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CYCLIC STEROIDAL HYDROXAMIC ACID DERIVATIVES

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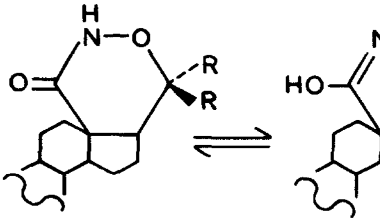
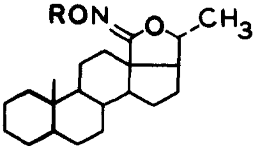
On oxidation of 18-oximino-20-hydroxypregnane derivatives with sodium N-chlorobenzenesulfonamide (chloramine B) (CB), Hora (1) reported that 6'-methyl-tetrahydro-1'2'-oxazino-(4',5': 13β, 17β)-18-norandrostane derivatives (I) were produced. The principal evidence for the existence of the tetrahydrooxazine ring was IR absorption at 3470 cm^{-1} (interpreted as NH), 3603 cm^{-1} (OH), 1640 cm^{-1} (C=N), and 1766 cm^{-1} (interpreted as C=O). Moreover, conversion of such products to a steroidal 18-carboxylic acid 18→20-lactones by means of nitrous acid was regarded as favoring the oxazine structure, since Noland *et al*. (2) had described a similar rearrangement of tetrahydrooxazines.

In the course of our work on C-18 functional steroids (3,4) we have attempted oxidation of the C-20 hydroxy group in 18-oximino steroids with N-bromoacetamide (NBA) in Et_2O-MeOH-H_2O and obtained mixtures of cyclic products. For example, treatment of IV with NBA gave compound A, $C_{21}H_{33}NO_2$ (mass spectrometry), m.p. 180-182°, [α]D-7°, identical with material made from the same starting material and CB by the method of Hora (1). 20β-Hydroxy-5α-pregnan-18-oic acid 18→20-lactone, m.p. 161-163°,

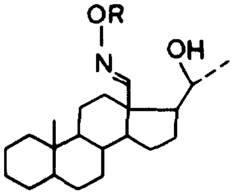


I R = H or CH_3



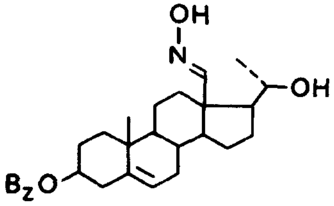
II R = H

III R = CH_3

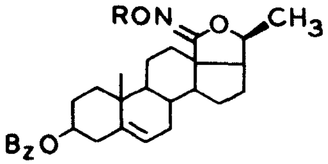


IV R = H

V R = CH_3

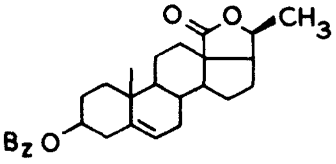


VI

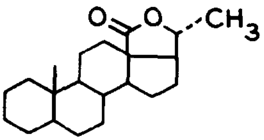


VII R = H

VIII R = NO



IX



X

[α]D + 11°, was isolated as a second product from the NBA reaction.

A clue that the oxazine structure is incorrect was given by the IR spectrum (CCl_4 solution) of A (Fig. 1) which showed only very small absorption at 3460 cm^{-1} and a larger band at 3600 cm^{-1}. The spectrum in $CHCl_3$ is essentially the same. These bands apparently correspond to the NH and OH absorption described by Hora. It is pertinent that the tetrahydrooxazines obtained by Noland show as the bands of highest frequency only ν_{max} 3390, 3160 cm^{-1} ($CHCl_3$) and that O-alkyl hydroxamates (5) (RC(O)NHOR) exhibit ν_{max} at frequencies no higher than 3470 cm^{-1} in all solvents examined. We observed bands at 1640 and 1670 cm^{-1} (CCl_4:$CHCl_3$) and 1670 cm^{-1} (KBr), but no 1766 cm^{-1} band was seen. Moreover, the 1766 cm^{-1} peak assigned to C=O by Hora does not agree in position with the C=O peak (1660-1675 cm^{-1}) of the tetrahydrooxazines of other workers (4,5).

Because of these anomalous spectral features, a chemical proof of structure was undertaken. Methylation of IV (CH_3I-Ag_2O) gave the oxime methyl ether V, m.p. 139-140°; [α]D + 27°. Treatment of V with NBA in ether-methanol-water produced a product, m.p. 133-134°; [α]D - 13°, identical with material obtained by methylation (CH_3I-Ag_2O) of compound A.

The only possible explanation for these facts is that the supposed tetrahydrooxazines are in fact cyclic alkyl hydroxamic acids. Thus, compound A would correspond to II and its methylated derivative to III. The obtainment of hydroxamic acid derivatives under these conditions is not wholly unexpected, as in presence of hypohalite, oximes are known (6) to form hydroxamic acid halides which react readily with alcohols to afford alkyl hydroxamic acids.

A reinvestigation of the nitrous acid degradation of the supposed tetrahydrooxazines was also undertaken. Treatment of VI with CB gave material which we formulate as VII; m.p. 205-209°; ν_{max}^{KBr} 3605, 3455, 1675 cm^{-1}; [α]D + 4°, (lit. (1) m.p. 207-209°; ν_{max} 3600, 3469 cm^{-1}

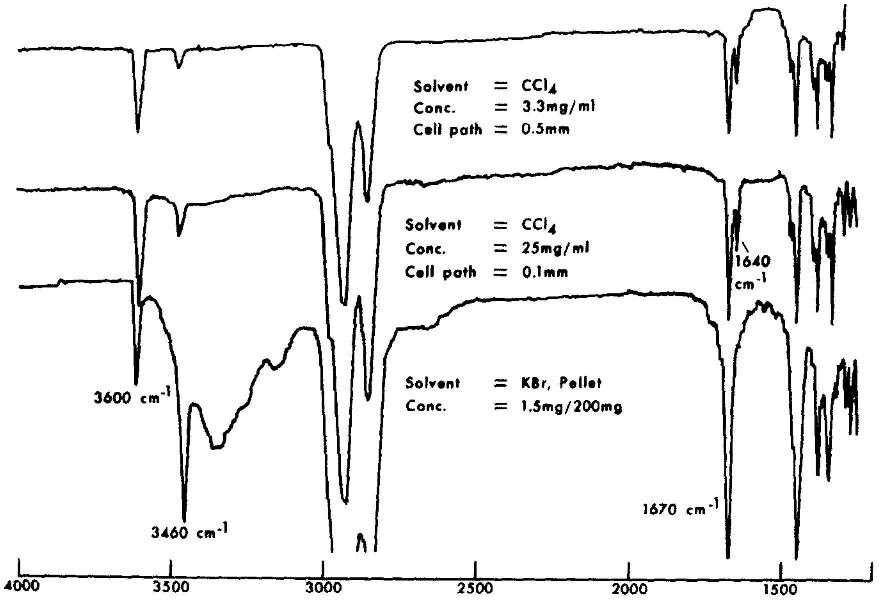


Fig. 1 : **Infrared spectra of 18-oximino-18→20-epoxy-5α-pregnane (II)**

for material obtained in the same way). The action of nitrous acid on VII gave VIII, m.p. 213-215°; ν_{max}^{KBr} 1710 (benzoate C=O), 1640 (C=N), 1565 (N=O) cm^{-1}, apparently identical with a product of unassigned structure, m.p. 218-219°, isolated in 64% yield by Hora (1) in the same way. No trace of the lactone IX, produced in 21% yield by Hora was produced under these conditions, although direct hydrolysis of II (10% H_2SO_4 in 95% ethanol, reflux for 24 hr.) have the corresponding 18-oic acid 18→20-lactone, m.p. 160-161°; ν_{max}^{KBr} 1755 cm^{-1}; [α]D + 11°, in 35% yield, together with starting material. It is noteworthy that the N=O and C=N bands in IX (1565 and 1640 cm^{-1} respectively) correspond well with nitrimines (7) (1560-1580 cm^{-1} for N=O) but not with nitroso derivatives of authentic tetrahydrooxazines (2,8) [1515-1520 cm^{-1} (N=O), and 1730-1748 cm^{-1} (C=O)]. Moreover, although Noland (2) reported that nitroso derivatives of authentic 1,2-oxazino-3-ones hydrolyze readily, VIII was unaffected after refluxing for 48 hrs. in 95% ethanol.

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