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# ASYMMETRIC SYNTHESIS AND CONFIGURATIONAL ASSIGNMENT OF (23R)-HYDROXYCHOLANIC ACID. BASE-INDUCED OXIDATIVE-HYDROLYSIS OF 23-BROMOCHOLANAL

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Previous work [1] has shown that monobromination followed by hydrolysis and periodate oxidation of steroid aldehydes provides a facile means for the stepwise degradation of the bile acid side chain. The hydrolysis of the bromoaldehyde by KOH-EtOH under nitrogen was shown to involve the intermediacy of the corresponding hydroxy-semiacetal [1b].

We report a novel stereospecific synthesis of the hitherto unknown (23)-hydroxycholanic acid (Va) by way of base-induced oxidative-hydrolysis of an epimeric mixture of 23-bromocholanal (I).

This study was aimed at establishing whether hydrolysis of (I), induced by bases of various strength in aqueous systems, under atmospheric oxygen, generates the corresponding α-hydroxy-aldehyde (II), or possibly lends itself to rearrangement, oxidation, and/or fragmentation products of the structures (III), (IVa) and (Va), depending on reaction conditions [2].

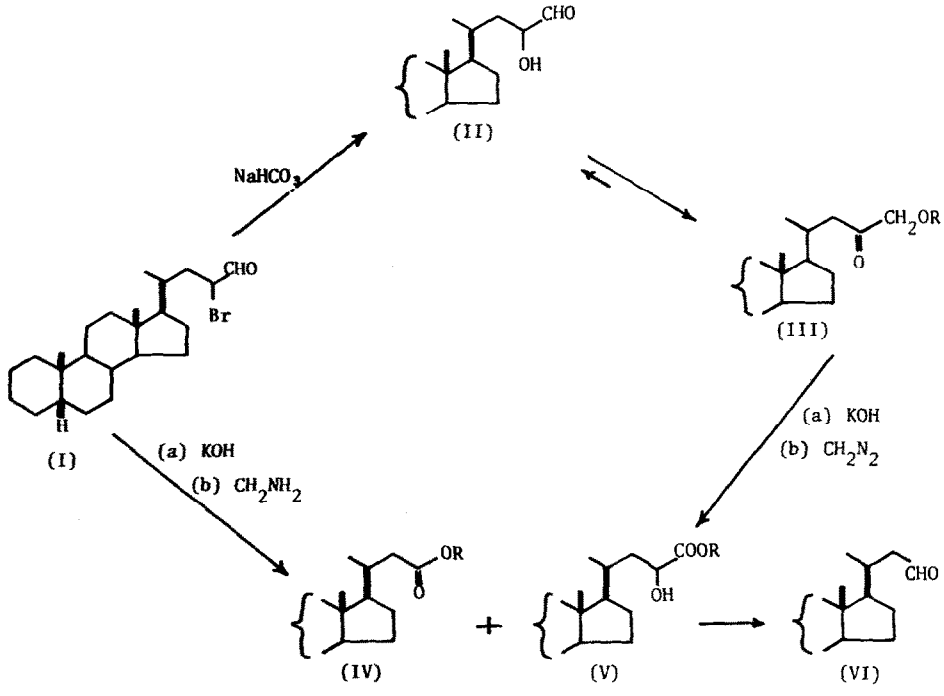
When a solution of the epimeric mixture of (I) [1a] (1.0 gr) in 90%-t-BuOH-10%-$H_2O$ (50 ml), containing sodium bicarbonate (1.0 gr), was refluxed for 18 hrs., the hitherto unknown rearrangement product 5αH-23-ketocholanol (III), m.p. 148° $[\alpha]_D^{20}$ +26° ($CHCl_3$, 1%) i.r.: 3460 (OH) and 1715 (C=O) $cm^{-1}$, was obtained in quantitative yield.

The 60 MHz n.m.r. (downfield from $Me_4Si$) of (IIIa) in $CCl_4$ exhibits resonances at τ 5.94 (2H, s, 24-$H_2$), 7.03 (1H, broad s, OH), 9.00 (3H, d, 21-$H_3$; J 6 Hz), 9.09 (3H, s, 19-$H_3$), 9.30 (3H, s, 18-$H_3$) in agreement with formulation (IIIa).

The ketol (IIIa) lends itself to easy cleavage by means of sodium periodate in acetone: acetic acid:water [3] to yield (70-80%) norcholanic acid (IVa), m.p. 176-177°[4]. In practice this sequence (I → III → IVa) constitutes a more convenient degradative route for the cholanic

acid sidechain.

Acetylation of (IIIa) by means of $Ac_2O$-AcOH in the presence of toluene-p-sulfonic acid afforded the hitherto unknown 24-acetoxycholan-23-one (IIIb), m.p. 108-109°, $[\alpha]_D^{25}$ +21° ($CHCl_3$, 1%), i.r.: 1712-1750 $cm^{-1}$, 1220-1240 $cm^{-1}$, n.m.r. ($CCl_4$) : τ 5.56 (2H, s, 24-$H_2$), 7.90 (3H, s, $CH_3CO$), 9.05 (3H, d, 21-$H_3$; J 6 Hz), 9.09 (3H, s, 19-$H_3$), 9.30 (3H, s, 18-$H_3$).




IIIa, R=H; IIIb, R=$CH_3CO$; IVa-Va, R=H; IVb-Vb, R=$CH_3$

When either (IIIa) or (I) (1.0 gr) was exposed to the action of a 2% solution of potassium hydroxide in a similar t-butanol-water mixture at room temperature under atmospheric oxygen and the product treated first with diazomethane in ether, and then chromatographed on silica gel, two different crystalline compounds, A and B, were obtained in a ratio, ranging from 1.5:1 to 1:1.5, respectively. Compound A, of higher Rf value (0.60*) was identified as methyl norcholanate(IVb), $[M]_D^{27}$ +70° ($CHCl_3$), 1%); i.r. ($cm^{-1}$): 1726, 1732: n.m.r. ($CCl_4$): τ 6.34 (3H, s, $OCH_3$), 9.02 (3H, d, 21-$H_3$; J 6 Hz), 9.30 (3H, s, 18-$H_3$), identical in all

respects to an authentic sample of (IVb).

T.l.c. analysis showed that compound B (Rf 0.45) comprised a 9:1-mixture of stereoisomers. The preponderant isomer was obtained by preparative t.l.c., and the pure product melted at 129-130°, $[\alpha]_D^{25}$ +20.1° ($CHCl_3$, 1%). It is assigned the methyl 23-hydroxycholanate structure (Vb) on the basis of: (i) its elemental analysis; (ii) its mass spectrum showing a molecular-ion peak at m/e 390; (iii) its absorption bands at 1720-1725 and 3450-3520 $cm^{-1}$ in the i.r. spectrum; (iv) its u.v. spectrum in $C_6H_{12}$, showing absorption at 210 mμ (ε 1=20); (v) its n.m.r. spectrum in $CDCl_3$ exhibiting upfield resonances at τ 8.99 (3H, d, 21-$H_3$); J 6 Hz) 9.09 (3H, s, 19-$H_3$), 9.31 (3H, s, 18-$H_3$), and a singlet at 6.27 (3H) assigned to methoxy group protons; (vi) its alkaline hydrolysis followed by periodate oxidation[3], affording norcholanal in high yield.

The assignment of (R)-configuration to C-23 in (Vb) is deduced from a) the Horeau method[5], and b) the o.r.d. measurement. Treatment of (Vb) with α-phenyl-butyric anhydride in pyridine gave the dextrorotatory α-phenylbutyric acid, $[\alpha]_D$ +1.7°, in 18.1% optical yield. The o.r.d. curve shows negative Cotton effect as follows: (c. 0.10, hexane), 25-27°[ϕ] - 11250°; $[\phi]_{240}$ - 15000° $[\phi]_{220}$ - 19400° (trough) $[\phi]_{210}$ - 14450°; $[\phi]_{207.5}$ - 12870°. This is in agreement with the prevailing view that α-hydroxy-acid derivatives of D-configuration should exhibit negative Cotton effect in o.r.d. [6].

The (23S)-epimer could not be isolated from the (I) → (Vb) conversion. However, it could be isolated in 90% optical purity from hydrolysis of 23-bromocholanic acid [7] by potassium hydroxide in t-butanol followed by esterification and separation by preparative t.l.c. on silical gel ($KGF_{254}$) with chloroform as eluent. The pure methyl (23S)-hydroxycholanate had $[\alpha]_D^{20}$ +33° ($CHCl_3$ 1%) (calcd.) [8], and gave absorption in the n.m.r. spectrum ($CCl_4$) at τ 9.33 (3H, s, 18-$H_3$).

The data presented above clearly indicate that the hydrolysis of (I) in weakly basic media, in the presence of air, does not involve oxidation, instead, it gives rise almost exclusively to the rearrangement product (IIIa). By contrast, the hydrolysis with strong base is accompanied by oxidation, leading both to fragmentation and oxidation products, IVa, and Va, respectively. Significantly, the oxidative-hydrolysis of (I) gives preference to the thermodynamically more stable epimer, thus providing the first entry to asymmetric syntheses of

α-hydroxy bile acids. The mechanism and stereochemistry of this reaction will be described in the full paper.

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