SOME SMALL POLYMERS OBTAINED FROM NITROGEN HETEROCYCLES

A Thesis
submitted for the
Degree of Doctor of Philosophy
in the
Australian National University

by
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January, 1968
The work described in this Thesis was carried out by the candidate at the Australian National University. Where the work of other chemists was used, appropriate acknowledgement is given.

Noriaki Yamamoto
I sincerely thank Professor Adrien Albert, F.A.A., Head of the Department of Medical Chemistry, for continuous help and encouragement throughout the work; and Drs D. J. Brown, T. J. Batterham, and W. L. F. Armarego for helpful discussions and advice.

Grateful acknowledgement is also made to the Australian National University for award of a Scholarship.

I also thank Mrs S. M. Schenk for so ably typing this Thesis.
Introduction.

Many polymers arise incidentally in the course of chemical syntheses. Until comparatively recently, most polymers, even oligomers of low molecular weight, were set aside for lack of any readily accessible means for determining their constitution. If these substances had no useful physical properties, suggesting use as artificial fibers, mouldable plastics, or materials for paints and varnishes, they were for the most part not subjected to further examination. This was particularly true of the oligomers which arose in heterocyclic chemical work.

Today, there is a wide variety of physical instruments which can give information of many kinds about the structure of complex molecules. The existence of such facilities has prompted the investigations described in this Thesis. It is essentially a study of two, three, and four-fold oligomers which arise by the action of acid on several simple substances with nitrogen containing rings.

In detail, these oligomers were compounds obtained by the action of acid on pteridine and 2-amino-3-formylpyrazine (Section 1), 4-methylpteridine
(Section 2), and quinazoline (Section 4). This study of quinazoline necessitated a prior investigation of the three anhydro-polymers of 2-aminobenzaldehyde (Section 3), which were produced (together with other heterocyclic oligomers) by the action of acid on quinazoline.

After classifying some of the main types of (nitrogenous) heterocyclic polymerizations already known, Section 5 proceeds with a brief discussion of the various types of polymers dealt with in the body of this Thesis.

(1) Introduction
(2) The Dimer of 4-Methylpteridine
(3) Nucleophilic Addition Reactions of 4-Methylpteridine
(4) 4,6,7-Trimethyl- and 2,4,6,7-Tetramethyl-pteridine
CONTENTS

Introduction

Section 1: Action of Acid and Alkali on Pteridine and the Structure of the Monoformyl-anhydro-trimer of 2-Amino-3-formylpyrazine.

(1) The Ring-opening Reaction of Pteridine 1
(2) The Trimer of 2-Amino-3-formylpyrazine 5

Section 2: The Structure of the Dimer of 4-Methylpteridine.

(1) Introduction 9
(2) The Dimer of 4-Methylpteridine 10
(3) Nucleophilic Addition Reactions of 4-Methylpteridine 25
(4) 4,6,7-Trimethyl- and 2,4,6,7-Tetramethyl-pteridine 31
Section 3: The Structures of the Anhydro-polymers of 2-Aminobenzaldehyde.

(1) Introduction 40
(2) Anhydro-tri-2-aminobenzaldehyde 40
(3) Anhydro-tetra-2-aminobenzaldehyde 51
(4) A Reaction Pathway for the Formation of the Trimer and the Tetramer 67
(5) 2-Amino- and 2-Methylamino-benzaldehyde 70

Section 4: Structures of Compounds obtained by the Action of Acid and Alkali on Quinazoline.

(1) The Action of dilute Acid and Alkali on Quinazoline: Formation of 2-amino-benzaldehyde and its Anhydro-polymers 77
(2) The Structure of Substance Q 81
(3) A Reaction Pathway for the Formation of Substance Q 86
Section 5: A General Discussion of the Oligomerization of Nitrogen Heterocycles.

Section 6: Experimental.

(1) Introduction

(2) Experimental in Section 1

(3) Experimental in Section 2

(4) Experimental in Section 3

(5) Experimental in Section 4

Bibliography.

Appendix: Publications.
Section 1: Action of Acid and Alkali on Pteridine and the Structure of the Monoformyl-anhydro-trimer of 2-Amino-3-formylpyrazine.

(1) The Ring-opening Reaction of Pteridine.

Pteridine (1.1) gives 2-amino-3-formylpyrazine (1.2) when boiled with hot dilute sulphuric acid, then neutralized with 2N-potassium hydroxide (Albert, Brown, and Wood, 1956). This reaction, which is so different from the action of acid on 4-methylpteridine under the same conditions as shown in Section 2, was re-examined to obtain information on its course.

An improved method for preparing pteridine is recorded in the Experimental part (p.103).

By periodical chromatographic sampling, it was found that pteridine, in the presence of either acid or alkali, decomposed to 2-amino-3-formylpyrazine (1.2) without producing any detectable substance. Pteridine, in dilute sulphuric acid (pH 1.8) at 70°, produced only a blue fluorescent spot [due to the pyrazine (1.2)] on a paper chromatogram when sampled within 15 minutes. The most likely intermediate, 2-formamido-3-formylpyrazine (1.3) (see below), was found to be completely hydrolysed within 10 min. under the
same conditions. For preparative purpose the aminopyrazine (1.2) was best obtained at pH 2.5 by an improved method (see Experimental part).

In 0.1 N-potassium hydroxide or N-sodium carbonate at 25°, pteridine decomposed partly to the pyrazine (1.2) within one and a half hours, then, after a prolonged time at this temperature, several products were gradually and simultaneously formed; these could not be identified. When pteridine was set aside in aqueous borax buffer (pH 9.2) for 3 days at 20°, most of the starting material was recovered, and chromatography showed the formation of only a small amount of the pyrazine (1.2). On heating pteridine in this buffer solution at 65° for 6 hr., 15% of the pyrazine (1.2) was isolated and most of the pteridine was unchanged.

2-Formamido-3-formylpyrazine (1.3), a possible intermediate in the ring-opening of pteridine, was obtained (in 26% yield) by stirring the pyrazine (1.2) at 5° with a mixture of acetic formic anhydride and sodium formate, together with a product of higher melting point (see below; 46% yield). The infrared (i.r.) and the 1H-nuclear magnetic resonance (n.m.r.)
(1.1)  

(1.2: \( R = H \))  
(1.3: \( R = \text{CHO} \))

(1.4)

(1.5)
Figure 1.1 Ultraviolet spectra of:

A, 2-amino-3-formylpyrazine in chloroform;
B, 2-formamido-2-formylpyrazine in water (pH 7.0);
C, the monoformyl-anhydro-trimer in chloroform.
spectra of the lower melting product were consistent with the structure (1.3) (cf. Experimental part). The long wave-length peak of the ultraviolet (u.v.) spectrum (Perrin, 1962) of the primary amine (1.2) underwent a strong hypsochromic shift in the N-formyl-derivative (1.3) as expected (cf. Fig. 1.1). The formamidopyrazine (1.3) was found to hydrolyse slowly to the primary amine (1.2) at pH 7.0, and more quickly in acid (see above). Attempted synthesis of pteridine from 2-formamido-3-formylpyrazine and alcoholic ammonia in a sealed tube at 870° caused profound decomposition.

(2) The Trimer of 2-Amino-3-formylpyrazine.

Elementary analysis and molecular weight determination of the above higher melting-point substance indicated the molecular formula C16H13N9O3. It was shown as follows to be a monoformyl-anhydro-trimer of the aminopyrazine (1.2). (It will be referred to here simply as "the trimer".) Hot N-acetic acid (or cold trifluoroacetic acid) regenerated the pyrazine (1.2) almost quantitatively, indicating that the trimer had bonds easily hydrolysed by acid. Infrared analysis (a Nujol mull) showed
that the trimer possessed imino groups (3320, medium; 3240 and 3170 cm\(^{-1}\), weak) (they resisted acetylation with acetyl chloride or acetic anhydride in pyridine) as well as two different kinds of carbonyl group (1700 and 1680 cm\(^{-1}\), both strong). One carbonyl group, which showed absorption at 1680 cm\(^{-1}\), was presumably the \(\text{C-}\) formyl group of \(\text{N-}\) substituted 2-amino-3-formylpyrazine, taking into account the absorption band (1680 cm\(^{-1}\)) of the aminoaldehyde (1.2). Another (1700 cm\(^{-1}\)) might be a \(\text{N-}\) formyl or else a \(\text{C-}\) formyl group non-equivalent to the above \(\text{C-CHO}\).

The u.v. spectrum of the trimer in chloroform (\(\lambda_{\text{max}}\ 266, 277, 314, 368 \text{ m\(\mu\)}; \log \varepsilon 4.27, 4.25, 3.94, 3.99) showed a slight complexity compared with that of the aminoaldehyde (1.2) in the same solvent (cf. Fig. 1.1). However, the longest wave-length absorption maxima of both compounds were significantly close. When the trimer was dissolved in 95% ethanol, it gave a spectrum almost identical with that of the aminoaldehyde (1.2) in ethanol with the exception of the approximately triple height of the extinction coefficients of the former, indicating that the trimer was decomposed by this solvent to the monomer (1.2) (this was confirmed by chromatography).
Although the trimer was not very soluble in deuteriochloroform (and less soluble in other suitable solvents), several weak peaks were detected between \( \tau 0 \) and \( 3 \) in the n.m.r. spectrum by an ordinary measurement; no signal was observed above \( \tau 3.0 \). The region, \( \tau -1.5 \) and \( 3.35 \), was scanned on a Perkin-Elmer R10 n.m.r. spectrometer with a computer of average transients attachment (Digital Equipment Corporation, PDP-8S; measured by Mr N. L. R. King, Department of Chemistry, ANU.), and the average of approximately 120 scans is shown in Fig. 1.3. The spectrum consisted of a triplet at \( \tau 2.47 \) (\( J=7.5 \) c/sec., 1H), two pairs of coupled doublets (i.e. at 1.86 and 1.69, \( J=2.0 \), 2H each; at 1.72 and 1.50, \( J=2.5 \), 1H each), a broad doublet at 0.73 (\( J=7.5 \), 2H), a doublet at 0.53 (\( J=9.5 \), 1H), a singlet at -0.02 (2H), and a broad doublet at -0.85 (\( J=9.5 \), 1H). After deuterium exchange, the broad doublets at \( \tau 0.73 \) and -0.85 disappeared with simultaneous collapse of the triplet at \( \tau 2.47 \) and the doublet at 0.53 to singlets, indicating the presumable presence of \((-NH)_{2}CH\) and \(-NHCHO\) groups. The two pairs of the doublets are undoubtedly due to the ring-protons of the three pyrazine nuclei, two of which are equivalent.
The singlet at \(-0.02\) are assigned to two identical C-formyl groups. Combination of these partial structures led to the only possible structure \((1.4)\) for the trimer, i.e. 2-di(2'-formylpyrazin-3-ylamino) methyl-3-formamidopyrazine. The assignments of the signals in the n.m.r. spectrum are shown in Fig. 1.3. The closeness of the longest wave-length maxima in the u.v. spectra of the trimer and the monomer \((1.2)\) supports the structure \((1.4)\), because \((1.4)\) possesses a partial structure similar to \((1.2)\). The absorption band at 1700 cm\(^{-1}\) in the i.r. spectrum (see above) is assigned to the N-CHO group.

It is interesting to analyse the fragmentation patterns of the mass spectrum of the trimer \((1.4)\) (Fig. 1.2; measured by Dr J. K. McLeod, Research School of Chemistry, ANU.). The main fragment ions are illustrated in Fig. 1.4. There are certain ambiguities for the assignments: elimination of the formylpyrazinylamino- (cleavage 1) or the formamidopyrazinyl- (cleavage 2) group from the parent ion \((m/e 379)\) could give either the ion \(a\) or \(b\) (respectively) at \(m/e 257\) (M-122). No evidence has been sought to decide whether this peak is due to a mixture of the two ions, or either
one of them. Lack of a metastable ion peak at m/e 255 suggests that the peak at 256 [apparently due to the ion (1.5) or d] is most likely to arise directly from the parent ion by loss of either of the above two pyrazine groups accompanied by intramolecular hydrogen shift; this process would simultaneously produce the pyrazine ion (1.2) or c at m/e 123 shown in the figure. Intense metastable ion peaks (at m/e 204, 203, and 175.5) indicate loss of a molecule of CO from the ion a or b (i.e., from the C-CHO or N-CHO) to produce an ion of m/e 229, and successive loss of two molecules of CO from the ion (1.5) or d to give ion peaks at 228 and 200. The peak at 227 could probably result from loss of a hydrogen radical from ions of m/e 228 (but no metastable ion peak was observed at 226). The peak at m/e 200 is presumably to be assigned to the ion f or g, which loses first a hydrogen radical, then a molecule of HCN to give ion peaks at 199 and 172 (these cleavages were confirmed by the metastable ions at m/e 198 and 148). Loss of a molecule of CO from either ion (1.2) or c would give rise to the abundant peak at m/e 95, probably
due to the radical ion \( h \) which further decomposes to the ion \( i \) (m/e 68) by loss of a molecule of HCN (metastable ion peaks at m/e 73.5 and 48.7 confirm this degradation).

The trimer is most likely formed by a simple Michael-type addition of the amino group of the unchanged starting material to the C=N side-chain of a dimer such as formula (1.5) which would arise by a condensation of the activated C-formyl group (by N-formylation) of the initial product (1.3) and the amino group of (1.2). When the reaction was carried out over a longer time and at a higher temperature, the yield of the dimer increased and that of the initial product (1.3) decreased proportionately. In addition, the higher the concentration of the starting material (1.2) in acetic formic anhydride, the higher the proportion of the dimer to substance (1.3).

The action of acid on 2-amino-3-formylpyrazine (1.2) was also examined. When this pyrazine was stirred in 0.1 N-hydrochloric acid at room-temperature for 12 hr., the effect of the acid was not appreciable, whereas under these conditions
2-aminobenzaldehyde was almost completely converted to the anhydro-trimer (Albert and Yamamoto, 1966) as will be explained in Section 3. On heating the pyrazine (1.2) in a pH 2 buffer solution, an inseparable mixture of several products was formed but most of the starting material remained unchanged.
Figure 1.2  Mass Spectrum of the Trimer

![Mass Spectrum of the Trimer](image)
Figure 1.3 $^1H$ N.M.R. Spectrum of the Trimer in CDCl$_3$
Figure 1-4 Fragment ions in the Mass spectrum of the Trimer

(*X: metastable ion)
Section 2: The Structure of the Dimer of 4-Methylpteridine

(1) Introduction.

It was shown (Albert, Brown, and Wood, 1956) that 4-methylpteridine, treated with boiling dilute sulphuric acid at pH 1.5, was converted to a stronger base for which a provisional structure N-(3-acetyl-2-pyrazinyl)formamidine (2.1, p.12) was proposed (after elementary analysis; C, H, N) from analogy with the known ring-opening of pteridine as described in Section 1. When it was found that the molecular weight in boiling water was twice that required by formula (2.1), the structure of the degradation product was re-examined by modern physical methods, as will now be described.

Perrin and Inoue (1962, 1963) found, by potentiometric and kinetic studies, that 4-methylpteridine adds water across the 3,4-double bond to give an equilibrated mixture containing a little of the hydrate, 3,4-dihydro-4-hydroxy-4-methylpteridine (2.2). In acid solution, as was recently shown by n.m.r. (Albert, Batterham, and McCormack, 1966), 4-methylpteridine gives the cation (2.3) which is
dihydrated across the two unshared double bonds of the pyrazine ring. The u.v. spectrum of the cation, which is almost identical with that of the cation of 5,6,7,8-tetrahydro-4-methylpteridine, supports structure (2.3) (cf. Table 2.1, p.38). Pteridine, because it lacks the sterically-hindering 4-methyl group, contributes a higher proportion of the 3,4-hydrate to the equilibrium states of both the neutral species (Perrin and Inoue, 1962 and 1963), and the cation (Albert, Batterham, and McCormack, 1966).

It is well established that heterocyclic rings become less sensitive to hydrolytic fission as the number of doubly-bound nitrogen atoms declines. Hence the cation of 4-methylpteridine (2.3) (which has only two of these atoms) is more likely to resist acid-catalysed ring-fission than the monohydrated cation of pteridine (which has three).

(2) The Dimer of 4-Methylpteridine.

The compound formed by the action of dilute acid on the pteridine was obtained in improved yield (57%) by prolonged heating at a slightly lower
temperature (the reaction also took place at 25°, but more slowly: 12% yield after 8 days). Periodic checking by paper chromatography showed no intermediates and no other major product. The substance was isolated as the hemi-sulphate (monocation), which was basified to give the neutral species; both species were identical (infrared spectra) with those previously obtained (p. 9). The hemi-sulphate was converted to the sulphate (dication) in dilute sulphuric acid at pH 4. Elementary analysis showed that all the neutral species, the hemi-sulphate, and the sulphate contained the equivalent of two molecules of 4-methylpteridine and three molecules of tightly bound water.

The infrared spectrum showed that the dimer (neutral species) contained hydroxy and imino groups (3300 and 3200 cm$^{-1}$, broad and strong). The lack of characteristic absorption for carbonyl- and primary amino-groups (between 1800 and 1610 cm$^{-1}$) completely ruled out structure (2.1). The characteristic absorption bands of the hemi-sulphate were at 1100 (broad and strong, S=0) and 1640 cm$^{-1}$
(2.1) \[
\begin{array}{c}
\text{C} \quad \text{OH}_3 \\
\text{N:CHNH}_2 \\
\end{array}
\]

(2.2) \[
\begin{array}{c}
\text{HO} \quad \text{XH} \\
\text{N:CHNH}_2 \\
\end{array}
\]

(2.3) \[
\begin{array}{c}
\text{HO} \quad \text{H} \\
\text{N:CHNH}_2 \\
\end{array}
\]

(2.4) \[
\begin{array}{c}
\text{HO} \quad \text{H} \\
\text{N:CHNH}_2 \\
\end{array}
\]

(a) \( R=H \);
(b) \( R=H \), protonated on 3 or 3';
(c) \( R=H \), protonated on 3 and 3';
(d) \( R=C_2H_5 \)

(2.5) \[
\begin{array}{c}
\text{HO} \quad \text{H} \\
\text{N:CHNH}_2 \\
\end{array}
\]
[sharp and medium, an aminopyrimidinium group involving N-3 and N-8 in formula (2.3)]. Ultraviolet spectral studies, in various aqueous buffer solutions (cf. Table 2.1 and Fig. 2.1), showed that the dimer existed as a neutral species between pH 8 and 11, as a dication below pH 3, and apparently as an anion above pH 13, with complete reversibility between all species. (The hemi-sulphate mentioned above contains the monocation.) Structural similarity between the dimer and the dihydrated form of the monomer is shown by the closeness between the u.v. absorption maxima of the neutral species of the dimer ($\lambda_{\text{max}} 267, 300 \mu\mu$; $\log \varepsilon 4.03, 4.16$) and those of the (unstable) neutral species obtained by suddenly basifying the dihydrated cation (2.3); also between the maxima of the dication of the dimer and of the monomer (2.3) (Table 2.1). Two overlapping $pK_a$ values, 4.19 and 6.28 (Table 2.1), were obtained by potentiometric titration with acid and resolved by a Noyes calculation (cf. Albert and Serjeant, 1962).
Figure 2.1 Ultraviolet spectra of the dimer at A, pH 2.0; B, 9.0; C, 14.

The n.m.r. spectrum in hexadeuterio-dimethyl sulfoxide consisted of peaks at 7.78 s (3H), 7.02 m (2H), 6.57 s (1H), 5.97 m (1H), 5.12 m (3H), 4.68 m (1H), 4.10 m (2H), 2.68 m (1H), 2.09 s (1H), 1.97 s (1H), and 1.96 m (ca. 2H). After deuterium exchange, the singlet at 6.57 and the multiplets at 4.68, 4.10, 2.68, and 2.09 almost disappeared. The spectrum of 4,5-diamino-4′-methylpyridine, in the same solvent and pH 2, also showed that the dimer contained an N,N′-disubstituted 4,5-diamino-4′-methylpyrididine ring, of which Me(6) and H(2) signals appeared at 7.78 and 2.09, respectively (see above). However, analysis of the multiplets at 5.97, 5.12, and 4.10 was difficult because of their broadness. Therefore the spectrum was examined in DCl/D2O solution and judged to be somewhat shifted, but thus confirming that the structure of the neutral species of the dimer persisted in the stable dication.
The n.m.r. spectrum in hexadeuterio-dimethyl sulfoxide consisted of peaks at \( \tau \) 7.78s(3H), 7.02m(2H), 6.57s(1H), 5.97m(1H), 5.12m(3H), 4.68m(1H), 4.10m(2H), 2.68m(1H), 2.09s(1H), 1.97s(1H), and 1.96m(ca 2H). After deuterium exchange, the singlet at \( \tau \) 6.57 and the multiplets at \( \tau \) 4.68, 4.10, 2.68, and 1.96 almost disappeared. The spectrum of 4,5-diamino-6-methylpyrimidine in the same solvent [\( \tau \) 7.79s, Me(6); 2.09s, H(2); 3.74 and 5.51m, \( \text{NH}_2 \)(4 and 5)] suggested that the dimer contained an \( N\_N'\)-disubstituted 4,5-diamino-6-methylpyrimidine ring, of which Me(6) and H(2) signals appeared at \( \tau \) 7.78 and 2.09, respectively (see above). However, analyses of the multiplets at \( \tau \) 7.02, 5.97, and 5.12 were difficult because of their broadness. Therefore the spectrum was examined in DCl/D\textsubscript{2}O solutions and was found to give very similar signals, thus confirming that the structure of the neutral species of the dimer persisted in the stable dication. This spectrum, obtained in 3N-DCl (Fig. 2.2) contained a singlet (3H) at \( \tau \) 7.47, two double doublets (2H) around 6.32, a double triplet (1H) at 5.35, three doublets (3H) around 4.6, and
singlets (1H each) at 1.59 and 1.41. Taking account of the n.m.r. spectrum of the dihydrated 4-methylpteridine cation (2,3) (Table 2.2, p. 39), the structure of the dimer appeared to be the trihydrated dimeric molecule (2,4,a), namely 5,6,7,8-tetrahydro-6-hydroxy-4-methyl-7-(5',6',7',8'-tetrahydro-6',7'-dihydroxypteridin-4'-ylmethyl)pteridine. The possibility that the condensation occurred at the 3,4-bond was eliminated by the n.m.r. spectrum, because the signals of the Me(4) and CH2(4') groups in a 3,4-adduct would have appeared as singlets further up-field than were found (cf. the chemical shift of the 3,4-hydrated cation of 2-amino-4-methylpteridine; Table 2.2).

The position of the substitution was assigned to C(7), rather than C(6), with reasonable certainty by analogy with the acid-catalysed Michael-type reaction product (2,6, p.26) from 7-hydroxy-6-methylpteridine and 6-hydroxy-7-methylpteridine [the C=N(7,8) bond of these hydroxypteridines was shown to be a stronger carbanion receptor than the C=N(6,5); Albert and Serjeant, 1964]. Furthermore the X-ray crystallography of pteridine has shown
(Hamor and Robertson, 1956) that the 3,4-double bond is the shortest bond (1.28 Å) and hence it is particularly ethylenic and likely to add Michael reagents; the second shortest bond is the 7,8-bond (1.32 Å), and the 5,6-bond is longer (1.36 Å). It has been shown above, on the evidence of the n.m.r. spectra that the steric effect of the methyl group of 4-methoxyteridine has prevented the condensation from taking place (G(4) not present). The intensity of the signal for C(4) is greater than that of bond-lengths). It is not taken into account in the three expanded multiplets in the n.m.r. spectrum (Fig. 2.2). Assignments of the signals for the spectra in DCl and hexadeuterio-dinatrium sulphoxide are recorded in Table 2.2. The complex of the signal from the 4-methoxy-teridine can be explained in terms of non-equivalence of the geminal protons due to restricted rotation around the 4',7-bond.

The intensities of the u.v. spectra of the dication and the neutral species of the dimer (Table 2.1) were nearly twice those of the cation (2.3).
(Hamor and Robertson, 1956) that the 3,4-double-bond is the shortest bond (1.28 Å) and hence it is particularly ethylenic and likely to add Michael reagents; the second shortest bond is the 7,8-bond (1.32 Å), and the 5,6-bond is longer (1.36 Å). It has been shown above, on the evidence of the n.m.r. spectrum, that the steric effect of the methyl group of 4-methylpteridine has prevented the condensation from taking place on C(4). Hence (from consideration of bond-lengths), it is most likely to have taken place on the 7,8-double-bond. That the dication has the structure (2,4,c) was confirmed by the complete analysis of the three expanded multiplets in the n.m.r. spectrum (Fig. 2.2). Assignments of the signals for the spectra in DCl and hexadeuteriodimethyl sulfoxide are recorded in Table 2.2. The complexity of the signal from the 4'-methylene group can be explained in terms of non-equivalence of the geminal protons due to restricted rotation around the 4',7-bond.

The intensities of the u.v. spectra of the dication and the neutral species of the dimer (Table 2.1) were nearly twice those of the cation (2.3)
and its (dihydrated) neutral species, respectively, as required by the respective molecular weights; this helps to verify the above structures (2.4, a and c). Taking into account the ionization constants of 5,6,7,8-tetrahydro-4-methylpteridine ($\text{pK}_a$ 6.74) and the dihydrated 4-methylpteridine (2.3) (5.51) (cf. Table 2.1), the two overlapping $\text{pK}_a$ values of the dimer (6.28 and 4.19) were found compatible with the proposed structure (2.4,a), in which the further ionization of the monocationic species (2.4,b) exerted the usual coulombic repression of the acceptance of a second proton, namely to give the dication (2.4,c).

That the u.v. spectrum of the neutral species was immediately reproduced when freshly prepared acid and alkaline solutions were rapidly adjusted to pH 9, indicates the presence of the same pattern and amount of covalent hydration in all species. The three non-anionic species of the dimer were stable: no spectroscopic change occurred at pH 2 and 9 after storage for one month at 20°C. The dimer, dissolved in 2N-NaOD, gradually produced a dark violet colour and began to decompose (within 5 min. at 33°C), but the n.m.r. spectrum measured...
within 3 minutes showed the presence mainly of a trihydrated species (2.4,a). There was no signal at lower field than \( \tau 1.8 \), eliminating the possibility of dehydration to the pyrazine ring, which would be expected to give proton signals between \( \tau 0 \) and 1.5 (cf. the spectrum of 4-methylpteridine in \( D_2O \) in Table 2.2). No dehydration occurred on drying the specimen at 150° in a high vacuum, as shown by elementary analysis and spectra (i.r. and n.m.r.). Most of the dimer was recovered after heating at 70° for 17 hr. in an aqueous buffer solution at pH 10. This strong binding of water by the neutral species stands in contrast to the behaviour of the neutral species of 4-methylpteridine which, when generated in the hydrated state by the action of alkali on the cation (2.3), gradually becomes anhydrous (\( t_{1/2} \approx 20 \) min., at pH 8; Inoue and Perrin, 1963). The unusually strong covalent binding of water by the dimer (neutral species) is best explained by strong intramolecular hydrogen bonds, as shown in the folded configuration (2.5; p. 12), one with which space models are entirely compatible.
The intensity of the molecular ion region in the mass spectrum of the dimer (Fig. 2.3) measured by Dr. Q.N. Porter, University of Melbourne) decreased with time, no doubt due to dehydration. The M-1 ion peak was slightly more intense than that of the molecular ion at m/e 346, which could probably be caused by the very ready loss of a hydrogen radical. Below these two peaks in the molecular ion region, weak peaks were observed at m/e 310, 292, 290, and 288; the first two peaks could be due to the two dehydrated ion peaks M-2H₂O and M-3H₂O, respectively. Besides the strongest peak, due to water, the spectrum below m/e 146 gave intense fragmentation peaks almost identical with those produced by 4-methylpteridine (Goto et al., 1965).

Above, several chemical reactions were carried out to confirm the proposed structure (2.4.a) when the dimer was refluxed in ethanol (with a trace of toluene-p-sulphonic acid), elementary analysis of the product proved that two hydroxyl groups were replaced by ethoxyl. The presence of an unreplaced hydroxyl group and at least one ether group was confirmed by the i.r. spectrum (3300 vs N-H), 1065 bs (C-O-C) cm⁻¹).
The intensity of the molecular ion region in the mass spectrum of the dimer (Fig. 2.3; measured by Dr. Q.N. Porter, University of Melbourne) decreased with time, no doubt due to dehydration. The M-1 ion peak was slightly more intense than that of the molecular ion at m/e 346, which could probably be caused by the very ready loss of a hydrogen radical. Below these two peaks in the molecular ion region, weak peaks were observed at m/e 310, 292, 290, and 289; the first two could be due to the two dehydrated ion peaks M-2H$_2$O and M-3H$_2$O, respectively. Besides the strongest peak, due to water, the spectrum below m/e 146 gave intense fragmentation peaks almost identical with those produced by 4-methylpteridine (Goto, et al, 1965).

Apart from the spectroscopic evidence mentioned above, several chemical reactions were carried out to confirm the proposed structure (2.4,a). When the dimer was refluxed in ethanol (with a trace of toluene-p-sulphonic acid), elementary analysis of the product proved that two hydroxyl groups were replaced by ethoxyl. The presence of an unreplaced hydroxyl group and at least one ether group was confirmed by the i.r. spectrum [3230 bs (OH), 1065 bs (C-O-C) cm$^{-1}$].
The n.m.r. spectrum clearly indicated no skeletal change and the presence of two ethoxyl groups (cf. Table 2.2). Because the hydroxyl group on C(6) in the formula (2.4,a; p.12) is much more sterically hindered [see formula (2.5)] than the others, this alcohohate is considered to have structure (2.4,d).

It was found that 4-methylpteridine in dilute sulphuric acid was oxidized by hydrogen peroxide to 6,7-dihydroxy-4-methylpteridine, which was unambiguously synthesized from 4,5-diamino-6-methylpyrimidine and oxalic acid. The physical properties of the product were in accordance with the structure (the u.v., n.m.r., and i.r. spectra are shown respectively in Table 2.1 and 2.2, and in the Experimental part). The u.v. spectrum and the two anionic pKₐ values were similar to those of 6,7-dihydroxypteridine (Table 2.1). The n.m.r. spectrum indicated that 6,7-dihydroxy-4-methylpteridine formed no hydrate in acid.

However on oxidation of the dimer under the same conditions, the product [which was isolated as a sulphate (C₁₄H₁₈N₈O₄,H₂SO₄) and gave the u.v. and n.m.r. (in DCl/D₂O and d₆-DMSO) spectra similar to those of the starting material] was found to possess
no carbonyl group (i.r. spectrum). Oxidation of the dimer with alkaline potassium ferricyanide or permanganate gave a mixture of several, inseparable products. When manganese dioxide (or acetic anhydride) in dimethyl sulphoxide was used for the oxidation, a reddish-brown substance (m.p. above 280°) was the principal product. The same substance was obtained in better yield in an attempted acylation of the dimer with acetic anhydride in pyridine (also with acetic formic anhydride in the presence of sodium formate, but in less yield). On the evidence of the elementary analysis, and the i.r. (3400 broad and weak, presumably an imino group; 1640 cm.\(^{-1}\) strong, a conjugated C=C group) and the u.v. spectra (the Experimental part; the long wave-length absorption maximum at 509 m\(\mu\) denotes a long conjugated pathway), the product was assigned the structure 3,7-dihydro-4-methyl-7-(pteridin-4-ylmethylene)pteridine (2-7). A compound with this skeletal structure has been obtained by the oxidation of compound (2.6) (Albert and Serjeant, 1964). The same structure exists also in pterorhodin, which occurs in the wings of the Javanese butterfly Appias nero (Pfleiderer, 1963) and apparently, other
species also. Pterorhodin (2.8) was synthesized by the oxidative condensation of xanthopterin and 7-methylxanthopterin (Hitchings, et al., 1949).

(3) Nucleophilic Addition Reactions of 4-Methylpteridine.

Much work has been done on nucleophilic addition reactions of pteridines [e.g. of 6-hydroxy- (Albert and Reich, 1961), 2-hydroxy- (Albert and Howell, 1962), 7-hydroxy- (Albert and McCormack, 1965), and 2-aminopteridine (Albert and McCormack, 1966)], all of which gave 1:1 adducts. Because 4-methylpteridine gives the di-adduct (2.3) in acid solution, it was necessary to examine the behaviour of the pteridine towards bulkier nucleophiles to see whether mono-adducts were preferred when the molecular complexity of the adducts was increased. This experiment was suggested by formation of the dimer, as described above.

An equivalent amount of 4-methylpteridine and barbituric acid was found to give an 1:1 adduct quickly and almost quantitatively in dilute acid. The i.r. spectrum showed carbonyl groups (1690 and 1660) and a hydroxy group (3120 cm\(^{-1}\)). In the
The n.m.r. spectrum of a benzylamine adduct of the 1:1 sttaking into account the reported chemical shifts of the Me(4) group in the 3,4-hydroxy- and 2-amino-pteridines (Table 2.2), the presence of two coupled doublets at 4.33 and 4.61 proved that the addition took place on the 3,4-bond of the pyrimidine ring. An ultraviolet spectral study, in perchloric acid solutions, confirmed this, as the absorption that the 1:1 adduct shows at 0-11, and methanolic, a zwitterion at 4.5-5.5, (Fig. 7.4) and the two approximate pK values were 4.0 and 6.0. The identification of the zwitterion of the 1:1 adduct was consistent with that of the long-term adduct of tetramethyl-pteridine, which has the same 6-position, because the presence of an acidic peak in the cation at 7.5 is usual for 7,8-dimethyl-pteridine.
n.m.r. spectrum (Na$_2$CO$_3$/D$_2$O solvent) the singlet at $\tau$ 7.65, attributed to the Me(4) group, eliminated the possibility of addition across the 3,4-bond such as occurs in 2-hydroxy- and 2-amino-pteridine (see above). The signal of such an aliphatic Me(4) group in the adduct would be expected to appear a little up-field, taking into account the reported chemical shifts of Me(4) group in the 3,4-hydrates of 2-amino-4-methyl- and 2,4,6,7-tetramethyl-pteridines (cf. Table 2.2). The presence of two coupled doublets at $\tau$ 4.35 and 2.61 proved that the addition took place on the pyrazine ring. An ultraviolet spectral study, in solutions of various pH, showed that the 1:1 adduct existed as a mono-cation below pH 1, and a monoanion at 8-11, and mainly as a zwitterion at 4.5-5.5 (Fig. 2.4). The two approximate p$K_a$ values were 4.0 and 6.0. The spectrum of the zwitterion of the adduct was almost identical with that of the anion. This showed that the trihydroxypyrimidinyl group is in the 7- (not the 6-) position, because 7,8-dihydro-4,6-dimethyl-pteridine has the same long-wave absorption peak in the cation as in the neutral species as is usual for 7,8-dihydropteridines.
generally, whereas 5,6-dihydro-4-hydroxypteridine and other 5,6-dihydro-derivatives undergo a large spectral shift when converted to the cation (Albert and Nagasawa, 1962; cf. Table 2.1). This assignment of structure (A.4) was confirmed by analogy with ultraviolet absorption (2,9) and comparison of bond-lengths, as was the case for the 1:1 adduct (2,10.b).

When two molar equivalent of barbituric acid were used instead of one, a 2:1 adduct (2,10.a) was isolated after prolonged stirring; the structure was confirmed by the i.r. and n.m.r. spectra of 5-hydroxy-4-methylpteridine b-bituric acid (A.4), readily gave the 1:1 adduct (2,10.b), the structure of which was consistent with the i.r. and the n.m.r. spectra. To confirm the position of the peripheral group in the adduct (2,9.a), an attempt was made to oxidise it (with hydrogen peroxide in dilute acid) to give a 4-methylpteridine and barbituric acid at A, pH 1.0; B, 5.0; C, 9.0.

Figure 2.4: Ultraviolet spectra of the 1:1 adduct of 4-methylpteridine and barbituric acid at pH 1.0; B, 5.0; C, 9.0.
generally; whereas 5,6-dihydro-4-hydroxypteridine and other 5,6-dihydro-derivatives undergo a large spectral shift when converted to the cation (Albert and Matsuura, 1962; cf. Table 2.1). This assignment of structure (2.9,a) was confirmed by analogy with substance (2.6) and comparison of bond-lengths, as was done for the dimer (p.16).

When two equivalents of barbituric acid were used instead of one, a 2:1 adduct (2.10,a) was isolated after prolonged stirring; the structure was confirmed by the i.r. and n.m.r. spectra. 6-Hydroxy-4-methylpteridine and barbituric acid readily gave the 1:1 adduct (2.9,b), the structure of which was consistent with the i.r. and the n.m.r. spectra. To confirm the position of the pyrimidinyl group in the adduct (2.9,a), an attempt was made to oxidise it (with hydrogen peroxide in dilute sulphuric acid at 25°) to the adduct (2.9,b) but this substance could not be detected among the many decomposition products. Upon treatment of 4-methylpteridine with approximately two equivalents of sodium hydrogen sulphite, the 5,6:7,8-di-adduct (2.10,b) was readily formed. The assignments of
the signals in the n.m.r. spectra of these adducts are shown in Table 2.2.

In order to confirm that the C=N(7,8) bond of 4-methylpteridined was involved in the formation of the dimer and in the 1:1 adduct with barbituric acid, a synthesis of 7-(or 6-)deuterio-4-methylpteridine was attempted through substitution of the hydroxy group in 7-(or 6-)hydroxy-4-methylpteridine with a chlorine atom. However chlorination of the hydroxypteridine by commonly used methods (e.g. phosphorus pentachloride in phosphoryl chloride or in phosphorus trichloride) was unsuccessful mainly because of the poor solubility of the starting material in the solvent. Refluxing 7-hydroxy-4-methylpteridine with phosphorus pentachloride in pentachloroethane (a method introduced for resistant examples by Albert and Clark, 1964) gave 7-chloro-4-dichloromethylpteridine, in poor yield (10%), and much intractable black tar. The structure of the chloropteridine was derived from elementary analysis, and from i.r., u.v., and n.m.r. spectra (Experimental part, p. 116).
Several attempts were made to see if the methyl group of 4-methylpteridine would react as a Michael-type donor with various substances that often act as acceptors at pH 2, such as 6-hydroxy- or 2-amino-pteridine (Albert and Serjeant, 1964; Albert and McCormack, 1966), but no condensation took place.

(4) 4,6,7-Trimethyl- and 2,4,6,7-Tetramethyl-pteridine.

A 4-methyl group, in those azanaphthalenes which have a pyrimidine ring in the molecule, is well known to reduce greatly the amount of hydration across the 3,4-bond (Albert and Armarego, 1965). Hence it was expected that the above trimethyl- and the tetramethyl-pteridines, (both substances hitherto unknown), might resist the hydronium-catalysed hydration across both the 3,4-bond and the pyrazine ring, and, consequently, might be stable even on heating under acidic conditions and give further information about the reaction pathway for the formation of the dimer from 4-methylpteridine. No hydration across
the 1,2-position of a pteridine has ever been reported.

Condensation of diacetyl with 4,5-diamino-6-methyl- and 4,5-diamino-2,6-dimethyl-pyrimidine respectively gave the trimethyl- and the tetramethyl-pteridine, the structures of which were consistent with the i.r. (no OH, NH, nor C=O group) and the n.m.r. (Table 2.2) spectra. The tetramethylpteridine was dissolved in DCl/D$_2$O (initial pH, 1.0) in order to examine the steric effect of the methyl groups on hydration. The n.m.r. spectrum of the tetramethyl-pteridine cation, measured within 4 minutes of acidification, showed that a species hydrated across the 3,4-bond was predominant at the initial stage (the assignments of peaks are shown in Table 2.2); this conclusion was reached by taking into account the reported chemical shifts of the 3,4-hydrated cations of 2-amino-4-methyl-, 6,7-dimethyl-, and 2,6,7-trimethyl-pteridine (cf. Table 2.2). The presence of 5,6:7,8-dihydration was excluded by the above n.m.r. spectrum, and any structure similar to that of the dimer (2,4,a) was similarly ruled out by the absence of a methylene signal. Also any possibility of ring-opening between the 3,4- or the
7,8-bond was eliminated by the lack of a carbonyl group peak in the i.r. spectrum of the DCl/D_2O solution (pH 1), in which the only absorption between 1800 and 1600 cm\(^{-1}\) was a medium-strong peak at 1636 cm\(^{-1}\) (assignable to the methylformamidinium group in the 3,4-hydrate). No clear n.m.r. spectrum was obtainable after setting the solution aside at 20\(^\circ\) for 30 min. because of decomposition (it became dark brown). 4,6,7-Trimethylpteridine in DCl solution decomposed so quickly that no spectrum could be obtained.

Hydration of the tetramethylpteridine was then studied through u.v. absorption (see Table 2.1 and Fig. 2.5). The spectrum of the cation, which remained unchanged for at least a week at 20\(^\circ\), resembled that of 2,6,7-trimethylpteridine (3,4-hydrate; cf. Table 2.1). The equilibrium pK\(_a\) value, 2.65 at 20\(^\circ\), was obtained spectrophotometrically (also 2.64, potentiometrically). The following non-equilibrium results were obtained in rapid-reaction apparatus (spectrophotometrically; cf. Perrin, 1965). When a freshly prepared solution at pH 2.0 was neutralized, a rapid dehydration reaction occurred
Figure 2.5 Ultraviolet spectra of 2,4,6,7-tetramethylpteridine at A, pH 0.0 (stable hydrated cation); B, 5.2 (anhydrous neutral species); C, 8.0 (rapidly dehydrating neutral species).
The u.v. spectrum of the unstable neutral species (hydrated across the 3,4-bond on the evidence of the n.m.r., u.v., and i.r. spectra mentioned above) is shown in Fig. 2.5, C; it closely resembles that of the 3,4-hydrate of pteridine (cf. Table 2.1). The $pK_a$ for the equilibrium between the two hydrated tetramethylpteridine species was found, from rapid spectrophotometric measurements, to be 6.71 at $20^\circ$. The observed value was slightly higher than the predicted approximate figure, 6.3, which was obtained by adding to 4.79 (the $pK_a$ value of 3,4-hydrated pteridine; Perrin, 1962), appropriate increments for the methyl groups (cf. Albert, Howell, and Spinner, 1962).

4,6,7-Trimethylpteridine gave, at various pH values, u.v. spectra similar to those of the tetramethylpteridine (Table 2.1). However spectra in acidic media changed slowly but irreversibly. The unstable, neutral molecule of the 3,4-hydrate of the trimethylpteridine was found to give an u.v. spectrum ($t_{1/2}$ for dehydration 4.0-4.5 sec. at pH 5.0 and 3.2 min. at 8.0, at $20^\circ$) similar to that of the
tetramethyl compound; however measurement was difficult because of the low value of the equilibrium $pK_a$ and gradual decomposition of the hydrated cation.

The steric hindrance to hydration exerted by a 4-methyl group in 4,6,7-trimethyl- and 2,4,6,7-tetramethyl-pteridine is revealed on their lower equilibrium $pK_a$ values (Table 2.1) compared with those of 6,7-dimethyl- and 2,6,7-trimethyl-pteridine (2.93 and 3.73, respectively; Table 2.1), because a decrease in the amount of hydrated species causes a decrease in the $pK_a$ values, whereas a methyl group otherwise always raises a $pK_a$ value, evidence of base-strengthening (Albert and Armarego, 1965).

Pteridine exists in acid as an equilibrated mixture containing more of the 3,4-hydrated cation (79%) than the 5,6:7,8-dihydrate, whereas the 4-methyl derivative, because of the sterically-hindering 4-methyl group, gives exclusively the dihydrated cation (2.3) [Albert, Batterham, and McCormack, 1966; also in the present work the n.m.r. spectrum of 4-methylpteridine was examined at pH 3 (the equilibrium $pK_a$ is 2.94); measurement, which was completed within 2 minutes of acidification, showed
the presence of a mixture of the anhydrous neutral species and the dihydrated cation (ca 3:1), but no signal due to the 3,4-hydrated species (or its cation) was observed. Ethyl 6,7-dimethylpteridine-4-carboxylate, in spite of steric hindrance exerted by the 6- and 7-methyl groups, has recently been shown (Clark, 1967) to give an equilibrated mixture of the (kinetically favoured) 5,6,7,8-dihydrated cation and the 3,4-hydrated cation. However in 4,6,7-trimethyl- and 2,4,6,7-tetramethyl-pteridine, the base-strengthening effect of the 4-methyl group (i.e. the methyl group in the ring which forms the cation) combined with the blocking effect of the 7- and 6-methyl group may probably stabilize the cation of the 3,4-hydrate and suppress all hydration across the pyrazine ring.
## Table 2.1

### Physical properties of some pteridines.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Ionizations (H₂O; 20°)</th>
<th>Spectrometry²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Species²</td>
<td>pKₐ</td>
</tr>
<tr>
<td><strong>Dimer (2,4, a)</strong></td>
<td>++</td>
<td>4.19±0.02</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>6.28±0.02</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pteridine³</strong></td>
<td>0¹</td>
<td>4.12±0.05</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>4.79±0.04</td>
</tr>
<tr>
<td></td>
<td>0⁺</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>0⁻</td>
<td>5.17±0.06</td>
</tr>
<tr>
<td></td>
<td>0⁻²</td>
<td>-</td>
</tr>
<tr>
<td><strong>4-Methyl-²</strong></td>
<td>0¹</td>
<td>2.94±0.13</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>5.51±0.03</td>
</tr>
<tr>
<td></td>
<td>0⁺</td>
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<tr>
<td><strong>5,6,7,8-Tetrahydro-4-methyl-²</strong></td>
<td>+</td>
<td>6.74±0.02</td>
</tr>
<tr>
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<td>-</td>
</tr>
<tr>
<td><strong>2,4,6,7-Tetramethyl-²</strong></td>
<td>0¹</td>
<td>2.65±0.03</td>
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<td>+</td>
<td>2.64±0.02</td>
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<tr>
<td></td>
<td>0⁺</td>
<td>6.71±0.06</td>
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<td></td>
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<td>1.74±0.05</td>
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<td><strong>6,7-Dihydroxy-4-methyl-²</strong></td>
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<td>10.17±0.08</td>
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<td><strong>7,8-Dihydro-4,6-dimethyl-³</strong></td>
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<tr>
<td></td>
<td>0⁻</td>
<td>-</td>
</tr>
<tr>
<td><strong>5,6-Dihydro-4-hydroxy-³</strong></td>
<td>+</td>
<td>2.94±0.04</td>
</tr>
</tbody>
</table>

- inflections are underlined (in italics).
- dication (++), cation (+), neutral species (0), anion (-),
dianion (--), the 3,4-hydrate (*), and the 5,6,7,8-dihydrate (**).
- Analytical wave-length in μm; an entry in this column indicates a spectrometric (otherwise potentiometric) determination (cf. Albert and
- Values from Perrin, 1962.
- Values from Brook and Ramage, 1955.
- Values from Albert, Brown, and Cheeseman, 1952.
- The anhydrous cation becomes hydrated so rapidly that it has not been independently observed.
- The extinction coefficients are calculated as 100% of the hydrated neutral species.
- Above this pH, the rate of dehydration is so fast that measurement is difficult.
### Table 2.2

<table>
<thead>
<tr>
<th>Compounds</th>
<th>H(2')</th>
<th>H(2)</th>
<th>H(6')</th>
<th>H(7)</th>
<th>H(6)</th>
<th>CH₂(4')</th>
<th>CH₃(4)</th>
<th>OC₂H₅</th>
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<tr>
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<td>1.97s</td>
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<td>4.58d⁺</td>
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<td>Diethoxy-analogue (2.4, d)</td>
<td>2.09s</td>
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<td>5.08d</td>
<td>6.00m</td>
<td>7.0m²</td>
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<td>J=2.8</td>
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**Pteridines**

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<th>H(6)</th>
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<td>(Me)²</td>
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<tr>
<td>4-Methyl-</td>
<td>0.58s</td>
<td>(6.88s)</td>
<td>0.66d⁺</td>
<td>0.48d⁺</td>
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<tr>
<td></td>
<td>1.48s</td>
<td>(7.45s)</td>
<td>4.74d⁺</td>
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<td>J=2.5</td>
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<tr>
<td>2-Amino-4-methyl-</td>
<td>-</td>
<td>(7.83s)</td>
<td>1.28⁺</td>
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</tr>
<tr>
<td>(7.04s)</td>
<td>(6.93s)⁺</td>
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<td>2,4,6,7-Tetramethyl-</td>
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<td>(7.93s)</td>
<td>(7.30s)</td>
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</tr>
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<td>(7.30s)</td>
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<td>4,6,7-Trimethyl-</td>
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<td>2,6,7-Trimethyl-</td>
<td>(7.30s)</td>
<td>3.52s</td>
<td>(7.30s)</td>
<td>(7.30s)</td>
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<tr>
<td>6,7-Dimethyl-</td>
<td>1.20s</td>
<td>3.42s</td>
<td>(7.30s)</td>
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<tr>
<td>6,7-Dihydroxy-4-methyl-</td>
<td>0.88s</td>
<td>(7.46s)</td>
<td>-</td>
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<tr>
<td>(2.9, a)</td>
<td>1.91s</td>
<td>(7.65s)</td>
<td>2.61d</td>
<td>4.35d</td>
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<tr>
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<td>2.10s</td>
<td>(7.74s)</td>
<td>-</td>
<td>4.57s</td>
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<tr>
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<td>(7.73s)</td>
<td>5.35bs⁺</td>
<td>4.92bs⁺</td>
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<tr>
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<td>1.58s</td>
<td>(7.53s)</td>
<td>4.86bs⁺</td>
<td>4.71bs⁺</td>
</tr>
</tbody>
</table>

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1. Sodium 3-trimethylsilylpropanesulphonate as internal standard, except for Solvents A and E where tetramethylsilane was used.  
2. A = [⁵⁷Cl]-dimethyl sulfoxide, B = 3N-DCl, C = D₂O, D = N-DCl (the solution: pH 1.5-1.0, E = deuterio-chloroform, F = 10D Na₂CO₃ in D₂O, G = 55 Na₂S₂O₅ in D₂O.  
3. The chemical shift is approximate.  
4. Values in parentheses indicate the chemical shifts of the methyl groups.  
5. The material is extremely unstable in dilute alkaline solution at 0.1M.  
6. All values from Albert, Batterham, and McCormack, 1966.  
7. Suffixes: b, broad; s, singlet; d, doublet; dd, double doublet; t, triplet; dt, double triplet; m, multiplet; j, coupling constants (c/sec.); * the 3,4-hydrate; ** the 5,6,7,8-dihydrate; t assignments were made according to the results of Goto and Matsuda, for mono-methylpteridine, 1963 and 1965.
Section 3: The Structures of the Anhydro-polymers of 2-Aminobenzaldehyde.

(1) Introduction

An anhydro-polymer is slowly formed from 2-aminobenzaldehyde on storage at room temperature, whereas mineral acid quickly produces not only this polymer but another one as well. Because similar substances were obtained by the action of hot acid on quinazoline (cf. Section 4), it seemed desirable to re-examine the structures suggested for the 2-aminobenzaldehyde polymers by Seidel and Dick (1927) on the basis of chemical reactions. The spectral properties of these polymers were found to be not in accord with these authors' proposal but pointed unequivocally to other structures, the derivation of which will be explained in this Section.

(2) Anhydro-tri-2-aminobenzaldehyde.

This substance, obtained when 2-aminobenzaldehyde is set aside with 0.1N-hydrochloric acid at room temperature (Seidel, 1926; Seidel and Dick, 1927),
has an empirical formula corresponding to three molecules of the aldehyde less two molecules of water (C_{21}H_{17}N_{3}O). Bamberger (1927) first assigned it the structure (3.1, p.46) on the evidence only of the molecular weight (measured ebullioscopically in pyridine) and the formation of a mono-N-methyl derivative with methanol and hydrogen chloride. Seidel and Dick (1927) preferred the tautomeric pair of formulae (3.1) and (3.2); the latter was used to explain the formation of a mono-acetyl (but no di-acetyl) derivative and the failure to condense the trimer directly with another molecule of 2-aminobenzaldehyde under the neutral conditions; but formula (3.1) was required to explain the formation of a di-nitroso derivative, a nitroso derivative of the acetyl compound, and the condensation with 2-aminobenzaldehyde in the presence of strong acid to give the anhydro-tetramer.

In the present work the i.r. spectrum of the trimer indicated the presence of an aliphatic hydroxy group (3200 cm\(^{-1}\), broad and strong) but no carbonyl group. An u.v. spectral study, made in water over a range of pH values, showed that
the trimer existed as a stable neutral molecule between pH 4 and 12.5. However below pH 3 it was at equilibrium with 2-aminobenzaldehyde. The ultraviolet spectra of the trimer had bands which were easily hydrolyzed by acid to re-form the monomer. In solution (e.g. 10^-5 mole/l) the rate of depolymerization was roughly proportional to hydrogen ion concentration, for the reaction was about complete in 20 min. at pH 0, 10 hr at pH 1.0, 3 days at pH 2.0, and 1 month at pH 3.0. The u.v. spectra of the trimer in ethanol (Fig. 3.1) showed maxima at 286 m\(_\lambda\) but no absorption above 300 m\(_\lambda\), which indicated lack of a highly conjugated system. The n.m.r. spectra (Fig. 3.2) consisted of a singlet (1H) at \(\delta = 6.7\), two doublets (2H each) at 4.93 and 4.43 (with \(v=4\) c/sec.), a singlet (3H) at 4.84, a broad singlet (4H) at 3.24, and a complicated multiplet from aromatic protons (18H). The dilute solutions contained more than a two-fold excess of thiourea, the azomethine group in the trimer. No such proton signal is usually expected between 6.3 and 8.3. This was interpreted to illustrate the absence of an azomethine group in the trimer.

**Figure 3.1** Ultraviolet spectra, in ethanol, of A, the trimer; B, the monoacetyl-trimer; C, the diacetyl-trimer; D, the diformyl-trimer.
the trimer existed as a stable neutral molecule between pH 4 and 12.5. However below pH 3 it was at equilibrium with 2-aminobenzaldehyde, indicating that the trimer had bonds which were easily hydrolysed by acid to re-form the monomer. In dilute solution \( (10^{-5} \text{ mole/l.}) \) the rate of depolymerization was roughly proportional to hydrogen ion concentration, for the reaction was almost completed within 20 min. at pH 0, 10 hr. at pH 1.0, 3 days at pH 2.0, and 1 month at pH 3.0. The u.v. spectrum of the trimer in ethanol (Fig. 3.1) showed peaks at 240 and 286 \( \mu \mu \) but no absorption above 320 \( \mu \mu \), which indicated lack of a highly conjugated system. The n.m.r. spectrum (Fig. 3.2) consisted of a singlet (1H) at \( \tau 6.73 \), two doublets (1H each) at 4.63 and 4.43 (both \( J=4 \) c/sec.), a singlet (1H) at 4.34, a broadened doublet (1H) at 3.53 \( (J=4) \), and a complicated multiplet from aromatic protons (12H) between 2.5-3.5. There was no signal at lower field than \( \tau 2.5 \), indicating the absence of an azomethine group \((-\text{CH=N-})\) in the trimer, because such proton signal is usually expected between
\[ \tau 1.5 \text{ and } 2.0 \] (cf. the value \[ \tau 1.50 \] obtained in the present work for the \( \text{CH}=\text{N} \) proton of benzylidenaniline, dissolved in carbon tetrachloride). After deuterium exchange, the doublets at \( \tau \, 4.63 \) and \( 4.43 \) collapsed to sharp singlets, that at \( 3.53 \) disappeared, and the singlet at \( 6.73 \) (attributed to a hydroxy group) almost disappeared. Because the trimer contains only one oxygen atom, the doublet at \( 3.53 \) was ascribed to an imino proton coupled with a vicinal methine proton \( (4.63, J=4 \, \text{c/sec.}) \), and the doublet at \( 4.43 \) to the methine proton of a secondary alcohol. No peak due to a methylene group was present. Consideration of these exchange phenomena and the possible mode of formation of the compound led to the partial structures: \(-\text{CH(OH)}\text{C}_6\text{H}_4\text{N(O)}\) and \(-\text{CH(-NH)}\text{C}_6\text{H}_4\text{N(O)}\). The trimer had another methine proton which gave a singlet at \( \tau 4.34 \), suggesting a partial structure, \(-\text{CH(-N-)}\text{C}_6\text{H}_4\text{N(O)}\) for the rest of the molecule. Combination of these three partial structures allowed only one total structure, namely \( 2,4:2',N-(\text{o-aminobenzo})-1,3:\alpha,2''-(\alpha\text{-hydroxytolueno})-1,2,3,4\text{-tetrahydroquinazoline} \) \( (3.3,a) \). A molecular model is shown as formula \( (3.4,a) \).
Figure 3.2: N.m.r. Spectrum of the Triazin in D_2O-DMSO-CDCl_3
This structure (3.2a) was confirmed by examination of the spectra of Selena's monopropyl derivative and of a diisopropyl derivative. The spectrum in addition of the monopropyl-trimer is similar to the n.o.r. spectrum (Table 3). This was consistent with the n.o.r. spectrum (Table 3). The spectrum in the 17-21 cm$^{-1}$ region showed a 17-21 cm$^{-1}$ peak in agreement with the n.o.r. spectrum (Table 3).
Slight variations in preparation gave specimens of the trimer with different melting-points (between 233-247°), although the i.r. spectra were identical (cf. Experimental part, p. 119). This could presumably be caused by different ratios of α- and β-configuration of the 7″-hydroxyl group in the trimer. N.m.r. data are recorded in Table 3 (p, 76).

This structure (3.3,a) was confirmed by examination of the spectra of Seidel's monoacetyl derivative (1926) and of a diacetyl derivative which, contrary to Seidel's report, was readily obtainable. The i.r. spectrum of the monoacetyl compound resembled that of the trimer, except for bands assignable to an N-acetyl substituent, e.g. 1660 cm⁻¹. This derivative still possessed a hydroxyl group (3200 cm⁻¹, broad and strong) but no ester group (no additional band near 1200 cm⁻¹). The u.v. spectrum in ethanol (Fig. 3.1, p. 42) resembled that of the starting material. Thus, the monoacetyl-trimer is considered to be the N-acetyl derivative (3.3,b). This was consistent with the n.m.r. spectrum (Table 3), in which the singlet from H(4) (τ 3.43) appeared at considerably
lower field than that of the proton in the trimer (τ 4.63). When the solution was shaken with a trace of 35% DCl, the singlet at τ 6.67, attributable to the 7"-hydroxy group, disappeared with simultaneous collapse of the doublet at τ 4.44 [from H(7")] to a singlet.

The u.v. spectrum of the diacetyl derivative (Fig. 3.1) closely resembled that of the monoacetyl-trimer. The i.r. spectrum showed no absorption band near 3300 cm.\(^{-1}\), which provided proof that the hydroxy group of (3,3,a) was acetylated, and this was confirmed by strong absorption bands at 1735 and 1215 cm.\(^{-1}\) due to the O-acetyl group, apart from the strong band at 1675 cm.\(^{-1}\) due to N-acetyl. The two clear singlets at τ 7.69 and 7.47 (3H each) in the n.m.r. spectrum are best assigned to an O-acetyl and a N-acetyl group respectively, using the signal at τ 7.40 (N-acetyl) in the monoacetyl-trimer as a guide. The singlet at τ 4.47 (1H) is assigned to H(2) because this proton appeared at τ 4.34 in the trimer and τ 4.28 in the monoacetyl-trimer, and it should not be greatly affected by the two
acetyl substituents. Although a complicated multiplet was found between $\tau$ 2.5 and 3.5, two sharp singlets at $\tau$ 3.31 and 3.16 (1H each) stood out, and are assigned to H(4) and H(7") (cf. Table 3). The diacetyl-trimer was found to contain no exchangeable hydrogen atom.

All this evidence points to a common skeleton for the parent substance and the mono- and di-acetyl derivatives, which are assigned structures (3,3, a, b, and c), respectively.

Similar treatment of the trimer with acetic formic anhydride gave a diformylated anhydro-trimer ($C_{23}H_{17}N_3O_3$). This material was also obtained (in the present work) from 2-aminobenzaldehyde as a minor product (20% yield) together with the major product (40%), 2-formamidobenzaldehyde, on treatment with acetic formic anhydride at 30°. The u.v. spectrum (Fig. 3.1, D) differed considerably from those of the trimer and its acetyl derivatives by having peaks at longer wave-length (315 and 350 μ), indicative of a skeletal change and the presence of a more highly conjugated system. The diformyl-trimer was found to possess two kinds of carbonyl i.r. bands at 1685 and 1665 cm.$^{-1}$ but no evidence
of an imino or a hydroxy group. This was confirmed by the n.m.r. spectrum (Fig. 3.3), in which singlets at \( t = 0.34 \) (1H) and 0.96 (2H) were assigned to formyl protons, consistent with the presence of one \( \text{C-CHO} \) and two equivalent \( \text{N-CHO} \), respectively. A sharp singlet (2H, \( t = 2.83 \)) stood out among a complicated multiplet (ca 12H, \( t = 9-9.2 \)). No other signal was present. The above evidence led to the structure (3.5), 2,4:2',6'-\text{N-(p-aminobenzo)}-1-formyl-3-formylphenazine, for the diformyl derivative of anhydro-tri-2-aminobenzaldehyde. The singlet (2H) at \( t = 2.83 \) is shown by arrows in formula (3.6) in which the reaction proceeds through a six-membered ring (transition state).

3) Anhydro-tetra-2-aminobenzaldehyde

This pale yellow substance is formed when 2-aminobenzaldehyde is set aside with stronger acid
of an imino or a hydroxy group. This was confirmed by the n.m.r. spectrum (Fig. 3.3), in which singlets at τ -0.34(1H) and 0.96(2H) were assigned to formyl protons, consistent with the presence of one C-CHO and two equivalent N-CHO, respectively. A sharp singlet (2H, τ 2.83) stood out among a complicated multiplet from aromatic protons (ca 12H, τ 1.9-3.2). No other signal was present. The above evidence led to the structure (3.5), 2,4:2',N-(o-formylamidobenzo)-1-formyl-3-(o-formylphenyl)-1,2,3,4-tetrahydroquinazoline for the diformyl derivative of anhydro-tri-2-aminobenzaldehyde. The singlet (2H) at τ 2.83 is assigned to the equivalent protons of H(2) and H(4). A plausible pathway to the diformyl-trimer in the presence of acetic formic anhydride is shown by arrows in formula (3.6) in which the reaction proceeds through a six-membered ring (transition state).

(3) Anhydro-tetra-2-aminobenzaldehyde

This pale yellow substance is formed when 2-aminobenzaldehyde is set aside with stronger acid
In the present work, many absorption bands were found to be characteristic of the trimer (p. 42). The u.v. spectrum showed that the u.v. spectrum shown in Fig. 3.8 and 3.7, respectively on p. 63 and 62. Thus it seemed that a; R=H, R'=H
b; R=Ac, R'=H
c; R=CHO, R'=H
d; R=Ac, R'=NO

(a- and hydrochloric acid) than the others, which form the structures (2.6) and (2.7) and the corresponding compounds of the three molecules of the trimer (C₂H₅NO₂·HCl) and (C₂H₅NO₂·HCl) dissolved in the condensation with aldehyde reagents such as benzylhydrazine, and the formation of a dinitrocarboxylic (dinitrobenzoic acid) derivative.

The u.v. spectrum shown in Fig. 3.8 and 3.7, respectively on p. 63 and 62. Thus it seemed that...
(e.g. 5N-hydrochloric acid) than is needed to form the trimer (3.3,a), followed by basification of the resulting red salt (Seidel, 1926; see below). It has an empirical formula corresponding to four molecules of the monomer less three molecules of water \((C_{28}H_{22}N_{4}O)\). Seidel and Dick (1927) assigned it the structure (3.7) on the grounds of the molecular weight (determined cryoscopically in naphthalene), the ready condensation with aldehyde reagents such as benzoylhydrazine, and the formation of a dinitroso derivative and a mononitroso-monoacetyl derivative.

In the present work, many absorption bands were found common to the i.r. spectra of the trimer and the tetramer, indicating that much skeletal similarity exists between the two compounds. Bands characteristic of the tetramer occurred at 3370 and 3330 cm\(^{-1}\) (weak; imino groups) and at 1660 cm\(^{-1}\) (broad and strong; a conjugated carbonyl group). The u.v. spectrum shown in Fig. 3.4 resembled that of the trimer (p. 42) except for the long wave-length maximum at 370 m\(\mu\) which resembled those of 2-aminobenzaldehyde (365 m\(\mu\)) and 2-methylamino-benzaldehyde (387 m\(\mu\)) (see Fig. 3.8 and 3.7, respectively on p. 63 and 62). Thus it seemed
It is consistent with the n.m.r. spectra in deuterio-chloroform (Fig. 3.5), in which signals for three diaphoric protons are found at almost the same positions as those of the tetramer. Assignments of those peaks are shown in Table 3. The signals from H(4) at 5.10 and H(10) at 0.96 (in that order) assign, respectively to H(3) and the NH group of C(7*). Simultaneously the H(4) signal (~ 4.65) sharpened, and the H(7*) doublet (~ 4.27) collapsed to a singlet. When the acetone solution was shaken with a drop of deuterium oxide, the doublet at ~ 4.43 became a singlet with the doublet at ~ 3.61 remaining unchanged. From these data, it is likely that the tetramer contains the skeleton of the title and an ununconjugated 2-aminobenzyaldehyde unit. The structure is presented as (3-8,4).

Figure 3.4 Ultraviolet spectra, in ethanol, of A, the tetramer; B, the monoacetyl-tetramer; C, the monoacetyl-mononitroso-tetramer.
likely that the tetramer contains the skeleton of the trimer plus an unconjugated 2-aminobenzaldehyde residue, and the structure is presented as (3.8,a). This is consistent with the n.m.r. spectrum in deuterio-chloroform (Fig. 3.5), in which signals from three aliphatic protons are found at almost the same positions as those of the trimer. Assignments of those peaks are shown in Table 3. The signals from H(4) at \( \tau = 4.65 \) appeared only as a broad singlet in deuterio-chloroform, but as the expected doublet \( (J = 5 \text{ c/s}) \) in acetone (Table 3). Deuterium exchange in the deuterio-chloroform solution caused stepwise disappearance of signals at \( \tau = 5.10 \) and 0.96 (in that order), assigned respectively to H(7') and the NH group of C(7''). Simultaneously the H(4) signal \( (\tau = 4.65) \) sharpened, and the H(7'') doublet \( (\tau = 4.27) \) collapsed to a singlet. When the acetone solution was shaken with a drop of deuterium oxide, the doublet at \( \tau = 4.43 \) became a singlet with simultaneous disappearance of the broad doublet at \( \tau = 3.61 \) assigned to H(7'); but the doublet due to NH(7'') \( (\tau = 0.80) \) remained unchanged. From these data,
Figure 3.5: N.m.r. Spectrum of the Tetramer in CDCl₃
the tetramer is assigned structure (1.4.a).

2,4:2',N-(o-aminobenzo)-1,3-2,4-[N-(N-formylaniline)
toluene]-1,2,3,4-tetrahydroaniline. The steric
model of the tetramer, shown as formula (3.4.a; p. 46)
suggests that the N-formylaniline group would
preferably have an α-configuration because of the
steric repulsion in the α-configuration, between
this group and the benzene ring (A) as well as (3.4.a).

The mass spectra of the trimer and the tetramer
Shannon (G. S. R. O., Sydney), confirmed the molecular
weights and could be rationalized in terms of the
structures (3.4.a) and (2.8.a).

The ultraviolet spectrum of the monoacetyl
dependent tetramer, indicating a common skeleton.
Characteristic i.r. absorption bands occurred at
3330 (weak and sharp; NH) and 1665 cm⁻¹ (strong
and broad; N-Ac), also a strong band at 1650 cm⁻¹
(conjugated CHO). A sharp singlet (3H) at 7.50
in the n.m.r. spectrum is assigned to the N-acetyl
group, and a singlet at 4.30 and a doublet at
4.26 (J = 6 c/sec.) (1H each) are undoubtedly due
the tetramer is assigned structure (3.8,a), 2,4:2', N-(o-aminobenzo)-1,3:a,2''-[α-(o-formylanilino) tolueno]-1,2,3,4-tetrahydroquinazoline. The steric model of the tetramer, shown as formula (3.4,b; p. 46) suggests that the o-formylanilino group would preferably have an α-configuration because of the steric repulsion, in the β-configuration, between this group and the benzene ring (A) in formula (3.4,b).

The mass spectra of the trimer and the tetramer (Fig. 3.6), measured and interpreted by Dr. J. S. Shannon (C.S.I.R.O., Sydney), confirmed the molecular weights and could be rationalized in terms of the structures (3.3,a) and (3.8,a).

The ultraviolet spectrum of the monoacetyl derivative (Fig. 3.4) closely resembled that of the parent tetramer, indicating a common skeleton. Characteristic i.r. absorption bands occurred at 3330 (weak and sharp; NH) and 1665 cm.\(^{-1}\) (strong and broad; N-Ac), also a strong band at 1650 cm.\(^{-1}\) (conjugated CHO). A sharp singlet (3H) at \(\tau 7.50\) in the n.m.r. spectrum is assigned to the N-acetyl group, and a singlet at \(\tau 4.30\) and a doublet at \(\tau 4.26\) (\(J = 5\) c/sec.) (1H each) are undoubtedly due
to H(2) and H(7") respectively (cf. Table 3). The signal of the imino proton [NH(7")] was split into a broad doublet (\(\tau = 0.95, J = 5 \text{ c/sec.}\)) by H(7"), in almost the same fashion as the NH(7") of the tetramer. The H(4) signal appeared at \(\tau = 3.13\), showing a lower-field shift, as observed in the spectrum of the monoacetyl-trimer (p. 47). After deuterium exchange, the doublet due to NH(7") disappeared and that from H(7") collapsed to a singlet. This monoacetyl-tetramer is accordingly considered to have structure (3.8,b; p. 52).

As the tetramer possesses two imino groups, several attempts were made to obtain a diacetyl derivative. On treatment with acetyl chloride in pyridine, or with acetic anhydride and zinc chloride, the tetramer gave only the monoacetyl derivative. Severer conditions, namely refluxing a solution of the monoacetyl-tetramer (3.8,b) in a mixture of acetic anhydride and acetic acid (1:1) gave the diacetyl-trimer (3.3,c; 83%) and 2-acetamidobenzaldehyde (11%). These products could reasonably be formed either by direct replacement of the 2-formylanilino group in the monoacetyl-tetramer...
by an acetoxyl group, or by complete depolymerization followed by reconstruction of the diacetyl-trimer from 2-amino- and 2-acetamido-benzaldehyde. After similar treatment, 2-aminobenzaldehyde gave only a 17% yield of the diacetyl-trimer, together with 2-acetamidobenzaldehyde (29%) [which has been prepared in good yield from 2-aminobenzaldehyde and acetic anhydride in cold ether (Friedländer and Göhring, 1884)]. Moreover 2-acetamidobenzaldehyde was recovered almost quantitatively after being heated with acetic anhydride and acetic acid under the above conditions. Thus it is concluded that conversion of the monoacetyl-tetramer to the diacetyl-trimer does not involve depolymerization but is a simple nucleophilic replacement. This result supports our conclusion that the trimer and the tetramer have a common nucleus.

Formylation of the tetramer with acetic formic anhydride gave a monoformyl-tetramer (3.8,c). This was confirmed by the u.v. and i.r. spectra (the Experimental part, p.124) which closely resembled those of the monoacetyl-tetramer. In the n.m.r. spectrum, peaks from the three aliphatic
protons [H(2), (4), and (7")] appeared at slightly lower field than those in the monoacetyl-tetramer (cf. Table 3). Deuterium exchange occurred similarly [i.e. the NH(7") doublet disappeared with simultaneous collapse of the H(7") doublet to a singlet].

Resistance of the 7"-imino group in the tetramer (3.8,a) to acetylation or formylation is consonant with the steric hindrance at this point as demonstrated above by the slowness of deuteration (p. 54).

The mononitroso-monoacetyl-derivative obtained by Seidel and Dick (1927), contained no imino group (there was no i.r. absorption near 3300 cm.\(^{-1}\) ), and the two carbonyl bands of the monoacetyl-tetramer (1665, N-Ac; 1650 cm.\(^{-1}\), CHO) were shifted to 1675 and 1695 cm.\(^{-1}\), indicating removal, by nitrosation, of the hydrogen bond between the formyl and the imino groups of the structure (3.8,b). The ultraviolet spectrum (Fig. 3.4, p. 53) showed a strong hypsochromic shift (relative to the spectrum of the tetramer) and rather resembled that of the diacetyl-trimer (Fig. 3.1, p. 42). A similar shift was then demonstrated in the long wave-length
peak (387 m\textmu) of 2-methylaminobenzaldehyde to 287 m\textmu on N-nitrosation (Fig. 3.7). In the n.m.r. spectrum, the acetyl and the formyl groups gave singlets at \(\tau\ 7.49\ (3H)\) and \(-0.08\ (1H)\) respectively; a broad singlet at \(\tau\ 4.63\ (1H)\) was assigned to the H(2). The remaining signal [from the aromatic protons and H(7"), and H(4)] was a complex multiplet between \(\tau\ 1.7\) and 3.4. Treatment with deuterium oxide showed the absence of exchangeable protons. Thus the monoacetyl-mononitroso-tetramer has structure (3.8,d; p. 52).

The red tetramer hydrochloride, obtained as an intermediate during the preparation of the tetramer mentioned above (p. 52), was found by Seidel (1926) to give analytical figures consonant with a complex of one molecule of the tetramer, three of hydrogen chloride, one of water, and one of uncombined 2-aminobenzaldehyde. No structure was proposed. It was found in the present re-investigation that the specimen, recrystallized from 5N-hydrochloric acid and dried at 130\(^\circ\), gave analytical figures consistent with the structure \(C_{28}H_{22}N_4O\), 2HCl (the tetramer dihydrochloride). Paper chromatography showed that 2-aminobenzaldehyde was absent.
Figure 3.7 Ultraviolet spectra of
A, 2-methylaminobenzaldehyde in H₂O;
B, 2-methylaminobenzaldehyde (monocation) in 2N-HCl;
C, N-nitroso-2-methylaminobenzaldehyde in H₂O.
Figure 3.8 Ultraviolet spectra of A, 2-aminobenzaldehyde in H$_2$O; B, 2-aminobenzaldehyde (monocation) in 1.6N-HCl; C, the tetramer hydrochloride in 5N-HCl.
The tremendous bathochromic shift between the u.v. spectrum of the hydrochloride (Fig. 3.8) and that of the free tetramer (Fig. 3.4, p. 83) indicated that the former contains a longer conjugated pathway. The long wave-length maximum at 467 mw especially suggested the presence of an azomethinium group (+CH=N+). After standing for 1 day at 40°C, the spectrum was transformed to that of the cation of 2-aminobenzaldehyde (Fig. 3.8), indicating polymerization to the monomer. The characteristic absorption bands in the i.r. spectrum were shown at 1630 (strong, CH=) and 3400 cm\(^{-1}\) (broad am. OH). The n.m.r. spectrum in trifluoroacetic acid (Fig. 3.9) consisted of a narrow intense multiplet (about 12H, 1.7-2.5) and a broader multiplet (about 6H, 2.5-3.4) and a slightly broadened singlet (2H) at 8.83. This singlet was assigned to an azomethine proton, because benzylideneaniline in trifluoroacetic acid gave a doublet at \(8 = 0.85\) (\(\gamma = 16\) c/sec.). No signal characteristic of a formyl group was found. From these results, the
The tremendous bathochromic shift between the u.v. spectrum of the hydrochloride (Fig. 3.8) and that of the free tetramer (Fig. 3.4, p. 53) indicated that the former contains a longer conjugated pathway. The long wave-length maximum at 467 m\(\mu\) especially suggested the presence of an azomethinium group \(-\text{CH=N-}\). After setting the acid solution aside for 1 day at 20\(^\circ\)C, the spectrum was transformed to that of the cation of 2-aminobenzaldehyde (Fig. 3.8), indicating depolymerization to the monomer. The characteristic absorption bands in the i.r. spectrum were shown at 1630 (strong; CH=\(\text{N}^+\)) and 3400 cm\(^{-1}\) (broad and medium; OH). The n.m.r. spectrum in trifluoroacetic acid (Fig. 3.9) consisted of a complicated multiplet (18H) between \(\tau\) 1.7 and 3.4 [namely a narrow intense multiplet (about 12H, \(\tau\) 1.7-2.5) and a broader multiplet (about 6H, \(\tau\) 2.5-3.4)] and a slightly broadened singlet (2H) at \(\tau\) 0.83. This singlet was assigned to an azomethine proton, because benzylideneaniline in trifluoroacetic acid gave a doublet at \(\tau\) 0.65 \((J = 16 \text{ c/sec.})\). No signal characteristic of a formyl group was found. From these results, the
most likely structure of the tetramer hydrochloride is considered to be (3.9, p.68), 1',2',3',4'-tetrahydro-4'-hydroxyquinazolino[2',3'-l]-1,12-dihydro-tribenzo[b,f,j]-1,5,9-triazacycloduodecahexane dihydrochloride. This entirely cyclic structure can explain the failure to condense with another molecule of 2-aminobenzaldehyde. A space model of the structure shows that the three benzene rings attached to the azomethine bonds can easily lie in the same plane, as required for extended conjugation and the absorption at 467 µ.

Structures of the trimer and the tetramer, identical with those proposed above, were published by McGeachin (1966) in Canada, in the same month (October) as the above results were published in England (Albert and Yamamoto, 1966).

Physiological activities of the trimer, the tetramer, and the tetramer hydrochloride on mouse cancer (Carcinoma C 1025 and Ridgway osteogenic Sarcoma) and Leukaemia (L 1210) were examined by Dr. C. Chester Stock, in the Sloan-Kettering Institute for Cancer Research, New York. Moderate, but not outstanding, leukaemic activity was demonstrated for the tetramer.
(4) A Reaction Pathway for the Formation of the Trimer and the Tetramer.

The relations of the formation and decomposition of the monomer (2-aminobenzaldehyde), trimer, tetramer, and the tetramer hydrochloride are illustrated as follows:

```
MONOMER  \[\text{H}^+\]  \[\text{dil. H}^+\]  TRIMER
conc. H^+  \[\text{dil. H}^+\]  \[\text{H}^+\]
```

"TETRAMER HYDROCHLORIDE"  \[\text{H}^+\]  "TETRAMER"

Pyridine-H₂O

Ultraviolet studies showed that equilibrium between the monomer and the trimer occurs in dilute acid (p. 43). In dilute acidic solution (10⁻⁵ M, below pH 3) the tetramer and its hydrochloride also decompose to the monomer. The monomer, trimer and tetramer all give the tetramer hydrochloride in stronger acid. Thus the tetramer is obtainable from the trimer via the "hydrochloride", although no tetramer was found when condensation of the trimer with 2-aminobenzaldehyde was attempted in pyridine or in phosphate buffer (pH 4). The trimer could be formed from some dimer, such as (3.10), to the
The group of which a third molecule of aldehyde is added; the product could give a similar product (§ 3.16) by simple amine formation. The "amino" attack is formally similar to the reaction of ethyl acetoacetate to benzylidene-ketene. The mechanism for the dimer (3.12) could then be visualized through the two reactions shown by structural formulae (3.12) and (3.13) which produce the tetramer (3.14).

The skeletons of the trimer and the tetramer are reminiscent of Tröger's Base (Jrger, 1954; Spielman, 1953; § 1.16) which is formed from benzaldehyde and o-methylaminoacetophenone. The spectra of these compounds, hitherto unrecorded, are shown in Fig. 3.3 and 3.7, respectively.

Large hypsochromic shifts, seen...
azomethine group of which a third molecule of 2-aminobenzaldehyde is added; the product could give the adduct (3.1, p.46) by simple anil-formation. The above nucleophilic attack is formally similar to the ready addition of ethyl acetoacetate to benzylidene-aniline. Cyclization to the trimer (3.3,a) could then follow through the two similar reactions shown by arrows in formula (3.11). The "tetramer hydrochloride" (3.9) may arise by parallel reactions involving a cyclotrimer. If, after basification, an aldehyde group is liberated, consecutive additions of imino groups across the two C=N bonds as shown in formulae (3.12) and (3.13) would produce the tetramer (3.8,a).

The skeletons of the trimer and the tetramer are reminiscent of Tröger's Base (Tröger, 1887; Spielman, 1935) (3.14) which is formed from p-toluidine and formaldehyde.

(5) 2-Aminobenzaldehyde and 2-Methylamino-benzaldehyde.

The u.v. spectra of these compounds, hitherto unrecorded, are shown in Fig. 3.8 and 3.7, respectively. Large hypsochromic shifts, seen
when the cations are formed, are in conformity with the principle of optical transparency of an aromatic group (de Borst, et al., 1938; Harberts, et al., 1936). Thus the spectrum of each cation is almost identical with that of benzaldehyde \([\lambda_{\text{max}}(0.1 \text{N-HCl}) 249, 280 \text{ m\u}}; \log \varepsilon 4.13, 3.13; \text{Vandenbelt, et al., 1954})].

2-Aminobenzaldehyde was sufficiently stable in dilute acidic solution \((10^{-5}\text{M})\) for spectrometric measurement of the ionization constant \((pK_a 1.36), \) which was found to be slightly lower than the known value of the 4-isomer \((1.74; \text{Forbes, et al., 1958})\).

To investigate the effect of storage on 2-aminobenzaldehyde (a subject of considerable interest to chemists using it in syntheses), chromatographic systems had to be found which could detect the monomer, trimer, and tetramer in the presence of one another. Such selectivity was obtained by: (i) spotting on paper which was then developed with light petroleum \((\text{b.p. 80-100}^\circ)\) saturated with methanol, and (ii) spotting on a thin-layer silica gel \((\text{Kieselgel G})\) plate, subsequently developed with chloroform-acetone \((9:1)\) as solvent; \(R_F\) values are shown in the Experimental section.
On storage at $20^\circ$, solid 2-aminobenzaldehyde formed mainly the trimer but also a trace of the tetramer; the recovery of unchanged 2-aminobenzaldehyde was 60 and 40% after 1 and 2 months respectively. At $5^\circ$ there was no change in this time. Attempts, on a preparative scale, to convert the trimer into the monomer by steam-distillation in ammonium hydroxide solution, or by continuous extraction of the suspension in a buffer (pH 1.36) by ether, gave only small yields.

Bamberger (1904) reported an anhydro-dimer ($C_{16}H_{16}N_2O$) of 2-methylaminobenzaldehyde. It was obtained as a by-product (8% yield) during the preparation of 2-methylaminobenzaldehyde (66% yield) by the action of dimethyl sulphate on anthranil. The molecular weight of the dimer was determined ebullioscopically in acetone, but no structure was presented. In the present re-investigation it was found that the action of N-hydrochloric acid on 2-methylaminobenzaldehyde at room temperature gave the same dimer almost quantitatively. The lack of absorption at 3500-3100 and 1800-1620 cm.$^{-1}$ in the i.r. spectrum indicated that the dimer possessed
neither hydroxy nor carbonyl group. The n.m.r. spectrum in deuteriochloroform showed a singlet (6H) at 6.90 due to two equivalent N-methyl groups, a singlet (2H) at 4.41 likely to be due to two equivalent methine protons similar to the aliphatic protons of both the trimer (3.3,a) and the tetramer (3.8,a) of 2-aminobenzaldehyde (cf. Table 3), and a complicated multiplet (8H) at 2.8-3.5 from aromatic ring-protons. These spectral results led to the only possible structure (3.15,a) for the anhydro-dimer of 2-methylaminobenzaldehyde, namely 2,6-epoxy-1,5-dimethyl-1,5-diaza-3,4:7,8-dibenzocycloocta-3,7-diene. One compound which has the same ring system (the epoxy-dibenzo-tetrahydro-diazocine) as that of the dimer (3.15,a) has been reported [i.e. the anhydro-bi-isatic acid (3.15,b) obtained by refluxing isatin with aqueous potassium hydroxide, followed by acidification of the resultant potassium salt; Stefanovic, et al, 1959]. The ultraviolet spectrum of the dimer (3.15,a) in ethanol (see Experimental part)
resembled that of N-methyl-o-toluidine in the same solvent ($\lambda_{\text{max}}$ 242, 292 m\(\mu\); log \(\varepsilon\) 3.96, 3.27: Wohl, 1939; Grammaticakis, 1949; Ramart-Lucas and Klein, 1949), and the extinction coefficients of the former were (as expected) approximately twice as large as those of the toluidine. The singlet at 4.41 in the n.m.r. spectrum mentioned above is assigned to \(\text{H}(2 \text{ and } 6)\). The dimer could simply be formed from a simpler cyclic dimer, shown in formula (3.16), by acid-catalysed elimination of a hydroxy group, followed by the internal ether formation (or both reactions may take place concertedly) as shown by arrows in the formula.
\[ (a: R = CH_3, R' = H) \]
\[ (b: R = H, R' = COOH) \]

\[ (3.15) \]

\[ (3.16) \]
Table 3

$^1$H-Nuclear magnetic resonance spectra

$^\dagger$-Values (p.p.m.)$^a$ for protons.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>H-2</th>
<th>H-4</th>
<th>H-7&quot;</th>
<th>OH-7&quot;</th>
<th>H-7'</th>
<th>Aromatic</th>
<th>CH$_3$CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3.3, a)$^b$</td>
<td>4.34s</td>
<td>4.63d</td>
<td>4.43d</td>
<td>6.73s</td>
<td>3.53bd</td>
<td>2.5-3.5m</td>
<td></td>
</tr>
<tr>
<td>(3.3, b)$^c$</td>
<td>4.28s</td>
<td>3.43s</td>
<td>4.45bd</td>
<td>6.67s</td>
<td>2.5-3.3m</td>
<td>7.40s</td>
<td></td>
</tr>
<tr>
<td>(3.3, c)$^d$</td>
<td>4.47s</td>
<td>3.31s$^*$</td>
<td>3.16s$^*$</td>
<td>2.5-3.3m</td>
<td>7.47s</td>
<td>7.69s</td>
<td></td>
</tr>
<tr>
<td>(3.8, a)$^d$</td>
<td>4.37s</td>
<td>4.65bs</td>
<td>4.27d (0.96bd)</td>
<td>5.10bs</td>
<td>1.9-3.5m (0.06s)$^+$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3.8, a)$^e$</td>
<td>4.40s</td>
<td>4.43d</td>
<td>4.09d (0.80bd)</td>
<td>3.61bd</td>
<td>1.9-3.5m (-0.03s)$^+$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3.8, b)$^d$</td>
<td>4.30s</td>
<td>3.12s</td>
<td>4.26d (0.95bd)</td>
<td>2.0-3.1m</td>
<td>7.50s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3.8, c)$^d$</td>
<td>4.22s</td>
<td>3.10s</td>
<td>4.19d (0.89bd)</td>
<td>2.0-3.2m</td>
<td>0.87**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3.8, d)$^d$</td>
<td>4.63bs</td>
<td>?</td>
<td>?</td>
<td>1.7-3.4m</td>
<td>7.49s</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tetramethylsilane as internal standard.  
$^b$ In hexadeuterodimethylsulphoxide and deuterochloroform (1:3, v/v).  
$^c$ In the same mixed solvent (2:1, v/v).  
$^d$ In deuterochloroform.  
$^e$ In acetone.  

The suffixes are: (b)s: (broad)singlet, (b)d: (broad)doublet, m: multiplet, $J$: coupling constant (cps.).  

$^*$ The assignment is uncertain.  
$^{**}$ The signal due to the CH$_2$(7') group.  
$^{+}$ The signal due to the -NH(7'')C$_6$H$_4$CHO(g) group.

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Section 4: Structures of compounds obtained by the quinazoline: formation of Aminobenzaldehyde and its Analogues. 

Quinazoline: Formulation of Aminobenzaldehyde and its Analogues. 

It is of historical interest that Gabriel (1902) evaporated quinazoline with hydrochloric acid without decomposition, and the residue contaminated with iron. In the present re-investigation, it was found that the quinazoline was partly decomposed to a residue with a yellowish color, and the observed chromatography that the quinazoline had partially decomposed to a residue with a yellowish color. 

In hexadeuterodimethylsulphoxide and deuterochloroform (1:3, v/v). In the same mixed solvent (2:1, v/v). In deuterochloroform. In acetone. The suffixes are: (b)s: (broad)singlet, (b)d: (broad)doublet, m: multiplet, $J$: coupling constant (cps.). 

* The assignment is uncertain. ** The signal due to the CH$_2$(7') group. 
$^+$ The signal due to the -NH(7''C$_6$H$_4$CHO(g) group.
Section 4: Structures of Compounds obtained by the Action of Acid and Alkali on Quinazoline.


Quinazoline (4.1) is stable in cold dilute acid and alkaline solutions. It is of historical interest that Gabriel (1903) evaporated quinazoline with hydrochloric acid repeatedly on the boiling water-bath and observed an orange colour and found that the residue contained ammonium chloride. He concluded that the quinazoline had partly decomposed to ammonia, formic acid, and 2-aminobenzaldehyde (the tetramer hydrochloride of which is orange).

In the present re-investigation, it was found (with the aid of paper chromatography) that quinazoline, when heated with hot dilute acid or hot strong alkali, gave 2-aminobenzaldehyde and its polymers (cf. Section 3). Quinazoline was heated at 90° for 1 hr. in aqueous solutions of graded hydrogen ion strength and the amount of quinazoline destroyed is shown in Fig. 4.1. All the solutions
between pH 7 and 12 remained unchanged under the above conditions. At pH 4-5 and 14, 2-aminobenzaldehyde was the only product (paper chromatography and n.m.r. spectrum); the ratios of the aldehyde and quinazoline were determined by measuring the intensities of the n.m.r. signals at 0.28 (due to the formyl group of the aminoaldehyde) and 0.84 [due to H(4) of quinazoline (Armarego and Willette, 1965; Katritzky et al., 1966), which existed predominantly as a neutral species in the above pH regions]. The values below pH 1.5 were calculated from the amounts of quinazoline recovered after neutralizing the acidic reaction mixtures, followed by extraction with dichloromethane. Between pH 1.5 and 3, 2-aminobenzaldehyde (produced from quinazoline by decomposition) was found to be partly converted to the anhydro-trimer (3.3,a), the anhydro-tetramer (3.8,a), and the monoformyl-tetramer (3.8,c); below pH 2, a new substance is formed, this is shown below to be a large polymer and will be referred to as Substance Q. Table 4 shows the yields of these degradation products obtained when quinazoline was refluxed for 1 hr. in buffer solutions (partly neutralized sulphuric acid; pH 2.0 and 1.5)(all the quinazoline was destroyed under those conditions).
Figure 4.1. Destruction of quinazoline at 90° for 1 hr.

Table 4. Decomposition products from quinazoline after refluxing for 1 hr.

<table>
<thead>
<tr>
<th>Products</th>
<th>pH 2.0</th>
<th>pH 1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-aminobenzaldehyde</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>the trimer</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>the tetramer</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>the monoformyl-tetramer</td>
<td>6</td>
<td>5.3</td>
</tr>
<tr>
<td>Substance Q (sulphate)</td>
<td>17</td>
<td>72</td>
</tr>
</tbody>
</table>
Also the Table shows that as the hydrogen ion concentration is increased, the yields of 2-aminobenzaldehyde and its anhydro-polymers decrease proportionally, but that of Substance Q increases.

It was already shown in Section 3 that the trimer was the only product formed by the action of cold dilute acid (pH 1) on 2-aminobenzaldehyde; the tetramer was obtainable only via the "tetramer hydrochloride" which was formed only in concentrated acid. However when the aminoaldehyde was heated under reflux in dilute acid for 1 hr., a small amount of the tetramer accompanied the trimer (the main product)(the reaction mixture remained yellow during the refluxing). This suggested that the tetramer could have been formed by a simple replacement reaction of the hydroxy group in the trimer with the amino group of the monomer [cf. formula (3.4), p. 46], because the tetramer hydrochloride has an intense red colour. The monoformyl-tetramer is most likely derived by combination of the tetramer and the formic acid produced during the above decomposition of quinazoline.
(2) The Structure of Substance Q.

"Substance Q", a pale yellow substance of high-molecular weight, was best obtained as the sulphate or the hydrochloride when quinazoline was refluxed with partly neutralized sulphuric acid (pH 1.5) or 0.1 N-hydrochloric acid, followed by basification with aqueous sodium carbonate. It re-produced the hydrochloride and the sulphate on acidification, and also gave a picrate. In an attempt to obtain the empirical formula of Substance Q by calculation from the elementary analysis, a good fit was obtained with \((\text{C}_{15}\text{H}_{13}\text{N}_{3}\text{O})_n\), consistent with an equimolecular adduct of quinazoline and 2-amino-benzaldehyde. The broadness of the peaks in the i.r. and the n.m.r. spectra suggested that Substance Q would most likely be a polymer of high-molecular weight. It possessed hydroxy (and possibly imino) groups (3300, broad and strong), but no carbonyl group (no strong absorption at 1800-1630 cm\(^{-1}\)). The n.m.r. spectrum in tetradeuterio-methanol with a trace of deuterium oxide (Fig. 4.2) showed only two broad multiplets at \(\tau\) 4.2-4.8 and 2.5-3.5 (the ratio of the intensities was approximately 1:4). These spectroscopic results
are consistent with the 1:1 adduct suggested above. Quinazoline is very reactive towards animal n-mercaptides which attack primary and secondary amine functions. Taking account of the proven value of 89 for the \( n(2) \) signal in the n.m.r. spectrum of 3,4-dihydroquinazoline in methanol the proton signal of the amide group in the \( n \) form of Substance 8 in the n.m.r. spectrum of Substance 10 can be compatible with the proposed structure (4.3.a). From the evidence of the elemental analysis, the hydrochloride, the sulphate, and the picrate would have the structures (4.4, a, b, and c), respectively. These were supported by the i.r. (e.g. 3200, broad and medium, \( \text{OH} \) and \( \text{NH} \) bands) and 1680 \( \text{cm}^{-1} \) strong, a formaldimine band at 3050, the n.m.r. spectra (three broad multiplets at \( 3 \) and 1, 1.9-3.5 ppm from aromatic protons), in a mixture of reactants.
are consistent with the 1:1 adduct suggested above.

Because quinazoline is very reactive towards anionoid reagents which attack position 4, it is suggested that Substance Q is a polymer of the 1:1 adduct (4.2,a) of quinazoline and 2-aminobenzaldehyde, with a structure such as that shown in formula (4.3,a). Taking account of the known value 2.89 for the H(2) signal in the n.m.r. spectrum of 3,4-dihydroquinazoline in methanol (Albert, 1966), the proton signal of the formamidino group in (4.3,a) should be masked by the aromatic ring protons (at 2.5-3.5). Thus the n.m.r. spectrum of Substance Q could be compatible with the proposed structure (4.3,a).

From the evidence of elementary analysis, the hydrochloride, the sulphate, and the picrate would have the structures (4.4, a, b, and c), respectively. These were supported by the i.r. (e.g. 3200, broad and medium, OH and NH groups; 1660 cm\(^{-1}\) strong, a formamidinium group) and the n.m.r. spectra [three broad multiplets at 1.3-1.8 (1H; formamidinium), 1.9-3.5 (8H, aromatic ring protons), and 3.5-4.2 (2H, aliphatic protons), in a mixture of
Acetylation of Substance Q in acetic anhydride-pyridine mixture at room temperature gave a diacetyl derivative, confirmed by the i.r. spectrum, which showed presence of $\nu$-Ac and $\pi$-Ac (at 1720 and 1690-1600 cm$^{-1}$), no hydroxy group (no absorption 3500-3100 cm$^{-1}$); all the peaks in the spectrum were very broad like those of the starting material and its salts. The n.m.r. spectrum in hexadeutero-dimethyl sulfoxide consisted of broad multiple peaks at 7.5-8.0 (two acetyl groups), 2.0-3.6 (aromatic ring and aliphatic protons, ca 10 H), 1.2-2.0 (1H, the formamidino group), supporting the structure (4.3.b) for the diacetyl derivative. The molecular weight determined to be about 1400, which led to the molecular weight determination of (4.3.b)(Substance Q and its salts were poorly soluble in these solvents, so that a skeletal change took place during the gentle acetylation, the most likely structure for

Figure 4.2. $^1$H-n.m.r. Spectrum of Substance Q in CD$_3$OD with a trace of D$_2$O.
pentadeuterio-pyridine and deuterium oxide as solvent of above salts.

Acetylation of Substance Q in acetic anhydride-pyridine mixture at room temperature gave a diacetyl derivative, on the evidence of the elementary analysis. This was confirmed by the i.r. spectrum, which showed the presence of O-Ac and N-Ac (at 1720 and 1690-1660) groups but no hydroxy group (no absorption at 3500-3100 cm$^{-1}$); all the peaks in the spectrum were very broad like those of the starting material and its salts. The n.m.r. spectrum in hexadeuteriodimethyl sulphoxide consisted of broad multiplets at 7.5-8.3 (two acetyl groups), 2.0-3.6 (aromatic ring and aliphatic protons, ca 10 H), and 0.5 (1H, the formamidino group), supporting the structure (4.3,b) for the diacetyl derivative. The molecular weight of the acetyl compound was found to be about 1400, which led to $n=4$ for the molecular formula of (4.3,b) (Substance Q and its salts were poorly soluble in solvents suitable for the molecular weight determination). Because it is unlikely that a skeletal change took place during the gentle acetylation, the most likely structure for
Substance Q appeared to be a linear polymer of the monomeric unit (4.3,a), where n is about four. The mass spectrum of the Substance Q sulphate was measured (by Dr J. A. Wunderlich, CSIRO, Melbourne). It showed mainly the intense peaks due to quinazoline and its fragments, all below m/e 130 (for quinazoline, see Batterham, Triffett, and Wunderlich, 1967). Although there were weak peaks even above m/e 500, the molecular ion peaks could not be confirmed.

(3) A Reaction Pathway for the Formation of Substance Q.

By periodical chromatographic sampling, it was found that an acidic solution of quinazoline (pH 1) at 87° exhibited first an intense blue fluorescent spot due to a certain initial product, then consecutively produced the dark spot due to Substance Q (cf. Experimental part). In stronger acid (e.g. 10N-hydrochloric acid) the proportion of the initial product to Substance Q seemed to be higher than at pH 1 (chromatography). The same blue spot gradually appeared when quinazoline was stirred...
with one molecular equivalent of 2-aminobenzaldehyde (but not with the anhydro-trimer) in dilute hydrochloric acid (pH 0.2) at 30°; after one day a considerable amount of Substance Q was obtained together with the anhydro-trimer of the aminoaldehyde. (On dissolving Substance Q in a large amount of N-hydrochloric acid, the blue fluorescent spot was also produced). The fact that the fluorescent spot due to the initial product only appeared after heating the acidified solution of quinazoline indicated that the product was a different substance from "quinazoline hydrochloride monohydrate" obtained by the action of hydrogen chloride on quinazoline in ether (Albert, Armarego, and Spinner, 1961), also different from 2-formamidobenzaldehyde (which gives a dark spot on paper chromatograms). Because quinazoline is stable and 2-aminobenzaldehyde gives only the anhydro-trimer in dilute acid at room temperature, the initial product is considered to be formed by a reaction of the degraded aminoaldehyde and the unreacted quinazoline under the above conditions; it is likely that its structure resembles that shown in formula (4.2,a). Several attempts
were made to isolate the intermediate substance, but it seemed to polymerize so easily during the separation that the pure material could not be obtained.

2-Aminoacetophenone was found to be stable in dilute acid under the conditions which convert 2-aminobenzaldehyde to the trimer (Section 3). Accordingly when molecular equivalents of quinazoline and the acetophenone were stirred in acid (pH 1.5) at room temperature, the 1:1 adduct (4,2,b) was obtained as the main product. This material gave, on a paper chromatogram with various developing solvents, an intense blue fluorescent spot of $R_F$ values identical with those of the initial product from quinazoline (see above). The adduct (4,2,b) showed a characteristic i.r. absorption at 3400, 3300 (both medium, 2NH) and 1650 cm.$^{-1}$ (strong, C=O). The n.m.r. spectrum in hexadeuterio-dimethyl sulfoxide with a trace of deuterium oxide was consistent with the structure (4,2,b); i.e. singlets at 7.53 and 4.42 [the acetyl and H(4) groups, respectively], a doublet at 2.34 ($J=1.5$ c/sec.; the N=CH-$N$), and a multiplet at 2.5-3.4 (8H, aromatic ring protons).
Polymerization of this adduct in dilute acid is probably prevented because of the steric hindrance by the acetyl methyl group, whereas the postulated adduct (4.2,a) appeared to polymerize easily under the same conditions.
Section 5: A General Discussion of the Oligomerization of Nitrogen Heterocycles.

It is a well-established characteristic of polymerization reactions that a monomer changes to a polymer via an activated intermediate (e.g. Marbel, 1959). Chemical activation of a monomer requires a (1) redistribution of electron densities in the bonds of the monomeric molecule (the intramolecular effect), and/or (2) a change of properties of existing (loose) intermolecular bonds between the reacting sites (intermolecular effect; an alteration of mutual orientation may suffice). For practical purposes, the reaction may start when the monomeric molecules have two or more functional groups which are already reactive enough to undergo spontaneous intermolecular condensations, but, more often, one or both of the condensing groups becomes reactive only if a new ionic species (or a free radical) is formed (e.g. by addition of acid, or a peroxide, or by supplying energy in the form of light). A polymeric compound of low molecular weight (i.e. an oligomer) can usually be obtained when the product
is stabilized (i.e., deactivated) by the steric hindrance imposed by its geometry, or else by a \( pK_a \) change during the earlier stage of the polymerization reaction. Formulae (5.1) to (5.10) illustrate some of the main types of nitrogen-containing heterocyclic oligomers previously known. These can be classified as follows.

(i) Heterocyclic oligomers from non-heterocyclic monomers, such as the dibenzodiazocine (5.1) obtained upon treatment of 2-aminobenzophenone with Lewis acids in an inert solvent (Metlesics and Sternbach, 1966).

(ii) Heterocyclic oligomers from heterocyclic monomers, which can be further divided into the following types:

(a) Oligomers formed by condensation of the side-chains. An example is provided by the dimerization of 2-amino-nicotinonitrile by heating in aqueous ammonia to give the triaza-naphthalene (5.2) (Taylor, et al, 1958).
b) Oligomers obtained by condensation of a side-chain of the monomer with the nucleus of another molecule of the monomer. An example is the dimer (5.3) formed from 2,4,4-trimethyl-1-pyrroline 1-oxide ("nitrone") on standing; cf. a review by Delpierre and Lamchen, 1965.

c) Oligomers where the nuclei join to one another by a single bond. Examples are the acid-catalysed polymerization of pyrroles and indoles. The trimer of pyrrole and the dimer of indole have structures (5.4) and (5.5), respectively. cf. a review by Smith, 1963.

d) Oligomers where the nuclei have become joined by a double bond. Examples are (a) biacridylidene (5.6), produced upon refluxing the monomer (acridine) with sodium carbonate in ethylene glycol (Albert and Catterall, 1965); (b) the orange substance (5.7) obtained by the action of alkali on 6-hydroxypteridine (Albert, 1955).

e) Oligomers in which monomers share two atoms [e.g. the products of the photodimerization of 2-pyridone (Taylor and Kan, 1963) and thymine (Blackburn and Davies, 1965; Anet, 1965); the
structures of the products are shown in formulae (5.8) and (5.9), respectively. This type (ii,ε) of condensation is in accordance with the Hoffmann-Woodward (1965) selection rules for concerted cis cycloaddition reactions, which predict that the dimerization of the above nitrogen heterocycles (the $2\pi \rightarrow 2\sigma$ process) will be photochemically allowed because of $m+n=4q$ for the monomers (where $m$ and $n$ are numbers of $\pi$-electrons of the starting materials and $q$ is an integer, 0, 1, 2, …). A cycloaddition is not thermally allowed for this system, but is permitted for the $m+n=4q+2$ electron systems.

(iii) Heterocyclic copolymers from two or more monomeric units, such as hexamethylenetetramine (5.10) formed from formaldehyde and ammonia.
Ph

$\text{N=Cl}$

Cl

Ph

$\text{N=C}$

Cl C=N

$\text{MeO-Me}$

$\text{Me} \text{~Me}$

$\text{CH~} 

2$

N

I

Ph

$\text{(5.1)}$

$\text{(5.2)}$

$\text{(5.3)}$

$\text{N}$

$\text{(5.4)}$

H

$\text{H}$

$\text{(5.5)}$

$\text{(5.6)}$

$\text{N}$

$\text{(5.7)}$

$\text{N}$

$\text{(5.8)}$

$\text{H}$

$\text{H}$

$\text{(5.9)}$

$\text{(5.10)}$

Classification of the various types of oligomers that might be obtained depends on the formation of the dimer of 2-amino-3-formylpyrazine and one of 2-formamido-3-formylpyrazine, is classified as a compound of type 3, by condensation of side-chains.

A plausible reaction mechanism for the formation of the dimer of 4-methylpyrazine (2.4.a.; Section 1) should be either a Michael-type addition of the methyl group of the monomer to the C=N(7) bond of another molecule, or a substitution to the pyrazine ring of the dehydrated dimer (5.10) by the Michael mechanism of anolysis of the monomer.

In the other case, the dimer is classified as type (11.2), namely union of the side-chain of one molecule with the nucleus of another. Anhydro-polymer of 2-aminobenzaldehyde and the anhydro-polymer of 2-methylenaminealdehyde belong to oligomers of this type, because the molecule is not heterocyclic. The most likely mechanism of formation was discussed on
Classification of the various types of polymers described in this Thesis will now be made.

The monoformyl anhydro-trimer of 2-amino-3-formylpyrazine (1.4; Section 1), which apparently arises by condensation of two molecules of 2-amino-3-formylpyrazine and one of 2-formamido-3-formylpyrazine, is classified as a compound of type (ii,a), i.e. condensation of side-chains.

A plausible reaction mechanism for the formation of the dimer of 4-methylpteridine (2.4,a; Section 2) would be either a simple Michael-type addition of the methyl group of the monomer to the C=N(7,8) bond of another molecule, or a substitution of the 7-hydroxy group in the dihydrated cation (2.3, p.12) by the methyl group of another monomer. In either case, the dimer is classified as type (ii,b), namely union of the side-chain of one molecule with the nucleus of another.

Anhydro-polymers of 2-aminobenzaldehyde and the anhydro-dimer of 2-methylaminobenzaldehyde belong obviously to oligomers of type (i), because the monomers are not heterocyclic. The most likely mechanism of formation was discussed on
p. 70 and 73. The diformyl-trimer (3,5) was produced by the action of acetic formic anhydride not only on the trimer (2,3,a) but also on the monomer (2-aminobenzaldehyde). This suggests an alternative, possible mechanism of formation shown in formula (5,11), where the reaction does not necessarily proceed via the trimer as described on p. 51.

The heterocyclic polymer (4,3) obtained by the action of acid on quinazoline (Section 4) is classified as type (iii), because it is a co-polymer.

Termination of all these polymerization reactions took place when substances of low molecular weight had been formed. The most evident reason for this is that the oligomers (1,4), (2,4,a), (3,3,a), (3,5), (3,9), and (3,15,a) were poorly soluble and separated from the reaction mixtures as precipitates. Other factors which assist chain-termination will now be mentioned.

It is not likely that the two (equivalent) CHO(2') groups in the monoformyl-trimer (1,4)
would be so active towards a nucleophile as the C-CHO group of the initial product (1.3); the NH(3) group is deactivated by the N-formyl group. The pK_a value of the two equivalent imino groups [i.e., 2NH(3')] is expected to be considerably lower (because of the electron withdrawing effect of the pyrazine ring) than that of 2-amino-benzaldehyde (pK_a 1.36; Albert and Yamamoto, 1966), possibly deterring intramolecular condensation of one of the imino groups with the CHO(2') group in the different pyrazine ring, whilst this condensation reaction was considered to take place during the formation of the trimer (3.3,a) and the diformyl-trimer (3.5) (cf. p.51 and 70). This would be the most probable reason for termination of the polymerization of 2-amino-3-formylpyrazine in a mixture of acetic formic anhydride and sodium formate.

The structure (2.4,a) of the dimer of 4-methylpteridine and its pK_a values (cf. Table 2.1) suggest a possibility of a further polymerization (e.g., formation of a tetramer from two molecules of the dimer), because the dimer still possesses
the Cyclic 2-amino groups which are considered to form unstable reaction products of the monomer under these conditions. However, when the 4-amino-dimine is heated in acid (pH 1.5) at 90° for a long time, the then-born oligomers described in the Experimental Section (p. 107), the yield of the dimer decreased proportionally, and the product was an intractable black tar (no other oligomers were obtained). Although the reaction was quenched (as the sulphate) at this stage, the preparative reaction times were long. As the product due to the geometry, the structures shown as the folded form (5.11).

Structures (5.12) and (5.13) are two different forms of the trimer (3.3.3) and the dehydrotrimer (3.5.), respectively. These are reminiscent of the structures of the trimer (3.3.3) of 2-methyl-aminobenzaldehyde, which consist of three or two, eightly or four hydroquinazoline rings (two dihedral angles for the dimer). This geometric stabilization could probably cause termination of the polymerization reactions.
the CH$_3$(4) and OH(7') groups which are considered to be similarly reactive as those of the monomer under the same conditions. However when 4-methylpteridine was heated in acid (pH 1.5) at 90° for a longer time than that described in the Experimental part (p. 107), the yield of the dimer decreased proportionally, and the product was an intractable black tar (no other oligomers were obtained). Although the dimer partly precipitated (as the sulphate) at the end of the above preparative reaction time, it might be a stable product due to the geometry, the structure being shown as the folded form (2.5).

Structures (5.12) and (5.13) are in different forms of the trimer (3.3,a) and the diformyl-trimer (3.5), respectively. These are reminiscent of the structure of the dimer (3.15,a) of 2-methylaminobenzaldehyde, and consist of three or two, tightly bound tetrahydroquinazoline rings (two dihydro-benzoxazine ring for the dimer). This geometrical stabilization could probably cause termination of the polymerization reactions,
followed by separation of the products from the reaction mixtures as precipitates.

Although the red tetramer hydrochloride (3.9) was apparently the main product when 2-aminobenzaldehyde was treated with strong acid, it was not obtained quantitatively (65% yield), suggesting other side-reactions, possibly further polymerization. The entirely cyclic structure (3.9) seemed to be the main reason for termination of the polymerization reaction to give the tetramer hydrochloride. On basification, it gives only the tetramer (3.8,a) (see p. 52).

Termination of the polymerization of the large co-polymer (4.4,a or b) could be caused by a steric strain when about four molecules of the monomeric unit (4.2,a) join linearly.
Section 6: Experimental

(1) Introduction.

Microanalyses were performed by Dr J. E. Fildes and her staff in the Micro-analytical Section of this Department. Compounds for analysis were dried over $\text{P}_2\text{O}_5$ at $80^\circ/0.01\text{ mm.}$ for 1 hr., unless otherwise indicated.

Paper chromatography was carried out on Whatman No. 1 (or sometimes No. 4) paper developed with 3% aqueous ammonium chloride (hence referred to as "$\text{NH}_4\text{Cl}$"), or with light petroleum (b.p. 80-100$^\circ$) saturated with methanol (hence designated as "pet.-MeOH"). Thin layer chromatography on silica gel (Kieselgel G) (0.2 or 0.5 mm. in thickness) was used with dichloromethane or chloroform-acetone (9:1, v/v.) as developers. Chromatograms were examined under two ultraviolet lamps with principal emission at 365 and 254 $\mu\text{m}$ respectively. When two substances had to be compared for identity, they were always run simultaneously.

Ultraviolet spectra were measured on a Shimadzu model RS 27 recording spectrophotometer or...
a Perkin-Elmer Spectracord model 4000A, and the
wave-length and intensity of each maximum checked
with an Optica manual instrument. Infrared
spectra of solids (in KBr discs or Nujol mulls)
were taken with a Unicam S.P.200 spectrophotometer;
the infrared spectrum of the solution of 2,4,6,7-
tetramethylpteridine in DCl/D2O (p.33) was taken
by Dr E. Spinner with a Perkin-Elmer 621 Grating
Infrared Spectrophotometer (CaF2 cells). Nuclear
(proton) magnetic resonance measurements were made
at 33.3° with a 60 Mc/sec. Perkin-Elmer spectro-

tube and the contents were vigorously shaken for
a few minutes, and re-examined. When no exchange
was observed, this tube was warmed on a water-bath
at about 45° for 1-3 hr. and set aside over night
at 22-25°, then measured again.

The names of new compounds are underlined at
their first mention in the body of the text.
Names occurring in paragraph headings are also
underlined, but this does not necessarily imply
that the compound is new.
(2) Experimental in Section 1.

Pteridine.—To 4,5-diaminopyrimidine (Brown, 1952) (3.2 g.), dissolved in boiling ethanol (20 ml.), was added a boiling suspension of polymeric glyoxal monohydrate (Raudnitz, 1948) (BDH, 2.4 g.; 1.1 equiv.) in ethanol (90 ml.); this mixture was heated under reflux for 30 min. The solvent was removed below 30°, and the residue sublimed at 110°/0.01 mm., giving pteridine as a yellow crystalline powder (93% yield, m.p. 137-138° raised on one recrystallization from benzene to 140° (Albert, Brown, and Cheeseman, 1951; 63% yield, m.p. 140°). It was found necessary to interrupt the sublimation several times and grind the cake.

2-Amino-3-formylpyrazine.—To pteridine (0.53 g.), dissolved in 0.25 N-sulphuric acid (20 ml.), was added enough N-sodium hydroxide (ca 1 ml.) to give pH 2.5, and the mixture was refluxed for 10 min. (final pH: 2.5). The cooled solution was taken to pH 7 with N-sodium hydroxide (or N-sodium hydrogen carbonate), saturated with sodium chloride, then extracted with chloroform. The extract (dried over Na₂SO₄) was evaporated to dryness at 20° in vacuo,
and the residue sublimed at 70°/0.01 mm., giving the pyrazine as a yellow powder (81% yield), m.p. 118-119° (Albert, Brown, and Wood, 1956; m.p. 120°). This was found identical with an authentic sample (infrared). The material gave a blue fluorescent spot on paper chromatography (R_F 0.7) with NH_4Cl.

The Action of Acetic formic anhydride on 2-Amino-3-formylpyrazine.—The pyrazine (0.20 g.) was dissolved in a cold mixture of anhydrous sodium formate (0.20 g.) and acetic formic anhydride (10 ml.), and the contents stirred at 5° for 1 day. The precipitate was filtered off and washed with a little cold ethanol, giving, after one recrystallization from chloroform-ethanol, 2-di(2'-formylpyrazin-3'-ylamino)methyl-3-formamidopyrazine as a pale yellow crystalline powder (47% yield), m.p. 230-231° [Found, for material dried over P_2O_5 at 85°/0.02 mm.: C, 51.2; H, 3.25; N, 32.6; M, 390, 400 (by a vapor pressure Osmometer Mechrolab Model 301A in chloroform at 37°). C_{16}H_{13}N_{9}O_{3} requires C, 50.65; H, 3.45; N, 33.25%; M, 379.3]. R_F 0.6 (thin-layer with chloroform-acetone).
The solvent of the above filtrate was removed at 20°/20 mm. using ethanol, and the residue was subjected to thin layer chromatography with dichloromethane (re-run four times). The band (R_F 0.7-0.85) which showed a dark colour under 254 µ light was collected and continuously eluted with boiling dichloromethane. Removal of the solvent at 20°/20 mm., followed by sublimation of the residue at 70°/0.01 mm., gave 2-formamido-3-formylpyrazine as a pale yellow powder (26% yield), m.p. 125-126°. A recrystallization from light petroleum (b.p. 60-80°) raised the melting point to 126-128° [Found, for material dried over CaCl_2 at 25°/20 mm.; C, 47.95; H, 3.7; N, 27.85. C_6H_5N_3O_2 requires C, 47.7; H, 3.35; N, 27.8%.

R_F 0.80 on paper (NH_4Cl). \nu_{\text{max}} 3300 (NH), 1690s (N-C=O), 1680s (C=O) cm^{-1}. \lambda_{\text{max}} (pH 7.0) 235, 266, 310, 325 µm; log e 3.84, 3.99, 3.75, 3.61.

^1^HCDCl_3/TMS 1.55 doublet (J=2.0 c/sec.), H(5); 1.49 doublet (J=2.0), H(6); 0.33 doublet (J=10.0), N-CHO; -0.11 singlet, C-CHO; -0.25 multiplet, NH. After deuterium exchange, the multiplet at -0.25 disappeared with simultaneous collapse of the doublet at 0.33 to a singlet].
The band \((R_F 0.5-0.65)\) which exhibited a blue fluorescence was also collected and eluted with boiling chloroform. After removal of the solvent at \(20^\circ/20\) mm., the residue (sublimed at \(55-60^\circ/0.01\) mm.) proved to be unreacted starting material (0.01 g.).

(3) Experimental in Section 2.

4-Methylpteridine.—Although this was previously obtained (Albert, Brown, and Wood, 1954) in 60% yield from 4,5-diamino-6-methylpyrimidine and polyglyoxal, the following preparative method is more satisfactory. To the pyrimidine (2.46 g.), dissolved in boiling ethanol (70 ml.), was added a boiling suspension of glyoxal monohydrate polymer (B.D.H., 1.67 g.; 1.1 equiv.) in ethanol (100 ml.), and the mixture refluxed for 30 min. After evaporation of the solvent at \(30^\circ\) under reduced pressure, the residue was covered with a layer of cotton and sublimed at \(110^\circ/0.01\) mm., giving the pteridine as a yellow powder (88% yield), m.p. 152-153.5\(^\circ\) (lit., 152-153\(^\circ\)). It was found necessary to interrupt the sublimation several times and grind the cake.
The dimer (2.4,a).—A solution of 4-methylpteridine (1.50 g.) in 0.5 N-sulphuric acid (24 ml.) was set aside for 15 min. at 30°, then heated at 95° (bath) for 40 min. (initial and final pH: 2.0). The solution was adjusted to pH 5.5 with sodium hydrogen carbonate and briefly warmed at 85°. After cooling, the precipitate was filtered off and washed with a little cold water, giving the dimer hemisulphate (57% crude yield). Two recrystallizations from water gave pale brown needles, decomposing ca 150° (Found, for material dried at 60°/0.01 mm.: C, 40.55; H, 5.2; N, 27.15; S, 3.8.

\[ \text{C}_{14}\text{H}_{18}\text{N}_8\text{O}_3 \cdot \frac{1}{2}\text{H}_2\text{SO}_4 \cdot \text{H}_2\text{O} \text{ requires } \text{C, 40.7; H, 5.1; N, 27.1; S, 3.9\%.} \]

For material dried at 110°/0.05 mm. for 40 min.: C, 42.45; H, 5.0; N, 28.0. \[ \text{C}_{14}\text{H}_{18}\text{N}_8\text{O}_3 \cdot \frac{1}{2}\text{H}_2\text{SO}_4 \text{ requires } \text{C, 42.55; H, 4.85; N, 28.35\%.} \]

Crude hemi-sulphate, recrystallized twice from very dilute sulphuric acid at pH 4, deposited the sulphate as colourless needles. It gradually became brown above 130° and decomposed above 150° (Found, for material dried at 110°/0.05 mm. for 1 hr.: C, 37.95; H, 4.6; N, 25.05. \[ \text{C}_{14}\text{H}_{18}\text{N}_8\text{O}_3 \cdot \text{H}_2\text{SO}_4 \text{ requires } \text{C, 37.85; H, 4.55; N, 25.2\%.} \]

Upon treatment
of the crude hemi-sulphate with a cold 10% solution (10 ml.) of sodium carbonate-sodium hydrogen carbonate (1:1), followed by two recrystallizations of the precipitate from 40 parts of boiling water (with carbon), the base was obtained as an ivory-white crystalline powder (47% yield based on 4-methylpteridine), decomposing ca 190° (darkened without melting) [Found, for material dried at 110°/0.01 mm.: C, 48.25; H, 5.2; N, 31.9; M, 313 (ebullioscopically in water); for material dried at 152°/0.05 mm. for 1 hr.: C, 48.95; H, 5.25; N, 32.55. \( \text{C}_{14}\text{H}_{18}\text{N}_{8}\text{O}_{3} \) requires C, 48.55; H, 5.25; N, 32.35%; M, 346]. It gives only one spot on paper chromatography \( (R_f 0.75, \text{with NH}_4\text{Cl}) \) in contrast to compound (2.6) which the cellulose resolved optically (Albert and Serjeant, 1964).

Reaction of the Dimer with Ethanol. - The substance (50 mg.), toluene-p-sulphonic acid monohydrate (2 mg.), and ethanol (10 ml.) were boiled for 9 hr. After evaporating the solvent, the residue was dissolved in ethanol passed through a column of neutral alumina (5 g.) and
eluted with ethanol. The elute gave 5,6,7,8-
tetrahydro-6-hydroxy-4-methyl-7-(5',6',7',8'-
tetrahydro-6',7'-diethoxypteridin-4'-ylmethyl)
pteridine (2.4,d) (64% yield) after removal of the
solvent and recrystallizing the residue from
ethanol-benzene; it gradually turned reddish brown
above 135° without melting [Found, for material
dried at 100°/0.01 mm.: C, 60.65; H, 6.25;
N, 23.65. C_{18}H_{26}N_{8}O_{3} requires C, 60.0;
H, 6.7; N, 23.35%. The presence of one molecule
of benzene was confirmed by n.m.r., τ 2.64 (6H)].
On recrystallization of the above material from
ethanol-light petroleum (b.p. 80-100°), the
substance was obtained benzene-free as an almost
colourless amorphous solid, gradually becoming
reddish brown above 120° without melting (Found:
C, 54.8; H, 6.3; N, 27.95. C_{18}H_{26}N_{8}O_{3}
requires C, 53.75; H, 6.5; N, 27.85%).

6,7-Dihydroxy-4-methylpteridine. 4,5-Diamino-
6-methylpyrimidine (0.25 g.) and oxalic acid
dihydrate (0.65 g.; 5 equiv.) were heated under a
slight vacuum 40-50 cm. Hg to 160° during 15 min.,
and maintained at 160-170° for 1.5 hr. The
product was extracted with boiling water (60 ml.) containing enough sodium hydroxide to maintain the mixture above pH 10. The filtrate was brought to pH 4 with acetic acid, concentrated to ca 10 ml. below 50° under reduced pressure, and set aside at 5° overnight. The precipitate was filtered off and washed with a little cold water, giving the crude 6,7-dihydroxy-4-methylpteridine as pale brownish yellow needles (83% yield). Two recrystallizations from 50 parts of boiling water gave yellow prisms which turned to a colourless powder on drying at 105°; the m.p. lay above 285° (Found, for material dried at 105°/0.5 mm.: C, 47.05; H, 3.75; N, 31.2. C7H6N4O2 requires C, 47.2; H, 3.4; N, 31.45%). The substance, recrystallized from water, contained water of crystallization (νmax 3570 cm.-1 etc.), lost on drying at 105°. The solubility in boiling water was about six times greater than that of 6,7-dihydroxypteridine (Albert, Brown, and Cheeseman, 1952). The mono-sodium salt was obtained as a colourless powder on stirring the dihydroxy-methylpteridine with 10% aqueous sodium hydrogen carbonate (νmax 1690 cm.-1).
Oxidation of 4-Methylpteridine with Hydrogen Peroxide. — To 4-methylpteridine (83 mg.), dissolved in N-sulphuric acid (0.75 ml.), 30% hydrogen peroxide (0.13 ml.; 2 equiv.) was added and the mixture set aside at 25° for 4 days (pH was 2.5 before and after). Enough solid sodium hydrogen carbonate to give pH 7.5 was added and the mixture set aside overnight at 5°. The precipitate was collected and washed with a little cold water, giving the crude mono-sodium salt of 6,7-dihydroxy-4-methylpteridine as a light brown powder (70% yield). After stirring with sodium acetate buffer solution (pH 4) and recrystallization from water, the neutral species was obtained as a yellow powder that was identical with authentic material (i.r. and chromatography).

Oxidation of the Dimer with Hydrogen Peroxide. — To the powdered dimer (0.10 g.) suspended in N-sulphuric acid (2 ml.), 30% hydrogen peroxide (0.1 ml.; 3 equiv.) was added, and the mixture was shaken at 37° until the precipitate almost dissolved (ca 15 min.), then filtered. After setting aside for 3 days at 25°, then overnight at 5°, the sulphate
was collected, after washing with a little cold water, as colourless needles (0.05 g.), which blackened without melting ca 170° (Found, for material dried at 25°/0.5 mm.: C, 37.1; H, 3.85; N, 24.55; S, 7.05. \( \text{C}_{14}\text{H}_{18}\text{N}_{8}\text{O}_{4}\cdot\text{H}_{2}\text{SO}_{4} \) requires C, 36.5; H, 4.4; N, 24.35; S, 6.95%). Basification with 10% sodium hydrogen carbonate gave the neutral species which decomposed during recrystallization from water.

**3,7-Dihydro-4-methyl-7-(pteridin-4-ylmethylene) pteridine (2.7).** - The finely ground dimer (80 mg.), suspended in 1:1 acetic anhydride-pyridine (1 ml.), was stirred at 25° for 2.5 hr. and set aside overnight at room temperature in the dark. The precipitate was filtered off and purified twice with a mixture of chloroform-ethanol, giving the pteridine as a reddish brown powder (60% yield). It became dark brown above 240° without melting (Found, for material dried at 100°/0.05 mm.: C, 58.15; H, 3.75; N, 36.9. \( \text{C}_{14}\text{H}_{10}\text{N}_{8} \) requires C, 57.95; H, 3.5; N, 38.6%. \( \lambda_{\max} \) (95% EtOH) 266, 290, 300, 455, 481, 509, 550 m\( \mu \); \( \log \epsilon \) 3.86, 3.94, 3.86, 4.29, 4.48, 4.46, 3.33.
\( \lambda_{\text{max}} \) (chloroform) 266, 280, 290, 304, 330, 460, 485, 515 \mu; \ \log e = 3.90, 3.92, 3.94, 3.87, 3.58, 4.31, 4.45, 4.33. The material is slightly soluble in a mixture of chloroform and ethanol but almost insoluble in water and other common organic solvents. It gives a single, yellow fluorescent spot on paper chromatogram (RF 0.03, with NH\(_4\)Cl) under 365 \mu light, and decomposes when dissolved in N-sulphuric or trifluoroacetic acid.

4-Methylpteridine and Barbituric acid. (a) Solutions of the pteridine (0.17 g.) in water (5 ml.) and of barbituric acid (0.15 g.; 1 equiv.) in water (25 ml.), were mixed (initial pH: 2.5) and set aside at 25° for 24 hr. in a dark place (final pH: 5.0), giving 7,8-dihydro-4-methyl-7-(2,4,6-trihydroxypyrimidin-5-yl)pteridine as a yellow powder (97% yield). This, suspended in 100 parts of water, was carefully dissolved by addition of 2N-sodium carbonate and the solution clarified by filtration. The filtrate was taken to pH 4 by careful addition of N-sulphuric acid. The precipitate was filtered off and washed well with water, giving the analytically pure material as a
pale yellow powder which gradually darkened above 250° without melting [Found, for material dried at 105°/1 mm.: C, 47.4; H, 3.55; N, 30.0.

C_{11}H_{10}N_{6}O_{3} requires C, 48.15; H, 3.65; N, 30.65%. 

\[ \lambda_{\text{max}} \text{ (pH } 8.0), 218, 260, 297, 302, 312 \text{ m}\mu; \log \varepsilon 4.22, 4.31, 3.86, 3.88, 3.82. \]

\[ \lambda_{\text{max}} \text{ (pH } 5.0), 218, 260, 297, 302, 312 \text{ m}\mu; \log \varepsilon 4.17, 4.27, 3.89, 3.92, 3.86. \]

\[ \lambda_{\text{max}} \text{ (pH } 1.0), 308, 414 \text{ m}\mu; \log \varepsilon 3.96, 3.24. \]

(b) Solutions of 4-methylpteridine (0.07 g.) in water (3 ml.), and of barbituric acid (0.14 g.; 2.2 equiv.) in water (25 ml.), were mixed and stirred at 25° for 24 hr. (initial and final pH: 2.5 and 3.0, respectively). The pale yellow precipitate, purified as above, gave 5,6,7,8-tetrahydro-4-methyl-6,7-dio-(2,4,6-trihydroxypteridine as a yellow powder (92% yield), above 230° it gradually became brown without melting (Found, for material dried at 110°/0.05 mm.: C, 44.6; H, 3.9; N, 27.15.

C_{15}H_{14}N_{8}O_{6} requires C, 44.8; H, 3.5; N, 27.85%. 

\[ \nu_{\text{max}} 3300, 3200, 1740, 1710, 1690, 1660, \text{ and } 1640 \text{ cm}^{-1} \text{ all broad and strong}. \]

7,8-Dihydro-6-hydroxy-4-methyl-7-(2,4,6-trihydroxypteridine was similarly obtained by the same procedures as a yellow powder
from 6-hydroxy-4-methylpteridine (Albert and Reich, 1961) and barbituric acid (1 equiv.) in 70% yield after two recrystallizations. The pteridine gradually became brown above 270° without melting (Found, for material dried at 110°/0.1 mm: C, 43.95; H, 3.75; N, 27.95. \( \text{C}_{11}\text{H}_{10}\text{N}_{6}\text{O}_{4}\text{.5H}_{2}\text{O} \) requires C, 44.15; H, 3.7; N, 28.1%.

\( \text{v}_{\text{max}} \) 3400bm, 3200bs, 1695bs, 1660bs cm\(^{-1}\).

4-Methylpteridine and Sodium hydrogen sulphite.

The pteridine (0.16 g.) and sodium metabisulphite (0.25 g.; 2.2 equiv.) were shaken in water (10 ml.) at 25° for 10 min. The solution, clarified by gravity filtration, was set aside at 25° for 30 min., then 0.20 g. more of the sodium salt was added. After setting aside at the same temperature for 3 hr. and at 5° for 0.5 hr. (final pH: 4), ethanol was added to the cold solution until crystals appeared, and the mixture chilled overnight. The colourless precipitate was filtered off and washed with (successively) 75% aqueous ethanol, absolute ethanol, and diethyl ether, giving the mono-sodium salt of 5,6,7,8-tetrahydro-4-methylpteridine-6,7-disulphonate as a colourless powder (56% yield).
It gradually became brown above 160° without melting (Found, for material dried at 25°/20 mm.: C, 23.65; H, 3.55; N, 15.35. \( \text{C}_7\text{H}_{11}\text{N}_4\text{O}_8\text{S}_2\text{Na} \) requires C, 23.0; H, 3.05; N, 15.3%).

7-Chloro-4-dichloromethylpteridine. — Finely ground 7-hydroxy-4-methylpteridine (Albert and Reich, 1961) (0.14 g.) was heated under reflux with pentachloroethane (20 ml.) for 15 min., phosphorus pentachloride (0.35 g.) was added, then the mixture boiled for 30 min. The solvent was evaporated at 60° (bath)/10 mm., and the residue extracted with cold benzene (2 x 10 ml.). After removal of the solvent at 40°/20 mm., extraction of the residue with boiling light petroleum (b.p. 40-60°, 100 ml.), followed by concentration of the extract to ca 3 ml., deposited the chloropteridine (10% yield). One recrystallization from this light petroleum gave pale yellow prisms, m.p. 84-85° [Found, for material dried over \( \text{CaCl}_2 \) at 25°/20 mm.: C, 33.9; H, 1.5; N, 22.25. \( \text{C}_7\text{H}_3\text{N}_4\text{Cl}_3 \) requires C, 33.7; H, 1.2; N, 22.45%]. No absorption band at 3500-3100, 1800-1600 cm.\(^{-1} \)
λ max (cyclohexane) 222, 297, 302, 307, 312, 321, 383 μm; log ε 4.09, 3.87, 3.94, 4.12, 4.00, 3.95, 2.22, respectively. ¹CDCl₃/TMS 2.10 singlet, CHCl₂(4); 1.03s, H(2)*; 0.34s, H(6)*.

(The assignments marked * are interchangeable)

4,6,7-Triethylpteridine—4,5-Diamino-6-methylpteridine (0.25 g.) and diacetyl (0.20 g.; 1.25 equiv.) were boiled in ethanol (5 ml.) for 1 hr. The solvent was removed in vacuo, and the residue was dissolved in benzene and passed through a column of neutral alumina (5 g.) which was eluted with benzene. After removal of the colourless fore-run, the yellow band was eluted. The solvent, removed at 20°/20 mm., left the trimethylpteridine as a yellow solid (71% crude yield). Two recrystallizations from light petroleum (b.p. 60-80°) gave the analytically pure material as pale yellow needles, m.p. 139-140° (Found, for material dried at 25°/0.01 mm.; C, 61.45; H, 5.75; N, 31.6. C₉H₁₀N₄ requires C, 62.05; H, 5.8; N, 32.15%).
2,4,6,7-Tetramethylpteridine.—This was prepared from 4,5-diamino-2,6-dimethylpyrimidine (Prasad, et al., 1959) and diacetyl in 65% yield according to the same procedures described for the above trimethylpteridine, followed by sublimation at 100°/1 mm. After two recrystallizations from light petroleum (b.p. 60-80°) the tetramethylpteridine was obtained as pale yellow needles, m.p. 124-125° (Found, for material dried at 25°/1 mm.; C, 63.85; H, 6.65; N, 29.4. C_{10}H_{12}N_{4} requires C, 63.8; H, 6.45; N, 29.75%).

(4) Experimental in Section 3.

Anhydro-tri-2-aminobenzaldehyde.—The substance, when prepared according to the directions of Seidel (1926) and recrystallized from ethanol, formed colourless leaflets (37% yield), m.p. 233-234° (decomp.) (Found: C, 77.4; H, 5.3; N, 12.7%; M (Rast), 288, 293. Calc. for C_{21}H_{17}N_{3}O: C, 77.0; H, 5.2; N, 12.8%; M, 327). \( \lambda_{\text{max}} (\text{EtOH}) \) 240, 286, 300\( \mu \); \( \log \varepsilon \) 4.23, 3.50, 3.33. The following preparative method is more satisfactory. To a suspension of 2-aminobenzaldehyde (1.50 g.) in
water (300 ml.), initially warmed at 60° for 3 min. and cooled to 25°, 2N-hydrochloric acid (10 ml.) was added with stirring. After vigorously stirring for 3 hr., the suspension was set aside for 16 hr. at 22-25° (initial and final pH: 1.2). The precipitate was collected, washed with dilute aqueous sodium bicarbonate, dried, and warmed with acetone (10 ml.). The trimer (80% yield), obtained by cooling and filtration, recrystallized from ethanol as colourless leaflets (87% recovery), m.p. 239° (decomp.). When the above suspension of the aldehyde in water was initially warmed at 40°, the trimer of melting point 245-247° (decomp.), was obtained after the similar treatment (53% total yield). The infrared spectra of these substances were identical with that of the trimer of m.p. 234°, and all gave single spots on paper (R_F 0.05; pet.-MeOH) and on thin layer (R_F 0.55; CHCl_3-acetone) chromatography.

**Monoacetyl-anhydro-tri-2-aminobenzaldehyde**—The procedures of Seidel (1926) were followed, but alcohol was preferred for recrystallization. The trimer (1.0 g.) gave, after acetylation and three
recrystallizations from ethanol, the monoacetyl-trimer as colourless prisms (68% yield), m.p. 228-229° (Seidel, 1926; m.p. 237°) (Found: C, 74.9; H, 5.1; N, 11.6. Calc. for C₂₃H₁₉N₃O₂: C, 74.8; H, 5.2; N, 11.4%). λ_max (EtOH) 237, 282 μ; log ε 4.27, 3.38.

Diacetyl-anhydro-tri-2-aminobenzaldehyde.—Acetyl chloride (0.2 ml.) was added to a cold solution of the trimer (0.1 g.) in pyridine (1 ml.). After the colourless deposit appeared, more acetyl chloride (0.3 ml.) and pyridine (1 ml.) were added, followed by stirring for 2 hr., cooling in ice and water. Then cold water (12 ml.) was added while cooling in ice, and the suspension stirred for 1 min., filtered, and washed with cold water. The pale brown solid was recrystallized from ethanol (72% yield). Two more recrystallizations from ethanol gave the diacetyl-trimer as colourless powder, m.p. 219-220°, easily soluble in pyridine, acetone, and chloroform, moderately in benzene (Found: C, 73.0; H, 5.3; N, 10.1. C₂₅H₂₁N₃O₃ requires C, 73.0; H, 5.1; N, 10.2%). λ_max (EtOH) 237, 274, 282 μ; log ε 4.26, 3.45, 3.38.
Diformyl-anhydro-tri-2-aminobenzaldehyde.—

Acetic formic anhydride (1.0 ml.) was added to a suspension of the trimer (0.20 g.) in light petroleum (b.p. 80-100°, 3 ml.), and the mixture was stirred for 3 hr. at 27°. The deposit, filtered and washed with a little ethanol, was recrystallized from ethanol to give the diformyl-trimer as colourless leaflets (0.20 g., 85% yield), m.p. 243-245° (Found, for material dried at 104°/0.01 mm.: C, 71.9; H, 4.4; N, 11.0%; M (Rast), 353, 340. C_{23}H_{17}N_{3}O_3 requires C, 72.05; H, 4.5; N, 11.0%; M, 383). \( \lambda_{\text{max}} \) (EtOH) 232, 248, 284, 315, 350 μ; \( \log \varepsilon \) 4.46, 4.34, 3.48, 3.28, 2.99.

Anhydro-tetra-2-aminobenzaldehyde.—

2-Aminobenzaldehyde (1.1 g.) and 5N-hydrochloric acid (8 ml.) were stirred, cooling in ice, until the solid dissolved (20 min.). The filtrate (frittered glass filter), set aside for 18 hr. at 22-25°, gave red needles (0.80 g.) which were warmed with a mixture (8 ml.) of pyridine and alcohol (2:3, v/v). To this solution, hot water (4 ml.) was added and the mixture warmed on a
steam-bath for 10 min. The yellow solution, refrigerated for 43 hr., deposited pale yellow prisms which, recrystallized from a mixture of pyridine, alcohol, and water (2:3:3, v/v/v.), gave the tetramer as pale yellow prisms (0.24 g., 19%), m.p. 233-234° [Found, for material dried at 105°/0.005 mm.: C, 77.9; H, 4.9; N, 12.95%; M (Rast), 400, 393. Calc. for C_{28}H_{22}N_{4}O: C, 78.1; H, 5.15; N, 13.0%; M, 430]. 

\( \lambda_{\text{max}} \) (EtOH) 230, 236, 259, 268, 286, 370 μm; log \( \varepsilon \) 4.57, 4.59, 4.19, 4.10, 3.57, 3.82, 

\( R_{F} \) 0.8 (paper and thin layer chromatography with pet.-MeOH and CHCl₃-acetone, respectively).

Monoacetyl-anhydro-tetra-2-aminobenzaldehyde.

The tetramer (0.54 g.) suspended in light petroleum (b.p. 80-100°, 2 ml.) was stirred with acetic anhydride (1 ml.) for 14 hr. at 22-25°. Removal of the solvent under reduced pressure left a pale yellow powder, which, recrystallized from acetone, gave the monoacetyl-tetramer as pale yellow prisms (67% yield), m.p. 263-265° [Found: C, 75.95; H, 5.0; N, 11.8. Calc. for C_{30}H_{24}N_{4}O_{2}: C, 76.25; H, 5.1; N, 11.9%], \( \lambda_{\text{max}} \) (EtOH) 229,
235, 260, 268, 282, 372 μμ; log e 4.61, 4.59, 4.19, 4.10, 3.46, 3.82. From the filtrate, 11% more material (m.p. 258-261₀) was obtained.

Acetylation of the tetramer with acetyl chloride in pyridine (25₀), or with acetic anhydride and zinc chloride (50₀), gave only the monoacetyl tetramer.

Acetylation of the monoacetyl-tetramer with hot acetic anhydride: The diacetyl-trimer and 2-acetamidobenzaldehyde.—The monoacetyl-tetramer (50 mg.), in acetic anhydride (1 ml.) and acetic acid (1 ml.), was refluxed for 2.5 hr. Removal of the solvent gave a residue which was warmed with ethanol (2 ml.) and set aside overnight at 22-25₀. The precipitate, collected and washed with a little ethanol, gave a colourless crystalline powder, m.p. 219₀. The filtrate, concentrated to about 1 ml., and warmed, then set aside for 4 hr. at 25₀ and chilled 1 hr., deposited crystals which, after washing with a little ethanol, gave more of the same solid. This was identical (infrared) with the diacetyl-trimer (84% yield). Removal of the solvent from the filtrate of the latter gave a small amount of viscous oil
which was warmed with water (2 ml.) and filtered (hot). The filtrate deposited crystals of 2-acetamidobenzaldehyde (11% yield), m.p. 68-69° (lit., 71°).

**Monoformyl-anhydro-tetra-2-aminobenzaldehyde.**—The tetramer (19 mg.), suspended in light petroleum (b.p. 80-100°, 0.4 ml.), was stirred with acetic formic anhydride (0.3 ml.) for 1.5 hr. at 30°. Solvent was removed and the residue was recrystallized from ethanol to give the monoformyl-tetramer as pale yellow prisms (79% yield), m.p. 273-274° (Found, for material dried at 105°/0.01 mm.: C, 75.7; H, 4.8; N, 12.4. \(\text{C}_{29}\text{H}_{22}\text{N}_{4}\text{O}_{2}\) requires C, 75.95; H, 4.8; N, 12.2%), \(\lambda_{\text{max}}\) (EtOH) 229, 235, 258, 268, 282, 370 m\(\mu\); \(\log \varepsilon\) 4.60, 4.59, 4.24, 4.13, 3.48, 3.82. \(\nu_{\text{max}}\) 3320(NH), 1680(N-CHO), 1650 cm.\(^{-1}\) (C-CHO).

**Monoacetyl-mononitroso-anhydro-tetra-2-aminobenzaldehyde.**—The procedure of Seidel (1926) was followed. After two recrystallizations from benzene, a 60% yield of the monoacetyl-mononitroso-tetramer was obtained, 191-193° (decomp.) (Seidel, 1926; m.p. 193°) (Found: C, 72.05; H, 4.7; N, 13.3.
Calc. for C₃₀H₂₃N₅O₃: C, 71.8; H, 4.6; N, 14.0%.

λmax (EtOH) 239, 274, 283 μ; log ε 4.22, 3.49, 3.42.

2-Methylnaminobenzaldehyde and N-nitroso-2-methylnaminobenzaldehyde. - 2-Methylnaminobenzaldehyde, b.p. 108-109⁰/9 mm. (lit. 111-112⁰/10 mm.), was prepared according to Barlin (1962), λmax (H₂O) 223, 230, 263, 267, 387 μ; log ε 4.33, 4.31, 3.80, 3.77, 3.72, λmax (2N-HCl) 247, 283 μ; log ε 4.05, 3.20, υmax (liq. film) 3380(NH), 1665(C=O) cm⁻¹, τ(CCl₄) 7.07d (J=5 c/s, Me), 2.4-3.6m (aromatic protons), 1.67m(NH), 0.16s(CHO). 2-Methylnaminobenzaldehyde (1.00 g.) and pentylnitrite (3.0 ml.) were refluxed in s-butanol (30 ml.) for 3.5 hr. Solvent was removed under reduced pressure (20 mm.) and the residue, recrystallized from light petroleum (b.p. 80-100⁰), gave N-nitroso-2-methylnaminobenzaldehyde as colourless needles (33% yield), m.p. 28-29⁰ (Found, for material dried over CaCl₂ at 20⁰/0.01 mm.: C, 58.75; H, 4.8; N, 17.2.

C₈H₈N₂O₂ requires C, 58.5; H, 4.9; N, 17.1%)

λmax (H₂O) 241, 287 μ; log ε 4.22, 3.53, υmax (liq. film) 1690, 1705 cm⁻¹ (C=O). τ(CCl₄) 6.58s(Me), 1.9-2.7m(aromatic Hs), 0.15s(CHO).
Anhydro-tetra-2-aminobenzaldehyde hydrochloride.—

The red needles, described above, were recrystallized from 5N-hydrochloric acid and dried over phosphorus pentoxide and sodium hydroxide at 130°/0.01 mm. for 1 hr., m.p. about 280° (blackened without melting when heated gradually, but when inserted at 260°, it immediately decomposed), and, dissolved in a mixture of pyridine, alcohol, and water, gave a single spot (RF 0.8; the same as the above tetramer) on paper chromatography in light petroleum-methanol (Found: C, 67.35; H, 5.2; N, 11.1; Cl, 14.1.

$C_{28}H_{22}N_4O_2\cdot2\text{HCl}$ requires: C, 66.8; H, 4.8; N, 11.1; Cl, 14.1%). $\lambda_{\text{max}}$(5N-HCl, within 8 min.) 220, 246, 307, 467 m\(\mu\); log $\varepsilon$ 4.26, 4.04, 3.93, 3.26.

Both the trimer and the tetramer, separately treated as above with 5N-hydrochloric acid, gave tetramer hydrochloride identical in infrared spectrum with the above.

2-Aminobenzaldehyde.— This, m.p. 39° (lit., 40°), was prepared according to Mann and Wilkinson (1957). $\lambda_{\text{max}}$(H$_2$O) 229, 260, 365 m\(\mu\); log $\varepsilon$ 4.32, 3.83, 3.59. $\lambda_{\text{max}}$(1.6 N-HCl) 246, 284 m\(\mu\); log $\varepsilon$ 4.06, 3.20.
pKₐ = 1.36 ± 0.05 (measured at 247 μ in HCl solutions of known E₀ at 20°. Rₚ 0.35, and 0.7 on paper (pet.-MeOH), and thin layer (CHCl₃-acetone) chromatography respectively.

When freshly prepared 2-aminobenzaldehyde was set aside for one month at 20°, much of the material melted at 37-38°. The material that remained unmelted was shown by paper chromatography to be a mixture of monomer, trimer, and a trace of the tetramer. The stored material was suspended in 2N-ammonium hydroxide and steam-distilled. The distillate, on refrigeration, deposited colourless leaflets of 2-aminobenzaldehyde. By extraction of the filtrate with ether more material was obtained (total yield 60%, m.p. 38-39°).

The residue in the steam-distillation flask, refrigerated for 1 day and filtered, gave a yellow solid which consisted mainly of the trimer with a small amount of monomer and a trace of tetramer (as shown by paper chromatography). The approximate yield of the trimer was 20%. Only 40% of 2-aminobenzaldehyde could be recovered in this way from a specimen that had been set aside for two months at 20°.
The Anhydro-dimer of 2-Methylaminobenzaldehyde.—

The methylaminoaldehyde (0.45 g.) was stirred with N-hydrochloric acid (3 ml.) at 25-30° for 2 days. The precipitate was filtered off, washed with cold water, and dried over CaCl₂ at 25°/20 mm., giving the crude dimer (94% yield). Two recrystallizations from ethanol gave analytically pure material (88% recovery), m.p. 138-139.5° (Bamberger, 1904; m.p. 139.5-140° from "ligroin") [Found: C, 76.2; H, 6.1; N, 11.2; M, 273, 278 (by a vapor pressure Osmometer in chloroform at 37°). Calc. for C₁₆H₁₆N₂O: C, 76.15; H, 6.4; N, 11.1%; M, 252.3].

λ max (95% EtOH) 246, 299 μ; log ε 4.26, 3.51.

(5) Experimental in Section 4.

Action of N-Sodium hydrogen sulphate on Quinazoline.—

(a) pH 2.0: A solution of quinazoline (Armarego, 1961) in N-sodium hydrogen sulphate (31 ml.) was refluxed for 1 hr. After cooling, the deposit was transformed to a powder by scratching; the suspension was stirred for 5 hr. and set aside for 12 hr., then chilled. The precipitate, filtered off and washed
with a little cold water, was stirred with chloroform (20 ml.) for 0.5 hr. at 25°. The Substance Q sulphate (see below) was obtained on filtration and washing with chloroform. The filtrate was passed through a silica gel column and eluted with chloroform. Removal of the solvent in vacuo gave a yellow powder (0.29 g.), which consisted of 2-aminobenzaldehyde and its anhydro-polymers (chromatography). The powder, warmed with ethanol (1 ml.) then chilled, deposited the trimer as a pale yellow powder, m.p. 233-234° after one recrystallization from acetone. The filtrate was subjected to thin layer silica gel chromatography with chloroform-acetone (9:1) as a developing solvent; the three bands (R_f 0.6-0.7, 0.8, and 0.9) were collected, eluted with chloroform, and afforded respectively the trimer, the tetrramer (m.p. 233-235°), and the monoformyl-tetramer (m.p. 269-271°). The yields of the above products are recorded in Table 4 (p. 78). Although 2-aminobenzaldehyde was not isolated as a pure material, the approximate yield was calculated by subtracting the amounts of the anhydro-polymers
from that of the above yellow powder (i.e. the chloroform-soluble part).

(b) pH 1.5: The same procedures as above were followed, and the results are recorded in Table 4.

Substance Q.—Quinazoline (2.6 g.) in 0.1N-hydrochloric acid (150 ml.; the solution, pH 1.1) was refluxed for 1 hr. and set aside overnight at 5°, depositing Substance Q hydrochloride (55% yield) as a pale yellow powder which after two recrystallizations from 0.01N-hydrochloric acid had m.p. 281-283° (decomp.) [Found, for material dried over KOH/CaCl₂ at 5°/20 mm. for 4 days: C, 59.65; H, 5.0; N, 13.75; Cl, 14.95. (C₁₅H₁₃N₃O₁.1.3HCl)₂, requires C, 60.3; H, 4.85; N, 14.05; Cl, 15.4%]. The hydrochloride was hygroscopic and decomposed on drying at a temperature higher than 5°.

On stirring the above Substance Q hydrochloride (50 mg.) with N-sodium hydrogen sulphate (pH 1.8; 7.5 ml.) at 25° for 1 hr., the Substance Q hemi-sulphate was obtained as a pale yellow powder after two recrystallizations of the precipitate from boiling water, m.p. ca 270° (gradually decomp.)
Substance Q picrate was obtained as a yellow crystalline powder by stirring the Substance Q hydrochloride with a saturated aqueous solution of picric acid (together with a trace of hydrochloric acid) at 25° for 1 hr.; then recrystallizing the deposit from methyl cellosolve-ethanol, m.p. 200-210° (gradually foaming) [Found: C, 53.25; H, 3.85; N, 16.95. \((\text{C}_{15}\text{H}_{13}\text{N}_3\text{O})_n\) requires C, 52.5; H, 3.35; N, 17.5%].

A suspension of the above hydrochloride or sulphate in 10% aqueous sodium carbonate was stirred at 25° for 2 hr.; the precipitate was filtered off and recrystallized twice from ethanol-water, giving Substance Q as a pale yellow powder (85-90% yield), m.p. ca 260° (gradually decomp.) [Found, for material dried at 105°/0.01 mm.: C, 71.8; H, 5.25; N, 16.2. \((\text{C}_{15}\text{H}_{13}\text{N}_3\text{O})_n\) requires C, 71.7; H, 5.2; N, 16.7%].

**Acetylation of Substance Q.**—The substance (0.10 g.), dissolved in a mixture of acetic anhydride
and pyridine (1:1; 2 ml.), was set aside at 25° for 2 days. The solvent was removed by repeatedly taking the preparation to dryness in vacuo in the presence of ethanol. The residue, after two recrystallizations from iso-propanol, gave the diacetyl derivative as an almost colourless crystalline powder (68% yield), m.p. 210-215° (gradually foaming) [Found: C, 68.3; H, 5.2; N, 12.0; M, 1400, 1410 (using chloroform in a vapor pressure osmometer at 37°). \((\text{C}_{19}\text{H}_{17}\text{N}_{3}\text{O}_{3})_4\) requires C, 68.05; H, 5.1; N, 12.5%; M, 1340].

A Chromatographic Study of the Degradation of Quinazoline.—Quinazoline (50 mg.), dissolved in 0.1N-hydrochloric acid (20 ml.; pH 1), was heated at 87° (bath), and the contents were periodically checked by paper chromatography with 3% aqueous ammonium chloride. The sky-blue fluorescent spot (RF 0.65) was gradually seen after 30 minutes heating; then a dark elongated spot (RF 0.2-0.4) due to Substance Q appeared after 60 min., when a large amount of quinazoline was still present (RF 0.75, dark spot).
Quinazoline and 2-Aminobenzaldehyde.— The powdered aldehyde (0.24 g.) was added at 3°C to a solution of quinazoline (0.26 g.; 1 equiv.) in N-hydrochloric acid (15 ml.; pH 0.2), and the mixture was vigorously stirred for 7.5 hr. and set aside overnight at 3°C. The precipitate, which mainly consisted of the aminoaldehyde and its anhydrotetramer (chromatography), was filtered off and purified by the same procedure described on p. 129, giving the trimer (46% yield) (infrared). To the above filtrate, diluted to 40 ml. with water, solid potassium hydrogen sulphate (2.0 g.) was added, and the mixture after stirring at 25°C for 1 hr. deposited Substance Q as sulphate (30% yield).

Quinazoline and 2-Aminoacetophenone.— This acetophenone (135 mg., prepared from o-nitrobenzoic acid: Reynolds and Hauser, 1950; Simpson et al., 1945) and quinazoline (130 mg.; 1 equiv.) were stirred in N-sulphuric acid (2.5 ml.; pH 1.8) at 25°C for 3 days; the contents were brought to pH 11 with 10% aqueous sodium carbonate-sodium hydrogen carbonate (1:1) and extracted thoroughly with
After being washed with cold water, the extract was evaporated to dryness in vacuo, and the residue was twice recrystallized from chloroform-benzene, giving 4-o-acetylanilino-3,4-dihydroquinazoline as pale yellow prisms (45% yield), m.p. 193-195° (Found: C, 72.6; H, 5.7; N, 15.45. C_{16}H_{15}N_{3}O requires C, 72.45; H, 5.7; N, 15.85%). R_{F} 0.65 (paper/3% aqueous NH_{4}Cl; a sky-blue fluorescent spot).

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Appendix: Publications

Albert and Yamamoto,
'The Structures of the Anhydro-polymers of 2-Aminobenzaldehyde', *J. Chem. Soc.* (B),
1966, 965.

Albert and Yamamoto,
'Pteridine Studies. Part XXXV. The Structure of the Compound formed by the action of dilute acid on 4-Methylpteridine', *J. Chem. Soc.* (C),
1968, in press.

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1968, prepared for publication.
The Structures of the Anhydro-polymers of 2-Aminobenzaldehyde

By Adrien Albert and Hiroshi Yamamoto

Reprinted from

JOURNAL
OF
THE CHEMICAL SOCIETY

SECTION B
Physical Organic Chemistry

1966
The Structures of the Anhydro-polymers of 2-Aminobenzaldehyde

By Adrien Albert and Hiroshi Yamamoto

The anhydro-trimer formed from 2-aminobenzaldehyde on storage or, more rapidly, in dilute acid, is assigned the structure 2,4,2',N-(o-aminobenzo)-1,3,2'-(o-hydroxytolueno)-1,2,3,4-tetrahydroquinazoline on the basis of ultraviolet, infrared, and nuclear magnetic resonance spectra. This replaces the previous formulation. The structure 1',2',3',4'-tetrahydro-4'-hydroxyquinazoline[2',3'-f]-1,3,4-tetrahydro-1,12-dihydrotribenzo[b,f,j]-1,5,9-triazacyclododecahexene dihydrochloride, is similarly assigned to the red anhydro-tetramer hydrochloride into which 2-aminobenzaldehyde is changed in concentrated acid, and 2,4,2',N-(o-aminobenzo)-1,3,2'-(o-(formylanilino)tolueno)-1,2,3,4-tetrahydroquinazoline, to the pale yellow anhydro-tetramer formed when this salt is basified.

The equilibria between these various polymers and the monomer are discussed. Quantitative data for the stability of 2-aminobenzaldehyde when stored are given for the first time.

One anhydro-polymer is slowly formed from 2-aminobenzaldehyde on storage at room-temperature, whereas mineral acid quickly produces two such polymers. When we obtained similar substances by the action of hot, dilute acid on quinazoline, it seemed desirable to re-examine the structures suggested for the 2-aminobenzaldehyde polymers by Seidel and Dick on the basis of chemical reactions. We found that the spectral properties of these polymers were not in accord with these authors' suggestions but pointed unequivocally to other structures now explained.

Anhydrotri-2-aminobenzaldehyde, obtained when 2-aminobenzaldehyde is set aside with 0,1N-hydrochloric acid at room temperature, has an empirical formula corresponding to three molecules of the aldehyde less two molecules of water (C21H17N3O). Bamberger first formulated structure (I) on the evidence only of the molecular weight (measured ebullioscopically in pyridine) and the formation of a mono-N-methyl derivative with methanol and hydrogen chloride. Seidel and Dick preferred the tautomeric pair (I) and (II); (II) was used to explain their inability to obtain a diacetyl derivative and to condense the trimer with another molecule of 2-aminobenzaldehyde under neutral conditions; (I) was used to explain the formation of a dinitrito-
derivative, a nitroso-derivative of the acetyl-compound, and the condensation with 2-aminobenzaldehyde in the presence of strong acid to give the anhydro-tetramer.

In the present work the infrared (i.r.) spectrum of the trimer indicated the presence of an aliphatic hydroxyl group (3300 cm\(^{-1}\), broad and strong) but no carbonyl group. Ultraviolet spectra showed that the trimer existed as a stable neutral molecule in aqueous solution between pH 4 and 12-5 but below pH 3 it was in equilibrium with 2-aminobenzaldehyde, indicating that the trimer had bonds which were easily hydrolysed by acid to re-form the monomer. In dilute solution (10\(^{-6}\) mole/l.) the rate of depolymerisation was roughly proportional to hydrogen-ion concentration, for the reaction was almost completed within 20 min. at pH 0, 10 hr. at pH 1-0, 3 days at pH 2-0, and 1 month at pH 3-0. The ultraviolet spectrum of the trimer in ethanol (Figure 1) showed peaks at 240 and 286 m\(\mu\) but no absorption above 320 m\(\mu\), which indicated lack of a highly conjugated system. The nuclear magnetic resonance (n.m.r.) spectrum consisted of a sharp singlet (1 H) at \(\tau 6·73\), a doublet (1 H) at \(\tau 4·63\) (\(J = 4\) c./sec.), a broadened doublet (1 H) at \(\tau 4·43\) (\(J = 4\) c./sec.), a singlet (1 H) at \(\tau 4·34\), a doublet (1 H) at \(\tau 3·53\) (\(J = 4\) c./sec.), and a complicated multiplet from the aromatic protons (12 H) between \(\tau 2·5\) and \(3·5\). There was no signal at lower field than \(\tau 2·5\), indicating the absence of an azomethine group (–CH=N–) from the trimer, the proton signals of which would be expected between \(\tau 1·5\) and 2-0 (cf. our value 1·50 for CH=N of benzylideneaniline in carbon tetrachloride). After deuterium exchange, the doublets at \(\tau 4·63\) and \(4·43\) collapsed to sharp singlets, that at \(\tau 3·53\) disappeared, and the singlet at \(\tau 6·73\) (attributed to a hydroxyl group) almost disappeared. The doublet at \(\tau 3·53\) was then ascribed to an imino-proton coupled to a vicinal methine proton (4·63, \(J = 4\) c./sec.) and the broad doublet, \(\tau 4·43\), to the methine proton of a secondary alcohol. No peak due to methylene groups was present. Consideration of these exchange phenomena and the possible modes of formation of the compound led to the partial structures: –CH(OH)–C\(_6\)H\(_4\)N–(o) and –CH(NH)–C\(_6\)H\(_4\)N–(o). The trimer had another methine proton which gave a singlet at \(\tau 4·34\), suggesting a partial structure, –CH(N–)–C\(_6\)H\(_4\)N–(o) for the rest of the molecule. Combination of these three led to the structure (IIIa)

\[
2·4·2·3·2\,\text{--}(\text{o-aminobenzo-})-3·1·3\,\text{--}(\text{o-hydroxytoluene})-1·2·3·4\,\text{--}\text{tetrahydroquinazoline for anhydrotrii-2-aminobenzaldehyde.}
\]

N.m.r. data are in the Table. Structure (IIIa) was confirmed by examination of the spectra of Seidel's monoacetyl derivative\(^2\) and of a diacetyl derivative which, contrary to Seidel's report, was readily obtainable. The i.r. spectrum of the monoacetyl compound resembled that of the trimer, except for bands assignable to an N-acetyl substituent, e.g., 1660 cm\(^{-1}\). This derivative still possessed a hydroxyl group (3200 cm\(^{-1}\), strong and broad) but no ester group (no additional band near 1200 cm\(^{-1}\)). The ultraviolet spectrum in ethanol (Figure 1) resembled that of the starting material and changed similarly after acidification. Thus, the monoacetyl-trimer is considered to be the N-monoacetyl derivative (IIIb).

This is confirmed by the n.m.r. spectrum, in which the singlet from H(4) (\(\tau 3·43\)) appeared at considerably lower field than that of the proton in the trimer (\(\tau 4·63\)). When the solution was shaken with a trace of 35% DCl, the singlet at \(\tau 6·67\), attributable to the 7\(^\prime\)-hydroxyl group, disappeared with simultaneous collapse of the doublet at \(\tau 4·45\) [from H(7\(^\prime\))] to a singlet.

The ultraviolet spectrum of the diacetyl derivative (Figure 1) closely resembled that of the monoacetyl-trimer. The absence of an i.r. band near 3300 cm\(^{-1}\) provided proof that the hydroxyl group of (IIIa) was acetylated, and this was confirmed by strong absorption bands at 1735 and 1215 cm\(^{-1}\), due to the O-acetyl group, apart from the strong band at 1675 cm\(^{-1}\).
due to N-acetyl. In the n.m.r. spectrum, two clear singlets at $\tau$ 7·69 and 7·47 (3 H, each) are best assigned to an O-acetyl and a N-acetyl group respectively, the singlet at $\tau$ 7·40 (N-acetyl) in the monoacetyl-trimer being used as a guide. The singlet at $\tau$ 4·47 (1 H) is assigned to H(2) because this proton absorbed at $\tau$ 4·34 in the trimer and at $\tau$ 4·28 in the monoacetyl-trimer, and would not be greatly affected by the two acetyl substituents. Although a complicated multiplet was found between $\tau$ 2·5 and 3·3, two sharp singlets at $\tau$ 3·31 and 3·16 (1 H each) stood out, and can be assigned to H(4) and H(7'). The diacetyl-trimer was found to contain no exchangeable hydrogen atom. All this evidence points to a common skeleton for the parent substance and the mono- and di-acetyl derivative, which are assigned structures (IIla, b, c), respectively.

Similar treatment of the trimer with acetic formic anhydride gave a diformylated anhydro-trimer ($\text{C}_{23}\text{H}_{17}\text{N}_{3}\text{O}_{3}$), of which the ultraviolet spectrum in ethanol (Figure 1, D) differed considerably from those of the trimer and its acetyl derivatives by having peaks at longer wavelength (315 and 350 m$\mu$), indicative of a skeletal change and the presence of a more highly conjugated system. The diformyl-trimer was found to possess two kinds of carbonyl i.r. bands at 1685 and 1665 cm.$^{-1}$ but no evidence of imino- or hydroxy-groups. This was confirmed by the n.m.r. spectrum, in which peaks were assigned to formyl protons observed as sharp singlets at $\tau$ -0·34 (1 H) and 0·96 (2 H), consistent with the presence of one C-CHO and two equivalent N-CHO, respectively. A sharp singlet (2 H, $\tau$ 2·83) stood out from a complicated aromatic multiplet (about 12 H, $\tau$ 1·9-3·2). No other signal was present. The above evidence led to the structure (IV) 2·4:2',N-(o-formamidobenzo)-1-formyl-3-(o-formylphenyl)-1,2,3,4-tetrahydroquinazoline for the diformyl derivative of anhydrotri-2-aminobenzaldehyde. The singlet (2 H) at $\tau$ 2·83 is assigned to the equivalent protons H(2) and H(4). A plausible pathway for the partial skeletal degradation of the trimer to the diformyl-trimer in the presence of

![Figure 1](image-url)  
**Figure 1** Ultraviolet spectra, in ethanol, of A, the trimer; B, the monoacetyl-trimer; C, the diacetyl-trimer; D, the diformyl-trimer

Acetic formic anhydride is shown by arrows in formula (V) in which the reaction proceeds through a six-membered ring transition state.

Anhydrotetra-2-aminobenzaldehyde is an almost colourless substance, formed when 2-aminobenzaldehyde is set aside with stronger acid (e.g., 5N-hydrochloric acid) than is needed to form the trimer (III, a), followed by basification of the resulting red salt (see below). It has an empirical formula corresponding to four molecules of the monomer less three molecules of water ($\text{C}_{28}\text{H}_{22}\text{N}_{4}0$). Seidel and Dick 1 assigned it the structure (VI) on the grounds of the molecular weight (determined cryoscopically in naphthalene 2), the ready condensation with aldehyde reagents such as benzoylhydrazine, 3 and the formation of a dinitroso-derivative 1 and of a mononitroso-monoacetyl-derivative.

We found many absorption bands common to the i.r. spectra of the tetramer and the trimer, which suggested skeletal similarity between the two compounds. Bands characteristic of the tetramer occurred at 3370 and 3330.
cm.\(^{-1}\) (weak; imino-groups) and at 1660 cm.\(^{-1}\) (broad and strong, a conjugated carbonyl). The ultraviolet spectrum (Figure 2) resembled that of the trimer except for the long-wavelength maximum at 370 m\(\mu\) which resembles those of 2-aminobenzaldehyde (365 m\(\mu\)) and 2-methylaminobenzaldehyde (387 m\(\mu\)) (see Figures 4 and 3, respectively). Thus it seemed likely that the tetramer contains the skeleton of the trimer plus an unconjugated 2-aminobenzaldehyde residue, and the structure is represented as (VIIa). This is confirmed by the n.m.r. spectrum, in which signals from the three aliphatic protons were found at almost the same positions as those from the trimer. Assignments of these peaks are shown in the Table. The signal of the H(4) at \(\tau 4.65\) appeared as only a broad singlet in deuteriochloroform, but as the expected doublet \((J = 5 \text{ c./sec.})\) in acetone (Table). Deuterium exchange in the deuteriochloroform solution caused stepwise disappearance of signals at \(\tau 5.10\) and 0.96, assigned, respectively, to H(7') and the NH group of C(7'). Simultaneously the H(4) signal \((\tau 4.65)\) sharpened and the H(7') doublet \((\tau 4.27)\) collapsed to a singlet. When the acetone solution was shaken with a drop of deuterium oxide, the doublet at \(\tau 4.43\) became a singlet with simultaneous disappearance of the broad doublet at \(\tau 3.61\) assigned to H(7'), but the doublet due to NH(7') \((\tau 0.80)\) remained unchanged.

From these results, the tetramer is assigned structure (VIIa), 2,4,2',2'-N-(2-aminobenzyl)-1,3:3',3'-\(N\)-[2-formylanilino]touleno]-1,2,3,4-tetrahydroquinazoline. The mass spectra of the trimer and the tetramer, measured and interpreted by Dr. J. S. Shannon (C.S.I.R.O., Sydney) confirmed the molecular weights and could be rationalised in terms of our suggested structures.

The ultraviolet spectrum of the monoacetyl derivative (Figure 2) closely resembled that of the parent tetramer, indicating a common skeleton. Characteristic i.r. absorption bands occurred at 3330 (weak and sharp; NH) and 1665 cm.\(^{-1}\) (strong and broad; N=O), also a strong band at 1650 cm.\(^{-1}\) (conjugated CHO). A sharp singlet (3 H) at \(\tau 7.50\) in the n.m.r. spectrum is assigned to the N-acetyl group, and a singlet at \(\tau 4.30\) and a doublet at 4.26 \((J = 5 \text{ c./sec.})\) (1 H each) are undoubtedly due to H(2) and H(7'), respectively. The signal of the imino-proton [NH(7')] was split into a broad doublet \((J 0.95, J = 5 \text{ c./sec.})\) by H(7'), in almost the same fashion as the NH(7') of the tetramer, and that of H(4) appeared at \(\tau 3.12\). After deuterium oxide exchange, the doublet due to NH(7') disappeared and that from H(7') collapsed to a singlet. This monoacetyl-tetramer is accordingly considered to have the structure (VIIb).

As the tetramer possesses two imino-groups, several attempts were made to obtain a diacetyl derivative. On treatment with acetyl chloride in pyridine or with acetic anhydride and zinc chloride, it gave only the monoacetyl derivative. Severer conditions, namely refluxing a solution of the monoacetyl-tetramer (VIIb) in a mixture of acetic anhydride and acetic acid \((1:1)\), gave the diacetyl-trimer (IIIc) \((83\%)\) and 2-acetamidobenzaldehyde \((11\%)\). These products could reasonably be formed either by direct replacement of the NH group in the monoacetyl-trimer by acetoxy-group, or by complete depolymerisation followed by reconstruction of the diacetyl-trimer from 2-amino- and 2-acetamido-benzaldehyde. After similar treatment, 2-aminobenzaldehyde gave only a 17% yield of the diacetyl-trimer (IIIc), together with 2-acetamidobenzaldehyde \((29\%)\) which has been prepared in good yield from 2-aminobenzaldehyde and acetic acid in cold ether \(^4\) and was recovered almost quantitatively after being heated with acetic anhydride and acetic acid under the above conditions. We conclude that the conversion of the monoacetyl-tetramer into the diacetyl-trimer does not involve depolymerisation but is a simple nucleophilic replacement. This result supports our conclusion that the trimer and the tetramer have a common nucleus.

Formylation of the tetramer with acetic formic anhydride gave a monoformyl-tetramer (VIIc) with absorption bands occurred at 3390 \((\text{weak and sharp; NH})\) and 1650 cm.\(^{-1}\) \((\text{strong and broad; N=O})\), ultraviolet and infrared spectra like those of the mono- and diacetyl derivatives (Figure 2) closely resembled that of the parent tetramer, two carbonyl, N=O; 1695 cm.\(^{-1}\) one hydrogen bond, imino-groups of the tetramer (VIIc). The trimer and the tetramer have a common nucleus. The n.m.r. spectrum of the monoacetyl-tetramer shows the 7''-imino-group to acetylation or formylation is consonant with the steric hindrance at this point as demonstrated above by the slowness of deuteration.

The mononitroso-monoacetyl derivative \(^1\) contained no imino-group.

\(^{1}\) P. Friedländer and C. F. Göhring, _Ber._, 1884, 17, 456.
no imino-group (no i.r. band near 3300 cm\(^{-1}\)), and the two carbonyl bands of the monoacetyl-tetramer (1665, N-Ac; 1650 cm\(^{-1}\), CHO) were shifted to 1675 and 1695 cm\(^{-1}\), indicating removal by nitrosation of the hydrogen bond between the aldehyde and the imino-groups of the structure (VIIb). The ultraviolet spectrum (Figure 2) shows a strong hypsochromic shift from that of the tetramer [A similar shift has now been demonstrated in the long-wavelength peak (387 m\(\mu\)) of 2-methylaminobenzaldehyde to 287 m\(\mu\) on N-nitrosation; see Figure 3]. In the n.m.r. spectrum, the acetyl and the aldehyde groups gave singlets at \(\tau\ 7.49\) (3 H) and \(-0.08\) (1 H), respectively; a broad singlet at \(\tau\ 4.63\) (1 H) is assigned to the H(2). The remaining signal [from the aromatic protons and H(7\('\)) and H(4\('\))] was a complex multiplet between \(\tau\ 1.7\) and 3.4. Treatment with deuterium oxide showed the absence of exchangeable protons. Thus the monoacetyl-monorosino-tetramer has structure (VIIId).

The red tetramer hydrochloride, obtained \(^2\) as an intermediate during the preparation of the tetramer (see above), was found by Seidel \(^2\) to give analytical figures consonant with a complex of one molecule of the tetramer, three of hydrogen chloride, one of water, and one of uncombined 2-aminobenzaldehyde. No structure was suggested. Our specimen, recrystallised from 3N-hydrochloric acid and dried at 150\(^\circ\), gave analytical figures consistent with the structure \(\text{C}_{28}\text{H}_{22}\text{N}_4\text{O}
\cdot 2\text{HC1}\) (the tetramer dihydrochloride). Paper chromatography showed that 2-aminobenzaldehyde was absent. The tremendous bathochromic shift between the ultraviolet spectrum of this hydrochloride (Figure 4) and that of the free tetramer (Figure 2) indicates that the former contains a longer conjugated path. The long-wavelength maximum at 467 m\(\mu\) especially suggests the presence of an azomethion group (-CH=N+H-). After the acid solution had been set aside for 1 day at 20\(^\circ\), the spectrum was transformed into that of the cation of 2-aminobenzaldehyde, indicating depolymerisation to the monomer. The i.r. spectrum showed characteristic absorption bands at 1630 (strong: CH=N) and 3400 cm\(^{-1}\) (broad and medium; -OH or water).

The n.m.r. spectrum (in trifluoroacetic acid) consisted of a complicated multiplet (18 H) between \(\tau\ 1.7\) and 3.4; namely, a narrow intense multiplet (about 12 H, \(\tau\ 1.7-2.5\)) and a broader multiplet (about 6 H, \(\tau\ 2.5-3.4\)). No signal characteristic of a formyl-group was found. A slightly broadened singlet (2 H) at \(\tau\ 0.83\) was assigned to an azomethine proton, because benzylideneaniline in trifluoroacetic acid gave a doublet at \(\tau\ 0.65\) (\(J = 16\) c./sec.). From these results, the most likely structure of the tetramer hydrochloride is considered to be (VIII).

A Reaction Pathway for the Formation of the Trimer and the Tetramer.—Ultraviolet studies (reported above) showed that equilibrium between the monomer and trimer
occurs in dilute acid. In stronger acid monomer, trimmer, and tetramer all give the "tetramer hydrochloride." Thus the tetramer is obtainable from the trimer via the "hydrochloride," although no tetramer was found when condensation of the trimer with 2-aminobenzaldehyde was attempted in pyridine or in phosphate buffer (pH 4).

The trimer could be formed from any dimer, even (IX), to one azomethine group of which a third molecule of 2-aminobenzaldehyde is added to give the adduct (I). This nucleophilic attack is formally similar to the ready addition of ethyl acetooacetate to benzylideneaniline. Cyclisation to the trimer (IIIa) could then follow through the two similar reactions shown by arrows in formula (X). The "tetramer hydrochloride" may arise by parallel reactions involving a cyclotrimer; if, after basification, an aldehyde group is liberated, consecutive additions of imino-groups across the two CN double bonds of formula (VIII) would produce the tetramer (VIIa).

The skeletons of the trimer and the tetramer are reminiscent of Tröger's Base (XI) which is formed from β-toluidine and formaldehyde.

**2-Aminobenzaldehyde and 2-Methylaminobenzaldehyde.**

-The ultraviolet spectra of these compounds, hitherto unrecorded, are shown in Figures 4 and 3, respectively. Large hypsochromic shifts are in conformity with the principle of optical transparency of an aromatic amino-group. Thus the spectra of the cations are almost identical with that of benzaldehyde [\(\lambda_{\text{max}}\) (0-1N-HCl) 249, 280 m\(\mu\) (log e 4-13, 3-18)].

2-Aminobenzaldehyde was sufficiently stable in dilute acidic solution (10-6 M) for spectrometric measurement of its ionisation constant (pKa 1.36, slightly lower than that of the 4-isomer, 1.74).

To investigate the effect of storage on 2-aminobenzaldehyde, chromatographic systems had to be found which could detect the monomer, trimer, and tetramer in presence of one another. Such selectivity was uncommon, but two suitable examples are given in the Experimental section.

Solid 2-aminobenzaldehyde formed mainly the trimer but also a trace of the tetramer on storage at 20°C, the recovery of 2-aminobenzaldehyde being 60 and 40% after 1 and 2 months respectively. At 5°C there was no change in this time. Attempts, for preparative purpose, to convert the trimer into monomer by steam-distillation in ammonium hydroxide solution, or by continuous extraction of the suspension in a buffer (pH 1-36) by ether, gave only small yields.

**EXPERIMENTAL**

Microanalyses were by Dr. J. E. Field and her staff. Paper chromatography (ascending) was carried out on Whatman No. 1 paper with light petroleum (b. p. 80-140°C) saturated with methanol, and thin-layer chromatography on silica gel (Kieselgel G) with chloroform-acetone (9:1) as solvent.

Ultraviolet spectra were measured on Shimadzu model RS 27 recording spectrophotometer or a Perkin-Elmer Spectronic model 4000A, and the maxima checked with an Optica manual instrument. Infrared spectra (KBr discs) were taken with a Unicam S.P. 200 spectrophotometer. Nuclear magnetic resonance measurements were made with a Perkin-Elmer spectrometer R 10. After the usual measurement, a drop of deuterium oxide [or 35% DC1 for substance (IIIb)] was added to the sample tube and the contents were vigorously shaken for a few minutes, and re-examined. When no exchange was observed, this tube was warmed on a water-bath at about 45°C for 1-3 hr. and set aside overnight at 22°C-25°C, then measured again.

**Anhydrotri-2-aminobenzaldehyde.**-This, prepared according to the direction of Seidel and recrystallised from ethanol, formed colourless leaflets (37% yield), m. p. 233°C-234°C (decomp.) (Found, for material dried at 80°/0·01 mm.: C, 77.4; H, 5.3; N, 12.7%; M(Rast). 288, 293. Calc. for C23H17N3O6: C, 77.0; H, 5.2; N, 12.8%; M, 327; \(\lambda_{\text{max}}\) (EtOH) 240, 286, 300 m\(\mu\) (log e 4.23, 3.50, 3.33). The following preparative method is more satisfactory. To a suspension of 2-aminobenzaldehyde (1.5 g.) in water (300 ml.), initially warmed at 60°C for 3 min. and cooled to 25°C, 2-nitrochlorohydric acid (10 ml.) was added with stirring. After vigorous stirring for 3 hr., the suspension was set aside for 16 hr. at 22°C-25°C (initial and final pH, 1-2). The precipitate was collected, washed with dilute aqueous sodium hydrogen carbonate, dried, and warmed with acetone (10 ml.). The trimer (80% yield), obtained by cooling and filtration, recrystallised from ethanol as colourless leaflets (87% recovery), m. p. 239°C (decomp.). The infrared spectrum of this substance was identical with that of the trimer of m. p. 234°C, and both gave single spots (Rf 0.05) on paper and (Rf 0.55) on thin-layer chromatography.

**Monoacetylanhydrotri-2-aminobenzaldehyde.**—The procedure of Seidel was followed, but alcohol was preferred for recrystallisation. The trimer (1.0 g.) gave, after acetylation and three recrystallisations from ethanol, the monoacetyl-trimer as colourless prisms (78% yield), m. p. 229°C-234°C (lit.,2 229°C (decomp.) (Found, for material dried at 80°/0·005 mm.: C, 74.9; H, 5.1; N, 11.6. Calc. for C23H16N3O6: C, 74.8; H, 5.2; N, 11.4%; \(\lambda_{\text{max}}\) (EtOH) 237, 282 m\(\mu\) (log e 4.27, 3.38).

**Diacetylanhydrotri-2-aminobenzaldehyde.**—Acetyl chloride (0.2 ml.) was added to a cold solution of the trimer (0.1 g.) in pyridine (1 ml.). After the colourless deposit appeared, more acetyl chloride (0.3 ml.) and pyridine (1 ml.) were added, followed by stirring for 2 hr., and cooling in iced-water. Then cold water (12 ml.) was added while cooling in ice, and the suspension stirred for 1 min., filtered, and washed with cold water. The pale brown solid was recrystallised from ethanol (72% yield). Two more recrystallisations from ethanol gave the diacetyl-trimer as colourless powder, m. p. 219-220°C, easily soluble in pyridine, acetone, and chloroform, moderately in benzene (Found, for material dried at 80°/0·01 mm.: C, 73.0; H, 5.3; N, 10.1. \(C_{25}H_{22}N_3O_6\) requires C, 73.0; H, 5.1; N, 10.1).


N, 10-2%); λ\text{max} (EtOH) 237, 274, 282 μm (log ε 4·26, 3·45, 3·38).

Formylandhydrortri-2-aminobenzaldehyde.—Acetic formic anhydride (1·0 ml.) was added to a suspension of the trimer (0·20 g.) in light petroleum (b. p. 80—100°, 3 ml.), and the mixture was stirred for 3 hr. at 27°. The deposit, filtered and washed with a little ethanol, was recrystallised from ethanol to give the formyl-trimer as colourless leaflets (0·20 g., 85% yield), m. p. 233—274° (Found, for material dried at 105°/0·01 mm.: C, 71·9; H, 4·4; N, 11·0%); M, 333; λ\text{max} (EtOH) 232, 248, 284, 315, 350 μm (log ε 4·46, 4·34, 4·38, 3·28, 2·99).

Anhydrotrihydrotri-2-aminobenzaldehyde.—2-Aminobenzaldehyde (1·1 g.) and 5N-hydrochloric acid (8 ml.) were stirred while cooled in ice until the solid dissolved (20 min.). The filtrate (fritted glass filter), set aside for 18 hr. at 22—25°, gave red needles (0·8 g.) which were warmed with a mixture (8 ml.) of pyridine and alcohol (2:3, v/v), and, dissolved in a mixture of pyridine, alcohol, and water (2 : 3 : 3, v/v), gave the diacetyl-trimer from the filtrate of the latter gave a small amount of viscous oil (0·8 (paper and thin-layer chromatography to be a mixture of monomer, trimer, and a trace of tetramer). The unmelted material was shown by paper chromatography to be a mixture of monomer, trimer, and a trace of tetramer (decomp.) (lit., 193°) (Found, for material dried at 80°/0·01 mm.: C, 72·05; H, 4·7; N, 13·3). Calc. for C₂₅H₂₆N₂O₅: C, 71·8; H, 4·6; N, 14·0%; λ\text{max} (EtOH) 239, 274, 283 μm (log ε 4·22, 3·49, 3·42).

2-Methylaminobenzaldehyde and N-Nitrosomethylaminobenzaldehyde.—2-Methylaminobenzaldehyde, b. p. 108—109°/0·01 mm. (lit., 111—112°/10 mm.), was prepared according to Barlin,8 λ\text{max} (H₂O) 223, 250, 263, 267, 387 μm (log ε 4·33, 3·41, 3·30, 3·77, 3·72); λ\text{max} (2N-HCl) 247, 283 μm (log ε 4·05, 3·20); \nu\text{max} (l.iq. film) 3380 (NH), 1665 (C=O) cm⁻¹; \tau (CCl₄) 7·07d (J = 5 c/sec., CH₃), 2·4—3·6m (aromatic H), 1·67m (NH), 0·16s (CHO). 2-Methylaminobenzaldehyde (1·00 g.) and pentyl nitrite (3·0 ml.) were refluxed in s-butanol (30 ml.) for 3·5 hr. Solvent was removed under reduced pressure (20 mm.) and the residue, recrystallised from light petroleum (b. p. 80—100°), gave N-nitrosomethylaminobenzaldehyde as colourless needles (0·40 g., 33% yield), m. p. 28—29° (Found, for material dried at 20°/0·01 mm.: C, 58·75; H, 4·8; N, 17·2). C₂₅H₂₆N₂O₅ requires C, 58·8; H, 4·9; N, 17·1%; λ\text{max} (H₂O) 241, 287 μm (log ε 4·22, 3·53); \nu\text{max} (liq. film) 1690, 1705 cm⁻¹ (C=O); \tau (CCl₄) 6·58s (CH₃), 1·9—2·7m (aromatic Hs), 0·15s (CHO).

Anhydrotetra-2-aminobenzaldehyde hydrochloride.—The red needles described above were recrystallised from 5N-hydrochloric acid and dried over phosphoric oxide and sodium hydroxide at 150°/0·01 mm. for 1 hr., m. p. about 280° (blackened without melting when heated gradually, but when inserted at 260°, it immediately decomposed), and, dissolved in a mixture of pyridine, alcohol, and water, gave a single spot (R₁ 0·8; the same as the above tetramer) on paper chromatography in light petroleum–methanol (Found: C, 67·35; H, 5·2; Cl, 14·1; N, 11·1). Calc. for C₂₅H₂₆N₂O₂·2HCl: C, 66·8; H, 4·8; Cl, 14·1; N, 11·1%; λ\text{max} (5N-HCl, within 8 min.) 220, 246, 307, 467 μm (log ε 4·26, 4·04, 3·93, 3·26).

Both the trimer and the tetramer, separately treated as above with 5N-hydrochloric acid, gave tetramer hydrochloride identical in infrared spectrum with the above.

2-Aminobenzaldehyde.—This, m. p. 39° (lit., 40°), was prepared according to Mann and Wilkinson,10 λ\text{max} (H₂O) 229, 260, 365 μm (log ε 4·32, 3·83, 3·59); λ\text{max} (1·6N-HCl) 246, 284 μm (log ε 4·06, 3·20), pKₐ 1·36 ± 0·05 (measured at 247 μm in HCl solutions of known H₃ at 20°, R₁ 0·35, and 0·7 on paper and thin-layer chromatography respectively.

When fresh 2-aminobenzaldehyde was set aside for one month at 20°, much of the material melted at 37—38°.

the tetramer. The stored material was suspended in 2N-ammonium hydroxide and steam-distilled. The distillate, on refrigeration, deposited colourless leaflets of 2-amino-benzaldehyde. By extraction of the filtrate with ether more material was obtained (total yield 60%, m. p. 38—39°). The residue in the steam-distillation flask, refrigerated for 1 day and filtered, gave a yellow solid which consisted mainly of the trimer with a small amount of monomer and a trace of tetramer (as shown by paper chromatography). The approximate yield of the trimer was 20%. Only 40% of 2-aminobenzaldehyde could be recovered thus after being set aside for two months at 20°.

We thank Drs. T. J. Batterham and W. L. F. Armarego for discussions, and Dr. J. S. Shannon for mass spectra. One of us (H. Y.) thanks this University for a Scholarship.

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