UNUSUAL REACTIONS OF STEROIDAL AND NON-STEROIDAL 1,5-DIOXIMES. STEREOCHEMISTRY AND MECHANISM OF FORMATION OF N-HYDROXY-PIPERIDINE ANALOGUES

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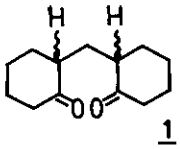
Abstract- 4,5-Secocholestane-3,5-dioxime on $NaBH_4$ reduction gave N-hydroxy-3β-methyl-4-aza-5α-cholestane and N-hydroxy-3α-methyl-4-aza-5β-cholestane. The stereochemistry of the products was fully established by converting the N-hydroxy compounds to N-chloro compounds which resulted in ^1H nmr signals separating out from the steroid envelope. The dioxime on reaction with NH_2OCH_3 underwent a regiospecific replacement of the oxime at C-3 by an oxime ether. In both these reactions this and other 1,5 dioximes exhibit unique behaviour not shown by isolated oximes. Arguments are presented pin-pointing a single mechanism involving a "oxadiaza" intermediate isomeric with the dioxime.

The conversion of a 1,5-dioxo compound to a N-hydroxypiperidine analogue by treatment with excess NH_2OH followed by reduction of the resulting product with $NaBH_4$ was reported by Gamov et al.[1] in 1974. They concluded that the products obtained from meso and dl forms of methylene-bis-2,2'-cyclohexanone 1 by reaction with 2 eq. of NH_2OH were 8-hydroxy-1,2,4,5-bis-tetramethylene-7-oxa-6,8-diazabicyclo-[3.2.1]-octanes 2. Reduction of 2 with $NaBH_4$ in ethanol gave N-hydroxyperhydro-acridines 3.



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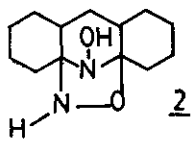

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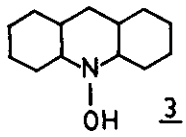

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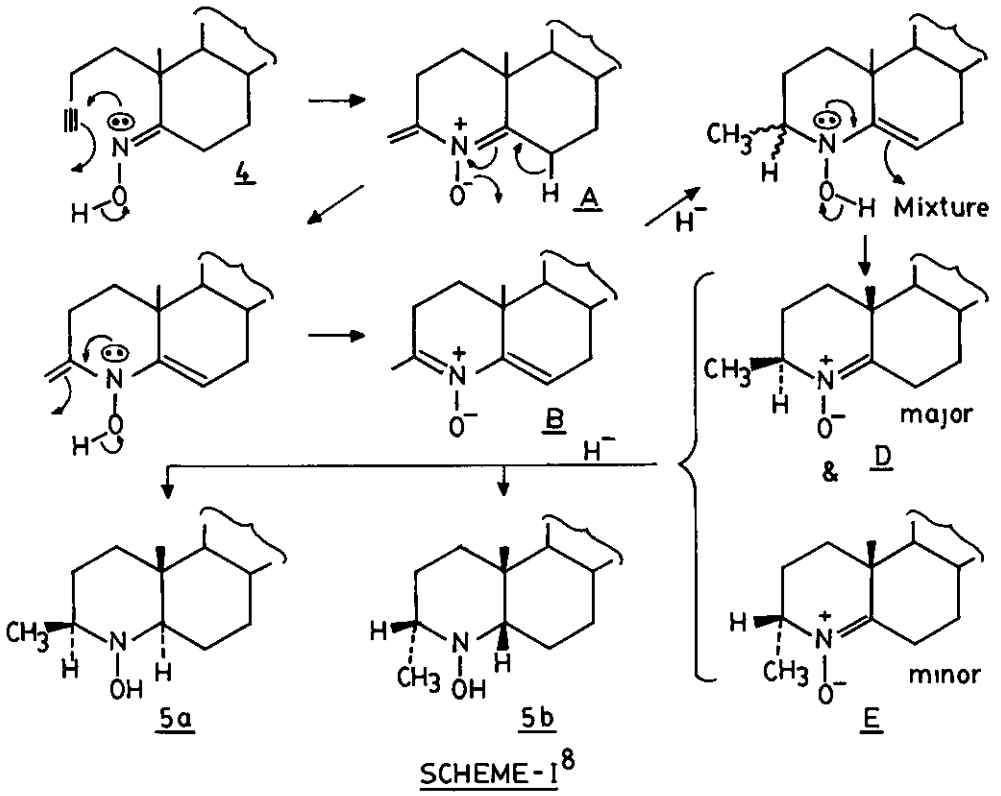
Compound 2 has the same molecular formula as the dioxime of 1 but the absence of absorption due to C=N between 1600-1700 cm^{-1} and the presence of a narrow band due to NH at 3220 cm^{-1} in ir[34] was cited by the authors[1] as the reason for the rejection of the dioxime structure in favour of 2. The $NaBH_4$ reduction of 2 to 3 is expected to be more facile than the oxazolidines[2] since formation of a nitrone intermediate from 2 should be more facile than that of an immonium ion[3]. Only small amounts of nitrone need to be present at equilibrium to get "trapped" by the hydride.

No mechanism was proposed[1] to explain the formation of the interesting heterocyclic species 2. It was, however, pointed out[1] that the formation of 2 rather than a 1,5-dioxime by reaction of a 1,5-dioxo compound with 2 eq. NH_2OH was exceptional. The possibility that equilibrium may exist between the two and that a dioxime may undergo $NaBH_4$ reduction by virtue of such an equilibrium has escaped attention. It has apparently been universally assumed that 1,5-dioximes will not react with $NaBH_4$ since oximes are resistant to reduction by this reagent under normal conditions[4].

As far as we are aware the first exception to this generalisation was discovered in Bombay[5]. The main focus of our attention at that time was, however, on another discovery. We had found that 4,5-secocholest-3-yn-5-one oxime 4 reacted readily with $NaBH_4$ to give N-hydroxy-3ε-methyl-4-aza-5ε-cholestane 5. But as reported briefly[6] several other ethynyl oximes had failed to react[7].

The $NaBH_4$ reduction of 4 gave two of the possible four stereoisomers having the structure 5 specifically 5a and 5b. The dioxime which had been found[5] to undergo $NaBH_4$ reduction was the dioxime of 4,5-secocholestane-3,5-dione and the product obtained on reduction was a mixture of the same two stereoisomers of 5 but in different proportions. Scheme I[8] represents what we regard as the most likely mechanism for the conversion of 4 to 5a and 5b produced in the proportion of 9:1. The assignment of configuration is on the basis of extensive transformations described later in this paper[9].

Preparation of 4 in good yields from 4,5-secocholest-3-yn-5-one could only be achieved using 1.5 eq. of NH_2OH under very carefully controlled conditions. Without such control and with excess NH_2OH[10] the product was the dioxime of 4,5-seco-cholestane-3,5-dione, 6. Its formation is via a series of heterocyclic intermediates. In its reactions leading either to heterocyclic products such as 5 or to non heterocyclic compounds, heterocyclic intermediates are involved.



SCHEME-I[8]

We have found it necessary to bring in a series of related studies to arrive at a definitive conclusion about the mechanism of reduction of 6 to 5.

Even the mechanism of formation of dioxime 6 via further reaction of 4 with NH_2OH is quite relevant and is discussed first. Since the O-methyl ether of 4 namely 7 is recovered unchanged under conditions in which 4 gives 6, the possibility of direct attack by hydroxylamine on the alkyne group is ruled out. Thus hydroxylamine attack has to be on one or both of the vinyl nitrones A or B shown in Scheme I. A further complication is that attack may be from the nitrogen or oxygen end. Not knowing whether kinetic or thermodynamic control was to be assumed, did not help either. Some of these complications could be disposed of by using not NH_2OH, but NH_2OCH_3 (actually methoxyamine hydrochloride + base) and examining the structure of the products. Such a study could be instructive though not necessarily conclusive.

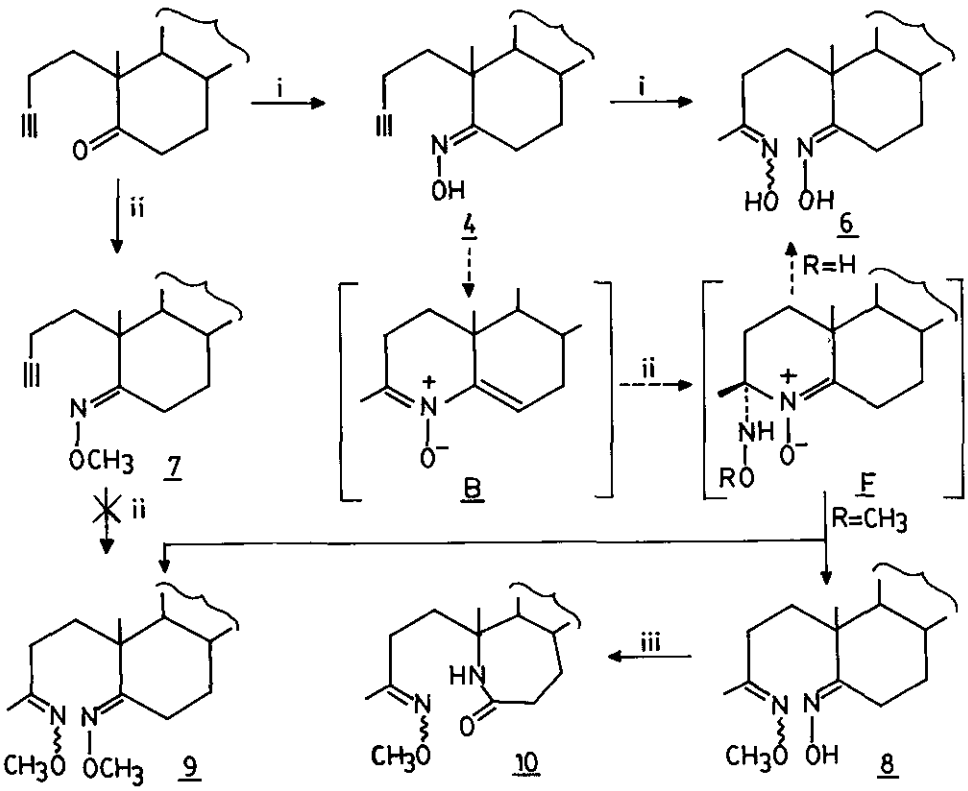
Treatment of 4 with this reagent gave a monomethyl ether of the dioxime in 25% yield accompanied by the dimethyl ether 9 in 50% yield. Only one of the two possible monomethyl ether was produced namely 8 (See Chart I). ^{1}H Nmr comparison of 4, 6, 7, 8 and 9 indicates that in all these compounds there is a distinct broad doublet of J = 14 Hz due to a deshielded 6α proton. This is seen at δ 3.33±0.02 in 4, 6 and 8 and at δ 3.17±0.01 in 7 and 9. Thus the configuration of the oxime of the ketone at C-5 is E in all these compounds and that the "conversion" of -OH of this oxime to $-OCH_3$ results in an upfield shift from δ 3.33 to 3.17. The structure tentatively assigned to 8 on this basis was confirmed by subjecting it to the Beckmann rearrangement by the action of p-toluenesulphonyl chloride in pyridine. Spectral evidence is completely in agreement with compound 10 expected to be formed by the migration of the 5-10 bond.

Formation of 8 to the exclusion of its isomer suggests that nucleophilic attack by the nitrogen of methoxyamine must be on the vinyl nitrone B derived from 4 (See Scheme I). It is of interest that we found it necessary[11] to postulate hydride attack on B rather than A to explain the stereochemistry of reduction of 4 by $NaBH_4$.

As indicated in Chart I the intermediate F is assumed to explain the reaction of methoxyamine as well as hydroxylamine. In the latter case the intermediate F (with R=H) is shown as giving the dioxime 6. But there is a distinct possibility of intramolecular attack by -OH at C-5 leading to the formation of an "oxadiaza" compound similar to 2 from this key intermediate.

This prompted us to subject the structural assignment of the dioxime 6, obtained from 4 to a closer scrutiny. We found that though this product was a single spot on tlc its hplc indicated the presence of equal amounts of two compounds. From ^{13}C nmr it could be concluded that the isomers differed only in the configuration of the oxime at C-3. Two signals each, could be assigned for the methylene and methyl carbons adjacent to the oxime at C-3. Downfield of δ 60 there were only two signals. These were at δ 159 and 164 and belonged to the sp^2 carbons at C-3 and C-5, providing strong evidence for the dioxime structure. Absence of any signals in the range δ 70 to 120 was a clear indication that "oxadiaza" isomer was absent. Its presence to the extent of 2% or less cannot be excluded on the basis of the nmr evidence.

Compound 6 is seen to be a mixture of (3E,5E) and (3Z,5E) isomers which were not separated. This is the mixture used in all reactions involving 6.



i. $NH_2OH \cdot HCl$, NaOAc, ii. $NH_2OCH_3 \cdot HCl$, NaOAc, iii. p-TsCl, Pyridine

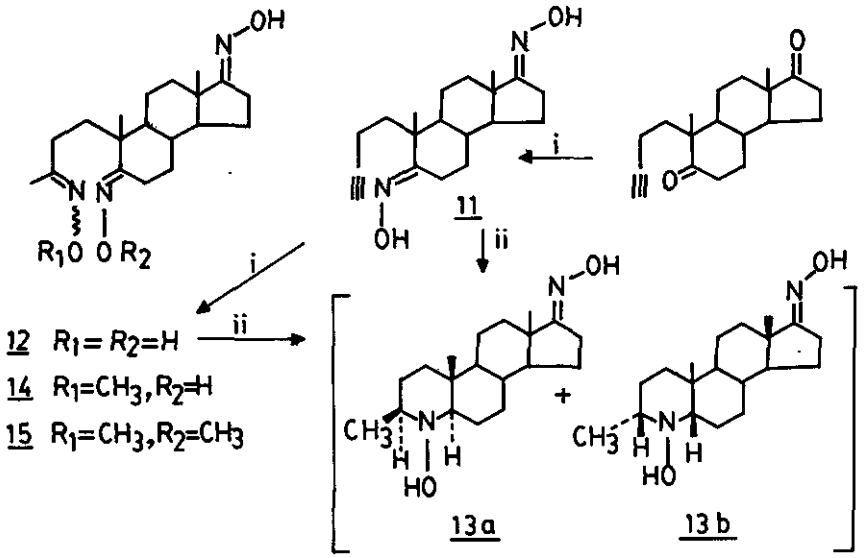
CHART-I

The next test we applied was a colour test. We were pleasantly surprised to find that a bluish green colour was produced on treatment of 6 with $FeCl_3$. This turned out to be a crucial observation. Isolated oximes do not give any colour with this reagent whereas certain N-substituted hydroxylamines do[12]. Thus there was every possibility that the "oxadiaza" isomer was present possibly in trace amounts. We reasoned that if equilibrium between this species and the dioxime exists then $NaBH_4$ should be able to reduce the dioxime via this species. Otherwise the reagent should simply serve to reductively remove this "impurity".

On stirring with $NaBH_4$ in ethanol for 24 h 6 gave 80% conversion. Only two products were obtained. They were 5a and 5b in the proportion of 5:3. Reductive cleavage of this to 3-methyl-4-azacholestanes forms part

of the stereochemical studies and is discussed later. A 4-aza-17β-aminoandrostane on bisquaternisation with excess CH_3I results in a compound having neuromuscular blocking activity[13].

To prepare an intermediate which could give a 3-methyl analogue of known stereochemistry was but one of the objectives for preparing 4,5-secoandrost-3-yne-5,17-dione dioxime 11. The required dione was obtained from androst-4-ene-3,17-dione by epoxidation followed by fragmentation. Treatment of either the dione or 11 with excess $NH_2OH.HCl$ in the presence of sodium acetate led to the trioxime 12 (See Chart II). This compound has in addition to the 1,5-dioxime system as in 6, an extra oxime at C-17 which should undergo all the typical reactions of an isolated oxime and thereby provide an "internal standard" from which to judge the unusual behaviour of the 1,5-dioxime system.



i, NH_2OH; ii, $NaBH_4$

Chart-II

The trioxime 12 gave a blue-green colour with $FeCl_3$. Reduction with $NaBH_4$ by refluxing for 5 h gave the reduction products 13a and 13b in an overall yield of 30%. The starting material was recovered to the extent of 45%[14].

Reductive cyclisation of the 1,5-dioxime system is seen to take place under conditions where the 17-oxime remains unaffected.

Compounds 13a + 13b were produced in 75% yield by $NaBH_4$ reduction of 11. This

reduction went to completion as judged by tlc, within 4 h.

In view of the similarity, but not identity, of behaviour of the acetylenic oximes 4 and 11 on the one hand and the "dioximes" 6 and 12 on the other when subjected to $NaBH_4$ reduction, it seemed likely that they would all react with NH_2OCH_3 under conditions wherein cyclohexanone oxime totally fails to react with this reagent. Refluxing 11 with methoxyamine HCl and sodium acetate in methanol led to disappearance of starting material in 8 h. The monomethyl ether 14 was obtained only in 25% yield. The major product[15] was the dimethyl ether 15. Yield of this was 65%. The oxime at C-17 did not react.

In the cholestane series in spite of using a large excess of methoxyamine the major product from 6 was the monoether 8 obtained in 80% yield. The minor product 9 was 12%. These compounds had been obtained earlier from the acetylenic oxime 4 by treatment with the same reagent. The similarity of behaviour is emphasised by the total regioselectivity in formation of monoether. Thus none of the isomer of 8 having a free oxime at C-3 is formed from either 4 or 6. Yet a major difference was noticeable. The major product from 4 was 9 whereas that from 6 was 8. Hence the possibility of both 4 and 6 reacting exclusively through a single common intermediate is ruled out.

Hence we shall confine ourselves henceforth only to the reactions of compounds not having an alkyne function.

A brief sum up of the key findings with the steroidal compounds is given below:-

1) 1,5-dioximes specifically 4,5-seco-3,5-steroidal dioximes have two oxime functions. If any species not having two sp^2 carbons but having instead carbons to which two hetero atoms are attached is also present then the ^{13}C nmr evidence indicates that the amount present must be less than 5%.
2) The possibility of some such species being present is indicated by the blue-green colour observed with $FeCl_3$.
3) There are distinct indications that the above species is not only present but is in equilibrium with the dioxime in that two unusual reactions are observed with these oximes which are not observed with isolated oximes. They are $NaBH_4$ reduction and reactions with methoxyamine.

In an effort to decide on the structure of the elusive species which acts as an intermediate a series of related compounds was treated with $NaBH_4$ or with methoxyamine or even with hydroxylamine.

Of the compounds already mentioned, compounds, 7, 8, 9, 14 and 15 were recovered

unchanged. The $FeCl_3$ "link up" still seems to be there. None of these gave any colour with $FeCl_3$.

We then turned our attention to examining a couple of open chain 1,5 dioximes to find out whether the behaviour observed above was general[16].

Freshly prepared glutaraldehyde dioxime had nmr spectrum indicating the presence of two oximes having the (1E,5E) configuration. On keeping, it isomerised to a (1E,5Z) isomer. This typical 1,5-dioxime gave a distinct yellow green colour with $FeCl_3$. Reaction with $NaBH_4$ gave a spot on tlc corresponding to N-hydroxy-piperidine. But the reaction was so slow that no attempt was made to isolate the product. The reaction with methoxyamine yielded the monomethyl ether 16 accompanied by a little dimethyl ether. The monomethyl ether does not give a $FeCl_3$ test and is resistant to reaction with NH_2OH or NH_2OCH_3 or $NaBH_4$

Another typical dioxime of a 1,5-diketone was obtained starting from sym.-collidine.[30] The dioxime of 4-methylheptane-2,6-dione 17 gave a distinct colour with $FeCl_3$. Here $NaBH_4$ reduction proceeded to the extent of 25% in 48 h. The product was N-hydroxy-2,4,6-trimethylpiperidine 19 having either a 2α,4α,6α or 2α,4β,6α configuration. In the mass spectrum a strong M^+ at 143 is accompanied by the base peak at m/z 128 due to loss of the methyl adjacent to nitrogen. It was a hygroscopic solid and had absorption at 3250 cm^{-1} in ir. In nmr[17] the axial protons at C-2 and C-6 are at δ 2.37. They are somewhat upfield due to being antiperiplanar to the lone pair on nitrogen. The methyls at C-2 and C-6 give a six proton doublet at δ 1.17(J=6Hz) while the doublet due to methyl at 4 is at δ 0.86.

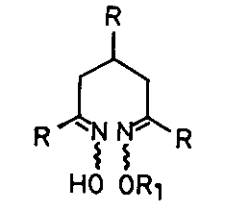
Treatment of 4-methylheptane-2,6-dione dioxime with methoxyamine gave 4-methyl-heptane-2,6-dione-2-(O-methyl)oxim-6-oxime 18. This monomethyl ether is the major product accompanied by some dimethyl ether. The monomethyl ether 18 was resistant to reaction with methoxyamine while both the mono and dimethyl ethers were recovered unchanged after reaction with $NaBH_4$

The intermediate which is presumed to be obligatory for the reaction with say $NaBH_4$ is obviously not being produced from the monoether of the 1,5-dioxime.

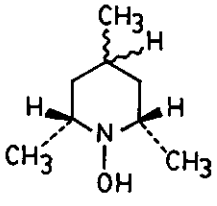
If the intermediate is indeed an "oxadiaza" compound obtainable from a 1,5-dioxime only, then it was best that we turn to a closer examination of the properties of a compound known to have the "oxadiaza" structure namely compound 2. Whether 2 was in equilibrium with detectable amounts of the corresponding dioxime in solution was also a point worth settling.

Gamov et al.[1] had separated by repeated fractional crystallisation two isomeric tetracyclic compounds which resulted from NH_2OH treatment of a mixture of meso and dl isomers of the starting 1,5-diketone, 1. They have assigned configuration to the two isomers as well as to the N-hydroxyperhydroacridines 3 produced from these by reaction with $NaBH_4$.

The mixture of stereoisomers of 2 was prepared as described by Gamov[1] and examined by ^{13}C nmr in $CDCl_3$+DMSO-d_6. Four signals downfield of δ 50 were at 85.05, 85.54, 99.54 and 101.33. Signals downfield of this were totally absent. If the dioxime was present it would certainly have been detected if the amount present was more than 5%. From the intensity of the signals it appears that out of the two tetracyclic isomers present and referred to as 2, one is present in larger amounts and gives rise to the signals at δ 85.05 and 99.54. The former represents a sp^3 carbon to which two nitrogens are attached while the latter clearly belongs to sp^3 carbon which is bonded to both nitrogen and oxygen. The compound gave a distinct green colour with $FeCl_3$



16 R=H, R_1= CH_3
17 R=CH_3, R_1=H
18 R=CH_3, R_1=CH_3



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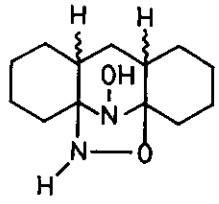

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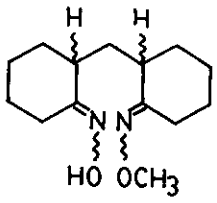

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CHART-III

Reaction of 2 with methoxyamine led to the formation of a bicyclic dioxime monomethyl ether 20 isolated in 60% yield accompanied by less than 10% of the dimethyl ether. Both compounds had a strong band at 1640 cm^{-1} in ir due to the presence of C=N. Besides using ir and nmr evidence the structure of the monoether, but not of the diether, was confirmed by CH analysis.

Of particular interest was a comparison of this dioxime monoether 20 with the host of other 1,5-dioxime monoethers such as 14, 16 and 18 in terms of its reactivity to $NaBH_4$ to NH_2OH or to NH_2OCH_3. It totally failed to react just as did the others. Thus in spite of having in-built features which would favour equilibrium with O-methyl ether of 2 the compound 20 does not lie on the path leading to the diether just as 14, 16 and 18 do not lie on the path leading to the corresponding diethers.

One word of caution. We do not claim that 2 has to break down to a bicyclic 1,5-dioxime to give the reactions observed with 2. These are all reactions that 2 can undergo directly or via nitrone intermediates.

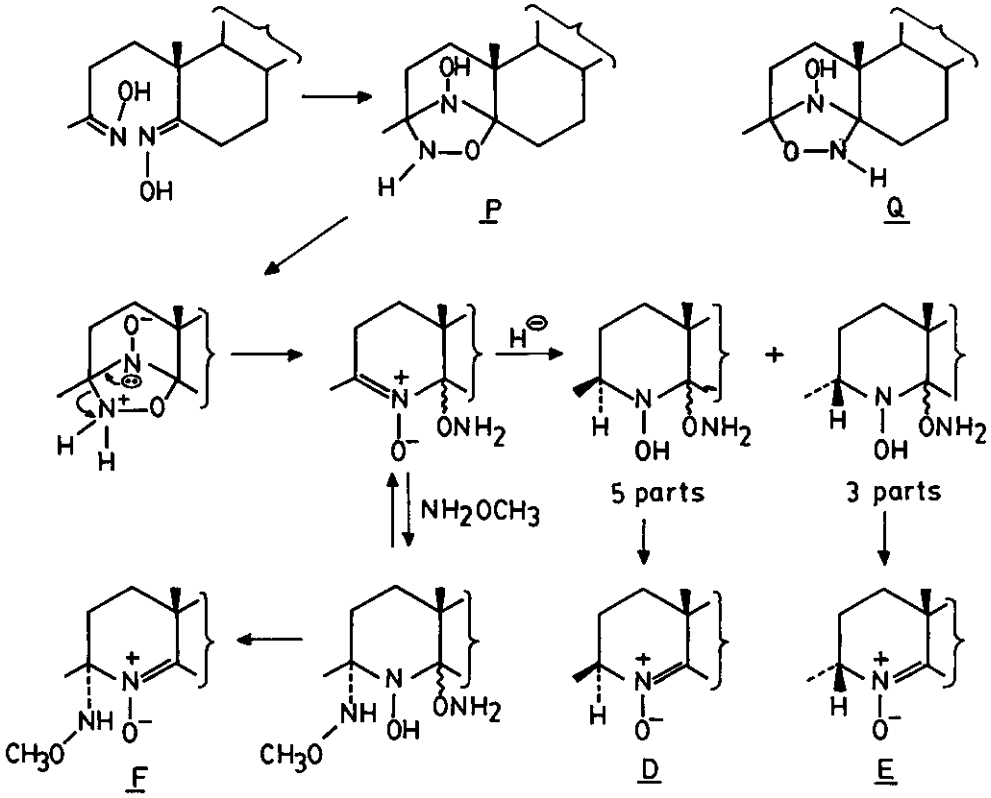
On the other hand we can reasonably conclude that the unusual reactions of 1,5-dioximes reported above proceed after their conversion to the "oxadiaza" isomer. Unless the initial conversion is fast the rate of reaction say with $NaBH_4$ is bound to be slower for the 1,5-dioximes than for 2 as is indeed observed.

In fact it may be necessary for E → Z or reverse isomerisation to give a 1,5-dioxime of proper stereochemistry to undergo facile transformation to the "oxadiaza" isomer.

The data collected about the structure, reactivity and regiospecificity in the transformation of the dioxime 6 to the monomethyl ether 8 by the action of methoxyamine play an important part in casting more light on the subject. Thus the dioxime 6 happens to be a mixture of dioximes having the structures (3E,5E) and (3Z,5E). The evidence is clear that the 5Z isomers are not present. Now if we specify that formation of the "oxadiaza" intermediate requires that the -OH of the oxime to be in proximity to the carbon to which it becomes bonded in the "oxadiaza" intermediate then oximes with either (3Z) or (5Z) configurations can react. In the case of 6 it follows that (3Z,5E) isomer would give rise to the oxadiaza intermediate P but not its isomer Q. See Scheme II. The reaction of 6 should then stop at 50% unless the (3E,5E) isomer is being isomerised to the (3Z,5E) one. It appears that the syn:anti isomerisation is slow only under strongly basic conditions and hence only for the $NaBH_4$ reduction in CH_3OH does one notice that the reaction virtually comes to a stop after 50% reduction[18]. It was hoped that work up at this stage may give the unreacted stereoisomer. But normal work up presumably restores the equilibrium proportion[19].

Scheme II suggests likely pathways for reaction of the (3Z,5E) isomer in 6 via P. Tentative suggestion is made that the reaction with $NaBH_4$ proceeds to give the intermediates D and E of Scheme I but in different proportions than obtained therein. The reaction with methoxyamine is also linked up with intermediate F of Chart II.

As pointed out on the first page those who obtained 2 did not propose any mechanism for its formation. The data collected above exclude a number of possibilities if the objective is to explain the formation of P to the exclusion of Q. This is possible only if the component of 6 having the configuration (3Z,5E) must make a



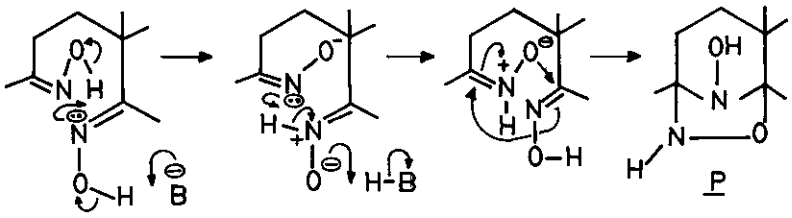
SCHEME-II

bond between the oxygen and C-5 without prior loss of sp^2 character at C-3.Without this restriction formation of Q remains a distinct possibility.

An attractive way of meeting this requirement is to use a 1,3-dipolar cycloaddition mechanism. There has been considerable speculation about the role of tautomeric 1,3-dipoles in cycloadditions[20]. Included among such compounds are those formed from an oxime by proton shift from oxygen to nitrogen, but ab initio calculations for intramolecular conversion of nitrosomethane to formaldehyde oxime by two 1,2 proton shifts indicate[21] that the energy required is too high for the process to be viable.

But there was a distinct possibility of a 1,2 proton shift occurring from an oxime oxygen to the nitrogen provided it could be assisted by a suitably positioned "neighbouring group". Such an assistance via hydrogen bonding has been proposed by

Grigg[22] to explain the 1:1 adduct formation between N-phenylmaleimide and 1,2,3-tricarbonyl-2-monooximes



Scheme-III

Scheme III uses a lone pair on a proximal nitrogen to assist the proton transfer. The basicity of this nitrogen can be increased by converting the -OH attached to it to $-O^-$ and restored when the $-O^-$ picks up a proton. Thus a role is assigned to both hydroxyls and provides a rationale for the failure of the monomethyl ether to react. A less attractive alternative is initial mutual proton transfer to give nitrones at both C-3 and C-5 and then either a stepwise or concerted addition to give an intermediate which gives P by proton transfer.

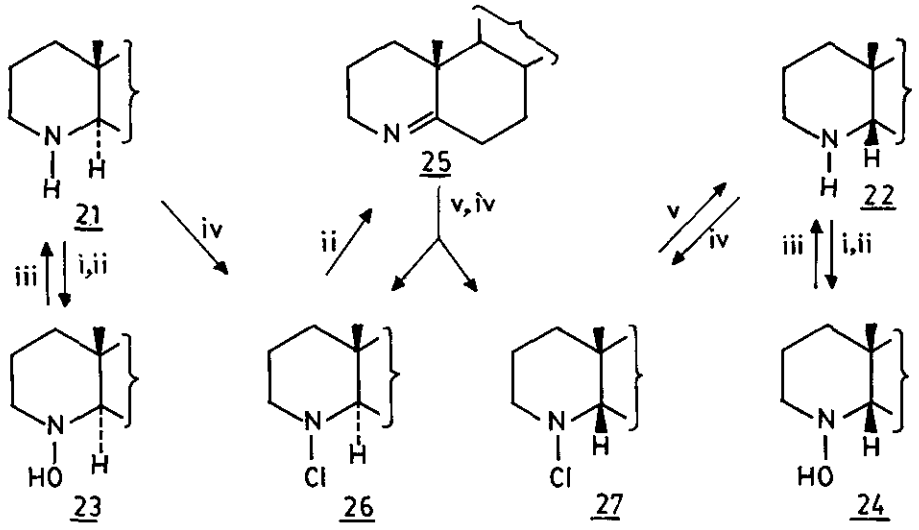
Stereochemical Studies

The primary concern here has been to establish beyond all doubt the configurations of the steroidal N-hydroxypiperidine analogues i.e. of the the two isomers 5a and 5b obtained by $NaBH_4$ reduction of 4 as well as 6.

We sought to do this primarily by use of nmr. We initially thought that nmr data from corresponding compounds not having a methyl at C-3 but with known configurations at C-5 may suffice. Thus we set out to make the known 4-aza-5α-cholestane 21[23] and 4-aza-5β-cholestane 22[24] with the intention of converting them to the corresponding N-hydroxy derivatives 23 and 24 respectively for the required nmr study.

Compound 21 was prepared as described[23]. The configuration of 21 rests on the method of its preparation[23]. In order to make 22 we chose to convert 21 to the imine 25 since it had been reported[24] that $LiAlH_4$ reduces 25 to a mixture of 21 and 22. For preparing 25 we treated 21 with N-chlorosuccinimide and the resulting N-chloro-4-aza-5α-cholestane 26 was dehydrochlorinated using methanolic KOH. From nmr it could be concluded that the product obtained after chromatography was pure 25. Though $LiAlH_4$ reduction proceeded as claimed the separation of 22 from

21 proved difficult. To overcome this difficulty the mixture of 21 and 22 was treated with N-chlorosuccinimide to give a mixture containing 26 and 27. These two could be readily separated by column chromatography. $LiAlH_4$ reduction of 27 gave pure 22. Stirring the 4-aza-cholestanes in dry benzene with benzoyl peroxide for 3 h resulted in the formation of the corresponding N-benzoyloxy derivatives[25]. Stirring the N-benzoyloxy derivative with methanolic KOH for 12 h hydrolysed them to the N-hydroxy compounds. Thus N-hydroxy-4-aza-5α-cholestane 23 was obtained from 21. The 5β isomer 24 was obtained similarly from 22. (See Chart IV).



i, Benzoyl peroxide; ii, KOH; iii, Zn/AcOH; iv, N-Chlorosuccinimide
v, $LiAlH_4$

CHART-IV

The nmr's of 23 and 24 proved far from satisfactory. A doublet of J=10Hz was seen at δ 3.3 in the former and at δ 3.27 in the latter. Both the arms of the doublets were relatively broad indicating couplings additional to the 10Hz. We tentatively assign them to the equatorial hydrogen at C-3 having a gem coupling of 10Hz. In the case of 23 there was a steady rise in absorption in going upfield from δ 2.7. Thus the remaining hydrogen at C-3 and the one at C-5 could not be assigned any chemical shift. The situation in the case of 24 was far better. On the edge of the steroid envelope a narrow, but not sharp, singlet stood out at δ 2.17 having $W_{\frac{1}{2}} = 6Hz$. The 5β H in 24 is equatorial and the only hydrogens it is expected

to couple with are the equatorial 6α H and the axial 6β H. Thus the signal at δ 2.17 can be assigned to the 5β H which in turn provides additional evidence for the correctness of the configurations assigned previously to 21 and 22. Examination of the nmr's of the corresponding chloro derivatives 26 and 27 proved to be an eye opener. The chlorine had served to deshield all the protons on the C-3 and C-5 carbons. Fig 1 gives the nmr of 27 in the region δ 1.5 to 4.0. Not only

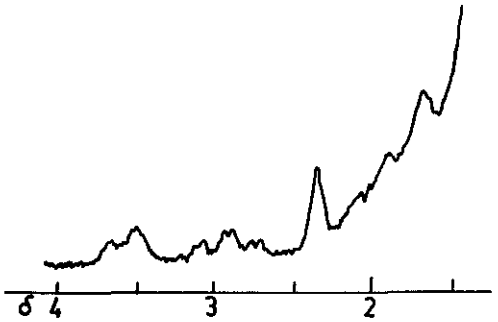


FIG. 1 nmr of 27

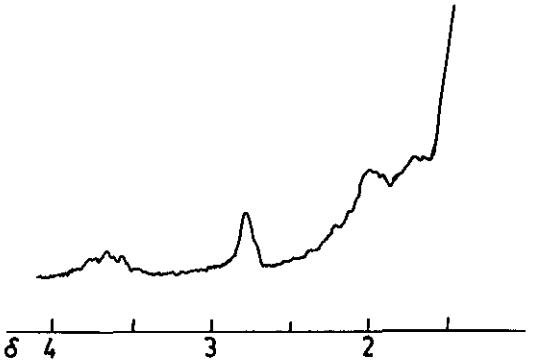


FIG. 2 nmr of 32

does the structure of 27 stand confirmed with the 5β H coming at δ 2.35 but one is forced to assign the signal centred at δ 2.92 as being due to the axial proton at C-3 having a diaxial coupling roughly equal to a geminal coupling and thereby giving the broad triplet. On the same considerations the signal at δ 3.6 is due to the equatorial proton. Because the A:B ring junction is cis the 3β proton is axial and the 3α proton is equatorial. The chemical shift difference between the two and the fact that the axial proton is shielded is definite. Whether it is due to the axial proton being antiperiplanar to the lone pair of electrons on nitrogen as expected with the N-Cl bond being equatorial we can only refer to contrasting views on the subject[26]. The nmr of 26 has signals due to the axial and equatorial protons at C-3 which are identical in the nature of their splitting to that noticed for 27. The chemical shifts are also practically identical.

These observations convinced us that assignment of configuration to the corresponding 3 methyl derivatives was best done using the correct N-chloro derivative. Conversion of an N-OH to N-Cl can be achieved by reduction of N-OH to N-H using activated Zn in glacial acetic acid followed by N-chlorination with N-chlorosuccinimide. In the present case we had to be certain that the conversion can be

achieved without changing the stereochemistry at C-3 and C-5. We had compounds of known configuration at hand which could establish that no isomerisation at C-5 was taking place. Thus 23 was converted to 26 via 21. In the same way 24 gave 27 free of any isomer.

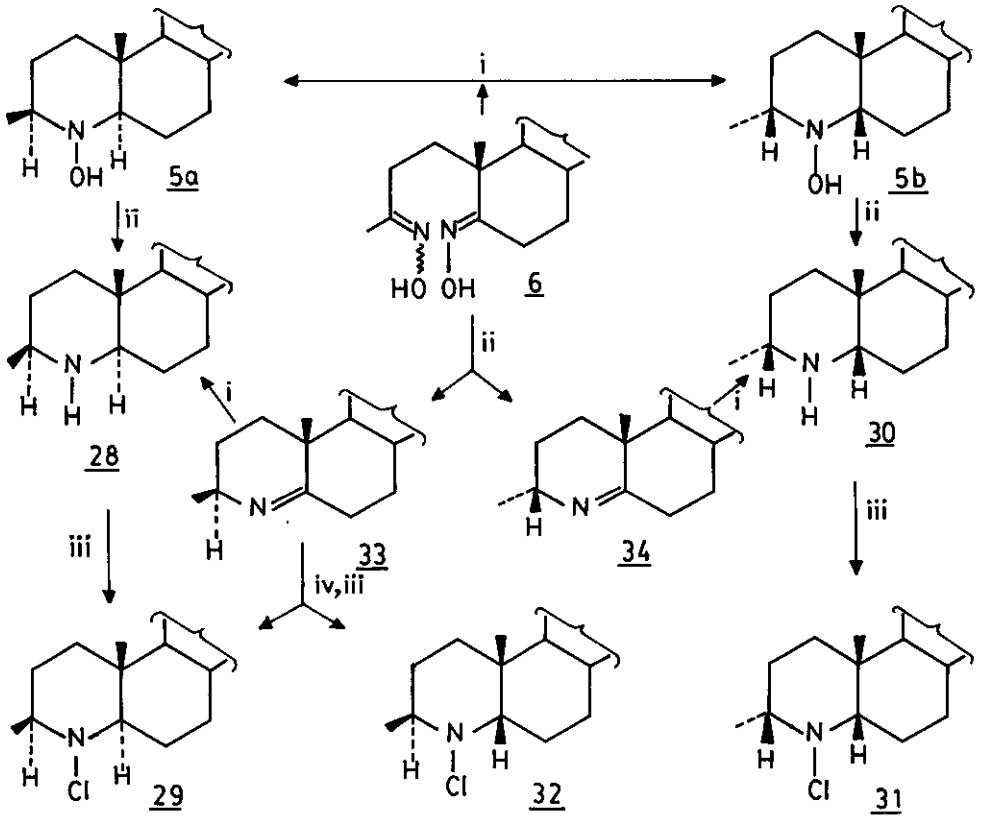
Treatment of 5a with Zn/HOAc gave 3β-methyl-4-aza-5α-cholestane 28 which on reaction with N-chlorosuccinimide gave the corresponding N-chloro derivative 29. In a similar fashion 5b was converted via 30 to the N-chloro derivative 31. With 29 and 31 unlike with 26 and 27 the single proton present at C-3 is split by a methyl group and is seen only as a multiplet. In nmr of 29 the multiplet is found at δ 2.76 while a doublet of doublet (J=10Hz and 3Hz) is seen at δ 2.33. It follows that the proton at C-5 is axial to both rings and has the 5α configuration. Since the C-3 proton is shielded and provided ring A is in the chair conformation then the signal at δ 2.76 must be due to the 3α (axial) proton. Hence 28 and 29 both have a 3β methyl and A:B trans junction. Compound 31 had in the nmr the typical 5β proton signal at δ 2.48. The proton at C-3 was responsible for a multiplet centred at δ 2.8. Assuming ring A to be in the chair conformation with the N-chloro bond equatorial the signal at δ 2.8 is assigned to an axial proton. Thus 31 must be N-chloro-3α-methyl-4-aza-5β-cholestane.

It was possible to remove the remote possibility that the protons at C-3 are not shielded because they are axial but because the methyl at C-3 was having a special shielding effect. We could do this because we were in a position to prepare the third of the four possible stereoisomeric N-chloro compounds and examine it in the nmr. Fig 2 gives the nmr of this compound in the region δ 1.5 to 4.0.

It must clearly belong to N-chloro-3β-methyl-4-aza-5β-cholestane 32 with the equatorial hydrogen at C-3 responsible for the signal at δ 3.67 characteristic of an unshielded proton unaffected by the presence of the methyl group at C-3 which has incidentally to take up an axial position.

Chart V describes how 32 was obtained. Configuration at C-3 in 33 follows from the fact that 29 is produced. Hence 32 has to be isomeric with 29 at C-5 as confirmed by nmr.

Thus 5a and 5b undoubtedly have the configurations depicted in Chart V. The stereoselectivity observed in $NaBH_4$ reduction of 33 and 34 has also come in useful (See Scheme I).



i $NaBH_4$, ii. Zn/AcOH, iii. N-Chlorosuccinimide, iv. $LiAlH_4$

CHART-V

EXPERIMENTAL

Melting points are uncorrected. Spectral data were recorded on the following instruments. Ir, Perkin-Elmer Model 397 spectrophotometer and only noteworthy absorptions (cm^{-1}) are listed. Nmr, Varian EM-360 L (60 MHz) spectrometer using tetramethylsilane as internal standard. Chemical shifts are quoted in ppm (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, b = broad).

$FeCl_3$ test : To a solution of compound in EtOH was added freshly prepared $FeCl_3$ solution by dissolving $FeCl_3$ in a 1:1 water-EtOH mixture.

4,5-Secocholest-3-yn-5-one oxime 4

Method 1 : To a solution of 768 mg (2 mmol) of 4,5-secocholest-3-yn-5-one[27] in

25 ml of MeOH were added $NaHCO_3$ (168 mg, 2 mmol) and hydroxylamine hydrochloride (139 mg,2 mmol)and the mixture was stirred at room temperature for 24 h The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, evaporated under vacuum (without heating). The residue was chromatographed on silica gel with CH_2Cl_2. Fractions containing 4 were combined together and the solvent was removed under reduced pressure without heating to give 4 as a colourless oil, 375 mg, yield 47%; ir (neat) : 3300 (C≡C-H, OH), 2100 (C≡C), 1640 cm^{-1} (C=N); nmr (CCl_4) δ : 8.93 (1H, b, NOH), 3.37 (1H, bd, J=14Hz, C-6α H), 1.75 (1H, s, C≡CH), 1.08 (3H, s, C-19 H), 0.72 (3H, s, C-18 H); Anal. compound unstable.

Method 2 : A mixture of 768 mg (2 mmol) of 4,5-secocholest-3-yn-5-one in MeOH(25 ml) 348 mg (5 mmol) of hydroxylamine hydrochloride and 410 mg (5 mmol) of AcONa was refluxed for 0.5 h. The reaction mixture was immediately diluted with 100 ml of water. The product was isolated as above and chromatographed to give 4, 530 mg, yield 66%.

$NaBH_4$ reduction of 4,5-secocholest-3-yn-5-one oxime 4 giving 5a and 5b

A mixture of 399 mg (1 mmol) of oxime 4 in 20 ml of MeOH and 100 mg of $NaBH_4$ was refluxed for 2 h. An additional 100 mg of $NaBH_4$ was added in two portions of 50 mg each and reflux was continued for 1h after each addition. After adding 100 ml of water to the reaction mixture, it was acidified with AcOH and extracted with Et_2O. The organic layer was washed with a solution of $NaHCO_3$, followed by water, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica gel with benzene to give in order of mobility :

N-Hydroxy-3α-methyl-4-aza-5β-cholestane 5b : An oil, 35 mg, yield 8.9%;α_D + 15° (c=0.01, $CHCl_3$), ir (nujol) : 3340 cm^{-1} (OH); nmr (CCl_4) δ : 2.33 (1H, m, C-3 H), 2.13 (1H, m, C-5 H), 1.17 (3H, d, J=6Hz, C-3 CH_3), 0.95 (3H, s, C-19 H), 0.65 (3H, s, C-18 H); Anal. calcd. for $C_{27}H_{49}NO$: C, 80.33; H, 12.24; N, 3.47; Found : C, 80.30; H, 12.60; N, 3.00.

N-Hydroxy-3β-methyl-4-aza-5α-cholestane 5a : A solid, 330 mg, yield 82%, mp 134-136°C; α_D + 40° (c=0.01, $CHCl_3$), ir (nujol) : 3480 cm^{-1} (OH); nmr ($CDCl_3$) δ : 3.70(1H, b, NOH), 1.15 (3H, d, J=6Hz, C-3 CH_3), 0.90(3H, s, C-19 H), 0.65 (3H, s, C-18 H); Anal. calcd.for $C_{27}H_{49}NO$: C, 80.33; H, 12.24; N, 3.47; Found : C, 80.82; H, 12.56; N, 3.50.

4,5-Secocholestane-3,5-dione dioxime 6

A mixture of 384 mg (1 mmol) of 4,5-secocholest-3-yn-5-one in 20 ml of MeOH, 350 mg (5 mmol) of hydroxylamine hydrochloride and AcONa (410 mg, 5 mmol) was refluxed for 7 h. The reaction mixture was diluted with water(100 ml) and the diluted mixture was extrated with $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was recrystallised from MeOH-hexane which gave 6 as a white solid, 350 mg, yield 81%; mp 112-115°C; α_D + 54° (c=0.01, $CHCl_3$); ir (nujol) : 3300 (OH), 1660 cm^{-1} (C=N); ^{1}H-nmr ($CDCl_3$) δ : 1.90(3H, s, C-3 CH_3), 1.10(3H, s, C-19 H), 0.71 (3H, s, C-18 H); Anal. calcd. for $C_{27}H_{48}O_2N_2$: C, 74.94; H, 11.10; N, 6.47; Found : C, 74.76; H, 10.80; N, 6.44; ms m/z : 432 (M^+) : ^{13}C-nmr[28] δ : 164, 159, 56.17, 56.02, 47.06, 42.93, 42.49, 39.62, 39.50, 26.16, 35.77, 35.01, 32.31, 30.21, 28.20, 28, 27.91,

24.25, 23.87, 23.62, 22.81, 22.69, 22.57, 22.45, 22.22, 21.18, 20.45, 20.34, 18.65, 13.58, 11.95; hplc : column, μ-porasil; solvent; EtOAc/cyclohexane (5:95); detector; uv; retention time, percentage : 3.90, 63.66%; 9.86, 36.34%.

4,5-Secocholest-3-yn-5-one O-methyloxime 7

A mixture of 384 mg (1 mmol) of 4,5-secocholest-3-yn-5-one in 20 ml of MeOH, 835 mg (10 mmol) of methoxyamine hydrochloride and 820 mg (10 mmol) of AcONa was refluxed for 2 h. The product was isolated as in 6. The residue was chromatographed on alumina with benzene to give 7, an oil, 370 mg, yield 90%; α_D + 42°(c=0.01, $CHCl_3$); ir (nujol) : 3320 (≡C-H), 2135 (C≡C), 1620 cm^{-1} (C=N); nmr (CCl_4) δ: 3.73 (3H, s, OCH_3), 3.18 (1H, m, C-6α H), 1.05 (3H, s, C-19 H), 0.7 (3H, s, C-18 H); Anal. calcd for $C_{28}H_{47}NO$: C, 81.31; H, 11.45; N, 3.38; Found : C, 81.50; H, 11.80; N, 3.10.

Reaction of 4 with NH_2OCH_3.HCl/AcONa giving 8 and 9

A mixture of 399 mg (1 mmol) of 4 in 20 ml of MeOH, 4.8 mg (5 mmol) of methoxyamine hydrochloride and 410 mg (5 mmol) of AcONa was refluxed for 6h. The product was isolated as in 6. The residue was chromatographed on silica gel with benzene-Et_2O to give in order of mobility :

4,5-Secocholestane-3,5-dione bis(O-methyloxime) 9 : A gummy mass, 230 mg, yield 50%; α_D + 35° (c=0.01, $CHCl_3$); ir (nujol) : 1640 cm^{-1} (C=N); nmr (CCl_4) δ : 3.78, 3.75 (6H, d, OCH_3 x 2), 3.17 (1H, d, J=14Hz, C-6α H), 1.82 (3H, s, C-3 CH_3), 1.07 (3H, s, C-19 H), 0.70 (3H, s, C-18 H); Anal. calcd for $C_{29}H_{52}N_2O_2$: C, 75.65; H, 11.30; Found : C, 75.50; H, 11.01.

4,5-Secocholestane-3,5-dione 3-(O-methyloxime) 5-oxime 8 : A solid, 120 mg, yield 27%; mp 87-89°C; α_D + 47° (c=0.01, $CHCl_3$); ir (nujol) : 3300 (OH), 1640 cm^{-1} (C=N); nmr (CCl_4) δ : 8.77 (1H, NOH), 3.77 (3H, s, OCH_3), 3.33 (1H, d, J=14Hz, C-6α H), 1.77 (3H, s, C-3 CH_3), 1.08 (3H, s, C-19 H), 0.70 (3H, s, C-18 H); Anal. calcd for $C_{28}H_{50}N_2O_2$: C, 75.33; H, 11.21; Found : C, 75.40; H, 11.15.

Beckmann rearrangement of 8 giving 10

To a solution of 223 mg (0.5 mmol) of 8 in dry pyridine (2 ml), 100 mg (0.52 mmol) of p-toluenesulphonyl chloride was added at 0°C. The reaction mixture was stirred for 15 min. The reaction mixture was diluted with 20 ml of water and acidified with dil. HCl. The acidified reaction mixture was extracted with Et_2O. The organic layer was washed with a solution of $NaHCO_3$ and followed by water, dried over Na_2SO_4 and the solvent evaporated. The residue was chromatographed on silica gel with benzene-Et_2O to give 4,5-seco-B-homo-5-azacholestane-3,5a-dione 3-(O-methyloxime) 10, 165 mg, yield 74%, a solid, mp 63-65°C; α_D + 54° (c=0.01, $CHCl_3$); ir (nujol) : 3200, 3050 (NH), 1640 cm^{-1} (C=O); nmr (CCl_4) δ : 7.73 (1H, b, NH), 3.77 (3H, s, OCH_3), 1.83 (3H, s, C-3 CH_3), 1.32 (3H, s, C-19, H), 0.70 (3H, s, C-18 H); ms m/z : 446 (M^+).

$NaBH_4$ reduction of 6 giving 5a and 5b

A mixture of 432 mg (1 mmol) of 6 in 20 ml of EtOH and 444 mg (12 mmol) of $NaBH_4$ was stirred for 24 h at room temperature. The product was isolated as in $NaBH_4$ reduction of 4. The residue was chromatographed on silica gel with benzene to give 5b, an oil, 127 mg, yield[29] 32% and 5a, a solid, 220 mg, yield 55%.

4,5-Secoandrost-3-yne-5,17-dione dioxime 11

A mixture of 230 mg (1 mmol) of 4,5-secoandrost-3-yne-5,17-dione[27] in 20 ml of MeOH, 350 mg (5 mmol) of hydroxylamine hydrochloride and 350 mg (5 mmol) of AcONa was stirred at 10-15°C for 10 h. The reaction mixture was diluted with 100 ml of ice cold water. The precipitated solid was filtered, washed with water and dried over P_2O_5 in vacuum to give 11, 240 mg, yield 76%, mp 176-178°C; ir (KBr) : 3420 (OH), 3260 (≡C-H), 2120 (C≡C), 1630 cm^{-1} (C=N); nmr δ : 8.90 (1H, m, NaOH, D_2O exch.), 3.30 (1H, d, J=10Hz, components m, C-6α H), 1.90 (s, ≡CH), 1.06 (3H, s, C-19 H), 0.95 (3H, s, C-18 H); Anal. compound unstable.

4,5-Secoandrostane-3,5,17-trione trioxime 12

A mixture of 230 mg (1 mmol) of 4,5-secoandrost-3-yne-5,17-dione in 20 ml of MeOH, 350 mg (5 mmol) of hydroxylamine hydrochloride and 350 mg (5 mmol) of AcONa was refluxed for 8 h. The reaction mixture was cooled to room temperature and diluted with 150 ml of water. The precipitated solid was filtered, washed with water and dried. The dried solid was recrystallised from MeOH to give 12, 250 mg, yield 72%, mp 132-135°C; α_D + 35° (c=0.01, $CHCl_3$); ir (nujol) : 3380 (OH), 1630 cm^{-1} (C=N); nmr ($CDCl_3$) δ : 9.2 (1H, m, NOH, D_2O exch.), 3.38 (1H, m, C-6α H). 1.80 (3H, s, C-3 CH_3), 1.10 (3H, s, C-19 H), 0.95 (3H, s, C-18 H); Anal. calcd for $C_{19}H_{31}N_3O_3$: C, 65.33; H, 8.84; N, 12.03; Found : C, 65.00; H, 9.10; N, 12.30; ms m/z : 349 (M^+).

4,5-Secoandrost-3,5,17-trione trioxime 12 from 11

A mixture of 260 mg (1 mmol) of 11 in 20 ml MeOH, 350 mg (5 mmol) of hydroxylamine hydrochloride and 350 mg (5 mmol) of AcONa was refluxed for 6 h. The trioxime 12 was isolated as above and recrystallised from MeOH, 250 mg, yield 72%; mp 132-135°C.

$NaBH_4$ reduction of 12 giving a mixture of 13a and 13b

To a solution of 349 mg (1 mmol) of 12 in 20 ml of EtOH was added 400 mg of $NaBH_4$ in portions at reflux temperature and refluxed for 5 h. The product was isolated as in $NaBH_4$ reduction of 4. The residue was chromatographed on silica gel with $CHCl_3$-Et_2O to give a mixture of N-hydroxy-3β-methyl-4-aza-5α-androstan-17-one oxime 13a and N-hydroxy-3α-methyl-4-aza-5β-androstan-17-one oxime 13b. 100 mg, yield[29] 31%, a solid, mp 169-172°C; α_D+30° (c=0.01, $CHCl_3$); ir (nujol) : 3300 (OH), 1630 cm^{-1} (C=N); nmr ($CDCl_3$) δ :3.45 (b, m), 1.20 (3H, d, J=6Hz, C-3 CH_3). 0.90-0.92, 0.95 (C-18 H and C-19 H in mixture); Anal. calcd for $C_{19}H_{32}N_2O_2$: C, 71.25; H,10.08; N, 8.75; Found : C, 71.03; H, 10.42; N, 9.00; ms m/z : 320 (M^+).

$NaBH_4$ reduction of 11 giving a mixture of 13a and 13b

Following the above procedure 334 mg (1 mmol) of 11 was reduced to give a mixture of 13a and 13b, 250 mg, yield 78%; a solid, mp 160-165°C; α_D+23.33° (c=0.01, $CHCl_3$); ir (nujol) : 3300 (OH), 1630 cm^{-1} (C=N); nmr ($CDCl_3$) δ : 3.45 (b, m), 1.20 (3H, d, J=6Hz, C-3 CH_3), 0.93, 0.95, 0.96 (C-18 H and C-19 H in mixture); Anal. calcd for $C_{19}H_{32}N_2O_2$: C, 71.25; H, 10.08; N, 8.75; Found : C, 70.80; H, 9.90; N, 8.30; ms m/z : 320 (M^+).

Reaction of 11 with NH_2OCH_3.HCl/AcONa, giving 14 and 15

A mixture of 410 mg (1.3 mmol) of 11 in 15 ml of MeOH, 435 mg (5.2 mmol) of methoxyamine hydrochloride and 640 mg (7.8 mmol) of AcONa was refluxed for 6 h. The product was isolated as in 6. The residue was chromatographed with benzene-acetone

to give in order of mobility:
4,5-Secoandrostane-3,5,17-trione 3,5-bis(O-methyloxime) 17-oxime 15 : 320 mg, yield 65%, amorphous solid, α_D+ 35° (c=0.01, $CHCl_3$); ir (nujol) : 3200 (OH), 1640 cm^{-1} (C=N); nmr (CCl_4) δ : 9.30 (1H, b, NOH, D_2O exch.), 3.78 and 3.74 (total 6H, OCH_3 x 2), 3.18 (1H, bd, J=14Hz, C-6α H), 1.83 (3H, s, C-3 CH_3), 1.07 (3H, s, C-19 H), 0.93 (3H, s, C-18 H); Anal. calcd for $C_{21}H_{35}N_3O_3$: C, 66.84; H, 9.28; N, 11.14; Found : C, 66.60;H, 9.20;N, 11.00;ms m/z : 377 (M^+).
4,5-Secoandrostane-3,5,17-trione 3-(O-methyloxime), 5,17-dioxime 14, 120 mg, yield 25%, a solid, mp 153-155°C, α_D + 53° (c=0.01, $CHCl_3$); ir (nujol) : 3250 (OH), 1640 cm^{-1} (C=N), nmr ($CDCl_3$) δ : 9.13 (2H, b, NOH x 2, D_2O exch.), 3.83 (3H, s, OCH_3), 3.38 (1H, bd, J=14Hz, C-6α H), 1.83 (3H, s, C-3 CH_3), 1.08 (3H, s, C-19 H), 0.93 (3H, s, C-18 H); Anal. calcd for $C_{20}H_{33}N_3O_3$: C, 66.12; H, 9.09; N, 11.57; Found : C, 65.97; H, 8.90;N, 11.20; ms m/z : 363 (M^+).

Glutaraldehyde dioxime[30]

A mixture of 39.5 g (0.5 mol) of dry pyridine in 200 ml of 'super dry' EtOH and 11.5 g (0.5 atom) of sodium was refluxed till all the sodium reacted. The reaction mixture was cooled and to the reaction mixture was added 17.38 g (0.25 mol) of hydroxylamine hydrochloride in minimum quantity of warm water, followed by rapid addition of conc. HCl(25 ml) in EtOH (50 ml).The mixture was refluxed for 1 h and alcohol removed under reduced pressure and the residual solution was cooled(0°C) for 10h to crystallisé glutaraldehyde dioxime. The crystallised glutaraldehyde dioxime was filtered, washed with water and recrystallised with MeOH, 10 g,yield 15%, mp 175-176°C,(lit.[30] mp 175-176°C);ir (nujol) : 3200-3100 (OH), 1650 cm^{-1} (C=N); nmr (DMSO-d_6) δ : 10.65 (2H, b, NOH x 2), 7.21 and 6.57 (2H, t, J=5.5Hz, -CH=N in E and Z isomers), 2.10(4H, m, CH_2-C=N), 1.40(2H, m, CH_2-C-C=N).

Reaction of glutaraldehyde dioxime with $NaBH_4$

To a refluxing solution of 260 mg (2 mmol) of glutaraldehyde dioxime in MeOH (20 ml) was added in portions 400 mg of $NaBH_4$ over a period of 10 h. The reaction mixture was analysed by tlc which showed a spot corresponding to standard N-hydroxy-piperidine. The reaction was very slow and even after prolonged reaction time sufficient conversion could not be achieved. Due to high solubility of N-hydroxy-piperidine, the isolation from the reaction mixture was not attempted.

Reaction of glutaraldehyde dioxime with NH_2OCH_3.HCl/AcONa giving 16

A mixture of 260 mg (2 mmol) of glutaraldehyde dioxime in MeOH (20 ml), methoxy-amine hydrochloride (835 mg,10 mmol) and 820 mg (10 mmol) of AcONa was refluxed for 8 h. The product was isolated as in 6. The residue was chromatographed on silica gel with $CHCl_3$-Et_2O to give in order of mobility :
Glutaraldehyde bis(O-methyloxime), 20 mg, yield 7%, an oil; ir (neat): 1640 cm^{-1} (C=N); nmr (CCl_4) δ : 7.2 and 6.43 (2H, t, J=5.5Hz, CH=N x 2 in E and Z isomers), 3.80and 3.73 (6H, s, OCH_3 x 2 in E and Z isomers), 2.17 (4H, m, CH_2-C=N x 2), 1.70(2H, m, CH_2-C-C=N).
Glutaraldehyde 1-(O-methyloxime) 6-oxime 16, 135 mg, yield 47%, an oil; ir (neat): 3250-3100 (OH), 1640 cm^{-1} (C=N); nmr ($CDCl_3$) δ : 9.50(1H, b, NOH), 7.34 and 6.58 (2H, t, CH=N x 2 in E and Z isomers), 3.80and 3.73 (3H, s, OCH_3 in E and Z isomers),

2.23 (4H, m, CH_2C=N x 2), 1.70 (2H, m, CH_2-C-C=N); Anal. calcd. for $C_6H_{12}N_2O_2$: C, 50.00; H, 8.33; N, 19.40; Found : C, 50.20; H, 8.30; N, 19.10.

4-Methylheptane-2,6-dione dioxime 17[30]

60.5 g (0.05 mmol) of 2,4,6-Collidine was reduced with 11.5 g (0.5 atom) of sodium by the procedure used for glutaraldehyde dioxime preparation from pyridine. After the removal of alcohol, the residue was extracted with a solution of 20% NaOH. The aqueous layer was washed with 200 ml of Et_2O twice, and neutralised. The neutralised mixture was extracted with Et_2O, the solvent removed and the product distilled under vacuum, 15 g, a gummy mass, yield 23% ir (nujol): 3250-3100 (OH), 1660 cm^{-1} (C=N); nmr ($CDCl_3$) δ : 9.50 (1H, b, NOH), 1.92 (6H, s, N=C-CH_3 x 2), 1.08 (3H, d, J=7Hz, C-4 CH_3).

N-Hydroxy-2,4,6-trimethylpiperidine 19

A mixture of 344 mg (2 mmol) of 17 in 15 ml of absolute ethanol and 400 mg of $NaBH_4$ was stirred at room temperature for 48 h. The product was isolated as in $NaBH_4$ reduction of 4. The residue was chromatographed on alumina with $CHCl_3$-Et_2O. Fractions containing 19 were combined together and the solvent was removed under reduced pressure to give 85 mg of 19, yield 30%, a hygroscopic solid, mp 67-68°C, ir (KBr): 3250 cm^{-1} (OH); nmr (CCl_4) δ : 6.20 (1H, b, NOH), 2.37 (2H, m, CH-N x 2), 1.85-1.25 (m, remaining protons), 1.20 (6H, d, J=6Hz, N-C-CH_3 x 2), 0.86 (3H, d, J=6Hz, C-4 CH_3); ms m/z : 143 (M^+).

Reaction of 17 with NH_2OCH_3.HCl/AcONa giving 18

*A mixture of 344 mg (2 mmol) of 17 in 25 ml of MeOH, 835 mg (10 mmol) of methoxy*amine hydrochloride and 820 mg (10 mmol) of AcONa was refluxed for 8 h. The product was isolated as in 6. The residue was chromatographed on silica gel with $CHCl_3$-Et_2O to obtain in order of mobility :

4-Methylheptane-2,6-dione bis (O-methyloxime), 33 mg, yield 9.6%, an oil; ir (neat): 1640 cm^{-1} (C=N); nmr (CCl_4) δ : 3.73 (6H, s, OCH_3 x 2), 1.73 (6H, s, CH_3-C=N x 2), 1.04 (3H, d, J=7Hz, C-4 CH_3).

4-Methylheptane-2,6-dione 2-(O-methyloxime) 6-oxime 18, 166 mg, yield 45%, an oil; ir (neat) : 3250 (OH), 1640 cm^{-1} (C=N); nmr ($CDCl_3$) δ : 9.60 (1H, b, NOH), 3.73 (3H, s, OCH_3), 1.80, 1.73, 1.70 (total 6H, CH_3-C=N in E and Z isomers), 1.07 (3H, d, J=7Hz, C-4 CH_3); Anal. calcd. for $C_9H_{18}N_2O_2$: C, 58.06; H, 9.68; N, 15.05; Found : C, 58.20; H, 9.65; N, 14.91.

8-Hydroxy-1,2,4,5-bis-tetramethylene-7-oxa-6,8-diazabicyclo[3.2.1]octane 2

It was prepared by the Gamov's procedure[1]. It was a solid, mp 159-164°C, (lit.[1] mp 159-164°C); ir (nujol) : 3210 (NH), 3100 cm^{-1} (OH); nmr (DMSO-d_6) δ : 1-3 (b, m), ^{13}C nmr[31] ($CDCl_3$+DMSO-d_6) : 101.33, 99.54 (C-1), 85.54, 85.05 (C-5), 41.1, 41.5 (C-2 and C-4), 22.80, 23.20, 24.50, 25.10, 29.20, 29.50, 29.60, 30.10, 32.90 (all CH_2).

Reaction of 2 with NH_2OCH_3.HCl/AcONa giving 20

A mixture of 238 mg (1 mmol) of 2 in 30 ml of MeOH, 418 mg (5 mmol) of methoxyamine hydrochloride and 418 mg (5 mmol) of AcONa was refluxed for 5 h. The product was isolated as in 6. The residue was chromatographed on alumina with benzene-Et_2O to give in order of mobility :

2,2'-Methylene-bis-cyclohexanone bis-(O-methyloxime), 20 mg, yield 7%, an oil; ir (neat) : 1640 cm^{-1} (C=N); nmr (CCl_4) δ : 3.70 (6H, s, OCH_3 x 2), 1.00-3.00 (20H,m),

2,2'-Methylene-biscyclohexanone 1-(o-methyloxime) 1'-oxime 20 : 140 mg, yield 56%, amorphous solid; ir (nujol) : 3250-3100 (OH), 1640 cm^{-1} (C=N); nmr ($CDCl_3$) δ : 8.3 (1H, b, NOH), 3.67 (3H, s, OCH_3), 1.00-3.00 (20 H, b, m); Anal. calcd for $C_{14}H_{24}N_2O_2$: C, 66.67; H, 9.52; N, 11.11; Found : C, 66.50; H, 9.40; N, 10.80.

4-Aza-5α-cholestane 21

To a refluxing solution of 4.19 g (10 mmol) of 3,5-seco-A-norcholestan-5-one-3-oic acid oxime[32] in 300 ml of dry n-pentanol was added 7 g of sodium in small portions over a period of 2 h. After all the sodium had reacted, the reaction mixture was cooled and diluted with water (100 ml). The diluted mixture was steam distilled to remove n-pentanol. The residue was extracted with Et_2O. The organic layer was washed with water, dried over Na_2SO_4 and the solvent evaporated. The residue was recrystallised from acetone to give 3.0 g, yield 92%, of 21, mp 114-115°C; α_D + 42° (c=0.01, $CHCl_3$), [lit.[23] mp 114-115°C, α_D + 40° (c=0.01, $CHCl_3$)]; ir (nujol) : 3270 cm^{-1} (NH); nmr (CCl_4) δ : 2.53 (1H, td, J_1=10Hz, J_2=3Hz, C-3α H), 0.90 (3H, s, C-19 H), 0.65 (3H, s, C-18 H).

Method A : General procedure for N-chlorination

A mixture of 1 mmol of azasteroid in 10 ml of hexane and 1.2 mmol of N-chloro-succinimide was stirred for 1 h at room temperature. The reaction mixture was filtered to remove suspended solid and the filtrate evaporated in vacuo. The residue was chromatographed on silica gel with hexane-benzene to give N-chloro derivative.

N-Chloro-4-aza-5α-cholestane 26

373 mg (1 mmol) of compound 21 was N-chlorinated by Method A to give 385 mg of 26, yield 94%; mp 99-100°C, α_D - 48.5° (c=0.01, $CHCl_3$); δ : 3.60 (1H, bd, C-3β H), 2.87 (1H, td, J_1=11Hz, J_2=3Hz, C-3α H), 2.18 (1H, dd, C-5α H), 0.92 (3H, s, C-19 H), 0.65 (3H, s, C-18 H); Anal. calcd for $C_{26}H_{46}NCl$: Cl, 8.71; Found : Cl, 8.69.

4-Azacholest-4-ene 25

A mixture of 815 mg (2 mmol) of 26 in 20 ml of MeOH and 5 ml of 10% methanolic KOH was stirred for 10 h. The reaction mixture was diluted with water (150 ml), acidified with 10% solution of AcOH and extracted with Et_2O. The organic layer was washed with a solution of $NaHCO_3$ followed by water, dried over Na_2SO_4 and the solvent evaporated. The residue was chromatographed on alumina with benzene to give 670 mg, yield 90%, of 25, mp 101-102°C, α_D + 76° (c=0.01, $CHCl_3$), [lit. mp 101-102°C[33], 103°C[24], α_D + 88° (c=0.01, $CHCl_3$)[24]]; ir (nujol) : 1650 cm^{-1} (C=N); nmr (CCl_4) δ : 3.50 (2H, m, C-3 H), 1.08 (3H, s, C-19 H), 0.70 (3H, s, C-18 H).

N-Chloro-4-aza-5β-cholestane 27 and 26 from 25 via $LiAlH_4$ reduction followed by N-chlorination

A mixture of 371 mg (1 mmol) of 25 in dry tetrahydrofuran (25 ml) and 400 mg of $LiAlH_4$ was refluxed for 6 h. The reaction mixture was cooled, unreacted $LiAlH_4$ destroyed by addition of ethyl acetate and the product was extracted with Et_2O. The organic layer was washed with water, dried over Na_2SO_4 and the solvent evaporated to dryness. The residue, 370 mg was N-chlorinated by Method A with 160 mg of N-chloro-succinimide to give in order of mobility :

27, 125 mg, yield 31%, an oil, α_D + 72° (c=0.01, $CHCl_3$); nmr (CCl_4) δ : 3.6 (1H, bd,

C-3α H), 2.91 (1H, td, J_1=11Hz, J_2=3Hz, C-3β H), 2.37 (1H, m, $W_{\frac{1}{2}}$=6Hz, C-5β H), 0.95 (3H, s, C-19 H), 0.65 (3H, s, C-18 H); Anal. calcd for $C_{26}H_{46}NCl$: Cl, 8.71; Found : Cl, 8.70.
26, 250 mg, yield 62%.

4-Aza-5β-cholestane 22
A mixture of 204 mg (0.5 mmol) of 27 in 30 ml of dry Et_2O and 100 mg of $LiAlH_4$ was stirred for 1 h. The unreacted $LiAlH_4$ was destroyed by addition of ethyl acetate and the product was extracted with Et_2O. The organic layer was washed with water, dried over Na_2SO_4 and the solvent evaporated to dryness. The residue was chromatographed on alumina with benzene to give 175 mg, yield 90%, of 22, an oil, α_D + 18° (c=0.01, $CHCl_3$),(lit.[24] α_D + 19°); ir (neat) : 3300 cm^{-1} (NH); nmr (CCl_4) δ : 3.10 (1H, d, J=10Hz, C-3α H), 2.60(1H, m, C-3β H), 2.37 (1H, m, $W_{\frac{1}{2}}$=6Hz, C-5β H), 0.87 (3H, s, C-19 H), 0.65 (3H, s, C-18 H).

Method B : General procedure for preparation of N-benzoyloxy derivative
A mixture of 1 mmol of azacholestane in 20 ml of dry benzene and 266 mg (1.1 mmol) of benzoyl peroxide was stirred at 60°C for 3 h. The peroxides were destroyed by addition of AcOH, KI and a solution of sodium thiosulphate. The organic layer was separated, washed with water, dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was chromatographed on silica gel with hexane.

N-Hydroxy-4-aza-5α-cholestane O-benzoate
Compound 21, 373 mg (1 mmol) was benzoylated according to Method B to give 240 mg of benzoate, 47%, a solid, mp 151-153°C, α_D - 0.77° (c=0.01, $CHCl_3$); ir (nujol) : 1740 cm^{-1} (C=O); nmr (CCl_4) δ : 7.93 and 7.40(5H, m, aromatic H), 3.47 (1H, m, C-3β H), 2.55 (1H, m, C-3α H), 2.23 (1H, d, J=12Hz, C-5α H), 1.13 (3H, s, C-19 H), 0.65 (3H, s, C-18 H).

N-Hydroxy-4-aza-5β-cholestane O-benzoate
Compound 22, 373 mg (1 mmol) was benzoylated according to Method B to give 240 mg of benzoate, yield 47%, an oil, α_D + 82° (c=0.01, $CHCl_3$); ir (neat) : 1740 cm^{-1} (C=O); nmr (CCl_4) δ : 7.93 and 7.40(5H, m, aromatic H), 3.60(1H, bd, J=10Hz, C-3α H), 2.63 (1H, m, C-3β H), 2.53 (1H, m, $W_{\frac{1}{2}}$=6Hz, C-5β H), 1.00(3H, s, C-19 H), 0.65 (3H, s, C-18 H).

Method C : General procedure for hydrolysis of benzoyl derivative
A mixture of 247 mg (0.5 mmol) of benzoate in MeOH(20 ml) and 1 ml of 10% solution of methanolic KOH was stirred at room temperature for 12 h. The product was isolated as in 25. The residue was chromatographed on silica gel with benzene to give N-hydroxy compounds.
N-Hydroxy-4-aza-5α-cholestane 23 : 150 mg, yield 77%, recrystallised from acetone to give colourless needles, mp 173-174°C; α_D + 16° (c=0.01, $CHCl_3$); ir (nujol) : 3325 cm^{-1} (OH); nmr ($CDCl_3$) δ : 7.67 (1H, b, NOH), 3.30 1H, bd, J=10Hz, C-3β H), 0.88 (3H, s, C-19 H), 0.65 (3H, s, C-18 H); Anal. calcd for $C_{26}H_{47}NO$: C, 80.21; H, 12.08; N, 3.60; Found : C, 80.10; H, 11.90; N, 3.20, ms m/z : 389 (M^+), 372 (M-OH).
N-Hydroxy-4-aza-5β-cholestane 24 : 150 mg, yield 77%, a solid, mp 87-88°C; α_D + 34° (c=0.01, $CHCl_3$); ir (nujol) : 3300 cm^{-1} (OH); nmr (CCl_4) δ : 8.43 (1H, b,

NOH), 3.27 (1H, d, J=10Hz, C-3α H), 2.43 (1H, m, C-3β H), 2.17 (1H, m, $W_{\frac{1}{2}}$=6Hz, C-5β H), 0.97 (3H, s, C-19 H), 0.65 (3H, s, C-18 H); Anal. calcd for $C_{26}H_{47}NO$: C, 80.21; H, 12.08; N, 3.60; Found : C, 80.00; H, 11.90; N, 3.20; ms m/z : 389 (M^+), 372 (M-OH).

Method D : General procedure for Zn/AcOH reduction

A mixture of 0.5 mmol of compound in 10 ml of AcOH and 500 mg of Zn was stirred at room temperature for 2 h. To the reaction mixture was added 50 ml of Et_2O and solid was filtered. The filtrate was washed several times with water, dried over Na_2SO_4 and the solvent was evaporated to dryness. The residue was chromatographed on alumina with benzene-Et_2O.

Zn/AcOH reduction of 23 to 21 followed by N-chlorination to convert into 26

Compound 23(300 mg)was reduced according to Method D to give 270 mg of 21. The compound 21 obtained was N-chlorinated according to Method A to give 280 mg of 26.

Zn/AcOH reduction of 24 to 22 followed by N-chlorination to convert into 27

Compound 24(300 mg) was reduced according to Method D to give 260 mg of 22. The compound 22 obtained was N-chlorinated according to Method A to give 260 mg of 27.

3β-Methyl-4-aza-5α-cholestane 28

Compound 5a[202 mg (0.5 mmol)] was reduced according to Method D to give 185 mg of 28, a solid, mp 90-92°C; α_D + 41° (c=0.01, $CHCl_3$); ir (nujol) : 3440 cm^{-1} (NH); nmr (CCl_4) δ : 2.60(1H, m, C-3α H), 2.13 (1H, bd, J=8Hz, C-5α H), 1.04 (3H, d, J=7Hz, C-3 CH_3), 0.90 (3H, s, C-19 H), 0.65 (3H, s, C-18 H); Anal. calcd for $C_{27}H_{49}N$: C, 83.64; H, 12.74; N, 3.61; Found : C, 83.20; H, 12.60; N, 3.40.

N-Chloro-3β-methyl-4-aza-5α-cholestane 29

Compound 28[387 mg (1 mmol)] was chlorinated according to Method A to give 400 mg of 29, yield 95%, a solid, mp 146-147°C; α_D - 37° (c=0.01, $CHCl_3$); nmr (CCl_4) : 2.76 (1H, m, C-3α H), 2.33 (1H, dd, J_1=11Hz, J_2=3Hz, C-5α H), 1.32 (3H, d, J=6Hz, C-3 CH_3), 0.92 (3H, s, C-19 H), 0.65 (3H, s, C-18 H); Anal. calcd for $C_{27}H_{48}NCl$: Cl, 8.42; Found : Cl, 8.30.

3α-Methyl-4-aza-5β-cholestane 30

Compound 5b[202 mg (0.5 mmol)] was reduced according to Method D to give 180 mg of 30, yield 93%, an oil, α_D + 14° (c=0.01, $CHCl_3$); ir (neat) : 3250 cm^{-1} (NH); nmr (CCl_4) δ : 2.60(1H, m, C-3β H), 2.37 (1H, $W_{\frac{1}{2}}$=6Hz, C-5β H), 1.03 (3H, d, J=7Hz, C-3 CH_3), 0.86 (3H, s, C-19 H), 0.65 (3H, s, C-18 H); Anal. calcd for $C_{27}H_{49}N$: C, 83.64; H, 12.74; N, 3.61; Found : C, 83.30; H, 12.50; N, 3.30.

N-Chloro-3α-methyl-4-aza-5β-cholestane 31

Compound 30[387 mg (1 mmol)] was chlorinated according to Method A to give 31; 390 mg yield 93%, a solid, mp 91°; α_D + 57° (c=0.01, $CHCl_3$); nmr (CCl_4) δ : 2.80(1H, m, C-3β H), 2.48 (1H, m, $W_{\frac{1}{2}}$=6Hz, C-5β H), 1.30(3H, d, J=6Hz, C-3 CH_3), 0.95 (3H, s, C-19 H), 0.65 (3H, s, C-18 H); Anal. calcd for $C_{27}H_{48}NCl$: Cl, 8.42; Found : Cl, 8.35.

Zn/AcOH reduction of 6 to give 3β-methyl-4-azacholest-4-ene 33 and 3α-methyl-4-azacholest-4-ene 34

A mixture of 864 mg (2 mmol) of 6 in 15 ml of AcOH and 860 mg of freshly activated

zinc was stirred at room temperature for 10 h. The products were isolated according to Method D to give in order of mobility :
33, 620 mg, yield 81%, a solid, mp 127-130°C; α_D + 33° (c=0.01, $CHCl_3$); ir (nujol): 1045 cm^{-1} (C=N); nmr (CCl_4) δ : 3.40(1H, m, C-3α H), 1.06 (3H, s, C-19 H), 0.70(3H, s, C-18 H); Anal. calcd for $C_{27}H_{47}N$: C, 84.07; H, 12.28; N, 3.60; Found : C, 84.30; H, 12.40; N, 3.37.
34, 80 mg, yield 10%, a solid, mp 95-96°C; α_D + 110° (c=0.01, $CHCl_3$); ir (nujol) : 1640 cm^{-1} (C=N); nmr (CCl_4) δ : 3.50(1H, m, C-3β H), 1.12 (3H, d, J=6Hz, C-3 CH_3), 1.07 (3H, s, C-19 H); 0.7 (3H, s, C-18 H); Anal. calcd for $C_{27}H_{47}N$: C, 84.07; H, 12.28; N, 3.60; Found : C, 84.20; H, 11.80; N, 3.80.

$LiAlH_4$ reduction of 33 followed by N-chlorination to give N-chloro-3β-methyl-4-aza-5β-cholestane 32 and 29

A mixture of 770 mg (2 mmol) of 33 in 50 ml of dry tetrahydrofuran and 760 mg (20 mmol) of $LiAlH_4$ was refluxed for 6h. The reaction mixture was cooled and the product isolated as in 22. The residue(765)mg was N-chlorinated according to Method A with 270 mg of N-chlorosuccinimide to give 32 in order of mobility :
32, 400 mg, yield 47%, mp 75°c; α_D + 100° (c=0.01, $CHCl_3$); nmr (CCl_4) δ : 3.67 (1H, m, C-3α H), 2.78 (1H, m, $W_{\frac{1}{2}}$=6Hz, C-5β H), 1.28 (3H, d, J=6Hz, C-3 CH_3), 0.95 (3H, s, C-19 H), 0.65 (3H, s, C-18 H); Anal. calcd for $C_{27}H_{48}NCl$: Cl, 8.42; Found : Cl, 8.39. The next to be eluted was 29, 380 mg, yield 45%.

$NaBH_4$ reduction of 33 and 34 to give 28 and 30 respectively

33 and 34 were reduced following the procedure used for $NaBH_4$ reduction of 6. The reduction was complete within 3 h. 33, 385 mg (1 mmol) gave 28, 340 mg, yield 88% and 34, 385 mg (1 mmol) gave 30, 365 mg, yield 94%.

Attempted reaction of 7, 8, 9, 14, 15, 16, 18 with $NaBH_4$

To a refluxing solution of 2 mmol of the compound was added 400 mg of $NaBH_4$ in portions over a period of 8-10 h. When the reaction mixture was analysed by thin layer chromatography, no spot other than the spot corresponding to R_f of starting material was observed. Work up as in $NaBH_4$ reduction of 4 yielded starting material only.

Attempted reaction of 7, 16, 18, 20 and cyclohexanone oxime with NH_2OCH_3/AcONa

A mixture of 1 mmol of the compound in 20 ml of MeOH, 418 mg (5 mmol) of methoxyamine hydrochloride and 410 mg (5 mmol) of AcONa was refluxed for 10 h. Tlc indicated that no reaction had taken place. Work up as in the preparation of 8 yielded starting material only.

Attempted reaction of 7 and 16 with $NH_2OH.HCl$/AcONa

A mixture of 1 mmol of the compound in 15 ml of MeOH, 348 mg (5 mmol) of hydroxylamine hydrochloride and 410 mg (5 mmol) of AcONa was refluxed for 8 h. Tlc indicated that no reaction had taken place. Work up as for 6 yielded starting material only.

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8. Only part structures are given. These are all cholestane derivatives.
9. The stereochemistry of the second hydride attack closely parallels the stereochemistry of the hydride reduction of the corresponding imines (See Chart V).
10. Actually $NH_2OH.HCl$ was used in the presence of $NaHCO_3$ or AcONa.
11. In case hydride attacks from α side on vinyl nitrone A at C-5 there is no compelling reason to exclude the subsequent β attack at the C-3 of the nitrone having a double bond at 3. Yet N-hydroxy-3α-methyl-4-aza-5α-cholestane is totally absent from the reduction products.
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14. The reaction seems to come to a standstill. It is suspected that out of the 3E,5E and 3Z,5E isomers present only one reacts and that under the strongly basic conditions interconversion is slow.
15. The specific position of the nmr signal between δ 3.1 and 3.6 due to 6α H indicated that there was a free oxime at C-5 in 14 while an O-methylated one was present at C-5 in 15.
16. This was felt necessary in view of our experience with δ etiynyl oximes whose unusual reactions appear to be confined to 4,5-secosteroids such as 4 and 11.
17. Henceforth the term "nmr" means "^{1}H nmr" Specific mention will be made of ^{13}C nmr where relevant.

18. This is definitely noticeable to a greater extent for 12 than 6.
19. This implies a faster isomerisation than expected from the work of R. E. Gawley and T. Garcia-Pons, Tetrahedron Lett., 1986, 27, 5185. Intramolecular assistance is presumably at work.
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34. This should read ir spectrum or nmr spectrum in place of ir or nmr respectively.

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