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THE LEAD TETRACETATE-IODINE REACTION OF CHOLANOL. ASSIGNMENT OF CONFIGURATION IN ISOMERIC 20,24-OXIDOCHOLANES

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As a part of a research project aimed at the functionalization of C-20 and C-21 in the cholanic acid series (1), the lead tetracetate reaction of cholanol (I) was undertaken.

Initially, we investigated the reaction of I (2) (m.p. 129.5-130.5°, $[\alpha]_D$ +24.4°, c. 4.8 in $CHCl_3$) with lead tetracetate in refluxing benzene over a period of 48-70 hrs. The reaction could not be effected at room temperature, and even at 78° it was incomplete after three days. This was evidenced by t.l.c. analysis of the reaction product which indicated the presence of 40-50% of starting material, together with some ten additional products (3). In the TLC the region below Rf 0.4 comprised a mixture of I with possibly IV. The region from Rf 0.4 to 0.6 displayed three distinct spots of comparable intensities which were identified as 20β,24-oxidocholane, II-B, (Rf = 0.41-0.47), 24-acetoxycholane (Rf = 0.47-0.53, m.p. 84-86°, $[\alpha]_D$+21.6°, c.4.2 in $CHCl_3$) and 20α,24-oxidocholane, II-A, (Rf = 0.53-0.59) (see Table 1). Preparative t.l.c. showed that the yields of II-A and II-B did not exceed 8-9% each.

We then applied the reaction of lead tetracetate (18 gr.) and iodine (10 mmoles) to I (10 mmoles) in 250 ml. carbon disulfide at room temperature. T.l.c. analysis showed that the conversion was 90% after 48 hrs. The chromatogram plate exhibited four spots of equal intensities, corresponding to II-B, II-A, III-B and III-A in increasing order of Rf values. Pure forms of each product in 20% yield were obtained by means of preparative t.l.c., amounting to a total yield of 80% or more. This communication is concerned with the characterization and assignments of structure of the two 20,24-oxidocholanes. The structure determination of the two iodo-20,24-oxido-cholanes, III-A and III-B, and the mechanism of their formation will be the subject of the following paper (4).

Both II-A and II-B analyzed as $C_{24}H_{40}O$ compounds, showing a molecular-ion peak at m/e 344 in the

CHART 1

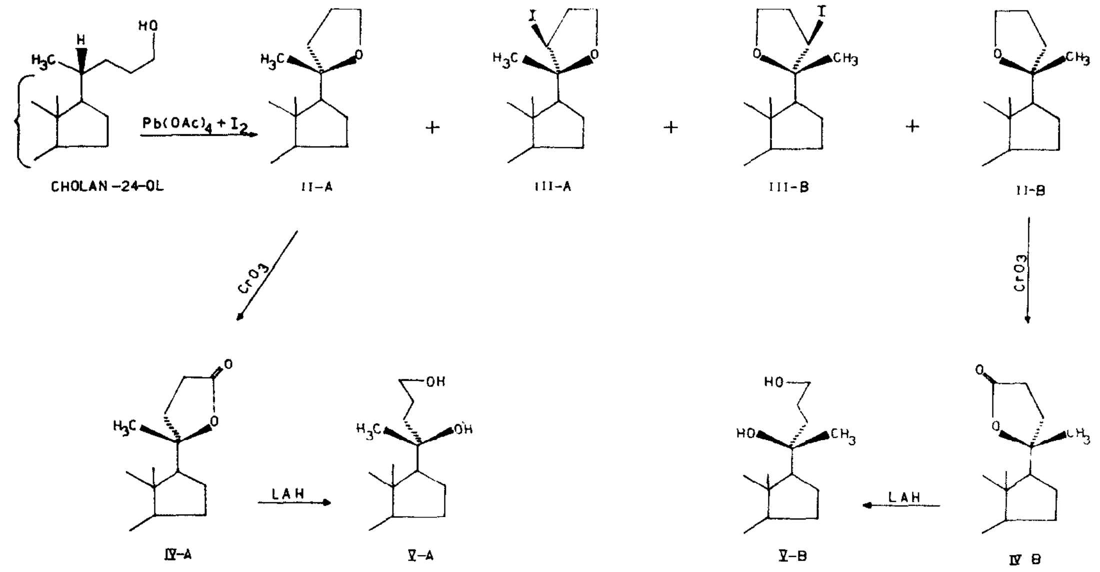
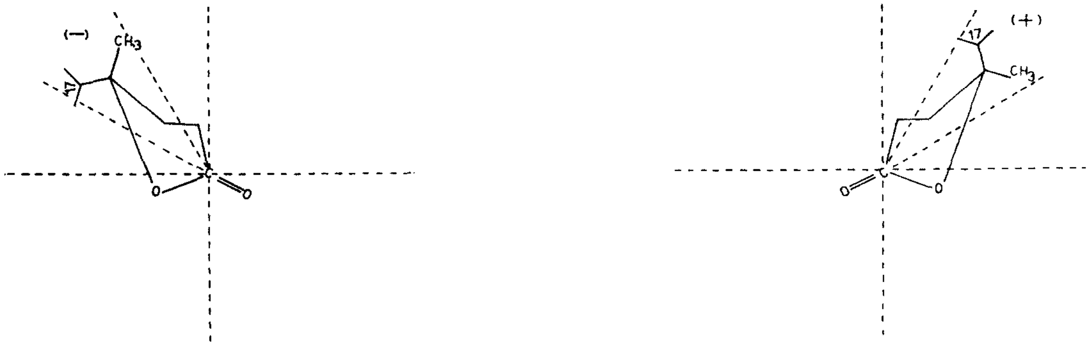


FIGURE 1. LACTONE SECTOR PROJECTION OF IV-A and IV-B



IV-A

IV-B

mass spectra. The C-21 methyl group protons of both isomers appear as singlets in the nmr spectra. It is less shielded in II-A than in II-B. The absorption band at 1050 cm^{-1}, which is attributable to the tetrahydrofuran grouping, is consistent with the 20,24-oxidocholane structure.

TABLE 1. ISOMERS OF 20,24-OXIDOCHOLANES (II), 20-HYDROXYCHOLANOIC ACID LACTONES (IV) AND 20,24-CHOLANEDIOLS (V).

Compound	M.P. °C	$[M]_D^{27}$	C. in $CHCl_3$	Rf[a]	FORMULA	ANAL. FOUND	
						C	H
II-A	113-114	+ 48.6	6.1	0.56	$C_{24}H_{40}O$	83.7	11.6
II-B	70-71	+ 41.7	2.6	0.44	$C_{24}H_{40}O$	83.6	11.5
IV-A	190	+ 127	4.8	0.19	$C_{24}H_{38}O_2$	80.5	10.4
IV-B	151	+ 36.7	4.9	0.16	$C_{24}H_{38}O_2$	80.6	10.6
V-A	165-166	+ 23	1.5	0.25[b]	$C_{24}H_{42}O_2$	79.4	11.4
V-B	135-136	+ 35.4	3.1	0.31[b]	$C_{24}H_{42}O_2$	79.7	11.7

a) Determined by TLC, Kieselgel G, benzene as eluent; b) Eluent: 1:1 chloroform-diethyl ether.

TABLE 2. ASSIGNMENTS AND CHEMICAL SHIFTS (in cps) FOR C-18 AND C-21 METHYL PROTONS IN ISOMERS OF II, IV, V AND 20-HYDROXYCHOLESTEROLS.

Methyl Group Protons	II-A	IV-A	V-A	20α-OH-Cholesterol[6]	II-B	IV-B	V-B	20β-OH-Cholesterol[6]
δ C-18	46	48	50	47.4	47.4	42	49	46.8
δ C-21	72	87	78	70.2	70	85	69	60

TABLE 3. CIRCULAR DICHROISM DATA ON ISOMERS OF II AND IV IN iso-OCTANE

Compound		Concentration g./l.	$\lambda_{m\mu}^{max}$	$\Delta \epsilon$	$10^{-2}[\theta]_{max}$
20α,24-Oxidocholane	(II-A)	1.545	195	+ 0.291	+ 9.60
20β,24-Oxidocholane	(II-B)	1.018	200	- 0.085	- 2.81
20α-Hydroxycholanoic acid lactone	(IV-A)	2.177	214	- 0.063	- 2.10
20β-Hydroxycholanoic acid lactone	(IV-B)	3.077	217.5	+ 0.463	+ 15.30

That the two isomers have the opposite configurations at carbon-20 is manifested by the opposite signs of the molecular ellipticity $[\theta]_{max}$ observed by circular dichroism (CD) studies (see Table 3). Chromic acid oxidation of II-A and II-B in acetic acid at room temperature provided the respective lactones, IV-A ($\bar{\nu}$ KBr 1775 cm^{-1}) and IV-B ($\bar{\nu}$ KBr 1760 cm^{-1}) in excellent yields.

The high melting lactone (IV-A) shows a fine structure and the CD of the R-band is negative. The isomeric lactone IV-B, by contrast, gives a positive effect at 2175 Å, the magnitude of which is about one order higher than in IV-A. If the Lactone Sector Rule (5) is applied for the half-chair conformation, the asymmetric carbon-20 of structure IV-B falls in the positive sector of the octant, whereas the asymmetric centre at C-20 in the case of IV-A falls in the negative sector, as actually observed (see Fig.1). Substantiation of the above absolute configuration assignments was provided by nmr analysis of the respective 20,24-cholanediols obtained from the lithium aluminium hydride reductions of IV-A and IV-B (see Table 2).

The stereochemistry around C-20 was also deduced from the diamagnetic shift of the C-21 methyl proton resonances in V-A and V-B. From the literature (6) it is known that the C-21 methyl protons in 20β-OH-cholesterol are more shielded than in 20α-OH-cholesterol. This allows one to correlate V-B with the 20β-OH series and V-A with the 20α-OH series since the C-21 methyl protons in V-B are more shielded than the C-21 protons in V-A (7).

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