Tetrahedron Letters No.14, pp. 1725-1728, 1968. Pergamon Press. Printed in Great Britain.

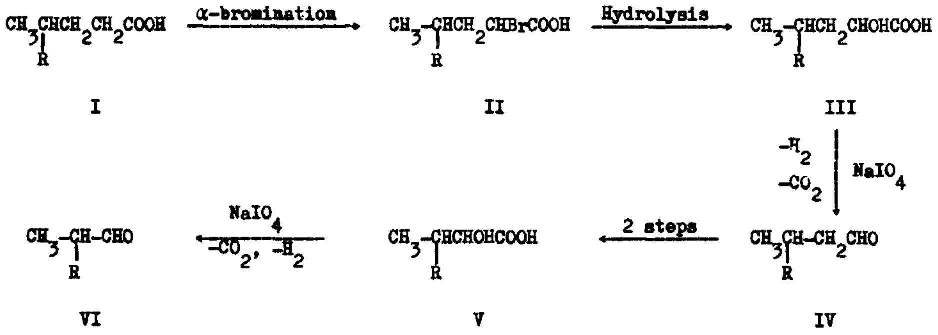
BILE ACID CHEMISTRY. III[1]. STEPWISE SIDE-CHAIN SHORTENING BY WAY OF SODIUM PER-IODATE OXIDATION OF α-HYDROXY BILE ACIDS INTO CORRESPONDING ALDEHYDES.

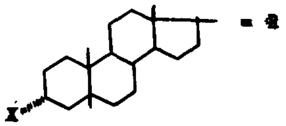
Yehuda Yanuka, Robert Katz and Shalom Sarel

Department of Pharmaceutical Chemistry, The Hebrew University School of Pharmacy,
Jerusalem, Israel

(Received in UK 27 December 1967)

We wish to report a new method for the stepwise degradation of the side-chain in bile-acids, in which one carbon atom is eliminated each time, as formulated below :





Ia, IIIa, IVa, X = OH

Ib, IIIb, IVb, X = H

Unlike the Barbier-Wieland route[2], the end products in this method are the corresponding aldehydes, which are accessible otherwise[3-6].

Although the periodate oxidation of α-hydroxy-acids has incidentally been reported for analytical purposes[7], no record of its utilization in aldehyde synthesis has been hitherto known, to our knowledge. This communication describes the preparation of two new steroidal aldehydes, 3α-hydroxy-nor-cholanal (IVa) and nor-cholanal (IVb), by sodium periodate oxidation of 3α,23-dihydroxy-cholanic acid (IIIa) and 23-hydroxy-cholanic acid (IIIb), respectively.

The α-hydroxy acids, IIIa (m.p.230°-231°) and IIIb (m.p.185°, $[\alpha]_D^{23}$ + 20°(EtOH,ca.2%) were available in high yields through the Sarel-Yanuka-Shalon method (I ⟶ II ⟶ III)[8].

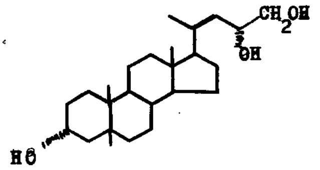
To a solution of IIIa in a 4:2:1-mixture of acetone:acetic acid:water, an excess of sodium periodate was added and stirred for 24 hrs., at 40-50°. The corresponding aldehyde, IVa, was readily isolated in pure form and in 90% yield, m.p.145°, $[\alpha]_D^{27}$ + 13°($CHCl_3$, ca.1%). Its structure derived from (i) its analysis (*anal*.found for $C_{23}H_{38}O_2$: C,79.1; H,10.6); (ii) infrared spectrum showing typical bands (cm^{-1}) at 2700 $(-\overset{O}{\overset{\|}{C}}-H)$ and 1715 (aldehydic carbonyl); and (iii) its nmr spectrum[9], exhibiting resonances attributable to one aldehydic proton (quartet centered at τ 0.19, J=2.5 cps) and one hydroxylic proton (τ 6.58).

Likewise, 23-hydroxy-cholanic acid (IIIb) furnished nor-cholanal (IVb) in 90% yield, m.p.133-135°, $[\alpha]_D^{27}$ + 8.0° ($CHCl_3$, ca.1%).

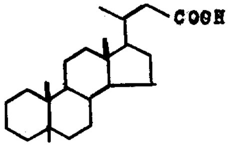
Anal. calcd. for $C_{23}H_{38}O$: C,83.6; H,11.6.
Found: C,83.6; H,11.8.

The presence of an aldehydic grouping in IIIb was inferred from (i) the infrared spectrum, showing absorption at 2700 cm^{-1} and 1730 cm^{-1}, and (ii) its nmr spectrum (CCl_4), giving resonance at τ 0.34 (1H,, J=2.5 cps).

For identification purposes, IIIa was first reduced by lithium aluminium hydride to give the corresponding triol, VII (m.p.223°; $[\alpha]_D^{23}$ + 26° (EtOH, ca. 2%); *anal*. found for $C_{24}H_{42}O_3$:75.9; H,11.1) and then oxidized by sodium periodate, using mixtures of either ethanol:acetic acid:water, or acetone:acetic acid:water, as solvents providing in quantitative yield the desired hydroxy-aldehyde, which was compared with IVa, obtained by the IIIa ⟶ IVa route. They were shown to be identical in all respects.



VII



VIII

Unlike the triol (VII), the α-hydroxy-acids IIIa and IIIb showed product dependence on solvent in the sodium periodate oxidations. Replacement of acetone by ethanol as a component in the solvent mixture, using IIIb as substrate, resulted in lower yields of the aldehyde (IVb). In addition we were able to isolate from the reaction mixture substantial amounts of its higher oxidation product, nor-cholanic acid (VIII) (m.p.176°, reported[10] m.p.175.5°-176.5°).

Furthermore, the yields in the III ⟶ IV conversions tend to increase as the reaction temperature increases. The yields of IVa and IVb increased from 20% to 50% to 90%, when the reaction temperature changed from 10-15° to 25-30° to 40-50°, respectively, while the reaction time (24 hrs) was kept the same throughout. We observed that, although the aldehydes (IVa and IVb) lent themselves to slight oxidation, its effect on the yields, however, was negligible after a period of 24 hrs.

That the formation of VIII cannot derive appreciably from the IVb ⟶ VIII path, was also evidenced from the isolation of sizable amounts of a labile compound, showing higher Rf valve than VIII in the TLC, and in the IR spectrum exhibited ethereal bands at 1060 cm^{-1} and 1100 cm^{-1}, which was completely converted into VIII on silica gel column. With a view to shed light on the mechanism of the reaction, structural study on this precursor is currently in progress.

For obvious reasons we performed a comparative study on the lead tetraacetate oxidation of IIIa and IIIb. We found that the reaction gave rise to a complex mixture, from which the desired aldehydes could be isolated in 50% yield, at most.

Detailed account on the utility of the IV ⟶ V ⟶ VI route in degradative work will be given in the full paper.

REFERENCES

1. Part I, S.Sarel and Y.Yanuka, J.Org.Chem., 24, 2018 (1959),
Part II, S.Sarel, Y.Yanuka and Y.Shalon, Israel J.Chem., 5, 48p (1967).

2. W.M.Hoehn and H.L.Mason, J.Amer.Chem.Soc., 60, 1493 (1938);
G.Lehman, L.Koppe and G.Hilgetag, J.prakt.chem., 32, 217 (1966).

3. A.Vern McIntosh, A.M.Searey, E.M.Meizer, and R.H.Levin, J.Amer.Chem.Soc., 71, 3317 (1949).

4. R.H.Levin, A.Vern McIntosch, and G.B.Spero, U.S.P. 2,623,054; Chem.Abst., 47, 10560 (1953).

5. H.Yashima, J.Biochem. (Japan), 54, 47 (1963).

6. K.E.Pfitzner and J.G.Moffatt, J.Amer.Chem.Soc., 87, 5661 (1965)

7. P.Fleury and J.Courtois, Bull.soc.chim.France, 190 (1948); Compt.rend., 237, 1019 (1953)

8. S.Sarel, Y.Yanuka, and Y.Shalon, Neth.P. 6,414,156 (1965); U.S.Patent 3,342,813 (1967); Brit.Patent 1,081,929 (1967).

9. NMR spectra were taken on an A-60 Varian, NMR Spectrograph in $CDCl_3$ or CCl_4 with TMS as internal reference.

10. J.W.Cook and G.A.D.Haselwood, J.Chem.Soc., 428 (1934).