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THE AUSTRALIAN NATIONAL UNIVERSITY

John Curtin School of Medical Research

Annual Report 1967

Department of Medical Chemistry

STAFF

Professor:

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Reader:

D.J. Brown, M.Sc. (Syd.), D.Sc., Ph.D. (Lond.), F.R.A.C.I.

Professorial Fellow:

D.D.Perrin, M.Sc. (N.Z.), D.Sc., Ph.D. (Lond.), F.R.A.C.I., F.R.I.C.

Senior Fellows:

E.Spinner, M.Sc. Tech., Ph.D. (Manc.), F.R.A.C.I.; W.L.F. Armarego, B.Sc., Ph.D. (Lond.), F.R.I.C. (from July, previously Fellow).

Fellow:

G.B. Barlin, M.Sc. (Syd.), Ph.D., F.R.A.C.I.

Microanalyst (Fellow):

Joyce E. Fildes, B.Sc. (Syd.), M.Sc., Ph.D. (Birm.).

Magnetic Spectroscopist (Fellow):

T.J. Batterham, B.Sc., Ph.D. (N.S.W.).

Research Fellows:

V.S. Sharma, M.Sc., Ph.D. (Agra)(until March); E. Kalatzis, B.Sc. (Alexandria), Ph.D. (Lond.)(until November); M.E.C. Biffin, B.Sc., Ph.D. (Lond.); B.D. Batts, B.Sc., Ph.D. (Q'ld.); R.M. Hoskinson, B.Sc., Ph.D. (N.S.W.)(until November); P.B. Ghosh, B.Sc. (Lond.), Ph.D. (East Anglia); D. Thacker, B.Sc., Ph.D. (Lond.) (from February); C.W. Childs, B.Sc., Ph.D. (Otago)(from March); P.S. Hallman, M.Sc., Ph.D. (Syd.)(from October).

Research Assistants:

B.T. England, B.Sc.; Svea-Reet Jaason, B.Sc. (N.S.W.).

Head Technician:

D.A. Maguire.

Department of Medical Chemistry

RESEARCH WORK

Introduction

Historically, the subject of Medical Chemistry has two origins, one in Pharmaceutical Chemistry and one in Biochemistry. From Pharmaceutical Chemistry it took the intense study of the chemistry of drugs and related substances, also the synthesis of potential drugs. The derivation from a part of Biochemistry occurred in 1949 when many biochemists left the International Union of Pure and Applied Chemistry to found the International Union of Biochemistry. These were mainly the biochemists interested in cellular components of large molecular weight, requiring special techniques for investigation. But others, whose special province was the chemistry of components of low molecular weight, preferred to stay within the parent organization and benefit from techniques being devised for the study of small molecules. Some of these workers and some from Pharmaceutical Chemistry became united as Medical Chemists engaged in the study of physico-chemical properties of small molecules as a clue to biological action.

By its inescapable preoccupation with water as a solvent and reagent, Medical Chemistry became sharply differentiated from Chemistry as such. Water is a complex polymer which is thought to contain on average 70 units of H_2O in each particle at body temperature. The current tendency of conventional chemistry is to avoid it by studying reactions in aprotic solvents, in liquefied gases, and even in fused salts and fused metals.

The Department of Medical Chemistry is concerned with the determination of ionization constants, and of the equilibria between essential metal cations and metal-binding components of the living cell, all in water. Several years ago it discovered that various heterocyclic molecules, related to bases active in body metabolism, have the property of building water covalently into their molecules; they shed it again in response to small changes in pH. Apart from this remarkable property,

the relative indestructability of heterocyclic substances in the body has singled them out for intensive study in this Department. The permanence of the genetic code, which is laid down in purine and pyrimidine heterocycles, the durability of the water-soluble vitamins in their traces in the body, and the smaller doses in which heterocyclic drugs are effective (compared to other drugs), all exemplify this principle.

New classes of 8-azapurines (Albert)

The 8-azapurines, notably 8-azaguanine which occurs in Streptomyces albus, have been shown to inhibit many kinds of experimentally-induced cancer in laboratory animals without harm to the host. However they proved inactive in patients because of more rapid metabolism by the body's enzymes, e.g. guanylase. This finding led to attempts to synthesize 8-azapurines having the 7-, 8-, or 9-nitrogen atom blocked by a simple alkyl-group such as methyl. The customary synthetic route to 8-azapurines via 4,5-diaminopyrimidines proved unavailing for these 7- and 8-blocked isomers. It is pleasing to report that two new reaction pathways have been discovered which provide convenient approaches to the 7- and the 8-methyl-8-azapurines. These reactions employ readily accessible 1,2,3-triazoles as starting materials. So far, most of our examples have carried a substituent in the 6-position (analogues of adenine, hypoxanthine, etc.). Eliminating this substituent has provided the parent substances; both of these readily underwent covalent hydration, which was surprising because the isomer, 9-methyl-8-azapurine does not combine with water.

Oligomers of heterocyclic substances (Albert, Yamamoto)

Many examples are known of dilute acids coverting members of biologically active heterocyclic families into less soluble material of higher molecular weight. Modern instrumentation, such as proton magnetic resonance spectroscopy, facilitated discovery of the nature of some of this "spoilt material". 4-Methylpteridine produces a somewhat bivalve-shaped dimer in which the methyl-group of one molecule is added across the 7,8-position of another. Cold dilute acid converts the

parent substance, pteridine, to 2-aminopyrazine-3-aldehyde, through the N-formyl-derivative of the latter, which readily gives an amidine-linked trimer. Quinazoline (benzopyrimidine) is changed by aqueous acid to 2-aminobenzaldehyde, whose polymerizing behaviour was discussed in last year's Report. In addition, the liberated 2-aminobenzaldehyde combines with unchanged quinazoline to produce a series of new condensation products ranging from monomer to tetramer.

Nucleophilic addition reactions of pteridines (Albert, McCormack)

Previous reports have recorded the surprising ability of certain pteridines to add (across a double-bond and in aqueous solution) such nucleophilic reagents as sodium bisulphite, barbituric acid, and ethanol. It was then found that 2-mercaptopteridine also behaves in this way, adding the reagent first to the 3,4-position, but sometimes transferring it later to the 5,6- and 7,8-positions. The S-methyl-derivative has a similar, but much weaker, affinity for these nucleophiles.

Pyrimidines and Purines (Brown)

Pyrimidines and purines, the families to which the coding bases of nucleic acids belong, have unusual and interesting chemical properties of which many are insufficiently known. Rearrangement-reactions abound, many of them dependent on ring-opening and -closing. In the further exploration of this field, the following four studies were undertaken.

(1) Sulphones and Sulphoxides (Brown, Ford)

It was found that simple amines do not effect the expected replacement of the substituent in 5-methylsulphonylpyrimidine and the corresponding sulphoxide. Instead the pyrimidine ring is opened to give (e.g. with amylamine) 2-methylsulphonyl-1,3-dipentyliminopropane. Methylsulphonylpurines undergo the normal replacement, of which the kinetics were studied to obtain better conditions for syntheses and also to provide better correlation of structure with reactivity in this family.

(2) The Hilbert and Johnson Rearrangement (Brown, Lee)

The rate of thermal rearrangement of 2-methoxypyrimidines to N-methylpyrimidones is being correlated with the Hammett sigma-values of substituted phenyl-groups inserted in the 5-position.

(3) Rearrangement of pyrimidines to pyrazoles (Biffin, Brown, Porter[2])

4-Methoxy-5-nitropyrimidine was found to react with hydrazines in a completely unexpected way to give 3-amino-4-nitropyrazoles. These were reduced to 4,5-diaminopyrazoles which were condensed with 1,2-dicarbonyl compounds to give some unusual ring-systems with fused pyrazole nuclei.

(4) The Dimroth-type rearrangement of quinazolines (Brown, England)

Quinazolines, which are benzo-pyrimidines, have been found to undergo the Dimroth rearrangement, in which an alkyl-group attached to a ring-nitrogen atom finally appears in an exocyclic amino-group. Preparation of the starting materials (2,3-dihydro-2-imino-3-methylquinazolines) has involved separation of cis- and trans-2-aminobenzaldoximes and the characterization of novel benzo-oxadiazepines, isomeric with quinazoline-N-oxides.

Penta-azanaphthalenes (Biffin, Brown)

The fundamental chemistry of the penta-azanaphthalenes, which include such highly biologically-active substances as toxoflavine and fervenulin is poorly understood. Hence an investigation was begun of the parent substances and such derivatives as should lead to meaningful correlations between structure and reactivity. Even the simplest members of the series have been found highly reactive towards nucleophilic substances and readily undergo covalent hydration.

Oxazoles (Brown, Ghosh)

The deuterium exchange rates and ionization constants of a series of oxazoles have been measured, and the proneness of these substances to ring-opening by nucleophilic reagents examined under physiological conditions.

Benzoxadiazoles (Ghosh, Whitehouse[3])

Several 7-substituted-4-nitrobenzoxadiazoles have been synthesized for trial as immuno-suppressive drugs. These highly fluorescent substances are also being examined as histochemical reagents.

Binding of metal cations by ligands present in blood and other tissues (Perrin)

The living cell and the fluids which bathe it have been likened to arenas where traces of many kinds of heavy metals are vigorously competed for by a variety of organic metal-binding substances (ligands). The following three projects are contributions to a study of the equilibria reached in this competition.

(1) Stability Constants (Perrin, Sharma, Childs)

Accurate stability constants of many complexes between metals and aminoacids have been determined under physiological conditions. The results have been applied to the computer programme described in last year's Report. This is being used to calculate the distribution of the various metals between the substances of lower molecular weight in blood plasma. The results obtained so far emphasize the importance of histidine as the binding agent for copper in this system.

(2) Mixed Complexes (Perrin, Sharma)

Mixed complex formation was found to be of general occurrence in systems containing a metal ion and more than one ligand. Resulting complexes are somewhat more stable than predicted on statistical grounds.

(3) Electrodes for bivalent cations (Perrin, Childs)

Electrodes, reversible to calcium and other bivalent metal ions, were examined as a means for determining stability constants of complexes with alkaline earth metal ions and other weakly complexing cations.

The deamination of amino-heterocycles (Perrin, Kalatzis)

A study of the kinetics of deamination of many aminopyrimidines and aminoacridines in alkaline solutions has shown that the aminopyrimidines require strong alkali for deamination, whereas the aminoacridines decompose under milder conditions. Two different reaction mechanisms have been proposed.

Tautomerism in 4-aminopyridines (Spinner, Batts)

Comparisons of ultraviolet and infrared spectra, and of ionization constants, among parent compound and methylated reference compounds have shown 4-nitraminopyridine to exist, wholly or largely, as the imino tautomer in the solid state and in water, but mostly as the amino tautomer in dioxane. Whereas in the cation of 4-aminopyridine the positive charge resides essentially on the amino nitrogen atom, in that of 4-nitraminopyridine it resides essentially on the ring nitrogen; the infrared spectra show different ring structures in the two cations.

Tautomerism in the 2-hydroxypyridine series (Spinner, Yeoh)

It has been found that when a saturated ring is annelated with the 5 and 6 positions of 2-hydroxypyridine, any ensuing strain greatly affects the tautomeric equilibrium. A compound containing a five-membered annelated ring, 2,3-dihydro-6-hydroxy-4-methylfuro[2,3-b]-pyridine, exists in the enol (as opposed to the amide) form to a much greater extent than does the six-membered counterpart, namely 2,3-dihydro-7-hydroxy-5-methyl[2,3-b]pyridine.

Vibration-spectral comparisons of carboxylate ions, nitro compounds, and nitronate ions (Kang, Spinner)

The NO stretching frequencies in substituted nitromethanes behave rather like the CO stretching frequencies in substituted acetate ions, the higher frequency being sensitive to the polar effect of the substituent and the lower one to its mass. In nitronate anions, on the other hand, both NO stretching frequencies behave alike, as expected in a system of C_{2v} symmetry: both are lowered as the mass of the substituent increases.

Secondary deuterium isotope effects on ionization constants (Batts, Spinner)

Small structural changes often affect the biological action of a molecule profoundly. One way of producing small but subtle changes in the chemical and physical properties of a molecule - which will undoubtedly prove medicinally useful at times - is to substitute deuterium for a non-labile protium. Work, on simple substituted

pyridines, aimed at elucidating these changes has shown that deuterium tends to be base-weakening in strongly electron-demanding environments, but base-strengthening otherwise.

Reduced Heterocyclic Compounds (Armarego)

Fully hydrogenated diazanaphthalenes have been little explored. They assume a new interest from the discovery that the paralysant, tetrodotoxin, is a perhydro-quinazoline. Catalytic reduction of naphthyridines in ethanol gave tetrahydro-naphthyridines, whereas catalytic reduction in acid medium or reduction with sodium and ethanol gave the decahydro-analogues. By means of nuclear magnetic resonance spectroscopy, it was found possible to distinguish between cis- and trans-fused decahydro-diazanaphthalenes.

Quinazoline studies (Armarego, Smith)

The hydration studies of a large number of quinazolines has been completed. The effects of substituents on the ratio of hydrated to anhydrous neutral species were shown to be comparable to those observed in the respective cations. The displacement of fluorine and chlorine from the benzo ring of quinazoline by methoxide ions followed the order of position 7>5>6 and 8, and the fluorine atom was displaced more readily than the chlorine atom.

Proton Magnetic Resonance Studies (Batterham)

Analysis of the p.m.r. spectra of substituted aromatic and hetero-aromatic systems has continued with the development of refined methods for de-composing these complex spectra.

An extensive study of the p.m.r. spectra of nucleosides led to the absolute stereochemistry of the cobamide-mediated reduction of adenosine to 2'-deoxyadenosine (with R.L. Blakley[4]).

Mass Spectra of Quinazolines (Batterham, Wunderlich[5])

Mass spectra of quinazoline and its derivatives showed that the system broke down by elimination of two molecules of hydrogen cyanide to give a benzyne radical ion. In substituted quinazolines pathways associated with the substituent were also observed.

Kinetic studies of chloropurines (Barlin)

There has been much confusion in the literature as to the relative reactivity of positions 2-, 6-, and 8- in the purine nucleus. Kinetic studies of the replacement of a chloro- by a methoxy- substituent in chloropurine anions have now shown that the 8-position is the least reactive and the 6-position the most. However in chloro-9-methyl-purines, which cannot form an anion, the 2-position is the least reactive and the 8-position the most.

Comparative kinetic studies of heterocycles (Barlin, W.V. Brown)

Methylsulphinyl derivatives of pyridine, pyridazine, quinoline, quinoxaline, phthalazine, and cinnoline have been made for the first time and the kinetics of their reactions with sodium methoxide studied. The surprising fact emerged, that there is little difference in reactivity between a methylsulphinyl- and a methylsulphonyl- group in these nuclei, but both groups are much more reactive than a methylthio-group. The use of alkyl groups bulkier than methyl is under investigation to evaluate the extent of steric hindrance in these reactions.

Quantitative Microanalyses (Fildes, Jaason)

Following the trend of biologists to submit ever smaller samples, research has been directed more and more to methods suitable for the submilligram region.

Investigation of a methylene-blue method for determining, spectrophotometrically, submilligram amounts of organically bound sulphur (over the 10-100 µg. range of S) is giving reasonable promise for development into a publishable method. Organic matter in the sample is first decomposed by reductive fusion with potassium metal in a sealed glass tube. The principal problems to be overcome are the variable blanks, due to traces of sulphur contaminants in the atmosphere.

A study of methods suitable for the determination of phosphorus (over the 0.1-3.0 mg. range of P) has shown that its spectrophotometric determination as phosphovanadomolybdate is more reliable than the usual molybdenum blue method.

The range of applicability of the F. & M. automatic analyser for carbon, hydrogen and nitrogen was further studied, with special reference to liquid samples, and to organic solids containing phosphorus, fluorine, and silicon.

TEACHING AND OTHER ACTIVITIES

There are seven students proceeding to the degree of Doctor of Philosophy and two Research Assistants are studying part-time for the Master of Science degree. Mr T. Kobayashi (Tokyo) joined the Department in November as Research Scholar. The following students received their Ph.D. degrees during the year: J.G. Catterall, R.V. Foster, J. Smith, J.W. Bunting, M.N. Paddon-Row, and I.G. Sayce.

Dr Spinner arranged the Department's weekly seminar series.

Dr Armarego returned from a year's study leave spent at the Milstead (Shell Research) Laboratories at Sittingbourne in Kent, England, where he worked with Dr J.W. Cornforth, F.R.S. on the synthesis of vitamin B_{12}.

Four Ph.D. theses were examined, for other Universities, by Professor Albert, Dr Brown, and Dr Perrin.

Professor Albert opened a symposium on "Biological Inorganic Chemistry", at the 39th A.N.Z.A.A.S. Congress, Melbourne, in January.

Professor Albert gave the first Memorial Lecture in honour of the late Professor S.E. Wright, at the Prince Henry Hospital, Sydney, in October.

Dr Brown was one of the invited speakers at the opening of the First International Heterocyclic Conference at Albuquerque (U.S.A.) in June, and again at the Gordon Research Conference on Heterocyclic Chemistry at Tilton (U.S.A.) in July. He also lectured in the Harvard University Medical School and the Agricultural University at Wageningen, Holland.

Dr Perrin was elected Titular Member of the Electroanalytical Commission of the International Union of Pure and Applied Chemistry, Regional Advisory Editor for the "Analyst", and Australasian representative for the Society for Analytical Chemistry.

Dr Armarego gave lectures in the Universities of London, Bristol, East Anglia, Salford and Strathclyde. Dr Spinner spoke at the Sixth Australian Spectroscopy Conference, Brisbane, in August. Dr Fildes gave an invited lecture to the R.A.C.I. Third Biennial Symposium of Analytical Chemistry, University of Newcastle, in May.

Specimens of substances discovered in the Department were requested by Professor D.O. Jordan (University of Adelaide); Dr Q. Porter (University of Melbourne); Dr R. Hoskinson (C.S.I.R.O., Melbourne); Dr J.J. McCormack (University of Vermont Medical School). A member of the Research School of Chemistry and one from the Department of Physical Biochemistry were guests in the Department for a few days for instruction in particular techniques.

Services for the first eleven months of 1967. The routine determination and interpretation of 1800 nuclear magnetic resonance spectra were made by Dr Batterham. Of these 300 were for other Departments of the School. Dr Perrin arranged the routine determination of 108 ionization constants, of which nine were requested from outside the Department. Routine determination of optical spectra supervised by Dr Spinner comprised 115 ultraviolet and 16 infrared spectra; half the latter were for members of other Departments.

The routine microanalytical service under Dr Fildes carried out 1972 microanalyses and special weighings on the 828 samples submitted by 51 research members of the John Curtin School and the Research School of Chemistry. These figures for microanalyses exceed the output for the 12 months of 1966 which was a record year. The atomic absorption spectrometer was much used by the Department of Physical Biochemistry, and also by the Research Schools of Chemistry, and of Social Sciences (Geography).

The Department's large-scale laboratory purified 500 gallons of solvents of which 40% were used by other Departments of the School. A large-scale batch of 4,5-diaminopyrimidine, valued at $4000, was synthesized in eight steps.

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