ROYAL SOCIETY OF CHEMISTRY

Heterocyclic Chemistry Group

Tenth Lakeland Heterocyclic Symposium

Grasmere 9-13th May, 1991

Sunderland Polytechnic
England
per Form 50

10th LAKELAND HETEROCYCLIC SYMPOSIUM

The Group is most grateful to the following organisations for their generous financial support of this meeting:

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The Secretary would also like to record his thanks to Mrs Mary Bower, and to the Grasmere Hoteliers for their help and cooperation.

TIMETABLE OF SCIENTIFIC PAPERS

Friday 10th May

Morning — Chairman: *Professor O. Meth-Cohn*

9.10-9.15 Welcome and Introductory Remarks

9.15-10.15 Professor G. Pattenden -

Synthetic Studies with Natural Pyrones, Pyridones, Butenolides and Maleimides

10.15-10.45 Dr J.A. Miller -

For Medicinal Purposes Only - Some Small Ring Heterocycles

10.45-11.15 COFFEE

11.15-11.45 Professor M.M. Campbell -

Synthesis in the Shikimate Pathway

11.45-12.45 Professor T.S. Livinghouse -

From Acylnitrilium Ions to Transition Metal Templates. Versatile New Methods for the Synthesis of Heterocyclic Ring Systems

LUNCH

Evening — Chairman: *Professor R.D. Chambers*

19.30-20.00 Professor H. Heaney -

Some Novel Pictet-Spengler Cyclisations using Non-Aqueous Reaction Conditions

20.00-21.00 Professor H. Heimgartner -

Synthesis of Heterocycles by Ring Expansions of 3-Amino-2*H*-azirines

Saturday 11th May

Morning — Chairman: *Professor G. Jones*

9.15-10.15 Professor J. Bergman -

Coupling Reactions of Indole Derivatives

10.15-10.45 Professor M.F.G. Stevens -

Antitumour Imidazotetrazinones: Heterocyclic Chemistry in the Major Groove of DNA

10.45-11.15 COFFEE

11.15-11.45 Dr J.N. Hay -

Heterocyclic Polymers - From Microchips to the Space Shuttle

11.45-12.15 Dr J. R. Malpass -

Bridging Nitrogen - Some Variations on an Azabicyclic Theme

12.15-12.45 Dr C.B. Chapleo -

A Guided Tour of Imidazole Cycling

LUNCH

Evening — Chairman: *Professor C.W. Rees*

19.30-20.15 Professor W. Flitsch -

Mitomycines: A New Approach

20.15-21.15 Professor L.A. Paquette -

Extending Classical Concepts of Reactivity and Conformation Theory: (a) Spirocyclic Tetrahydrofurans as Chemical Probes and Ligands; (b) Furanocembranolide Synthesis and Interconversion

Sunday 12th May

Morning

Chairman: *Dr J.V. Greenhill*

9.15-10.15 Professor W. Steglich -

Some New Aspects of Oxazolinone and Oxazinone Chemistry

10.15-10.45 Dr P.N. Edwards -

Aromatase Inhibitors Based on the Naphtho-[2,1-b]furan-2(1*H*)-one Skeleton

10.45-11.15 COFFEE

11.15-11.45 Dr G. Kneen -

The Synthesis and Fungicidal Properties of 2-Cyano-4-aroylimidazoles

11.45-12.45 Dr R.W. Alder -

Some Ins and Outs of Medium-Ring Heterocycles

LUNCH

Monday 13th May

Morning — Chairman: *Professor M.F.G. Stevens*

9.30-10.15 Professor H.M.L. Davies -

Novel Entry to the Tropane System by Reaction of Rhodium(II) Acetate Stabilised Vinyl-carbenoids with Pyrroles

10.15-10.45 Dr C.L. Habraken -

Further Adventures in *N*-Nitropyrazole Territory

10.45-11.15 COFFEE

11.15-11.45 Dr P.D. Bailey -

Asymmetric Synthesis *via* the Aza-Diels-Alder Reaction

11.45-12.30 Professor R. Neier -

A Novel Pyrrole Synthesis. A Model for the Biosynthesis of Porphobilinogen?

12.30-12.40 Closing Remarks

LUNCH

10th LAKELAND HETEROCYCLIC SYMPOSIUM

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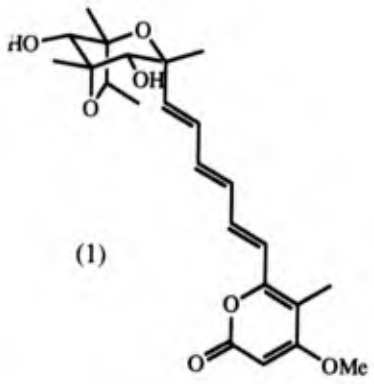
Dr R.C. Young	SmithKline Beecham Research

Synthetic Studies with Natural Pyrones, Pyridones, Butenolides and Maleimides

Gerald Pattenden

(Department of Chemistry, The University, Nottingham NG7 2RD England)

Pyrones e.g. citreoviridinol (1) and asteltoxin (2), *pyridones*, *e.g.* funiculosin (3) and illicicolin H (4), *butenolides*, *e.g.* patulin (5) and calycin (6), and *maleimides*, *e.g.* thiolutin (7) and pukeleimide (8) are families of secondary metabolites that occur widely in Nature, and several members show profoundly interesting biological properties.



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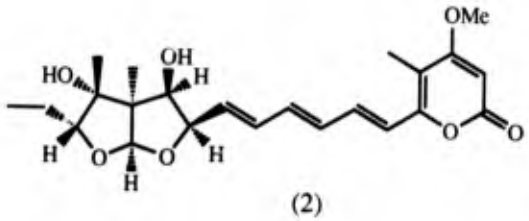

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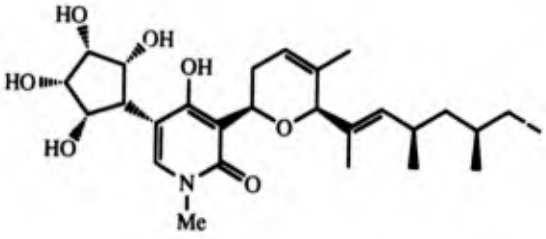

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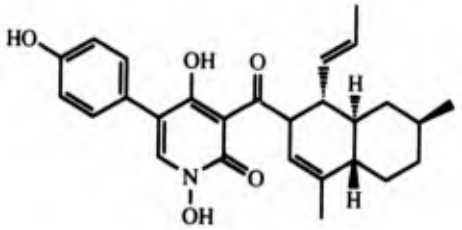

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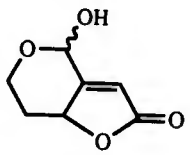

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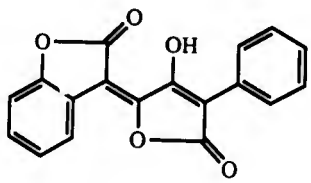

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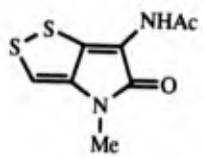

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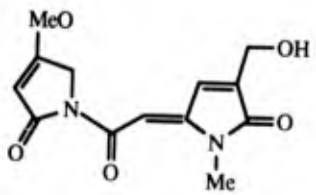
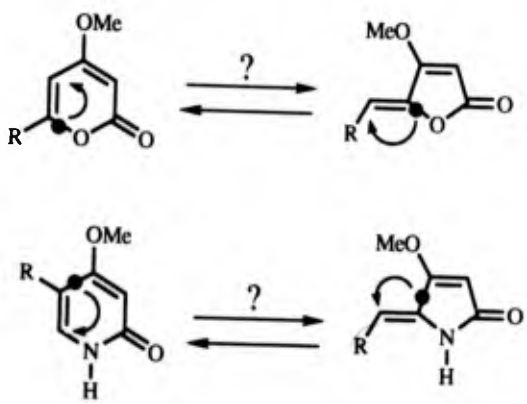


(8)

4-Oxy-2-pyrones are isomeric with 4-ylidenetetronic acids; similarly 4-ylidenetetramic acids are isomeric with 4-oxy-2-pyridones. It is possible that naturally occurring 2-pyrones and tetronic acids, and natural 2-pyridones and tetramic acids are interrelated biogenetically as 1,2-shift isomers (Scheme).



Scheme

The lecture will summarise some synthetic adventures within these families of natural products and also give some consideration to their biogenetic interrelationships.

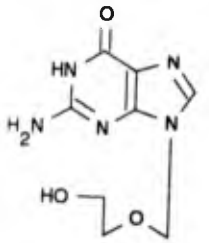
ABSTRACT FOR GRASMERE: MAY 1991

"FOR MEDICINAL PURPOSES ONLY - SOME SMALL RING HETEROCYCLES"

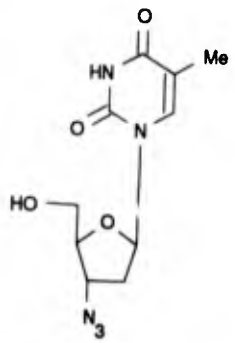
Dr. Allen Miller,
Wellcome Research

Analogues of the natural nucleosides continue to provide most of today's clinically useful anti-viral drugs. Their anti-viral properties generally result from inhibition of one or more of the key viral processing enzymes, or from incorporation into viral DNA or RNA, and subsequent chain termination of nucleic acid synthesis. The early analogues generally involved changes in the natural bases, and only following the success of acyclovir (1), and then zidovudine (2), was attention turned in earnest to analogues in which the sugar ring was modified.

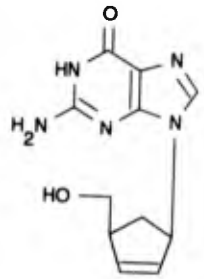
During the eighties, cyclopentanoid nucleosides, such as carbovir (3), attracted immense attention, but one variant of the nucleoside analogue type remained relatively unexplored - that of substitution of the sugar ring oxygen by sulphur, to give thiolanes. Although the corresponding 4-thiafuranose sugars have been reported in the literature, examples of their transformation into nucleoside analogues have been relatively rare. In part this has been due to the lack of robust, general routes to 4'-thianucleosides (4), and the subject of the presentation will be the development of just such a route.



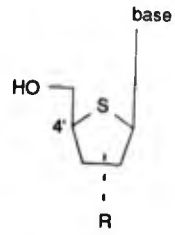
ACYCLOVIR (1)



ZIDOVUDINE (2)



CARBOVIR (3)



4'-THIANUCLEOSIDES (4)

The targets (4) represent a considerable synthetic challenge, as well as being of high potential on both therapeutic and, possibly, commercial grounds. Not only must the obligatory (in terms of our understanding of the mode of anti-viral action) hydroxymethyl and base ligands be *syn* to each other, but also the absolute configuration of C-4' must be as shown in (4). Moreover, a range of ligands, R in (4), must be accessible in a stereocontrolled fashion in order to maximise the structural options for synthesis and testing.

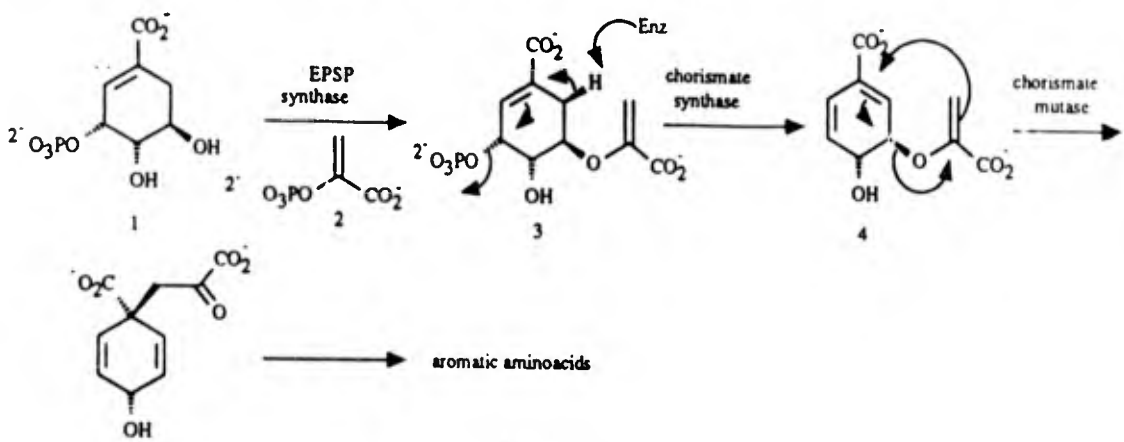
So much for flat heterocyclic chemistry! Approaches to this problem will be analysed, and detailed discussion of one answer will be presented.

SYNTHESIS IN THE SHIKIMATE PATHWAY

Malcolm M. Campbell* and Malcolm Sainsbury
School of Chemistry, University of Bath, Bath, BA2 7AY.

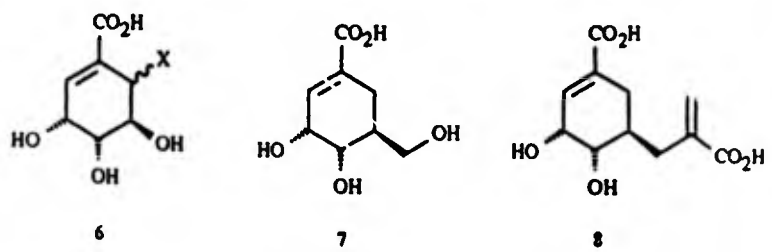
Shikimic acid has a key role in the biosynthesis of aromatic aminoacids in plants and in microorganisms (Scheme 1). Shikimate 3-phosphate (1), mediated by EPSP synthase, reacts with enol pyrophosphate (2) to give the enol pyruvate (3). Chorismate synthase then effects an *anti*-1,4-elimination of phosphate to give (4) which is further enzymically transformed by chorismate mutase into prephenate (5).

BIOSYNTHETIC PATHWAY AND POINTS OF ATTACK



Scheme 1

There is much potential in this reaction cascade for the rational design of inhibitors of each of the enzymic steps, and in consequence for the synthesis of enzyme inhibitors of plant biosynthesis or for the inhibition of microbial biosynthetic pathways.



Scheme 2

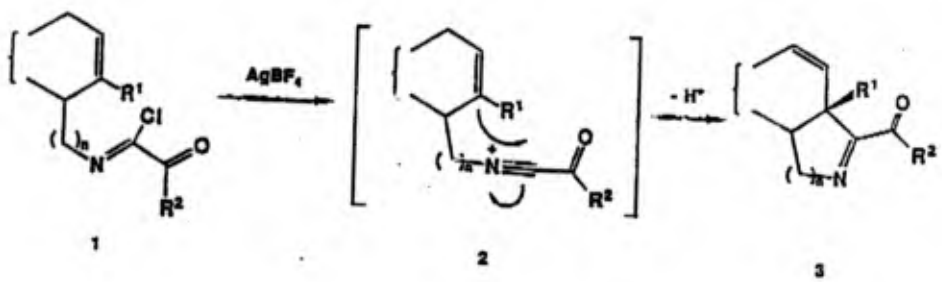
We will describe stereocontrolled synthetic routes from furan and from pyridine precursors, leading to substrate mimetics such as (6), (7) and (8).

From Acylnitrilium Ions to Transition Metal Templates. Versatile New Methods for the Synthesis of Heterocyclic Ring Systems.

Thomas S. Livinghouse
Department of Chemistry
Montana State University
Bozeman MT, USA

ABSTRACT

Complex heterocyclic ring systems, that are not readily available by way of conventional iminium ion cyclizations, can often be constructed expediently by the use of acylnitrilium ion initiated heteroannulations (**Scheme 1**). This lecture will focus on the application of this method, as well as complementary procedures mediated by transition metals, to the synthesis of naturally occurring skeletal systems.



Scheme 1

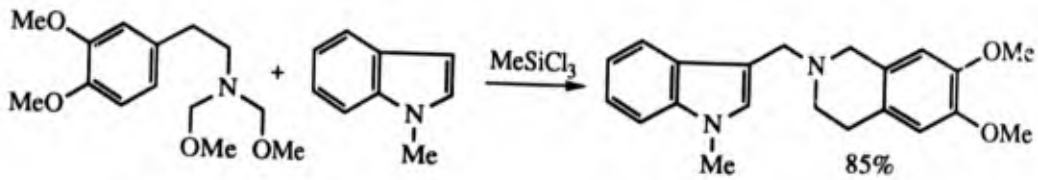
Some Novel Pictet-Spengler Cyclisations Using Non-Aqueous Reaction Conditions

Harry Heaney

Department of Chemistry, Loughborough University of Technology, Leicestershire, LE11 3TU

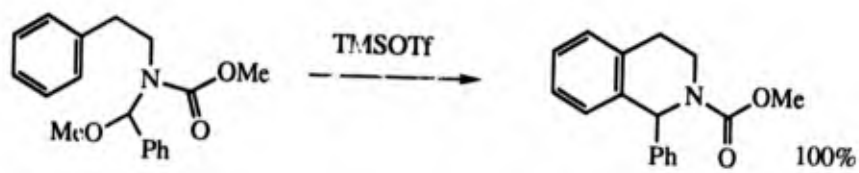
We will discuss two types of Pictet-Spengler cyclisations that result in the efficient formation of 1,2,3,4-tetrahydroisoquinolines.

The formation of bis-aminol ethers from primary amines provides reagents that can function as a di-cation equivalent and hence react sequentially either with the same or different nucleophiles. bis-(*N,N*-Methoxymethyl)-3,4-dimethoxy-β-phenylethylamine is one example and reactions with chlorosilane derivatives in the presence of π-excessive heterocycles such as indole result in a tandem reaction in which cyclisation is followed by reaction with the added heterocycle.

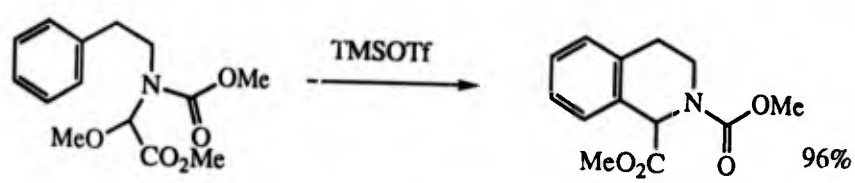


Other examples will include reactions with other heterocycles and stepwise reactions with benzenoid derivatives including *p*-methoxyphenyltributyl stannane which results in the formation of sendaverine methyl ether.

The formation of *N*-α-methoxyalkyl-β-phenylamine derived carbamates allows the generation of activated iminium species which cyclise readily to afford 1-substituted 1,2,3,4-tetrahydroisoquinoline derivatives, for example 1-phenyl-2-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline, in good yields.



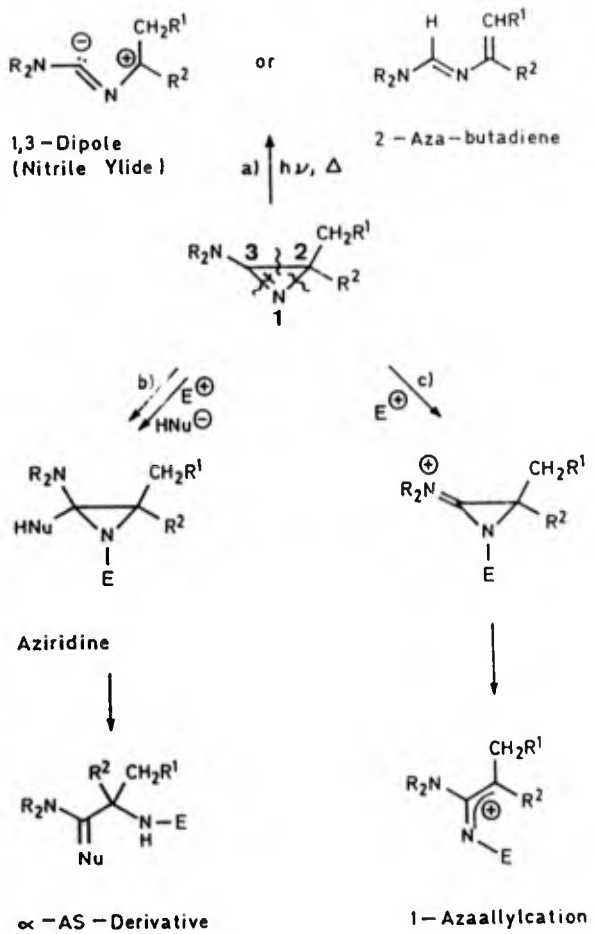
The method has also been extended to allow the preparation of the related 1–methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline.



SYNTHESIS OF HETEROCYCLES BY RING EXPANSIONS OF 3-AMINO-2H-AZIRINES

HEINZ HEIMGARTNER
Organisch-chemisches Institut der Universität Zürich,
Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

The 3-amino-2*H*-azirines are three-membered-ring amidines with an endocyclic C=N bond. The presence of a nucleophilic amidine group, which is part of the strained azirine structure, is responsible for the reactivity of these easily accessible heterocycles. Synthesis and structure of 3-amino-2*H*-azirines will be discussed.



Almost all reactions of these aminoazirines proceed by opening of the three-membered ring. Thereby, each of the bonds may be selectively cleaved, depending on the reagents and the reaction conditions. The following reactive intermediates, which may be used as building blocks for new nitrogen heterocycles, are formed:

The three types of ring cleavage will be demonstrated with some typical reactions leading to five-to-eight-membered heterocycles.

The main part of the lecture concerns syntheses of heterocycles *via* cleavage of the azirine C=N bond. Starting materials in these reactions are NH-acidic heterocycles, phenols, carboxylic acids, and their derivatives. The common feature of all these reactions is the activation of the azirine by protonation ($E^+ = H^+$), followed by a nucleophilic attack on the amidinium C-atom. The postulated intermediate is an aziridine which undergoes ring opening leading to α-amino acid derivatives. With a few examples it is shown that activation of the aminoazirine can also be accomplished by complexation with *Lewis* acids (*e.g.* BF_3).

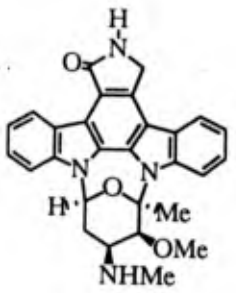
The term "ring expansion" is used in a rather general context for reactions leading to heterocycles which contain the azirine fragment as a part of the new ring. Accordingly, *N*-substituted cyclic amidinium systems and *C*-substituted aziridines as well as ring opened building blocks like aminoacid derivatives, which may or may not be isolated, are considered as intermediates.

Review: H. Heimgartner, *Angew. Chem. Int. Ed. (E)* **1991**, *30*, in press.

Coupling reactions of indole derivatives.

Jan Bergman
Department of Organic Chemistry, Royal Institute of Technology
S-100 44 Stockholm, SWEDEN

In connection with studies of indolocarbazole alkaloids such as staurosporin (**1**), we have synthesized e.g. 2 by a iodine promoted coupling of the trianion of indole-3-acetic acid.[1,2]



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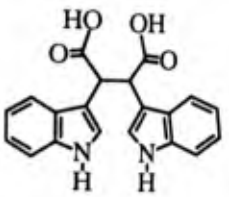

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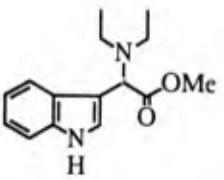
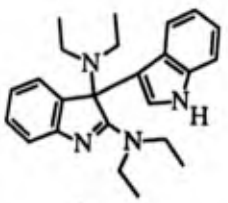


3

Couplings promoted by $FeCl_3$ have also been extensively studied. Thus $FeCl_3$-$(C_2H_5)_2NH$ and methyl indole-3-acetate yields **3**, a useful intermediate for elaboration to unsymmetrical indolocarbazole alkaloids. Similar treatment of indole and 2-methylindole, with $FeCl_3$ -$(C_2H_5)NH$, gave, after work-up, **4** and **5b**, respectively.

Ring-opening and recyclization of the intermediate **6** explains the formation of **5b**, whose structure was proven by addition of CH_3Li followed by $K_3Fe(CN)_6$ to calycanin (**5a**).



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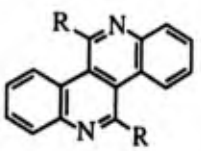
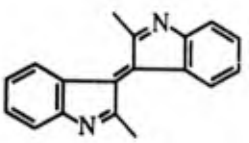


5 a R=H
b R=Me



6

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2. J. Bergman, S. Bergman and J.-O. Lindström, Tetrahedron Letters, **30**, 5337 (1989).

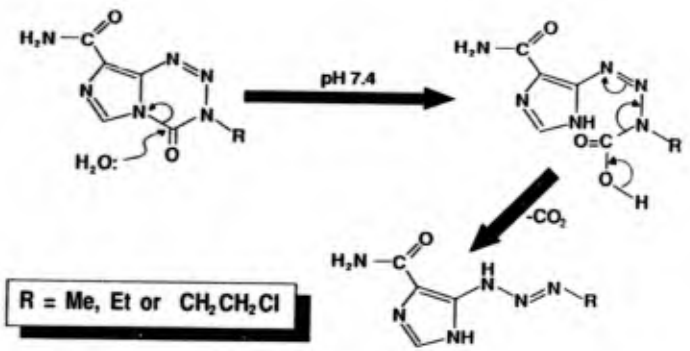
ANTITUMOUR IMIDAZOTETRAZINONES: HETEROCYCLIC CHEMISTRY IN THE MAJOR GROOVE OF DNA.

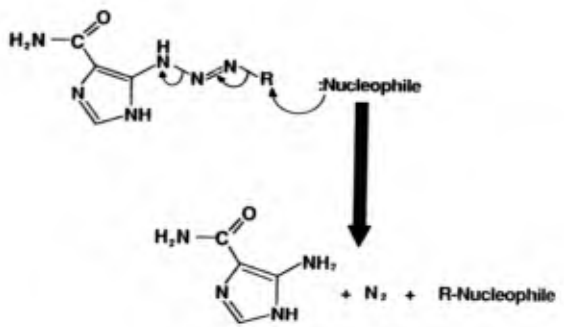
A. S. Clark, P.R. Lowe, C.E. Sansom, C.H. Schwalbe and M.F.G. Stevens, CRC Experimental Chemotherapy Group, Pharmaceutical Sciences Institute, Aston University, Birmingham B4 7ET

The X-ray crystal structure of the antitumour imidazotetrazinone temozolomide has been determined and reveals a doubly hydrogen-bonded dimer as the asymmetric unit. In both molecules the 8-carboxamide substituent is coplanar with the bicyclic heterocycle and forms a weak intramolecular NH...N hydrogen bond to the imidazole nitrogen atom N(7). The energy barrier to rotation of the carboxamide group of approximately 20kJmol^{-1} indicates that interconversion between rotamers should be possible in solution. In temozolomide and the related drug mitozolomide, N(7) is more negatively charged than N(1), which favours the formation of hydrogen bonds to the former atom in spite of their poor geometry.

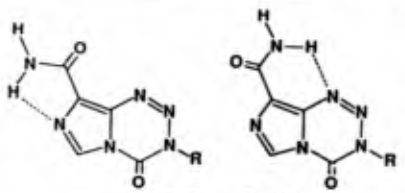
Both temozolomide and DTIC are prodrugs and are believed to exert their antitumour activity by conversion to 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC). DTIC and MTIC offer the same possibilities for carboxamide group rotation and an additional opportunity for tautomerism *via* exchange of a proton between N(1) and N(3) on the imidazole ring. In the crystalline state of DTIC both tautomers are present but the 3H-tautomer gains extra stability from a weak intramolecular NH...O hydrogen bond to the carboxamide O atom. The potential for intact DTIC to bind reversibly (i.e. non-covalently) to the same DNA major-groove sites as temozolomide and mitozolomide has not been recognised hitherto: however, only binding of its active monomethyl metabolite (MTIC) can have tumour-inhibitory consequences.

We have proposed recently a new model in which the imidazotetrazinone prodrugs are preferentially ring-opened to their alkylating forms by water "activated" in the nucleophilic microenvironment of guanine-rich DNA sequences (A.S. Clark, M.F.G. Stevens, C.E. Sansom and C.H. Schwalbe, 1990, *Anti-Cancer Drug Design*, *5*, 63). The results of the present crystallographic and molecular modelling studies, coupled with molecular orbital calculations, now allow us to rationalise accurately structure-activity relationships in antitumour imidazotetrazinones and related bicyclic heterocycles.

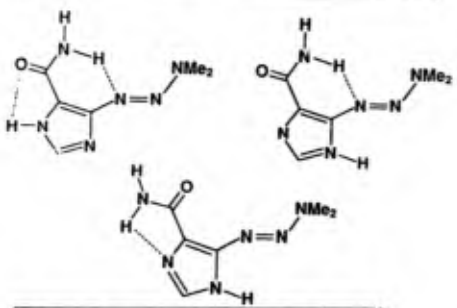




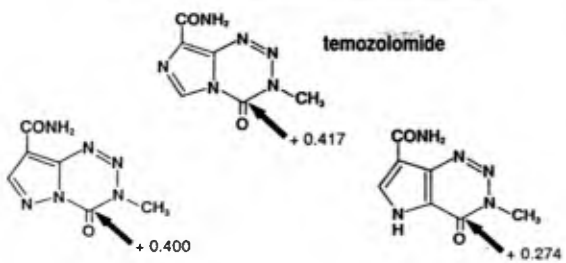
Intramolecular hydrogen bonding in antitumour imidazotetrazinones



Intramolecular hydrogen bonding possibilities in DTIC



Partial charges at C (4) in analogues of temozolomide



HETEROCYCLIC POLYMERS - FROM MICROCHIPS TO THE SPACE SHUTTLE

J N Hay
Kobe Steel Europe Ltd
Research Laboratory
Surrey Research Park
Guildford
Surrey

Polymers containing heterocyclic groups in the main chain are becoming increasingly important commercially due to the often excellent balance of properties they exhibit. They are currently found in applications as diverse as insulating layers in integrated circuits and components in the space shuttle. Their use is expected to expand rapidly, but full realisation of their potential is likely to be dependent on improvements in their synthesis and a deeper understanding of chemical processes occurring during their manufacture and use.

The synthesis of polymeric heterocycles is subject to a number of considerations which may not be so important in the preparation of their discrete heterocyclic analogues. The reaction which forms the heterocyclic ring should occur in essentially quantitative yield since even a relatively modest polymer molecular weight may require more than 50 ring-forming reactions to take place in each chain. Purification of an impure polymer is not a trivial task. If high molecular weight, or tight control of molecular weight, is required then the monomer precursors need also to be of very high purity. Many heterocyclic polymers are formed via condensation polymerisation, with the result that some small molecule(s) is eliminated as a by-product. Frequently, this molecule is a volatile such as water. This can lead to problems during polymer processing, where reaction of any residual functional groups will lead to volatile evolution and formation of voids in the component.

A further complication arises from the fact that many of the resultant polymers are insoluble in common solvents. Polymerisation reactions are therefore frequently carried out in high boiling point polar aprotic solvents which are difficult to remove in some cases. Precipitation of the polymer during the synthesis usually results in incomplete reaction. The rigidity of the polymers, which contributes to their insolubility, also means that they tend to have very high viscosities in the molten state.

From the foregoing, it might reasonably be assumed that the polyheterocycles have little to commend them! Despite the drawbacks, however, these polymers offer a range of desirable properties not possessed by any other class of polymers. Perhaps their main advantage is their high temperature performance. The presence of predominantly heterocyclic and aromatic units confers high thermo-oxidative stability on the polymers and also results in high glass transition temperatures (softening point). This allows them to be used in applications with service temperatures as high as 400°C. More widespread application would undoubtedly result from the development of improved synthetic routes to the polymers.

The main synthetic routes currently used to prepare polymeric heterocycles will be discussed and their advantages and disadvantages highlighted. The basic principles will be illustrated with particular reference to polyimides, by far the most important heterocyclic condensation polymer. The main synthetic routes described will be

1) the diamine / dianhydride reaction
2) variants of 1, eg use of diisocyanates, thioanhydrides etc.
3) in-situ polymerisation ('PMR' approach)
4) polymerisation of preformed bis-imides
5) activated aromatic nucleophilic substitution reactions

Other polymer types worthy of mention include polybenzimidazoles and polyphenylquinoxalines. Some of the ways in which chemists have helped to solve problems limiting the practical use of such condensation polymers will be outlined. The importance of reliable analytical methods will also be mentioned.

Some alternative approaches to heterocyclic polymers will be described. These include the hetero Diels-Alder reaction, which should be irreversible under the conditions of use of the polymer. This can be achieved by the first formed product eliminating a small molecule to give the final heterocycle. Another approach is to form the required polymer via a thermally induced rearrangement reaction. This is illustrated by the isobenzoxazole - acridone rearrangement.

An idealised solution to the general problems associated with polyheterocycle synthesis will be presented. This so-called oligomer approach utilises smaller preformed polymer chains, end-capped with 'latent' reactive groups. At elevated temperatures, these groups thermally rearrange to reactive intermediates which can either react with each other or other available functional groups to form heterocyclic linking groups in the final polymer. The likely advantages of such an approach will be outlined and ideas solicited!

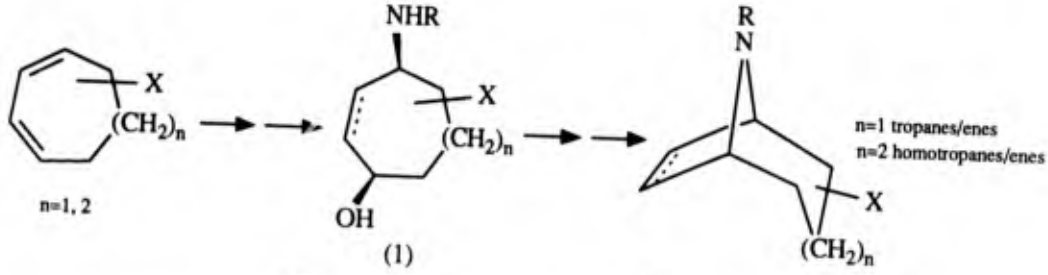
Bridging Nitrogen — Some Variations on an Azabicyclic Theme

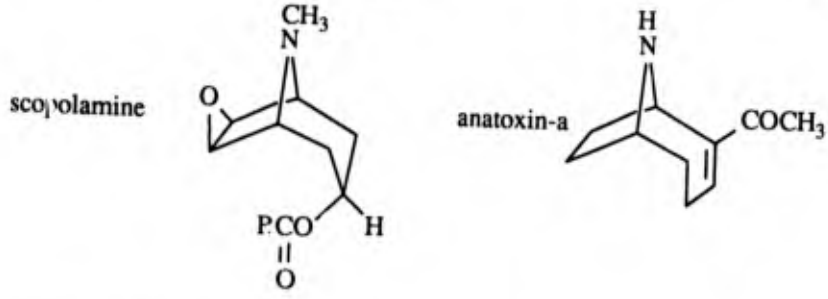
John R Malpass

Department of Chemistry, University of Leicester

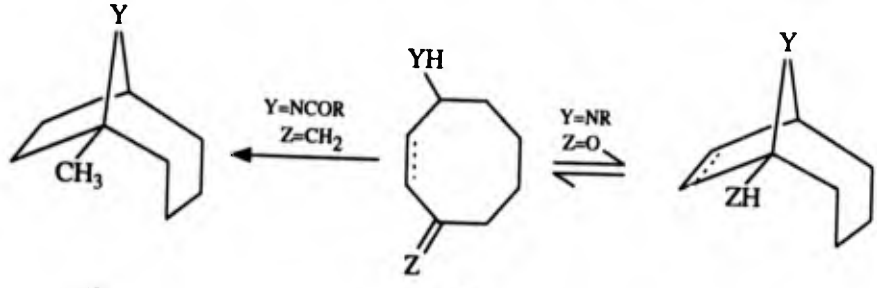
Nitrogen has most unusual properties when it bridges a 6-membered ring in 7-azabicyclo[2.2.1]-heptanes/enes (7-azanorbornanes/enes). Very high configurational stability at nitrogen allows study of invertomer preferences and of stereoelectronic control in reactions at nitrogen; ^{15}N nmr studies show dramatic deshielding of the nitrogen and contribute to a picture in which strain is not the major factor in determining the properties of the bridging nitrogen, in this environment.

Extension of our studies to higher homologues will be described including 8-azabicyclo[3.2.1]-octanes/enes (tropanes/enes) and 9-azabicyclo[4.2.1]nonanes/enes (homotropanes/enes). Simple intramolecular cyclisations based on intermediates (1) are aimed especially at the elusive trop-6-enes, potential precursors to scopolamine analogues.





General routes to the higher homologues are not well developed although anatoxin-a has aroused intense synthetic interest. Application of the intramolecular cyclisation approach to simple homotropanes/enes will be described; observations on radical cyclisations [e.g. to (3)] and on the balance of the mono-/bicyclic tautomeric equilibrium in aminoketones (2) ⇌ (4) will also be presented.



(3) (2) (4)

"A GUIDED TOUR OF IMIDAZOLE CYCLING"

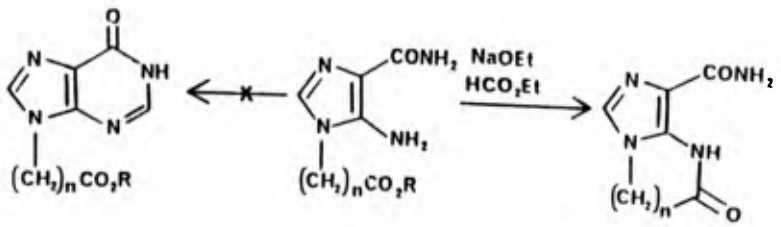
P R Birkett[a], C B Chapleo[a,b] and G Mackenzie[a]

a. Humberside Polytechnic, Hull

b. Reckitt & Colman Products, Hull

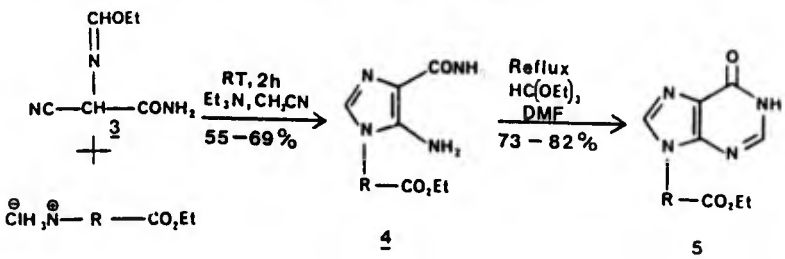
SYNTHESIS OF α- AND ß-(HYPOXANTHIN-9-YL AND ADENIN-9-YL) CARBOXYLATES

Purine derivatives, including those possessing the α-(purin-9-yl) carboxylic acid moiety are of interest because of their antitumour and antiviral activities[1]. Additionally α-(hypoxanthin-9-yl) carboxylic acids and their ß- and γ-homologues have potential as inhibitors of the enzyme purine nucleoside phosphorylase[2]. Surprisingly it has been reported that attempts to prepare ß- and γ-purine-9-yl carboxylate homologues (1) proved to be unsuccessful[3] ; alternatively fused imidazoles (2) were obtained.



1 2

Utilisation of the Shaw methodology[4], which provides an efficient route to substituted imidazoles and hence to the corresponding purines, has resulted in a convenient synthesis of ethyl α- and ß-hypoxanthin-9-yl carboxylates. Reaction of N-carbamoyl (or cyano)-cyanomethyl formimidate (3) with the appropriate aminoester salt afforded in good yield the imidazole carboxylates (4a-c) derived from glycine, alanine and ß-alanine[5]. Previous attempts to obtain hypoxanthines of type (5) involved direct alkylation of 6-chloropurines[3] or cyclisation of imidazoles[3]. This latter procedure resulted only in the intramolecular cyclisation products (2). In contrast to this earlier study[3] use of triethylorthoformate in DMF enabled the cyclisation to proceed smoothly to give the hypoxanthines[5] (5) in very good yield. Similarly the adenin-9-yl derivatives were also obtained in excellent yield. When optically active aminoesters are utilised in the synthesis of imidazoles (4) and (6) chiral integrity is maintained in the purines (5) and (7)[6].



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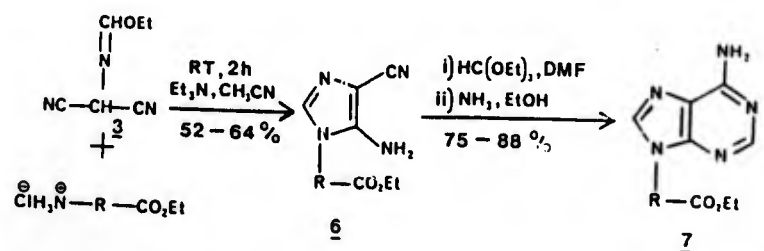
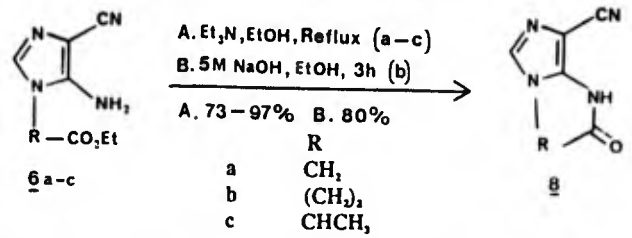
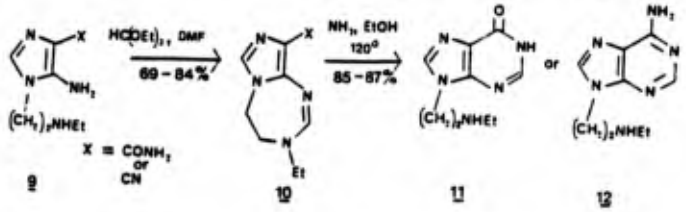


6 7

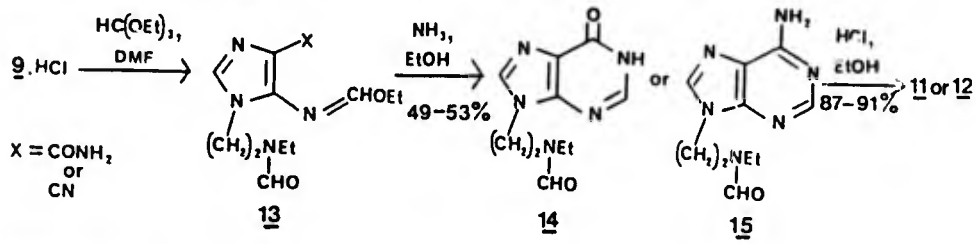
Intramolecular cyclisations, similar to those already reported[3] have been observed with the cyanoimidazoles (6a-c). In contrast to the earlier study[3] cyclisation to generate the fused five membered ring products were also observed.



Although the above synthetic strategy is general for purines, imidazoles (9) derived from N-ethyl-ethylenediamine gave good yields of the novel imidazotriazepines (10) when treated with triethylorthoformate; the structures were determined from spectroscopic data. However it was recognised that ammonia would effect a ring opening of (10) to give the exocyclic amidines which would subsequently undergo the desired cyclisation to give the purines; the corresponding purines (11) and (12) were thus obtained in good yield directly from the reaction of (10) with ammonia under pressure.



Formation of the triazepines was successfully avoided by using the imidazoles (9) as their hydrochloride salts. Now reaction presumably resulted in the formation of the protected imidate (13); intramolecular cyclisation being prevented due to the N-formyl protection at the side chain amine function. Further reaction with ammonia resulted in the protected purines which were readily deprotected under acid conditions to yield the parent purines (11) and (12).



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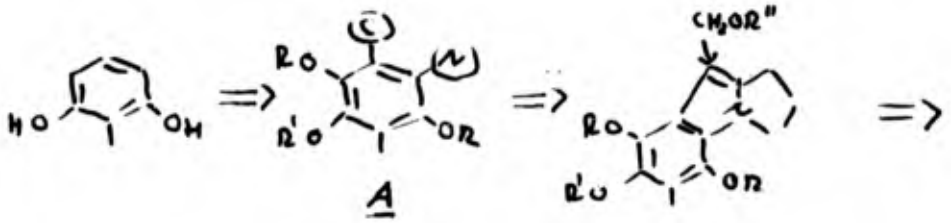
3. Bridson, P.K., McGowan, A., Wilson, C.M., Yeh, Y.M. J. Het. Chem. 24, 1155 (1987).
4. Shaw, G., Warrener, R.N., Ralph, R.K., Butler D.N. J. Chem. Soc. 1648 (1959); Mackenzie, G., Shaw, G.J. Chem. Research (M). 2145 (1977); (S) 184 (1977).
5. All new compounds gave satisfactory analytical and spectroscopic data.
6. Birkett, P.R., Chapleo, C.B., Mackenzie, G. unpublished results.

Mitomycines: A New Approach

Willi Flitsch, Stephan Köbbing and Wolfgang Micke
Universität Münster

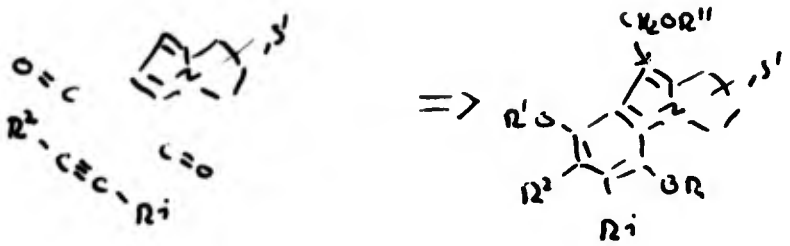
Attempts to synthesize mitomycines and mitosenes have been based on a general strategy comprising hexasubstituted benzene derivatives A:



A

The preparation of A takes about 15 steps rendering these syntheses laborious limiting, moreover, the versatility of this method.

A new versatile 2-step route to mitosenes is presented allowing a synthesis of hithero unknown derivatives.



Extending Classical Concepts of Reactivity and Conformation Theory: (a) Spirocyclic Tetrahydrofurans as Chemical Probes and Ligands; (b) Furanocembranolide Synthesis and Interconversion

Professor L.A. Paquette
Ohio State University

The acid-catalyzed dehydration of unsymmetrically substituted 1,4-diols will be shown to proceed with high levels of stereochemical retention. Furthermore, conversion to the spirocyclic tetrahydrofurans occurs with preferential loss of the primary rather than the tertiary hydroxyl, as judged by suitable ^{18}O labelling. These data reflect a reversal in the normal expectations based on commonly observed S_N1 reactions. The remarkable departure from traditional chemical behaviour stems from a previously unappreciated kinetic factor and is attributed to effective competition from so-called *associative S_N reactions*. In this context, proximal substitution by an electro-negative heteroatom will be shown to be of value as a tool for effecting stereocontrolled cyclization under acidic conditions.

This chemistry will subsequently be applied to the preparation of a new class of preorganized ionophoric polyethers, the belted spirocyclic tetrahydrofurans. The ground-state conformational preferences of these molecules, established by X-ray crystallography, will be shown to reflect the thermodynamic importance of gauche C-O/C-O sigma bond interactions. The coordinative abilities of these ionophores toward alkali metal ions will be outlined, with commentary on molecular structure as a function of the locus and number of binding sites.

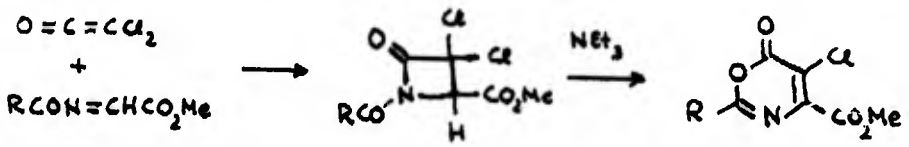
In the second half of the lecture, a retrosynthetic analysis and strategy for the total synthesis of pseudopterolide and allied pseudopteranes will be presented. The scheme is dependent upon the early elaboration of suitably 2,5-difunctionalised 3-furoate esters and their efficient diastereoselective coupling with an aldehydo ester to achieve construction of the butenolide subunit. A dual selenenylation strategy is next implemented for the oxidation of both relevant pendant groups. Following chemospecific introduction of the final structural component by palladium (0) catalysis, the formidable challenge of macrocyclization has been examined. The transition state requirements for these reactions will be discussed, as will the requirements underlying the ability to transform pseudopterolide *reversibly* into tobagolide.

Some New Aspects of Oxazolinone and Oxazinone Chemistry

Wolfgang Steglich

Institut für Organische Chemie und Biochemie der Universität Bonn,
Gerhard-Domagk-Straße 1, D-5300 Bonn 1, Germany

The use of acylimino esters and oxazolinone anions as kationic and anionic glycine equivalents respectively, opens new routes to modified amino acids and peptides. The combination of both reagents affords azlactones of triamino tricarboxylic acids with high diastereoselectivity. In some cases, the products can be converted into azetidinone derivatives. The reaction of acylimino esters with dichloroketene yields *N*-acylated 3,3-dichloroazetidin-2-ones **1** which undergo ring enlargement to 5-chloro-6*H*-1,3-oxazin-6-ones **2** on treatment with triethylamine. The oxazinones **2** react with ynamines under formation of pyridine derivatives.



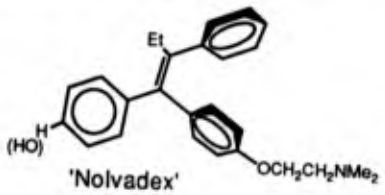
1 **2**

In the last part of the lecture the conversion of *N*-acylamino acids and peptides into 5-glycosyloxyoxazole derivatives is described. These novel compounds can be considered as masked derivatives of amino acids and peptides which release the parent compounds on treatment with glycosidases. During this work the first 3,4-dihydroxyoxazole derivatives have been prepared.

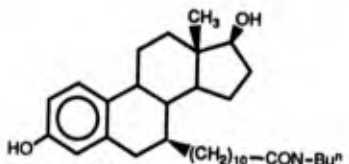
Aromatase inhibitors based on the naphtho[2,1-b]furan-2-(1H)one skeleton.

P.N.Edwards and M.S.Large

The growth of certain neoplasms, particularly breast cancer in women, can be oestrogen (E) dependent. This growth response, which is mediated through the variable modulating action of E/oestrogen receptor (E/ER) complexes on the expression of a number of genes, can be reduced or prevented by many different therapeutic modalities. By far the most successful has been the ICI drug 'Nolvadex', which, in its own right and as a phenolic metabolite, competes effectively with E for binding to ER: the drug/ER complex produces gene, cell type and species specific changes which in the majority of cases results in anti-tumour effects in ER+ tumours. However, a small proportion of ER+ tumours fail to respond or become tolerant.



'Nolvadex'

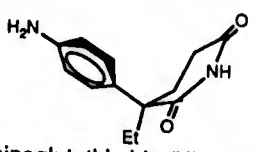


(1)

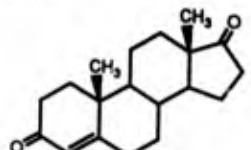
The recent discovery in ICI of pure E antagonists such as compound 1 provides hope for such cases in the future, but the use of drugs which inhibit E biosynthesis is an alternative, clinically proven therapeutic approach. Inhibition of the final enzyme in this biosynthetic pathway - aromatase(oestrogen synthetase), provides the most selective target, and extensive research by several groups over many years has produced a very wide variety of inhibitors (P.A.Cole & C.H.Robinson, J.Med.Chem.,1990,33,2933). Unfortunately, those agents so far tested clinically have significant side-effects through lack of specificity: aminoglutethimide, one of the earliest agents, inhibits several steroidal hydroxylases and needs cortisone replacement co-therapy; 4-hydroxy-androstenedione has androgenic effects, and even the very recent agent, CGS16949A, inhibits 11- and 18-hydroxylase to a significant degree.

The lecture will disclose compounds such as 2 and convey some of the chemical and biological findings discovered during our work on naphthofuranones.

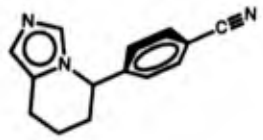
We thank Mr Chris Green for experimental assistance.



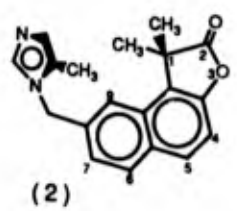
aminoglutethimide (Ki = 600nM)



4-hydroxyandrostenedione (Ki = 50nM)



CGS16949A (Ki = 1.5nM)



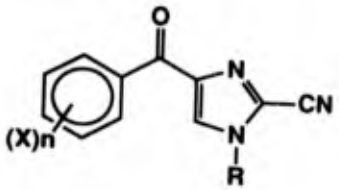
(2)

THE SYNTHESIS AND FUNGICIDAL PROPERTIES OF 2-CYANO-4-AROYLIMIDAZOLES

Clive L.Cornell, Philip J.Dudfield, Geoff Kneen and Stephen D.Lindell

Schering Agrochemicals Limited,
Chesterford Park Research Station,
Saffron Walden, Essex CB10 1XL

2-Cyano-4-aroylimidazoles of type (1) possess potent antifungal properties with potential use in agriculture [A.D.Buss, P.J.Dudfield and J.H.Parsons, EP 88 3022600 (1988) to Schering Agrochemicals Limited]. Of particular interest is their ability to control the two commercially important crop pathogens, *Phytophthora infestans* (potato blight) and *Plasmopara viticola* (vine downy mildew).



R = SO_2NMe_2, CO_2Et, $SO_2{}^iPr$

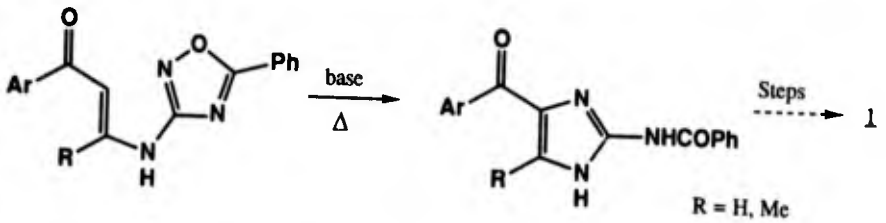
X = halogen, alkyl, haloalkyl, alkoxy

n = 0 - 3

1

At the onset of our interest in this structural class, 2-cyano-4-aroylimidazoles were unknown in the chemical literature. A number of synthetic routes have been developed which exploited the direct cyanation of imidazoles in the 2-position [P.J.Dudfield, C.T.Ekwuru, K.Hamilton, C.E.Osbourn and D.J.Simpson, *Synlett* (5), 277 (1990)], and these will be described.

An alternative approach to compounds (1) utilised the Boulton-Katritzky rearrangement of the readily synthesised oxadiazoles (2) to the 4-aroylimidazoles (3).



R = H, Me

2 3

Significant differences in the efficiency of the rearrangement to (3) were observed between (2) R = H and (2) R = Me, and a mechanistic basis for this observation will be discussed.

SOME INS AND OUTS OF MEDIUM-RING HETEROCYCLES

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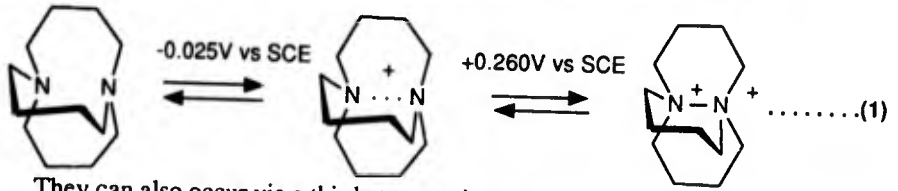
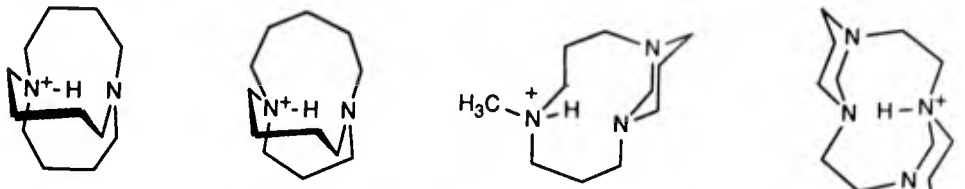
Medium ring heterocycles, and especially bicyclic medium ring systems with heteroatoms at both bridgeheads, provide ideal platforms for investigating interactions between heteroatoms.[1] These interactions can be direct, as in the redox system shown in equation (1):-



.....(1)

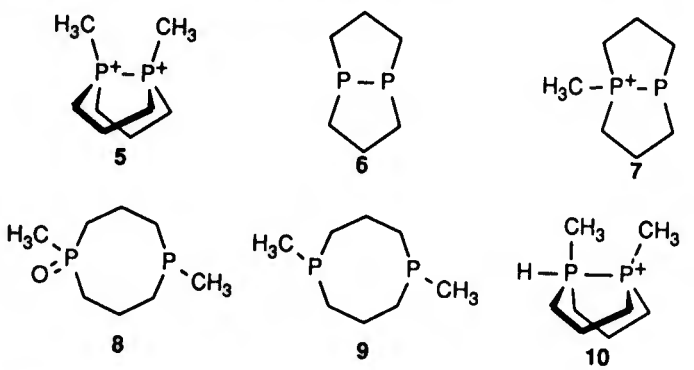
They can also occur via a third atom, as in transannular and intrabridgehead hydrogen bonding.



1 **2** **3** **4**

Neutron diffraction structures of **1** and **2** show that **1** has a linear symmetrical hydrogen bond, but the nearly-linear hydrogen bond in **2** is of the double minimum type. In **3** and **4**, the hydrogen bonds induce structural anomeric effects in the aminal units.

Second row elements like phosphorus offer further possibilities for interactions, and we have recently begun to explore these. Dication **5**, prepared from the known **6**,[2] via **7**, may be electrochemically active (cf. equation (1)). Dication **5** is very water-sensitive, hydrolysing rapidly to **8**, which can be reduced to diphosphine 9; this may be a useful ligand for transition metals. Will **9** protonate like the corresponding diamine to give a transannularly hydrogen-bonded cation? Preliminary evidence suggests that this and related diphosphines do something quite different; they protonate with P-P bond formation to give ions like **10**!



5 **6** **7** **8** **9** **10**

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1 R. W. Alder, *Tetrahedron*, **1990**, *46*, 683-713.
2 K. Issleib and P. Thorausch, *Phosphorus and Sulphur*, **1978**, *4*, 137-144.

NOVEL ENTRY TO THE TROPANE SYSTEM BY REACTION OF RHODIUM(II) ACETATE STABILIZED VINYLCARBENOIDS WITH PYRROLES

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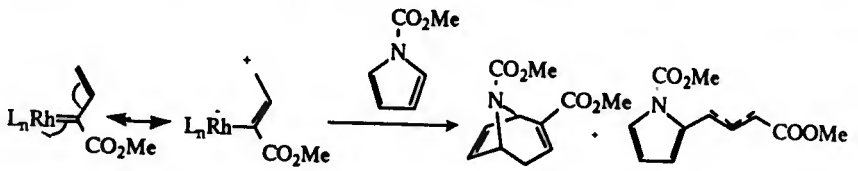
The 8-azabicyclo[3.2.1]octane structure is the basic skeleton of the tropane alkaloids. A new process to generate this system based on the reaction of rhodium stabilized vinylcarbenoids with pyrroles will be described. Vinylcarbenoids have been shown to react with dienes, resulting in a direct entry into seven-membered rings.[1-4] The transformation proceeds by a tandem cyclopropanation/Cope rearrangement, which ensures that excellent stereocontrol is obtained. Further extension of this chemistry to pyrroles, would allow a direct access into the tropane system.

Vinylcarbenoids with two electron withdrawing groups readily form 8-azabicyclo[3.2.1]octadienes on reaction with N-(alkoxycarbonyl)pyrroles.[4] The reaction of vinylcarbenoids possessing a single electron withdrawing group is complicated because these intermediates exhibit electrophilic character at the vinyl terminus as well as the carbenoid center. Due to this unprecedented reactivity, significant quantities of alkylation products are formed instead of the bicyclic structures. By appropriate choice of solvent and ligands, however, the bicyclic structures can be made to become the exclusive products. Recent studies applying this chemistry to actual natural products as well as compounds of neurochemical interest will be discussed.



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1. Davies, H. M. L.; Smith, H. D.; Korkor, O. *Tetrahedron Lett.* 1987, **28**, 1853.
2. Davies, H. M. L.; Clark, D. M.; Alligood, D. B; Eiband, G. R. *Tetrahedron* 1987, **43**, 4265.
3. Davies, H. M. L.; McAfee, M. J.; Oldenburg, C. E. M. *J. Org. Chem.* 1989, **45**, 930.
4. Davies, H. M. L.; Young, W. B.; Smith, H. D. *Tetrahedron Lett.* 1989, **30**, 4653.

FURTHER ADVENTURES IN N-NITROPYRAZOLE TERRITORY

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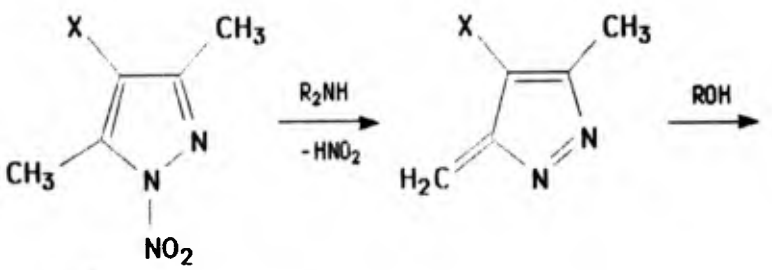
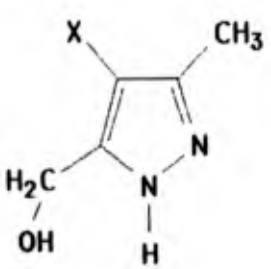
The chemistry of N-Nitroazoles has been extensively studied over the past two decades in Leiden[1]. One of the reactions reported is a functionalization of a CH_3 group[2]. Reacting **1a** with amines in alcohol solution gives the hydroxymethyl- and alkoxymethylpyrazoles **2a** and **3a**. We assume that the first step is the formation of a diazafulvene followed by addition of H_2O and ROH

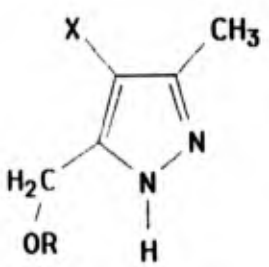


1, a: X=NO_2



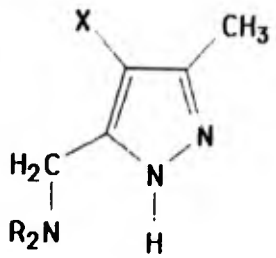
2, a: X=NO_2

\+



3, a: X=NO_2
R=CH_3, C_2H_5 or $isoC_3H_7$

We will discuss the reaction of N-Nitropyrazoles **1b-d** (X=Cl, Br, I) affording the di-alkylaminomethylpyrazoles **4** in excellent yields.



4, X=Cl, Br, or I

R_2N- = piperidyl, pyrrolidyl, morpholyl or $(C_2H_5)_2N$-

We will also present the results of reacting **1b-d** with an excess of DBU and DBN.

1. Leading references: C.L.Hebraken et al, *J.Org. Chem.*, **36**, (1971) 3081, 3084; **42**, (1977), 2893; **44**, (1979),4156; **49**, (1984), 2197, 3310; **51**, (1986), 4656 and *J. Heterocyclic Chem.*, **24**, (1987), 1653. J.G.Buchanan et al, *Progress in the Chemistry of Organic Natural Products*, **44**, (1983), 243-299; *J. Chem. Soc. Perkin Trans.* **1**, (1989), 925.
2. C.L.Hebraken and S.M.Bonser, *Heterocycles*, **7**, (1977), 259.

ASYMMETRIC SYNTHESIS VIA THE AZA-DIELS-ALDER REACTION

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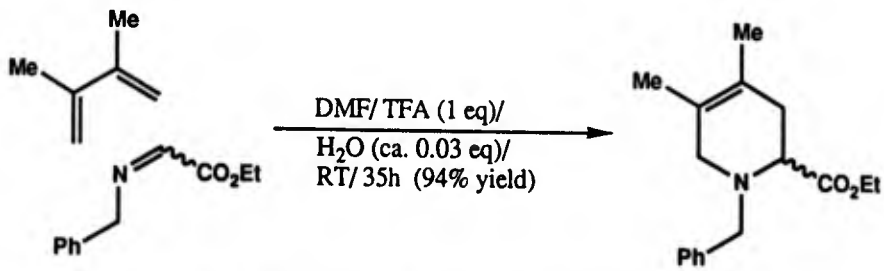
Summary. Optically active pipecolic acid derivatives can be prepared by the aza-Diels-Alder reaction of simple dienes with the imine derived from ethyl glyoxylate and chiral 1-phenylethylamine; the cyclo-addition reactions are regio-specific, highly diastereo-selective within the heterocyclic ring (>92% *exo* with cyclic dienes, and 100% *endo* with acyclic dienes), and lead to high asymmetric induction in most cases (average d.e. = 72%).

The piperidine ring system is one of the most commonly occurring heterocyclic units in natural products; short, versatile, stereo-controlled routes to substituted piperidines are consequently of great value. One of the most attractive synthetic approaches is to use aza-Diels-Alder chemistry, and we recently described the reaction of $PhCH_2N{=}CHCO_2Et$ with a range of dienes (Tetrahedron Lett., 1989, 30, 6781); for example, in the presence of TFA (1 eq) and H_2O (cat.), the adduct with 2,3-dimethylbutadiene could be obtained in 94% yield (Scheme 1), and reactions with other dienes enabled us to show that the cyclo-additions were regio-specific and highly diastereo-selective.

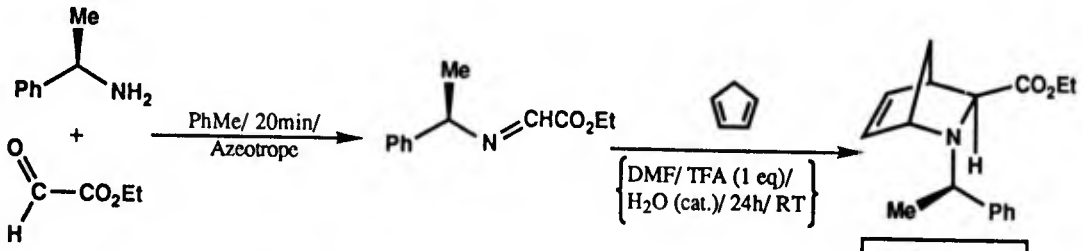


Scheme 1. Reaction between 2,3-dimethylbutadiene and $PhCH_2N{=}CHCO_2Et$

A simple, yet important, extension of this chemistry was to replace the achiral benzyl group on the imine by a chiral 1-phenylethyl moiety, in order to generate optically active pipecolic acid derivatives. We were hopeful that high asymmetric induction might be observed because the chiral carbon of the auxiliary would be bonded directly to one of the atoms involved in the cyclo-addition reaction.

Formation of the chiral imine was readily achieved by condensation of (R)-1-phenylethylamine with ethyl glyoxylate, and the Diels-Alder reactions were conducted using the standard conditions developed from the achiral work. The cyclo-adducts were formed as single regio-isomers in all cases, and were isolated in moderate to high yields (average 53%, non-optimised), confirming the ease and efficiency of this procedure. The dienes employed included cyclopentadiene, cyclohexadiene, penta-1,3-diene, 2-methylbutadiene, 2,3-dimethylbutadiene and hexa-2,4-diene.

It was immediately apparent that the reactions had proceeded with excellent diastereoselectivity within the heterocyclic ring, and further studies revealed that the *exo* adducts were favoured using cyclic dienes (92-97% *exo*), whilst acyclic dienes yielded products resulting exclusively from an *endo* transition state. Moreover, the chiral auxiliary had effected high asymmetric induction in most cases, giving ready access to a range of optically active pipecolic acid derivatives [average diastereomeric excess (d.e.) = 72%]. Particularly noteworthy were the cyclopentadiene adducts, which were obtained in 82% yield; the major *exo* product (preferred over the *endo* isomer by a ratio of 30:1) was formed with a d.e. of 89% - see Scheme 2.



Scheme 2. The aza-Diels-Alder reaction between the chiral imine [derived from ethyl glyoxylate and (R)-1-phenylethylamine] and cyclopentadiene.

The cyclo-adducts from the Diels-Alder reactions contain a number of valuable features for further elaboration. In particular, the carboxylic ester gives access either to pipecolic acid derivatives, or to the enormous range of naturally occurring 2-alkylated piperidines, whilst regio- and stereo-controlled reactions on 4,5-didehydro derivatives of piperidine and pipecolic acid are well documented. Finally, the chiral auxiliary allows continuous monitoring of optical integrity, but can be readily removed by hydrogenolysis (H_2/ $Pd(OH)_2$-C).

Thus, the chiral imine derived from optically active 1-phenylethylamine and ethyl glyoxylate is an effective dienophile in the aza-Diels-Alder reaction; in the presence of TFA (1 eq) and water (catalytic), the cyclo-adducts can be obtained in a single step in moderate to high yields, with complete control of regiochemistry, and with excellent *exo/endo* selectivity. Moreover, high asymmetric induction is observed in most cases (average 72% d.e.) and, as both enantiomers of 1-phenylethylamine are readily available, the method is applicable to the synthesis of either (R)- or (S)-pipecolic acid derivatives. We are currently determining the absolute stereochemistry of a number of such derivatives, in order to ascertain the direction of asymmetric induction, and we are also elaborating key aza-Diels-Alder adducts towards natural product target molecules such as carpamic acid.

In this lecture, I would describe our stereocontrolled route to pipecolic acid derivatives, discuss the asymmetric induction that can be achieved (including the absolute stereochemistry of the products), and present our synthetic work directed towards naturally occurring piperidine alkaloids.

A NOVEL PYRROLE SYNTHESIS. A MODEL FOR THE BIOSYNTHESIS OF PORPHOBILINOGEN?

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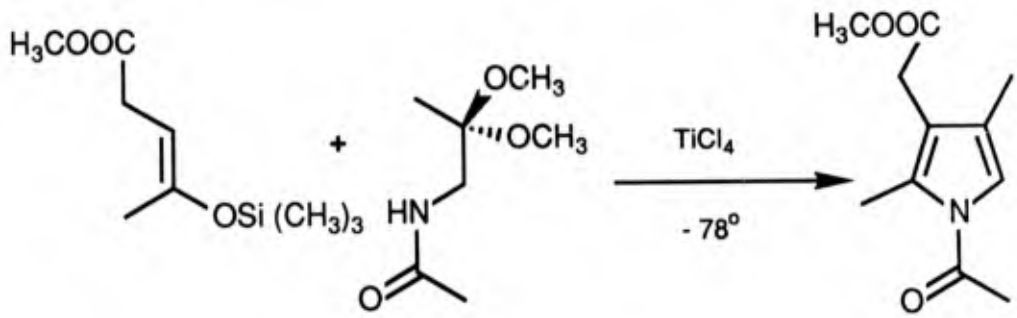
The importance of pyrroles stems from the fact, that they are the dominant sub-unit in the characteristic coloring matters of nature[1]. The biosynthetic pathway to the universal pyrrole building block, the porphobilinogen (PBG) has been used as stimulus for developping a new pyrrol synthesis.

Pyrroles can be obtained using a Lewis acid catalysed cross-aldol reaction. The process can give pyrroles via a two step sequence, aldol reaction intramolecular cyclisation, or in some cases directly in a one pot procedure[2].



The method allows to obtain alkyl substituted pyrroles in a regiospecific manner. The scope and the limits of this method will be presented and the analogy of this chemical process with the proposed mechanism for the formation of porphobilinogen by the enzyme δ-aminolevulinic acid dehydratase will be discussed.

To study the mechanism of the enzymatic process a series of inhibitors were synthesized. Three categories of inhibitors have been studied: substrate analogues, product analogues and finally inhibitors which resemble postulated intermediates of the enzymatic reaction sequence.

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2 Meunier, A., Neier, R., Synthesis **1988**, 381