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SYNTHETIC STUDIES IN STEROIDAL SAPOGENINS AND ALKALOIDS—III

THE SYNTHESIS AND STEREOCHEMISTRY OF ISOMERIC 16-HYDROXY- AND 16-OXO-5,17(20)-PREGNADIEN-3β-OLS*

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Abstract—All the isomers of 5,17(20)-pregnadiene-3β, 16-diol and 5,17(20)-pregnadien-3β-ol-16-one have been synthesized and the structures assigned on basis of NMR spectra. The selectivity of manganese dioxide oxidation of allylic alcohols has indicated that in this reaction abstraction of carbinyl hydrogen is the step which is sensitive to steric hindrance.

IN CONNECTION with a synthetic project on steroidal alkaloids and sapogenins[1] *cis*-5,17(20)-pregnadien-3β-ol-16-one was needed. Huang-Minlon and Chung Tung-shun reported the preparation of a ketone with this gross structure by reaction of hydrazine hydrate with 16α, 17α-epoxypregnenolone,[2] but in our hands, chromatography of the product furnished, in addition to the pyrazole IV, two diol fractions. The fraction, m.p. 182–183° corresponded to that described[2] but was found to be a mixture (later identified as IIa, ca. 75% and IIIa, ca. 25%). The second fraction, m.p. 191–193°, was homogeneous (TLC) and was assigned structure IIa on the basis of its method of preparation, NMR spectrum and subsequent reactions. When the hydrazine reaction was carried out under conventional Huang-Minlon conditions (190–195°) the total diol fraction decreased considerably. Reaction under Wharton conditions[3] (118°), on the other hand, furnished a diol mixture (65%) with increased proportion of the *trans*-isomer IIIa.

Oxidation of the crude diol fraction (182–185°) with manganese dioxide[4] and chromatography of the product on acid-washed alumina afforded pure *cis*-ketone Va and pure *trans*-diol IIIa. Under these conditions the *cis*-diol IIa is selectively oxidized. When a stronger oxidant[5] was used, a complex mixture resulted in which the 3-OH group was partially oxidized to a 3-oxo-4,6-diene system, as evidenced by formation of a di-DNP derivative. Benn and Dodson†[6a] reported having difficulty in selective manganese dioxide (method of preparation not specified) oxidation of an allylic 16-hydroxy-$\Delta^{17(20)}$ system, while Beard *et al.*[7] were able to oxidize both *cis*- and *trans*-17(20)-5α-pregnen-16α-ols with commercial active manganese dioxide. In agreement with our observation, Sciaky and Faccino[6b] have also found the 3-acetate of II is readily oxidized by manganese dioxide, whereas the 3-acetate of III is unaffected.

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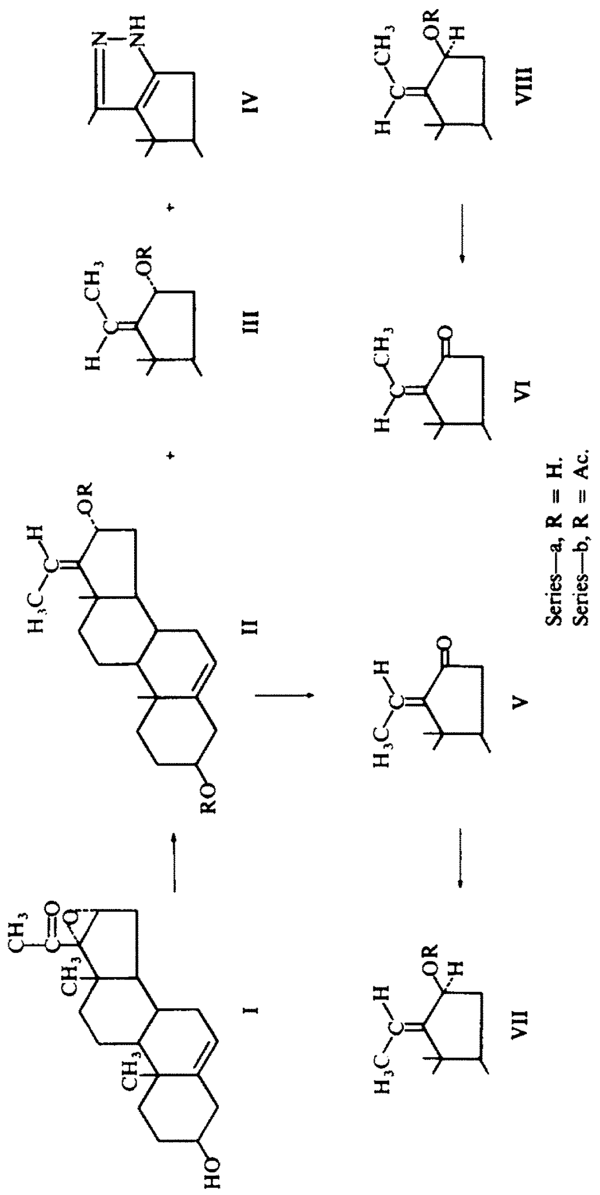
[*] Abstracted from Ph.D. thesis submitted by A. L. Rampal, 1966, Panjab University.

[†] While this work was in progress two communications describing the reaction of hydrazine hydrate with epoxypregenenolone appeared. There are minor differences in physical constants reported for some of the common compounds (Experimental).



Series—a, R = H.
Series—b, R = Ac.

From models it can be seen that the C-21 Me group shields both the C-16 hydrogen and the C-16 OH group to a greater extent in IIIa than in IIa. Resistance to oxidation in IIIa could arise from steric hindrance thus preventing attack of either of these sites by the reagent. In the case of diol VIIIa, the C-16 OH group is more hindered while C-16 hydrogen is relatively accessible. As oxidation of this diol proceeds readily, it seems that in manganese dioxide* oxidation of allylic alcohols the critical step which is sensitive to steric hindrance is the abstraction of carbinyl hydrogen.[8,9] The distance between the C-18 hydrogen and the 16--hydroxyl oxygen atom, as estimated from Dreiding models, is about 4 Å in the diol VIIIa, and any steric acceleration of oxidation in this compound may be considered unimportant.[10]

Both *cis*-Va and *trans*-VIa ketones are reasonably stable to diffused day light. Only on prolonged standing isomerization is detected. This is in contrast to observation of Beard *et al.*[7] who reported extreme light sensitivity of similar *cis*- and *trans*-ketones. Equilibration to a 1 : 1 mixture, however, readily occurs in presence of bases. The *trans*-ketone VIa gives the expected pink 2,4-dinitrophenylhydrazone, while this derivative of the *cis*-ketone Va is distinctly lighter in colour, suggesting pyrazoline formation. A cyclic structure, however, is not supported by the IR spectrum of the DNP of Va.

In order to complete the series, 16β-*cis*-diol VIIa was synthesized by reduction of the *cis*-ketone Va. The stereochemistry of the four isomeric diols and the two ketones was largely adduced from NMR spectral evidence. The relevant frequencies are given in Table 1. As a basis for assignment, similar compounds have been described,[6a,7] and only features of fresh interest are discussed here.

TABLE 1. NMR SPECTRA OF ISOMERIC DIOLS AND KETONES

Compound	C-18 Methyl proton	C-20 Vinylic proton	C-21 Methyl proton
IIa (X)	55		102, 109
IIb (X)	55		100, 108
IIIa (X)	46		101, 108
IIIb (X)	47		92, 99
IIIb (Y)	48		92, 99
VIIIa (X)	56		98, 105
VIIIb (X)	55		91, 97
VIIa (X)	63		100, 108
VIIb (Y)	62		98, 106
Va (X)	64	390	108, 115
Va (Z)	47	397	88, 96
VIa (X)	57	343	122, 129
VIa (Z)	43	238	125, 132

The downfield shift of ca. 10 c/s in the position of the C-18 Me resonance, observed in IIa and VIIIa as compared to IIIa has been attributed by Benn and Doddson[6a] to the deshielding effect of the β-oxygen in VIIIa and of the C-21 Me group in IIa. In confirmation of this explanation a paramagnetic shift of about 17 c/s has been observed in C-18 Me absorption of the diol VIIa in which both the above factors are operative. In fact in the diacetate VIIb, the C-18 and C-19 peaks coincide, whereas in the diol VIIa the former appears 1 c/s lower field, which is unusual in normal steroids.[11]

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* These conclusions about the mode of oxidation are valid only for the type of manganese dioxide used.

It has been observed[12] that in the NMR spectra of ketones, a change of solvent from deuterio-chloroform to benzene causes a shift which is dependent on the position of the absorbing proton relative to the CO group. In the *cis*-ketone Va the C-21 Me protons which are in front of the reference plane show an upfield solvent shift, whereas the C-20 vinylic proton which is behind this plane moves downfield in changing from deuteriochloroform to deuteriobenzene. Converse solvent shifts obtain in the *trans*-ketone VIa, thereby confirming the assigned stereochemistry.

The calculated molecular rotatory contribution for acetylation of 16β-OH group in *cis*-diol VIIa is −24 as compared to the literature[13] value of +64. A similar deviation, but in opposite direction, for acetylation of *cis*-diol IIa has been observed by Benn and Doddson.[6a] Both the *trans*-diols IIIa and VIIIa exhibit the expected molecular rotaroty contributions for acetylation. The deviation in the *cis*-series is considered to reflect distortion of ring D in 17(20)-pregnenes with this configuration.[6a]

EXPERIMENTAL

M.ps are uncorrected. Microanalyses are by Mr. B. N. Anand, Panjab University, Chandigarh. TLC were run on silica gel (N.C.L., Poona) impregnated with 15% plaster of Paris. Ether, pet. ether (40–60°) and AcOEt (5:5:1) mixture was used for developing the plates. Relative amounts of compounds in mixture were estimated from intensity and size of spots, and the values are **approximate**. Acetylations were carried out at room temp overnight with pyridine and Ac_2O. The spectra were recorded on a Varian A-60 spectrometer at 60 Mc/s. The numbers indicate resonance frequencies of protons expressed in c/s in direction of decreasing field strength relative to an internal TMS standard. X, Y and Z refer to $CDCl_3$, CCl_4 and deuteriobenzene respectively as solvents.

16α, 17α-Epoxy-5-pregnen-3β-ol-20-one (I). The epoxide I, m.p. 187–190°, was prepared according to the method of Julian *et al.*[14]

Reaction of hydrazine hydrate with epoxide I

Method A. A mixture of hydrazine hydrate (6 ml, 80%), epoxide I 3·0 g), KOH (3·0 g) and diethylene glycol (30 ml) was refluxed at 120° for 1 hr. The condenser was removed and a temp of 160° maintained for 3 hr. The mixture was cooled and diluted with water, dried (2·8 g, m.p. 185–193°) and chromatographed on alumina (60 g). Benzene-$CHCl_3$ (5:1) eluted a solid (1·4 g) which after crystallization from benzene melted at 182–183°. TLC showed it to be a mixture of two products (R_f 0·38, 75%; R_f 0·45, 25%). Further elution with benzene–$CHCl_3$ (1:1) furnished material (150 mg), m.p. 191–193° which was homogeneous on TLC (R_f 0·38). Crystallization from benzene afforded pure *cis*-diol IIa, m.p. 192·5–193°, $[\alpha]_D$ −83°. (Found: C, 79·95, H, 10·13. Calc. for $C_{21}H_{32}O_2$: C, 79·70; H, 10·19%.) Lit. m.p.[2] 182–183°, $[\alpha]_D$ −89°; m.p.[6b] 197–198°, $[\alpha]_D$ −82°; m.p.[6a] 190–191·5°, $[\alpha]_D$ −89°. The diacetate of the diol IIa was crystallized from MeOH, m.p. 161–163°, $[\alpha]_D$ −80°. (Found: C, 75·23; H, 8·98. Calc. for $C_{25}H_{36}O_4$: C, 74·96; H, 9·06%.) Lit. m.p.[6b] 160–162°, $[\alpha]_D$ −83·5°; m.p.[6a] 163–165°, $[\alpha]_D$ −89·5°.

The pyrazole IV (110 mg) was eluted from the above chromatogram with EtOH, m.p. 302–305°, $[\alpha]_D$ −77°. Lit. m.p.[2,6] 302–304°.

Method B. The reaction was carried out at 190–195° for 5 hr and the mixture worked up as above. The total diol fraction isolated was about 30%.

Method C. A suspension of the epoxide (1·0 g) in hydrazine hydrate (10 ml, 98%) was heated at 90° for 1 hr and then refluxed at 118° for another hr. The reaction mixture was processed as above. Total yield of the diol fraction was 630 mg (65%). Comparative TLC with method A product showed that the proportion of the *trans*-diol IIIa was greater in the mixture.

Manganese dioxide. Manganese dioxide A was prepared according to the method of Attenburrow *et al.*,[5] and manganese dioxide B according to the procedure of Mancera *et al.*[4]

Oxidation of the diol mixture with manganese dioxide A. A soln of the diol mixture (Method A, 100 mg) in $CHCl_3$ (15 ml) was shaken with MnO_2 A (10 g) for 30 hr at room temp and then filtered. Evaporation of $CHCl_3$ yielded a gum which resisted crystallization. On treatment with DNP reagent a mixture of derivatives separated, from which a pure DNP was obtained by repeated crystallization from AcOEt, m.p. 217–218°. (Found: N, 16·45; $C_{33}H_{34}N_8O_8$ requires: N, 16·70%.)

Oxidation of the diol mixture with manganese dioxide B. A soln of the diol mixture (method A, 2·26 g) in $CHCl_3$ (200 ml) was shaken with MnO_2 B (23 g) at room temp till complete disappearance (TLC) of the *cis*-diol IIa (ca. 30 hr). The solid was removed by filtration and the solvent was distilled off to obtain a crystalline residue which was chromatographed on acid-washed alumina (20 g). Pet ether (40–60°)-benzene (1:1) eluted V (1·1 g, 50%), m.p. (159–160°. Two crystallizations from acetone raised the m.p. to 172–172·5°, $[\alpha]_D$ −208°, ν_{max} 1710, 1645 cm^{-1}. (Found: C, 80·18; H, 9·965. Calc. for $C_{21}H_{30}O_2$: C, 80·21; H, 9·62%.) Lit. m.p.[2] 164–166°, $[\alpha]_D$ −219°.

An ethanolic soln of this ketone gave a pink DNP derivative which soon changed into a yellow solid. It was purified by repeated precipitation from $CHCl_3$ soln by addition of pet. ether (40–60°), m.p. 241–242°, ν_{max} 3560, 3325 cm^{-1}, λ_{max} 382 mμ, ε 16,400. (Found: N, 11·28. $C_{27}H_{34}N_4O_5$ requires: N, 11·31%.)

Elution of the above chromatogram with benzene and benzene–$CHCl_3$ (1:1) gave another fraction, m.p. 175–185°. Three crystallizations from acetone afforded pure *trans*-diol IIIa, m.p. 219–220°, $[\alpha]_D$ −71°. (Found: C, 79·65; H, 10·22. Calc. for $C_{21}H_{32}O_2$: C, 79·70; H, 10·19%.) Lit. m.p.[6b] 218–220°, $[\alpha]_D$ −84·5°, m.p.[6a] 219–222°, $[\alpha]_D$ −73°. The diacetate crystallized from MeOH, m.p. 150–151°, $[\alpha]_D$ −114°. (Found: C, 75·10; H, 9·10. Calc. for $C_{25}H_{36}O_4$: C, 74·96; H, 9·06%.) Lit. m.p.[6b] 134–136°, $[\alpha]_D$ −95°, m.p.[6a] 149–151·5°, $[\alpha]_D$ −116°.

cis-5,17(20)-Pregnadiene-3β, 16β-diol (VIIa). A slurry of *cis*-ketone V (500 mg), LAH (300 mg) and ether (100 ml) was stirred at 0° for 3 hr. Excess reagent was decomposed by addition of water (1 ml) and 50 KOHaq (2 ml) and the mixture was filtered leaving a cake which was extracted with ether. The combined ethereal extract was washed with water and dried. The residue left after evaportation of solvent was crystallized from benzene to obtain VIIa (400 mg, 80%), m.p. 195–197°. Three more crystallizations furnished an analytical sample, m.p. 198–199°, $[\alpha]_D$ −30°. (Found: C, 79·55; H, 10·21. $C_{21}H_{32}O_2$ requires: C, 79·70; H, 10·19%.) The diacetate crystallized from MeOH, m.p. 131–133°, $[\alpha]_D$ −35°. (Found: C, 74·78; H, 9·00. $C_{25}H_{36}O_4$ requires: C, 74·96; H, 9·06%.)

trans-5,17(20)-Pregnadiene-3β, 16β-diol (VIIIa). This diol, m.p. 182–183°, was prepared according to the method of Benn and Dodson.[6a]

Oxidation of VIIIa *with manganese dioxide B.* The diol VIIIa (25 mg) in $CHCl_3$ (3 ml) was oxidized with MnO_2 B (250 mg) as above. TLC of the crude product revealed almost complete oxidation. It was chromatographed on acid-washed alumina (5 g). Crystallization from AcOEt of the solid (20 mg) obtained from benzene–pet. ether (40–60°) fraction furnished pure *trans*-ketone VIa, m.p. 144–145°, $[\alpha]_D$ −255°, ν_{max} 1645, 1710 cm^{-1}. (Found: C, 80·36; H, 9·57. Calc. for $C_{21}H_{30}O_2$: C, 80·21; H, 9·62%.)

A pink DNP derivative obtained in the usual way was crystallized from EtOH, m.p. 220–221°; ν_{max} 3560, 3325 cm^{-1}; λ_{max} 380 mμ, ε 20,600. (Found: N, 11·43. $C_{27}H_{34}N_4O_5$ requires: N, 11·31%.)

Isomerization of the cis-*ketone* V. A soln of *cis*-ketone V (20 mg), $KHCO_3$ (200 mg) and water (2 ml) in MeOH (10 ml) was refluxed for 1 hr. The solvent was evaporated, the residue was washed with water and dried. On TLC it was found to be a mixture (ca 1:1) of *cis*-ketone V (R_f 0·62) and *trans*-ketone VI (R_f 0·72).

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