Synthesis of 2,6-Disubstituted Piperidines, Oxanes, and Thianes

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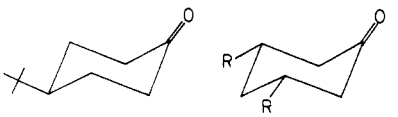
I. Introduction

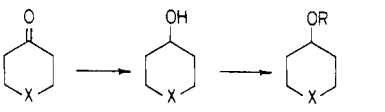
Investigations on the stereochemistry of cyclohexanes have been based mostly on the conformationally anchored 4-*tert*-butylcyclohexanone (1) and 3,5-disub-



1 2. R = Me, Ph, t-Bu

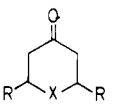
stituted cyclohexanones (2), as evidenced from the extremely large number of papers and monographs[1-6] on these systems.

Similar investigations on piperidin-4-ones (3), oxan-4-ones (4), and thian-4-ones (5), collectively termed in this review as heteran-4-ones, and of the heteran-4-ols



3. X = NH
4. X = O
5. X = S

6 7. R = Ac, Me



8a. R = Aryl
8b. R = Alkyl

(6) and other derivatives (7) are based conveniently on 2,6-diarylheteran-4-ones (8a) and 2,6-dialkylheteran-4-ones (8b), although a number of other substituents could also be incorporated at the 2 and 6 positions to render the cis systems conformationally rigid and the trans systems mobile.[7-14]

II. Scope and Limitations

In this review we attempt to focus on the various methods of synthesis of 2,6-disubstituted heteran-4-ones (8) in view of the various stereochemical studies[15-40] that have been made on these compounds. One of the reasons for the wide interest in the synthesis and stereochemistry of the heteranes is the close similarity of the conformational properties of the non-heteroatom sites of the heteranes to those of the carbocyclic systems and the special characteristics of the heteroatoms that enhance the conformational mobility. Another reason for the wide study is the occurrence of the heterane systems in natural products such as the piperidine alkaloids, carbohydrates, and macrolides. The problem of dependence of reactivity on the stereochemistry also enhances the interest in this subject. Yet another reason for interest being shown by some investigators in this field appears to be the clinical use of suitably substituted heteranes and the large number of ways available for making changes in the structures of the anticipated pharmacologically active synthetic compounds.

In this review almost all the 2,6-disubstituted piperidines have been included except for a few *N*-alkyl and *N*-acyl derivatives where the 2,6-dialkylpiperidines were employed simply as the amine components for the synthesis of alkylamines and amides with a view to examining their pharmacological activity. The major class of 2,6-disubstituted oxanes is the carbohydrates and related compounds. These have been the subject of many reviews and books too numerous to list, and therefore discussions on the carbohydrates and related systems are not included in this review. However, the

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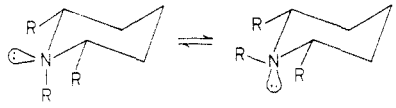
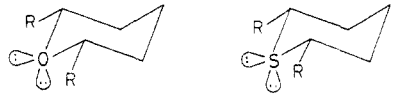
interest in the macrolides and the products of their hydrolysis has resulted in a large amount of significant work on substituted oxanes, and therefore, a few pertinent classes of compounds of this group are discussed. Previous reviews[7-14] on the heteranes are more general treatments incorporating the unsubstituted heteranes, monosubstituted heteranes, and disubstituted heteranes. This review, on the other hand, is devoted exclusively to 2,6-disubstituted heteranes, with or without substituents at other positions (9–11).



9a 9b



10 11a

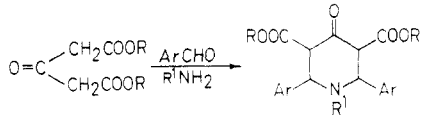
11b 11c

The literature has been covered to the middle of 1981, and almost all pertinent references have been included. A few valuable contributions might have been missed in spite of our thorough recheck.

III. Synthesis of Piperidines

A. Piperidin-4-ones

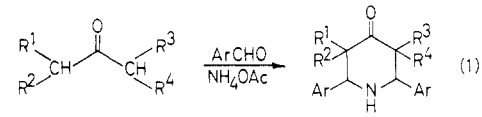
Baliah and his co-workers[41-46] developed an elegant method of synthesis of 2,6-diarylpiperidin-4-ones based on the earlier work of Petrenko-Kritschenko et al.[47-50] The earlier reaction involves the condensation of an ester of acetonedicarboxylic acid with an aromatic aldehyde and ammonia or a primary amine, leading to the formation of 2,6-diaryl-4-oxopiperidine-3,5-dicarboxylates or their N-substituted derivatives (12).



12. R = Me, Et
R^1 = H, Me, Et, Ph, $PhCH_2$

The reaction was later extended to aliphatic aldehydes and several amines by Mannich et al.[51-54] The classical Robinson synthesis of tropinone[55] is indeed an extension of the Petrenko-Kritschenko reaction.

The importance of the further work by Baliah et al. lies not only in the simplicity of their procedure but also in the use of acetone and other aliphatic ketones in the place of the esters of acetonedicarboxylic acid. The yields are also very high, with practically no side reactions of any consequence.[41] A large number of piperidin-4-ones (13) have thus been synthesized by employing various aldehydes and ammonium acetate or amines with aliphatic ketones containing α-hydrogen atoms on both sides of the carbonyl group (eq 1).[56-61]



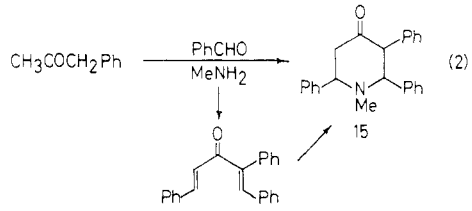
R–R_4 = H, Me, Et, Ph (1)

13

14. R^1–R^3 = H
R^4 = Me, Et, Pr, Bu

Only aromatic aldehydes undergo this modified reaction.

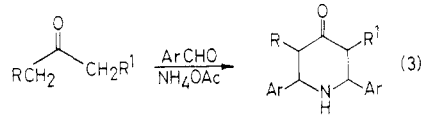
3-Alkylpiperidin-4-ones (14) have been obtained by employing alkyl methyl ketones with varying chain lengths (eq 1).[43] The cyclocondensation of benzyl methyl ketone with benzaldehyde and methylamine gives 2,3,6-triphenylpiperidin-4-one (15).[61] The same compound has also been obtained by the addition of methylamine to 1,2,5-triphenyl-1,4-pentadien-3-one, a byproduct of the previous reaction (eq 2).[61] The 3,5-



(2)

15

disubstituted piperidin-4-ones (16) are formed when both symmetric and unsymmetric aliphatic ketones are employed (eq 3).[41,44,62,63]



(3)

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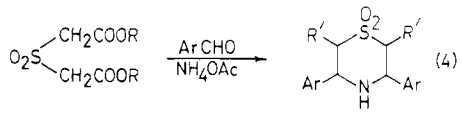
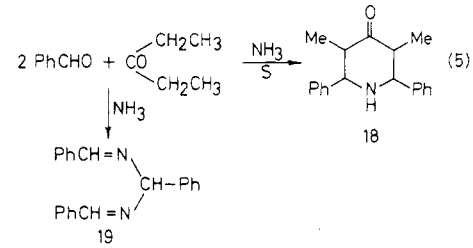
Sulfonyldiacetic acid and its esters also undergo condensation, yielding thiomorpholine derivatives (17)[64,65] in excellent yields (eq 4, R = H, Me, Et).



(4)

17. R′ = H, COOR

When ammonia is passed into a mixture of benzaldehyde and diethyl ketone containing a little sulfur, a vigorous exothermic reaction occurs leading to the formation of 2,6-diphenyl-3,5-dimethylpiperidin-4-one (18) in good yield (eq 5).[66] In the absence of sulfur the



(5)

18

19

piperidin-4-one is not formed; only the imine 19 is formed and the diethyl ketone is unchanged.[66] In similar experiments, butan-2-one, heptan-4-one, and dibenzyl ketone were employed. These ketones do not

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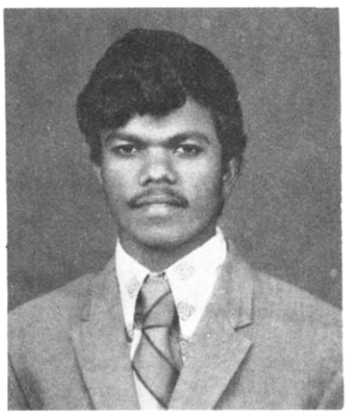
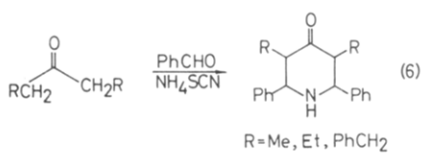


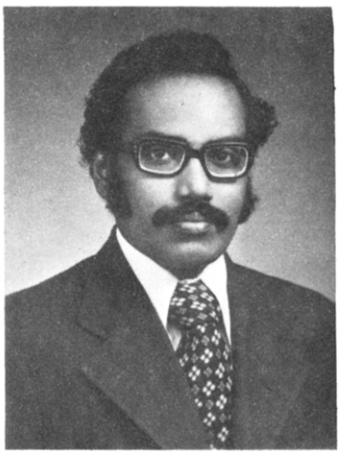
L. Chandrasekaran was born at Madurai in 1961. He obtained his B.Sc. (special) degree and M.Sc. degree from the American College in 1979 and 1981, respectively. His research work for the M.Sc. degree was on studies about piperidines and their stereochemistry and on some benzopyrans.

give piperidin-4-ones in the presence of sulfur but give them in the presence of NH_4SCN (eq 6).[66]

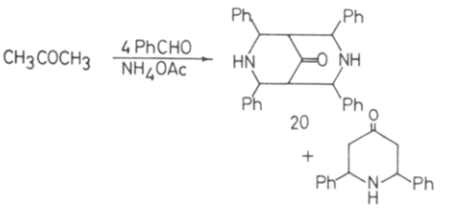


(6)

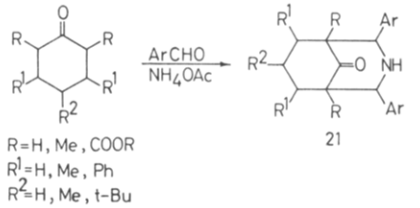
While all aromatic aldehydes other than benzaldehyde give the expected piperidinones as the only nitrogen-containing compounds when the reaction is carried out with acetone and ammonium acetate, benzaldehyde reacts a step further to give 2,4,6,8-tetraphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**20**).[42,67] This, being sparingly soluble in the reaction medium, ethanol or acetic acid, gets separated first and the simple piperidin-4-one is isolated as the hydrochloride. Interest on similar bicyclic systems resulted in the

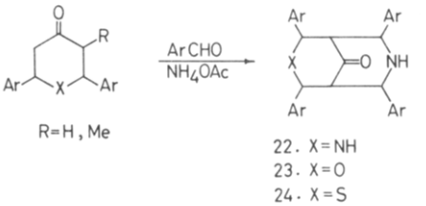


R. Jeyaraman was born at Sengundrapuram (near Madurai) in Tamilnadu, India, in 1944. He obtained his B.Sc. degree in 1966 from the Madras University and the M.Sc. degree in 1968 from Madurai University after carrying out both courses at the American College, Madurai. He then worked for his Ph.D. degree with Dr. V. Baliah at Annamalai University on the synthesis and stereochemistry of saturated heterocyclics. From 1971 he was a member of the Faculty of Annamalai University and its Pre-University College until 1978 when he moved to the American College. During 1981–1982 he did postdoctoral research with Prof. R. A. Abramovitch at Clemson University. At present he is on leave from the American College and working with Prof. R. W. Murray at the University of Missouri—St. Louis. His research areas are synthesis and stereochemistry of heteranes, applications of NMR and CMR spectroscopy and mass spectrometry to stereochemical problems, synthesis of anticancer agents, singlet oxygen and ozone chemistry, air pollution, and studies on novel rearrangements and cyclizations involving nitrenium ion intermediates.



synthesis of 3-azabicyclo[3.3.1]nonan-9-ones (**21**)[68,69] and

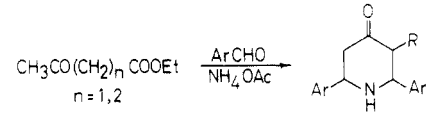




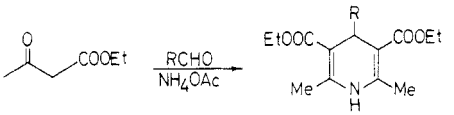
3,7-diazabicyclo[3.3.1]nonan-9-ones (**22**)[67,70–72] in a similar way starting from cyclohexanones and piperidin-4-ones, respectively. Oxan-4-ones and thian-4-ones undergo condensation to give 3-oxa-7-azabicyclo[3.3.1]nonan-9-ones (**23**) and 3-thia-7-azabicyclo[3.3.1]nonan-9-ones (**24**),[73–78] respectively. The chemistry of 3-azabicyclo[3.3.1]nonanes (3-ABNs), 3,7-diazabicyclo[3.3.1]nonanes (3,7-DABNs), 3-oxa-7-azabicy-

clo[3.3.1]nonanes (3-O-7-ABNs), and 3-thia-7-azabicyclo[3.3.1]nonanes (3-T-7-ABNs) has been reviewed recently.[79]

Ethyl acetoacetate and ethyl levulinate have also been employed as the ketone component for the synthesis of piperidin-4-ones (**25** and **26**).[80-83] With ethyl aceto-



25. R = COOEt
26. R = CH_2COOEt



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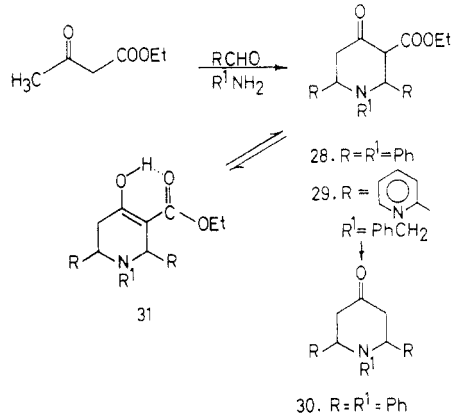
acetate, aromatic aldehydes give the piperidin-4-ones (**25**) while aliphatic aldehydes give 1,4-dihydropyridines (**27**).

Treatment of ethyl acetoacetate with benzaldehyde and aniline in absolute ethanol in the presence of malonic acid gives ethyl 1,2,6-triphenyl-4-oxopiperidine-3-carboxylate (**28**).[51,84-87] Hydrolysis of the



31

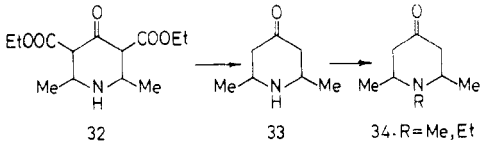
28. R = R^1 = Ph
29. R =
R^1 = $PhCH_2$

30. R = R^1 = Ph

ester (**28**) with 10% HCl in acetone gives 1,2,6-triphenylpiperidin-4-one (**30**).

Pyridine-2-carboxaldehyde in a similar way gives the 2,6-dipyridyl derivative (**29**). The esters **28** and **29** exist in the enol form (**31**) in CCl_4 solution as evidenced from their IR spectra.[86,88-90]

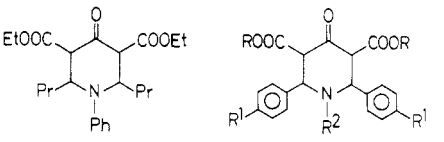
A number of piperidin-4-ones have been obtained from acetonedicarboxylic acid and its esters.[91-108] The 2,6-dimethylpiperidin-4-one (**33**) obtained from the



32 33 34. R = Me, Et

ester (**32**) is subsequently converted to the *N*-methyl and *N*-ethyl derivatives (**34**) by treatment with methyl and ethyl *p*-toluenesulfonates.[109] Use of aniline instead of ammonia in the condensation with diethyl acetonedicarboxylate and *n*-butyraldehyde gives diethyl 2,6-dipropyl-4-oxopiperidine-3,5-dicarboxylates (**35**).[110]

Acetonedicarboxylic acid and its esters give two geometric isomers of piperidin-4-ones (**36**).[47] However, the report[47] that *N*-methyl-2,6-diphenylpiperidin-4-one

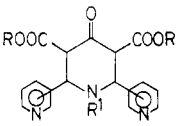


35 36. R = Et, R^1 = H, R^2 = Et
37. R = Me, Et
R = H, Me, MeO

is obtained as two geometric isomers needs to be reexamined.

Allylamine, benzylamine, phenethylamine, and 2-hydroxyethylamine also react with acetonedicarboxylate and aromatic aldehydes,[111] yielding *N*-alkyl derivatives (**37**, R^2 = CH_2=$CHCH_2$, CH_2=$C(Me)CH_2$, $MeOCH_2CH_2$, $PhCH_2$, $HOCH_2CH_2$, $PhCH_2$, $PhCH_2CH_2$).

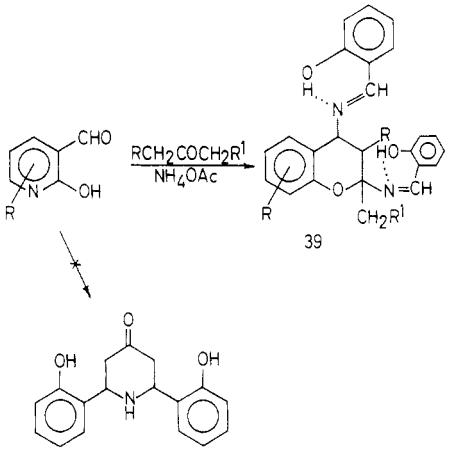
Pyridinecarboxaldehydes also react with acetonedicarboxylic esters.[93,94,112] The 2-pyridyl, 3-pyridyl, 4-pyridyl, and 3-methyl-2-pyridyl derivatives (**38**) were



38. R = Me, Et
R^1 = H, Me, CH_2CH_2OH
$PhCH_2$, $PhCH_2CH_2$

prepared, and their preferred conformations have been established by NMR spectroscopy.[93,98,113,114]

Though salicylaldehyde and substituted salicylaldehydes are reported to react with ketones and ammonia to form piperidin-4-ones,[101,115,116] we have established[117] with IR, NMR, and mass spectral data that the products are substituted benzopyrans (**39**) and not piperidin-4-ones.



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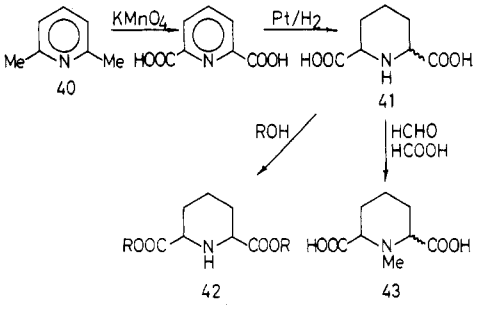
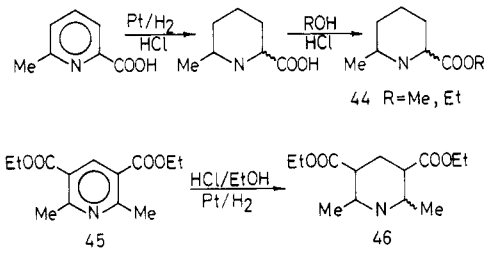
B. Catalytic Hydrogenation of Pyridines

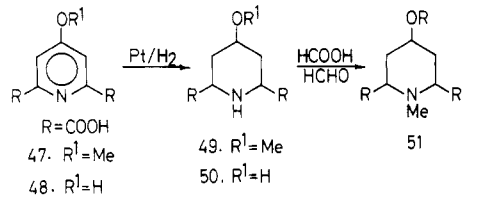
One of the methods of obtaining piperidine-2,6-dicarboxylic acid (**41**) has been to oxidize 2,6-lutidine (**40**) with alkaline permanganate followed by hydrogenation over platinum.[118-121] The dialkyl ester (**42**) and the *N*-methyl derivative (**43**) of the piperidine-2,6-dicarboxylic acid (**41**) have been prepared.[119,120,122] Adkins et al. employed a large number of 2,6-disubstituted pyridines for hydrogenation successfully and established



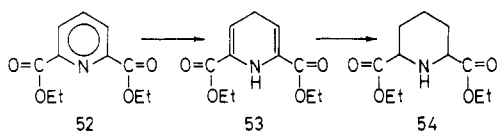
the appropriate conditions.[118] Ethyl 6-methylpiperidine-2-carboxylate (44) has been obtained in a



similar way.[123] Isomeric piperidine-3,5-dicarboxylates (46) are obtained from the corresponding pyridine 45 by hydrogenation.[124,125] The 4-methoxy- and 4-hydroxypyridine-2,6-dicarboxylic esters (47 and 48)

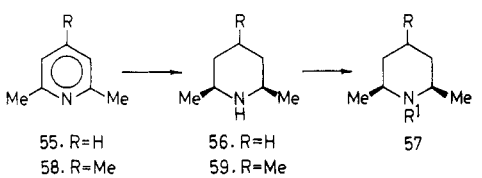


have been hydrogenated over Pt to give the corresponding piperidine derivatives (49 and 50), which, on treatment with formaldehyde–formic acid, give the *N*-methyl derivatives (51).[126] Diethyl pyridine-2,6-dicarboxylate (52) is hydrogenated first to the dihydro



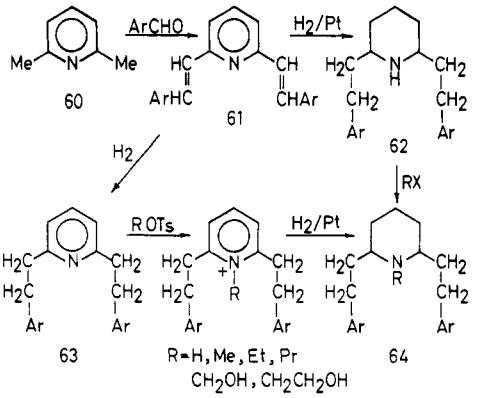
derivative (53) and then to the piperidine (54).[127]

Catalytic hydrogenation of 2,6-lutidine (55) over Pt, Ni, or RuO_2 gives *cis*-2,6-dimethylpiperidine (56), which has been converted to many *N*-alkyl derivatives (57).[109,118,128-133] Dialkylpyridines (55 and 58) have been



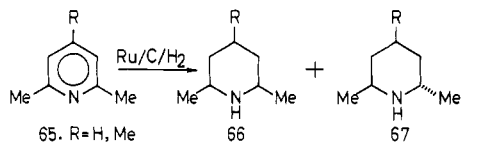
reduced to the *cis*-dialkylpiperidines 56 and 59 in 88–100% yield with Ru/C catalyst in tetrahydrofuran at 150 °C.[134] When mixtures are formed, the *cis*- and *trans*-2,6-dimethylpiperidines are separated by VPC,[135] fractional distillation,[136,137] or fractional crystallization of the hydrochlorides.[137]

The 2,6-distyrylpyridines 61, obtained by condensing 2,6-lutidine (60) with aromatic aldehydes, give the

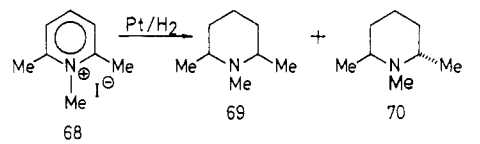


2,6-diphenethylpiperidines 62 on catalytic reduction.[138-145] The corresponding *N*-alkylpiperidines (64) are obtained by treating the 2,6-diphenethylpyridine (63) with methyl or ethyl *p*-toluenesulfonate to give the *N*-alkylpyridinium salt followed by catalytic hydrogenation.[133,139]

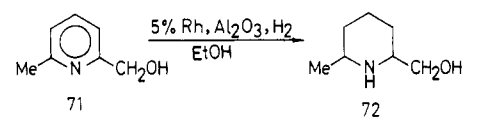
The pyridines (65) are reduced by Re_2S_7 catalyst and by RuO_2 and Rh–C catalysts to the corresponding piperidines (66 and 67).[146-148]



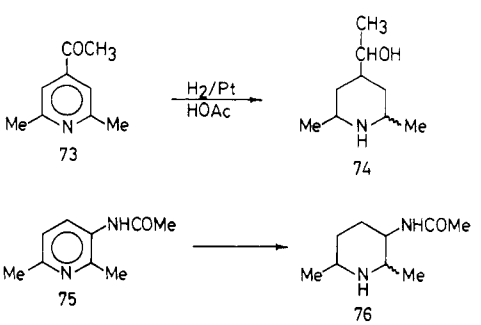
The cis and trans isomers of 1,2,6-trimethylpiperidine (69 and 70) are obtained by catalytic hydrogenation of 2,6-dimethylpyridine methiodide (68) over Pt catalyst and separation of the mixture by alumina column chromatography.[149-152]



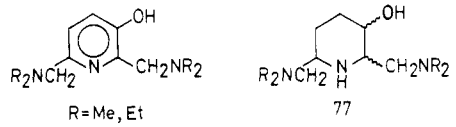
The *cis*-6-methylpiperidyl-2-carbinol (72) is obtained as the only product in the catalytic reduction of 6-methylpyridyl-2-carbinol (71) or by reduction with sodium.[153] By studies of the NMR spectrum it has been shown to be the cis isomer.[154]



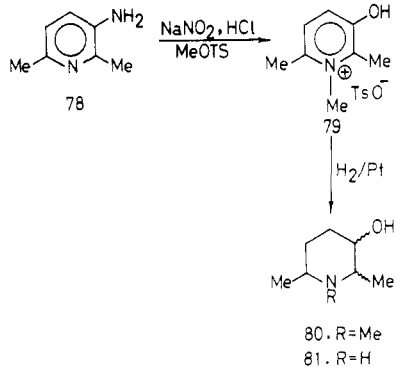
A mixture of 4-(1-hydroxyethyl)-2,6-dimethylpiperidines (74) is obtained by reducing 4-acetyl-2,6-trimethylpyridine (73) over Pt catalyst in acetic acid.[155]



Similarly isomers of 3-acetamido-2,6-dimethylpiperidine (76) were prepared from the corresponding 3-acetamidopyridine (75).[155] Catalytic hydrogenation of 2,6-bis(dialkylaminomethyl)-3-hydroxypyridines yields the isomeric 3-piperidinols (77).[156] Hydrogenation of 3-

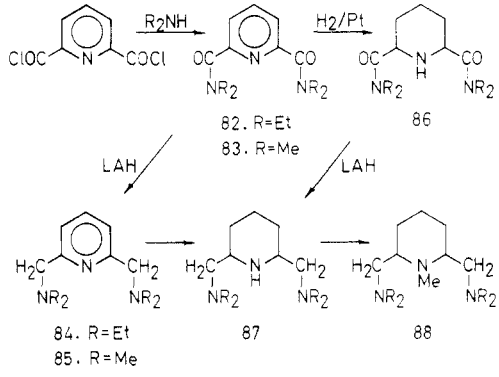


hydroxy-1,2,6-trimethylpyridinium tosylate (79), obtained from 2,6-dimethyl-3-aminopyridine (78), gives 3-hydroxy-1,2,6-trimethylpiperidine (80).[157] Similarly

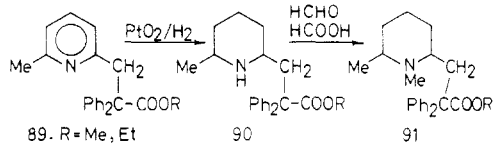


isomeric 3-hydroxy-2,6-dimethylpiperidines (81) have been prepared.

The diamides 82 and 83 and the diamines 84 and 85, obtained from pyridine-2,6-dicarboxylic acid, were reduced by $LiAlH_4$ to the corresponding piperidines (86 and 87) and to the *N*-methylpiperidines 88.[158]

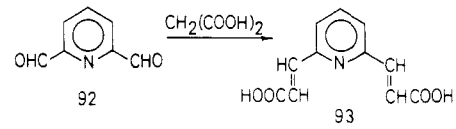


Hydrogenation of methyl or ethyl 1,1-diphenyl-2-(6-methyl-2-pyridyl)propionate (89) over Adam's catalyst at room temperature under 1 atm gives the piperidine derivative 90, which has been converted to the *N*-

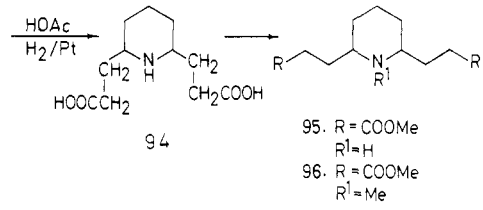


methyl derivative 91. All the piperidines possess analgesic properties.[159]

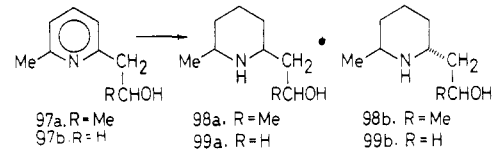
Pyridine-2,6-dicarboxaldehyde (92) also serves as a useful starting material for the synthesis of a number of piperidines. It reacts with malonic acid in the presence of piperidine to give the unsaturated acid 93, which, on catalytic hydrogenation, produces the pi-



peridine derivative 94.[160] The esters 95 and 96 have been prepared from this piperidine.[160]

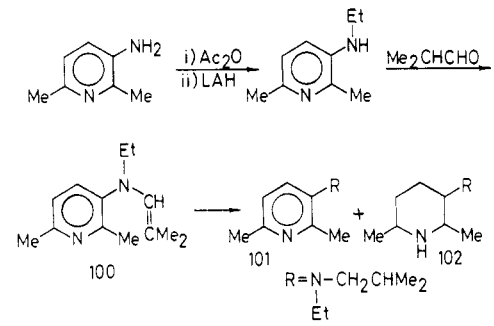


Hydrogenation of 2-methyl-6-(2-hydroxypropyl)-pyridine (97), obtained by the reaction of the monolithium salt of 2,6-lutidine with acetaldehyde, gives *cis*- and *trans*-2-methyl-6-(2-hydroxypropyl)piperidine (98a and 98b). The 2-methyl-6-(hydroxyethyl)piperidines

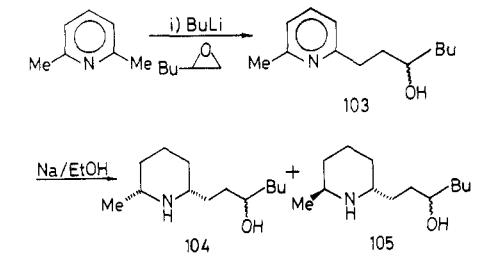


(99a and 99b) are obtained by hydrogenation of the corresponding pyridine over Pt/C.[161]

The pyridine enamine 100, on treatment with hydrogen in the presence of Adam's catalyst, gives the reduced amine 101 and the corresponding piperidines (102).[162]



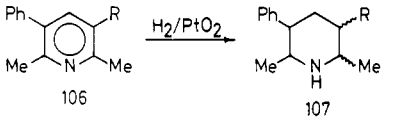
Treatment of 2,6-dimethylpyridine with *n*-BuLi and then with 1-hexene oxide gives pyridine alcohol 103, hydrogenation of which gives the piperidine derivative 104. Reduction of 103 with Na/EtOH gives an 80:20



mixture of 104 and 105. Seeding an acetonitrile solution of the crude mixture with 104 initiates crystallization of that isomer, the mother liquor containing approximately equal parts of 104 and 105. Spinning-band distillation effects the final separation of the *trans*-piperidine alcohol 105.[163]

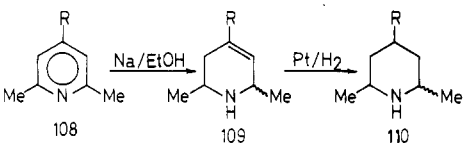
Several 3-carboxylic acid derivatives (107) of 2,6-di-

methylpiperidine were obtained by hydrogenating the pyridines **106** (R = $CONMe_2$, COOEt, $CONH_2$, $COOH_2$, COOH, $CONEt_2$) over PtO_2.[164]



106 **107**

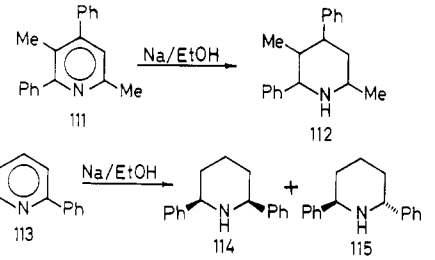
In addition to the catalytic hydrogenation of pyridine derivatives, reduction with sodium and alcohol has been employed over a long period for the conversion of pyridines to piperidines. Thus the 2,6-dimethylpyridines **108** (R = H, Et), on reduction with sodium



108 **109** **110**

and alcohol, give the dihydropyridines **109**, which, on further catalytic hydrogenation, give mixtures of *cis*- and *trans*-2,6-dimethylpiperidines (**110**).[130,165]

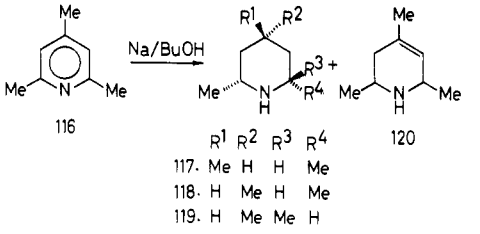
Similarly 3,6-dimethyl-2,4-diphenylpyridine (**111**), on reduction with Na/EtOH, gives the piperidine **112**.[166]



111 **112** **113** **114** **115**

The cis and trans isomers of 2,6-diphenylpiperidine (**114** and **115**) were obtained by starting from 2,6-diphenylpyridine (**113**).[117]

Chromatographic separation of the mixture of products obtained by reducing 2,4,6-trimethylpyridine (**116**)

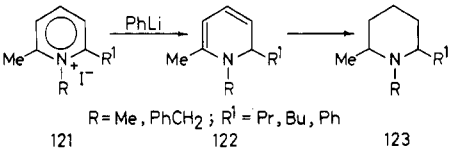


116 **120**

	R^1	R^2	R^3	R^4
117.	Me	H	H	Me
118.	H	Me	H	Me
119.	H	Me	Me	H

with sodium in ethanol yielded the trimethylpiperidine isomers **117–120** in the ratio 55:12:14:12 while reduction with sodium in butanol diminished the proportion of **117**, the ratio being 41:16:18:14 of the piperidines **117**, **118**, **119**, and **120**, respectively.[168]

The *N*-alkyldihydropyridines **122** are formed from the corresponding pyridinium iodides **121** by reaction with an alkyllithium. The piperidines **123** are obtained

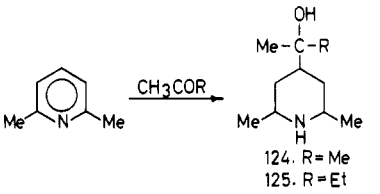


R = Me, $PhCH_2$; R^1 = Pr, Bu, Ph

121 **122** **123**

from the pyridinium salts via a mixture of dihydro and tetrahydro isomers and reduction over Pd/C.[169]

In a few instances electrolytic reductions have been employed to obtain the piperidine derivatives. Reduction of 2,6-dimethylpyridine in excess of acetone and 20% H_2SO_4 on lead electrodes gives 2,6-dimethyl-4-(2-hydroxypropyl)piperidine (**124**). Similar reduction in

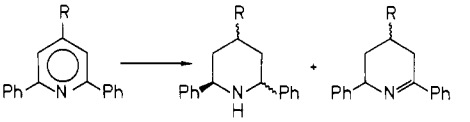


124. R = Me
125. R = Et

butan-2-one gives the corresponding 2-hydroxybutyl derivative **125**.[170]

Electrochemical reduction of 2,4,6-trimethylpyridine (**116**) in 20% H_2SO_4 on lead cathode (12 A, 6 h) in the absence of acetone gave a mixture of the isomers **117**, **118**, **119**, and **120** in the ratio 29:14:15:42.[168]

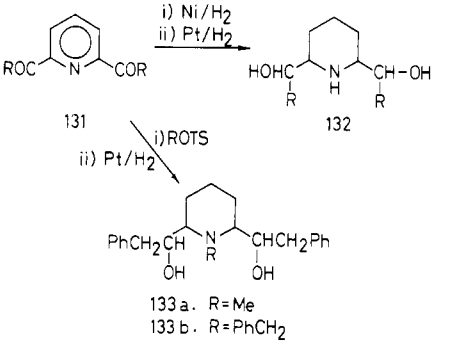
Another method of converting a pyridine to a piperidine is through the formation of the potassium radical ions followed by hydrolysis. Thus the potassium radical ions obtained from 2,6-diphenylpyridine (**126**)



126. R = H
127. R = Ph
128. R = H
129. R = Ph
130

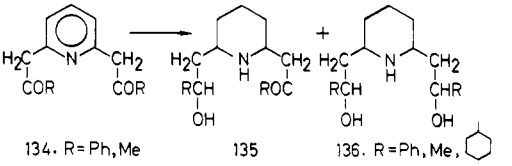
and 2,4,6-triphenylpyridine (**127**), on hydrolysis, give mixtures of *cis*- and *trans*-2,6-diphenylpiperidines (**128**) and 2,4,6-triphenylpiperidines (**129**) in addition to the tetrahydropyridine derivatives (**130**).[171] When the hydrolysis is carried out in D_2O the products are 83–100% deuterated.[171]

When carbonyl substituents are attached to the pyridine ring either the pyridine ring alone or one or both of the carbonyl groups in addition to the pyridine ring are reduced. The ketones **131** (R = Et, Pr, Bu, Ph), on hydrogenation, give the diols **132**.[172] Under vigorous



131 **132**
133a. R = Me
133b. R = $PhCH_2$

conditions phenyl groups present in the substituents are also reduced. Thus treatment of the pyridine derivative **131** (R = $PhCH_2$) with methyl or benzyl *p*-toluenesulfonate followed by catalytic hydrogenation leads to the diols **133a** and **133b**.[172] Pyridines containing the group CH_2COR in the 2,6-positions (**134**),

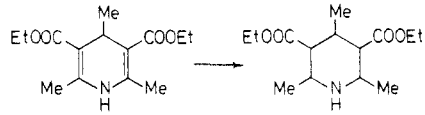


134. R = Ph, Me **135** **136**. R = Ph, Me,

on catalytic hydrogenation, produce different products in which one or both of the carbonyl groups are reduced

or the phenyl group also is hydrogenated (**135**, **136**).[174]

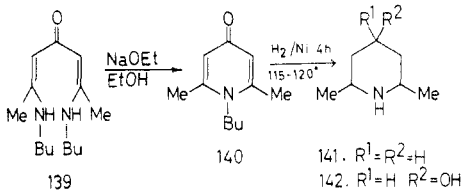
Dihydropyridines, which are easily accessible through condensations, are easily converted to the piperidines by catalytic hydrogenation. Diethyl 2,4,6-trimethyl-3,5-piperidinedicarboxylate (**138**) is obtained from the



137 138

dihydrocollidinedicarboxylate (**137**) by hydrogenation.[175]

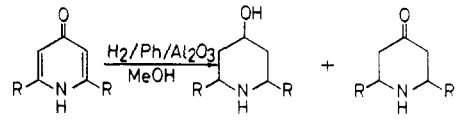
Heating a mixture of dehydroacetic acid and butylamine for 3 h and refluxing the resulting enamine (**139**)



139 140 141. $R^1=R^2=H$ 142. $R^1=H$ $R^2=OH$

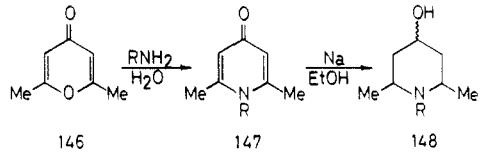
with EtONa in ethanol yield the dihydropyridinone **140**, which, on catalytic hydrogenation, gives *N*-butyl-2,6-dimethylpiperidine (**141**) and the corresponding alcohols (**142**).[176]

Hydrogenation of chelidamic acid (**143**) over 5% Rh on Al_2O_3 followed by esterification gives 42% dimethyl *cis,cis*-4-hydroxy-2,6-piperidinedicarboxylate (**144**) and 10% of the ketone **145**.[177]



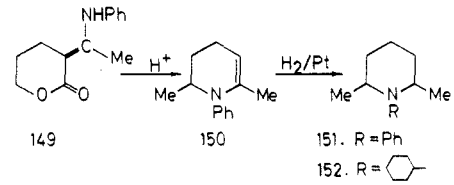
143. R=COOH 144. R=COOMe 145. R=COCMe

Pyrones could also be converted to piperidinols. The simple 2,6-dimethylpyrone (**146**) reacts with aqueous solutions of amine forming dihydropyridinones (**147**), which, on reduction with Na/EtOH, give the 2,6-dimethylpiperidinols (**148**).[178]



146 147 148

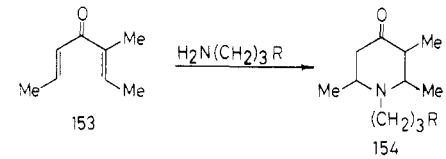
Enamino lactone **149**, on acid treatment, gives the tetrahydropiperidine **150**, which, on hydrogenation with PtO_2/HCl, gives the piperidine derivatives **151** and **152**.[179]



149 150 151. R=Ph 152. R=

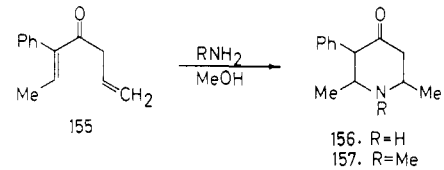
C. Cyclization Methods

Substituted piperidin-4-ones have been prepared by the addition of primary amines to the appropriate conjugated ketones. The cyclization reaction was performed with 5-methylhepta-2,5-dien-4-one (**153**) yielding the piperidin-4-ones **154** (R = NMe_2, NEt_2, OMe, OEt, OPr, OBu) by employing different substituted amines.[180]



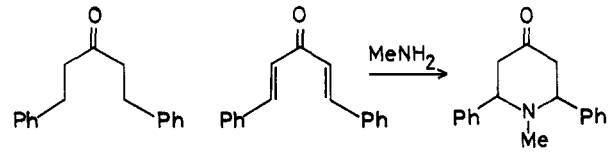
153 154

A solution of the unsaturated ketone **155** in methanol with concentrated aqueous ammonia heated in an autoclave yields 2,6-dimethyl-3-phenylpiperidin-4-one (**156**).[181] A similar treatment with methylamine yields the *N*-methyl derivative **157**.[181]



155 156. R=H 157. R=Me

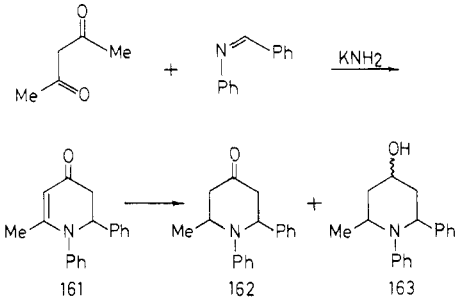
The report[182] of the formation of 2,6-diphenyl-1-methylpiperidin-4-one (**160**) by the addition of methylamine to dibenzylacetone (**158**) is apparently erroneous.



158 159 160

It is evident that methylamine does not add to dibenzylacetone to give the piperidin-4-one. An examination of the original patent,[183] quoted in the concerned paper, indicates that it is dibenzalacetone (**159**) that has been used but not dibenzylacetone.

Another method of synthesis of piperidin-4-ones is through the condensation of ketones with Schiff bases; e.g., the reaction of acetylacetone with benzylideneaniline in the presence of excess of KNH_2 in liquid ammonia yields the 2,3-dihydro-6-methyl-1,2-diphenyl-4(1*H*)-pyridone (**161**), which, on hydrogenation

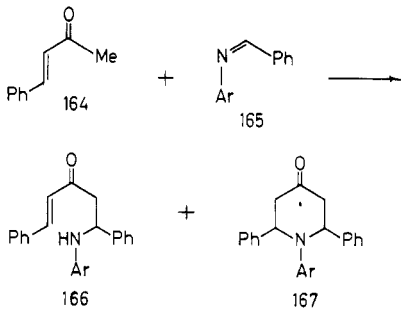


161 162 163

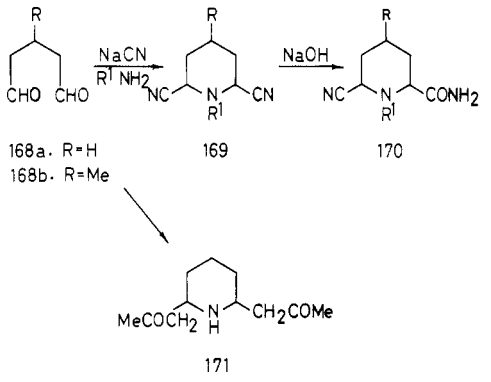
in acetic acid with Pt, is converted to a mixture of the ketone **162** and the alcohol **163** while reduction with excess of $NaBH_4$ gives the alcohol **163**.[184]

The condensation of Schiff bases with conjugated ketones also gives 2,6-diarylpiperidin-4-ones. Thus the Schiff bases **165** react with benzalacetone (**164**), giving the unsaturated compound **166** or the piperidin-4-one **167**.[185-187] The piperidin-4-one is also formed when a mixture of the Schiff base and acetone in alcohol is allowed to stand for several days.[186,187]

Piperidines can be obtained by starting from glutaraldehyde (**168a**) and 3-methylglutaraldehyde (**168b**)



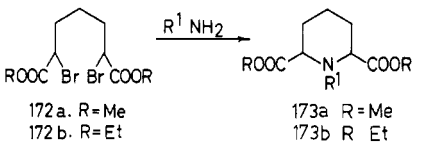
by the Strecker aminonitrile synthesis followed by cyclization. Treatment of the glutaraldehydes **168** with



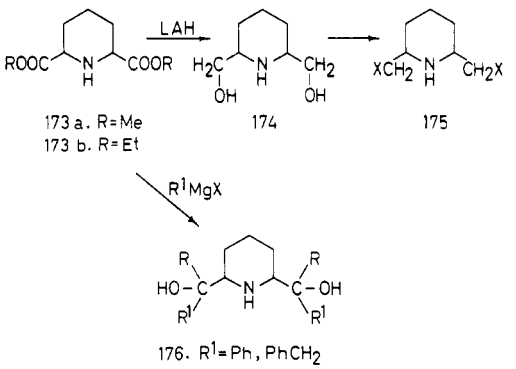
HCN and NH_4Cl or any other primary amine gives the 2,6-dicyanopiperidines **169** (R = H, Me, Et, *i*-Pr, *t*-Bu, $CH_2CH{=}CH_2$, Ph, NH_2, $PhCH_2$, Ph_2CH, $PhCH_2CH_2$).[188-190] In the presence of aqueous alkali the amide **170** is obtained.[191]

A one-step condensation of glutaraldehyde, ammonium chloride, and acetoacetic acid leads to 2,6-diacetonylpiperidine (**171**), the structure of which has been established by the X-ray diffraction analysis of its *N*-benzoyl derivative.[192]

Dialkyl *cis*-2,6-piperidinedicarboxylates (**173a** and **173b**) can be prepared from a mixture of dialkyl *meso*-α,α-dibromopimelates (**172a** and **172b**) and a



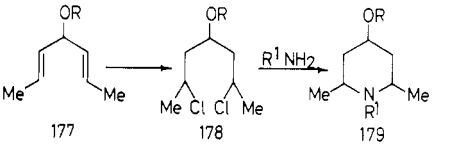
primary amine (R^1 = Me, OH, Ar) by boiling the mixture with benzene for 40 h.[193-198] The esters **173a** and **173b** (R^1 = H) have been converted to several 2,6-disubstituted piperidines. On reduction with $LiAlH_4$ the esters **173a** and **173b** give *meso-cis*-2,6-bis(hydroxymethyl)piperidine (**174**).[199,200] The alcohol reacts with



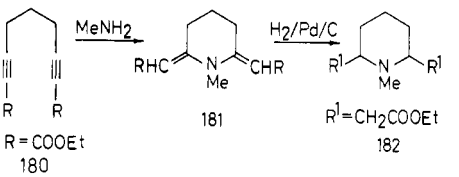
thionyl chloride or hydrobromic acid or hydriodic acid, yielding 2,6-bis(halomethyl)piperidines (**175**).[201,202]

The ester **173b** has been converted to the tertiary alcohols **176** by reaction with suitable Grignard reagents.[203]

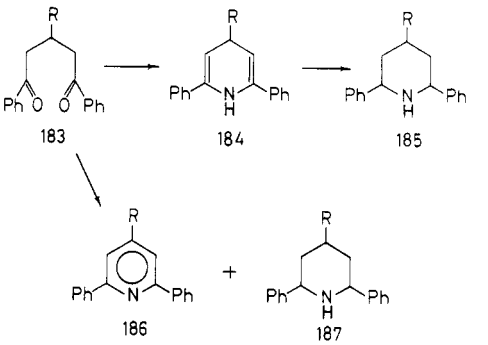
The diallylcarbinol ester **177** (R = PhCO) is converted into its chloride **178** and treated with ammonia or a primary amine to effect piperidine ring closure, leading to the 2,6-dimethylpiperidines **179** (R^1 = Me, $PhCH_2CH_2$).[204]



The acetylenic acid derivative **180** has been used for the synthesis of piperidines. Addition–cyclization with $MeNH_2$ leads to the unsaturated compound **181**, which, on hydrogenation over Pd/C, gives the diethyl piperidine-2,6-diacetate **182**.[205]



The condensation of a 1,5-diketone with amines is another synthetic route to piperidines. The 1,5-diketone **183** and ammonia in alcohol–chloroform solution yield the dihydropyridine **184**, which on hydrogenation gives 2,6-diphenyl-4-(*o*-hydroxyphenyl)piperidine (**185**).[206]

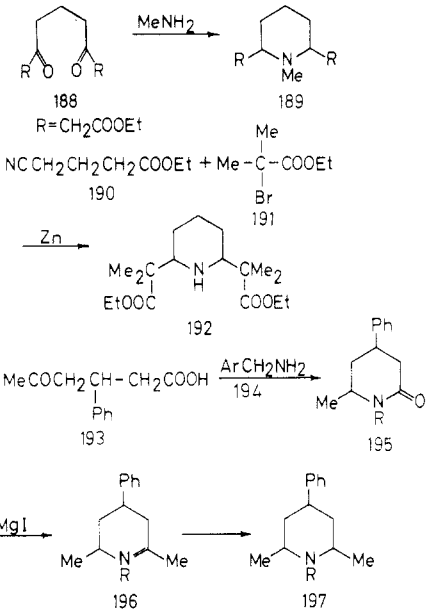


When a mixture of the 1,5-diketone **183** (R = H, Ph, *m*-anisyl) and an excess of formate–formamide reagent is heated for 5 h at 180–185 °C, a mixture of 2,6-diphenylpyridines **186** and 2,6-diphenylpiperidines **187** is formed.[207-209] Hydrogenation of the pyridines or the mixture gives piperidines.

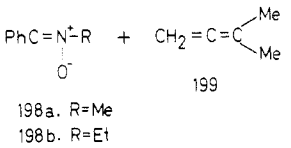
Diethyl 3,7-diketoazelate (**188**) reacts with methylamine in ethanol at 140–150 °C, yielding 1-methyl-2,6-bis(carbethoxymethylene)piperidine (**189**).[210]

Condensation–cyclization takes place when a mixture of ethyl γ-cyanobutyrate (**190**) and ethyl α-bromoisobutyrate (**191**) is heated with zinc in benzene, leading to the formation of the piperidine **192**.[211]

The reaction of the δ-keto acid **193** with homoveratrylamine (**194**) followed by cyclization and reduction with Raney Ni/H_2 gives the 2-piperidinone **195**. This 2-piperidinone reacts with MeMgI, giving the tetrahydropyridine derivative **196**, which, on further catalytic hydrogenation, gives 1-homoveratryl-2,6-dimethyl-4-phenylpiperidine (**197**).[212]

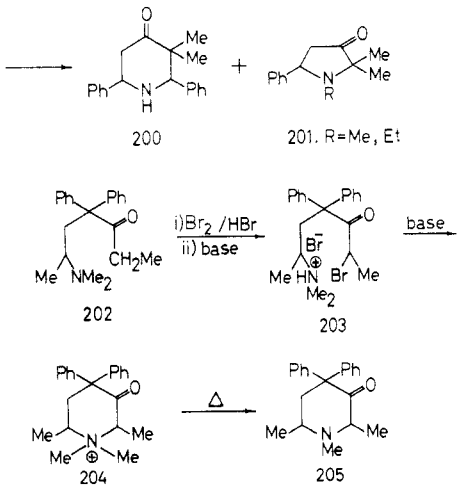


The cycloaddition reaction of the *C*-phenyl-*N*-alkyl-azomethines **198a** and **198b** with the allene **199**



yields 3,3-dimethyl-2,6-diphenylpiperidin-4-one (**200**) and the pyrrolidinone **201**.[213,214] However, the same piperidinone could be very easily obtained as the only product by the condensation of methyl isopropyl ketone with benzaldehyde and ammonium acetate.[50]

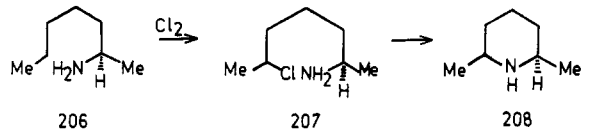
Internal alkylation of amines also leads to piperidines. The amino ketone **202** is brominated to give the α-



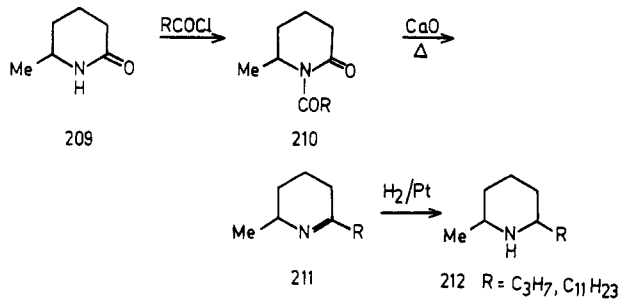
bromo ketone **203**, which in the form of free base spontaneously cyclizes to give the quaternary salt **204**. When the quaternary salt is heated, the *N*-methylpiperidin-3-one **205** is obtained.[215]

Radical chlorination of (*R*)-1-methylhexylamine (**206**) leads to the 5-chloro derivative **207**. This cyclizes to give a mixture of *cis*- and *trans*-2,6-dimethylpiperidines (**208**).[216,217]

By use of the Mundy rearrangement,[218,219] several 2,6-disubstituted piperidines have been synthesized. The Mundy rearrangement involves heating an *N*-aryl-

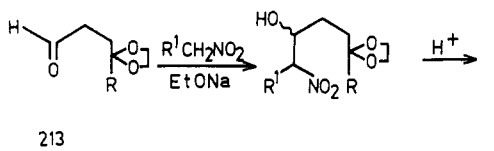


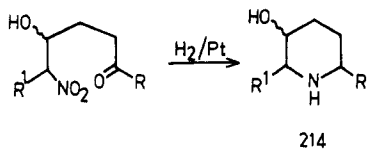
lamide with calcium oxide to obtain imines. Thus the piperidin-2-one **209** is converted to the *N*-acylamide



210, which, on pyrolysis with CaO, gives the tetrahydropyridine **211**. On hydrogenation, this tetrahydropyridine gives the piperidine **212**.[220]

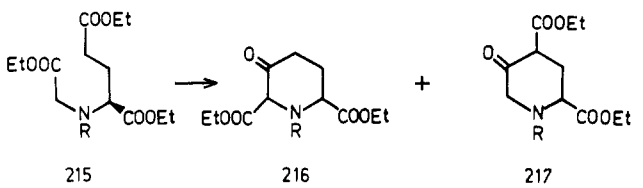
Addition of a nitroalkane to the aldehyde **213** followed by acid treatment and hydrogenation gives epimeric pairs of the 3-hydroxypiperidine **214**.[221] The



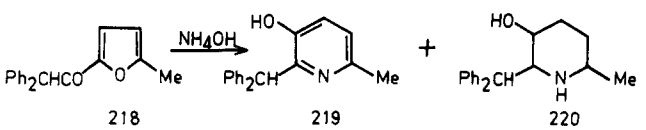


configuration and conformation of the alcohols have been established by NMR spectroscopy.[221a]

The condensation of ethyl L-glutamate with ethyl bromoacetate and benzoylation of the crude reaction product yield optically active diethyl *N*-benzoyl-*N*-((ethoxycarbonyl)methyl)-L-glutamate (**215**). Its Dieckmann ring closure gives a mixture of the piperidines **216** and **217**.[222]



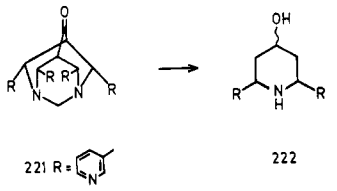
A case of ring opening and cyclization leading to the formation of 2,6-disubstituted piperidines involves heating 5-methyl-2-furyl benzhydryl ketone (**218**) with



aqueous NH_3 and methanol in an autoclave at 150–160 °C for 12 h. This gives a mixture of the pyridine **219** and the piperidine **220**.[223] Quast and co-workers have studied recently the ring opening and cyclization of

2,6-diarylpiperidin-4-ones.[224]

Though the Petrenko-Kritschenko reaction, hydrogenation of pyridines, and cyclization methods are the chief methods of building up the 2,6-disubstituted piperidine skeleton, a few cases of the formation of 2,6-disubstituted piperidines during ring cleavage of bicyclic and tricyclic compounds exist. One such instance is the formation of 2,6-di-3-pyridylpiperidin-4-ol (**222**) during

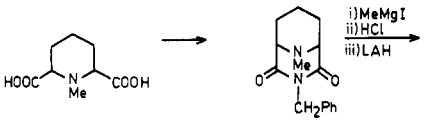


221 R =

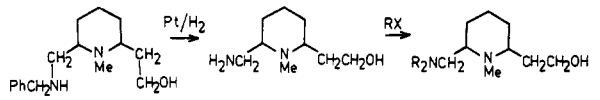
222

the hydrogenation of the diazaadamantan-9-one **221**.[225]

The diamines **225**, **226**, and **227** are obtained from *N*-methylpiperidine-2,6-dicarboxylic acid (**223**) through the formation of the benzylimide **224** and treatment of the imide with MeMgI followed by reduction with $LiAlH_4$.[225]

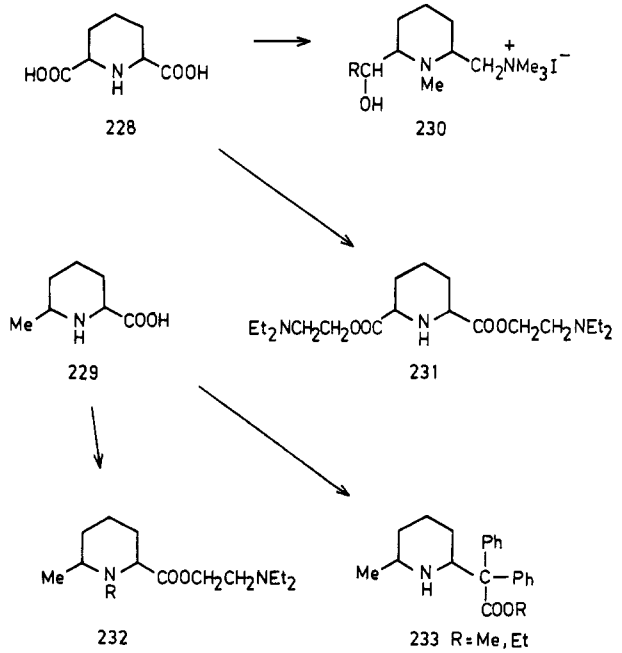


223 224



225 226 227

Piperidine-2,6-dicarboxylic acid (**228**) is reported to have been converted to the quaternary salts **230** and the amine **231** while 6-methylpiperidine-2-carboxylic acid (**229**) is converted to the esters **232** and **233**.[226,227] The

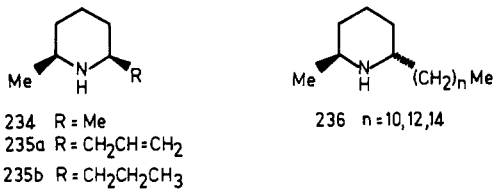


228 230 229 231 232 233 R = Me, Et

exact methods or scheme were not available to us.

D. Piperidine Alkaloids with 2,6-Substituents

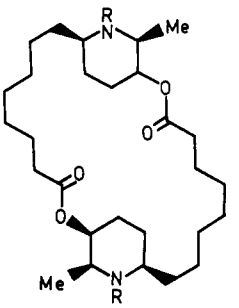
A minor subgroup of the piperidine alkaloids contains the 2-alkyl-6-methyl-piperidine skeleton,[228,229] the representatives being 2,6-dimethylpiperidine (**234**), the pine



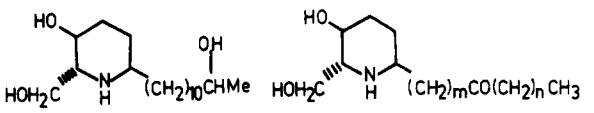
234 R = Me
235a R = $CH_2CH{=}CH_2$
235b R = $CH_2CH_2CH_3$

236 n = 10, 12, 14

alkaloid pinidine (**235a**),[230,231] alkaloids of the fire-ant venom (**236**),[232-235] and hydroxylated alkaloids such as carpaine (**237**),[236-238] prosopine (**238**),[239] isoprosopinine



237 R = H

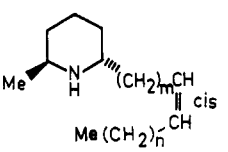


238

239a m = 6 n = 4
239b m = 9 n = 1

(**239a**),[240] and prosopinine (**239b**).[239a] The commonly employed method of synthesis of piperidines, viz., by the reduction of pyridine rings, has been employed for the synthesis of many alkaloids such as pinidine (**235a**),[161] dihydropinidine (**235b**),[241] carpaine derivatives,[242] and fire-ant alkaloids.[233-235]

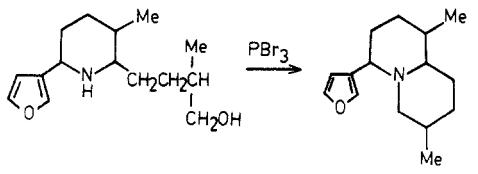
The venoms of the fire ants of the species *Sobnopsis xyloni*, *S. geminata*, *S. richteri*, and *S. invicta* are found to contain a series of alkaloids, most of which are *trans*-2-methyl-6-alkylpiperidines (**240–242**) with small



240 m = 8 n = 4
241 m = 3 n = 7
242 m = 5 n = 7

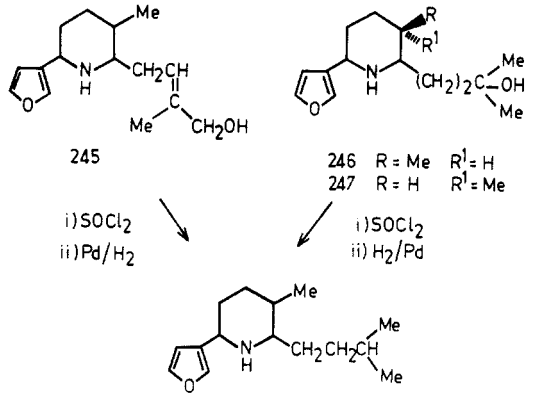
amounts of the cis isomer.[232,233-235,243-248] These are used to block neuromuscular transmission[245] and are also employed as antibacterial agents.[246]

The alkaloid secodihydrocastoramine (**243**), isolated from the roots of *N. japonicum*, has a furan substituent in the 2-position.[249] This alkaloid, on cyclization by PBr_3, gives an epimer of deoxycastoramine (**244**).[249] Nuphamine, another alkaloid isolated from the *N. japonicum* root, has a double bond in the side chain (**245**)[250] while the alkaloids nupharamine (**246**) and



243 244

epinupharamine (**247**) are the secondary alcohol derivatives.[251,252]



245 246 R = Me R¹ = H; 247 R = H R¹ = Me

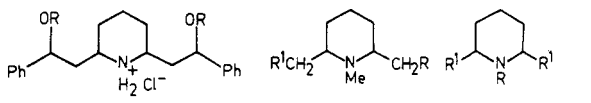
248

The alkaloid nuphamine (**245**) gives the dihydrodeoxypiperidine (**248**), which is (−)-deoxynupharamine, on reaction with thionyl chloride and subsequent catalytic hydrogenation.[253] Nupharamine (**246**) also is converted to the same dihydrodeoxypiperidine (**248**) under the same conditions.[253-255] Nuphamine, on catalytic hydrogenation, gives secodihydrocastoramine.[253]

The alkaloid pinidine isolated from *Pinus sabiniana* Dougl[256] and also found to be a constituent of *P. jeffreyi* and *P. torreyana* has been shown to be one of the optically active forms of *cis*-2-methyl-6-(2-propenyl)-piperidine (**235a**) by conversion to the *cis*-2-methyl-6-propylpiperidine (**235b**) and comparison with a sample obtained from hydrogenation of 2-methyl-6-propylpyridine.[241]

Dihydropinidine (**235b**) has been synthesized by another route also as indicated in Scheme I.[257] The yield in this synthesis is 60% whereas the earlier method by *N*-acyl lactam rearrangement it was only 15%.[220]

Norlobelandinine (**249**) has been isolated from *Lobelia polyphylla* in 1.4% yield.[258] Iodine reacts with



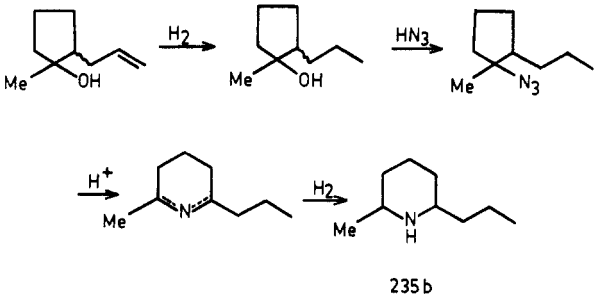
249b R = H

250 R = R¹ = CHOHPh
251 R = CHOHPh, R¹ = COPh
252 R = R¹ = COPh
253 R = R¹ = Me
254 R = H, R¹ = CH_2CH_2Ph

lobelanidine (**250**) to give lobeline (**251**) and lobelanine (**252**).[259a] The action of lobeline (**251**), lobalanine (**252**), 1,2,6-trimethylpiperidine (**253**), and 2,6-diphenethylpiperidine (**254**) on respiration and blood pressure has been examined.[259b] The alkaloids affect both while the other two piperidines have no effect on respiration but cause a decrease in blood pressure.

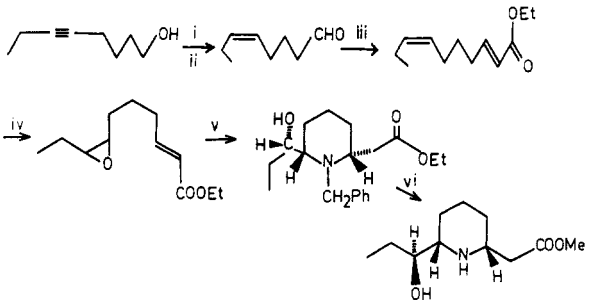
The structure of the alkaloid palustrine (**255**) has been established on the basis of the formation of 6-(α-hydroxypropyl)piperidine-2-acetic acid (**256**) by Hoffmann degradation, hydrogenation, and hydrolysis of dihydropalustrine.[260] Methyl dihydropalustraminate (**257**), obtained from palustrine (**255**) by Hoffmann degradation, has been synthesized from 5-octyn-1-ol, according to Scheme II.[261] Dihydropalustramic acids and their epimers have also been synthesized.[262]

SCHEME I

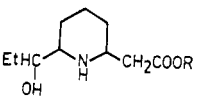


235b

SCHEME II

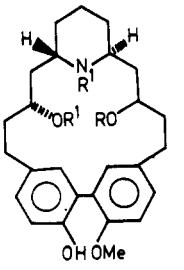


255



256 R = H
257 R = Me

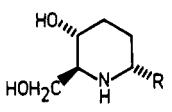
Three piperidine alkaloids, lythranine (**258**), lythranidine (**259**), and lythramine (**260**), belong to the lythranine group.[263]



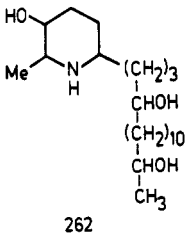
258 R = Ac, R¹ = H
259 R = R¹ = H
260 $R^1R^1 = -CH_2-$

Several 3-hydroxypiperidines have been isolated from plant extracts. Prosopinone and a related alkaloid, prosipinone D, isolated from *Cassia carnaval*, have been shown to have structures **261** and **262**, respectively, by the application of IR, UV, NMR, and mass spectral data.[264]

The relative and absolute configurations of prosopine (**263**) and prosopinine (**264**) have been established.[239a,265]

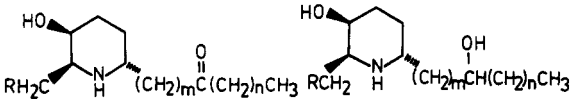


261 R = $(CH_2)_{10}COMe$
263 R = $(CH_2)_{10}CHOHMe$
264 R = $(CH_2)_9COEt$



262

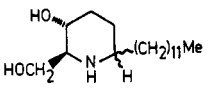
Along with these two a few more alkaloids, isoprosopinines A (**265**) and B (**266**) prosophylline (**268a**), pro-



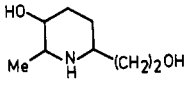
265 m=6, n=4, R=OH
266 m=9, n=1, R=OH
267 m=6, n=4, R=H

268a R=OH, m=6, n=4
268b R=H, m=6, n=4

sofrine (**268b**), and prosofrinine (**267**), have been extracted from the leaves of *Prosopis africana* and their structures established.[239] Deoxyprosopinine (**269a**) and deoxyprosophylline (**269b**) have been synthesized.[240]



269a βH
269b αH



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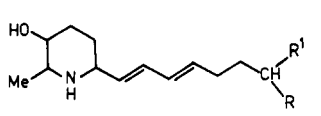
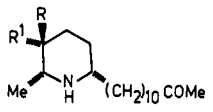
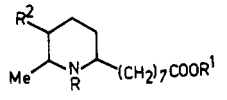


271 RR^1 = =CHCH=CHEt
272 R=OH, R^1=CH_2CH=CHEt



273 R^1=OH, R=H
274 R^1=H, R=OH



275 R=R^1=H, R^2=OH
276 R=Me, R^2=H, R^1=Et
277 R=$COOCH_2Ph$, R=H, R^2=OH

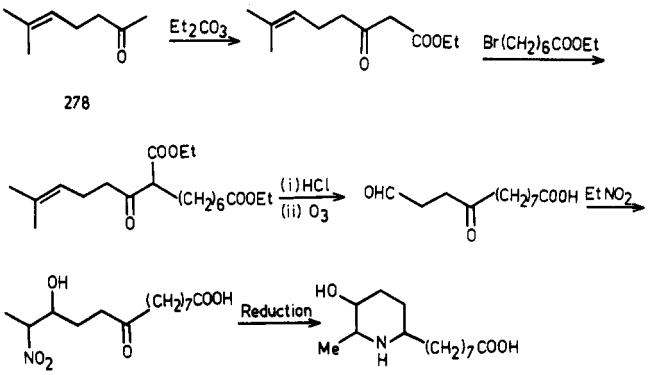
The alkaloid julifloridine (**270**) has been isolated from *P. juliflora* along with a few more alkaloids.[266] The structures of cryptophorine (**271**) and crytophorinine (**272**), isolated from the leaves of *B. cryptophorus*, have been determined from spectral data.[267]

The alkaloids (±)-cassine (**273**) and (±)-3-isocassine (**274**), isolated from *Cassia excelsa*, have been synthesized by the nitroethane condensation technique.[268]

Carpamic acid (**275**) is obtained by the hydrolysis of the alkaloid carpaine (**237**).[242] Ethyl *N*-methylcarpamate has been converted to ethyl deoxy-*N*-methylcarpamate (**276**) by treatment with thionyl chloride and catalytic hydrogenation.

Carpamic acid (**275**) is obtained by the hydrolysis of the alkaloid carpaine (**237**).[242] Ethyl *N*-methylcarpamate has been converted to ethyl deoxy-*N*-methylcarpamate (**276**) by treatment with thionyl chloride and catalytic hydrogenation. The configuration of the substituents at C-2 and C-6 has been established as cis to each other by comparing the melting points and the IR spectra of a (−)-isomer obtained by catalytic

SCHEME III



278

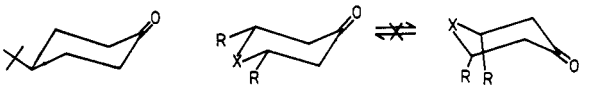
275

hydrogenation and reduction of deoxycarpyrinic acid with that obtained from *cis*-deoxycarpamate. On the basis of the failure to oxidize carpamic acid to the 3-ketone and the failure of ethyl carpamate to undergo epimerization, the orientation of the OH has been assigned as equatorial.[242]

N-((Benzyloxy)carbonyl)carpamic acid (**277**), on lactonization, yields the bis((benzyloxy)carbonyl) derivative of carpaine. Hydrogenation of **277** in absolute ethanol containing a small amount of HCl over Pd/C produces carpaine (**275**).[269] Carpamic acid (**275**) has been synthesized from 6-methylhept-5-en-2-one (**278**) according to Scheme III.[270–272]

E. 4-Hydroxypiperidines

The presence of the reactive carbonyl group in 4-*tert*-butylcyclohexanone (**279**) has enabled a large number of workers to obtain many epimeric pairs of 4-*tert*-butylcyclohexane derivatives by converting the sp^2 carbon to an sp^3 carbon.[273–280] Many useful intermediates have also been obtained by converting the C=O bond into C=C and C=N bonds. A similar trend is observed in the case of 2,6-disubstituted heteranes (**280**), which are the basic conformationally rigid models

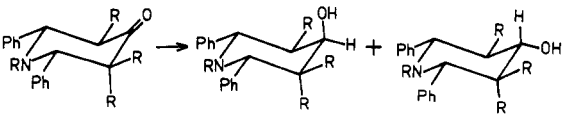


279 ≡ 1

280 X = NR, S, O

for the study of the stereochemistry of reactions in six-membered heterocyclics. The intramolecular interactions and stereochemical courses of reactions have differed significantly in many cases from those of the alicyclic analogues.

After synthesizing a significantly large variety of piperidin-4-ones (**281**), Baliah et al. reduced them to the secondary alcohols (**282**, **283**).[44,62,281] The MPV re-



281
R = H or alkyl

282
β-form

283
α-form

duction, reduction by sodium and alcohol, catalytic hydrogenation, and complex metal hydride reductions lead to isomeric mixtures of secondary alcohols.[56,58,182,281–283] The mixture is usually separated by column chromatography over alumina[44,283] or by paper

chromatography.[284] The stereochemistry of the alcohols and their reactivity have been studied by various spectral methods and kinetic techniques.

The stereoselectivity of the reduction with complex metal hydrides and the influence of solvent on the ratio of the epimeric pairs of alcohols have been studied.[285]

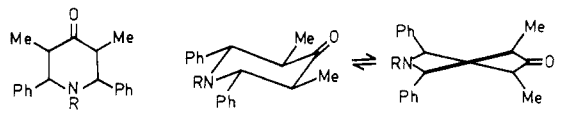
The isomeric alcohols have been designated as α and β forms.[283] The α form has the OH group cis to the 2,6-diaryl groups and is equatorially oriented in a chair form (**283**). The β isomer has the OH trans to the phenyl groups, the orientation being axial (**282**).

Sodium–alcohol reduction of a variety of 2,6-diarylpiperidin-4-ones afforded only the more stable equatorial isomer (**283**), as in the case of tropinone and related ketones.[286]

Reduction by the Meerwein–Ponndorf–Verley (MPV) method on the other hand affords only the β isomer.[58,283] However, reduction of 2,6-di-*p*-anisyl-1,3,5-trimethyl-4-piperidinone yields about 6% of the α isomer also.

Lithium aluminum hydride reduction of the piperidin-4-ones usually gives the α isomers predominantly. Reduction of 3,5-dimethyl-2,6-diaryl-4-piperidinone and its *N*-methyl derivative affords[283] considerable amounts of the β isomer.

The *N*-H ketone **284a** gives about 16% of the β isomer and the *N*-Me ketone gives 36% of the β isomer.

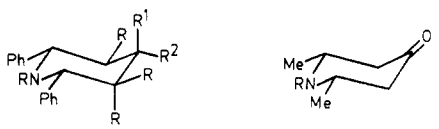


284a R=H
284b R=Me

285a 285b

For the 3,5-dimethylpiperidines (**284a, 284b**) the most stable conformation is a flattened chair in which the 3,5-methyl groups are equatorial. When this piperidine is reduced with $LiAlH_4$, the equatorial approach of the reducing agent to the carbonyl carbon is hindered by the axial hydrogens attached to C-3 and C-5. The approach of $LiAlH_4$ to the C-4 carbonyl will, therefore, be axial, resulting in the formation of the equatorial isomer (α isomer). The 3,5-dimethyl derivatives appear to be in an equilibrium involving the chair (**285a**) and flexible (**285b**) forms. In the flexible form the attack of $LiAlH_4$ from the equatorial side does not seem to be seriously hindered and hence produces the β isomer in addition to the major α isomer. It may be noted that the β isomer was not obtained[56] previous to this work since the isomers were separated by fractional crystallization and not by column chromatography.

The 4-acetoxy derivatives (**286a, 286b**) of 2,6-diarylpiperidines have been prepared from the individual pure isomers of the alcohols.[287] These acetoxy derivatives are useful as good suppressors of the polarographic maxima of lead, oxygen, and nickel.[288]

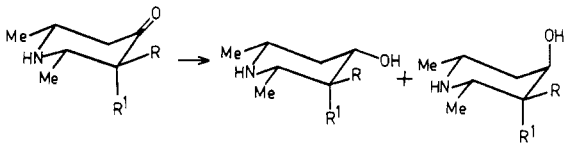


286a R=H, Me
R^1=H, R^2=OAc
286b R=H, Me
R^1=OAc, R^2=H

287 R=H
288 R=Me

The 2,6-dimethyl derivatives also have been examined similarly. 2,6-Dimethylpiperidin-4-one (**287**) and its *N*-methyl derivative (**288**) have been reduced with sodium and alcohol. Reduction of 1,2,6-trimethylpiperidin-4-one (**288**) with sodium and ethanol gives a liquid boiling at 100–110 °C (12 mm).[51,289] Since the predominant formation of the equatorial isomer was assumed in such reductions, no attempts to separate and identify the isomers were made in most of the earlier studies.[289]

The reduction of the isomers of 2,3,5-trimethylpiperidin-4-one (**289** and **290**) with hydrogen over nickel



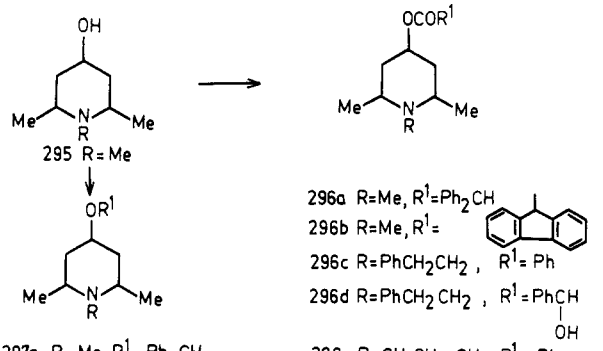
289 R=Me, R^1=H
290 R=H, R^1=Me

291 R=Me, R^1=H
293 R=H, R^1=Me

292 R=Me, R^1=H
294 R=H, R^1=Me

as well as by Na/alcohol yields a mixture of epimeric alcohols, the α form (**291, 293**) predominating in each case. The MPV method of reduction gives only the β isomer (**292, 294**). The alcohols obtained from the trans ketone (**289**) were named α and β forms and those obtained from the cis ketone (**290**) γ and δ isomers. The α and γ isomers have equatorial OH while the other two have axial OH.[290]

From the 1,2,6-trimethylpiperidin-4-ol (**295**), the diphenylacetic acid esters (**296a**) and 9-fluorenecarboxylic acid esters (**296b**) have been prepared.[291–293] The reaction of the piperidinol **295** with Ph_2CHBr gives the 4-alkoxy derivative **297a**.[294] These compounds possess antihistaminic and anticholinergic properties.[294] The benzoate (**296c**) and mandelate (**296d**) of 2,6-dimethyl-*N*-phenethyl-4-hydroxypiperidine are known to possess anesthetic properties.[293,295] The benzoate (**297b**) of *N*-allyl-2,6-dimethyl-4-hydroxypiperidine also has therapeutic properties.[296]



295 R=Me

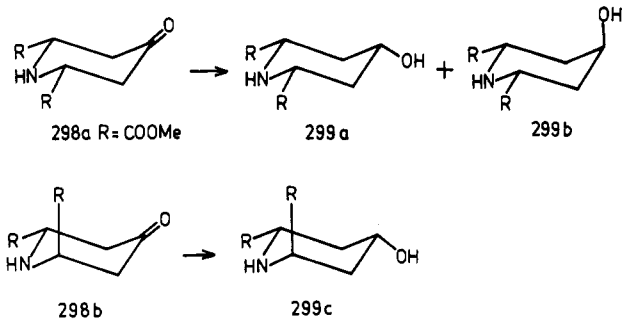
296a R=Me, R^1=Ph_2CH
296b R=Me, R^1=
296c R=$PhCH_2CH_2$, R^1=Ph
296d R=$PhCH_2CH_2$, R^1=PhCH(OH)

297a R=Me, R^1=Ph_2CH
297b R=$CH_2CH{=}CH_2$, R^1=COPh

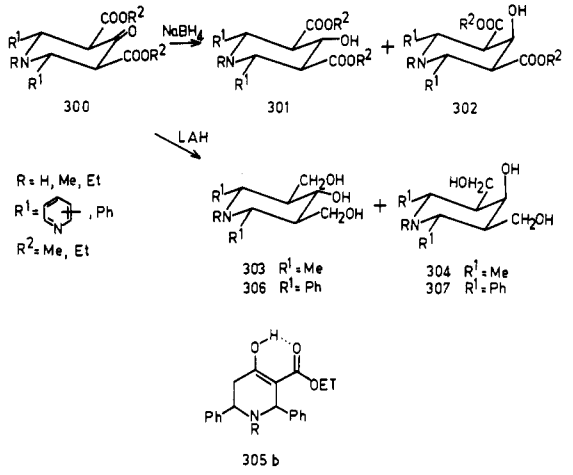
296e R=$CH_2CH{=}CH_2$ R^1=Ph

Alcohols were obtained by the reduction of a mixture of *cis*- and *trans*-methyl 4-oxopiperidine-2,6-dicarboxylates (**298a** and **298b**).[297] The alcohols were separated by fractional crystallization. The equatorial alcohol (**299a**) formed from the cis compound was obtained first. The mother liquor, after acidification, gave the hydrochloride of the alcohol (**299c**) derived from the trans isomer. The second alcohol (**299b**) derived from the cis compound was isolated from the mother liquor after the separation of **299c**. The configurations of all three alcohols were assigned from their NMR spectra.[297]

The 2,6-diarylpiperidin-4-ones with ester groups at



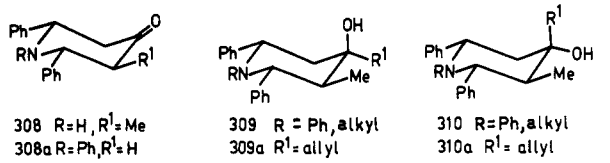
the 3- and 5-positions (**300**), on reduction, produce either 4-ols (**301** and **302**) or triols (**303** and **304**) depending upon the reagent and the piperidin-4-one employed. Reduction of the keto esters **300** with $NaBH_4$



gives a mixture of epimeric alcohols.[298,299] The composition of the epimeric mixture is found to depend on the solvent employed for reduction. Reduction in anhydrous alcohols at room temperature gives the alcohols **301** and **302** in 90% yield in the ratio 15:85 while reduction in these solvents at −15 °C gives only **302**. In dioxane, dimethylformamide, diglyme, and methylene chloride 60–70% yields of **301** and **302** in the ratio 1:9 are obtained. In the presence of water as well as in water alone, the ratio becomes 6:4. This increase of the yield of equatorial alcohol (**301**) has been explained by considering the electrostatic effect of the neighboring carbonyl dipoles on the course of the reaction. The directive effects appear to be most effective in nonpolar solvents, with the consequent formation of **301**. In a polar solvent the effect is diminished and the reduction takes the normal course of that of an unhindered ketone with the formation of **302**.

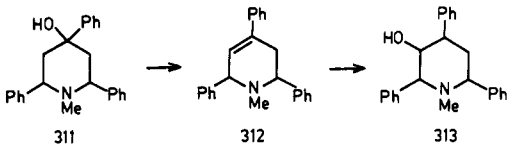
The keto forms (**305a**) of diethyl 4-oxo-2,6-diphenylpiperidine-3,5-dicarboxylate and its *N*-alkyl derivatives are reduced by $NaBH_4$ to the epimeric alcohols **301** and **302** (R′ = Ph) while reduction with $LiAlH_4$ produces epimeric pairs of the triols **306** and **307**. However, the enol forms (**305b**), stabilized as chelates, are not reduced by $LiAlH_4$.[97] The triols contain a higher percentage of the trans isomer, the OH occupying the axial position.[99]

Epimeric pairs of tertiary alcohols have been prepared by the Grignard addition to the piperidin-4-ones.[44,300-302] The tertiary *cis*-2,6-diphenyl-3-methylpiperidin-4-ols (**309, 310**) are obtained by the interaction

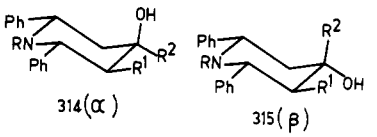


of the piperidin-4-ones (**308**) with Grignard reagents or with PhLi.[301,302] The alkyl group at CH enters preferentially cis to the substituents at C-2 and C-6. The configurations of the alcohols have been established from their NMR spectra. The addition of allylmagnesium bromide to 1,2,6-triphenyl-4-piperidinone (**308a**) also affords isomeric tertiary alcohols **309a** and **310a**.[303]

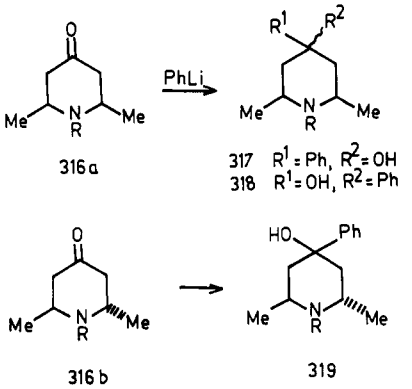
The 2,4,6-triphenylpiperidinol **311** has been dehydrated to the tetrahydropyridine **312** from which the 3-hydroxy derivative **313** was obtained.[304]



On the basis of ^1H NMR spectral data it was shown that in the α isomers (**314**) of the tertiary alcohols and their *N*-methyl derivatives the 4-substituent group is equatorially oriented. The β isomers (**315**) of these have axial 4-substituent.[302]

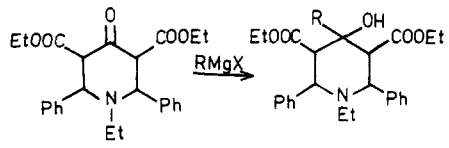


Isomeric 2,6-dimethyl-4-phenyl-4-hydroxypiperidines (**317, 318**) and the corresponding *N*-phenethyl derivatives have been prepared and separated. The configurational assignments were made on the basis of their reactions.[305]



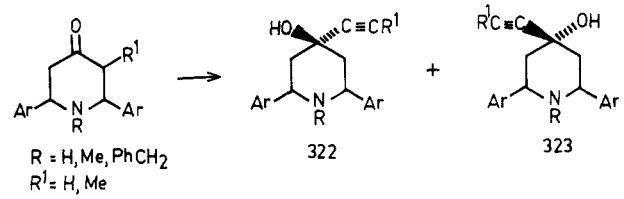
Addition of PhLi to a mixture of the cis and trans isomers (**316a** and **316b**) of 2,6-dimethylpiperidin-4-one gives the three possible piperidinols **317, 318,** and **319** in the ratio 9:2:1.[306] The 4-acetoxy derivatives of these piperidin-4-ols have been obtained.[307]

Phenylmagnesium bromide adds to diethyl 1-ethyl-2,6-diphenyl-4-piperidinone-3,5-dicarboxylate (**320**), yielding exclusively one alcohol (**321**). Similarly alkylmagnesium bromides add to produce the 4-alkyl derivatives.[308,309]



320 321 R = alkyl, Ph

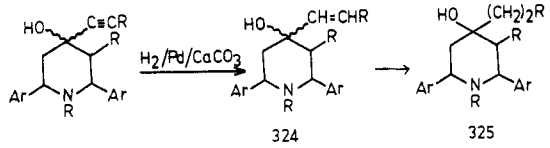
One largely reported class of 4-substituted 2,6-diarylpiperidines is the addition products of piperidin-4-ones with acetylene or its derivatives (**322**, **323**).[310-315]



R = H, Me, $PhCH_2$
R^1 = H, Me

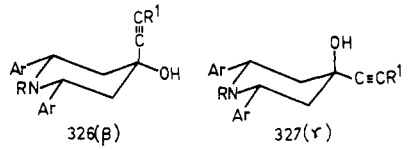
322 323

In many cases the acetylenic compounds have been hydrogenated over Pd–$CaCO_3$ to the ethylenic product (**324**), which, on further hydrogenation over Ni or Zr modified Raney Ni, gives the 4-ethylpiperidin-4-ol (**325**).[310,314,316]



324 325

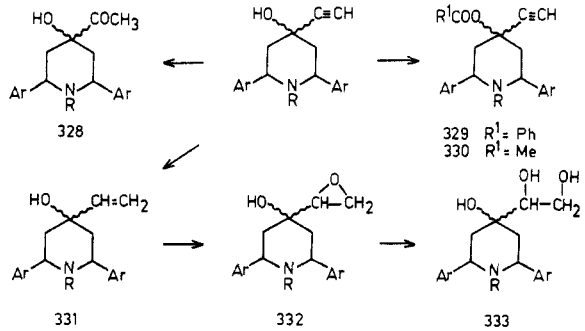
Hydrogenation of the acetylenic piperidinols has been carried out in methanol with Ni or Pd catalyst on various carriers ($BaSO_4$, $CaCO_3$, SiO_2, C) or on Pt catalyst.[317] The β isomer (**326**) is found to undergo hydrogenation at a faster rate than the γ isomer (**327**). A



326(β) 327(γ)

second mole of hydrogen adds much more slowly. With Pd catalyst, the effectiveness of the carriers was found to be in the order $BaSO_4 > CaCO_3 > SiO_2 > C$. The activity of the metals forms the order Pd > Ni > Pt.[317]

The acetylenic piperidinols are converted to methyl ketones (**328**) by standard procedures, involving treatment with mercuric sulfate and dilute sulfuric acid.[310,314]



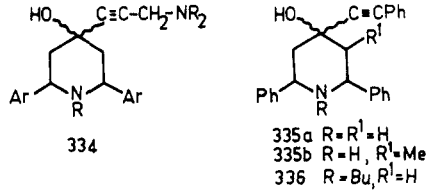
328 329 R^1 = Ph
330 R^1 = Me

331 332 333

The addition products, on treatment with alkyl halides, yield the corresponding *N*-alkyl derivatives which react with benzoyl chloride in benzene to yield the hydrochloride of 1-alkyl-2,6-diphenyl-4-ethynyl-4-piperidyl benzoate (**329**).[311] Similarly the acetates (**330**) have been obtained.[318]

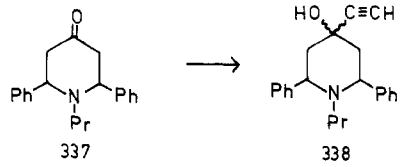
The oxiranylpiperidinol **332** is obtained by the treatment of the appropriate vinylic piperidinol (**331**) with an excess of performic acid.[319,320] The oxiranylpiperidinol **332**, on hydrolysis with H_2SO_4, gives the triol **333**.[320]

The acetylenic piperidinols undergo Mannich condensation with formaldehyde and dialkylamines in the presence of CuCl in dioxane to yield the amine **334**.[312,314]



334 335a R = R^1 = H
335b R = H, R^1 = Me
336 R = Bu, R^1 = H

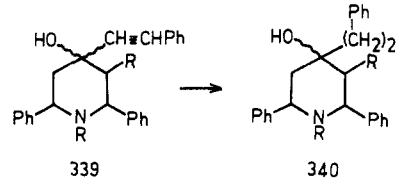
Phenylacetylene also reacts with piperidin-4-ones. It adds to 2,6-diphenylpiperidin-4-one, giving **335a**, which is alkylated with butyl iodide to form **336**.[321,322] Phenylacetylene also reacts with 2,6-diphenyl-3-methylpiperidin-4-one to give the corresponding tertiary alcohol (**335b**).[323] 3-*n*-Propyl-2,6-diphenylpiperidin-4-one (**337**), on treatment with acetylene, gives an epimeric



337 338

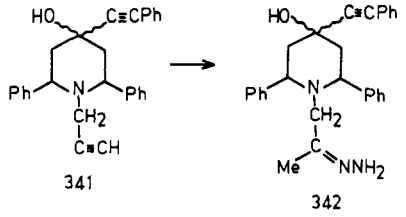
mixture of alcohols (**338**).[324,325] The mixture has been separated and the configurations of the alcohols have been established.

As in the case of acetylene addition compounds, the phenylacetylene addition compounds also are hydrogenated in stages to the 4-phenylvinyl (**339**) and 4-phenethyl (**340**) derivatives.



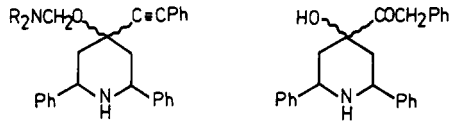
339 340

Alkylation of the piperidinol **335a** with 3-bromopropyne gives the N-alkylated derivative **341**, which, with hydrazine hydrate, gives the hydrazino derivative (**342**).[326]



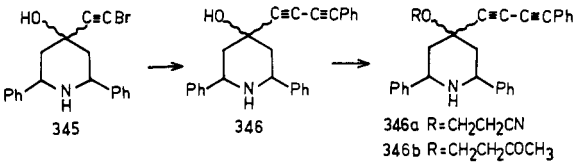
341 342

The acetylenic piperidinol **335a** reacts with paraformaldehyde in the presence of CuCl and R_2NH in benzene to give the amino ether **343**. Hydration of **335a** with mercuric sulfate and dilute sulfuric acid gives the ketone **344**.[322]



343 344

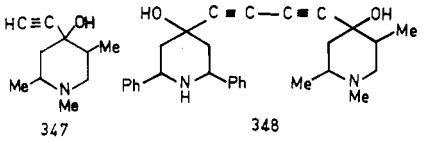
Several conjugated acetylenic compounds have also been prepared. The reaction of phenylacetylene, CuCl, NH_2OH, and $BuNH_2$ with the 4-bromoethynyl derivative **345** gives **346**. Treatment of the tertiary alcohols



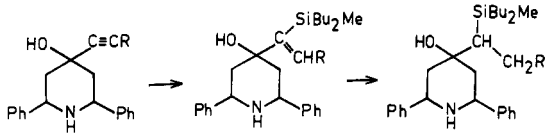
345 346 346a R=CH_2CH_2CN 346b R=$CH_2CH_2COCH_3$

346 with acrylonitrile gives **346a**, which has been converted to the methyl ketone **346b**.[327] The coupling reaction between the acetylenic piperidinols themselves yields conjugated systems. Condensation of the acetylenic piperidinol **345** with the β isomer of **347** in the presence of CuCl leads to the butadiyne derivative **348**.[328,329]

Refluxing Bu_2MeSiH with the acetylene addition compound **349** in toluene containing a catalytic amount of H_2PtCl_6 in propan-2-ol solution gives **350**, which has been reduced to the saturated alcohol **351**.[330,331]

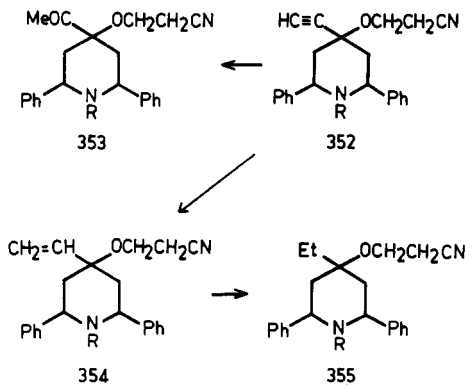


347 348



349 350 351

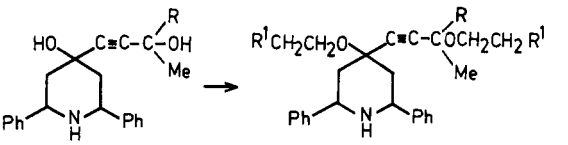
The 4-cyanoethoxy derivative **352**, obtained by addition of the corresponding alcohol to acrylonitrile, reacts with $HgSO_4$–H_2SO_4, giving the ketone **353**.[332]



353 352 354 355

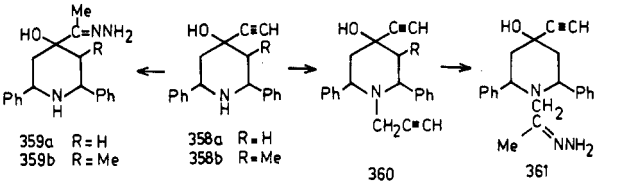
Hydrogenation of **352** over $Pd/CaCO_3$ in alcohol gives the ethylenic alcohol **354**, while a similar hydrogenation over Raney Ni gives the 4-ethyl derivative **355**.

The 4-ethynyl derivative **349** (R = H), on reaction with a ketone, yields tertiary alcohol **356**. This, on addition to acrylonitrile, gives the dinitrile **357a**, which has been converted to the acid **357b** and the ester **357c**.[333,334]



356 357a R=CN 357b R=COOH 357c R=COOEt

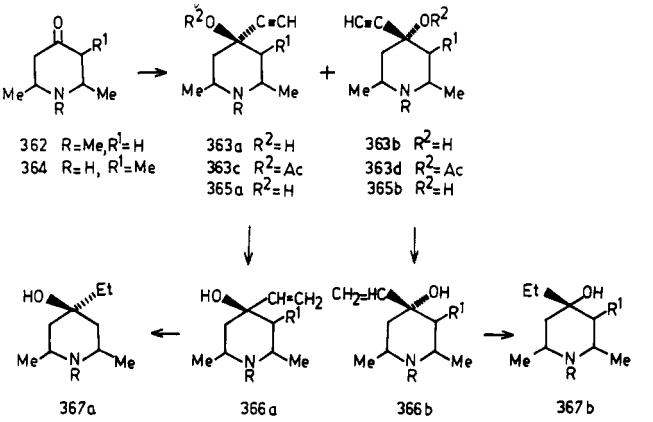
The reaction of 4-ethynylpiperidin-4-ols **358a** and **358b** with hydrazine hydrate gives **359a** and **359b**, re-



359a R=H 359b R=Me 358a R=H 358b R=Me 360 361

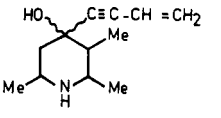
spectively.[313,315,326] Treatment of **358a** with 3-bromopropyne gives the corresponding *N*-alkyl derivative **360**, which, on treatment with hydrazine hydrate, gives **361**.[313,335]

The addition of acetylene to 1,2,6-trimethylpiperidin-4-one (**362**) gives a mixture of the alcohols **363a** and **363b**, which have been separated. They have



362 R=Me,R^1=H 364 R=H, R^1=Me 363a R^2=H 363c R^2=Ac 365a R^2=H 363b R^2=H 363d R^2=Ac 365b R^2=H 367a 366a 366b 367b

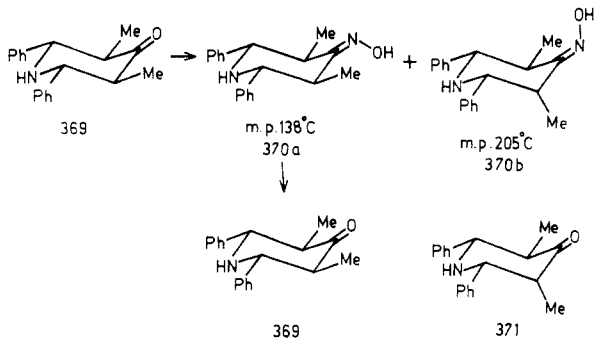
been converted to the acetoxy derivatives (**363c**, **363d**) also. The conformations and configurations of the alcohols and esters have been determined by their IR and NMR spectra.[336] The addition of acetylene to 2,5,6-trimethylpiperidin-4-one (**364**) gives the 4-ethynyl derivatives **365a** and **365b**. These also have been hydrogenated to the alkenes (**366a**, **366b**) and alkanes (**367a**, **367b**).[337] The addition of vinylacetylene to 2,5,6-trimethylpiperidin-4-one in a similar way gives the tertiary alcohol (**368**).[338]



368

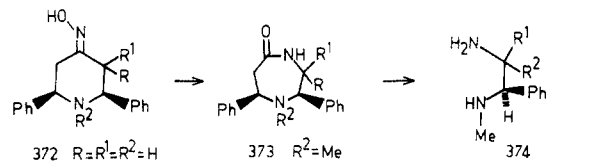
F. 4-Aminopiperidines

Though the formation of oximes from ketones is a common reaction, the conformational rigidity of the 2,6-diphenylpiperidine ring makes it possible to identify two isomeric oximes in certain cases. Two oximes (**370a** and **370b**) are obtained from *cis*-3,5-dimethyl-*cis*-2,6-



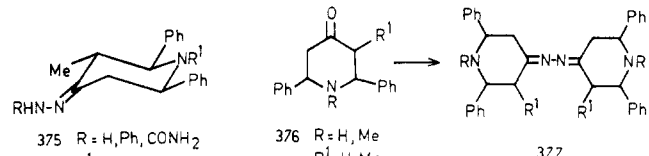
diphenylpiperidin-4-one (**369**). These have been separated by preparative TLC.[339] However, the *N*-methyl derivative gives only one oxime. Deoximation of the oxime **370a** by heating with $NaHSO_3$ gives 100% of the cis piperidinone (**369**) while the trans oxime (**370b**) gives a mixture of the cis (**369**) and trans (**371**) piperidinones in an 80:20 ratio. At room temperature the trans oxime gives the trans ketone (**371**) exclusively, the equilibrium mixture containing part of the unhydrolyzed oxime. Haller et al.[340] isolated the trans ketone (**371**) from the semicarbazone.[340] The $A^{(1,3)}$ strain[341] between the substituent at the exocyclic double bond and the methyl group causes the formation of the anti isomers. A change in the ring conformation from cis to trans avoids the $A^{(1,3)}$ strain in the dimethylpiperidinone oxime.

A single isomer of the oxime **372** from 2,6-diphenylpiperidin-4-one has been reported.[342] Lyle et al.[343]

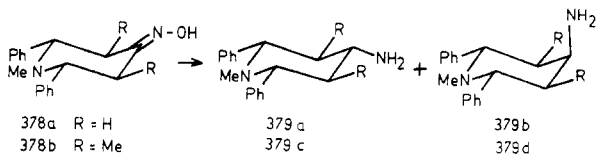


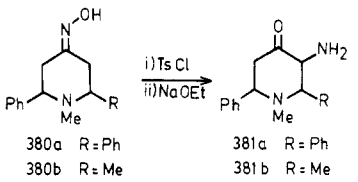
established the configuration of the (+)-1-methyl-2,6-diphenylpiperidin-4-one oxime (**372**, R = R′ = H) by conversion to the lactam **373** and hydrolysis to the diamine **374**, the configuration of which was established by standard methods.[343a] Similarly 3-alkyl- and 3,3-dimethylpiperidinones have been converted to the diamines.[343b]

For the purpose of studying the anisotropic effects of the hydrazone group on the adjacent protons, the hydrazones, phenylhydrazones, and semicarbazones of the piperidin-4-ones **375** have been prepared. The reaction of the ketone **376** with hydrazine hydrate gives diastereomeric mixtures of **377**.[344]



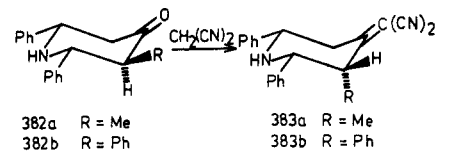
Reduction of 2,6-diphenylpiperidin-4-one oxime (**378a**) with $LiAlH_4$ gives the amines **379a** and **379b** in the ratio 70:30, while 3,5-dimethyl-2,6-diphenylpiperidin-4-one oxime (**378b**) gives the amines **379c** and **379d** in the ratio 20:80 because of steric factors.[345,346] The configurations have been established by NMR studies on the amines and their acetyl derivatives.[345] Alkylation of the diamines from the oxime **378a** has also been studied.[346,347] The piperidin-4-one oximes **380a** and **380b** undergo Neber rearrangement to yield the 3-aminopiperidin-4-ones (**381a** and **381b**).[348,349]

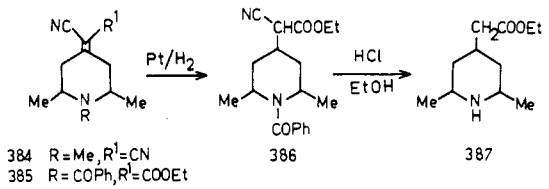




G. Other 4-Substituted Piperidines

Because of the high reactivity of the carbonyl group in piperidin-4-ones, a large number of substituents have been introduced at the 4-position. Malononitrile was condensed with 2,6-diphenyl-3-methylpiperidin-4-one (**382a**) and 2,3,6-triphenylpiperidin-4-one (**382b**) and the products **383a** and **383b** were obtained.[350] In this reaction the compounds **383a** and **383b**, in which the $A^{(1,3)}$ strain is avoided by epimerization, are formed. In the dicyanomethylenepiperidines the substituents at the 3-position are axial, although in the parent ketones they are equatorial. The condensation of malononitrile takes place with 1,2,6-trimethylpiperidin-4-one, giving the 4-cyanomethylene derivative (**384**).[351]

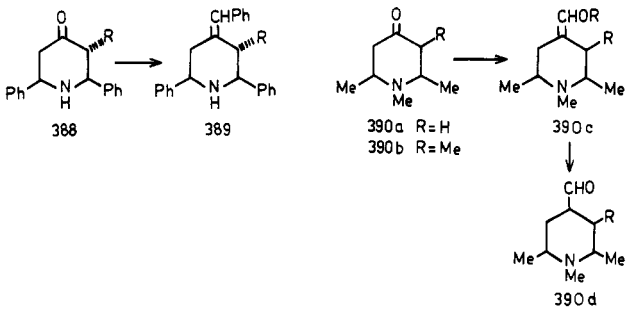




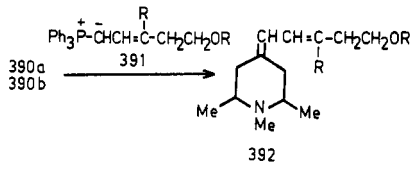
In a similar way ethyl cyanoacetate reacts with the *N*-benzoyl derivative of 2,6-dimethylpiperidin-4-one to give the 4-methylene compound **385**. This has been reduced to the saturated compounds **386** and **387**, which exist as isomeric mixtures.[352] The isomers have been separated.[352]

Several instances of the Wittig reaction performed with 2,6-disubstituted piperidin-4-ones are known. Treatment of $Ph_3P{=}CHPh$ with the 2,6-diphenylpiperidin-4-one **388** gives the methylene derivative **389**.[353] The Wittig condensation of $Ph_3P{=}CHOR$ (R = Me, Et, Bu) with 1,2,6-trimethylpiperidin-4-one (**390a**) and 1,2,3,6-tetramethylpiperidin-4-one (**390b**)

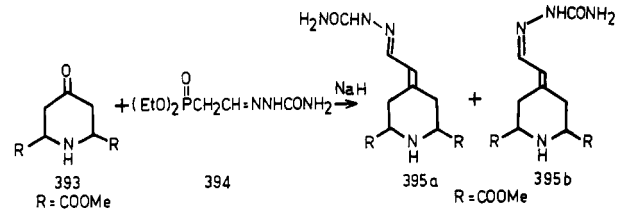
gives the 4-methoxymethylene derivatives **390c**, which,



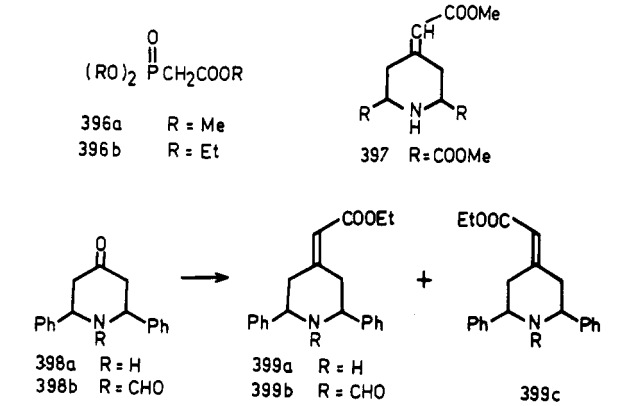
on hydrolysis, give the 4-carboxaldehydes **390d**.[354] The reaction of the ketones **390a** and **390b** with the ylide **391** gives the alkoxypentenylidenes **392**.[355]

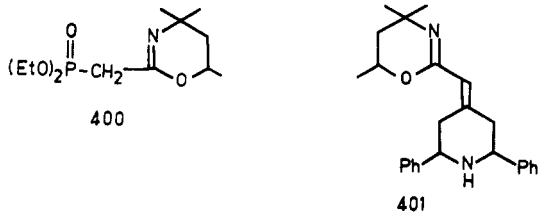


Dimethyl *cis*-4-oxopiperidine-2,6-dicarboxylate (**393**) was converted into the semicarbazones of 2,3-dihydrobetalamic acid dimethyl ester **395a** and **395b** by a



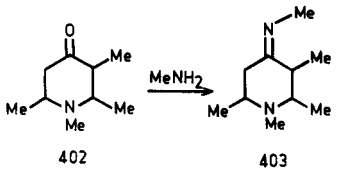
modified Horner–Wittig reagent, **394**.[356] Similarly the piperidine-2,6-dicarboxylate **393** reacts with the reagent **396a** to give the triester **397**. For the same study 2,6-

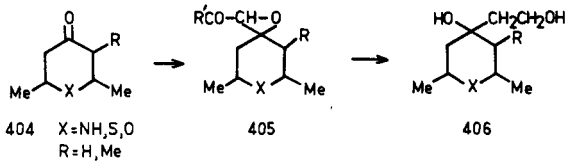




diphenylpiperidin-4-one (**398a**) was condensed with the Wittig reagents **396b** and **400** to give the unsaturated compounds **399a** and **401**, respectively. The *N*-formyl derivative **398b** gives the products **399b** and **399c** in high yield.

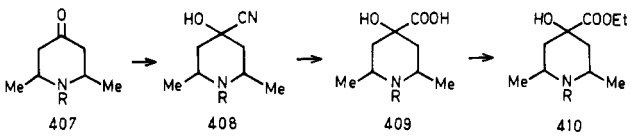
Methylamine gives Schiff base **403** when heated in a sealed tube with 1,2,5,6-tetramethylpiperidin-4-one (**402**).[357] The glycidic acid derivatives **405** (X = O, S,





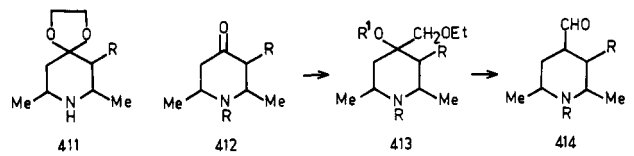
NMe) are formed by the condensation of the corresponding heterocyclic ketone **404** with $ClCH_2COR$ (R = NH_2, MeNH, Me_2N, PhNH, Et_2N). The glycidic esters are formed by condensing the ketone with ethyl chloroformate.[358] These have been reduced to the diols **406**.[359]

The 4-hydroxy-4-carboxylic acids **409** are obtained by the addition of HCN to the *N*-alkyl-2,6-dimethylpiperidinones **407** (R = H, Et, $CHMe_2$, $PhCH_2$, $PhCH_2CH_2$) and subsequent hydrolysis of the cyano-

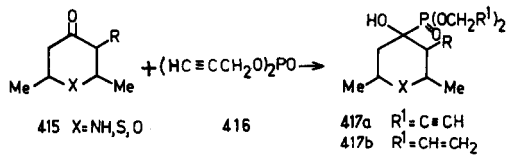


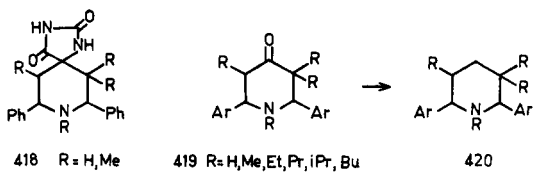
hydrins **408**. Esterification of the acid **409** gives the ester **410**.[360]

Ketals are easily formed from the piperidin-4-ones. The ketals **411** from ethylene glycol and 2,6-dimethylpiperidin-4-ones are prepared by normal methods.[361,362]



The mercuric chloride catalyzed reaction of the piperidin-4-ones **412** with $ClCH_2OEt$ in THF yields 4-ethoxymethyl derivatives **413**. Hydrolysis of the hem-



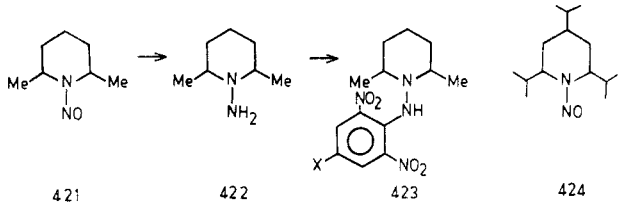


iacetals in formic acid affords the free 4-carboxaldehydes (414).[363,364]

The reaction of dipropargyl phosphonate (416) with 2,6-dimethylpiperidin-4-ones and related heteranes (415) in the presence of sodium propargoxide gives 4-substituted compounds (417a).[365a,b] Diallyl 4-piperidinylphosphonates (417b) have also been prepared.[365c] Spirohydantoins (418) have been obtained[56] from 2,6-diphenylpiperidin-4-ones. Many piperidin-4-ones 419 have been reduced to the piperidines 420 by the Wolff–Kishner method.[44,366-370]

H. *N*-Nitrosopiperidines and Related Compounds

The *N*-nitroso derivatives and *N*-amino derivatives of many substituted piperidin-4-ones and piperidines have been obtained and their conformations studied. *N*-nitroso-2,6-dimethylpiperidine (421) is prepared by

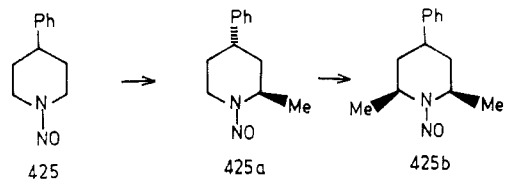


421 422 423 424

treating 2,6-dimethylpiperidine with NOCl or with nitrous acid.[371-379] Reduction of the nitroso compound with $LiAlH_4$ gives the *N*-aminopiperidine 422.[371,380] Electrolytic reduction also gives the amine 422.[381] The amine 422 reacts with 4-substituted 2,6-dinitrochlorobenzene to give the *N*-arylamino derivative 423.[382]

Though the nitroso compounds are generally carcinogenic, blocking of the α positions by methyl groups reduces the carcinogenic activity.[383] The relative rates of *N*-nitrosation of piperidine, 2-methylpiperidine, 2,6-dimethylpiperidine, and 2,2,6,6-tetramethylpiperidine with HNO_2 are found to be 100:20:10:1, indicating the steric hindrance of the methyl group.[384] *N*-Nitroso-2,4,6-triisopropylpiperidine (424) has also been obtained.[385]

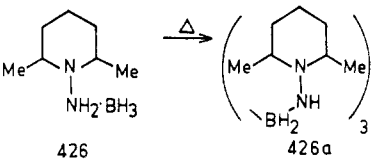
Another method of synthesizing *N*-nitroso-2,6-dimethylpiperidines is to alkylate the unsubstituted *N*-nitrosopiperidines at the α position. Thus alkylation of the *N*-nitroso-4-phenylpiperidine 425 anion with



425 425a 425b

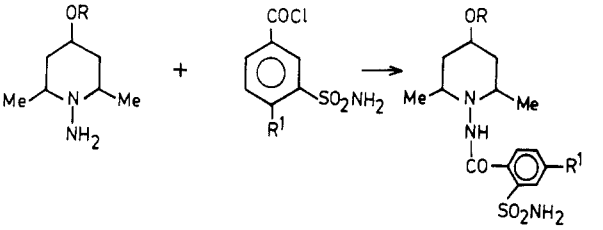
methyl iodide yields 2-alkyl (425a) and 2,6-dialkyl (425b) derivatives.[386] Monoalkylation gives solely the 2-axial alkyl derivative. A second methylation of the monomethyl derivative gives the 2,6-diaxial derivative. No isomer having trans methyl groups has been detected in this reaction. However, the trans isomer dominates over the cis by three times at equilibrium. The high stereoselectivity is explained in terms of stereoelectronic control for axial attack.[386]

The *N*-amino derivative (422) of 2,6-dimethylpiperidine combines with BH_3 to give the adduct 426, which, on pyrolysis, gives the trimer 426a.[374,377]

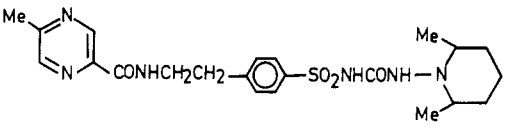


426 426a

The benzamidopiperidines 428, examined for their use as diuretics, have been synthesized from 1-amino-



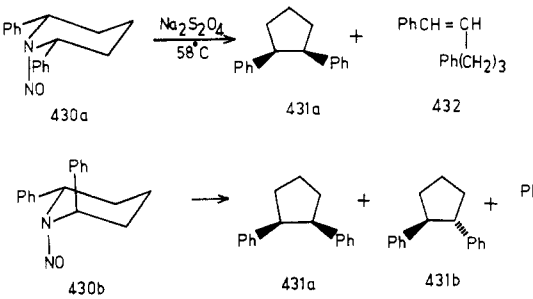
427 428



429

2,6-dimethyl-4-alkoxypiperidines by treatment with the substituted benzoyl chloride 427 in the presence of NaOH.[387-389] Similarly, the sulfonamide 429, used for the treatment of diabetes, is obtained from 1-amino-2,6-dimethylpiperidine.[390]

N-Nitroso derivatives (430a, 430b) are also formed from 2,6-diarylpiperidines.[167,380,391-393] Though 1-



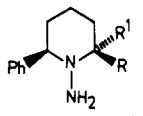
430a 431a 432

430b 431a 431b 432

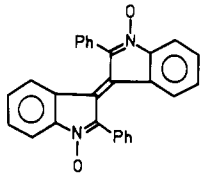
nitroso-2,6-dimethylpiperidin-4-one (421) undergoes reduction to the 1-amino derivative when reduced with $Na_2S_2O_4$, the diphenyl compounds 430a and 430b do not give the 1-amino derivative, but instead form non-nitrogenous compounds.[392] *cis*-2,6-Diphenyl-1-nitrosopiperidine (430a), on reduction with $Na_2S_2O_4$, produces 21% 1,5-diphenyl-1-pentene (432) and 57% *cis*-1,2-diphenylcyclopentane (431a). From *trans*-2,6-diphenyl-1-nitrosopiperidine (430b) is obtained 60% of a mixture of *cis*- and *trans*-1,3-diphenylcyclopentane (431a and 431b) and 19% 1,5-diphenyl-1-pentene (432).

The *cis*- and *trans*-1-nitroso-2,6-diphenylpiperidines (430a and 430b) are, however, conveniently reduced by $LiAlH_4$ to the 1-aminopiperidines 433a and 433b, respectively.[167] The five-membered rings are also formed when the *N*-aminopiperidines are oxidized with EtOH/HgO.[167,380,392,393] The cis isomer 433a gives *cis*-1,2-diphenylcyclopentane (431a) and 1,5-diphenyl-1-pentene (432) in the ratio 65:25.

The reaction of the *N*-aminopiperidine 433a with $KMnO_4$ also gives 35% cyclopentane.[167] The trans



433a R = Ph, R¹ = H
433b R = H, R¹ = Ph



434

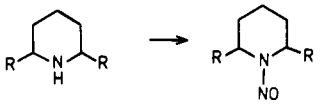
isomer **433b**, on the other hand, reacts with HgO, giving 59% *trans*-1,2-diphenylcyclopentane (**431b**) and 12% *cis*-1,2-diphenylcyclopentane (**431a**) along with 14% 1,5-diphenylpentene (**432**).

Reduction of *cis*- and *trans*-1-nitroso-2,6-diphenylpiperidines with lithium in liquid ammonia also gives only the same hydrocarbon products.[392] From *cis*-1-nitroso-2,6-diphenylpiperidine (**430a**) is obtained 26% 1,5-diphenyl-1-pentene (**432**) and 45% *cis*-1,2-diphenylcyclopentane (**431a**). From *trans*-1-nitroso-2,6-diphenylpiperidine (**430b**) is obtained 91% of a mixture of *cis*- and *trans*-1,2-diphenylcyclopentane.

The products obtained from both *N*-nitrosopiperidines and *N*-aminopiperidines are the same, suggesting a common intermediate for the mercuric oxide oxidation of the *N*-aminopiperidines and the sodium hydrosulfite reduction of *N*-nitrosopiperidines. The mechanism for the formation of the cyclopentanes and the pentene has been discussed.[393]

cis-1-Amino-2,6-diphenylpiperidine (**433a**) is deaminated when treated with the indole derivative **434** with the formation of 50% *cis*-2,6-diphenylpiperidine and 40% 1,5-diphenylpent-1-ene.[394]

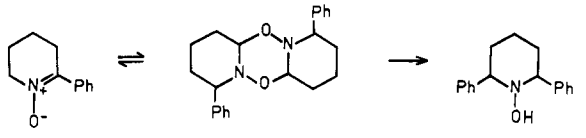
N-Nitroso compounds (**436a** and **436b**) have been prepared from 2,6-dicyanopiperidine (**435a**) and 2,6-dicarbomethoxypiperidine (**435b**).[395,396]



435a R = CN
435b R = COOMe

436a R = CN
436b R = COOMe

The *N*-OH derivative of 2,6-diphenylpiperidine (**438**) has been prepared[397] by the addition of PhMgBr to 2,3,4,5-tetrahydro-2-phenylpyridine *N*-oxide (**437**). The *N*-hydroxy compound was reduced to 2,6-diphenylpiperidine.[397]



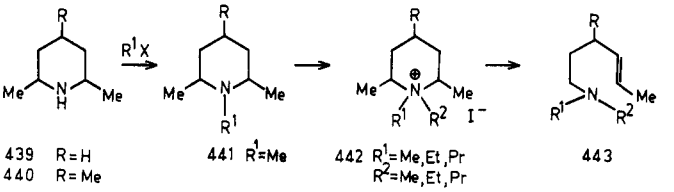
437

438

I. *N*-Alkylpiperidines

Various *N*-alkylpiperidines have been prepared with a view to studying their pharmacological properties.[398-406] Most of these derivatives have been prepared from 2,6-dimethylpiperidine because of the structural similarity with naturally occurring alkaloids and because of the easy methods of synthesis.

cis-2,6-Dimethylpiperidine (**439**) reacts with methyl iodide in the presence of potassium carbonate, with dimethyl sulfate in the presence of potassium carbonate in acetone, or with formaldehyde and formic acid, giving the *N*-methyl derivative (**441**).[133,407-409] The trans



439 R = H
440 R = Me

441 R¹ = Me

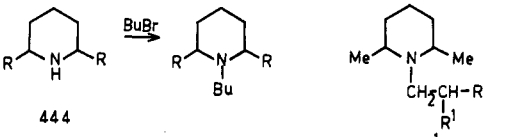
442 R¹ = Me, Et, Pr
R² = Me, Et, Pr

443

isomer also reacts in the same way. The 2,4,6-trimethylpiperidines **440** give the *N*-methyl derivatives **441** (R = Me), the optical properties of which have been discussed, but not the conformational and configurational possibilities.[409]

The quaternary salts **442** obtained from 2,6-dimethylpiperidine are reported as good antiseptics, antispasmodics, antihistaminic agents, and germicides.[408] Studies on the Hofmann degradation of 2,4,6-trialkylpiperidinium iodides indicate that elimination occurs preferentially in the piperidine ring, giving **443** rather than in the 2-alkyl chain, except when the alkyl group is methyl. This is attributed to a steric effect in the polar transition state.[410]

The 2,6-disubstituted piperidines **444** (R = Me, Ph, $PhCH_2CH_2$) have been allowed to react with butyl



444

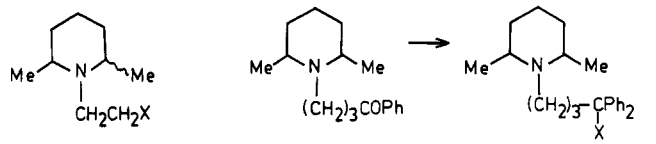
445a R = H, R¹ = OH
445b R = H, R¹ = CH_2OH
446 R = Ph, R¹ = OH

bromide at 150–155 °C for 6 and 12 h, and the relative reactivities have been examined. When a single substituent is present the methyl group is found to be as effective as the larger groups in diminishing the rate of alkylation. When substituents are present on both the 2- and 6-positions, the methyl group is more effective than the larger groups.[411,412]

The reaction of 2,6-dimethylpiperidine with 2-chloroethanol or 3-chloropropanol in the presence of NaI in absolute ethanol and sodium ethoxide gives the *N*-alkylated piperidines **445a** and **445b**.[130,413,414]

The reaction of 2,6-dimethylpiperidine with styrene oxide yields 1-phenyl-2-(2,6-dimethylpiperidino)ethanol (**446**).[413,415]

Treating *cis*- or *trans*-2,6-dimethylpiperidine with ethylene oxide or ethyl bromoacetate, followed by reduction with $LiAlH_4$ and chlorination of the hydroxy derivative **447a** with thionyl chloride, gives the 2-



447a X = OH
447b X = Cl
447c X = $NHNH_2$

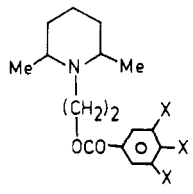
448a

448b X = OH
448c X = CN

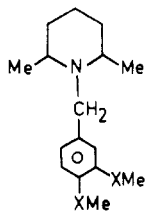
chloroethyl derivative **447b**, which, on treatment with hydrazine hydrate, gives **447c**.[416]

The ketone **448a** reacts with PhMgBr or PhLi to produce the tertiary alcohol **448b**, the cis isomer of which shows antiarrhythmic activity.[400] Similarly, the nitrile **448c** has anticholinergic activity.[399]

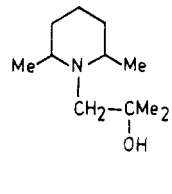
The 3,4,5-trihalobenzoates **449**, prepared by treating the ω-bromoalkyl-3,4,5-trihalobenzoates with 2,6-dimethyl- and 2,6-diethylpiperidines, are useful as hypotensives and central nervous system depressants.[401,402]



449 X=Cl, Br



450a X=O
450b X=S



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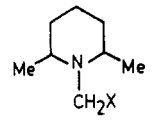
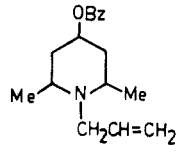


452 X=CN
453 X=CH_2NH_2



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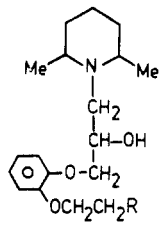
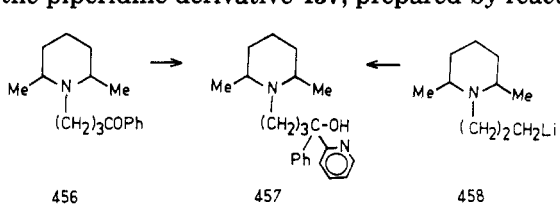


455 R=OMe, SMe

The benzyl derivatives **450a** and **450b** and the tertiary alcohol derivative **451** have been obtained and their properties described.[417-419]

The cyanomethyl derivative **452** and the aminoethyl derivative **453** have been obtained by the reaction of 2,6-dimethylpiperidine with acetonitrile and subsequent reduction of the product.[420,421]

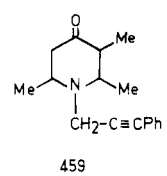
The α form of 1-allyl-2,6-dimethyl-4-piperidyl benzoate hydrochloride (**454**) is an anesthetic. The β-piperidinopropanols **455**, prepared by refluxing 1,2-epoxy-3-(2-methoxyethoxyphenoxy)propane with 2,6-dimethylpiperidine, are antiarrhythmics and local anesthetics.[422] Antiarrhythmic property is also exhibited by the piperidine derivative **457**, prepared by reaction



456 457 458

of the cis isomer of **456** with 2-lithiopyridine or by reaction of the cis isomer of **458** with 2-benzoylpiperidine.[423]

Phenylacetylene reacts with HCHO and 2,3,6-trimethylpiperidinone to give the *N*-(1-phenylpropynyl) derivative **459**.[424] The amide **460** also has useful pharmacological properties.[425]



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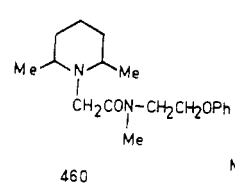

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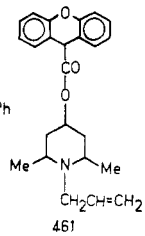

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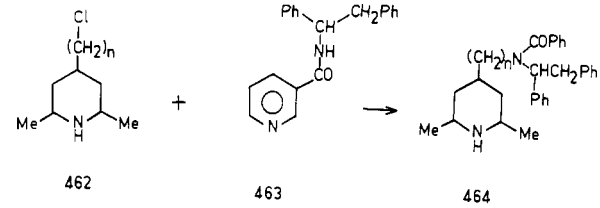
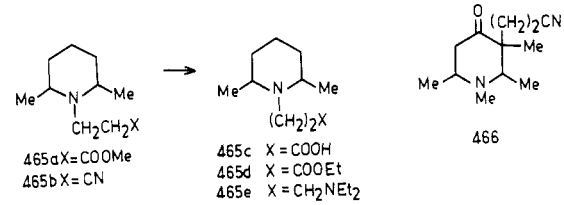
The 9-xanthenecarboxylic acid ester of 1-allyl-2,6-dimethylpiperidin-4-ol (**461**) has been prepared.[426] It



462 463 464

amide **463** and the piperidinoalkyl halides **462** in the presence of sodamide, have spasmolytic activity.[405]

The piperidines also add to acrylic acid derivatives to give several useful compounds. Methyl acrylate reacts with 2,6-dimethylpiperidine in methanol to give 1-(β-(carbomethoxy)ethyl)-2,6-dimethylpiperidine (**465a**).[427]



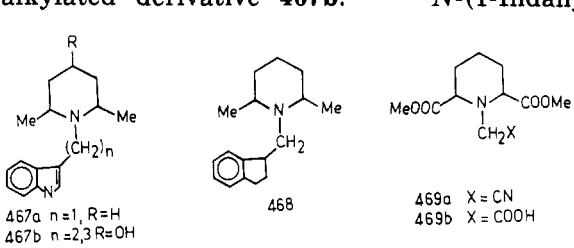
465a X=COOMe
465b X=CN

465c X=COOH
465d X=COOEt
465e X=CH_2NEt_2

466

Heating 2,6-dimethylpiperidine with excess acrylonitrile containing a trace of water for 30 h on a steam bath gives β-piperidinopropionitrile **465b**, which has been converted to other acid derivatives **465c-d**.[428a] Michael addition of 1,2,3,6-tetramethylpiperidin-4-one to acrylonitrile gives the 3-substituted derivatives (**466**).[428b]

Substituted piperidines are condensed with HCHO and indole in the presence of glacial acetic acid to form the indolylalkyl derivatives **467a**, having strong oxytocic effect.[406] Both 2,6-dimethyl- and 2,4,6-trimethylpiperidines have been employed. Indolylalkyl halides also react with 2,6-dimethylpiperidin-4-ol to yield the *N*-alkylated derivative **467b**.[429] *N*-(1-Indanyl-



467a n=1, R=H
467b n=2,3 R=OH

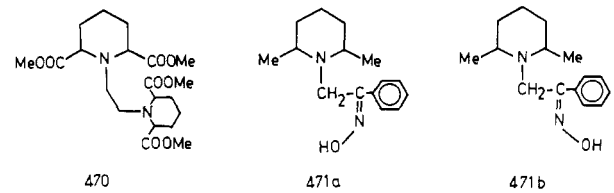
468

469a X=CN
469b X=COOH

methyl)-2,6-dimethylpiperidine (**468**) is prepared by the reaction of 1-formylindan with 2,6-dimethylpiperidine in cyclohexane, followed by catalytic hydrogenation.[430]

Dimethyl *cis*-piperidine-2,6-dicarboxylate condenses with HCHO in the presence of HCN, giving the 1-cyanomethyl derivative **469a**, which, on hydrolysis, gives the 1-carboxymethyl derivative **469b**.[431]

Ethylene-*N*,*N*′-bis(2,6-methoxycarbonyl)piperidine (**470**) obtained from 2,6-dicarboxypiperidine by reaction with ethylene dibromide forms metal complexes.[432]

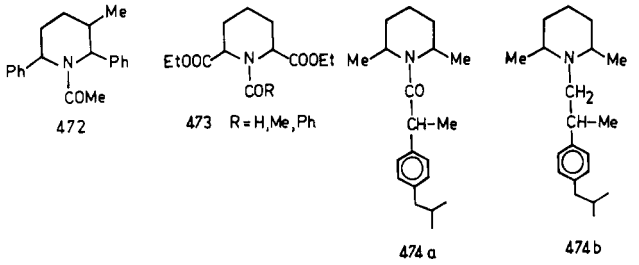


470 471a 471b

The photoaddition of 2,6-dimethyl-*N*-nitrosopiperidine to styrene gives a mixture (48%) of high-melting (161–164 °C) and low-melting (61–66 °C) compounds that show no distinctive differences in their NMR spectra. On the basis of their solubility and melting points the compound with higher melting point has been assigned the anti configuration (**471b**) and the other the syn configuration (**471a**).[379]

J. *N*-Acyl- and *N*-Chloropiperidines

The N-acetylation of 2,6-diphenylpiperidine has failed to take place under various conditions, indicating the steric hindrance for the approach of the reagent to NH.[433] However, it has been reported that the *N*-acetyl derivative **472** of 3-methyl-2,6-diphenylpiperidin-4-one

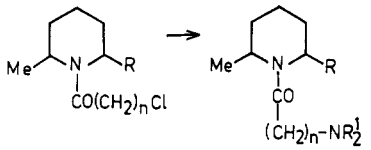


472 473 R = H,Me,Ph 474a 474b

can be prepared by refluxing it with 1,4-diazabicyclo-[2.2.2]octane in acetic anhydride and ethyl acetate for 6 h.[301] The *N*-acetyl derivative and various *N*-acyl derivatives **473** of piperidine-2,6-dicarboxylates are known.[434,435]

The isomers of 2,6-dimethylpiperidine react with a large number of acyl halides.[436–441] The reaction of α-(4-iso-butylphenyl)propionyl chloride with 2,6-dimethylpiperidine in the presence of Et_3N gives the amide **474a**. This can be reduced with $LiAlH_4$ to the *N*-phenethyl derivative **474b**, which has antiinflammatory activity.[442]

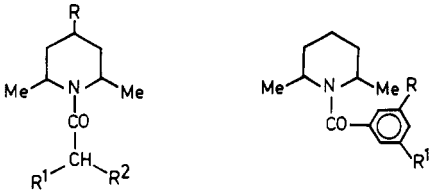
cis-2,6-Dimethylpiperidine reacts with β-chloropropionyl chloride and chloroacetyl chloride, giving the *N*-(β-chloropropionyl) and *N*-chloroacetyl derivatives **475a** and **475b**, which, on reaction with amines, give the



475a n=1 R=Me
475b n=2 R=Me
475c R=COOEt

476a R^1=Me
476b R^1=Et
476c R^1R^1=

diamines **476a,b**.[443,444] Other piperidines such as ethyl 6-methylpipercolinate (**475c**) also react in the same

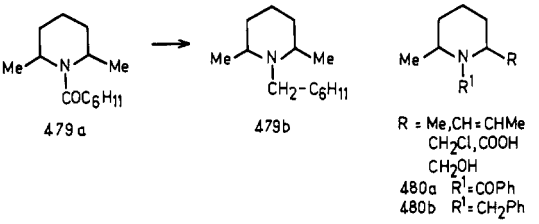


477 R = H,Me
R^1 = H,Cl,Me,Ph
R^2 = H,$PhCH_2CMe_2$

478a R = H,Me
478b R = H,OMe,Me

way.[444] Acetylation and benzoylation of 2,6-dimethyl- and 2,4,6-trimethylpiperidines give acetyl and benzyl derivatives.[445–448] Several other *N*-alkanoyl derivatives (**477**) of 2,6-dimethyl- and 2,4,6-trimethylpiperidines have been prepared.[403,449–453]

The methoxybenzoyl derivative (**478b**) is obtained from 2,6-dimethylpiperidine and reduced with $LiAlH_4$.[454] The 3,5-dimethylbenzoyl derivative (**478**, R,R′ = Me) is used as an insect repellant.[455] Treatment of 2,6-dimethylpiperidine with cyclohexanecarbonyl chloride yields the amide **479a**, which, on reduction with



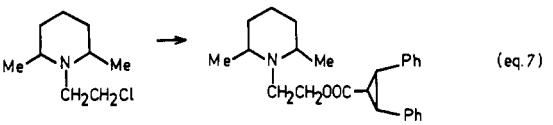
479a 479b

R = Me,CH=CHMe
CH_2Cl,COOH
CH_2OH
480a R^1=COPh
480b R^1=CH_2Ph

$LiAlH_4$, gives (2,6-dimethylpiperidino)methylcyclohexane (**479b**).[456]

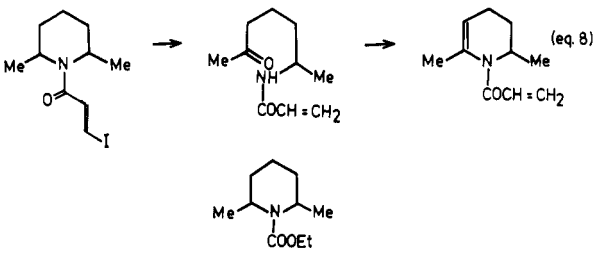
The *N*-glycosides of 2,6-diphenylpiperidin-4-one hydrochloride are obtained by heating the piperidine with glucose in MeOH.[457]

The benzoyl derivatives **480a** and the corresponding *N*-phenylmethyl derivatives **480b** have been prepared.[137] Treatment of 2,2-diphenylcyclopropanecarboxylic acid with NaOH and 2,6-dimethylpiperidino-β-chloroethane hydrochloride gives the ester (eq 7).[458]



(eq 7)

The *N*-β-iodoacrylyl derivative of 2,6-dimethylpiperidine, when irradiated, yields a ring-cleaved product which may be recyclized to a tetrahydropyridine (eq 8).[459] The reaction of 2,6-dimethyl-

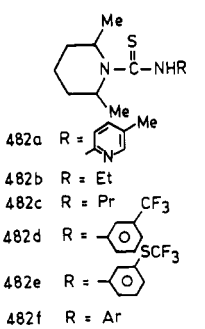


(eq 8)

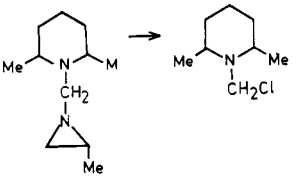
481

piperidine with ClCOOEt gives the carbamate **481**.[460]

Treatment of 2-amino-5-methylpyridine with CS_2 in triethylamine followed by methylation gives methyl 5-methyl-2-pyridinedithiocarbamate, which, on refluxing with 2,6-dimethylpiperidine, gives **482a**.[461] Other

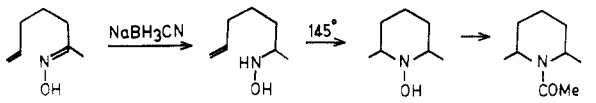


482a R =
482b R = Et
482c R = Pr
482d R =
482e R =
482f R = Ar



483a 483b

SCHEME IV

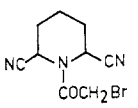


dithiocarbamates (**482b, 482c**) are prepared from the piperidine, MeOH, CS_2, Et_3N, and an alkyl halide.[462-464]

The thiourea derivatives (**482d–f**) are obtained from the piperidines by condensation with arylthiocyanates.[465-467] They are used for treating helminth infections.

The reaction of 2,6-dimethylpiperidine with *N*-(hydroxymethyl)-2-methylaziridine gives the *N*-methylaziridyl derivative **483a**, which reacts with acetyl chloride to give 1-(chloromethyl)-2,6-dimethylpiperidine (**483b**).[468]

Bromoacetyl chloride is employed to acylate 2,6-dicyanopiperidine to the *N*-bromoacetyl derivative **484**,



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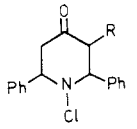
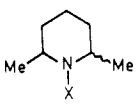


485a R = H
485b R = Me

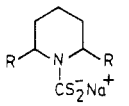
which is effective in the control of certain bacterial diseases of fruit trees.[469]

N-Chloro-2,6-diphenylpiperidin-4-ones (**485a**) are formed by passing chlorine through a solution of the piperidinone hydrochloride in ethanol–water.[470] They behave as very good oxidizing agents similar to *N*-chlorosuccinimide. The kinetics of oxidation of cyclohexanone oxime have been studied by using *N*-chloro-3-methyl-2,6-diphenylpiperidin-4-one (**485b**) as the oxidizing agent.[471] *N*-Hydroxy and *N*-acetyl derivatives of 2,6-dimethylpiperidine have been obtained as shown in Scheme IV.[472]

The *N*-chloro compounds **486a** have been obtained from *cis*- and *trans*-2,6-dimethylpiperidine and a neutral halogenating agent such as NaOCl or *N*-chlorosuccinimide.[217,473,474] To obtain pure samples the re-



486a X = Cl
486b X = F



487 R = alkyl

action is carried out in a buffer medium at 0 °C in the presence of dichloromethane as the solvent in which the *N*-chloro derivative is extracted as soon as it is formed.[473] The *N*-fluoro derivatives (**486b**) of *cis*- and *trans*-2,6-dimethylpiperidine have also been obtained.[473,475]

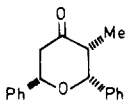
The sodium salts (**487**) of *N*-carbodithioic acid of 2,6-dialkylpiperidines have been obtained and their NMR spectra examined. It was shown that on formation of these derivatives a conformational inversion occurs.[476]

IV. Synthesis of Oxanes

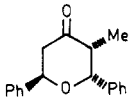
Compounds of the oxane and thiane series find wide use in industry as universal solvents, plasticizers, polymer stabilizers, and components of the rocket fuels.[477] The oxanes have also biological applications. Several natural products including antibiotics possess the oxane ring skeleton.

A. Oxan-4-ones by Condensation

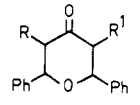
The formation of 2,6-diphenyl-3-methyloxan-4-one[478,479] was reported in 1902. A couple of years later Japp and Maitland[478] obtained a mixture of stereoisomeric 2,6-diphenyl-3-methyloxan-4-ones (**488a** and **488b**) by condensing benzaldehyde with 2-butanone in



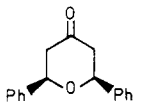
488a



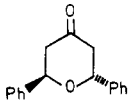
488b



489 R = Me, R^1 = Me
490 R = H, R^1 = Et



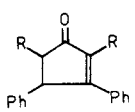
491a



491b

the presence of a base. A 1968 report[480] provides a convenient method of synthesizing pure *cis*-2,6-diphenyl-3-methyloxan-4-one. There are also modified procedures for its synthesis.[481,482] The 3,5-dimethyl- and 3-ethyl-2,6-diaryloxan-4-ones (**489, 490**) are also obtained in a similar way. One or both of the isomers (**491a, 491b**) of 2,6-diphenyloxan-4-one were known[483-485] for some time, but their stereochemistry was not studied. Baxter and Whiting[480] prepared several *cis*- and *trans*-2,6-diaryloxan-4-ones and established their stereochemistry by NMR spectra.

The condensation of benzaldehyde with methyl *n*-propyl ketone by the method of Japp and Maitland[478] was reported[486] to give only the cyclopentenone **492** and



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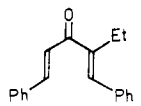

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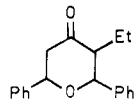
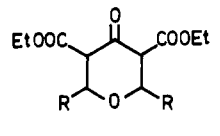


494

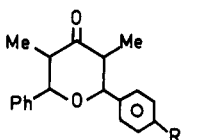
the dibenzylidene derivative **493**. However, when the reaction mixture was allowed to stand, the 2,6-diphenyloxan-4-one (**494**) was obtained.

The cis and trans isomers of 2,6-diphenyloxan-4-one are easily obtained from acetonedicarboxylic acid.[482-485] By condensation with benzaldehyde in the presence of dry hydrogen chloride at −5 to −10 °C and by subsequent decarboxylation, the cis isomer **491a** is obtained. The condensation, when carried out at room temperature, affords the trans isomer (**491b**).[482,484,487]

Diethyl acetonedicarboxylate also reacts with both aliphatic and aromatic aldehydes to yield oxan-4-ones (**495**).[488] Unsymmetrical 2,6-diaryloxan-4-ones (**496**) with different aryl groups were obtained by the reaction of monobenzylidenebutan-3-one with aromatic aldehydes.[489] The keto amide **497** reacts with benzaldehyde in an ethanol–water solution of NaOH to give the oxan-4-one **498**.[490] Acetonedicarboxylic acid reacts with chloral hydrate to give 2,6-bis(trichloromethyl)oxan-4-one (**499**).[491]



495 R = Me, Et, Bu, Ph



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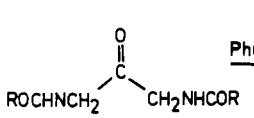

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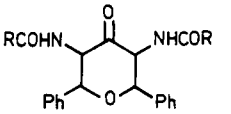
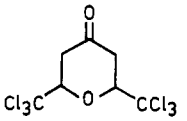
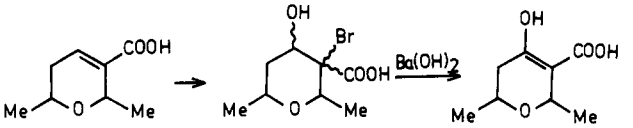


498 R = Ph, $PhCH_2$, $PhCH_2CH_2$, Me, OEt



499

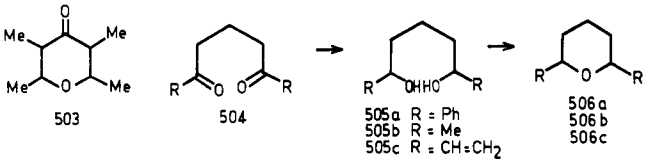
The acid **500**, obtained from dicrotonaldehyde, is converted to 2,6-dimethyloxan-4-one.[492] From the



500 501 502

unsaturated acid **500** the bromohydrin **501** is readily obtained. Treatment of **501** with boiling barium hydroxide solution yields **502**, which, on heating, gives 2,6-dimethyloxan-4-one.

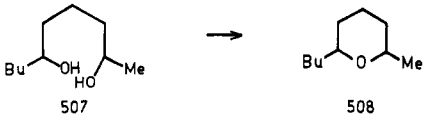
The tetramethyloxan-4-one **503** is obtained by repeating twice the aldol condensation of diethyl ketone with acetaldehyde.[493]



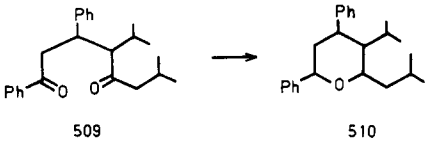
503 504 505a R = Ph; 505b R = Me; 505c R = $CH=CH_2$ 506a 506b 506c

B. Oxanes by Cyclization

The 1,5-diketones **504**, on reduction, give the racemic diols **505**, which can be cyclized to *cis*- and *trans*-2,6-disubstituted oxanes **506**.[494,495] Cyclization of the heptane-2,6-diols **505b** with anhydrous pyridine and *p*-toluenesulfonyl chloride yields 2,6-dimethyloxane (**506b**).[496] The cis and trans isomers of 2,6-divinyloxane (**506c**) have been obtained by the cyclization of nona-1,8-diene-3,7-diol (**505c**).[497] Similarly, 2-methyl-6-alkyloxanes **508** are also formed from unsymmetrical alcohols (**507**).[498]



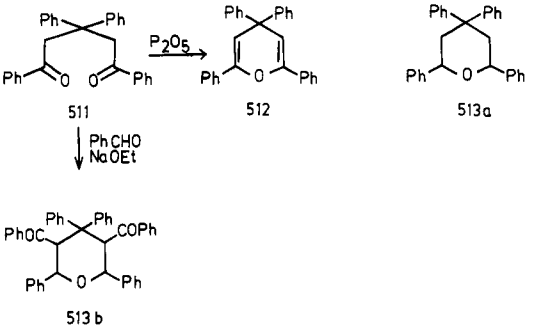
507 508



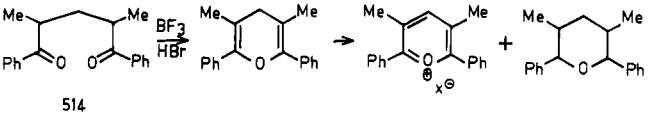
509 510

The reduction of the diketone **509**, followed by cyclization, gives 2,4-diphenyl-5-isopropyl-6-isobutyloxane (**510**), six isomers of which have been isolated.[499]

Dehydrocyclization of the 1,5-diketone **511** yields the pyran **512**, which, on catalytic hydrogenation, gives the oxane **513a**, while condensation of the 1,5-diketone with benzaldehyde in the presence of NaOEt gives the tetraaryloxane **513b**.[500,501]



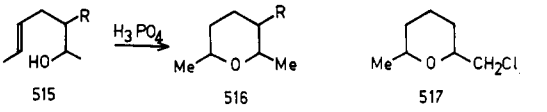
511 512 513a 513b



514

The disproportionation reaction of pyrones is also a method of obtaining oxanes.[502,503] Disproportionation reaction of the 1,5-diketone **514**, takes place with acid reagents through a stage of formation of the 4*H*-pyran, which undergoes further transformation with the formation of the disproportionation products.

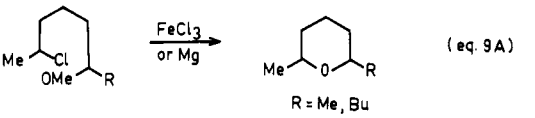
The secondary alcohols **515**, prepared from Grignard addition to aldehydes, give the oxanes **516**[504] on heating



515 516 517

with a catalytic amount of H_3PO_4. Similarly, cyclization of 1-chloro-2,6-heptanediol gives 2-(chloromethyl)-6-methyloxane (**517**).

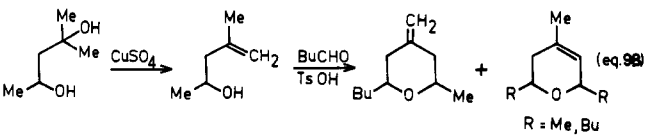
Aliphatic γ- and δ-methoxy halides are cyclized with ferric chloride or magnesium to the 2,6-disubstituted oxanes (eq 9A).[505-507]



(eq. 9A)

R = Me, Bu

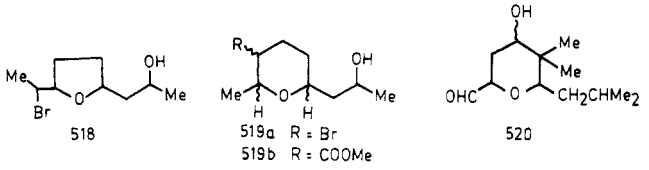
A mixture of 2-methyl-6-butyloxane derivatives can be obtained by refluxing 2-methylpentane-2,4-diol with a catalytic amount of $CuSO_4$ and keeping the resulting alkenol with BuCHO and TsOH (eq 9B).[508,509]



(eq. 9B)

R = Me, Bu

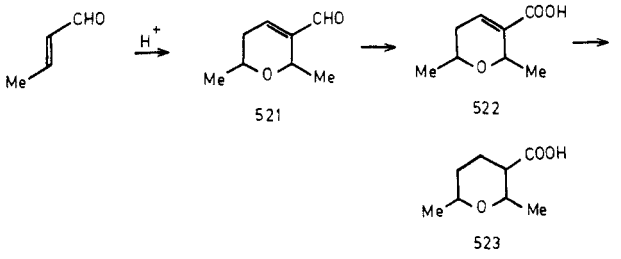
Intramolecular alkoxybromination of the diastereomeric *trans*-2-nonene-6,8-diols with AcNHBr gives 2-(1-bromoethyl)-5-(2-hydroxypropyl)tetrahydrofuran (**518**) and 3-bromo-2-methyl-6-(2-hydroxypropyl)oxane



518 519a R = Br 519b R = COOMe 520

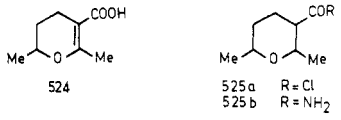
(**519a**)[510] in a 4:1 ratio. The latter can be converted to the ester **519b**.[510] The oxan-4-ol **520** has been synthesized in five steps.[510a]

One of the earliest methods of synthesis of 2,6-dimethyloxanes involves the dimerization of crotonaldehyde with a strong acid to give the aldehyde **521**.



521 522 523

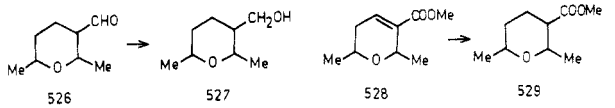
The sodium salt of the acid **522**, on hydrogenation, gives the oxane **523**.[511-516] The oxane **523** can also be obtained from **521** by hydrogenation over nickel followed by oxidation with ammonium vanadate and manganese(II) acetate.[517] The dihydropyran **524** is also formed as an



524 525a R = Cl 525b R = NH_2

intermediate in the hydrogenation over nickel.[511,513,517] The oxane **523** has been converted to the acid chloride **525a** and the amide **525b**.[518]

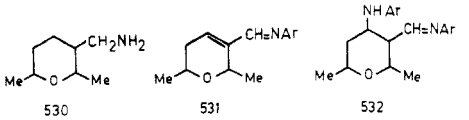
The oxane-3-carboxaldehyde **526** itself may be obtained from **521** by hydrogenation and converted to the 3-hydroxymethyl derivative **527**.[519,520] The aldehyde



526 527 528 529

521 is oxidized with $Ba(OH)_2$ and silver nitrate in water, and the resulting acid **522** is treated with diazomethane to give the ester **528**, which, on catalytic hydrogenation over platinum, gives the oxane **529**.[514]

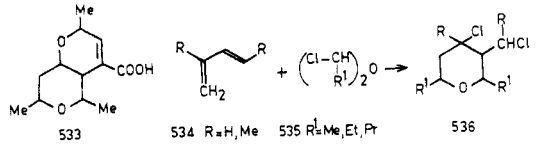
The oxane-3-carboxaldehyde **526**, obtained by hydrogenation of **521**, on reaction with anhydrous ammonia followed by catalytic hydrogenation, yields the amine **530**.[521]



530 531 532

Dicrotonaldehyde (**521**) reacts with a primary amine to give the dihydropyran **531**, which, with excess amine, gives the oxane **532**.[516,522]

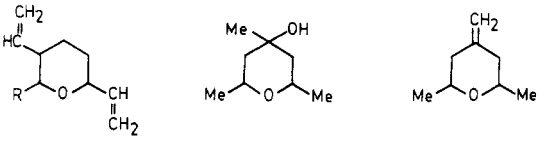
Oxidation of trimeric crotonaldehyde gives the oxane derivative **533**.[523]



533 534 R = H, Me 535 R = Me, Et, Pr 536

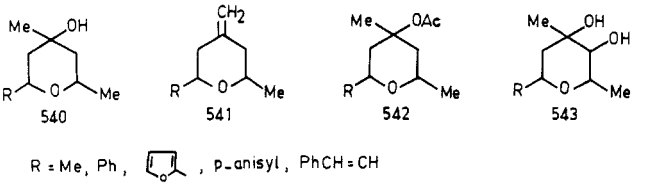
Treatment of the butadienes **534** with the α-haloalkyl ether **535** in the presence of $ZnCl_2$ and hydroquinone gives the oxanes **536**.[524-526b]

The 3,6-divinyloxanes **537** are formed when butadiene is heated with triphenylphosphine–palladium chloride complex, NaOPh, and an aliphatic or aromatic aldehyde.[527-531]



537 538 539

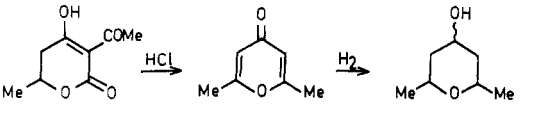
When but-2-ene is heated with acetaldehyde in the presence of H_2SO_4, oxanol **538** is obtained[532] in low yield. The same compound can also be obtained from isobutylene and acetaldehyde.[533,534] The 4-methylene derivative **539** is also obtained as a byproduct.[534] In a similar way 2-methyl-4-hydroxy-1-pentene reacts with acetaldehyde or benzaldehyde in the presence of acid catalysts like H_2SO_4, H_3PO_4, $FeCl_3$, HCl, TsOH, etc., to yield 2,6-disubstituted oxan-4-ols (**540**).[535-537a] The *cis*-dimethyl derivatives only are formed. Along with the oxan-4-ols, 2,6-dialkyl-4-methyleneoxanes (**541**) are sometimes formed.[537b-d] The oxan-4-ol **540** is converted to the oxane-3,4-diol **543** through the formation of acetate **542** and oxidation by permanganate.[535]



540 541 542 543

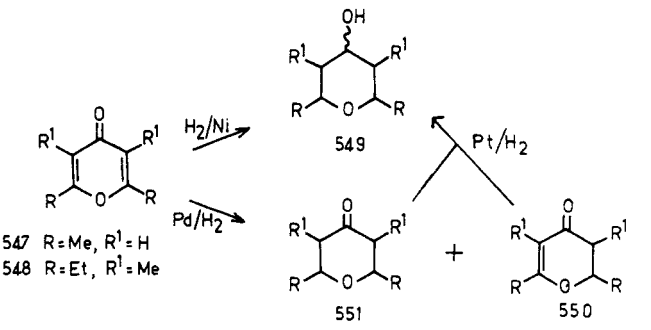
R = Me, Ph, , p-anisyl, PhCH=CH

Treatment of dehydroacetic acid (**544**) with HCl gives 2,6-dimethylpyrone (**545**), complete hydrogenation of which gives the oxan-4-ol **546**.[538-540]



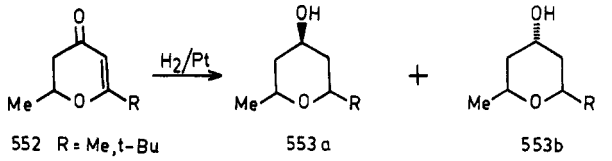
544 545 546

Hydrogenation of 2,6-dimethyl-4-pyrone (**547**) with Raney nickel gives the oxan-4-ol **549** while with Pd a



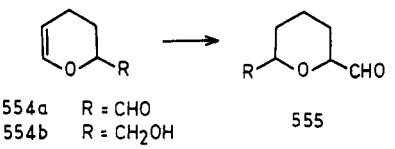
547 R = Me, R^1 = H 548 R = Et, R^1 = Me 549 550 551

mixture of 2,6-dimethyldihydro-4-pyrone (**550**) and the corresponding oxan-4-one (**551**) are formed that can be finally converted to the oxan-4-ols **549**.[541-543] Hydrogenation of 2,6-diethyl-3,5-dimethyloxan-4-one (**551**, R′ = Me) and the corresponding oxan-4-ol (**549**, R′ = Me).[544] Catalytic hydrogenation of the dihydropyran **552** gives the oxan-4-ols **553a** and **553b**.[545]



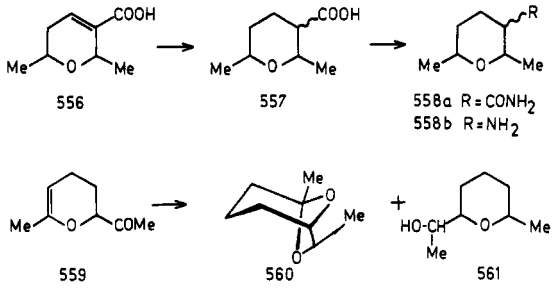
552 R = Me,t-Bu 553a 553b

The dihydropyrans **554a** and **554b**, on heating with CO and H_2 in an autoclave at high pressure with Rh_2O_3 catalyst, yield the oxanes **555**.[546]



554a R = CHO
554b R = CH_2OH 555

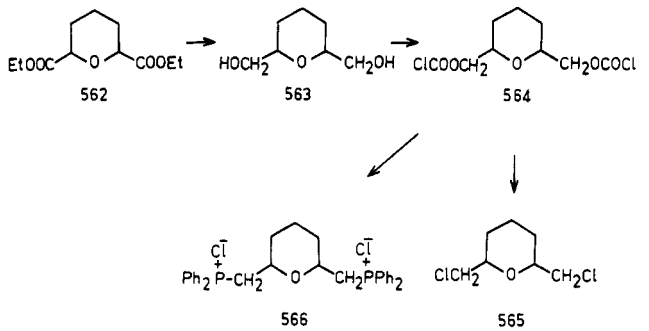
Hydrogenation of the trans *dl* mixture of the dihydropyran **556** gives two stereoisomers of the 3-carboxyoxane **557**. The isomeric acids are converted to the amides **558a** and 3-aminooxanes **558b**.[547]



556 557 558a R = $CONH_2$
558b R = NH_2
559 560 561

Low-pressure hydrogenation of the ketone **559** over Pd/C gives the dioxa bicyclic compound **560** along with the oxane **561**.[548]

Diethyl oxane-2,6-dicarboxylate (**562**),[542] on reduction with $LiAlH_4$, gives the diol **563**, which reacts with chloroformic acid to form the ester **564**. This ester, in

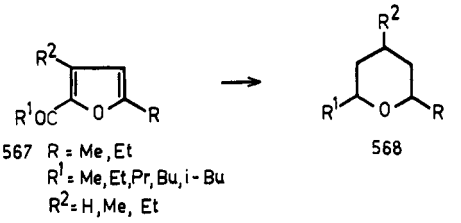


562 563 564 566 565

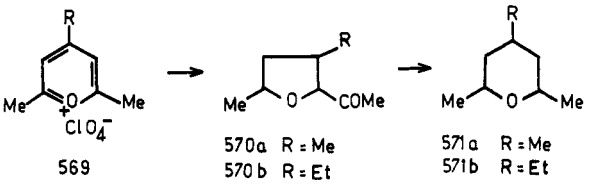
the presence of catalytic amounts of triphenylphosphine, gives 2,6-bis(chloromethyl)oxane (**565**) while with equivalent amounts forms the phosphonium chloride **566**.[549]

When 2-alkyl-5-acylfurans (**567**) are hydrogenated over the Pt, Pd, Ir, Os, Rh, or Ru catalyst supported on carbon, 2,6-dialkyloxanes (**568**) are formed.[550-557]

When a mixture of 2,4,6-trimethylpyrylium perchlorate (**569**) and hydrogen peroxide is steam distilled 3,5-dimethyl-2-acetylfuran (**570a**) is formed. By a similar method 2-acetyl-3-ethyl-5-methylfuran (**570b**) is also obtained. Hydrogenation of these acetyl derivatives over Pt–C gives 2,4,6-trimethyloxane (**571a**) and 2,6-dimethyl-4-ethyloxane (**571b**), respectively.[553,558]

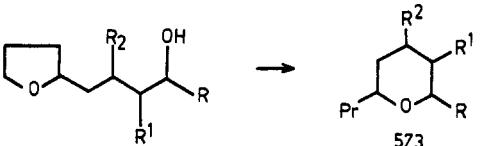


567 R = Me, Et
R^1 = Me, Et, Pr, Bu, i-Bu
R^2 = H, Me, Et 568



569 570a R = Me 570b R = Et 571a R = Me 571b R = Et

Isomerization of the tetrahydrofuryl derivatives **572** over Pt–C in the vapor phase yields the oxanes **573**.[559,560]

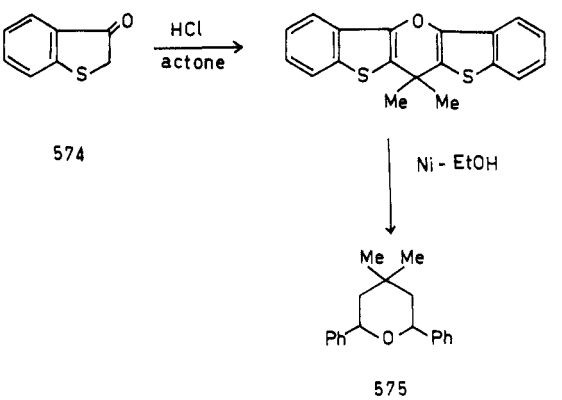


572

R	R^1	R^2
Me	H	Et
Et	H	Et
Pr	Me	H

573

A novel desulfurization technique provides a means of obtaining 4,4-dimethyl-2,6-diphenyloxane (**575**). Desulfurization of 2,3-dihydrothianaphthen-3-one (**574**) with Raney nickel in refluxing ethanol gives the oxane **575**.[561]

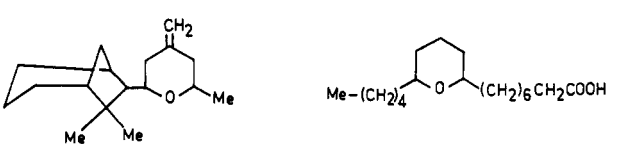


574 575

Thermal lead tetraacetate reaction of 5,5-dimethyl-2-heptanol (**576**) produces the pyran **577** in addition to other products.[562]

576 577

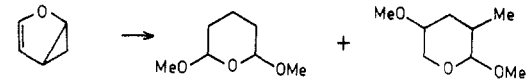
The addition of camphene oxide in hexane to 2-methyl-1-penten-4-ol in the presence of H_2SO_4 gives the bicycloheptyloxane **578**.[563]



578 579

Oxymercuration–demercuration of dienes and unsaturated alcohols yields diols, tetrahydrofurans, and oxanes.[564] Thus a mixture of methyl octadecadienoate, mercuric acetate, THF, and water is shaken for 4 days, $NaBH_4$ and aqueous NaOH are added, and the mixture is extracted with ether to yield a mixture from which the oxane **579** was separated by TLC.[564]

Treatment of 2-oxobicyclo[3.2.0]hex-3-ene with NH_4Cl in MeOH gives 2,6-dimethyloxane (**580**) along with other products.[565]



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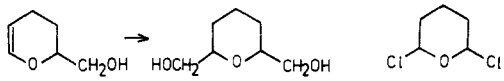
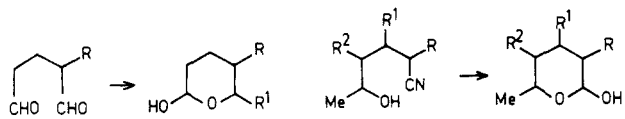


581 **582** **583**

Hydroxyformylation of the dihydropyran **581** in the presence of $Co_2(CO)_8$ gives 2,6-dimethyloloxane (**582**).[566]

The halogenation of oxanes under UV radiation gives 2,6-dihalooxanes.[567] Thus simple oxane reacts with chlorine, giving 2,6-dichlorooxane (**583**) in 40% yield along with other products.

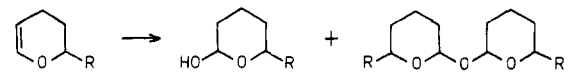
Many 6-substituted oxan-2-ol derivatives (**585**) were prepared by the reaction of a suitable dialdehyde, usually a glutaraldehyde derivative (**584**), with a Grignard reagent or any other appropriate reactant.[568]



584 **585** **586** R = Me, Et, Pr; R^1 = H, Me, Et, Pr; R^2 = Me, Et **587**

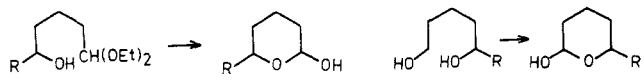
A few 6-methyl-2-hydroxyooxanes (**587**) with alkyl substituents at the 3- and 4-positions were obtained from the nitriles **586** by hydrogenation and reaction with HCHO[569] or with semicarbazide followed by hydrolysis.[570]

The 2-alkyl-2,3-dihydro-4*H*-pyran **588**, on stirring with dilute HCl, gives 6-hydroxy-2-alkyloxane **589a** in addition to the dimer **589b**.[571]



588 R = Me, *i*-Pr, t-Bu, t-amyl **589a** **589b**

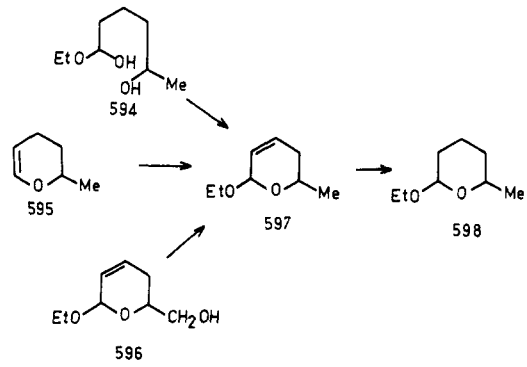
Several 6-alkyl-2-hydroxy- or -2-alkoxyoxanes have been synthesized. Hydrolysis of the ketal **590** with sulfuric acid gives 6-alkyl-2-hydroxyoxanes (**591**).[572-574]



590 R = Me, Et, Bu **591** **592** R = $CH_2CH{=}CH_2$ **593**

Treatment of the diol **592** with H_2SO_4–$K_2Cr_2O_7$ gives 6-allyloxan-2-ol (**593**).[575]

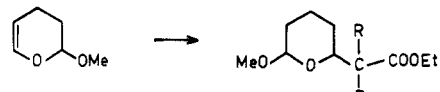
The derivatives of 2-alkoxy-6-methyldihydropyrans are of interest since they are structural fragments in many important antibiotics such as magnamycin, picromycin, etc. Three general methods are available for the synthesis of 2-ethoxy-6-methyl-Δ^3-dihydropyran:[576] (1) by cyclization of 1,1-diethoxy-2-hexen-5-ol (**594**)



594 **595** **596** **597** **598**

obtained by the condensation of propylene oxide with propargylaldehyde acetate,[577] (2) from δ-caprolactone through 6-methyl-Δ^2-dihydropyran (**595**) with subsequent bromoalkylation and dehydrobromination,[578] and (3) by the reduction of 2-ethoxy-6-(hydroxymethyl)-Δ^3-dihydropyran (**596**) through its tosylate and iodide.[579] Catalytic hydrogenation of the dihydropyran **597** over Raney nickel leads to the formation of 2-ethoxy-6-methyloxane (**598**).[576]

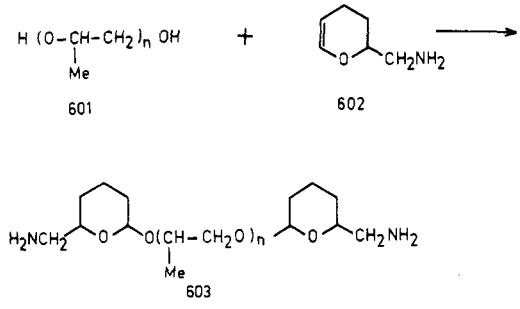
Compounds possessing active methylene groups add to 2-hydroxy-3,4-dihydro-2*H*-pyran (**599**). Thus



599 **600** R = H, MeCO, COOEt, CN

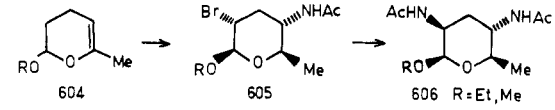
treatment of **599** *with an equimolar amount of the active methylene compound in the presence of a catalyst such as TsCl, BF_3–Et_2O, $AlCl_3$, $ZnCl_2$, etc., gives the oxanes* **600**.[580]

Polypropylene glycol (**601**), *treated with* 2-(aminomethyl)-3,4-dihydro-2*H*-pyran (**602**) *in the presence of* dry HCl, gives the dimerized product **603**.[581]



601 **602** **603**

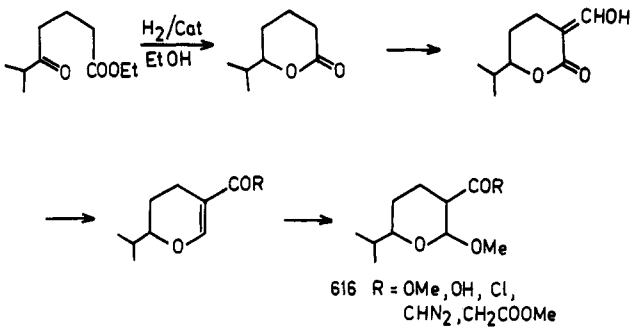
Hydroboration–amination of 2-ethoxy-6-methyl-3,4-dihydro-4*H*-pyran (**604**) with subsequent bromination gives the bromo derivative **605**, which, on treatment with sodium azide, hydrogenation, and resolution, gives ethyl *N*,*N*′-diacetyl-D-kasugaminide (**606**).[582]



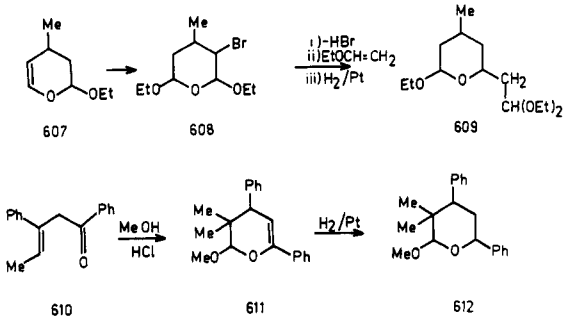
604 **605** **606** R = Et, Me

Bromination of the dihydropyran **607** with bromine

SCHEME V

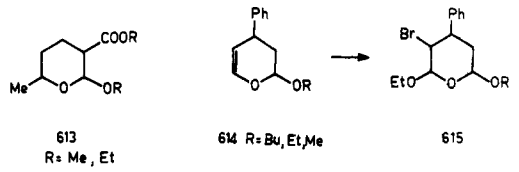


in the presence of ethanol and KOH gives the 3-bromo derivative **608**, which can be converted to the 6-alkyl derivative **609**.[583,584]



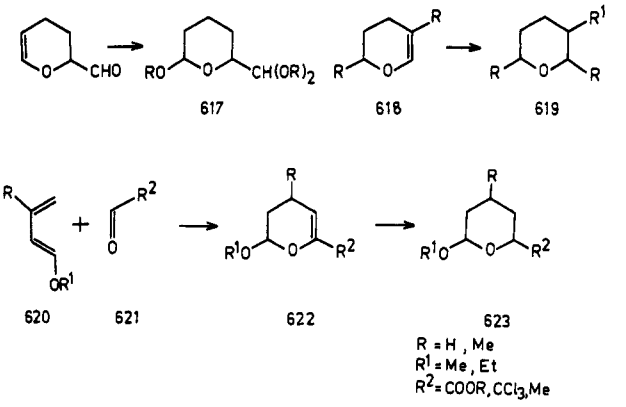
The aldehyde **610**, on shaking with MeOH–HCl for several hours, gives the 2-methoxydihydropyran **611**, which, on hydrogenation, gives the oxane **612**.[585]

The oxane **613** is prepared by the alcoholysis of an α-acyllactone or an α-acylthiolactone with anhydrous methanol or ethanol containing a strong acid.[586,587]



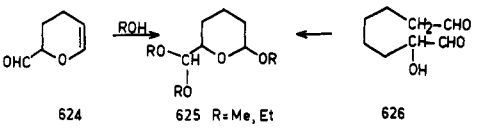
Heating cinnamaldehyde with alkoxyethylene in the presence of hydroquinone gives **614**, which, on treatment with NBS in absolute ethanol, gives **615**.[587] The 6-isopropyl-2-methoxyoxane **616** was prepared as given in Scheme V.[588]

The 6-alkoxy-2-(dialkoxymethyl)oxanes **617** are formed when a substituted 2-formyldihydropyran is treated with anhydrous aliphatic alcohol with HCl or H_2SO_4 as catalyst.[589] In the presence of an acid, 2-acetaminoethanol adds to the dihydropyran **618** to give the oxane **619**.[590]

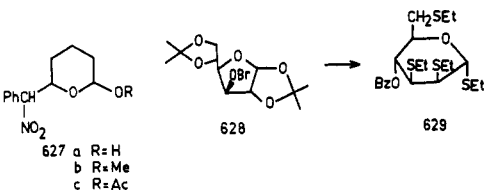


The Diels–Alder reaction of the diene **620** with the aldehydes **621** forms trans isomers of the dihydropyran **622**, which, on thermal isomerization, yield the oxanes **623**.[591]

Alcohols add to 2-formyl-3,4-dihydropyran (**624**), the dimerization product of acrolein, in the presence of HCl to give the alkoxyoxanes (**625**).[592,593] The trialkoxy derivative is also obtained from 2-hydroxyhexanedialdehyde **626** by ketalization and cyclization.[593a] Other 2,6-disubstituted oxanes have also been obtained.[594-600a]

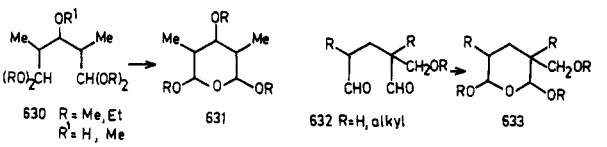


Base-catalyzed reaction of glutaraldehyde and $PhCH_2NO_2$ yields the oxane **627a**. Its *O*-methyl and acetyl derivatives (**627b, 627c**) have been obtained.[600b]

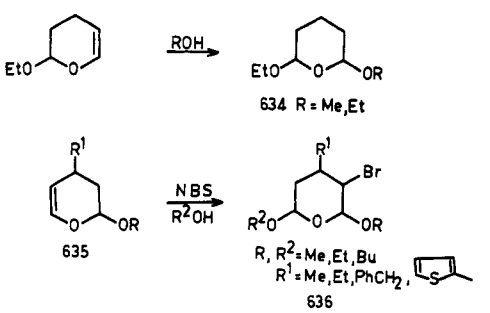


A novel method of obtaining the thio analogues of carbohydrates is exemplified in the reaction of 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**628**) with EtSH/HCl to give **629**. The thio group is introduced first at C-1 and then successively at C-2, C-3, and C-6 by intramolecular migration.[601]

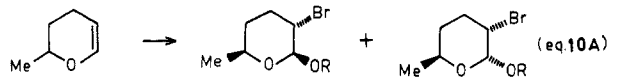
A general method of obtaining 2,6-dialkyloxyoxanes is the formation of an internal ketal from a dialdehyde.[602-608] The dialdehyde acetals **630**, on treatment with HCl, give the 2,4,6-trialkoxyoxanes (**631**).[603-606] Treatment of 2-(alkoxymethyl)-2,4-dialkylpentanedials (**632**) with aliphatic alcohols in the presence of acids gives the 2,6-dialkoxy-3,5-dialkyl-3-alkoxymethyloxanes (**633**).[607,608]



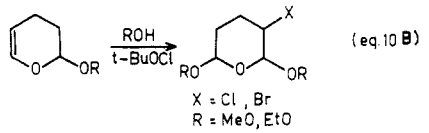
Another convenient method of obtaining the 2,6-dialkoxyoxanes (**634**) employs the alcoholysis of 6-alkoxy-2,3-dihydropyran.[596,606,609-614]



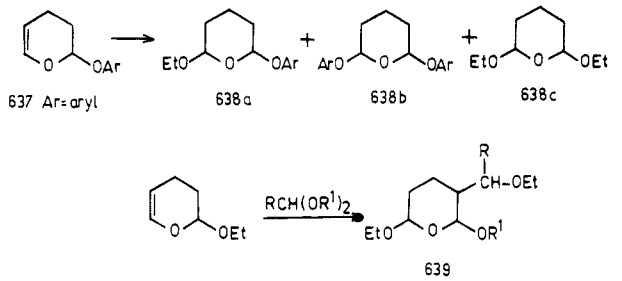
Bromination of the alkoxydihydropyrans **635** with NBS in the alcohols ROH gives the 2,6-dialkoxy-3-



The electrophilic addition of *tert*-butyl hypochlorite or hypobromite to 2-alkoxy-3,4-dihydro-2*H*-pyrans in alcoholic solvents yields cis/trans mixtures of the 1,2-addition products (eq 10B).[617,618]



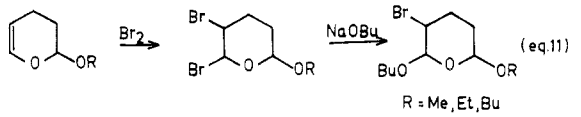
The condensation of vinyl aryl ether with acrolein gives the dihydropyran **637**. A mixture of this di-



hydropyran and anhydrous ethanol is treated with dry HCl–dioxane to yield 21% of **638a**, 35% of **638b**, and 10% of **638c**.[619]

The acid-catalyzed addition of acetals to 2-alkoxy-3,4-dihydro-2*H*-pyran gives the dialkoxyoxane **639**.[620,621]

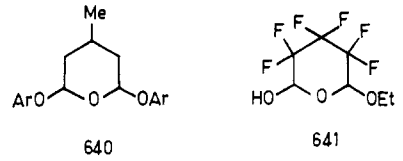
The bromination of 6-alkyl- and 6-alkoxy-Δ^5-dihydropyrans by bromine gives a dibromide, which, on treatment with NaOBu, gives 3-bromooxane (eq 11).[622,623] The electrochemical bromoalkylation of 2-

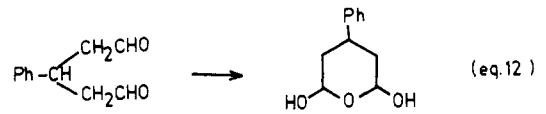


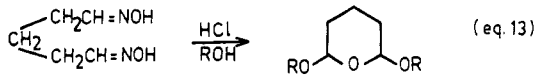
alkoxy-Δ^5-dihydropyrans with trans addition gives 2,6-dialkoxy-3-bromooxanes.[624] Methyl vinyl ketone adds to methyl acrylate when heated in an autoclave, giving 2-carbomethoxy-6-methyl-2*H*-3,4-dihydropyran, which, on catalytic hydrogenation, gives 2-carbethoxy-6-methyloxane.[625]

Other methods of obtaining 2,6-dialkoxyoxanes are also available. A mixture of aryl vinyl ether, crotonaldehyde, and a phenol in HCl–dioxane gives the 2,6-diaryloxyoxanes (**640**).[626,627] 3-Phenylglutaraldehyde, on standing with water for several days, yields the 2,6-dihydroxy-4-phenyloxane (eq 12).[628] When the oxime of glutaraldehyde is kept with nitroethane in ethanol or butanol with HCl and $CaCl_2$, 2,6-diethoxyoxane or 2,6-dibutoxyoxane is formed (eq 13).[629] Fluorinated oxanes (**641**) have also been prepared by an analogous method.[630]

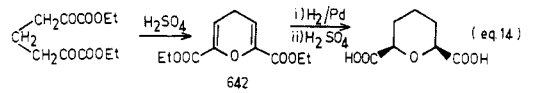
A convenient method of preparing oxane-2,6-dicarboxylic acid is the condensation of diethyl oxaloacetate with HCHO, subsequent hydrolysis, and cy-





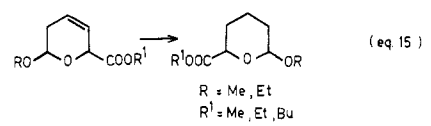


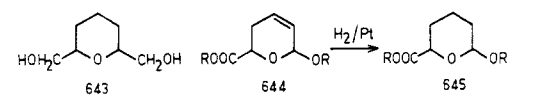
clization of the resulting diethyl 2,6-dioxoheptanedioate to the pyran **642**. The pyran, on catalytic reduction,



yields the oxane (eq 14).[631] Pyran-2,6-dicarboxylic acid can also be hydrogenated.[632]

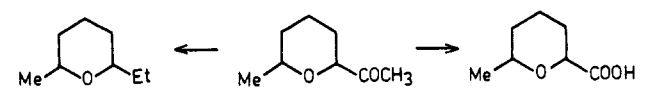
The pyran derivatives that can be obtained from the dimer of crotonaldehyde are easily converted to the esters of 6-alkoxyoxane-2-carboxylic acids in a similar way (eq 15).[633] Hydroformylation of 5,6-dihydro-4*H*-





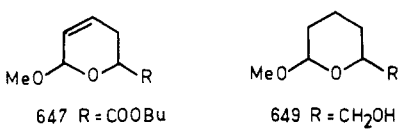
pyrans gives preferentially 2-substituted oxanes. Thus 6-(hydroxymethyl)-5,6-dihydro-4*H*-pyran, on hydroformylation, gives **643**.[634]

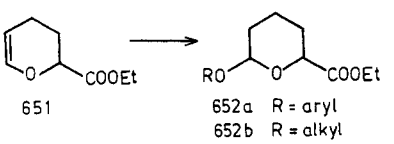
The dihydropyran **644** obtained by the condensation of 1-alkoxy-1,3-butadiene with butyl glyoxalate gives the oxane **645**[635,636] on catalytic hydrogenation. The dimeric methyl vinyl ketone, on catalytic hydrogenation, gives the ketone **646**, which is converted to the acid



by NaOBr and the 6-ethyl derivative by Wolff–Kishner reduction.[637]

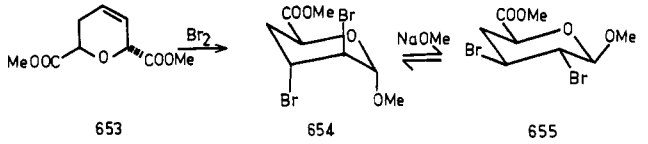
Reduction of the dihydropyran **647** with $LiAlH_4$ gives



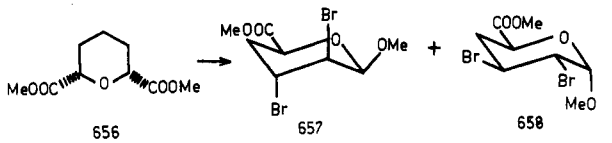


the alcohol **648**, which, on hydrogenation in MeOH over PtO_2, gives **649**.[638] Hydrogenation of the dihydropyran **647** gives the oxane **650**, which may be reduced to the alcohol **649**.[638] Ethyl 3,4-dihydropyran-2-carboxylate **651**[639] reacts with phenols and alcohols to form ethyl 6-aryloxyoxane-2-carboxylates **652a**[640] or the 6-alkoxy analogues **652b**.[640]

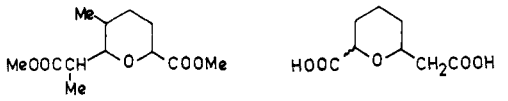
The isomeric bromo derivatives of oxane-2-carboxylic acid are also obtained and their stereochemistry studied. Bromination of the trans isomer **653** in methanol



653 654 655



656 657 658

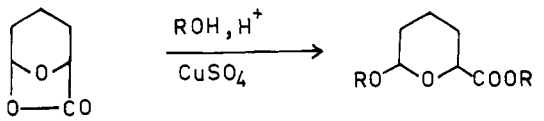


659 660

gives the dibromo derivative **654**. Bromination of the cis compound **656** gives **657** and **658**.[641] Isomerization of **654** gives **655**.[641] The oxane derivative **659** is obtained as one of the major oxidation products of grisorixin.[642]

The oxane-2-acetic acid derivative **660** was isolated from civet (*V. civetta*), and two diastereomeric products were also synthesized.[643] Thus a solution of 2-ethoxyoxane and BF_3/Et_2O gives a polymeric ester, which, on treatment with NaOH, gives 6-carboxyoxane-2-acetic acid.[644] The mechanism of the reaction is not clear.

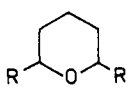
One method of formation of 6-alkoxyoxane-2-carboxylate **662** is by the reaction of 7-oxo-6,8-dioxa-



661 R = Me, Et, allyl 662

bicyclo[3.2.1]octane **661** or its 1,4-dimethyl derivative with an appropriate alcohol in the presence of $CuSO_4$ and sulfuric acid.[645,646] The starting lactones are obtained from acrolein dimer or methacrolein dimer by oxidation with silver oxide[639] or oxygen[647] by the Tischenko reaction[648] or by the Cannizzaro reaction.[649]

Treatment of glutaraldehyde with ammonium cyanide gives substantial yields of 2,6-dicyanooxane **663a**, which can be converted to the diamide **663b**.[650]

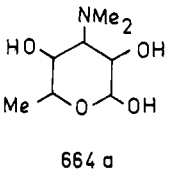


663a R = CN
663b R = $CONH_2$

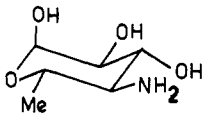
C. Natural Products

The extensively studied area of natural products of the oxane group is the carbohydrates, which have substituents at the 2- and 6-positions in addition to other positions in the cyclic structures. This wide area is not included in this review. However, a few specific derivatives that occur in other classes of compounds like macrolides[651,652] are covered here.

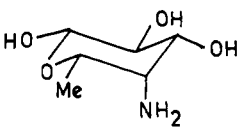
Several 4-amino-4,6-deoxy sugars (**664**) have been isolated from (i) the antibiotic amicetin,[653,654] (ii) the lipopolysaccharide of *Chromobacterium violaecum*,[655] and (iii) strains of *E. coli*.[656] Amosamine (**664a**), ob-



664a



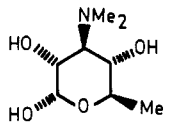
664b



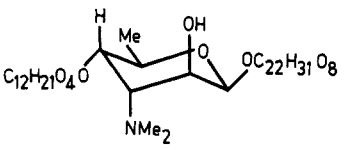
664c

tained from the antibiotic amicetin, is 3,6-dideoxy-4-dimethylamino-D-glucose. Viosamine (**664b**), obtained from *C. violaceum*, is 4-amino-4,6-dideoxy-D-glucose.[657] The 4-amino sugar isolated from *E. coli* strain Y-10 was shown to be 4-amino-4,6-dideoxy-D-galactose (**664c**).[656]

Mycaminose (**665**),[658] which constitutes the basic portion of antimicrobial agents such as magnamycins,[659-661] spiramycine,[659,662] and leucomycins, is a 3,6-dideoxy-3-dimethylaminohexose.[663] In magnamycin



665



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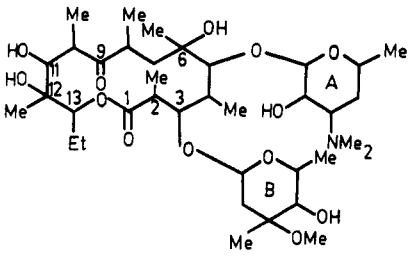
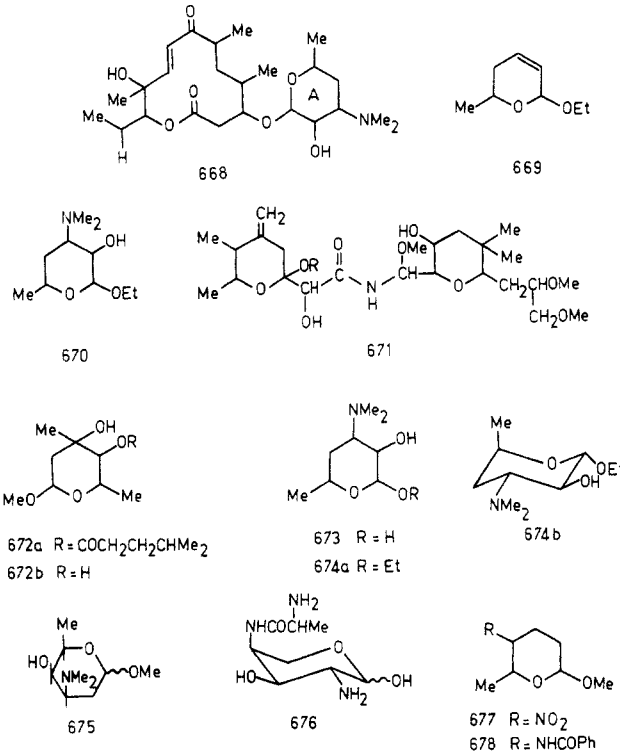


667

(**666**) it is linked glycosidically to a 17-membered lactone and a neutral sugar. Mycarose is linked by its glycosidic group to the 4-hydroxy group of mycaminose.[658,664] The early synthesis of mycaminose involves the preparation of methyl 3-amino-3,6-dideoxy-α-D-glucoside by the Fischer nitromethane cyclization reaction followed by N-methylation to the dimethylamino compound, which, on hydrolysis, yields 3,6-dideoxy-3-(dimethylamino)-β-D-glucose.[665] Other methods are also available.[652]

Erythromycin A (**667**) contains a 14-membered lactone ring which is joined to desosamine (A) and cla-



The macrolide DL-picrocin (**670**) was synthesized from 5,6-dihydro-2-ethoxy-6-methylpyran (**669**)[623b] by oxidation with perbenzoic acid and subsequent treatment of the epoxide with 33% aqueous dimethylamine.[623a]

Paderin, isolated from *Paederus fuscipes*, is a substituted 5,5-dimethyloxan-3-ol (**671**).[668]

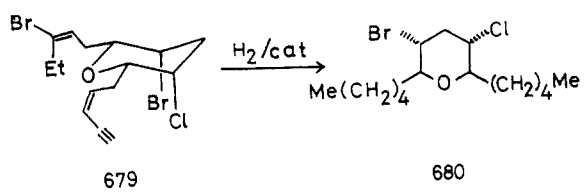
Methanolysis of the antibiotic magnamycin yields a base and the methyl 4-isovalerylglucoside (**672a**) of the sugar mycarose (**672b**).[669]

The isomer 2-ethoxy-4-(dimethylamino)-6-methyloxan-3-ol (**674a**), obtained from desosamine **673**, the amino sugar component of a significant member of the macrolide antibiotics,[670-673] shows a relatively large $J_{2,3}$ coupling constant of 6.1 Hz, and the conformation **674b** was proposed.[672]

Methanolysis of megalomycin A gives D-rhodosaminide (**675**) as one of the products.[674a] The isolation of L-rhodosamine was simultaneously reported.[674b] The antibiotic prumycin is a diamine and has been identified as 4-(D-alanylamino)-2-amino-2,4-dideoxy-L-arabinose (**676**).[675]

Methyl *N*-benzoyl-α,β-DL-tolylposaminide (**678**) is obtained by the condensation of 2-hydroxynitropropane with acrolein followed by cyclization to give 5-nitro-2-methoxy-6-methyloxane (**677**), which is reduced with Raney nickel and benzoylated.[676]

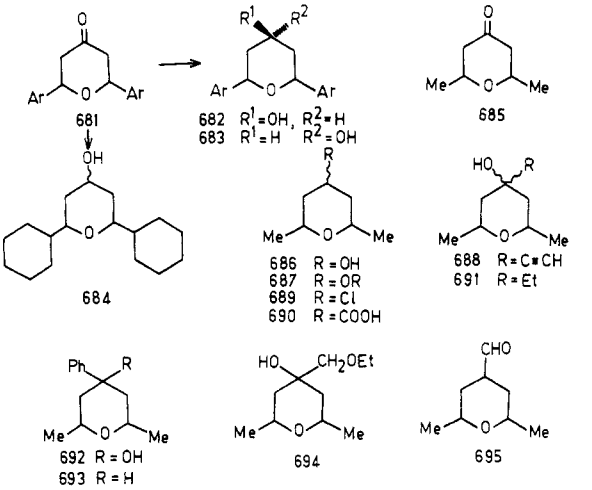
The structure and stereochemistry of dactylyne (**679**),



isolated from the sea hare *Aplysia dactylomela*, have been determined by X-ray diffraction.[677,678] Catalytic hydrogenation of **679** gives octahydromonodebromodactylene (**680**).[677]

D. 4-Substituted Oxanes

Several oxan-4-ones have been reduced to the epimeric mixture of oxan-4-ols. Reduction of 2,6-diaryloxan-4-ones (**681**) with $NaBH_4$ and aluminum isoprop-



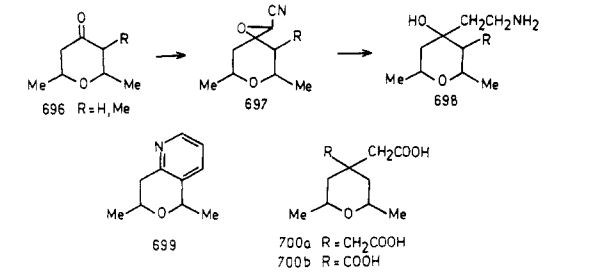
oxide gives a mixture of *cis*- and *trans*-oxan-4-ols (**682**, **683**).[482,679,680] When reduced with Pt/H_2, 2,6-diaryloxan-4-ones give dicyclohexyloxan-4-ols (**684**).[538]

Reduction of 2,6-dimethyloxan-4-one (**685**) with Raney nickel, aluminum isopropoxide, or Mg in MeOH gives a mixture of stereoisomeric alcohols (**686**).[538,681] The alcohol obtained by the Pt-catalyzed reduction of 2,6-dimethyloxan-4-one has been converted to the ether **687** and the 4-chloro compound **689** by treatment with PCl_3, which, on treatment with Mg/CO_2, gives the oxane-4-carboxylic acid **690**.[681]

Treatment of ethynylmagnesium bromide in THF with 2,6-dimethyloxan-4-one **685** yields the 4-ethynyl derivative **688**, which, on hydrogenation over Raney Ni, gives the 4-ethyl derivative **691**.

Phenylmagnesium bromide adds to 2,6-dimethyloxan-4-one to give the 4-phenyl-4-hydroxy derivative (**692**), which, on reaction with silver oxide and subsequent reduction over Pt, gives 4-phenyl-2,6-dimethyloxane (**693**).[682] The Grignard reagent, obtained from $ClCH_2OEt$ and Mg, reacts with 2,6-dimethyloxan-4-one to give the 4-ethoxymethyl derivative **694**, which has been dehydrated in H_2SO_4 and hydrolyzed to the 4-carboxaldehyde **695**.[683]

The oxan-4-ones **696** react with $ClCH_2CN$ in *t*-BuOH/*t*-BuOK to give the epoxide **697**, which, on reduction with $LiAlH_4$, gives the amine **698**.[684]



The pyranopyridine **699** is formed when 2,6-di-

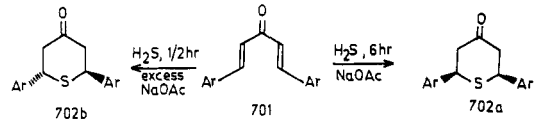
methyloxan-4-one reacts with $H_2NCH{=}CHCHO$.[685]

The condensation of 2,6-dimethyloxan-4-one with ethyl cyanoacetate in excess of anhydrous NH_3 and acidification of the resulting ammonium salt yield a dicyano imide, which, on gentle stepwise hydrolysis, gives the 4,4-diacetic acid **700a**.[686] The 4-carboxylic acid derivative **700b** has also been obtained.[686]

V. Synthesis of Thianes

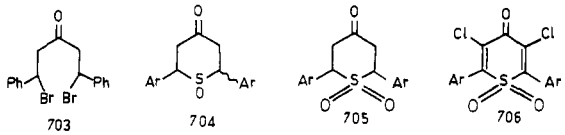
A. Thian-4-ones

An early method of synthesis of 2,6-diarylthian-4-ones (**702**) is by the simple addition of H_2S to α,α'-diolefin



702b 701 702a

ketones (**701**) in very faintly alkaline solutions. The reaction takes place smoothly, yielding both *cis*- (**702a**) and *trans*-2,6-diarylthian-4-ones (**702b**) depending upon the amount of base used and the time and rapidity of passage of H_2S.[487,701-708] This method of Arndt et al.[705,709] is the best method of preparing 2,6-diarylthian-4-ones. The same workers obtained 2,6-diphenylthian-4-one (**702a**) from the dibromide **703** by treating it with sodium sulfide.[487]

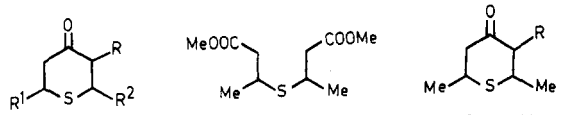


703 704 705 706

The 2,6-diarylthian-4-ones are oxidized to the 1-oxide **704** by bromine and to the 1,1-dioxide **705** by hydrogen peroxide–acetic acid.[701,704,707] The sulfone **705**, on heating with PCl_5, gives the 3,5-dichlorothiopyrone **706**.[707]

Baliah and co-workers[701,702,710-715] obtained various 2,6-diarylthian-4-ones and 3-alkyl-2,6-diarylthian-4-ones and established their conformations and configurations. The optimum conditions for the formation of *cis*- and *trans*-thian-4-ones have also been determined. When hydrogen sulfide is passed into an ethanolic solution containing the diarylideneacetone **701** and a definite amount of sodium acetate for 6 h until equilibrium is established, the cis isomer is obtained. If hydrogen sulfide is passed rapidly into a mixture containing an excess of sodium acetate for 30 min, the trans isomer is obtained. The unreacted unsaturated ketone and the polymeric sulfide may be easily separated.

The 3-methyl- and 3-ethylthianes **707a–d** were also obtained by the same method.[715,716]



	R	R^1	R^2
707a	Me	Ph	Ph
707b	Et	Ph	Ph
707c	Me	Me	Me
707d	Me	Me	Et

708

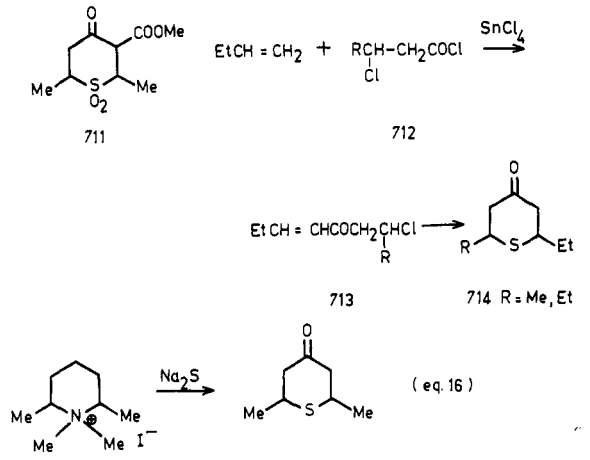
709 R = COOMe
710 R = H

Various aromatic aldehydes and pyridinecarboxaldehydes have been used for the synthesis of 2,6-diarylthian-4-ones by the Arndt method, with the use of ethanol or dioxane as the solvent.[701,717-719]

A convenient method of synthesizing 2,6-dimethylthian-4-one (**710**) involves the Dieckmann condensation of the diester **708**. The ester is cyclized in the presence of sodium methoxide or sodamide.[720-722] The keto ester **709** is hydrolyzed with HCl to give the thian-4-one **710**. The 4-oxothiane 1,1-dioxide **711** has been obtained by oxidation of the thian-4-one **710** or by oxidation–hydrolysis of the ester **709**.

Another closely related method of formation of thian-4-ones involves substitution–addition. The acid chloride **712** reacts with but-1-ene in the presence of $SnCl_4$ to give the β-chloro ketone **713**, which, on treatment with sodium sulfide in methanol, gives the thian-4-one **714**.[723] This appears to be an excellent method of obtaining unsymmetrical thian-4-ones.

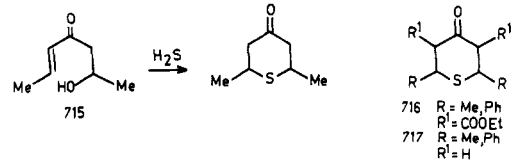
An attractive alternative for the synthesis of thian-4-ones is the conversion of a piperidin-4-one to the quaternary salt and treatment with sodium sulfide.[724] By this method 2,6-dimethylpiperidin-4-one is converted to 2,6-dimethylthian-4-one (eq 16).



711 712 713 714 R = Me, Et

Since 2,6-diarylpiperidin-4-ones do not form quaternary salts, this method is not applicable to them. However, if electron-withdrawing ester groups are present in the 3- and 5-postions, the formation of the corresponding thian-4-one takes place smoothly by treatment of the piperidinone directly with sodium sulfide.[725,726]

2,6-Dimethylthian-4-one can also be formed by heating the unsaturated ketone **715** with H_2S in aqueous methanolic H_2SO_4 in an autoclave.[727]



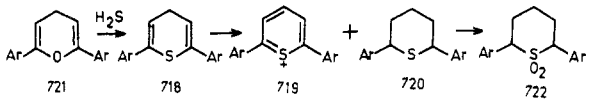
715

716 R_1 = Me, Ph
R^1 = COOEt
717 R = Me, Ph
R^1 = H

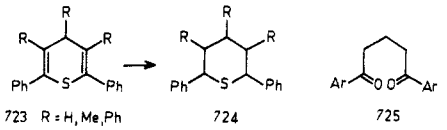
A direct condensation–addition employing the easily available diethyl acetondicarboxylate yields the thian-4-ones in good yields. The acetonedicarboxylic ester, on treatment with piperidine and an aldehyde in ethanol and finally with H_2S, yields the 3,5-dicarbethoxythian-4-ones **716**. The ester may be hydrolyzed and decarboxylated to the thian-4-one **717**.[728-730]

B. Thianes

A method of synthesis of 2,6-diarylthianes studied mostly by Russian workers is based on the disproportionation reaction of suitable thiopyran derivatives. When 2,6-diaryl-4*H*-thiopyran (**718**) is treated with a



721 718 719 720 722



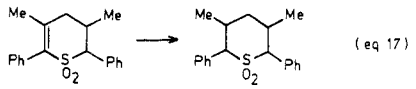
723 R = H, Me, Ph 724 725

strong acid, it is converted to a mixture of the thiopyrylium salt **719** and the thiane **720** at various rates depending on the nature of the substituents.[501,731,732] The thianes obtained in this way have been converted to the sulfones (**722**).[501] Alternatively, the reaction of 4*H*-pyrans (**721**) with H_2S in the presence of HCl in acetic acid yields a mixture of the three sulfur analogues **718**, **719**, and **720**.[501,733]

The hydrogenation of thiopyrans **723** in the presence of Pd/C or Rh/C at 100 °C and 50 atm gives the thianes **724** in good yield.[477,734]

The reaction of 1,5-diketones **725** with H_2S–CF_3CO-OH also leads to a mixture of the thiopyrylium salts **719** and the thianes **720**.[735-739]

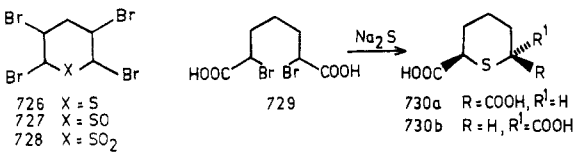
Hydrogenation of thiopyran 1,1-dioxides to thiane 1,1-dioxide is also possible. Thus 3,5-dimethyl-2,6-diphenyl-2,3-dihydrothiopyran 1,1-dioxide over a nickel catalyst yields 3,5-dimethyl-2,6-diphenylthiane 1,1-dioxide (eq 17).[477]



(eq 17)

2,3-Dimethyl-6-isopropylthiane has been formed by starting from 2,6-dimethylocta-2,6-diene through a series of steps (Scheme VI).[740]

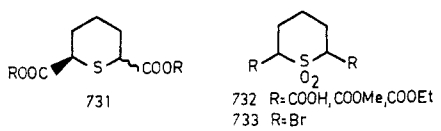
Halogen-substituted thianes have also been synthesized. The addition of bromine to thiopyran in $CHCl_3$ at −35 °C yields 2,3,5,6-tetrabromothiane (**726**),



726 X = S
727 X = SO
728 X = SO_2

729

730a R = COOH, R¹ = H
730b R = H, R¹ = COOH



731

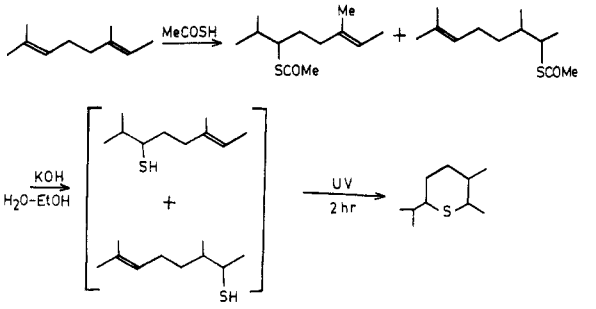
732 R = COOH, COOMe, COOEt
733 R = Br

which, on oxidation with H_2O_2 in HOAc, yields the sulfoxide **727** and sulfone **728**.[741]

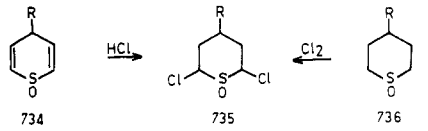
cis-2,6-Thianedicarboxylic acid (**730a**) was prepared by the action of sodium sulfide on α,α′-dibromopimelic acid (**729**) in water. Evaporation of the mother liquor gives the trans isomer **730b**.[742,743] The methyl and ethyl esters (731) of the acids were prepared.[744]

trans-2,6-Thianedicarboxylic acid (**730b**) has been resolved into its enantiomers by using quinine. The dextrorotatory acid is obtained with a maximum rotation of 91° and the levorotatory isomer with the maximum rotation of −11.5°.[745]

SCHEME VI



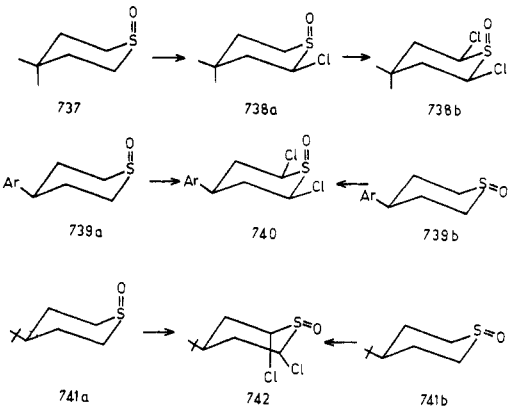
Hydrogen chloride adds to 4*H*-thiopyran 1-oxide (**734**) to yield 2,6-dichlorothiane 1-oxide (**735**, R = H).[746]



734 735 736

The dichloro compound is also formed when thiane 1-oxide **736** is chlorinated by employing *tert*-butyl hypochlorite, sulfuryl chloride, or chlorine in pyridine.[747]

The 4-substituted thiane 1-oxides are also chlorinated at both α-positions with *tert*-butyl hypochlorite and pyridine, chlorine and pyridine, or sulfuryl chloride in the presence of CaO.[748] Chlorination of 4,4-dimethylthiane 1-oxide (**737**) gives the monochloro (**738a**) as well as the dichloro (**738b**) derivatives.[748]



737 738a 738b

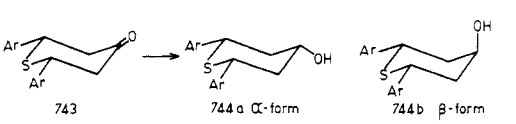
739a 740 739b

741a 742 741b

Both the *cis*- and *trans*-4-arylthiane 1-oxides (**739a** and **739b**), on chlorination, give the same dichloro compound **740** in which the aryl group is forced to the axial position. The *cis*- and *trans*-4-*tert*-butylthiane 1-oxides (**741a** and **741b**) also undergo chlorination, producing the same dichloro derivative **742**. However, in this case the two chlorine atoms occupy axial positions.[748]

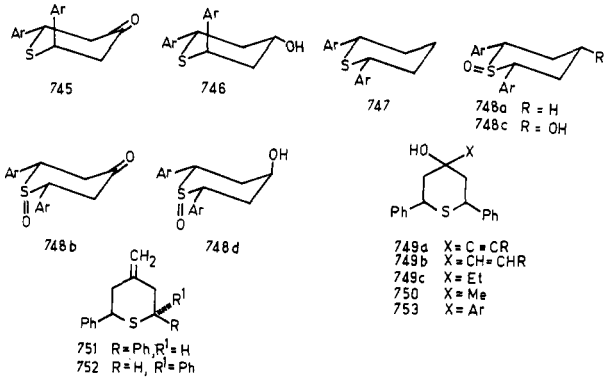
C. 4-Substituted Thianes

The *cis*-2,6-diarylthian-4-ones **743** are converted to a mixture of epimeric alcohols **744a** and **744b** by various



743 744a α-form 744b β-form

methods of reduction, while the trans isomers **745** give only one alcohol (**746**) in each case.[487,701] Reduction of the thian-4-ones **743** with $LiAlH_4$ yields the equatorial alcohols exclusively.[701]



The MPV reduction of the cis isomer **743** produces more of the axial alcohol than the equatorial alcohol (3:1) while in the reduction of the trans thianones (**745**) the alcohol (**746**) formed is equatorial since ring flipping would lead to the stable equatorial isomer.[701]

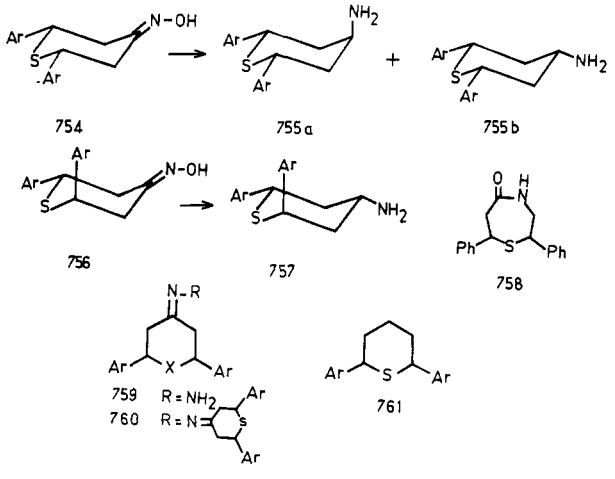
The thian-4-ones, thian-4-ols, and thianes **743**, **744a**, **744b**, and **747** have been converted to sulfoxides by stereospecific oxidation with bromine water.[701,749]

The thiane **747** gives mainly the equatorial *S*-oxide **748a** by equatorial electrophilic attack while the ketone **743** gives the axial oxide **748b**. The 4-hydroxy derivatives **744a** and **744b** give the trans oxides **748c** and **748d** involving neighboring group participation by the 4-substituent.[749]

As with the piperidin-4-ones, 2,6-diphenylthian-4-one (**743**, Ar = Ph) has also been treated with acetylenes to give a mixture of isomeric addition products (**749a**).[750] The isomers were separated and converted, by catalytic hydrogenation in stages, to the 4-vinyl derivatives **749b** and the 4-ethyl derivatives **749c**.[750]

cis-2,6-Diphenylthian-4-one reacts with MeMgBr to give two isomeric tertiary alcohols **750**,[701] which, on dehydration with P_2O_5, give the same dehydration product **751**.[703,751,752] The trans isomer **745** gives a noncrystalline product, which, on dehydration, gives **752**.[703] Similarly, arylmagnesium bromides add to the thian-4-one **743** to give a mixture of isomers **753**.[701,752]

The oximes **754** and **756** are formed readily from the thian-4-ones **743** and **745**.[711,753] The oxime **754**, on

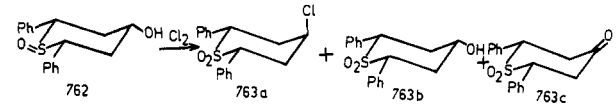


reduction with $LiAlH_4$, gives a mixture of amines **755a** and **755b**.[711] The corresponding trans aminothianes **757** have also been prepared.[711] The epimeric 4-amino-2,6-diaryltetrahydrothiopyrans are obtained by the $LiAlH_4$ reduction of the oximes. The *cis*-2,6-diarylthian-4-ones give more of the axial amines (**755a**) whereas the *trans*-2,6-diarylthian-4-ones give one amine only (**757**), as expected.

The oxime **754** (Ar = Ph) undergoes Beckmann rearrangement, yielding 2,7-diphenyl-5-oxo-1-thia-4-azacycloheptane (**758**).[753b]

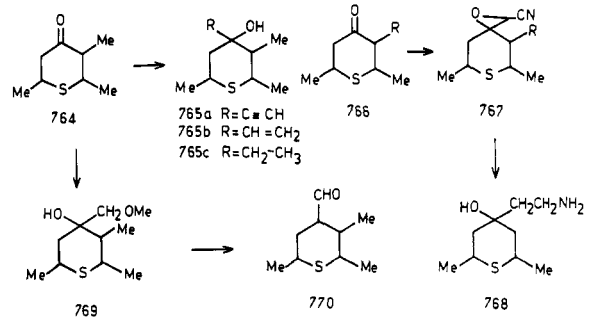
The hydrazones (**759**) obtained from 2,6-diarylthian-4-ones and their sulfones are converted to the azines (**760**) by acid-catalyzed partial hydrolysis.[753] Treatment of the ketone **743** (Ar = *p*-anisyl) with hydrazine hydrate affords the azine **760** directly.[753a] Reduction of the ketone with zinc amalgam and ethanolic hydrochloric acid gives the thianes (**761**).[703,712,751]

The reduction of chlorine with the *cis*-4-hydroxythiane 1-oxide (**762**) has been studied.[754] Chlorination



of the *cis*-thiane 1-oxide **762** gives a mixture of *trans*-4-chlorothiane 1,1-dioxide (**763a**), *cis*-4-hydroxythiane 1,1-dioxide (**763b**), and 4-oxo-*cis*-2,6-diphenylthiane 1,1-dioxide (**763c**).

Additions, substitutions, and reductions have been carried out on 2,6-dimethylthian-4-ones. Acetylene adds to the thian-4-one **764** to yield 4-ethynyl-4-

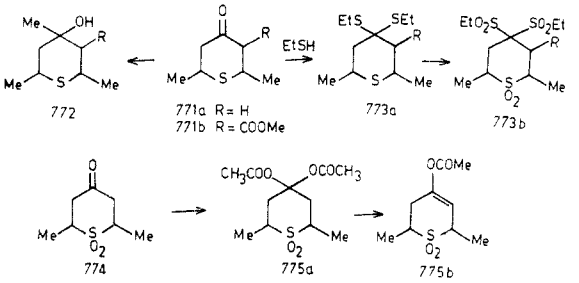


hydroxy-2,3,6-trimethylthiane (**765a**), which, on partial hydrogenation, gives the 4-vinyl analogue **765b** and on continued hydrogenation gives the 4-ethyl derivative **765c**.[755]

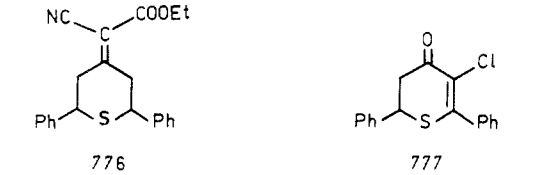
The ketone **766** condenses with $ClCH_2CN$ in the presence of *t*-BuOH/*t*-BuOK to give **767**, which, on reduction with $LiAlH_4$, gives the amine **768**.[684]

Ethoxymethylmagnesium chloride adds to the thian-4-one **764** to give the 4-(ethoxymethyl)-4-hydroxythiane **769**, which, on refluxing in aqueous HCOOH followed by treatment with acid, gives the thiane-4-carboxaldehyde **770**.[756] Methylmagnesium iodide adds to 2,6-dimethylthian-4-one, giving 2,4,6-trimethylthian-4-ol (**772**) in good yield.[757]

The thian-4-ones **771a** and **771b** react with ethanethiol, producing the thioketals **773a**, which, on oxidation with $KMnO_4$, give the trisulfones **773b**.[758] In the presence of perchloric acid, acetic anhydride reacts with the thian-4-one **774**, yielding the 4,4-diacetoxy derivative **775a** and the enol acetate **775b**.[721]



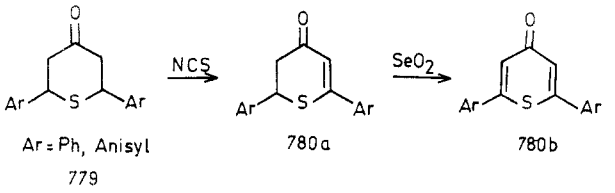
Heating a mixture of 2,6-diphenylthian-4-one and cyanoacetic ester at 150 °C for 6 h gives 2,6-diphenyl-4-(cyanocarbethoxymethylene)thiane (**776**).[759]



The dihydrothiopyranone **777** is formed when 2,6-diphenylthian-4-one reacts with SO_2Cl_2 in carbon tetrachloride followed by heating with 2,4,6-trimethylpyridine.[760]

2,6-Diphenylthiopyran-4-one (**778a**) was prepared by Arndt et al.[709] in poor yield (15%) by the reaction of the thian-4-one **743a** with PCl_5 followed by treatment with a base. The same procedure when applied to the 2,6-di-*p*-anisylthian-4-one (**743b**) gives the 3,5-dichlorothiapyran-4-one **778b**.[753]

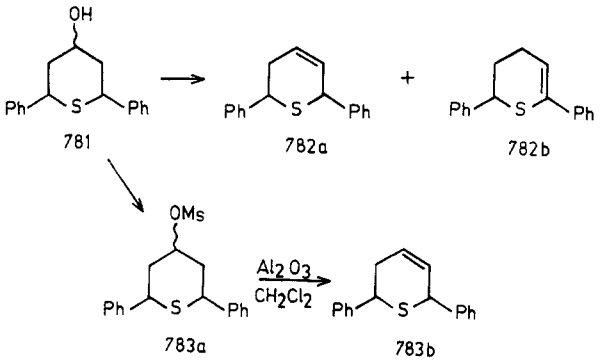
Two relatively useful methods for the conversion of the thian-4-one to the thiopyran-4-one have recently been described.[761,762] Oxidation of the thian-4-ones **779**



with NCS and pyridine gives the dihydro-4*H*-thiopyranones **780a**, which, on dehydrogenation with SeO_2 in toluene, give the thiopyran-4-ones **780b** in good yield.[761] The (2-thienyl)thian-4-one (**779**, Ar = 2-thienyl) has also been prepared but without further separation has been employed for the conversion to thiopyran-4-one (**780b**).[761]

Another method is the treatment of the thian-4-one with XeF_2 when the dihydrothiopyranone **780a** and thiopyranone **780b** are formed successively.[762]

2,6-Diphenylthian-4-ol (**781**) has been converted to the dihydropyrans **782a** and **782b**. The earlier method involves dehydration under acid catalysis[681,763] or pyrolysis in the presence of anhydrous magnesium sulfate.[757] The Bamford–Stevens reaction on the tosylhydrazone of the thian-4-one produces the dihydrothiopyran **782b** in low yield.[480]



In an attractive recent method the thian-4-ol **781** is treated with methanesulfonyl chloride to yield the methanesulfonate **783a**, which gives the dihydrothiopyran **783b** on dehydromesylation employing activated neutral alumina.[764]

VI. Conclusion

In this review we have attempted to bring together much of the information on the synthesis of three selected classes of heteranes with substituents at the 2 and 6 positions. The stereochemistry of many heteranes with a nearly rigid geometry around the heteroatom, viz., those with *cis*-2,6-substituents, has been discussed in detail by several authors while the stereodynamics of the corresponding trans systems is rarely dealt with. On the contrary, the dynamics of hydrogen and other groups attached to nitrogen in the piperidine series (with 2,6-disubstituents) has been the most popular subject for many investigators.

In general, the 2,6-disubstituted heteranes are excellent models, similar to *tert*-butylcyclohexyl derivatives, for the study of a variety of aspects of stereochemistry, including reaction mechanisms involving heteroatom participation, conformational mobility at the second half of the ring (involving carbons 3, 4, and 5), and correlation of configurations with spectroscopic phenomena such as Bohlmann bands, magnetic nonequivalence, half-band widths, coupling constants, etc.

In addition, these heteranes are suitable synthons for the development of many heterosteroids, alkaloids, bicyclic and polycyclic systems, macrocycles, and antibiotics. The possible biological activities of many of the 2,6-disubstituted heteranes and the similarity of some of them with certain natural products are a few among the many other attractions of 2,6-disubstituted heteranes.

It is with this view that the various synthetic routes for 2,6-disubstituted heteranes have been presented here. The ease of formation of most of the heteranes and the simplicity of experimental techniques are the promising factors for interest in these systems.

Note Added in Proof. Many important articles on the synthesis and stereochemistry of 2,6-disubstituted piperidines, oxanes, and thianes have appeared recently.[765–793]

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