Tetrahedron Letters No.21, pp. 2265-2269, 1966. Pergamon Press Ltd.
Printed in Great Britain.

THE STEREOCHEMISTRY OF 10-HYDROXY-3,5-CYCLOSTEROIDS

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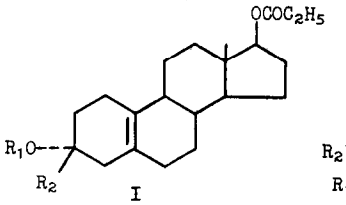
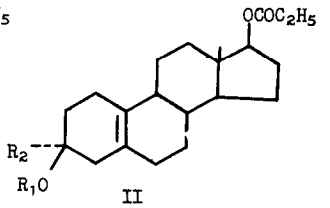
(Received 14 February 1966)

We have reported (I) that solvolysis reactions of the 5(10)-unsaturated 3α- and 3β- mesylate esters Ia and IIa take place with



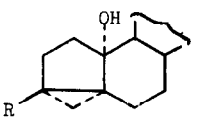
I



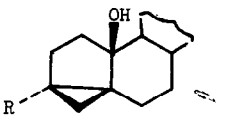
II

a: $R_1 = CH_3SO_2$, $R_2 = H$ b: $R_1 = CH_3SO_2$, $R_2 = D$ c: $R_1 = H$, $R_2 = D$

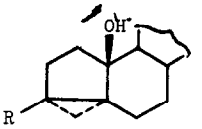
double bond participation as evidenced both kinetically (in HOAc) and by the formation (in aqueous acetone) of 10-hydroxy-3,5-cyclosteroids which were tentatively assigned structures IIIa and IVa, respectively.



III



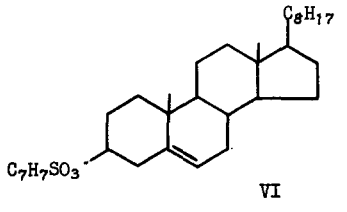
IV



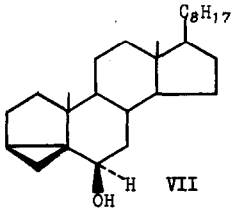
V

a: R = H b: R = D

These transformations may be viewed as homoannular variants of the familiar isosteroid transformation (2) of cholesteryl tosylate (VI) to i-cholesterol (VII) and it was by this presumed analogy that the stereoformulas IIIa and IVa were suggested.



VI



VII

In a similar solvolysis study (employing 17-keto analogs of I and II), W. F. Johns (3) was led to identical stereochemical conclusions except that the C-10 configuration of the α-mesylate solvolysis product was left unassigned. It was pointed out that, though a 10α-alcohol structure (as III) might be expected on stereoelectronic grounds, this would at the same time require ring B to assume a boat form. On the other hand, conversion of the α-mesylate to a 10β-alcohol (as V) entails no such encumberance and was considered by Johns to be mechanistically admissible. We wish to present spectroscopic (NMR) evidence in support of this latter formulation.*

Our originally proposed structures IIIa and IVa for the two solvolysis products both contain the angular hydroxyl and C-4 methylene groups as cis substituents on the newly formed 5-membered ring and the mutual proximity of these groups is clearly seen in models. If the α-mesylate solvolysis

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* Our attempts to investigate these configurational questions by chemical means have so far failed.

product is represented not by IIIa but by the 10β-alcohol structure Va, then the two groups would be trans oriented and relatively distant. We had expected that these two possibilities would be distinguishable by NMR methods since it is by now well established that hydroxyl groups exert a pronounced deshielding effect on spacially proximate protons (4).

The spectra of both solvolysis products were examined with particular attention to the high field (cyclopropane)region.* The pertinent signals were exceedingly complex, however, and partly overlapped with other high-field resonances. This difficulty was circumvented through the synthesis of the corresponding 3-deuterated derivatives.

Cautious addition of ethereal $LiAlD_4$ (1 equivalent) to a cold (-20°) stirred solution of 17β-hydroxy-estr-5(10)-en-3-one propionate in ether led to a mixture of the 3-deuterio-3α- and 3β- alcohols Ic and IIc. The pure epimeric alcohols, obtained by chromatography on alumina, were free of C-3 proton signals but were otherwise identifiable with the corresponding nondeuterated samples (1). The derived mesylate esters Ib and IIb, after solvolysis in buffered (KOAc) aqueous acetone at 80°, gave 3,5-cyclosteroids m.p. 129-131° and 113-114°, respectively. Neither melting point was depressed on admixture with the previously described (1) nondeuterated analog. Each product showed a weak but sharp absorption band in the infrared near 3050 cm^{-1}, whereas the deuterium-free compounds displayed doublets in this region.

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* All NMR spectra were run at 100 Mc/sec. on a Varian HA-100 spectrometer. Tetramethylsilane was employed as an internal standard (0.0 ppm) but the spectra were first obtained in its absence so as to avoid obscuring high field signals.

The 100 mc NMR spectra (figure 1) of the deuterated cyclosteroids proved to be strikingly informative. The C-4 methylene protons of the

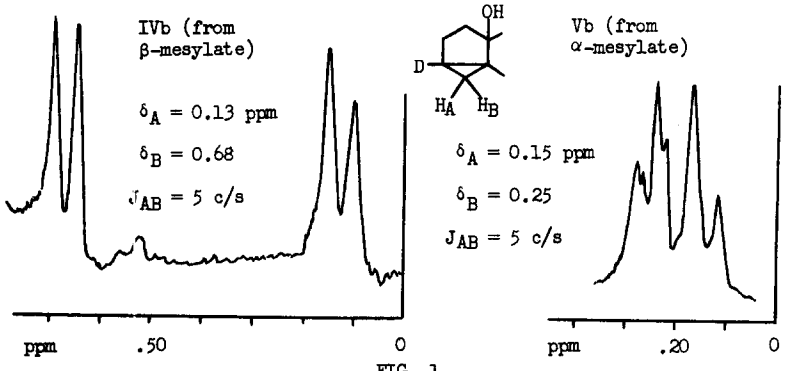

FIG. 1
NMR spectra (high field) of solvolysis products IVb and Vb in $CDCl_3$

β-mesylate solvolysis product are widely separated in chemical shift and give rise to an AX pattern. For reasons discussed above, this confirms its previous formulation as IVb in which the juxtaposition of the angular hydroxyl group and the 4β- proton is evident in a model. The C-4 methylene protons of the α-mesylate solvolysis product are, by contrast, relatively close in chemical shift and appear as an AB quartet.*+ The latter result

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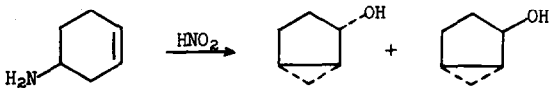
* The low field half of this quartet is further split by long range proton coupling which is removed by irradiation at 2.32 ppm. We wish to thank Prof. C. Moreland for skillfully performing the decoupling experiment.

\+ Rerunning these spectra in benzene solution caused only a general upfield shift (0.10-0.12 ppm) of the cyclopropane proton resonances. Changing to dimethyl sulfoxide - d_6, however, noticeably altered the cyclopropane region of compound IVb. The chemical shift difference between the 4α- and 4β- protons was now increased to approximately 0.67 ppm.

can not easily be reconciled with formula IIIb in which the angular hydroxyl and cyclopropane methylene groups are cis. This product must, then, be assigned the trans structure Vb.

It appears that the stereochemistry of the incoming hydroxyl group in the above solvolysis reactions is influenced by product stability and is not governed stereoelectronically by the configuration of the leaving group. This conclusion is clearly in agreement with Hanack's recent finding (5) that nitrous acid deamination of Δ^3-cyclohexenylamine gives comparable amounts of cis- and trans- bicyclo[3.1.0]hexanol-2 along with monocyclic products.*



Acknowledgment: This work was supported by Grant AM 09279 from the National Institute of Health, U. S. Public Health Service.

* We are very grateful to Prof. Hanack for kindly providing copies of the unpublished NMR spectra of these substances. We had hoped that they would provide models for our compounds IVa and Va but the complexity of these curves prevented the required analysis.

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