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TRANSFORMED STEROIDS—XX

DIRECTION OF THE OXIDE CYCLE OPENING OF THE STEREOISOMERIC 16,17-OXIDES OF DEHYDROPREGNENOLONE 20-HYDRAZONE

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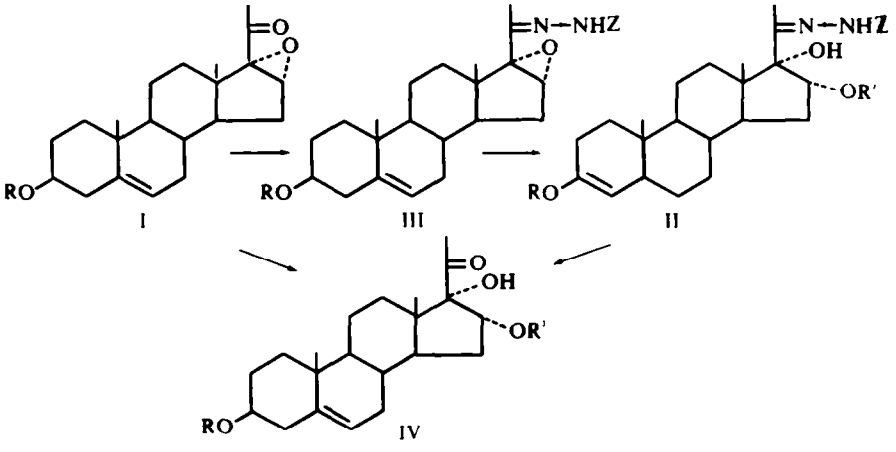
Abstract—Opening of the oxide cycle in stereoisomeric 16,17-oxides of dehydropregnenolone caused by the action of acetic acid in the presence of diphenylhydrazine is strictly selective and takes place at C(17) only. With the 16α,17α-oxide *cis*-opening is the case and results in 16α-acetoxy-3β,17α-dihydroxypregn-5-en-20-one, whereas the 16β,17β-oxide involves a 16 → 17 hydride shift and leads to 3β-hydroxypregn-5-en-16,20-dione. These results corroborate the mechanism of the reaction described as a reversible electronic shift in the hydrazone fragment of the side chain.

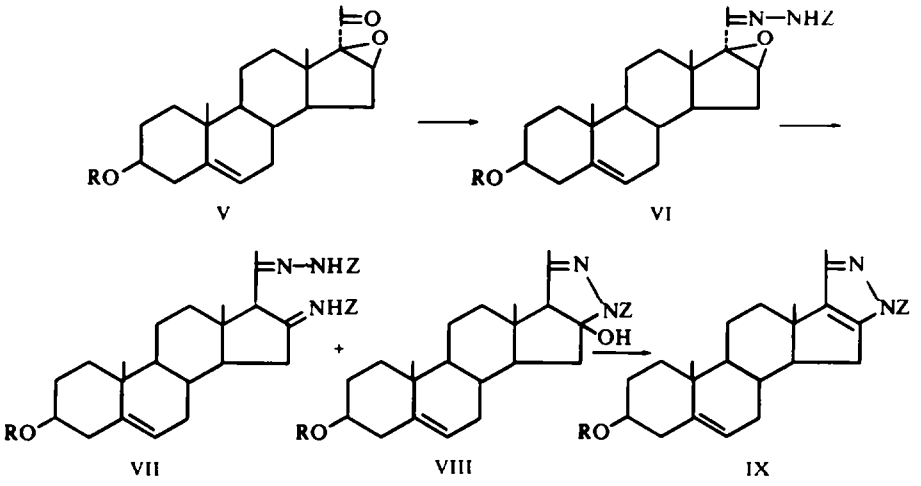
IT IS generally accepted that the interaction of keto-oxides with nucleophillic reagents proceeds as proton-catalysed trans-diaxial opening. However, as originally established by Colton[2] and later by Petrow *et al.*[3] the 16α,17α-oxide of dehydropregnenolone (I) in acetic acid in the presence of hydrazine derivatives yields the 16-acetate of *cis*-16α,17α-diol 20-hydrazone (II, R^1 = Ac) only.

A careful study of this reaction[4,5] has shown that its first step involves the formation of the epoxy hydrazone (III) which undergoes further a sterically abnormal opening of the oxide ring. A cleavage of the C_{17}-O bond take place exclusively with initial formation of the 17-acetate followed by an acetyl group migration which results in the stable 16-acetate.



The reaction of epimeric 16β,17β-oxide (V) with acetic acid in the presence of hydrazine derivatives also proceeds[6,7] with initial formation of the epoxy hydrazone (VI) but its further transformation differs sharply from that observed in the α-series.

Thus 3β-hydroxypregn-5-en-16,20-dione dihydrazone (VII) and 3'-substituted 3β-hydroxyandrost-5-en-(16,17c-2'-hydroxy-5'-methylpyrazoline (VII) are formed instead of 16,17-diol derivatives. A decrease in the amount of hydrazine may result in the exclusive formation of the cyclized derivative. As it might be expected, hydroxypyrazoline (VIII) is readily dehydrated under acidic conditions to yield the corresponding pyrazole (IX).



In the present work the reaction of epoxyketones (I and V) with acetic acid and diphenylhydrazine was investigated. Treatment of the keto-oxide (I) with these reagents resulted in the formation of 16α- acetoxy-3β,17α-dihydroxypregn-5-en-20-one diphenylhydrazone (X) identical to that obtained from the triol 16-acetate (IV, R' = Ac). The 20-diphenylhydrazone (XI) of 3β-hydroxypregn-5-en-16,20-dione has been produced exclusively when the keto-oxide (V) was subjected to the above treatment. The former compound was also obtained from the diketone (XII). No hydrazone formation took place in position 16, presumably due to steric hindrance. The position of the hydrazone group is established by the sodium borohydride reduction of the diketone hydrazone (XI) followed by acetylation to form 3β,16α-diacetoxypregn-5-en-20-one diphenylhydrazone (XIII). The latter was shown to be identical with the sample obtained from 3β-acetoxy-16α-hydroxypregn-5-en-20-one (XIV).

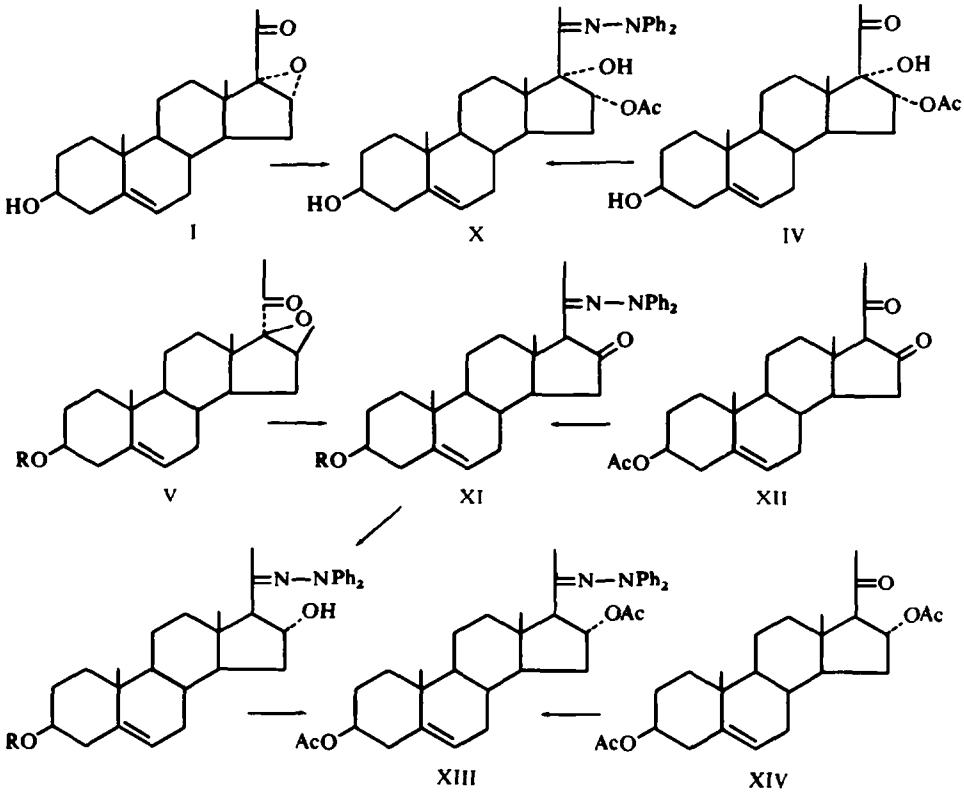
The difference in the reaction of the 16α,17α-epoxy hydrazone (III) and its 16β,17β-isomer (VI) observed provides a basis for speculation on the reaction mechanism.

The C(20) carbonyl C atom is the most electrophilic centre in the original epoxyketones (I and V) therefore the reaction starts with the formation of the hydrazones.

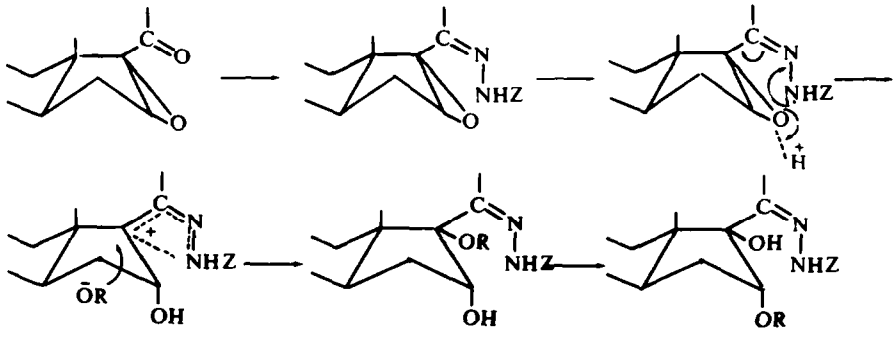
But in the latter it is the epoxide O atom rather than the hydrazone group that acts as a proton-attracting centre.

At the same time a reversible shift of the lone N-electron pair along the conjugated chain seems to occur thus facilitating the C_{17}—O bond cleavage. The resulting cation is stabilized by the conjugation in a fixed configuration determined by the sterochemistry of the side chain in the original hydrazone.

The further destiny of this cation appears to be determined by two factors; (i) presence of adequate amount of nucleophylic reagent in the reaction medium, and (ii) the possibility to attack the appropriate side of the molecule which is determined by the configuration of the stabilized cation, i.e., on the possibility to comply with the electronic and steric requirements of the process.

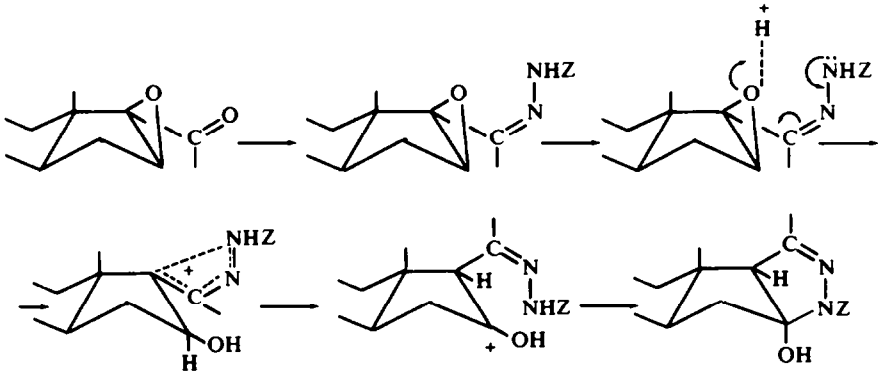


Both requirements may be met when 16α,17α-oxide react in acetic acid or in aqueous dioxan and the reaction proceeds as a nucleophilic attack from the rear side of the molecule (Scheme I).



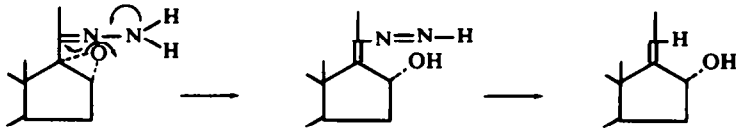
SCHEME 1.

In the case of 16β,17β -oxide hydrazone a front attack at C(17) is known to be hindered. Thus the reaction proceeds through a 16→17 hydride shift followed either by cyclization to pyrazoline or by formation of the 16,20-diketone derivatives (Scheme II).



SCHEME II.

The mechanism postulated has a formal similarity with that suggested by Huang-Minlon for the reduction of 20-keto-16α,17α-oxide[8] to allylic alcohols and by Angelici *et al.*[9] for the reaction of the 16α,17α-oxide (I) with phenylhydrazine under basic conditions (Scheme III).



SCHEME III.

A substantial difference, however, may be observed. In the mentioned schemes the bond shift caused by proton elimination is irreversible whereas only a reversible electronic shift occurs in the mechanism proposed now for the proton catalysed reaction.

Confirmation of this reversibility was found in the oxide ring opening of oxides (I and V) in the presence of diphenylhydrazine since the intermediate hydrazone was deprived of the H atom in the hydrazone fragment and was hence incapable of the irreversible bond shifts.

EXPERIMENTAL

M.ps were determined on a Kofler block. IR spectra were performed on Zeiss UR-10 spectrophotometer in KBr. TLC was carried out on silica gel (KSK, 100–150 mesh, iron free, 20% of water) in ether–petrol, ether solvents with detection by H_2SO_4. Optical rotations were measured in $CHCl_3$ solns.

16α-*Acetoxy*-3β,17α-*dihydroxypregn*-5-*en*-20-one *diphenylhydrazone* (X)

(i) A soln of α-oxide I (500 mg) in AcOH (5 ml) was treated with a soln of diphenylhydrazine (500 mg) in the same solvent (2 ml) for 2 days. The crystalline ppt was crystallized from MeOH and afforded X

(220 mg), m.p. 190–193° (193–194° from ether-heptane), $[\alpha]^{23}$ −20°, (*c* 1·23), R_f 0·43 (Found: C, 75·57; H, 8·07; N, 4·79. Calc. for $C_{35}H_{44}O_2N_2$: C, 75·54; H, 7·91; N, 5·03); IR spectrum: 3550–3400, 1733, 1593, 1495 cm^{-1}. The mother liquor after filtration was poured into water, extracted with $CHCl_3$, the extract washed with water and evaporated. The residue was treated with ether. Evaporation left a mixture (300 mg) of X and the parent α-oxide I which was chromatographed preparatively on two plates (300 × 200 mm) of silica gel (2 mm thickness). The fractions collected were crystallized from MeOH to yield 180 mg of X, m.p. 188–191° and 165 mg of α-oxide I, m.p. 185–188°. The total yield of X was 400 mg.

(ii) The 16-acetate IV (100 mg) was added to a soln of diphenylhydrazine (100 mg) in AcOH (10 ml) and the mixture set aside for 2½ days at room temp. The mixture was then diluted with water and the product isolated with $CHCl_3$. Working up and evaporation gave a crystalline residue, which was crystallized from MeOH to yield X (80 mg), m.p. and mixed m.p. 190–193°.

3β-*Hydroxypregn-5-en*-16,20-*dione* 20-*diphenylhydrazone* (XI, R = H)

A soln of diphenylhydrazine (100 mg) in AcOH (3ml) was added to a soln of V, (R = H; 100 mg) in the same solvent (1 ml) and the mixture was allowed to stand for 20 hr. at room temp. The resulting product was then diluted with water and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with water and evaporated. Crystallization from aqueous MeOH yielded 100 mg of the XI (R = H) 209–211°, $[\alpha]_D^{23}$ −45° (*c* 1·136), R_f 0·39. (Found: C, 80·23; H, 8·25; N, 5·83. Calc. for $C_{33}H_{40}O_2N_2$: C, 79·84; H, 8·06; N, 5·64%); IR spectrum: 3600–3400, 1640, 1595, 1500 cm^{-1}.

3β-*Acetoxypregn-5-en*-16,20-*dione* 20-*diphenylhydrazone* (XI, R = Ac)

(i) A soln of diphenylhydrazine (160 mg) in AcOH (6 ml) was added to a soln of V, (R = Ac); 150 mg), in the same solvent (2 ml) and the mixture was allowed to stand over-night at room temp. The usual treatment produced after crystallization from aqeous acetone 120 mg XI, (R = Ac), m.p. 192–194°, $[\alpha]_D^{23}$ −29° (*c* 0·71) R_f 0·76. (Found: C, 77·90; H, 7·91; N, 5·40. Calc. for $C_{35}H_{42}O_3N_2$: C, 78·01; H, 7·80; N, 5·20%); IR spectrum: 1740, 1655, 1595, 1500 cm^{-1}.

(ii) The monohydrazone XI, (R = H; 30 mg) was acetylated with Ac_2O (0·25 ml) in pyridine (0·5 ml) overnight at room temp. The reaction mixture was worked up in the usual way and the product was crystallized from aqueous MeOH, yielding XI, (R = Ac) m.p. and mixed m.p. 180–183°.

(iii) A soln of diphenylhydrazone (30 mg) in AcOH (1 ml) was added to a soln of XLL (30 mg) in the same solvent (1 ml) and the mixture was allowed to stand for one night. XI, (R = Ac) m.p. and mixed m.p. 190–191° was obtained in the usual way and was recrystallized from aqueous MeOH.

3β,16α-*Diacetoxypregn-5-en*-20-*one* 20-*diphenylhydrazone* (XIII)

(i) A soln of $NaBH_4$ (40 mg) in water (1·5 ml) was added to a soln of XI, (R = Ac; 300 mg) in THF (9 ml) at 0°. The mixture was left overnight at 20° and more $NaBH_4$ (40 mg) was added. The reaction mixture was allowed to stand for one day more at room temp the solvent was evaporated at 20°, diluted with water and extracted with ether. The extract was washed with water and evaporated. Preparative TLC on silica gel followed by crystallization from ether hexane afforded 160 mg evidently 3-acetate hydrazone of 16β-epimer, m.p. 156–158° (in capillary), R_f 0·75, IR spectrum: 3240–3220, 1740, 1595, 1500 cm^{-1} and 50 mg 3-acetate hydrazone XV, m.p. 155–157°, R_f 0·6, IR spectrum 3460–3400, 1735, 1595, 1500 cm^{-1}. (Found: N, 5·23. Calc. for $C_{35}H_{44}O_2N_2$: N, 5·18%). The latter compound was acetylated with Ac_2O in pyridine to XIII, m.p. 172–174° (from aq. MeOH in capillary).

(ii) A soln of XIV (70 mg) and diphenylhydrazine (70 mg) in dioxan (2 ml) was treated with AcOH (0·1 ml).

The mixture was allowed to stand for 2 days at room temp and then diluted with water and extracted with ether. The extract was washed with water and evaporated. Preparative TLC followed by crystallization from aqueous MeOH yielded, a fraction (60 mg. m.p. 155–159°, R_f 0·6), which was acetylated in the usual way to from XIII, m.p. and mixed m.p. 177–178° (from aq. MeOH in capillary). An analytical sample was crystallized from aqueous MeOH and had m.p. 187–189°, $[\alpha]_D^{23}$ -65° (c 1·206), R_f 0·75. (Found: C, 75·92; H, 8·03. Calc. for: $C_{37}H_{45}O_4N_2$, C, 76·29; H, 7·9); IR spectrum: 1733, 1725, 1630, 1595, 1495 cm^{-1}.

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