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THE AUSTRALIAN NATIONAL UNIVERSITY

John Curtin School of Medical Research

Annual Report 1966

Department of Medical Chemistry

STAFF

Professor:

A. Albert, B.Sc.(Syd.), Ph.D., D.Sc.(Lond.), F.R.A.C.I., F.A.A.

Reader:

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

Professorial Fellow:

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

Senior Fellow:

E. Spinner, M.Sc.Tech., Ph.D.(Manc.), F.R.A.C.I.

Microanalyst (Fellow):

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

Fellows:

W. L. F. Armarego, Ph.D.(Lond.), F.R.I.C.; G. B. Barlin, M.Sc.(Syd.), Ph.D.(A.N.U.), F.R.A.C.I.; T. J. Batterham, Ph.D.(N.S.W.) (from October, previously Research Fellow).

Research Fellows:

N. W. Jacobsen, M.Sc.(W.Aust.), Ph.D.(A.N.U.) (resigned November); V. S. Sharma, M.Sc., Ph.D.(Agra); E. Kalatzis, B.Sc.(Alex.), Ph.D.(Lond.); M. E. C. Biffin, Ph.D.(Lond.); B. D. Batts, Ph.D.(Queensland); R. M. Hoskinson, Ph.D.(N.S.W.) (commenced February); P. B. Ghosh, B.Sc.(Lond.), Ph.D. (East Anglia, England) (commenced June).

Visiting Research Fellow:

J. J. McCormack, Ph.D.(Yale), U. S. National Institutes of Health Postdoctoral Fellow (until May).

Research Assistants:

B. T. England, B.Sc.(A.N.U.)(from January).

Svea-Reet Jaason, B.Sc.(N.S.W.)(from May).

Head Technician:

D. A. Maguire.

RESEARCH WORK

Introduction

Medical chemistry is the study of chemical families in which strong and highly selective biological effects reside. It covers (i) the organic chemical syntheses of these substances, their analysis, and the study of their chemical properties, (ii) the study of their physical properties and attempts to correlate these with molecular structure, and beyond this with biological properties, and (iii) the inorganic co-ordination chemistry of biologically-active metal cations.

In this Department the subject is being developed by (a) studies of the heterocyclic chemistry of substances related to the nucleic acid bases, especially the physical and organic chemistry of pteridines, pyrimidines, and purines, and (b) quantitative studies of equilibria involving biologically-potent heavy metal cations with biologically-occurring ligands.

Covalent hydration of 8-azapurines (Albert)

Although, in 1965, no hydration could be detected in members of the purine family, the 8-azapurines have now been found to have a high affinity for water, which they add across the 1,6-double bond (and hence eliminate it). This hydration can be repressed by inserting a methyl-group in the 6-position, where it offers the expected steric and electronic hindrance, but the similar effect of a 9-methyl group was unexpected and will be investigated further.

Covalent hydration has considerable biological importance: the presence of a hitherto unexpected alcoholic group must alter the pattern of distribution in the body. Moreover hydration can produce a substance which can serve as a depot for a more biologically active substance if this is obtainable by gentle oxidation. Thus the hydrated form of 2-amino-8-azapurine is readily oxidized in vitro to 8-azaguanine which is highly active against cancer in the rat, but is eliminated too fast from the human body to be a useful drug. The possibility that hydrated 2-amino-8-azapurine may act as a precursor of 8-azaguanine is being tested for us by Dr. Chester Stock in the Sloan-Kettering Institute (New York).

Nucleophilic additions in pteridines (Albert, McCormack)

The surprising ability of certain pteridines to add Michael reagents, demonstrated here last year, has been extended to 2-aminopteridine which gives 2-amino-3,4-dihydro-4-substituted pteridines with the following nucleophilic reagents: sodium hydrogen sulphite, dimedone, 4,6-dihydroxypyrimidine, barbituric acid, 2-thiobarbituric acid, nitromethane, and even ethanol and methanol.

The oxidation of heterocyclic hydrazines (Albert, Catterall)

In a comprehensive study of the best conditions for replacing a hydrazino-group by hydrogen in heterocyclic compounds, two reagents proved to be outstandingly reliable, (a) oxygen in the presence of ethanolic alkali, and (b) aqueous cupric sulphate. This replacement reaction is useful for the synthesis of many nitrogen heterocyclic substances required in medical chemistry, and enough knowledge has now been obtained for the reaction to be undertaken with more confidence than formerly.

Polymers of 2-aminobenzaldehyde (Albert, Yamamoto)

When 2-aminobenzaldehyde is stored at room temperature, a trimer is formed, whereas acidic conditions produce the salt of a tetramer which is changed on neutralization, to another tetramer of more complex structure. These substances do not have the simple

constitution assigned to them in the literature, but are cage molecules whose exact structures have now been determined by physical methods (principally ultraviolet, infrared, and proton magnetic resonance spectroscopy).

Pyrimidines (Brown)

The quite special importance of the pyrimidines nucleus in Nature is indicated by the new types of pyrimidine constantly being discovered in ribonucleic acids (both transport and microsomal). To increase knowledge of the chemistry of this still imperfectly understood nucleus, the following studies were undertaken.

Nucleophilic displacements in pyrimidines

(Brown, Foster, Ford)

Aminolyses of 2- and 4-methoxy (or methylthio) pyrimidines bearing C-methyl, 5-bromo-, or 5-nitro groups have proved of value for preparing the corresponding alkylaminopyrimidines in the absence of solvent. The rate constants indicate mild deactivation by methyl groups, moderate activation by a bromo substituent, and profound activation by the nitro group.

Pyrimidine 2- and 4-sulphones and sulphoxides have been found to undergo facile reactions with nucleophiles. Rate constants for their aminolysis indicate a slightly greater reactivity than the corresponding chloropyrimidines, and some 10^5 times the reactivity of the thioethers from which they were derived. The work has been extended to the purine series.

The Dimroth Rearrangement

(Brown, Paddon-Row, England)

The facilitating effect of electron-withdrawing groups on Dimroth Rearrangement of 1-alkyl-1,2-dihydro-2-iminopyrimidines has been further explored: 5-halo, 5-carbamoyl, or 5-cyano substituents increase the rate in that order; so too does replacement of the N-alkyl group by an allyl, 2'-hydroxyethyl, benzyl, or p-nitrobenzyl group. The introduction of a 5- or N-prop-2'-ynyl group leads not only to rapid Dimroth Rearrangement but also to

interesting isomerizations in the side chain to yield allenyl and prop-1'-ynyl derivatives as well as bicyclic products.

Dimroth Rearrangement proceeds rapidly and normally in anhydrous secondary amines, e.g. diethylamine, but not in primary amines (abnormal aliphatic products). No reaction occurs in tertiary amines. This behaviour is consistent with the previously postulated mechanism in aqueous media. Rearrangements of 1,4-dialkyl-1,2-dihydro-2-iminopyrimidines proceed so very sluggishly that hydrolysis to the corresponding oxopyrimidines overrides the reaction. While the reason for this was being sought by proton magnetic resonance techniques, in collaboration with Dr T. Batterham, a new and rapid (acid/base catalysed) deuteration of the 4-methyl groups in such molecules was discovered.

The "Christmas Rearrangement" (Brown, Paddon-Row)

This reaction, first discovered in this Department in December 1965, is exemplified by the isomerization of 1-aryl(or benzyl)-4-mercapto-1,2,3,5,7-penta-azaindene to 4-aryl(or benzyl) amino-1-thia-2,3,5,7-tetra-azaindene. It has now been shown that each rearrangement reaches an equilibrium (from either component) in the molten state or by boiling in an alcohol or other solvent. In most cases the equilibrium constant favours the thiatetra-azaindene, but in alkali the acidic mercapto compound is favoured. Electron-withdrawing p-substituents increase the rate of equilibration, and a rectilinear plot is obtained for Hammett's sigma-values against log k_f (rate of fission for the penta-azaindene).

The Hilbert and Johnson Rearrangement (Brown, Lee)

The effect of substitution on the rate of thermal rearrangement of alkoxypyrimidines has been further explored. The measured rate differences are quite small with the exception of that occasioned by a nitro group.

5-Nitropyrimidines (Brown, Biffin, Lee)

Attempts to make 5-nitropyrimidine in many laboratories have failed. Following the general study of hydrazino heterocycles,

mentioned above, 4,6-dihydrazino-5-nitropyrimidine was oxidized by silver oxide in methanol to give 5-nitropyrimidine in good yield. Its cation was covalently hydrated, the first example of this phenomenon in a single ring heterocycle. Similar reactions have been used to make related compounds.

Equilibria between metal cations and organic complexing substances (Perrin, Sharma, Sayce)

To throw more light on quantitative aspects of metal-complex equilibria in biological systems, a computer programme has been developed for calculating the concentrations of metal complexes (including polynuclear, mixed, and hydrolysed species) in multi-metal multi-ligand systems, by using the values of their stability constants. Such systems, also serve as models of metalloenzyme-substrate interactions. Stability constants of such complexes for several bivalent metal ions with representative ligands have been obtained from potentiometric measurements: calculations were carried out with a general computer programme into which were fed the titration data and the known constants for complexes containing only one type of ligand. Quantitative equilibria under physiological conditions between histidine and bivalent metal ions, including copper(II), have been elucidated. Sulphur-containing ligands readily form polynuclear complexes with metal ions: stability constants of some of these complexes have been obtained. However penicillamine, for steric reasons, forms only mononuclear complexes.

Rapid-reaction techniques (Perrin, Bunting)

Ionization constants have been found for unstable hydrated cations in the quinazoline, triazanaphthalene, and 8-azapurine series, also the equilibrium proportions and the kinetics, all by using a modified Britton-Chance type apparatus with quartz capillary reaction cell, spherical lenses, cathode tube display, and rapid-repeat photography.

Nitrosation and deamination (Perrin, Kalatzis)

Rates of hydrolytic deamination of neutral molecules of 9-amino-, 9-methylamino-, and 9-dimethylaminoacridine were found to be independent of the hydroxyl ion concentration of the solution. The mechanism of the diazotisation of 4-aminopyridine has been elucidated. In acid solutions the resulting 4-pyridine diazonium ion (like the corresponding 2-isomer and the N-nitroso derivatives of α- and γ-methylamino-N-heteroaromatic bases) readily undergo hydrolysis.

Carboxylate ion structure (Spinner and, in part, Kang)

Vibration-spectral studies of the bond structure of the carboxylate grouping have been continued. In crystalline sodium formate the (time- and space-averaged) crystallographic site symmetry of the formate ion is C_{2h}^6, and the ionic symmetry C_{2v}; if the local, short-term, symmetry of the ion were the same as the crystallographic symmetry, no crystal splitting of fundamental vibration bands would be permitted. Actually the infrared band of HCO_2Na at 1366 $cm.^{-1}$ does show crystal-splitting, very prominently after isotopic dilution with DCO_2Na, and irrespective of the precise method of crystallization of the specimen or the precise conditions of examination (disc or mull).

If the CO_2^- grouping had C_{2v} symmetry the two carboxylate stretching frequencies would show a roughly similar susceptibility to intra- or inter-molecular environmental effects. Actually, in benzenoid carboxylate ions the frequency near 1600 $cm.^{-1}$ moves over a range of 150 $cm.^{-1}$ according to the polar effect of the substituent, while that near 1400 $cm.^{-1}$ does not vary with substitution, especially in aqueous solution. In solid group I and group II metal salts of substituted acetic acids, a regular pattern of cation effects on carboxylate stretching frequencies is normally observed, irrespective of the substituent in the anion; exceptions attributable to crystal packing effects are rate: replacement of a univalent metal ion by an isoelectronic divalent one has little effect on the carboxylate stretching frequency near 1600 $cm.^{-1}$, but raises that near 1400 $cm.^{-1}$ considerably.

Fine structure of pyridines (Spinner, Batts)

A study of deuterated and other substituted 4-pyridones has shown that there is no localized carbonyl stretching vibration in these compounds; instead, mixed C=O/C=C stretching occurs.

A vibration-spectral study of the bond structure of the 4-aminopyridine cation by means of ring deuteration, nitrogen deuteration and nitrogen methylation would make it appear that this ion has an amidinium ion (pyridone-like) structure, and not a pyridinium ion structure, or one intermediate between the two. This is at variance with widely-held opinion based on ionization constants.

Vibrational assignments and vibrational mixing in some pyridines and pyridinium ions have been elucidated by ring deuteration.

Physical properties of Di- and Tri-azanaphthalenes (Armarego)

The infrared and n.m.r. spectra of many families of di- and tri-azanaphthalene (also 1,4,5,8-tetra-azanaphthalene) were studied to form a background of reference for contemplated synthetic work. The difficult study of the (very small) proportion of hydrated bases in the neutral species (mainly anhydrous) of twenty-eight quinazolines was commenced.

5-Membered heterocyclic rings (Barlin)

Many 5-membered heterocyclic nuclei of great biochemical interest (e.g. imidazole) contain two opposing influences. Electron release by a singly bound nitrogen atom is opposed by the electron attraction exerted by the doubly-bound nitrogen atom. To evaluate the relative strength of these effects, the reactivity of the bromine atom in a series of bromo-*N*-methyl-tetrazoles, -triazoles and imidazoles with piperidine in ethanol was measured by studying the kinetics of its reaction. The results showed, by comparison with those obtained for 2-bromopyridine, that from two to three doubly bound nitrogen atoms were required in azoles to overcome electron release from the singly bound atom and

reach the reactivity of 2-bromopyridine. Some large positional effects were also observed.

Kinetics of the methylsulphonyl-group as a leaving group (Barlin, W. V. Brown)

A series of new methylsulphonyl-derivatives of pyridine, pyridazine, pyrazine, quinoline, isoquinoline, quinoxaline, cinnoline and phthalazine have been prepared. A study of the kinetics of replacement of the methylsulphonyl group by methoxide ion in methanol showed that the methylsulphonyl group is very readily exchanged. Wherever direct comparisons were possible, the methylsulphonyl compounds were found to be from 40 to 100 times more reactive than the corresponding chloro compound. The methylsulphonyl group in the above series of compounds was found also to be readily replaced by hydroxide ion, ammonia, methylamine, n-propylamine, hydrazine, sodium hydrogen sulphide and sodium cyanide.

The site of protonation of azoles (Barlin, Batterham)

The proton magnetic resonance spectra of various charged species of thirty five azoles were measured. This data reveals the site of protonation in imidazoles and 1,2,4-triazoles. Solvent effects were also examined.

Proton Magnetic Resonance studies (Batterham)

p.m.r. spectra of many families of nitrogen-heterocycles have been determined and interpreted, during the year. The surprising observation was made that the pteridine cation, after hydration in the 3,4-position, transfers this water to the 7,8-. and adds a second molecule in the 5,6-, positions (with Albert and McCormack). The stereochemistry of cobamide-mediated hydrogen transfer in the biosynthesis of deoxyribonucleotides has been decided (with R. L. Blakley). See also above under Brown.

TEACHING AND OTHER ACTIVITIES

Of the Department's twelve scholars proceeding to the degree of Doctor of Philosophy, three satisfied their examiners during the year: of these, two (Mr. J. Smith and Mr. R. V. Foster) have taken up research work in pharmaceutical industry and one (Mr. J. G. Catterall) has a postdoctoral fellowship at the University of Warwick, Coventry. Three other scholars (Mr. M. Paddon-Row, Mr. I. G. Sayce, Mr. J. Bunting) have presented their theses and are awaiting examination. One new scholar (Mr. G. B. Yeoh) commenced during 1966. One of the twelve scholars (Mr. J. Bunting) holds a Commonwealth Postgraduate Award, and one (Mr. P. Ford) a C.S.I.R.O. Postgraduate Studentship.

Dr. E. Spinner arranged the Department's programme of seminars, which were held at fortnightly (sometimes weekly) intervals. Dr. T. J. Batterham gave a course on Nuclear Magnetic Resonance to the School in February and March.

The Department helped organize the Third National Convention of the Royal Australian Chemical Institute including the Fourth Australian Heterocyclic Symposium in Canberra (Aug. 15-18). Papers were presented by Drs. Brown (Chairman), Barlin, Batterham, Batts, Kalatzis, Spinner, and Messrs. W. V. Brown, Bunting, England, Lee, Paddon-Row, and Yamamoto.

Professor Albert spent eight months in the Northern Hemisphere on study leave, mainly as an Honorary Research Associate at University College (six months). He also visited Departments of Chemistry and Pharmacology in Istanbul, Bucharest, Cluj (Rumania), Belgrade, Catania, Rome, Milan (one month in the Istituto di Farmacologia of the University), basel, Zurich, Hamburg, Kiel, Stuttgart, Münster, Bonn, Copenhagen, Stockholm, Paris, Vienna, Philadelphia, Seattle, and Vancouver, then took part in the 9th International Cancer Congress (Tokyo) and visited Universities in Tokyo, Sendai, Nagoya, Osaka, and Kyoto. He gave thirty lectures in various centres of research on selectively toxic agents.

Four Ph.D. theses were examined, for other Universities, by Dr. D. J. Brown.

Specimens of substances discovered in the Department have been sent on request to Dr. P. Handler (Biochemistry Department, Duke University, N.C.); Dr. J. Jacobus (Division of Medicinal Chemistry, U. S. Department of the Army); Dr. M. Gordon (Smith Kline & French, Philadelphia); Dr. D. Shugar (Poland); Dr. Chester Stock (Sloan-Kettering Institute for Cancer Research); Dr. W. Jacobson (Cambridge); Dr. A. R. Peacocke (Nuffield Department of Clinical Biochemistry, Oxford).

Large scale equipment was put at the disposal of the Biochemistry Department of this School for the processing of nucleotides; also the Canberra Fire Brigade used our large scale plant for the dilution of concentrated sulphuric acid. Absolute and s.v.r. grades of alcohol were routinely purified for the whole of the John Curtin School, thus reducing the cost from $10.00 to 38¢ per winchester bottle. Four organic syntheses were carried out for other Departments. The large-scale laboratory was in use on 40 per cent of the working days of the year.

A computer of average transients for the enhancement of the sensitivity of the Perkin-Elmer R10 nuclear magnetic resonance spectrophotometer was installed in December. The determination and interpretation of 1500 nuclear magnetic resonance spectra were made of which 300 were for other Departments in this School. Spectroscopic service work in Dr. Spinner's section comprised the determination of 227 ultraviolet and 12 infrared spectra.

The Analytical Chemistry section of the Department carried out 1943 microanalyses and micro-weighings, on 859 samples, for the whole of the John Curtin School, representing a 10 per cent increase over the average for the previous five years, and a 12 per cent increase over last year. Analyses carried out for the Inorganic Chemistry Unit of the Research School of Chemistry exceeded those for 1965 by 44 per cent. About 2.5 per cent of the carbon, hydrogen, and nitrogen analyses were completed on the new

gas-chromatographic F. and M. Analyser which was installed in June, but was out of service through a defect between early August and November. This semi-automatic apparatus has proved particularly useful for perchlorates and azides which often explode in the furnace. At the request of the School Committee, thorough analytical checks were applied to fifteen "Analytical Grade" chemicals of Australian manufacture, which were compared simultaneously with the leading imported brands. It was found that the overall quality of many of the local manufactured chemicals conformed to the standards recommended by the American Chemical Society (Dr. Fildes and Miss Jaason).

During the year, the Perkin-Elmer Atomic Absorption Spectrophotometer was used frequently by research members of other Departments in this University (Biochemistry, Physical Biochemistry, Experimental Pathology, Geography and Zoology); the Department of Geography (Research School of Pacific Studies) has also been helped with pH measurements.

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