7.22
Tricyclic Systems: Central Carbocyclic Ring with Fused Five- and Six-membered Rings

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7.22.1 INTRODUCTION
7.22.2 THEORETICAL METHODS
  7.22.2.1 Molecular Orbital Methods
  7.22.2.2 Molecular Mechanics and Related Methods
  7.22.2.3 Other Methods
7.22.3 EXPERIMENTAL STRUCTURAL METHODS
  7.22.3.1 X-ray Methods
  7.22.3.2 PE Spectroscopy
  7.22.3.3 IR Spectroscopy
  7.22.3.4 UV/Visible and Fluorescence Spectroscopy
  7.22.3.5 Mass Spectrometry
  7.22.3.6 NMR Spectroscopy
7.22.4 THERMODYNAMIC ASPECTS
  7.22.4.1 Solubilities and Chromatographic Behavior
  7.22.4.2 Tautomerism
7.22.5 REACTIVITIES OF FULLY CONJUGATED RINGS
  7.22.5.1 Electrophilic Attack at Carbon
  7.22.5.2 Nucleophilic Attack at Carbon
  7.22.5.3 Reactions With Radicals and Electron-deficient Species
  7.22.5.4 Reductions
7.22.6 REACTIVITIES OF NONCONJUGATED RINGS
  7.22.6.1 Isomers of Aromatic Compounds in Equilibrium with a Fully Conjugated Derivative
  7.22.6.2 Dihydro Derivatives
  7.22.6.3 Tetrahydro and Higher Derivatives
7.22.7 REACTIVITIES OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS
  7.22.7.1 Alkyl Groups
  7.22.7.2 Sulfur Groups
7.22.8 REACTIVITIES OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS
7.22.9 RING SYNTHESES
  7.22.9.1 Synthesis of Compounds with a Central Four-membered Ring
    7.22.9.1.1 With one heteroatom in each heterocyclic ring
    7.22.9.1.2 With two heteroatoms in one heterocyclic ring and one in the other
  7.22.9.2 Synthesis of Compounds with a Central Five-membered Ring
    7.22.9.2.1 With one heteroatom in each heterocyclic ring
    7.22.9.2.2 With two heteroatoms in one heterocyclic ring and one in the other
7.22.1 INTRODUCTION

There is no corresponding chapter in the first edition of Comprehensive Heterocyclic Chemistry (CHEC-I) that relates to the material presented here. Although some 6-4-5, 6-5-5, and 6-7-5 fused compounds have been reported, the great majority of tricyclic ring systems with a central carbocyclic ring and fused five- and six-membered heterocyclic rings are of the 6-6-5 variety. Of these, separate treatment has been reserved for the imidazo[4,5-g]-, imidazo[4,5-f]-, or imidazo[4,5-h]quinazoline-based benzo-separated purines (Section 7.22.12.1), the furocoumarins and furochromones (Section 7.22.12.2), the pyrrolo[3,2-g]isoquinoline-based tetracyclic ellipticines (Section 7.22.12.3), and the pyrrolo[2,3-f]quinoline quinone (PQQ) and related compounds (Section 7.22.12.4); each is an important class of compounds with special applications. Brief mention is made of two pyrrolo[3,4-g]quinoline-based tetracyclic ergolide drugs (Section 7.22.12.5). Although duocarmycins B1 and C1 (pyrindamycin B) are pyrrolo[3,2-f]quinoline-based members of an important new class of antitumor antibiotics \(<91JCA6645>\), these compounds are not covered in depth as the number of investigations on them is limited. Separate sections cover synthetic work related to the benzo-separated purines (Section 7.22.11.1), the furocoumarins and furochromones (Section 7.22.11.2), the ellipticines (Section 7.22.11.3), and PQQ and related compounds (Section 7.22.11.4). Structural formulae, equations, and schemes are presented fully in the synthetic sections, but only when there is a particularly strong reason to do so in the nonsynthetic ones.

7.22.2 THEORETICAL METHODS

7.22.2.1 Molecular Orbital Methods

Molecular orbital computational analysis by PM3–Cl–UHF semiemipirical methods have been used to support the contention that preferable HSOMO–LUMO interactions produce a favored biradical and explain the site selectivity in the sensitized photochemical \([2+2]\) cycloadduct formation of 2-pyrones with electron-deficient ethylenes \(<92BCJ354>\). The lowest ionization energies, dipole moment, and dominant electronic configurations of a 5-methylidenated version of 7-nitrosooxazol[4,5-g]cyclopenta[e]pyrimidine of unknown origin were calculated by the ADC(3) \textit{ab initio} method \(<92CPH11>\). An extensive semiemipirical and \textit{ab initio} investigation into the mechanism of oxidation of methanol by PQQ is cited in Section 7.22.12.4.
7.22.2.2 Molecular Mechanics and Related Methods

An ab initio computation of the structure of 5,6-dihydropyrrolo[3,2-\(h\)]quinoline at the STO-3G level provided data of importance to a Monte Carlo simulation study of the relative binding of guests dimethyl urea and imidazolodine to a macrocyclic host whose structure contains the above-mentioned quinoline as a hydrogen bond accepting and donating subunit \(\langle93JACS79\rangle\). The x-ray crystal structure of vernolepin, a 6-6-5 saturated tricyclic diactone, was used to help define the scope and limitations of a computer program written to conduct a systematic conformational analysis of saturated polycyclic ring systems \(\langle84T3729\rangle\).

7.22.2.3 Other Methods

In a demonstration that a spatial correspondence between apomorphine and certain ergoline alkaloids indicates their dopaminergic activity (DA) is due to binding at the same receptor site, the molecular electrostatic potential (MEP) patterns of heterocycles representative of substructures of the larger fragments were calculated by ab initio SCF computations at the HF/STO-3G level \(\langle86JMC1418\rangle\). Among the potent DA agonists central to this study were an octahydropyrrolo- and pyrazolo[3,4-\(g\)]quinoline, both tricyclic ergoline partial structures synthesized by Eli Lilly chemists.

7.22.3 EXPERIMENTAL STRUCTURAL METHODS

7.22.3.1 X-ray Methods

Of the x-ray crystal structure determinations made of 6-4-5, 6-5-5, 6-6-5, and 6-7-5 fused heterocycles, many are of furocoumarin/furochromone, ellipticine, and PQQ derivatives because of their importance to biomedical investigations. Mention is made of these in their respective sections (7.22.12.2–7.22.12.4). A bibliography which lists the remaining structures, arranged according to central ring size and ring system formula, is presented in Table 1.

<table>
<thead>
<tr>
<th>System</th>
<th>Formula</th>
<th>Heterocyclic base unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–4–5</td>
<td>C(_6)O–C(_7)–C(_8)N</td>
<td>3-Oxa-11-azatricycl[6.3.0.1(0^2)]undecane</td>
<td>90CPB370</td>
</tr>
<tr>
<td>6–5–5</td>
<td>C(_6)O–C(_7)–C(_8)O</td>
<td>5,9-Dioxatricycl[6.4.0.0(1^2)]dodecanol</td>
<td>90JCS(P1)751</td>
</tr>
<tr>
<td>6–6–5</td>
<td>C(_6)N–C(_7)–C(_8)N</td>
<td>Pyrrolo[3,4-f][benz][pyran, decahydro-</td>
<td>90JOC3555, 93JOC4979</td>
</tr>
<tr>
<td>C(_6)N–C(_7)–C(_8)O</td>
<td>Pyrrolo[3,2-f]isoquinoline, octahydro-</td>
<td>84JOC5109</td>
<td></td>
</tr>
<tr>
<td>C(_6)N–C(_7)–C(_8)N</td>
<td>Pyrrolo[2,3-g]quinoline, dihydro-</td>
<td>91AX(C)561</td>
<td></td>
</tr>
<tr>
<td>C(_6)N–C(_7)–C(_8)N</td>
<td>Pyrazolo[3,4-g]quinoline, octahydro-</td>
<td>83JMC1112</td>
<td></td>
</tr>
<tr>
<td>C(_6)N–C(_7)–C(_8)NO</td>
<td>Oxazolo[5,4-f]isoquinoline, tetrahydro-</td>
<td>92AX(C)1243</td>
<td></td>
</tr>
<tr>
<td>C(_6)N–C(_7)–C(_8)NS</td>
<td>Thiazolo[4,5-f]quinoline, hexahydro-</td>
<td>91JMC2736</td>
<td></td>
</tr>
<tr>
<td>C(_6)N–C(_7)–C(_8)NS</td>
<td>1,2,5-Thiadiazolo[3,4-d]quinaxoline, dihydro-</td>
<td>92H(33)337</td>
<td></td>
</tr>
<tr>
<td>C(_6)N–C(_7)–C(_8)NS</td>
<td>1,2,3-Thiadiazolo[5,4-f]isoquinoline, tetrahydro-</td>
<td>89JMC1566</td>
<td></td>
</tr>
<tr>
<td>6–7–5</td>
<td>C(_6)O–C(_7)–C(_8)O</td>
<td>2,9-Dioxatricycl[9.3.0.1(4^2)]tetradecane</td>
<td>90AX(C)875</td>
</tr>
</tbody>
</table>

In addition to focused crystallographic structural studies, x-ray methods have been applied to problems of developing models for the topography of enzymes' active sites, or inhibitors of the same. For example, the x-ray crystallographically derived structural parameters of three 7-alkylated 2,4-diaminopyrrolo[3,2-f]quinazolines were among 62 of these heterocycles employed in the 3D QSAR development of a distance geometry model for the inhibition of dihydrofolate reductases \(\langle84JMC901\rangle\). Finally, in an application of an iterative protein crystal structure analysis approach to enzyme inhibitor design, a set of novel imidazolo[4,5-g]tetrahydroquinoline inhibitors of thymidylate synthetase was developed in a systematic fashion by using newly generated enzyme–inhibitor complex data as feedback for structural modification \(\langle92JMC847\rangle\).
7.22.3.2 PE Spectroscopy

The 5-methylidenated version of 7-nitrosooxazolo[4,5-g]cyclopenta[e]pyrimidine (1) was the only tricyclic ring structure among 36 heterocycles examined by ab initio computational analysis for their lowest ionization energies related to experimentally determined molecular photoelectron spectroscopic (PES) data \(92\text{CPH11}\). It is not clear if this compound’s preparation has been reported, nor whether its PE spectrum has ever been obtained.

![Image](1)

7.22.3.3 IR Spectroscopy

The assignment of lactone ring size (six instead of five) in an f-fused benzofuran tricycle was confirmed by an IR absorption frequency for the lactone carbonyl group present at 1740 cm\(^{-1}\), instead of at 1760 cm\(^{-1}\) where it is present in a known 5-6-5 analogue \(85\text{JCS(P1)747}\). The absence of a C=S IR stretching frequency at 1250 cm\(^{-1}\) in (pyrano[2,3-g]benzothiazol-2-yl)benzamides distinguished them from the isomeric thiol-substituted pyrimidy[5,4-f]-fused flavones \(94\text{BCJ2326}\). The IR spectrum of 1,4-benzodioxano[6,7-c]furoxan was found to exhibit characteristic bands in the 1580–1620 cm\(^{-1}\) region \(88\text{JHC803}\).

7.22.3.4 UV/Visible and Fluorescence Spectroscopy

9-(Phenylsulfonyl)furo[2,3-g]quinoline and its parent unsubstituted heterocycle were found to have very similar absorption maxima; hence, the sulfone group does not provide an additional conjugative effect \(83\text{JOC774}\). In addition, furo[2,3-g]quinoline and its isomeric furo[3,2-g] counterpart were found to exhibit UV absorption maxima that are almost identical. An absorption maximum at 435 nm consistent with the presence of a 2H-1,4-benzothiazine chromophore was one of the key pieces of data that enabled the structure determination of compounds based upon the new 1,2-dihydro-3H,8H-pyrrrolo[2,3-h][1,4]benzothiazine skeleton \(87\text{T5357}\). The UV spectrum of 1,4-benzodioxano[6,7-c]furoxan was found to exhibit four characteristic band maxima in the 350–480 nm region \(88\text{JHC803}\).

Many of the fully aromatic 6-6-5 tricycles show good fluorescence properties, and in some instances this has been utilized in biochemical applications. The reader is directed to the literature cited in Section 7.22.12.1 (benzo-separated purines) for examples of how the sensitivity of the fluorescence properties of tricyclic fluorophores to environmental conditions can be utilized to analyze the binding parameters associated with biomacromolecules. Of particular interest in this regard is a method known as fluorescence–polarization titration \(83\text{B2347}\).

7.22.3.5 Mass Spectrometry

The use of mass spectrometry for structure identification is of particular importance to studies in which the quantity of analyte is limited. For example, certain carcinogenic monoamino, dialkylated imidazo[4,5-f]quinoxalines and imidazo[4,5-f]quinolines present in a few ppb in heated food of
muscle origin have been identified in this way \(<92M\text{I }722-01, 92M\text{I }722-02\>). When the quantity of material is more substantial, however, complex fragmentation patterns such as the positive ion generated from saturated tricyclic acetal lactone (2) can be elucidated \(<90\text{JPR}122\>.

![Image](2)

### 7.22.3.6 NMR Spectroscopy

Often used in concert with mass spectrometry, NMR spectroscopy remains an invaluable structural diagnostic tool of particular importance to tricyclic natural products chemistry. For example, the tricyclic phenolic compound moracin P (3) was one of eight previously known compounds identified together with two new isoprenoid-substituted flavanones in isolates of the root bark of mulberry trees \(<89\text{H}(29)807\>). In a series of studies of 6-7-5 tricyclic natural products, 1D and 2D \(^1\)H and \(^13\)C NMR spectroscopy were employed extensively in the structure determination of sesquiterpene lactones (4)-(8) found among the aerial natural products of toxic plants \(<85\text{P}1378, 90\text{P}551, 90\text{P}3875\>.

![Image](4)

![Image](5)

![Image](6)

![Image](7)

![Image](8)

In another example of the utility of NMR to structure determination, \(^13\)C—\(^13\)C chemical shift-correlated NMR spectroscopy has been used to establish the regioisomeric identity of a disubstituted dihydropyrrolo[2,3-\(h\)]quinoline (9) \(<91\text{A8687}\>). The structure of one (LL-D253\(\gamma\)) of the two minor metabolites of an antibiotic chromone has been revised to that of (10) with the help of \(^1\)H-coupled \(^13\)C NMR spectral analyses of related chromones that revealed diagnostic \(^1\)H—\(^13\)C long-range couplings \(<92\text{JCS}(P)12271\>.

![Image](9)

![Image](10)

The stachybotrins A and B (11) and (12), two new aromatic alkaloids with antibacterial and antifungal activity, were isolated from an aquatic isolate of a new species of the genus *Stachybotrys*
Tricyclic Systems: Central Carbocyclic Ring, 5- and 6-membered Rings

Their structures were determined primarily by analysis of high field 2D (HMBC, HMQC, COSY, and NOESY) NMR data.

A correction of structure from (13) to the azaphilone structure (14) for monochaetin, a metabolite elaborated by the fungus Monochaeta compta, was made possible by examination of the long-range $^1H$-$^{13}C$ connectivity pattern as determined by the heteronuclear selective population inversion (SPI) NMR technique $^{86}JCS(P1)1975$.

One of six chromenone glycosides isolated from the tubers of Eranthis hyemalis and structurally identified by a combination of FAB–MS and 2D (COSY, COLOC) NMR techniques was compound (15), a $\beta$-d-glucopyranoside of 7-(hydroxymethyl)-2,3-dihydro-2-(1-hydroxy-1-methylethyl)-4-methoxy-5$H$-furo[3,2-$g$][1]benzopyran-5-one $^{91}HCA611$.

Some unusual substituent-derived chemical shift effects have been noted in certain tricyclic systems. Upon formation of 9-(phenylsulfonyl)furo[2,3-$g$]quinoline by furan ring annelation $^{83}JOC774$), an unusually strong deshielding (to ca. 9.7-9.75 ppm) of the former C-4 proton of the quinoline (the C-8 one in the furoquinoline numbering system) was noted. The assumption was that the formation of the third ring of the tricyclic system forced the sulfone substituent into a conformation which causes deshielding of the (former) C-4 proton. Together with UV spectroscopic data, a close examination of the $^1D$-$^1H$ and $^1H$-$^{13}C$ NMR spectral characteristics was sufficient to permit the structure determination of compounds based upon the new 1,2-dihydro-$3H,8H$-pyrrolo[2,3-$h$][1,4]benzothiazine skeleton $^{87}T5357$.

7.22.4 THERMODYNAMIC ASPECTS

7.22.4.1 Solubilities and Chromatographic Behavior

Both analytical LC and quantitative TLC have been used successfully in the separation of all the regioisomers ([2,3-$g$] vs. [2,3-$h$]) and stereoisomers (trans-fused vs. cis-fused) of octahydro, pyrrolo-fused isoquinolines $^{84}JOC5109$.
7.22.4.2 Tautomerism

In a study reporting the resolution and x-ray crystal structure-determined absolute configuration of trans-4,4a,5,6,7,8a,9-octahydro-5-propyl-1H(or 2H)-pyrazolo[3,4-g]quinoline, an ergoline-related dopamine agonist, it was noted that in the solid state, the pyrazole ring is protonated on the 1-nitrogen rather than on the 2-position \(<83\text{JMC1112}\>). It was suggested that solutions contain a mixture of the 1 and 2 protonated tautomers. The rapid degenerate equilibrium between 1,4-benzodioxano[6,7-c]furoxan N-oxide forms has been probed by variable temperature \(^1\)H NMR, and a \(\Delta G^*\) of 13.1 kcal mol\(^{-1}\) for this process was calculated \(<88\text{JHC803}\>.

7.22.5 REACTIVITIES OF FULLY CONJUGATED RINGS

7.22.5.1 Electrophilic Attack at Carbon

As expected, the 1-position of 8,9-dihydropyranol[3,2-e]indoles is susceptible to acylation under conditions (POCl\(_3\)/DMF, oxaly chloride) known to be effective at the 3-position of indoles \(<92\text{JMC3625}\>). The electrophilic introduction of fluorine into the furan ring of the furochrome nucleus of khellin has been accomplished \(<87\text{TL4003}\>\) in excellent yield (82–84\%) by the action of either BrF (HF/dibromantin/THF/\(\text{CH}_2\text{Cl}_2/4\text{°C}\)) or poly HF/NBS/\(\text{CH}_2\text{Cl}_2/0\text{°C}\) to afford trans-3-bromo-2-fluoro-2,3-dihydrokhellin (16). These methods nicely circumvent the problem of oxidative demethylation known to be associated with treatment of benzofurans with \(\text{CF}_3\text{OF}\) in freon at \(-78\text{°C}\). Transformation of compound (16) into other 2,3-disubstituted-2,3-dihydrokhellins and into the 2-fluoro and 3-fluoro versions of khellin itself was accomplished.

![Diagram](image)

The substitution pattern of TIOH-mediated electrophilic aminomethylation of psoralens (furocoumarins) by \(N\)-(hydroxymethyl)phthalimide has been elucidated \(<85\text{JHC75}\>). Multiple phthalimidoated adducts were obtained when a B-ring hydroxy or methoxy activating group was present, and these resisted simple cleavage with \(\text{NH}_2\text{NH}_2\). However, this two-step procedure to aminomethyl group introduction worked well when the psoralens contained only methyl substituents.

7.22.5.2 Nucleophilic Attack at Carbon

Nitrogen nucleophiles in the form of aryl amines readily displace a chloro substituent at the 9-position of the 1H-pyrazolo[3,4-f]quinoline \(<92\text{JMC4595}\>\) and 1H-imidazo[4,5-f]quinoline ring systems \(<92\text{BC1579}, 92\text{JMC4595}\>\). Similarly, aryl hydrazines readily displace the chloro group of 8-(ethoxycarbonyl)-substituted 9-chloropyrazolo[4,3-f], [3,4-f]-, and imidazo[4,5-f]quinolines, but this is then followed by spontaneous cyclization to give the pyrazolones \(<90\text{JMC2640}\>\). 4,9-Dibromo-1,2,5-thiadiazole[3,4-g]quinoxaline has been found unreactive towards nucleophilic displacement by \(t\)-butylmalononitrile or malononitrile anion in the presence of palladium(II) catalyst \(<92\text{H(33)337}\>\).

7.22.5.3 Reactions With Radicals and Electron-deficient Species

In the potentially biomimetic transformation shown in Equation (1), a photogenerated aryl(methylene)oxyl radical generated by fragmentation of a thioxopyridyl ester undergoes 6-endo cyclization onto the 5-position of an isoflavone, and the radical cycloadduct formed apparently abstracts a pyridinemethio moity and undergoes a thermal elimination of pyridine-2 thiol to give the pentacycle \(<89\text{CC1613}\>\). Without the unsaturation such as that introduced in this last step, the central rings of compounds like (17) are known to be susceptible to ring opening upon treatment with primary amines \(<86\text{H(24)1109}\>\).
7.22.5.4 Reductions

TCNQ derivatives fused with 1,2,5-thiadiazolo and pyrazino units (4,9-bis(dicyanomethylene)-1,2,5-thiadiazolo[3,4-f]quinoxalines) undergo reversible four-stage one-electron reductions, as determined by cyclic voltammetry \(\langle 92\text{JMC}337\rangle\).

7.22.6 REACTIVITIES OF NONCONJUGATED RINGS

7.22.6.1 Isomers of Aromatic Compounds in Equilibrium with a Fully Conjugated Derivative

Oxazolo[4,5-h]quinolin-2(3H)-ones could be acylated effectively at the N-3 position with reagents such as AcCl, ethyl chloroformate, trans-cinnamoyl chloride, and dimethyl carbamoyl chloride \(\langle 85\text{JMC}1255\rangle\).

7.22.6.2 Dihydro Derivatives

Most of the reports on the reactivity of dihydro derivatives of the tricycles are concerned with the ease of oxidation to fully aromatic ring systems. Certain 6,7-dihydropyranol[2,3-f]indazol-2(7H)-ones have been found to be very resistant to full aromatization upon treatment with DDQ in refluxing benzene, providing the pyranol[2,3-f]indazol-2(7H)-ones in only two instances after extended (12 d) reaction time \(\langle 84\text{JHC}361\rangle\). On the other hand, methyl 1,2-dihydro-3H,8H-pyrrolo[2,3-f][1,4]benzothiazine-2-carboxylates not bearing a 2-alkyl substituent were found to be quite reactive towards a presumed autoxidative decomposition to red orange oligomeric materials \(\langle 87\text{T}5357\rangle\). Yet a third reactivity has been found for certain 4,5-dihydrothiazolo[4,5-f]quinolines, which in 8-cyano-7-oxo-4,5,6,7-tetrahydro form was found to require aeration in refluxing EtOH (2 h) in the presence of DBU to afford the 4,5-unsaturated derivative (77%) \(\langle 89\text{H}(29)1517\rangle\).

7.22.6.3 Tetrahydro and Higher Derivatives

The furan ring of the N-benzyl furan-fused tetrahydroquinolinequinone \((18; X = O)\) suffers reduction under debenzylation conditions \((H_2, \text{Pd/C})\) affording compound \((19)\) (89%) \(\langle 91\text{JOC}6379\rangle\). The thiophene derivative \((18; X = S)\) gives a similar overreduction product, but in low yield only,
even when one equivalent of palladium is used. The N-benzyltetrahydropyridine rings of both systems (18), however, are easily oxidized with three equivalents of DDQ in benzene to give the quinolinequinones (20) (35–37%).

![Chemical Structures](image)

7.22.7 REACTIVITIES OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

7.22.7.1 Alkyl Groups

Decarboxylation of 5,7-dimethyl-8-oxo-6-aza-8H-indeno[2,1-b]thiophene-4-carboxylic acid could be effected by heating an admixture of it and copper powder (87H(26)1535). Direct sublimation in vacuo afforded the desired product (58%). 9-Chloro-2- and 3-methyltriazolo[4,5-f]quinoline-7-carboxylic acids are decarboxylated under similar conditions (93H(36)259). The cyano group of 8-cyano-7-oxo-4,5,6,7-tetrahydrothiazolo[4,5-f]quinolines can be converted into an amino group by conc. HCl mediated hydrolysis to the amide, followed by Hofmann rearrangement (89H(29)1517).

7.22.7.2 Sulfur Groups

Reductive desulfurization of 9-(phenylsulfonyl)furo[2,3-g]quinoline and its 2-methyl derivative can be effected by treatment with LAH in THF solution at reflux, but proceeded poorly with aluminum amalgam, the reagent of choice for the reductive cleavage of vinyl sulfones (83JOC774). Raney nickel was used to remove a thiomethyl substituent from the central ring of a furochromone direct precursor to visnagan (89JOC4481).

7.22.8 REACTIVITIES OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

Although reactions at ring heteroatoms have been conducted and reported on members of this class of heterocycles, in general the outcome of these is not reflective of a unique characteristic of the tricyclic framework.

7.22.9 RING SYNTHESSES

7.22.9.1 Synthesis of Compounds with a Central Four-membered Ring

7.22.9.1.1 With one heteroatom in each heterocyclic ring

4-Ethoxycarbonyl-5-phenyl-1H-pyrrole-2,3-dione (a dioxopyrrolone) undergoes head-to-tail regiochemical photocycloaddition with dihydropyran to give the cis-syn-trans adduct (21) in 19% yield (Equation (2)) (90CPB370). The structure and stereochemistry of this product, which arises via a $[\pi2s + \pi2a]$ process in an endo encounter complex, was determined by x-ray analysis.
Dihydro-4H-thiin-4-one, upon irradiation in neat furan, affords the tricyclic photoproduct (22) isolated in 5% yield after chromatographic separation (Equation (3)) \(92\text{HCA}1925\). This product is also formed (by GC) when 1:1 furan/MeCN or furan/MeOH is employed as solvent. Excitation of the dihydrothiinone is thought to be followed by an intersystem crossing, producing a triplet that reacts with furan to give a triplet 1,4-biradical intermediate as a mixture of diastereomers. Intersystem crossing from this mixture then provides the singlet biradical diastereomer from which the product is derived.

\[
\begin{align*}
\text{O} &+ \text{O} \quad \text{hv} \quad 5\% \\
(22) & \\
\end{align*}
\]

As shown in Equation (4), the sensitized irradiation of a mixture of 4,6-dimethyl-2-pyrone and maleic anhydride, or of 4,6-dimethyl-5-ethoxycarbonyl-2-pyrone and maleimide, gives the mixed photoadducts (23) and (24) in ca. 20% yields \(90\text{BCJ}3456, 92\text{BCJ}354\). As with many other \([2 + 2]\) cyclocondensation reactions involving heterocycles, these are thought to proceed via biradical intermediates.

\[
\begin{align*}
\text{O} &+ \text{O} \quad \text{hv, sens.} \quad 19-20\% \\
(23) & R=H, X=O \\
(24) & R=\text{CO}_2\text{Et}, X=\text{NH} \\
\end{align*}
\]

7.22.9.1.2 With two heteroatoms in one heterocyclic ring and one in the other

Sensitized UV irradiation of 1,3-dimethyluracil with 1-methyl-3,4-dibromomaleimide in acetone solution gives the cis-anti-cis-[2 + 2] cycloadduct (25) (41%) (Equation (5)) \(83\text{AG(E)161}\). The presence of methyl substituents at the C-5, C-6, or both of these loci resulted in a severe reduction of yield (1–8%). With 1,3,5-trimethyluracil as starting material, a small amount of the cis-syn-cis-[2 + 2] cycloadduct (3%) was obtained along with the cis-anti-cis-isomer. For the latter, a diamagnetic shifting of the C–Me group by the imide C=O moiety was noted in its \(^1\text{H}\) NMR spectrum.

\[
\begin{align*}
\text{O} &+ \text{O} \quad \text{hv} \quad 1-41\% \\
(25) & R^1=\text{H}, \text{Me}; R^2=\text{H}, \text{Me} \\
\end{align*}
\]

Photochemical cyclocondensation of 1,3-diacetylimidazolin-2-one with 3,4-dihydro-2-methoxy-2H-pyran in acetone solution gives a mixture of four stereoisomeric [2 + 2] cycloaddition products.
(26) in 75–80% combined yield. A single isomer can be obtained by recrystallization (Equation (6)) \<83CJC1158>. The mixture of photoadducts was further elaborated, in nine steps, to (±)-biotin.

\[
\begin{align*}
\text{MeO} & \quad \text{N} \\
\text{MeO} & \quad \text{N}
\end{align*}
\]

\[
\text{hv} \quad 75–80\%
\]

\[\text{(26)}\]

7.22.9.2 Synthesis of Compounds with a Central Five-membered Ring

7.22.9.2.1 With one heteroatom in each heterocyclic ring

(i) By synthesis of a heterocyclic ring

Acid-catalyzed removal of a TMS protecting group from a bicyclic lactone in methanol solution proceeded with intramolecular acetylation after conjugate addition of methanol to an α,β-unsaturated ketone side chain. By this route the 6-5-5 tricyclic acetal (27) is obtained in excellent yield (Equation (7)) \<90JCS(P1)751>. Hemiacetal derivatives of the acetics were also prepared, and were found to exist in equilibrium with their open hydroxy-ketone forms by \(^1\)H NMR.

\[\text{TMSO}^{\text{MeOH, } H^+} \quad \text{RO} \quad \text{MeO} \quad \text{OMe} \quad \text{MeOH, } H^+ \quad \text{RO} \quad \text{MeO} \quad \text{OMe} \]

\[\text{(27) } R=\text{Ph, } 3-\text{ClC}_6\text{H}_4\]

(ii) By synthesis of the carbocyclic ring

Cyclization of a 4-(3-thienyl)-3,5-pyridinedicarboxylic acids in hot H\(_2\)SO\(_4\) was shown to be a viable route to the substituted 8-oxo-6-aza-8\(H\)-inden0[2,1-\(b\)]thiophenes (e.g. (28)) (Equation (8)) \<87H(26)1535>. In the case of the dimethylated carboxylic acid shown, the neutral tricyclic heterocycle (28) is obtained in 21% yield.

\[\text{29} \quad \text{H}_2\text{SO}_4 \quad 21\% \quad \text{29} \quad \text{H}_2\text{SO}_4 \quad 21\% \]

(iii) By synthesis of two contiguous rings

Chromium- and molybdenum-based carbene complexes condense with ketoalkynes along a CO insertion pathway to afford tricyclic pyran-containing lactone products (29) in variable yield (Equation (9)) \<90JA1645, 91JA5459>. 

\[\text{29} \quad \text{H}_2\text{SO}_4 \quad 21\% \quad \text{29} \quad \text{H}_2\text{SO}_4 \quad 21\% \]
7.22.9.2.2 With two heteroatoms in one heterocyclic ring and one in the other

As shown in Equation (10), the 1,3-dipolar cycloaddition of in situ generated carboethoxyformonitrile oxide to a dihydropyran has been used to construct the terminal isoxazoline ring of the tricyclic heterocycle (30) \(^*\). The \([\pi_4s + \pi_2s]\) pericyclic product is obtained as a 70/30 inseparable mixture of diastereomers in 50% yield.

\[
\begin{align*}
(\pm) & \quad \text{Pri} \quad \text{O} \\
\text{EtO}_2C-\text{C}=\text{N}-\text{O} & \quad \xrightarrow{50\%} \quad \text{Pri} \quad \text{O} \\
(\pm) & \quad \text{CO}_2\text{Et} 
\end{align*}
\]

In an early step in an enantioselective total synthesis of certain prostaglandins \(^*\), application of the Prins reaction conditions to an unsaturated bicyclic lactone or ether (Equation (11)) afforded tricyclic heterocycles (31) containing cyclopentane-fused tetrahydrofuran and 1,3-dioxane units in 4–10% yield. The major products in each case were bicyclic diacetate derivatives of the starting material.

\[
\begin{align*}
(\pm) & \quad \text{O} \\
\text{X} & \quad \xrightarrow{(\text{CH}_2\text{O})_2, \text{HOAc, cat. } \text{H}_2\text{SO}_4, 4\text{–}10\%} \quad (\pm) \\
\text{X} & \quad \text{O} \\
(\pm) & \quad \text{N} \\
\text{H}_2 & \quad \text{O} \\
(31) & \quad X=\text{O}, \text{H}_2
\end{align*}
\]

7.22.9.2.3 With two heteroatoms in each heterocyclic ring

An intramolecular nitrile oxide cycloaddition reaction of a 1,3-dioxolane monocyclic precursor provided the construction of the two five-membered rings of the isoxazoline (32), a precursor to prostaglandin F\(_{2\alpha}\) (Equation (12)) \(^*\).

\[
\begin{align*}
\text{O} & \quad \text{X} \\
\text{N} & \quad \xrightarrow{\text{NaOCl, 65–75%}} \quad (\pm) \\
\text{O} & \quad \text{N} \\
(32) & \quad \text{O}
\end{align*}
\]

7.22.9.3 Synthesis of Compounds with a Central Six-membered Ring

7.22.9.3.1 With one heteroatom in each heterocyclic ring

(i) By synthesis of a heterocyclic ring

(a) By formation of one bond. A minor by-product in the pyrolysis (Equation (13)) of 7-allyloxy-5-methoxychromone has been assigned the structure of the dihydrofuran-fused 5-methoxychromone
Tricyclic Systems: Central Carbocyclic Ring, 5- and 6-membered Rings

(33) on the basis of its $^1$H NMR spectrum $^{92}$CS(Pl)2271. The major product (68\%) is the C-8 allyl-bearing 7-hydroxy-5-methoxychromone.

$$\text{(33)}$$

In a report describing new syntheses of substituted quinolines, furo[2,3-\textit{g}]quinolines (34) and (35) were prepared in high yield from the same 7-allylquinolinol (Scheme 1) $^{83}$JOC774. Reductive desulfonflylation of these tricycles with LAH gave 2-methylfuro[2,3-\textit{g}]quinoline (36) and the unsubstituted parent heterocycle (37), respectively. The latter could also be prepared in good yield by a simultaneous desulfurization-aromatization route from 5-(phenylsulfonyl)-6-oxo-5,6,7,8-tetrahydroquinoline. The versatility of this second route is demonstrated by the synthesis of the isomeric furo[3,2-\textit{g}]quinoline (38) shown in Scheme 2.

$$\text{(34)} \xrightarrow{i, I; \text{ii, DBU}} \text{(35)} \xrightarrow{i, \text{NaO}_4, \text{cat. OsO}_4; \text{ii, HOAc, H}_2\text{SO}_4} \text{(36)}$$

$$\text{LAH, THF, 66 °C} \xrightarrow{\text{HOAc, H}_2\text{SO}_4} \text{(37)}$$

$$\text{(38)}$$

Scheme 1

In an application of a novel radical chain reaction based on $O$-alkyl tin dithiocarbonates, the disubstituted dihydrofuro[3,2-\textit{h}]quinoline (39) was prepared in good yield from an 8-allyloxy-7-iodoquinoline precursor (Equation (14)) $^{92}$JA7909.

$$\text{(39)} \xrightarrow{\text{hv, 8 h, cat. (Ph}_3\text{Sn)}_2} \text{(39)}$$

A convenient access to fully unsaturated furo[3,2-\textit{h}]quinolines (40) via $S_{RN1}$ reactions between 5-chloro-7-iodo-8-isopropoxyquinoline and ketone enolates is shown in Equation (15) and affords these compounds in very good yield $^{87}$H(26)1863.
As shown in Equation (16), reaction of an allyl α-iodoaryl ether with tributyltin hydride in the presence of the activated alkene ethyl acrylate gives a mixture of 2-substituted dihydrofuro[3,2-h]quinolines (41) \(^\text{<89H(28)373>}\).

\[
\begin{align*}
\text{Cl} &+ \text{CO}_2\text{Et} &\xrightarrow{\text{Bu}^3\text{SnH, PhMe}} &\xrightarrow{72\% \text{ (combined)}} &\text{Cl} \\
\text{Cl} &+ \text{CO}_2\text{Et} &\xrightarrow{\text{Bu}^3\text{SnH, PhMe}} &\xrightarrow{72\% \text{ (combined)}} &\text{Cl} \\
\end{align*}
\]

The reduction of a nitroketone with H\(_2\) and Raney nickel in EtOH directly provided the bridged myosmine (42) (76%), presumably via an intermediate amino ketone which undergoes an intramolecular Schiff base cyclization (Equation (17)) \(^\text{<83JOC492>}\).

In one of the last transformations in a multistep synthesis of 1,2-dihydro-8-epi-vermolepin (43), nucleophilic intramolecular substitution at an iodomethyl group was promoted by heating an ester precursor with an equivalent of NaOAc in DMF (Equation (18)) \(^\text{<95TL311>}\). Molecular mechanics analysis of the precursor produced a minimum energy conformer that showed the hydroxyl substituent too distant from the iodomethyl group to have interfered with this high yield transformation.

As shown in Equation (19), 1-(2-dimethylaminoethyl)-8,9-dihydropyrano[3,2-e]indoles (44), rotationally restricted phenolic analogues of the neurotransmitter serotonin, were prepared in good yield from 5-hydroxyindoles in a cyclization reaction using an intramolecular variant of the Mitsunobu reaction \(^\text{<91TL3345, 92T1039>}\). The borane complex could be dissociated with CsF and Na\(_2\)CO\(_3\) in refluxing EtOH.
In a TTN-mediated oxidative rearrangement route to certain linear pyranoisoflavones, the aurones (2-alkylidene-6,7-dihydro-4-methoxy-7,7-dimethyl-5H-furo[3,2-g][1]benzopyran-3(2H)-diones) (45; R¹ = R² = H, OMe) were obtained in low yields (Equation (20)) \( \langle 89BCJ826, 92H(34)505 > \). A signal at \( \delta \) 6.45 ppm in the \(^1H\) NMR spectrum due to the benzylidene proton was noted as being characteristic of the aurone system.

The lactone (46) was obtained in 65% yield via reduction of a ketoester with sodium borohydride in MeOH and subsequent acidic workup (Equation (21)) \( \langle 90H(30)223 > \).

(b) By formation of two bonds. A study of the reaction of 2-substituted nitroarenes with vinyl Grignard reagents was undertaken to develop a new approach to the synthesis of 7-substituted indoles \( \langle 89TL2129 > \). One of the findings was that treatment of 5-nitroquinoline with three equivalents of vinylmagnesium bromide affords, upon workup, pyrrolo[2,3-f]quinoline (47) in moderate yield (Equation (22)).

As shown in Equation (23), the condensation of \( m \)-diacetylbenzene with two equivalents of 8-hydrazinoquinoline gives the bis(pyrido[3,2-g]indole) (48) in a Fischer synthesis upon cyclization of the intermediate bis(quinolinylhydrazone) with ppa \( \langle 93JA872 > \).

The improved synthesis of an antipsychotic pyrrolo[2,3-g]isoquinoline from an areca alkaloid shown in Scheme 3 \( \langle 84JOC5109 > \) began with a condensation of arecolone with dimethyl or diethyl malonate to give diketone (49). This diketone could be isolated and characterized as either the hydrochloride salt or the free base but was more conveniently subjected in crude form to Knorr
reaction conditions (2-oximido-3-pentanone, Zn, HOAc) affording the 1H-pyrrolo[2,3-\textit{g}]isoquinolin-4-one (50) in 45% overall yield. By analytical LC and quantitative TLC, this compound was found to be ca. 90% of the desired linear, trans-fused product. By-products present in the amounts of 6–11% and 1–3% were isolated and characterized as, respectively, the [2,3-\textit{g}] cis-fused and [2,3-\textit{h}] trans-fused isomers. X-ray crystallographic analysis was used to confirm the latter structure. A very minor by-product, detected by TLC, was believed to be the [2,3-\textit{h}] cis-fused isomer.

\[
\text{Me}^N\text{N} + \text{RO}_2\text{C}-\text{CO}_2\text{R} \xrightarrow{\text{ii}, \text{KOH}, \text{H}_2\text{O}; \text{iii}, \text{HCl}, \text{H}_2\text{O}} \text{Me}^N\text{N} + \text{RO}_2\text{C}-\text{CO}_2\text{R} \rightarrow \text{Me}^N
\]

(49)

In a model reaction used to support the structure identification of a neutral polyaza ‘cleft’ for enolate complexations, the disubstituted dihydropyrrolo[2,3-\textit{h}]quinoline (51) was prepared by alkylation of 7-bromo-5,6,7,8-tetrahydro-8-quinolone with ethyl 3,3-diamino-2-propenoate (Equation (24)) \(91\text{J}_{9687}\). The regioisomeric residence of the two substituents in this product was supported by \(^{13}\text{C}-^{13}\text{C} \) shift-correlated NMR spectroscopy.

\[
\text{Br} + \text{EtO}_2\text{C}-\text{NH}_2 \xrightarrow{\text{Et}_3\text{N}, \text{THF}} \text{Br} + \text{EtO}_2\text{C}-\text{NH}_2 \rightarrow \text{Br} + \text{EtO}_2\text{C}-\text{NH}_2
\]

(24)

Treatment of a hydroxy carbaldehyde precursor with chloroacetone in refluxing THF in the presence of potassium carbonate and 18-crown-6 resulted in the formation of the 2-acetyl furochromone (52) in 53% yield (Equation (25)) \(84\text{TL}2953\).

\[
\text{CHO} + \text{Cl} \xrightarrow{\text{K}_2\text{CO}_3, \text{THF, 18-crown-6}} \text{CHO} + \text{Cl} \rightarrow \text{CHO} + \text{Cl}
\]

(25)

In the first reported syntheses \(92\text{T}1039\) of either of the fused indole heterocycles shown in Equation (26), dihydropyrano[3,2-\textit{e}] and [2,3-\textit{f}]indoles (53) and (54) were prepared from a mixture of nitrodihydrobenzopyrans via condensation with DMFDMA (DMF dimethyl acetal) followed by reductive cyclization of the resulting \(\beta\)-aminostyrene derivatives. The isomers were separated by flash chromatography.
Synthesis of furochrome (55) was accomplished in 56% overall yield from a 5-acetyl-6-ethoxybenzofuran via BF$_3$·Et$_2$O-mediated deethylation (70%) followed directly by a Claisen-type condensation of the resultant hydroxyketone and EtOAc (Equation (27)) \(\langle 89JOC4481\rangle\).

(ii) By synthesis of the carbocyclic ring

(a) By formation of one bond. An LDA-mediated cyclization of a heterobiaryl precursor was followed by oxidation (Equation (28)) to prepare the pyrido- and thieno-fused ortho-naphthoquinone (56) in 74% yield \(\langle 93TL2437\rangle\).

(b) By formation of two bonds. In a study of diene-transmissive Diels–Alder reactions \(\langle 90BCJ284\rangle\), cycloaddition of a substituted 1,4-dihydrothiane and maleic anhydride or \(N\)-(p-methoxyphenyl)maleimide gave 4-oxa-10-thia- and 10-thia-4-aza- versions of the substituted tricyclo [7.4.0.0$^2$.8]trideca-8,11-diene-3,5-diones (57) in good yield (Equation (29)). The starting material is itself a Diels–Alder adduct of an \(\alpha,\beta: \alpha',\beta'\)-unsaturated thioketone and DMAD.

In another study of Diels–Alder reactions, but with dienopyranosides \(\langle 90JOC3555\rangle\), condensations of these carbohydrate-derived dienes with maleimide or its \(N\)-phenyl derivative gave anelated pyranosides (58) in a highly stereoselective manner, giving single products in some cases (Equation (30)). Double bond migration products (59) were also obtained, but these were discovered to have been generated by the presence of a trace of acid. Conducting the condensations in the presence of Et$_3$N or (Pr)$_2$NEt prevented this migration.
Tricyclic Systems: Central Carbocyclic Ring, 5- and 6-membered Rings

(iii) Synthesis of two contiguous rings

Heating the 1,1-disubstituted alkene with excess sarcosine ethyl ester in xylene with molecular sieves in a sealed tube at 180°C (7 h) afforded (60) (40%) (Equation (31)) <84JA7175>. This product was then processed in two steps to (±)-Sceletium alkaloid A₄.

Although obtained only in low yields upon troublesome chromatography of product mixtures that contained much polymeric material, the tricyclic benzo[3]furan and benzothiophene lactones (61) were shown to be isolable products from attempted Diels–Alder reactions on the allene ester precursors shown in Equation (32) <85JCS(P1)747>. Although it was noted in the case of the two thiophenes that the tricyclics appeared to be forming from a precursor (presumably a dihydro form) on the chromatographic column, it was not possible to convert the crude suspected cycloaddition adducts directly into the aromatics by dehydrogenation with DDQ. Complex mixtures were obtained instead. It is possible that the actual Dienophiles in these Diels–Alder reactions are alkynes. In a related study, the bis-lactone (62) was also obtained (Equation (33)) <86H(24)881>.
The generation of a pyrrole-2,3-quinodimethane was demonstrated by trapping it in intramolecular Diels–Alder fashion, as shown in Equation (34) \( \langle 92 \text{CC}1401 \rangle \). Diastereomerically pure octahydropyrrolo[2,3-b]quinoline (63) was obtained (84\%) when its imine precursor was subjected to conditions that effect both carboxylation at the imino nitrogen (by CICO\(_2\)Me) and deprotonation at the methyl group (by Pr\(_2\)NEt) to give a 2,3-dimethylene-2,3-dihydropyrrrole intermediate which cyclized directly.

\[
\begin{align*}
\text{CICO}_2\text{Me, Pr}_2\text{NEt,} & \quad \text{PhMe}, \quad 180^\circ \text{C}, \quad 40 \text{ min} \\
\text{84\%} & \\
\text{MeO}_2\text{C} & \quad \text{Tos} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

(63)

In a similar heterocyclic quinodimethane ring construction strategy, the hexacyclic adducts (64) were isolated in good yield upon condensation of appropriately functionalized indole imines with (±)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid chloride (Equation (35)) \( \langle 88 \text{JA}2242 \rangle \). In a demonstration of the utility of this new method for indole alkaloid synthesis, further transformations conducted on compound (64; \( R^1 = R^2 = H, \ R^3 = \text{Et} \)) were shown to lead to (−)-16-methoxytabersonine.

\[
\begin{align*}
\text{PhMe,} & \quad 110^\circ \text{C}, \text{1.25 h} \\
64–75\% & \\
\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}; & \quad \text{R}^1 = \text{CO}_2\text{Me}, \text{R}^2 = \text{R}^3 = \text{H}; \\
\text{R}^1 = \text{R}^2 = \text{H}, \text{R}^3 = \text{CO}_2\text{Me}; & \quad \text{R}^1 = \text{O-MOM}, \text{R}^2 = \text{R}^3 = \text{H}; \\
\text{R}^1 = \text{R}^3 = \text{H}, \text{R}^2 = \text{O-MOM}; & \quad \text{R}^1 = \text{R}^2 = \text{H}, \text{R}^3 = \text{Et}
\end{align*}
\]

(64)

(iv) Synthesis of both heterocyclic rings

Based on the fact that the thermal rearrangement of 1,1-dimethylprop-2-ynyl aryl ethers is known to afford chromenes, it was expected and then found that the pyrano[2,3-g]indole (65) forms by sequential indolization and regioselective rearrangement via thermolysis of the appropriate azido ester precursor (Equation (36)) \( \langle 84 \text{JCS(P1)}1333 \rangle \). This transformation proceeded in remarkably high yield (94\%) simply upon heating the azide for 3 h in toluene at reflux. The intermediate, unarranged 1,1-dimethylprop-2-ynloxyindole was not isolated.

\[
\begin{align*}
\text{PhMe,} & \quad 110^\circ \text{C}, \text{3 h} \\
94\% & \\
\text{CO}_2\text{Et} & \quad \text{O} & \quad \text{H}
\end{align*}
\]

(65)

(v) Synthesis of all three rings

In a study of annelation reactions of 4-alkynylcyclobutenones \( \langle 91 \text{JOC}6104 \rangle \), thermolysis of a 4-alkynyl-4-(propargyloxy)cyclobutene was observed to give a high yield of a quinone methide as evidenced by the formation of a hetero-Diels–Alder product in the presence of butoxyethene as a
trapping agent (Equation (37)). Adduct (66) was isolated in excellent yield as a 2:1 mixture of diastereomers.

\[
\begin{align*}
\text{PhO} & \quad \text{OMe} \\
\text{O} & \quad \text{OMe} \\
& + \quad \text{OBu}^n \\
\rightarrow & \quad \text{MeO} \quad \text{OMe} \\
& \quad \text{BuO}^n \quad \text{BuO} \\
\end{align*}
\]

In a study of rhodium-catalyzed \([2+2+2]\) cycloadditions of alkynes \(<88\text{JCS(P1)1357}\rangle\), the intramolecular \([2+2+2]\) cycloaddition of 4,9-dioxadodeca-1,6,12-triyne catalyzed by Wilkinson's catalyst \([\text{PPh}_3]\text{RhCl}\) over a prolonged period of time gave the dihydroxybenzo- and tetrahydrofurofused 6-6-5 tricyclic benzene derivative (67) in moderate yield (Equation (38)). It should be noted that an analogous bis-tetrahydrofuro-fused 5-6-5 tricyclic compound could be prepared (74%) under similar conditions, but after only 3 h at room temperature.

\[
\begin{align*}
\text{OO} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\rightarrow & \quad \text{O} \quad \text{O} \\
\end{align*}
\]

7.22.9.3.2 With two heteroatoms in one heterocyclic ring and one in the other

(i) Synthesis of the heterocyclic ring

(a) By formation of one bond. As shown in Scheme 4, isoxazoles (68) or (70), prepared from the corresponding o-hydroxyketoximes by acetylation followed by thermal cyclization, led to 3,7,7-trimethyl-7\(H\)-pyrano[3,2-f]-1,2-benzisoxazole (69) or 2,2,9-trimethyl-7\(H\)-pyrano[2,3-e]-1,2-benzisoxazole (71) upon sequential reduction with NaBH₄ and dehydration with TsOH \(<89\text{H(28)711}\rangle\). The pyrano[1,2]benzisoxazoles (69) and (71) were obtained in excellent overall yield from the ketoximes.

![Scheme 4](image)

The four (pyrano[2,3-g]benzothiazol-2-yl)benzamides (72) shown in Equation (39) were obtained in good yield by heating 6-aminoflavone-derived thiourea precursors in POCl₃ containing PCl₅, \(<94\text{BCJ2326}\rangle\).
The key steps in the preparation of novel antihypertensive 7H-1,4-dioxano[2,3-e]indoles are the condensation of a 2,3-dihydro-1,4-benzodioxan-5-carbaldehyde with methyl α-azidoacetate and the thermolytic ring-closure of the resulting vinyl azide to give ester (73), obtained in 65–75% overall yield from the carbaldehyde (Equation (40)) (92JMC3058). Compound (73) was processed further by removal (TBAF) of the TBDMS group, tosylation (TsCl, pyridine) of the resulting alcohol, and displacement (R¹R²NH, K₂CO₃, pyridine) of the tosylate group with amines.

Thermal cyclization was also the route employed to prepare 9-hydroxy-7-methyl-1H-pyrazolo[3,4-f]quinoline (74) from the 6-aminoindazole/ethyl acetoacetate condensation adduct shown in Equation (41) (92JMC4595). The hydroxyl substituent of compound (74) was then converted (POCl₃, DMF) to a chloro, which in turn was displaced by treatment with aryl amines to give tricycles with potent in vivo immunostimulatory activity like that noted for regioisomeric 1H-imidazo[4,5-f]quinolines but unlike the inactive pyrazolo[4,3-f]quinolines. Although it was noted with some interest that none of the linear tricyclic isomer had been isolated, this finding actually parallels that reported earlier for the similar condensation of 1- and N(6)-alkyl and unsubstituted 6-aminoindazoles with diethyl ethoxymethylenemalonate (83JHC1351).

Isoxazole rings were annelated onto 5-nitroquinoline and isoquinoline-based α-nitrobenzyl-p-tolylsulfones by treatment with potassium phenoxide, which acted as both base and reductant (Equation (42)) (95H(40)187). In the cases of quinolines as starting materials, product benzisoxazoles (75) both with and without phenoxy substitution were obtained, but in the case of an isoquinoline starting material no phenoxy-substituted product was generated. The reaction is thought to proceed via a nitrosobenzylsulfone carbanion intermediate, and can be applied to nitronaphthalenes but not to less active nitrobenzenes.
As shown in Scheme 5, isatin (77) was synthesized according to the Sandmeyer procedure whereby the α-oximinomalide (76) formed by condensation of chloral hydrate, NH₂OH, and the appropriate ethylenedioxo aniline was cyclized by concentrated H₂SO₄ (95MC906). This isatin was then used to 2-oxo-1,2-dihydroindol-3-ylidene a tricyclic ketone to give one of those in a series of camptothecin analogues tested for activity as topoisomerase I inhibitors.

Scheme 5

(b) By formation of two bonds. The isoxazole analogue (78) of a 2-acetyl furochromone has been prepared (79%) by slow addition of hydroxylamine O-sulfonic acid to a hydroxy carbaldehyde precursor in a two phase system (H₂O/CH₂Cl₂) containing two equivalents of sodium bicarbonate (Equation (43)) (84TL2953).

Scheme 6

4-Dialkylamino-3,3-dichloro-4,5,6,7-tetrahydropyrano[2,3-ε]indazol-2(3H)-ones (79) were obtained in good yield by the cyclocondensation of 5-(dialkylamino)methylene derivatives of 1,5,6,7-tetrahydro-4H-indazol-4-one with dichloroketene prepared in situ from Cl₂CHCOCl and Et₂N (Scheme 6) (84JHC361). Compounds (79) readily underwent dehydrochlorination upon treatment with DBN to give the 6,7-dihydropyranono[2,3-ε]indazol-2(7H)-ones (80), but these proved to be very resistant to full aromatization with DDQ in refluxing PhH, although extended reaction time (12 d) did afford two 3-chloro-4-dimethylaminopyrano[2,3-ε]indazol-2(7H)-ones in 40–76% yield.

In an example of the Combes synthesis of quinolines, acid-catalyzed condensation of 4(7)-aminobenzimidazole with excess acetylacetone afforded 5,7-dimethylimidazo[4,5-h]quinoline (81), albeit in low yield (Equation (44)) (91T7459).

Scheme 6

4-Oxo-1H-4,5,6,7-tetrahydro-5-indoleacetic acids gave the tetrahydroindolol[4,5-c]pyridazino-3(2H)-ones (82) upon condensation with hydrazine in ethanol (Equation (45)) (92H(34)1303). Stereo-
chemical determinations of the products (82) were made by comparing the ring 1H—1H coupling constants to those of a cis-fused tricyclic lactone derived from one of the tetrahydro-5-indoleacetic acid starting materials.

As part of an examination of an oxidative coupling of methyl 6-hydroxyindole-2-carboxylate with primary amines which enabled the development of a facile preparation of 2-substituted methyl pyrrolo[2,3-c]benzoxazole-5-carboxylates, the reaction of this indole with 1,2-diaminoethane and excess MnO2 gave compound (83) in an apparent intramolecular interception of a transient intermediate o-quinone monoimine (Equation (46)) <88JOC5163>.

A series of substituted imidazotetrahydroquinoline thymidylate synthetase inhibitors (84) was prepared <92JMC847> according to imidazole ring annellation of 6,7-diamino-1,2,3,4-tetrahydroquinolines by condensation with appropriate electrophilic reagents (e.g., CNBr, HCl(OMe)), Im(CS). In a separate study, a series of aryl[e]fused pyrazolo[4,3-c]pyridines with potential anxiolytic activity <90JMC2640>, substituted pyrazolo[4,3-f]-, [3,4-f]-, and imidazo[4,5-f]quinolines (85) were prepared by pyridine ring annellation of aminoindazoles or an aminobenzimidazole via [(arylamino)methylene]malonates by a modified Gould–Jacobs cyclization with the use ofPOCl3 at reflux.

In an example of one of the more promising cross processes of diene-transmissive hetero-Diels–Alder reactions of bis(silyloxy) cross-conjugated trienes <94CL1833>, 3-(methoxymethylene)-2,4-bis(trimethylsilyloxy)-1,4-pentadiene was first condensed with N-methylmaleimide to give an endo mono-cycloadduct: this in turn was condensed with DEAD to give the cross bis-adduct (86) upon workup with MeOH (Equation (47)). It was established by 1H NMR that the initially formed ring of the product (86) had the trans configuration, indicating that the stereochemistry of the initial endo monocycloadduct had been inverted during the formation of the second ring.

Condensation of dopachrome methyl or ethyl esters with cysteine ethyl ester in pH 6.8 aqueous phosphate buffer led to the 1,2-dihydro-3H,8H-pyrrolo[2,3-h][1,4]benzothiazines (87), as shown in
Equation (48) \textsuperscript{(87T5357)}. A mechanism similar to that commonly accepted for the formation of \textit{2H}-1,4-benzothiazines via condensation of \(\beta\)-aminothiols with simple \(\alpha\)- and \(\rho\)-benzoquinones was suggested. It was noted that the products (87; \(R^1 = H\)) rapidly decompose to oligomeric materials whereas the others are much more stable to this presumed oxidative lability.

\begin{equation}
\text{R}^1\text{Et}, \text{R}^2=\text{Me} ;
\text{R}^1=\text{Et}, \text{R}^2=\text{Me};
\text{R}^1=\text{Et}, \text{R}^2=\text{H};
\end{equation}

Condensation of 1- and \(N\)(6)-alkyl and unsubstituted 6-aminindazoles with diethyl ethoxy-methylenemalonate in Dowtherm A at elevated temperature gave the ethyl 6,9-dihydro-9-oxopyrazolo[3,4-\(f\)]quinoline-8-carboxylates (88) (Equation (49)) \textsuperscript{(83JHC1351)}. The 6-ethyl-8-carboxylic acid derivative is a potent antibacterial agent.

The oxazolo[4,5-\(h\)]quinolin-2(3\(H\))-ones (89) and 2,5-disubstituted oxazolo[4,5-\(h\)]quinolines (90) were prepared as new antiallergic agents by oxazole ring annelation conducted by condensing 7-amino-8-hydroxyquinoline intermediates with phosgene, \(\sigma\)-ester, or imidate reagents (Scheme 7) \textsuperscript{(85JMC1255)}.

[4,5-\(f\)]Thiazole ring annelation onto 6-bromo-3-cyano-5-oxo-5,6,7,8-tetrahydro-2(1\(H\))-quinolinone was effected by treatment with thioformamide and its derivatives under mild conditions, giving the 8-cyano-7-oxo-4,5,6,7-tetrahydrothiazolo[4,5-\(f\)]quinolines (91) in good yield (Equation (50)) \textsuperscript{(89H(29)1517)}.

Together with syntheses of 2-amino-8,9-dihydrothiazolo[4,5-\(f\)]- and [4,5-\(f\)]isoquinoline and 2-amino-4,5-dihydrothiazolo[5,4-\(h\)]isoquinoline based upon an \(\alpha\)-bromoketone/thiourea condensation similar to that described above, a direct thiazole ring annelation method for an \(N\)-protected octahydroquinolin-5-one has been developed. This involves the trapping of a kinetic enolate with TMS—Cl followed by regioselective bromination (NBS) and condensation with thio-
urea (89H(29)1517). This sequence (Equation (51)) gave the cis-fused 2-aminooctahydrothiazolo[4,5-f]quinoline (92) in 53% overall yield. By a similar sequence, a trans-octahydroquinolin-5-one gave a trans-fused version of compound (92), indicating that the starting ketones were fairly stable toward epimerization under the reaction conditions.

\[
\text{BOC} \quad \begin{array}{c}
\text{N} \\
\text{O}
\end{array} 
\xrightarrow{\begin{array}{c}
i, \text{LDA, THF, } -78^\circ \text{C;} \\
\text{ii, NBS, THF, } 0^\circ \text{C;} \\
\text{iii, } \text{H}_2\text{NCSNH}_2, \text{THF}
\end{array}} \quad \text{BOC} \quad \begin{array}{c}
\text{N} \\
\text{S} \\
\text{NH}_2
\end{array}
\]

(51)

(ii) **By synthesis of the carbocyclic ring**

(a) By formation of two bonds. The thermal cycloaddition of N-phenylmaleimide to the very reactive 2,3-(ethylenedisulfonyl)-1,3-butadiene or its bisthioether analogue gave the tricyclic cycloadducts (93) (Equation (52)) (92CB499).

\[
\text{X} = \text{SO}_2, \text{S}
\]

5-Anilino - 5a,8a-dihydro - 1,3,7-trimethyl - 1H - pyrrolo[3,4-g]quinazoline - 2,4,6,8(3H,5H,7H, 9H)-tetrones (94) were obtained in good yield by the sequential treatment of 5-formyl-1,3,6-trimethyluracil with (i) aniline to form the 6-methylene-5-(phenylamino)methylene derivative, via a [1,5]-hydrogen shift in the aldimine, and (ii) maleimide to achieve the central ring-forming cycloaddition reaction (Equation (53)) (90BCJ2938).

\[
\text{i, PH}_2\text{NH, dioxane, } 25^\circ \text{C}
\]

\[
\text{Me} \quad \begin{array}{c}
\text{N} \\
\text{CHO} \\
\text{R}
\end{array} 
\xrightarrow{\begin{array}{c}
i, \text{N-methylmaleimide}
\end{array}} \quad \text{Me} \quad \begin{array}{c}
\text{N} \\
\text{NMe} \\
\text{NMe}
\end{array}
\]

(53)

(iii) **By synthesis of two contiguous rings**

The Rh$_2$OAc$_2$-catalyzed nitrogen extrusion from the diazoketone shown in Equation (54) leads to isoxazole (95) after aromatization of the central ring (89H(29)1003). The formation of the tricyclic ring system is thought to proceed through a furq[3,4-d]isoxazole intermediate that undergoes intramolecular Diels–Alder reaction and then fragmentation.

\[
\text{N} = \text{CO}_2\text{Me}
\xrightarrow{\begin{array}{c}
i, \text{Rh}_2\text{OAc}_2, \text{CICH}_2\text{CH}_2\text{Cl, } 83^\circ \text{C;} \\
\text{ii, } \text{TsOH, CICH}_2\text{CH}_2\text{Cl}
\end{array}} \quad \text{N} = \text{CO}_2\text{Me}
\]

(54)
7.22.9.3.3 With two heteroatoms in each heterocyclic ring

As shown in Scheme 8, a common ketone precursor led to the pyrazolo[4,3-g]- and thiazolo[5,4-g]-fused 1,4-benzoazines (96) and (97) (87JMC580). For the synthesis of compound (96) the ketone was condensed with HCO₂Et and subsequently cyclized with hydrazine. For the synthesis of the thiazole (97) α-bromination of the ketone was followed by condensation with thiourea. The linear tricyclic structures (96) and (97) were supported by ¹H and ¹³C NMR spectroscopic analyses.

![Scheme 8](image)

4-Dialkylamino-4,5,6,7-tetrahydro-3H-1,2-oxathiino[6,5-e]indazole 2,2-dioxides (98) were obtained (35–50%) by the cyclocondensation of 5-(dialkylamino)methylene derivatives of 1,5,6,7-tetrahydro-4H-indazol-4-one with sulfene prepared in situ from MsCl and Et₃N (Equation (55)) (84JHC361).

![Equation 55](image)

7.22.9.3.4 With more than two heteroatoms in either heterocyclic ring

In an unexpected outcome, 8-quinolino condensed with tetrasulfur tetranitride in refluxing toluene to give 1,2,5-thiadiazolo[3,4-h]quinoline (99) (25%) (Equation (56)) (91BCJ68).

![Equation 56](image)

The condensation of aminobenzotriazoles with DMAD gave (Z)-conjugate addition adducts which underwent ring closure in boiling Dowtherm to give triazolo[4,5-f]quinolinones (100) (Equation (57)) (93H(36)259). The quinolinone form of the product (100) is supported by ¹³C NMR spectroscopic evidence. It was found that ring closure to the tricycle fails in the absence of an N-methyl substituent; retro-Michael addition takes place instead.

![Equation 57](image)

A series of tetrahydrothiadiazoloisoquinolines that could potentially reduce the formation of epinephrine by inhibiting phenylethanolamine-N-methyltransferase has been prepared (89JMC1566).
In connection with this study, syntheses of 1,2,3-thiadiazolo[4,5-\(h\)]isoquinoline (102) (Scheme 9), 5-chloro-1,2,3-thiadiazolo[5,4-\(h\)]isoquinoline (104) (Scheme 10), and 1,2,5-thiadiazolo[3,4-\(h\)]isoquinoline (105) (Equation (58)) were developed. 7-Aminoisooquinoline and 8-amino-5-chloroisooquinoline each condensed with sulfur monochloride to give the dithiazolisoquinolin-2-iium chloride hydrochlorides (101) and (103), respectively, in excellent yield. Nitrous acid treatment of these intermediates gave compounds (102) and (104) in moderate yield. Treatment of 7,8-diaminoisoquinoline with SOCl\(_2\) gave the tricyclic product (105) directly and treatment with nitrous acid gave 1,2,3-triazolo[4,5-\(h\)]isoquinoline (106).

\[
\text{Scheme 9}
\]

\[
\text{Scheme 10}
\]

In a study of the diene-transmissive Diels–Alder reactions \(<90\text{BCJ}284>\), cycloaddition of a substituted 1,4-dihydrothiadiazine and maleic anhydride or \(N\)-(\(p\)-methoxyphenyl)maleimide gave substituted bicyclo[4.4.0]dec-10-enes (107) in good yield (Equation (59)) \(<90\text{BCJ}284>\). The starting thiazidine is itself a Diels–Alder adduct of an \(\alpha,\beta:\alpha',\beta'-\)unsaturated thioketone and dead.

\[
\text{Equation (58)}
\]

1,4-Benzodioxano[6,7-\(c\)]furoxan (108) (Equation (60)), which was available previously via NaOCl oxidation of 6-amino-7-nitro-1,4-benzodioxane, has been prepared using a simpler route from 6,7-dinitro-1,4-benzodioxane via azide-for-nitro displacement and pyrolysis of the crude intermediate azide, in spite of a report that pyrolysis of 6-azido-7-nitro-1,4-benzodioxane fails to generate (108) in various solvents and at different temperatures \(<88\text{HC}803>\). Di- or trinitro-1,4-benzodioxanes were subjected to a similar nucleophilic displacement with azide ion to afford the bent tricyclic 1,4-
benzodioxano[5,6-c]furoxans (109) (Equation (61)). Heating compound (109; \( R = \text{NO}_2 \)) in toluene under reflux, or even neat in the solid-state, results in complete and irreversible rearrangement to the linear tricyclic isomer via a Boulton–Katritzky rearrangement.

![Chemical structure](image)

\[
\text{(108)}
\]

\[
\text{(109): } R=\text{H, NO}_2
\]

6,7-Disubstituted and unsubstituted 1,2,5-thiadiazolo[3,4-\(g\)]quinoxaline-4,9-diones (110) have been prepared in good yield by condensation of 5,6-diaminobenzo[\(c\)[1,2,5]thiadiazole with \( \alpha \)-dicarbonyl reagents (Equation (62)) \( \langle 92\text{H}(33)337 \rangle \). These quinones were then converted into 1,2,5-thiadiazolo-, pyrazino-fused TCNQ analogues by condensation with malononitrile in the presence of TiCl\(_4\) in dry pyridine. The x-ray crystal structure determination of the product derived from compound (110; \( R^1 = R^2 = \text{H} \)) has been accomplished.

\[
\text{(110): } R^1=R^2=\text{H, Me, Ph}
\]

7.22.9.4 Synthesis of Compounds with a Central Seven-membered Ring

7.22.9.4.1 With one heteroatom in each heterocyclic ring

(i) By synthesis of a heterocyclic ring

(a) By formation of one bond. Ozonolysis of the vinyl substituent on a pyrido[2,3-\(b\)]cycloheptanone unexpectedly gave, upon reductive workup, the tricyclic ketal lactone (111) as a mixture of \( \text{cis} \)- and \( \text{trans} \)-fused isomers (Equation (63)) \( \langle 94\text{SC273} \rangle \).

![Chemical structure](image)

\[
\text{(111)}
\]

(ii) By synthesis of the carbocyclic ring

(a) By formation of one bond and fragmentation of another. As shown in Equation (64), the thermolysis of a divinylcyclopropane precursor induced a [3,3]-sigmatropic rearrangement and
Tricyclic Systems: Central Carbocyclic Ring, 5- and 6-membered Rings

smoothly generated the 6-7-5 tricyclic cycloheptadiene derivative (112) \( \langle 92\text{JOC5559} \rangle \). It was suggested that this rearrangement occurs via a boat transition state.

7.22.9.4.2 With two heteroatoms in one heterocyclic ring and one in the other

(i) By synthesis of a heterocyclic ring

(a) By formation of two bonds. Bromination of a pyrido[2,3-\( h \)]cycloheptanone followed by condensation with thiourea led to the construction (Equation (65)) of the fused thiazole ring of the amine (113), isolated in excellent yield \( \langle 91\text{JMC2736} \rangle \).

\[
\text{Br}_2, 48\% \text{ HBr, 25 °C}; \quad \text{H}_2\text{NCSNH}_2, \text{H}_2\text{O}, 100 °C \quad 93\%
\]

(113)

A 6-7 bicyclic, erythro diastereomer aminoalcohol precursor derived from 5,6,7,8-tetrahydro-9\( H \)-cyclohepta[\( h \)]pyridin-9-one was condensed with diethyl carbonate to afford the 6-7-5 tricyclic cis-fused oxazol-2-one (114) (Equation (66)) \( \langle 84\text{JMC20} \rangle \).

\[
(\pm) \text{NH}_2 \quad \xrightarrow{(\text{EtO})_2\text{CO}} \quad (\pm) \text{N} \quad \xrightarrow{(\text{EtO})_2\text{CO}} \quad \text{NH}_2
\]

(114)

7.22.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

As shown in Equation (67), monotosylhydrazones of PQQ and PQQ-triesters can undergo photogenerated Wolff rearrangements \( \langle 93\text{HCA1674} \rangle \). The photogenerated \( \pi \)-diazoketone leads to a carbene-mediated ring contraction to give a ketene that can be trapped with either water or methanol. The latter workup affords 4-methoxycarbonylated versions of 1,4-dihydropyrrolo[2',3':3,4]cyclopenta[1,2-\( h \)]pyridin-2,6,8-tricarboxylic acids (115), while the former gives 4-unsubstituted ones due to \textit{in situ} decarboxylation at the 4-position.
Ring opening (Equation (68)) of the versatile synthon 1,3,5,7-tetraethia-s-indacene-2,6-dione with sodium t-amylate followed by 1,2-dibromoethane alkylation gave the tricyclic 1,4-dithiane (116) (35%) 〈87JOC3285〉. In a related ring transformative reaction (Equation (69)), reduction of 4,8-dimethylbenzo[1,2-d:4,5-d’]bis-1,2,3-trithiole with sodium borohydride followed by alkylation with 1,2-dibromoethane afforded the 1,4-dithiane-containing tricyclic monothiole (117) (35%) 〈89TL3453〉.

\[
\text{O} \quad \begin{array}{c}
\text{S} \\
\text{S} \\
\text{O} \\
\end{array} \quad (68)
\]

\[
\text{O} \quad \begin{array}{c}
\text{S} \\
\text{S} \\
\text{S} \\
\end{array} \quad (116)
\]

\[
\text{O} \quad \begin{array}{c}
\text{S} \\
\text{S} \\
\text{S} \\
\end{array} \quad (117)
\]

N-Benzyl-1,2,3,4-tetrahydrocyclobuta[b]pyridine-5,6-dione (118) functions as a synthon of the unstable pyrido[cyclobutenedione and undergoes regiospecific introduction of unsaturated nucleophiles at the more reactive carbonyl group to give the 1,2-adducts (119) (Scheme 11) 〈91JOC6379〉. These in turn undergo a thermolytic ring expansion in vessels open to air to give the furan- and thieno[3,2-g]-fused tetrahydroquinolinequinones (120) in good yield. The use of furanyl-3-yllithium in this sequence gave a furan[2,3-g]-fused analogue in 83% yield.

\[
\text{N} \quad \begin{array}{c}
\text{Bn} \\
\text{O} \\
\end{array} \quad (118)
\]

\[
\text{N} \quad \begin{array}{c}
\text{Bn} \\
\text{OH} \\
\end{array} \quad (119) \ R=2\text{-furyl}, 2\text{-thienyl}
\]

\[
\text{Bn} \quad \begin{array}{c}
\text{O} \\
\end{array} \quad (120) \ X=O, S
\]

Scheme 11

One product from the oxidation of a-santonin by KMnO₄ (Equation (70)) has been shown to be the ketodilactone (121) 〈94TL8117〉. This ring transformation is thought to occur via manganese metalloccycle formation at the 4,5-double bond followed by a ring opening/ring closing oxygen atom insertion at the 3,4-single bond.

\[
\text{O} \quad \begin{array}{c}
\text{O} \\
\text{Bn} \\
\end{array} \quad (121)
\]

One of the key steps of a short and efficient synthesis of (+)-8-deoxyvernolepin from (−)-a-santonin 〈94JOC6395〉 was the 1,4-fragmentation of the γ-hydroxystannane (123) to give the δ-valerolactone (124) in quantitative yield (Scheme 12). The hemiacetal (123), prepared from the ester (122) by acetal group hydrolysis, was irradiated in cyclohexane in the presence of (dialkoxymido)benzene (DAIB) and iodine under a stream of oxygen to suppress a radical 1-for-Bu₅Sn substitution reaction that had previously caused the yield of product (124) to be only 70%. A different total synthesis of (+)-8-deoxyvernolepin from (−)-a-santonin along a route involving a spiro lactone has also been reported 〈87JCS(P1)2833〉.

Cyclocondensation of 1,4-diarylpyridazino[4,5-d]pyridazines with a ketene N,S-acetal, generated in situ by treatment of 2-methylthiol-1-methyl-1-pyrrolinium iodide with DBU, proceeded smoothly.
to give a cycloadduct which underwent spontaneous aromatization to give the 1,4-diaryl-6-methylpyrrolidino[2,3-g]phthalazines (125) (Equation (71)).<ref>91T3959</ref>

\[
\begin{align*}
S &+ MeS \\
\text{MeS} &
\end{align*}
\]

(71)

(125) R=Ph, 4-MeO\text{Ph}

### 7.22.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS

#### 7.22.11.1 Benzo-separated Purines

The development of compounds in which the pyrimidine ring and the imidazole ring of the purine system are separated by a benzene ring to form an extended or 'stretched-out' purine model was undertaken in the mid-1970s by Leonard and co-workers. Reviews covering the literature through the mid-1980s relate synthetic and other aspects of these compounds <ref>82ACR128, B-84MI 722-01, 84PAC1025, 85MI 722-01, 86T1917</ref>. A general description of these structurally unique purine analogues appears in Section 7.22.12.1, while the highlights of the more recent synthetic developments in this field are summarized here.

The attempt to prepare deoxy-\textit{lin}-benzoadenosine (127) directly from \textit{lin}-benzoadenosine was abandoned when efforts to prepare pure 3',5'-di-O-benzoyl-\textit{lin}-benzoadenosine gave unstable mixtures. This was attributed to the increased nucleophilicity of the exocyclic amino group of \textit{lin}-benzoadenosine compared to adenosine. In the successful preparation (Scheme 13), treatment of the \textit{lin}-benzoadenosine precursor 8-(methylthio)-3-(\textit{S}-\textit{O}-acetyl-\textit{\beta}-\textit{D}-ribofuranosyl)imidazo[4,5-g]quinazoline (126) with \textit{NH}_3OH \cdot \text{AcOH} afforded a mixture of the 3',5'- and 2',5'-di-O-acetyl nucleosides in ca. 4:1 ratio <ref>84B3868</ref>. The mixture was converted to a separable mixture of diacetylribonucleosides, and free-radical reductive deoxygenation of the 2'-thiobenzoyl isomer with \textit{Bu}_3SnH afforded the diacetyl deoxyribonucleoside in good yield. Treatment with ethanolic \textit{NH}_3 in a pressure vessel at 150°C afforded compound (127). The monophosphate was prepared by condensation with pyrophosphoryl chloride in \textit{m}-cresol. The diphosphate was prepared by chemical phosphorylation of the monophosphate via the morpholidate. Pyruvate kinase was used to phosphorylate the diphosphate, affording the triphosphate.

\[
\begin{align*}
\text{SMe} &
\end{align*}
\]

(126)

R=2,3,5-tri-\textit{O}-acetyl-1-\textit{\beta}-\textit{D}-ribofuranosyl

\[
\begin{align*}
\text{NH}_2 &
\end{align*}
\]

(127) R=2-deoxy-1-\textit{\beta}-\textit{D}-ribofuranosyl

i, \textit{NH}_3OH \cdot \text{HPO}_4\text{Ac}, \text{pyridine}, 25°C, 72 h; ii, \text{PhC(Cl)Cl}=\text{N}^+\text{Me}_2\text{Cl}; \text{CH}_2\text{Cl}_2, 25°C, 48 h; iii, \text{H}_3\text{S}, \text{pyridine}, 25°C, 30 min; iv, \text{Bu}_3\text{SnH}, \text{cat. AlBN, PhMe, 110°C}, 8 h; v, \text{NH}_3, \text{EtOH}, 130–145°C, ca. 24 h

Scheme 13
The use of cycloaddition reactions for the synthesis of partially reduced heterocyclic systems was shown to be an attractive approach to dihydrobenzimidazoles, dihydroquinazolines, and dihydro-<i>lin</i>-benzopurines (Scheme 14) (\textsuperscript{86}JOC\textsuperscript{616}). The dihydroxylation of the Diels–Alder adduct dimethyl 3,6-dihydrophthalate (128) with OsO\textsubscript{4} and NMO followed by protection of the diol as the iso-propylidene derivative afforded compound (129). Saponification, dehydration with ethoxyethyne, and rearrangement with TMS—N\textsubscript{3} effected conversion to the substituted tetrahydroisatoic anhydride (130), and subsequent treatment with formamidine acetate yielded compound (131). The substituents at the 6,7-positions of compound (131) were not amenable, however, for annelation of an imidazole.

![Diagram](image_url)

Since the methodology for annelating the pyrimidine ring was already in place, an alternative route of constructing the dihydrobenzimidazole unit prior to addition of the pyrimidine ring was selected (Scheme 15). When the substituted dihydrobenzimidazolone (132) (prepared in 77\% overall yield from 1,3-diacetyl-4,5-dimethylimidazolin-2-(1\textit{H})-one via a 4\(\pi + 2\pi\) cycloaddition route) was heated with a catalytic amount of TsOH in benzene or toluene, two equivalents of isobutylene and one equivalent of H\textsubscript{2}O were lost, and anhydride (133) deposited in 85\% yield when the solution was cooled. A Curtius rearrangement was carried out with an excess of TMS—N\textsubscript{3} in refluxing MeCN to give the substituted dihydroisatoic anhydride (134). Conversion to the dihydro-<i>lin</i>-benzopurinedione (135) was possible if a solution of the precursor (134) in NMP was deoxygenated prior to the addition of formamidine acetate and heated at 100°C (1 h). Compound (134) proved to be useful for the synthesis of 4,9-dihydro-<i>lin</i>-benzouracil (136): brief reaction with urea in a melt at 180 ± 5°C gave (136) in 73\% yield. It was possible to aromatize the central ring of compound (135) by heating with p-chloranil in glacial AcOH: the product, <i>lin</i>-benzouracil (137), had been identified previously as the final enzymatic oxidation product of <i>lin</i>-benzohypoxanthine (and <i>lin</i>-benzoxyanthine) with xanthine oxidase.

The substituted indazole (138), an intermediate in the synthesis of <i>prox</i>-benzisoallopurinol (139), suffered extensive decarboxylation to 6-aminoindazole when heated with formamide at 180°C in an attempt at direct synthesis. This difficulty was eliminated by heating the acid (138) with excess formamidine acetate in EtOH giving compound (139), and the extended analogue of allopurinol, in >80\% yield (Equation (72)). The generality of this reaction with respect to substituted isoanhydrides and anthranilic acids was demonstrated by the synthesis of a variety of substituted quinazolin-4-(3\textit{H})-ones (\textsuperscript{86}JOC\textsuperscript{616}).

A convenient synthesis (Scheme 16) of <i>lin</i>-benzopurines through a common intermediate has been developed (\textsuperscript{87}JOC\textsuperscript{2933}). 5,6-Dimethylbenzimidazole (140) was oxidized by KMnO\textsubscript{4} to benzimidazole-5,6-dicarboxylic anhydride (141) (48\%) and conversion to 1-acetylbenzimidazole-5,6-dicarboxylic anhydride (142) (93\%) was effected by heating with Ac\textsubscript{2}O. The five-membered cyclic anhydride was then enlarged to a six-membered oxazinedione ring by treatment with TMS—N\textsubscript{3}. The mixture of 1- and 3-acetylimidazo[4,5-<i>g</i>]-7,5-benzoxazine-6,8(5\textit{H})-diones (143) was then used directly as the pivotal intermediate for the synthesis of <i>lin</i>-benzohypoxanthine (144), <i>lin</i>-benzoanthine (145), <i>lin</i>-benzoguanine (146), and <i>lin</i>-benzoadenine (147). Formamidine acetate in DMF or Cellosolve was used to convert (143) to imidazo[4,5-<i>g</i>]quinazolin-8(7\textit{H})-one (144) in 86\% overall yield from (142). Fusion with urea produced imidazo[4,5-<i>g</i>]quinazoline-6,8(5\textit{H},7\textit{H})-dione (145) in
an overall yield of $\geq 55\%$. Upon treatment with cyanamide and KOBu$^+$ in DMF 8-aminomimidazo[4,5-$g$]quinazolin-8(7$H$)-one (146) was obtained (59\% overall yield). Direct conversion of the intermediate (143) to 8-aminomimidazo[4,5-$g$]quinazoline (147) (56\% overall yield) was accomplished by sequential treatment with: (i) anhydrous NH$_3$ in anhydrous DMF; (ii) POCl$_3$; and (iii) concentrated NH$_4$OH.

The selective reduction of the central ring of lin-benzopurines by means of excess lithium in liquid NH$_3$, containing one equivalent of HOBu$^+$ gave the 4,9-dihydro-lin-benzopurines (148) (Equation (73)) $^{88}$JOC3873. Although lin-benzohypoxanthine gave 4,9-dihydro-lin-benzohypoxanthine (148; R = H) as the major product (40\%), it was accompanied by lin-benzopurine (149) (20\%) (Scheme 17). The reduction of lin-benzoadenine (150) with excess Li in NH$_3$ (heterogeneous) at $-78\,^\circ$C yielded lin-benzopurine (149) almost exclusively (by TLC analysis). An attempt to prepare 4,9-dihydro-lin-benzoadenine (154) by P$_2$S$_5$ conversion of 4,9-dihydro-lin-benzohypoxanthine (151) to 4,9-dihydro-8-thioimidazo[4,5-$g$]quinazoline (152), methylation to 4,9-dihydro-8-(methylthio)-imidazo[4,5-$g$]quinazoline (153), and displacement of the 8-SMe group with NH$_3$ failed in the last step (Scheme 18). However, it was possible to obtain 4,9-dihydro-lin-benzoadenine (154) by reduction of compound (150) with Li in MeNH$_2$ and HMPT at $-6.5\,^\circ$C (Equation (74)).

The synthesis of 3,7-dimethylimidazo[4,5-$g$]quinazoline-6,8(5$H,7$H)-dione and imidazo[4,5-$g$]quinazoline-6,8(5$H,7$H)-dione, the 1-methyl and 1,9-dimethylated versions (155) of lin-benzoxanthine, respectively, has been achieved using an approach (Equation (75)) based upon an imidazole ring assembly on 7-chloro-3-methyl-6-nitroquinazoline-2,4(1$H,3$$'H$)-dione, effected by treatment with NH$_3$ or MeNH$_2$ followed by reductive cyclization in HCO$_2$H $^{84}$JHC791. In this same investigation, the 9-(formylamino)-lin-benzoxanthine derivatives (156) were obtained from 7-hydratino-6-nitro-quinazoline-2,4(1$H,3$H)-dione precursors.
Tricyclic Systems: Central Carbocyclic Ring, 5- and 6-membered Rings

908

(140) $\xrightarrow{\text{KmNO}_{4}, \text{HOBu}^t, 25-70^\circ C, 4.25 \text{ h}}$ 48%

(141) $\xrightarrow{\text{Ac}_2\text{O}, 145-150^\circ C, 3 \text{ h}}$ 93%

(142)

$\text{i, NH}_3, \text{DMF, 10^\circ C, 30 min; ii, POCl}_3, 15-70^\circ C, 2.25 \text{ h; iii, NH}_4\text{OH, H}_2\text{O, 100^\circ C, 1 h}}$

(143) ca. 1:1

$\xrightarrow{\text{TMS-N}_3, \text{MeCN, 25-95^\circ C, 3 h}}$

(147)

$\xrightarrow{\text{H}_2\text{CN}, \text{KOBu}^t, \text{DMF, 155^\circ C, 3 h}}$ 56%

$\xrightarrow{\text{H}_2\text{NCONH}_2, \text{DMF, 155^\circ C, 5 h}}$ 55%

$\xrightarrow{\text{HCl(=NH}_3\text{NH}_2+\text{AcOH, DMF, 155^\circ C, 3 h}}$ 86%

Scheme 16

(146) $\xrightarrow{\text{H}_2\text{NCN}, \text{KOBu}^t, \text{DMF, 155^\circ C, 3 h}}$ 40-93%

(148) $\text{R=H, OH, NH}_2$

Scheme 17

(149) $\xrightarrow{\text{Li, HOBu}^t, \text{NH}_3, -78^\circ C, 35 \text{ min}}$ 20%

(150) $\text{Li, NH}_3, -78^\circ C, 35 \text{ min}$ 52%

Scheme 18

(151) $\xrightarrow{\text{P}_2\text{S}_5, \text{H}_2\text{S, pyridine, 115^\circ C, 8 h}}$ 56%

$\xrightarrow{\text{Mel, KOH, MeOH, 25^\circ C, 1 h}}$ 82%

(153)
Using the same general approach, a large number of *lin-* (157) and *prox-* (158)–(159) benzo-separated analogues of theophylline, caffeine, isocaffeine, and the potent cyclic nucleotide phosphodiesterase (PDE) inhibitor 3-isobutyl-1-methylxanthine (IBMX), among others, were prepared as potential PDE inhibitors or as potential A<sub>1</sub> or A<sub>2</sub> adenosine receptor antagonists (86JMC972, 89JMC2247). For the most part, their syntheses utilized 7- or 5-chloro-6-nitroquinoxaline-2,4(1H,3H)-dione as precursors, and an amination/reductive cyclization sequence for imidazole ring construction.

The first synthesis of *prox*-benzoguanine (160; R = NH<sub>2</sub>) was accomplished by using a similar sequence on 2-amino-5-chloro-6-nitroquinoxaline-4(3H)-one (86JOC4067). This same report described a simplified preparation of *prox*-benzohypoxanthine (160; R = H) involving the catalytic hydrogenation of 3-amino-2,6-dinitrobenzonitrile in HCO<sub>2</sub>H. Compound (161), the carbocyclic derivative of *lin*-benzo-separated 2',3'-dideoxyinosine (DDI, a potent anti-HIV antiviral drug) was prepared in two steps from 7-chloro-6-nitroquinoxaline-4(3H)-one and the appropriate racemic aminocyclopentane (89MI 722-01).

*lin*-Benzohypoxanthine derivatives in the form of the alkylated imidazo[4,5-g]quinazoline-
4,8,9(3H,7H)-triones (162) have been synthesized by Fremy radical oxidation of 4-amino-imidazo[4,5-\textit{g}]quinazolines or by nitrogen dioxide oxidation of their 4,9-unsubstituted derivatives \cite{86JOC4784,88JOC7355}. As neither approach afforded the desired \textit{lin}-benzoxanthine derivatives (163), these imidazo[4,5-\textit{g}]quinazoline-4,6,8,9(3H,5H,7H)-tetriones were obtained instead by xanthine oxidase-mediated oxidation of the corresponding triones (162). A 48\% HBr-mediated reduction was utilized to generate the 4,9-dihydroxylated forms (164) and (165) of \textit{lin}-benzohypoxanthine and \textit{lin}-benzoxanthine. These could be re-oxidized to their benzoquinone form by treatment with DDQ.

For all those \textit{lin}-benzohypoxanthine and \textit{lin}-benzoxanthine quinone derivatives possessing a leaving group at the 2\textit{x} position described above, the requisite 3-methylimidazo[4,5-\textit{g}]quinazoline precursors were synthesized by annelation of an imidazole ring onto 6-amino-7-(methylamino)quinazolin-4(3H)-one by acylicative cyclization. By contrast, the precursors to those \textit{lin}-benzohypoxanthine quinone derivatives (166) possessing a leaving group at the 6\textit{z} position were synthesized by annelation of a pyrimidine ring onto ethyl 6-(\textit{\alpha}-methoxyacetamido)-2-(methoxy-methyl)-1-methylbenzimidazole-5-carboxylate by aminative cyclization \cite{89JOC3611}. Catalytic hydrogenation to the 7-amine then permitted the same Fremy’s salt-mediated oxidation described above to be used in the generation of the imidazo[4,5-\textit{g}]quinazoline-4,8,9(3H,7H)-triones. By this same synthetic route, the 2,6-bis(bromomethyl)-3-methyl-\textit{lin}-benzohypoxanthine-4,9-quinone (167) was also prepared.

The preparation of \textit{lin}-benzoinosine-4,9-quinone (168) was carried out by regioselective ribosylation of 4-nitroimidazo[4,5-\textit{g}]quinazolin-8(3H,7H)-one followed by nitro group reduction, Fremy oxidation, and deacetylation \cite{91JOC776}. 4-Amino-\textit{lin}-benzohypoxanthine (169; \(R = \text{H}) was prepared (80\%) by sodium dithionite reduction of 5-nitroimidazo[4,5-\textit{g}]quinazolin-8(3H,7H)-one, but
the corresponding secondary amine riboside \((169; R = 1-\beta-D\text{-ribofuranosyl})\) deribosylated rapidly in water and could not be isolated.

As part of an investigation into modifications on the heterocyclic base of acyclovir (9-[2-hydroxyethoxy)methyl]-9H-guanine (Zovirax) a potent anti-HSV antiviral drug, the lin-benzoguanine derivatives \((170)\) have been prepared using a silylation/alkylation sequence conducted on lin-benzoguanine itself \((85JMC982)\). Unfortunately, compound \((170; R^1 = H, R^2 = \text{CH}_2\text{O(}\text{CH}_2\text{)OH})\) did not show any inhibition of HSV-1, although it did exhibit some ability to compete with acyclovir for the binding site on the viral thymidine kinase. Finally, a 1995 communication describes the synthesis of certain lin-benzo-separate 7-deazaadenines (aminopyrrolo[3,2-g]quinazolines) \((171)\) as ATP competitive inhibitors of the epidermal growth factor receptor (EGFR) \((B-95MI 722-01)\).

\[
\begin{align*}
\text{(168)} & \quad R = 1-\beta-D\text{-ribofuranosyl} \\
\text{(169)} & \quad R = \text{H, 1-}\beta-D\text{-ribofuranosyl}
\end{align*}
\]

\[
\begin{align*}
\text{(170)} & \quad R^1 = \text{H}, R^2 = \text{CH}_2\text{O(}\text{CH}_2\text{)OBz}; \\
& \quad R^1 = \text{CH}_2\text{O(}\text{CH}_2\text{)OBz}, R^2 = \text{H}; \\
& \quad R^1 = \text{H}, R^2 = \text{CH}_2\text{O(}\text{CH}_2\text{)OH}
\end{align*}
\]

\[
\begin{align*}
\text{(171)} & \quad R = \text{alkyl}
\end{align*}
\]

7.22.11.2 Furocoumarins and Furochromones

A general description of these compounds appears in Section 7.22.12.2.

7.22.11.2.1 Synthesis using chromium carbene complexes

Wulf and co-workers have utilized chromium carbene complexes to synthesize nonlinear furocoumarins \((87TL1381, 88IA7419, 88OM3246)\). The reactions of 2-furyl chromium carbene complexes with derivatives of pent-4-ynoic acid were utilized in the preparation of the naturally occurring compounds sphonadin \((172; X = \text{O})\) and heratomin (Scheme 19). An analogous method using a 2-thienyl chromium carbene complex was employed to synthesize the unnatural thiosphonadin \((172; X = \text{S})\). The use of a 3-furyl chromium carbene complex afforded another unnatural furocoumarin. Once the intermolecular approach to compounds \((172; X = \text{O, S})\) had been demonstrated to be general in nature, an alkynie was tethered to the 2-furyl complex to determine whether or not the reactions would occur in an intramolecular fashion. The reaction did take place, but in high yield only when a terminal trimethylsilyl group was resident on the alkynie moiety. This discovery enabled these investigators to develop convergent syntheses of sphonadin \((172; X = \text{O})\) (Scheme 20) and angelicin \((173)\) (Scheme 21).

\[
\begin{align*}
\text{(CO)}_2\text{Cr} + \text{CO}_2\text{Me} & \quad \xrightarrow{i, \text{ii or iii}} \quad 42-55\% \\
\text{OMe} & \quad \xrightarrow{\text{iii or iv}} \quad 40-69\%
\end{align*}
\]

\[
\begin{align*}
\text{(172)} & \quad X = \text{O, S}
\end{align*}
\]

\[\text{i, THF, 85 °C, 18 h; ii, air, PhH, TsOH, 4 Å sieves, 85 °C;}
\[\text{iii, air, SiO}_2; \text{iv, 5% Pd/C, Ph}_2\text{O, 259 °C; v, ddc, PhMe, 110 °C}\]

Scheme 19
7.2.11.2 Other methods

The last step in the synthesis of the sulfur- and selenium-containing psoralen analogues (174) (7H-thieno[3,2-g][1]benzothiopyran-7-one, 7H-seleno[3,2-f][1]benzothiophen-7-one, 2H-selenolo[3,2-g][1]benzothiopyran-2-one, and 7H-selenolo[3,2-g][1]benzoselenopyran-7-one) was the polyphosphoric acid silyl ether (PPSE)-mediated cyclization of benzothiophenes or selenophenes shown in Equation (76) <92H(34)1119>.

Kanematsu and co-workers found that furo[2,3-f]inden-7-one could be converted to psoralen (175) using a Baeyer–Villiger oxidation followed by dehydrogenation (Equation (77)) <84JA6735>. Conversion of the indanone to its oxime followed by a Beckmann rearrangement and dehydrogenation was used to produce 8-azapsoralen (176) (Equation (78)). While a methoxylated furo[2,3-f]inden-7-one did not afford methoxsalen under the same conditions, 8-methoxy-3-(phenylthio)inden-7-one did produce the desired furocoumarin (177) (20%) under Baeyer–Villiger oxidation conditions (Equation (79)) <94TL9617>. Several furocoumarin natural products substituted at the 2-position (178; R = H, 2-allyl, C(OH)Me₂) have been prepared via a Wittig reaction using a 4-hydroxybenzofuran-5-carbaldehyde (Equation (80)) <95T3087>.
7.22.11.3 Ellipticines

A general description of these compounds appears in Section 7.22.12.3.

7.22.11.3.1 Synthesis using cycloaddition reactions

Gribble and co-workers utilized the cycloaddition of the suitably substituted furo[3,4-b]indole (179) with 3,4-pyridyne (generated in situ from 3-chloro-4-iodopyridine and an alkyllithium reagent) followed by a tandem oxygen-bridge extrusion/deprotection to afford a mixture of ellipticine and isoellipticine (Scheme 22) \(^{(84JOC4518)}\). MO calculations supporting a regioselective HOMO/LUMO interaction between (179) and an acrylate led these investigators to the route shown in Scheme 23 in which reaction of compound (179) and a suitably protected 5,6-dihydropyridone gave a single carbazole pyridone product which gave ellipticine after amide reduction and palladium-catalyzed dehydrogenation/debenzylolation \(^{(90TL1081,92JOC5878)}\).
Tricyclic Systems: Central Carbocyclic Ring, 5- and 6-membered Rings

(179) i, ii \[\text{R'=MeOC}_2\text{H}_2\text{CH}_2\] \[\text{iii} \to \text{R'=C}_2\text{H}_5\]

R=4-MeOC\text{H}_2\text{C}_2\text{H}_2

i, N-(4-methoxyphenyl)-5,6-dihydro-2-pyridone, TMS-OTf; CH\text{Cl}_2; ii, NaHCO\text{3}, H\text{2}O; iii, LAH, THF; iv, Pd/C

\text{Scheme 23}

7.22.11.3.2 Other methods

Saulnier and Gribble used a tetracyclic keto lactam to prepare ellipticine by treatment with MeLi followed by NaBH\text{4} reduction of the resultant rearranged tetracyclic diol (Scheme 24) \langle82\text{JOC}2810\rangle. Modifications of this method have been used to prepare several analogues of ellipticine \langle83\text{JOC}2690, 83\text{TL}3831, 85\text{JOC}5451, 86\text{MI} 722-01, 89\text{JOC}3264, 92\text{JOC}5891\rangle.

Ellipticine and olivace have both been synthesized via a Bischler–Napieralski cyclization and subsequent aromatization of alkylamidocarbazoles, as shown for the preparation of compounds (181) (Equation (81)) \langle90\text{JOC}4528\rangle.

6-Azido-5,7-dimethyl-6-phenylisoquinoline (182) has been used to prepare ellipticine via a nitrene insertion reaction (Equation (82)) \langle89\text{TL}297\rangle.

7.22.11.4 Pyrroloquinolinequinone and Related Compounds

A general description of these compounds appears in Section 7.22.12.4. PQQ is also known as methoxatin.

Fischer indole cyclization and transformation of a nitrile to an ester (Pinner synthesis) to yield diethyl 5-hydroxy-1\text{H}-pyrrolo[2,3-\text{f}]quinoline-2,7-dicarboxylate (183) was performed in one step by
treatment of either a 5-quinolylhydrazone or an acetylated azo precursor with saturated ethanolic HCl (Scheme 25) \(<85JA7198, 87JOC1942\>). Compound (183) was then oxidized with 

can to afford the decarboxymethoxatin (184), an analogue of PQQ. Although the yield of product was very low, a 

Doebner reaction was used as the key step in the preparation of diethyl 5-methoxy-1H-pyrrolo[2,3-

f]quinoline-2,9-dicarboxylate (185), which is the precursor to an isomeric decarboxymethoxatin (Equation (83)) \(<87JOC1942\>). 7,9-Didecarboxymethoxatin has also been synthesized in order to 

compare its chemical (e.g., acid-base, electrochemical) properties to those of methoxatin \(<85JA3328\>.

\[
\begin{align*}
\text{(183)} & \quad \text{i, NaNO}_2, \text{HCl, H}_2\text{O, 5 °C; ii, ethyl } \alpha\text{-methylacetoacetate; iii, HCl, EtOH; iv, CAN,}\ H_2\text{O, MeCN, 5 °C} \\
\text{(184)} & \quad \text{Scheme 25}
\end{align*}
\]

Furo- and thieno- analogues (187; X = O, S) of PQQ have been prepared via the cyclization of a 

6-amino-5-hydroxybenzofuran or benzothiophene with the dimethyl ester of 4-ketogluataconic acid, 

followed by oxidation (HNO\(_3\)) of the triesters (186) to the ortho-quinones (Scheme 26) \(<94HCA100\>.

\[
\begin{align*}
\text{(185)} & \quad \text{MeO} \\
\text{(186)} & \quad \text{MeO}_2\text{C} \\
\text{(187)} & \quad \text{MeO}_2\text{C} \\
\text{Scheme 26}
\end{align*}
\]

7.22.12 IMPORTANT COMPOUNDS AND APPLICATIONS

7.22.12.1 Benzo-separated Purines

Leonard and co-workers have synthesized \textit{de novo} analogues of the purines, and especially of 

adenine, that differ from the natural bases, ribonucleosides, or ribonucleotides by defined dimen-
sional changes. With these dimensional probes, it is possible to assess the size of the space available or required for the purine (e.g., adenine) moiety in enzyme–coenzyme binding sites. In the best cases, the dimensional probes also serve as fluorescent probes. Several reviews on the subject covering the literature through the mid-1980s are available (82ACR128, B-84MI 722-01, 84PAC1025, 85MI 722-01, 86T1917). A survey of the synthetic developments in this class of compounds appears in Section 7.22.11.1.

The initial synthetic target was 8-aminoimidazo[4,5-g]quinazoline (147), to which Leonard and co-workers gave the trivial name lin-benzoadene. The prefix refers to the linear disposition of the three rings in compound (147), and the numbering is as shown. The formal insertion of a spacer into the center of the adenine ring system, in this case a benzene ring (actually four additional carbon atoms), stretches the natural adenine linearly by 2.4 Å, the width of the benzene ring known accurately from many x-ray structure determinations. The stretched-out analogue (147) has the advantage of retaining unobstructed the normal binding sites, e.g., N-1, N-6, and N-7 of adenine. Similar to lin-benzoadene (147) in containing the binding sites analogous to the 1,N6 binding sites found in adenine and related nucleosides and nucleotides are prox-benzoadene (188) and dist-benzoadene (189). In the abbreviated nomenclature, prox for proximal and dist for distal refer to the spatial relationship of the amino groups to the imidazole ring in the respective compounds. The rings are angled within a common plane. The term benzo presents no ambiguity since only when the ring is central is it devoid of nitrogen and accordingly ‘benzo’. The structural differences between (147), (188), and (189) reside in the spatial relationships of the pyrimidine and imidazole rings with respect to the central benzene ring and in the nature of the internal hydrogen bonding likely to occur in isomers (188) and (189). They are not actually dimensional probes since they also involve orientational changes.

The concept of dimensional probes of binding and activity has stimulated the synthesis of analogues of (147), (188), and (189) that differ from natural bicyclic bases, ribonucleosides, and ribonucleotides by defined dimensional changes. These have found application in numerous biochemical investigations, including ones of the enzymes pyruvate kinase and Escherichia coli DNA polymerase I (84B3868), adenosine deaminase (calf intestinal mucosa) and xanthine oxidase (buttermilk) (88JOC3873), the cGMP-dependent protein kinase (85B1122, 88B1988), and the catalytic subunit of cAMP-dependent protein kinase (83B2347, 83B6310, 84B4350, 88B1988). Benzo-separated purines have been developed as potential PDE inhibitors (86JMC972), potential A1 or A2 adenosine receptor antagonists (89JMC2247), as reductive alkylators (86JOC4784, 87B7355, 89JOC3611, 91JOC776), as potential antiviral agents (85JMC982, 89MI 722-01), and as ATP competitive inhibitors of the epidermal growth factor receptor (EGFR) (B-95MI 722-01).

### 7.22.12.2 Furocoumarins and Furochromones

The furocoumarins, both linear (190) and bent (191), and furochromones (192) are photoactive compounds which are often utilized in conjunction with UV light in the treatment of skin disorders such as psoriasis and vitiligo (90MI 722-01, 91MI 722-01). As a result of this interest, many x-ray crystal structure determinations of furocoumarin and furochromone analogues have been made. Compounds (193)–(200) are some of these (86AX(C)1849, 87AX(C)2369, 88AX(C)676, 88AX(C)1475, 89AX(C)1520, 90AX(C)437, 90AX(C)2146, 91AX(C)2144). Many are naturally occurring substances. Some of the linear furocoumarins, or psoralens as they are often called, have been found to be highly mutagenic and/or carcinogenic, perhaps often as a consequence of their ability to intercalate between base pairs in DNA and form double-stranded crosslinks by undergoing two [2 + 2] cycloadditions per molecule. As a result, research on the family of compounds known as the bent
Tricyclic Systems: Central Carbocyclic Ring, 5- and 6-membered Rings

furocoumarins has taken on new importance, since these derivatives are not as able to crosslink DNA. A survey of the synthetic developments in this class of compounds appears in Section 7.22.11.2.

7.22.12.3 Ellipticines

Ellipticine (201) and its analogues have been a strong focus of investigation ever since the discovery that the parent compound showed good antitumor activity (for reviews, see 〈85H(23)1277, B-90MI 722-02, 91SL289〉). Since that initial discovery, some of the ellipticine derivatives that have been used in chemotherapeutic clinical trials include elliptinium (202), ditercalinium (203), datelliptium (204), and pazellipticine (205). Because of the mixed results seen up to 1990, though, it is evident that additional structural modification will be required before any ellipticine derivative finds wide use as a chemotherapeutic agent. To support some of the ongoing efforts to improve upon the activity of these compounds, x-ray crystal structures of several ellipticine analogues and related compounds have been determined. Compounds (206)–(212) are some of these 〈83AX(C)631, 84AX(C)1871, 88AX(C)386, 88AX(C)1797, 88AX(C)2123, 88AX(C)2126〉. A survey of the synthetic developments in this class of compounds appears in Section 7.22.11.3.

7.22.12.4 Pyrroloquinolinequinones and Related Compounds

Pyrroloquinolinequinone (213) (2,7,9-tricarboxy-1H-pyrrolo[2,3-f]quinoline-4,5-dione, PQQ) (trivial name: methoxatin) has been identified as a co-factor in many enzymes, including those that oxidize MeOH to HCHO in methylotrophic and autotrophic bacteria. Quinoproteins appear in mammalian systems as well, and methoxatin itself (213) has even been identified as an inhibitor of HIV-1 reverse transcriptase (for PQQ reviews, see 〈91MI 722-02, 95MI 722-02〉). Interest in under-
standing the co-enzymic behavior of PQQ has led investigators to determine the x-ray crystal structure of its tribasic salt (214) \(93\text{AX(C)2093}\) and the 1,3,5-trinitrophenylhydrazone (215) of a triester derivative \(85\text{AX(C)89}\). The chemistry of PQQ (213) is noteworthy in that nucleophilic attack at the quinone ring occurs most often at C-5 instead of at C-4 \(89\text{MI 722-02}, 93\text{HCA1674}, 95\text{JA3278}\). \(^{13}\text{C}\) NMR and IR spectroscopic data support the contention that the electrophilicity at C-4 is diminished relative to that at C-5 by conjugative interaction with the pyrrole ring nitrogen \(94\text{HCA100}\). A theoretical study in 1995 employing semiempirical (AM1, PM3) and \textit{ab initio} (3-21G, 6-31G, and 6-31G**) procedures has been conducted to examine three possible molecular mechanisms for the oxidation of MeOH by PQQ (213) \(95\text{JA8807}\). A survey of the synthetic developments in this class of compounds appears in Section 7.22.11.4.

### 7.22.12.5 Ergolides

Pergolide mesylate (216) (Permax) \(89\text{MI 722-03}\) and cabergoline (217) (Dostinex) \(94\text{MI 722-01}\) are an antiparkinsonian and antiprolactin agent, respectively, with pyrrolo[3,4-\(g\)]quinoline-based
Tricyclic Systems: Central Carbocyclic Ring, 5- and 6-membered Rings

![Chemical Structures](image)

tetracyclic structural ergolide frameworks. They are both potent, long-acting dopamine agonists, and the latter is in clinical trials for Parkinson's disease and other maladies.