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A NOVEL REDUCTIVE CYCLIZATION INVOLVING ATTACK BY AN OXIME ON AN UNCONJUGATED ALKYNE. A NEW ROUTE TO 4-AZA STEROLS.

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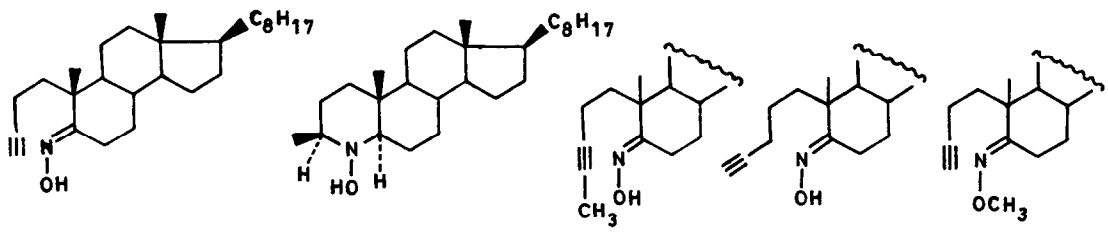
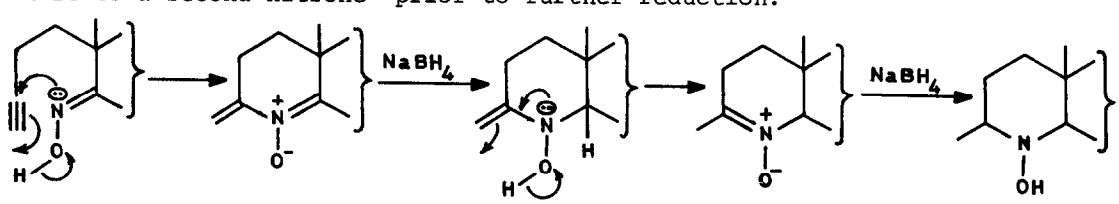
Abstract: N-hydroxy-3-methyl-4-aza sterols were produced by the action of $NaBH_4$ on oximes of δ-ethynyl-5-oxo-4,5-secosterols. An unsaturated nitrone intermediate accounts for this reaction as well as for the facile transformation to dioximes of 3,5-dioxo-4,5-secosterols.

The oxime 1, prepared[2] from 4,5-secocholest-3-yn-5-one, on treatment with $NaBH_4$ in methanol, yielded the reductively cyclized compound 2 in 90% yield[3]. Since this reagent does not normally reduce either an alkyne or an oxime[4] it was clear that some unusual transformation was involved wherein an intermediate susceptible to sodium borohydride reduction was being formed. Another remarkable observation was that the secocholestane derivatives 3,4 and 5 were totally resistant to sodium borohydride reduction under the same conditions.



1 2 3 4 5

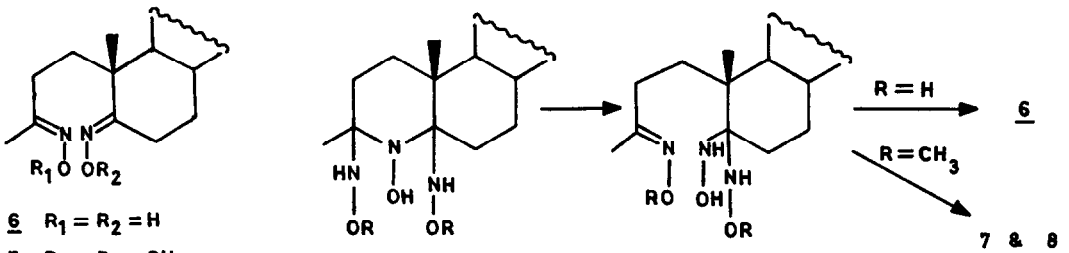
A cyclization demanding appropriate positioning of the triple bond relative to the electron pair on nitrogen as well as to the proton attached to oxygen could account for the selectivity. As shown in Scheme I the cyclization would lead to an unsaturated nitrone readily reducible to a vinyl hydroxylamine. The latter was presumed to undergo a facile [2,3] sigmatropic shift to a second nitrone[5] prior to further reduction.



SCHEME I

Formation of cyclic nitrones by displacement of a chloro[6] or a tosyloxy[7] group to an oxime by attack by the lone pair of electrons on nitrogen is known. But attack on an unconjugated alkyne has not been observed before. Yet the same has also to be invoked to explain the reactions of 1 with excess hydroxylamine and with NH_2OCH_3. The former converts 1[8] to the dioxime 6, while the latter gives a mixture of the di- and mono- ethers 7 and 8. Neither reagent affects compounds 3,4 and 5.

Substituting NH_2OH or NH_2OCH_3 for "hydride" in Scheme I should lead to 9,R=H or 9,R=CH_3. Conversion of former to 6 and the latter to 7 and 8 can be expected to follow[9].



6 $R_1 = R_2 = H$

7 $R_1 = R_2 = CH_3$

8 $R_1 = CH_3$, $R_2 = H$

9

Reactions with $NaBH_4$, NH_2OH and NH_2OCH_3 were also carried out on the dioxime of 4,5-secoandrost-3-yne-5,17-dione. Same transformations were observed as with 1. One notable feature was that in all the corresponding products the oxime at the 17 position was still present.

REFERENCES AND NOTES:

1. *We are grateful to the University Grants Commission, New Delhi, for the award of research fellowships to KGA and PPD.*
2. *Isolation of this monooxime, made by using NH_2OH, HCl and NaOAc in MeOH, was possible only under carefully controlled conditions. It was used immediately.*
3. *Compound 2, besides analysing for $C_{27}H_{49}NO$ had prominent peaks in the mass spectrum at m/e=403(M^+) and 386 (M^+-17). The monoacetate of 2 had IR (nujol) 1770, 1300, 1210, 940 cm^{-1}; ^1H NMR (60MHz,CCl_4)δ2.6 (broad, 1H, 3αH), 2.0 (broad, 1H, 5αH), 1.93 (s,3H, COMe), 1.05 (d,J=5.5Hz, 3H,3βMe), 1.02 (s,3H,19Me), 0.63 (s,3H,18Me). Detailed structural and stereochemical assignments of compounds 1 to 8 will from part of a forthcoming full paper of much wider scope.*
4. *No acid is present. For reduction of oximes with $NaBH_4$ in the presence of acids see G.W. Gribble, R.W. Leiby and M.N.Sheehan., Synthesis., 856 (1977).*
5. *For reactions of nitrones see G.R.Delpierre and M.Lamchen, Quart. Rev. of Chem. Soc. (London), 19, 329 (1965).*
6. *H.R. Brandman and R.T.Conley, J.Org. Chem., 38, 2236 (1973).*
7. *G. Stork, S.D. Darling, L.T. Harrison and P.S. Wharton., J.Amer. Chem. Soc., 84,2018 (1962).*
8. *The dioxime 6 was, of course, produced directly by the action of excess NH_2OH on 4,5-secocholest-3-yn-5-one. We thank P.M. Pradhan for this observation.*
9. *A plausible explanation can be given as to why cleavage of 9 occurs preferentially at the 3,4 bond, but requires assumptions as to the correct stereochemistry of 9.*

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