The Chemistry of Heterocycles

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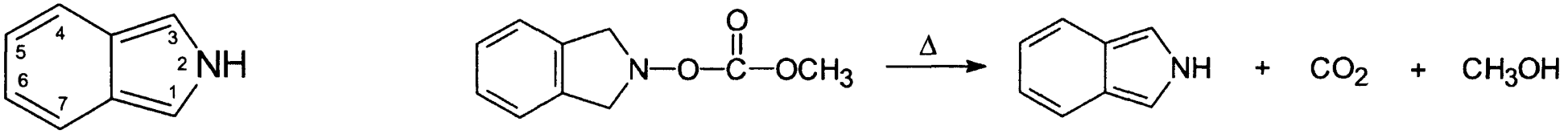
The Chemistry of Heterocycles, (Second Edition).

By Theophil Eicher and Siegfried Hauptmann, Wiley-VCH Veriag GmbH, 2003

5.14 Isoindole

[A-C] The name isoindole is admissible for benzo[*c*]pyrrole. Although isoindole has an *ortho*-quinonoid structure, it can be isolated; it is characterized spectroscopically and chemically:



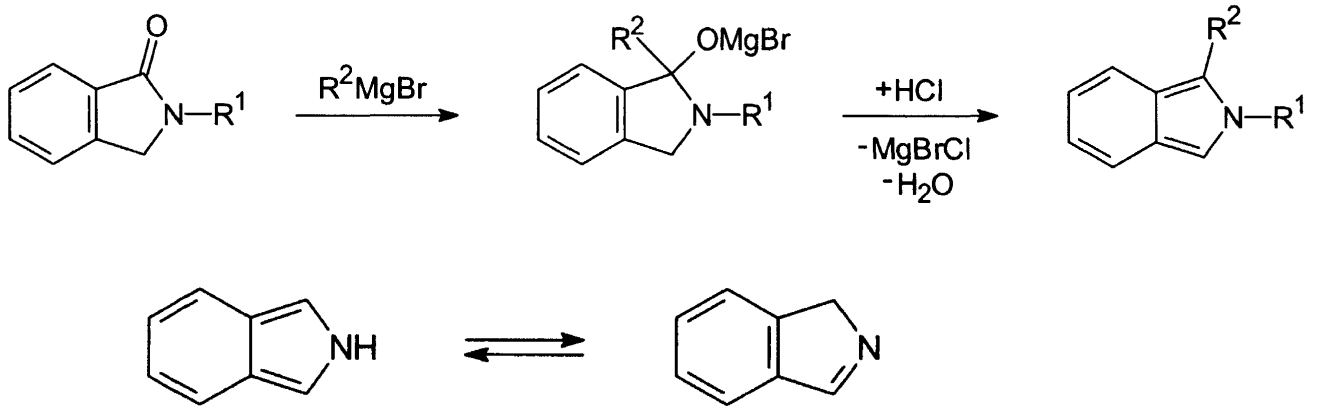
2-(Methoxycarbonyloxy)-1,3-dihydroisoindole (obtained from 2-hydroxy-1,3-dihydroisoindole and methyl (4-nitrophenyl)carbonate) was pyrolyzed in vacuo at 500 °C and isoindole condensed on a cold-finger condenser filled with liquid nitrogen.

Isoindole crystallizes in colorless needles, darkens at room temperature and polymerizes. Solutions in dichloromethane kept under nitrogen are more stable.

They give a red color with EHRLICH'S reagent and form the corresponding DIELS-ALDER adducts (*endo*:*exo* = 2:3) with *N*-phenylmaleinimide.

Isoindoles substituted on the pyrrole ring are thermally more stable and can, for instance, be prepared from 2-substituted 1,3-dihydroisoindol-1-ones by the following route.

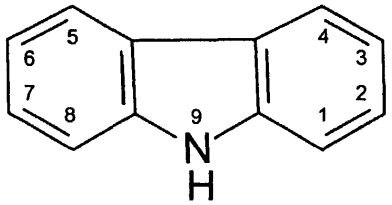
A tautomeric equilibrium exists between isoindoles unsubstituted in the 2-position and the corresponding 1*H*-isoindoles:



Isomerizations in which an H-atom changes its position in a heterocyclic system are known as annular tautomerisms. This is a special case of prototropy (prototropic rearrangement).

For isoindole, the position of the equilibrium depends to a large extent on the type of the substituent in the 1- and/or 3-position. The 1-phenyl compound exists in the 2*H*-form and couples with benzenediazonium chloride in the 3-position.

5.15 Carbazole



[A,B] The numbering of carbazole (benzo[*b*]indole) predates the introduction of systematic nomenclature and is retained for historical reasons.

Carbazoles behave like *o*,*o*'-disubstituted diphenylamines. However, the basicity of carbazole, pK_a = -4.94, is much lower than that of diphenylamine (pK_a = 0.78), and also lower than that of indole and pyrrole.

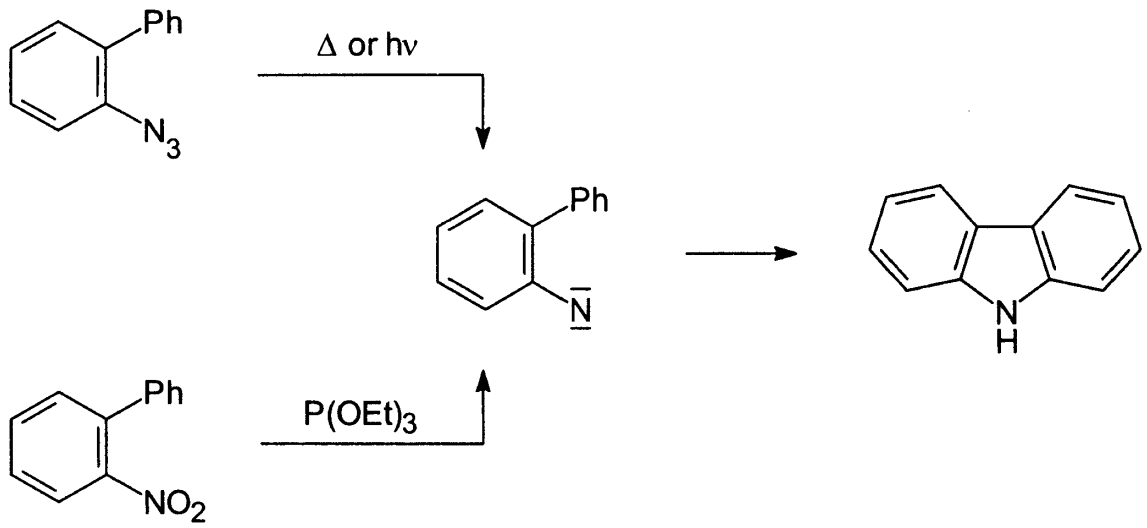
As a consequence, carbazole is insoluble in dilute acids but only soluble in coned H_2SO_4 with protonation of the N-atom. On pouring the solution into water, carbazole precipitates without polymerization.

The NH-acidity of carbazole pK_a = 17.06 corresponds approximately to that of indoles and pyrroles. For this reason, carbazole is convertible into *N*-metallated compounds which can be subjected to electrophilic substitution on nitrogen.

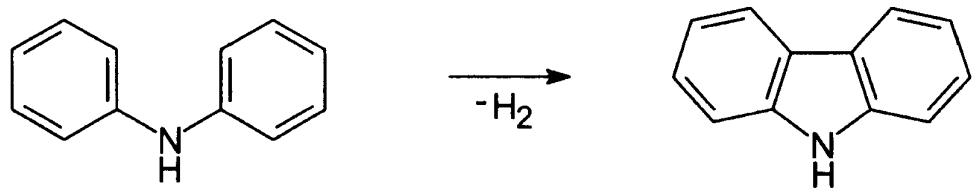
Carbazole reacts with electrophiles faster than benzene. Substitution occurs regioselectively in the 3-position, e.g. in the VILSMEIER-HAACK formylation.

There are very few addition and ring-opening reactions of carbazoles.

[C] *ortho*-Substituted biphenyl derivatives are a starting point for the synthesis of carbazoles, e.g.:



Thermolysis or photolysis of 2-azidobiphenyl produces a nitrene, as does deoxygenation of 2-nitrobiphenyl with triethyl phosphite. The nitrene cyclizes immediately to give carbazole. Carbazoles can also be made by cyclodehydrogenation of diphenylamines.



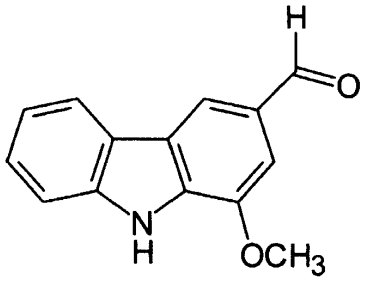
This reaction can be carried out photochemically or with palladium(II) acetate in acetic acid.

[D] Carbazole forms water-insoluble crystals of mp 245 °C, bp 355 °C, and occurs in the anthracite fraction of coal tar.

A few alkaloids are derived from carbazole, e.g. murrayanine **1** (1-methoxycarbazole-3-carbaldehyde) and ellipticine **2**, which is a carbazole system with a fused pyridine ring.

Ellipticine is one of the substances which can intercalate into human DNA. The molecule is inserted between two paired bases. Ellipticine derivatives are approved in some countries for use as cytostatic agents.

Pharmaceuticals containing a carbazole system are rare, but one example of these is the beta-blocker carazolol **3** [1-(carbazol-4-yloxy)-3-(isopropylamino)propan-2-ol]:



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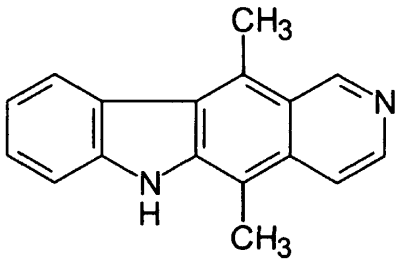

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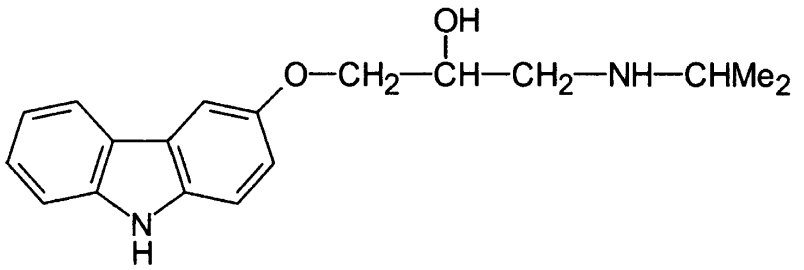

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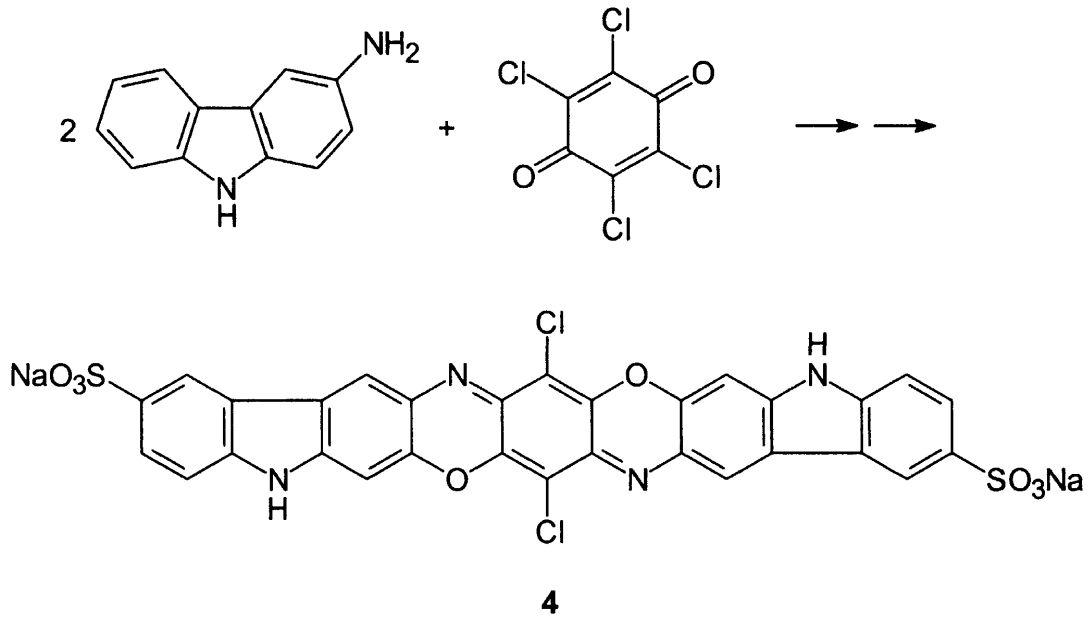
The textile dye Sirius Light Blue **4** is produced by a double cyclocondensation of 3-aminocarbazole with chloranil followed by sulfonation:



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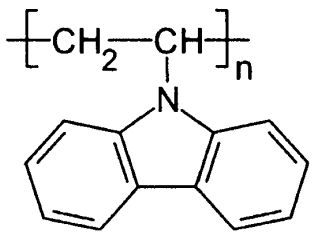
Carbazole is vinylated in the 9-position by acetylene. The resulting polymer **5** (poly-*N*-vinylcarbazole) proves to be a photoconductor:



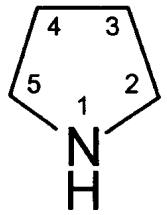
5

Photoconductors are substances which, upon irradiation, increase their electric conductivity. They find use in electrophotography as well as in copying processes.

5.16 Pyrrolidine

[A] The pyrrolidine molecule is practically without strain, nonplanar and conformationally mobile. As in the case with tetrahydrofuran, the twist and envelope conformations are preferred. The activation energy for pseudorotation is 1.3 kJ mol^{-1}.

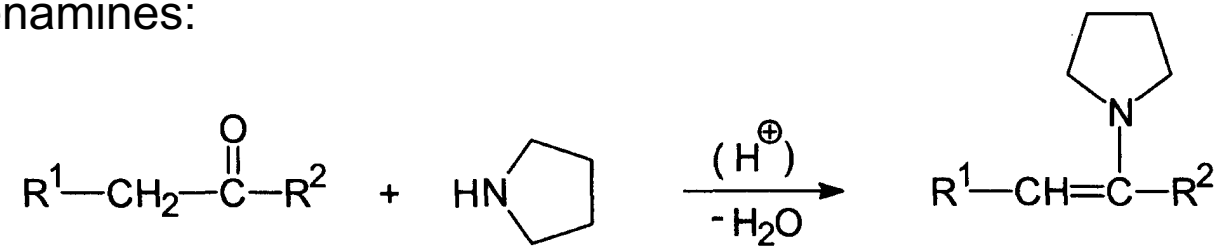
The chemical shifts in the NMR spectra lie in the region characteristic for cycloalkanes and dialkylamines.



	^{1}H-NMR ($CDCl_3$) δ (ppm)	^{13}C-NMR ($CDCl_3$) δ (ppm)
H-2/H-5:	2.75	
H-3/H-4:	1.53	
C-2/C-5:		47.1
C-3/C-4:		25.7

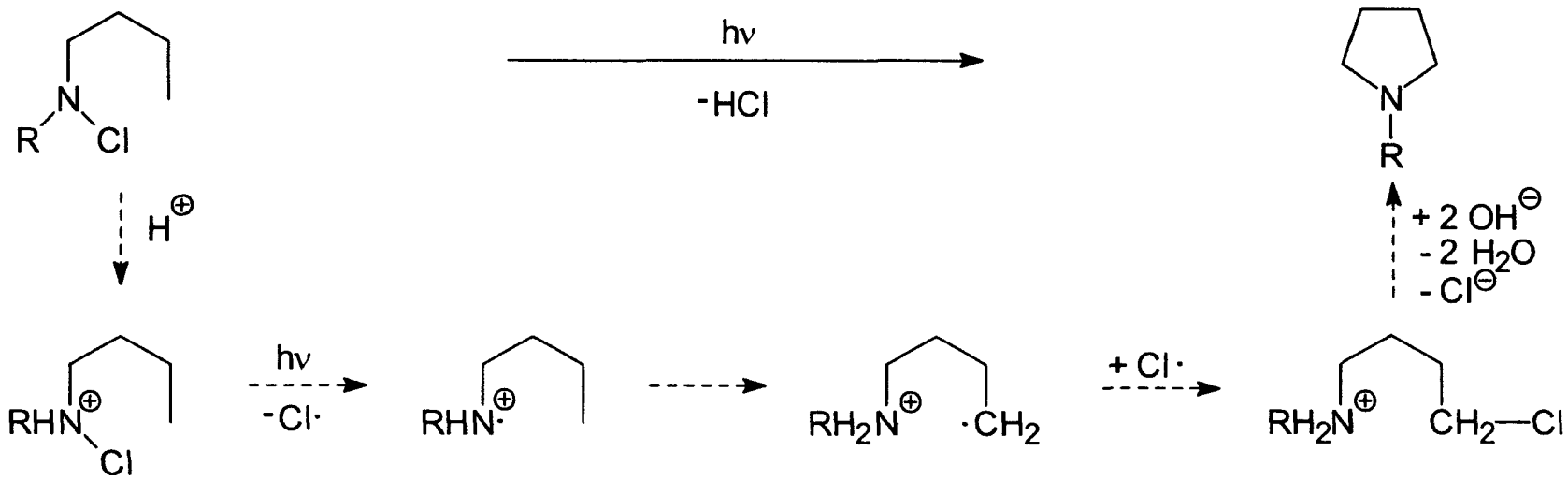
[B] Pyrrolidines and *N*-substituted pyrrolidines undergo reactions typical of secondary or tertiary alkylamines. They can be alkylated, quaternized, acylated and nitrosated.

The basicity and nucleophilicity of pyrrolidines are greater than those of diethylamine (pyrrolidine pK_a = 11.27, diethylamine pK_a = 10.49). Because of these properties, pyrrolidine is very suitable for the conversion of carbonyl compounds into enamines:



[C] Pyrrolidine and *N*-substituted pyrrolidines are produced commercially by ring transformation of tetrahydrofuran with ammonia or primary amines at 300 °C on aluminium oxide catalysts.

N-Substituted pyrrolidines are also accessible by photodehydrohalogenation of *N*-alkyl-*N*-chloroamines (HOFMANN-LÖFFLER reaction):



The reaction is first carried out in acid solution. The photolysis of the *N*-chloroammonium ions produces an aminium radical ion which, by abstraction of an H-atom from the methyl group, is converted into an alkyl radical.

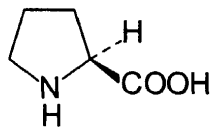
The latter initiates a chain reaction by abstracting a Cl-atom form a new *N*-chloroammonium ion. After addition of a base, the cyclodehydrohalogenation occurs via the corresponding δ-chloroalkylamine involving an intramolecular nucleophilic substitution.

[D] Pyrrolidine is a colorless, water-soluble liquid of a penetrating amine-like odor, of bp 89 °C. It fumes in air owing to salt formation with carbon dioxide.

Pyrrolidin-2-one, often called pyrrolidone, is the lactam of 4-aminobutyric acid. Pyrrolidone is prepared from butano-4-lactone and ammonia at 250 °C. It is colorless, water-soluble, of mp 25 °C and bp 250 °C (decomp). Pyrrolidone is vinylated by acetylene. Poly-(*N*-vinylpyrrolidone) has proved useful as a plasma substitute in blood transfusion.

1-Methylpyrrolidin-2-one is a colorless, water-soluble liquid, bp 206 °C, made from butano-4-lactone and methylamine. As a solvent is used the industrial extraction of acetylene from gas mixtures.

Proline (pyrrolidine-2-carboxylic acid), is one of the 20 essential amino acids.



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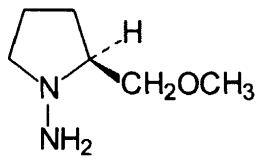
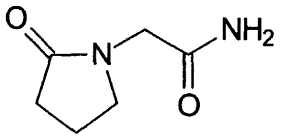


2 (SAMP)



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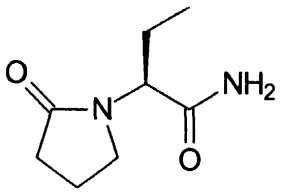

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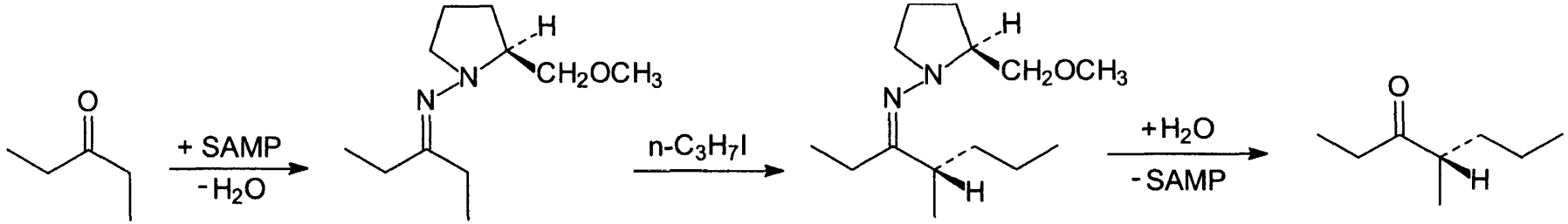
(*S*)-(-)-Proline 1, colorless crystals, mp 220°C, $[\alpha]^{20}_{D}$ -80 (water), occurs abundantly in collagen. It is produced by acid-catalyzed hydrolysis from gelatin.

Piracetam **3** is medicinally used as anticonvulsant and antiepileptic. Levetiracetam **4** is a chiral second-generation analogue of **3** providing a useful alternative for adjunctive therapy to conventionally anticonvulsants, e.g. benzodiazepines.

The designation 'chiral pool' was introduced to denote an available source of enantiomerically pure natural products. These include the (*S*)-amino acids, as well as (*S*)-lactic acid, (*S*)-malic acid, (*R*,*R*)-tartaric acid and β-D-glucose.

Their chirality can be utilized for asymmetric syntheses, demonstrated by an example of the chiral auxiliaries (*S*)- and (*R*)-1-amino-2-(methoxymethyl)pyrrolidine developed by ENDERS and abbreviated as SAMP (**2**) and RAMP. They are synthesized from (*S*)- or (*R*)-proline in several steps.

The enantioselective synthesis of the insect pheromone (*S*)-4-methylheptan-3-one **8** by alkylation of pentan-3-one **1** using these chiral auxiliaries:



The ketone **5** reacts with SAMP to give hydrazone **6**. The possibility of internal asymmetric induction exists in **6**, so that the following alkylation (action of lithium diisopropylamide in diethyl ether, followed by 1-iodopropane at -110°C) occurs diastereoselectively.

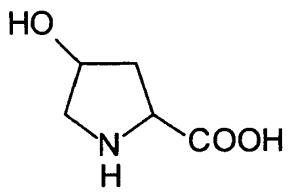
In the final step, the auxiliary SAMP is hydrolytically removed from **7**. Thereby, the α-alkylated ketone **8** is formed with ee = 99.5%. The use of RAMP as auxiliary would thus produce the (*R*)-enantiomer of **8**.

Although it appears to be an enantioselective synthesis, it is in fact a multi-step synthesis in which steps 6 → 7 represent a diastereoselective reaction. Nowadays chiral auxiliaries are at our disposal for the approach to the most varied synthetic problems.

4-Hydroxyproline **9** is a proteinogenic amino acid, occurring mainly in collagen. It can be separated from the hydrolysis products of gelatin.

Several alkaloids are derived from pyrrolidine, e.g. hygrin **10**, a minor alkaloid of the coca plant, as well as nicotine.

The vasodilator buflomedil **11** and the antihypertensive captopril **12** are drugs containing a pyrrolidine ring.



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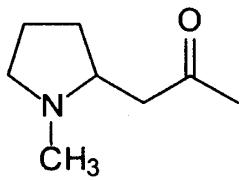

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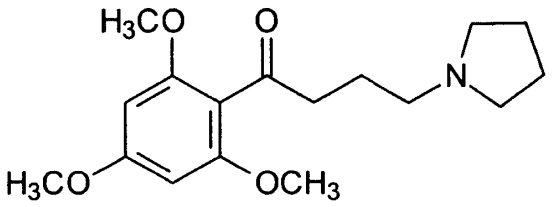

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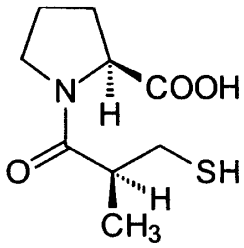
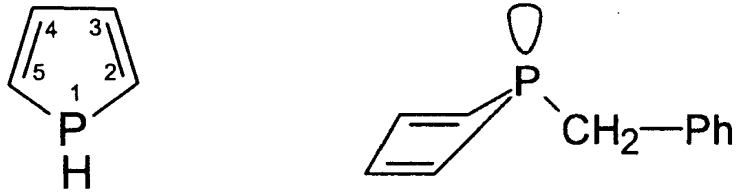


12

5.17 Phosphole

[A-C] Phosphole polymerizes rapidly. 1-Substituted phospholes are thermally more stable. X-Ray studies of 1-benzylphosphole show that the molecule is not planar and that phosphorus retains its pyramidal structure.

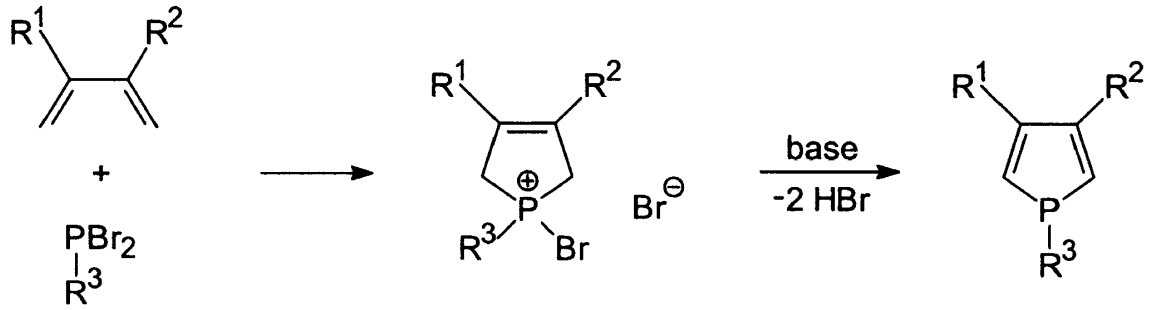


Consistent with this finding, the NMR spectra show that phosphole has a lower aromaticity than furan.

Phospholes are weak bases and react with strong acids to give phospholium salts. The cleavage of the exocyclic P-C bond by lithium in boiling THF is an interesting reaction of 1-phenyl- and 1-benzylphosphole.

The phosphole anion is planar, aromatic and iso-π-electronic with furan and thiophene.

Phospholes are accessible by [4+1] cycloaddition of buta-1,3-dienes with alkyl- or aryldibromophosphanes followed by dehydrobromination.



Summary of the general chemistry of five-membered heterocycles with one heteroatom:

• The parent compounds of the monocyclic five-membered heterocycles with one heteroatom are aromatic. When considering the three most important systems only, it appears that the aromaticity increases as follows: furan < pyrrole < thiophene (< benzene). This sequence also applies to the respective benzo[*b*] condensed systems.

• Because of their aromaticity, these compounds undergo electrophilic substitution, with the reactivity decreasing in the following order: pyrrole > furan > thiophene (» benzene). Substitution occurs regioselectively in the 2-position. The corresponding benzo[*b*] condensed systems react more slowly. Substitution occurs on the five-membered ring, but in this case, the regioselectivity is reduced.

• The reactivity as 1,3-dienes in [4+2] cycloadditions is greatest for furan which is also the system most liable to undergo ring-opening.

• The benzo[*b*] condensed systems do not react as 1,3-dienes but undergo [2+2] cycloadditions.

• The benzo[*c*] condensed systems have o-quinonoid structures. Their resonance energy is, therefore, lower than that of the corresponding benzo[*b*] condensed systems. The compounds prove to be reactive 1,3-dienes.

• Some heterocycles are accessible by cyclodehydration, namely:

— furans from 1,4-dicarbonyl compounds
— benzo[*b*]furans from α-phenoxycarbonyl compounds
— benzo[*b*]thiophenes from α-(phenylsulfanyl)carbonyl compounds
— indoles from *N*-acyl-*o*-toluidines or α-arylamino ketones
— dibenzofurans from 2,2'-dihydroxybiphenyls
— tetrahydrofuransfrom 1,4-diols

• Cyclocondensation is an important synthetic method starting from:

— 1,4-dicarbonyl compounds (thiophenes, pyrroles)
— α-halocarbonyl compounds and β-keto carboxylic esters (furans, pyrroles)
— α-amino ketones and β-keto carboxylic esters (pyrroles)
— 1,3-dicarbonyl compounds or β-chlorovinylcarbonyl compounds (thiophenes, selenophenes, tellurophenes)
— carbonyl compounds and CH-acidic nitriles (aminothiophenes)

• Indoles are obtained by specific cyclizations (FISCHER synthesis, REISSERT synthesis, BATCHO-LEIMGRUBER synthesis, NENITZESCU synthesis), as are carbazoles from biphenylene or diphenylamines and pyrrolidines (HOFMANN-LÖFFLER reaction).

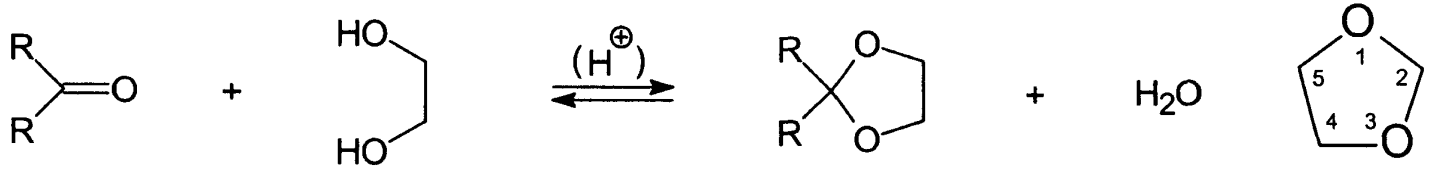
Ring transformations make possible the preparation of furans, thiolane, pyrrolidine and pyrrolidin-2-one.

The importance of five-membered heterocycles with one heteroatom, of the benzo and dibenzo condensed systems and of the partially or completely reduced compounds as natural products, pharmaceuticals, and starting materials or auxiliaries for syntheses is much greater than for three- or four-membered heterocycles, apart from oxirane.

5.18 1,3-Dioxolane

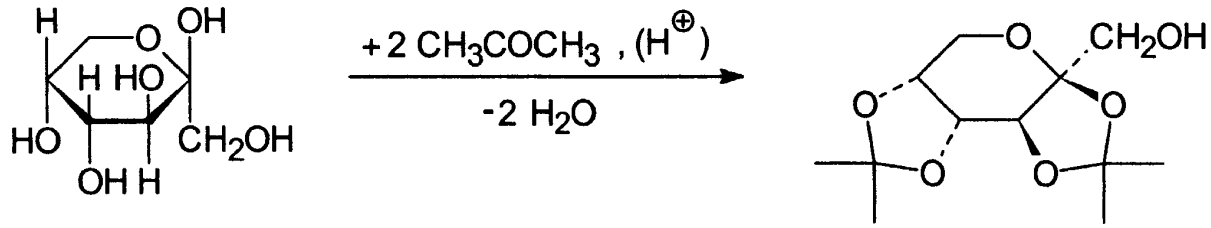
1,3-Dioxolanes can be viewed as cyclic acetals or ketals. The ring is nonplanar and conformationally mobile.

1,3-Dioxolanes are prepared by Cyclocondensation of aldehydes or ketones with 1,2-dioles in benzene and with *p*-toluenesulfonic acid as catalyst. Quantitative yields are realized by removing the resulting water by azeotropic distillation.



1,3-Dioxolanes are stable to bases. They are hydrolyzed by dilute acids even at room temperature in a reversal of their formation. The conversion of aldehydes and ketones into 1,3-dioxolanes is one of the most important methods for the protection of the carbonyl function in multistep syntheses.

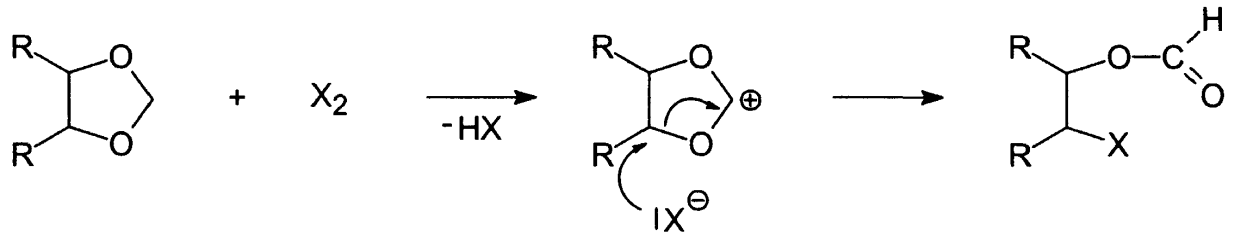
It is also the standard method for blocking two vicinal *cis*-positioned hydroxy groups in a carbohydrate, via reaction with acetone, e.g.:



β-D-fructopyranose

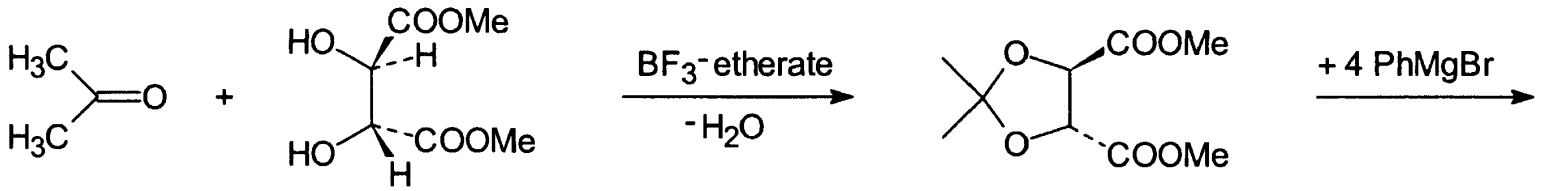
2,3:4,5-di-O-isopropylidene-β-D-fructopyranose

Halogens react with 1,3-dioxolanes via 1,3-dioxolan-2-ylium salts to give β-haloalkyl formates:

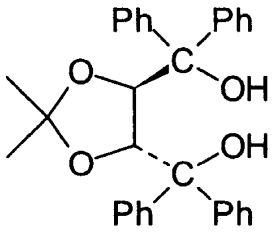


1,3-Dioxolane, a colorless liquid, bp 78 °C, is soluble in water.

(4*R*,5*R*)- and (4*S*,5*S*)-2,2-Dimethyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanol were prepared from enantiomeric methyl tartrates as follows:



(R,R)-(+)-dimethyl tartrate



(4R,5R)-(-)-enantiomer

The compounds form chiral metal complexes as well as chiral clathrates and can be used as auxiliaries for asymmetric syntheses.