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STRUCTURE DETERMINATION AND MECHANISM OF FORMATION OF IODO-OXIDO-CHOLANES FROM LEAD TETRACETATE-IODINE REACTION OF CHOLANOL

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In the preceding paper (1) we described the structure and the stereochemistry of the two isomers, 20α,24-oxidocholane II-A and 20β,24-oxidocholane II-B, obtained from the lead tetracetate-iodine reaction of cholanol I. This communication deals with the structure determination of the two additional iodo-oxidocholanes, III-A and III-B, formed in the same reaction in about 20% yield each.

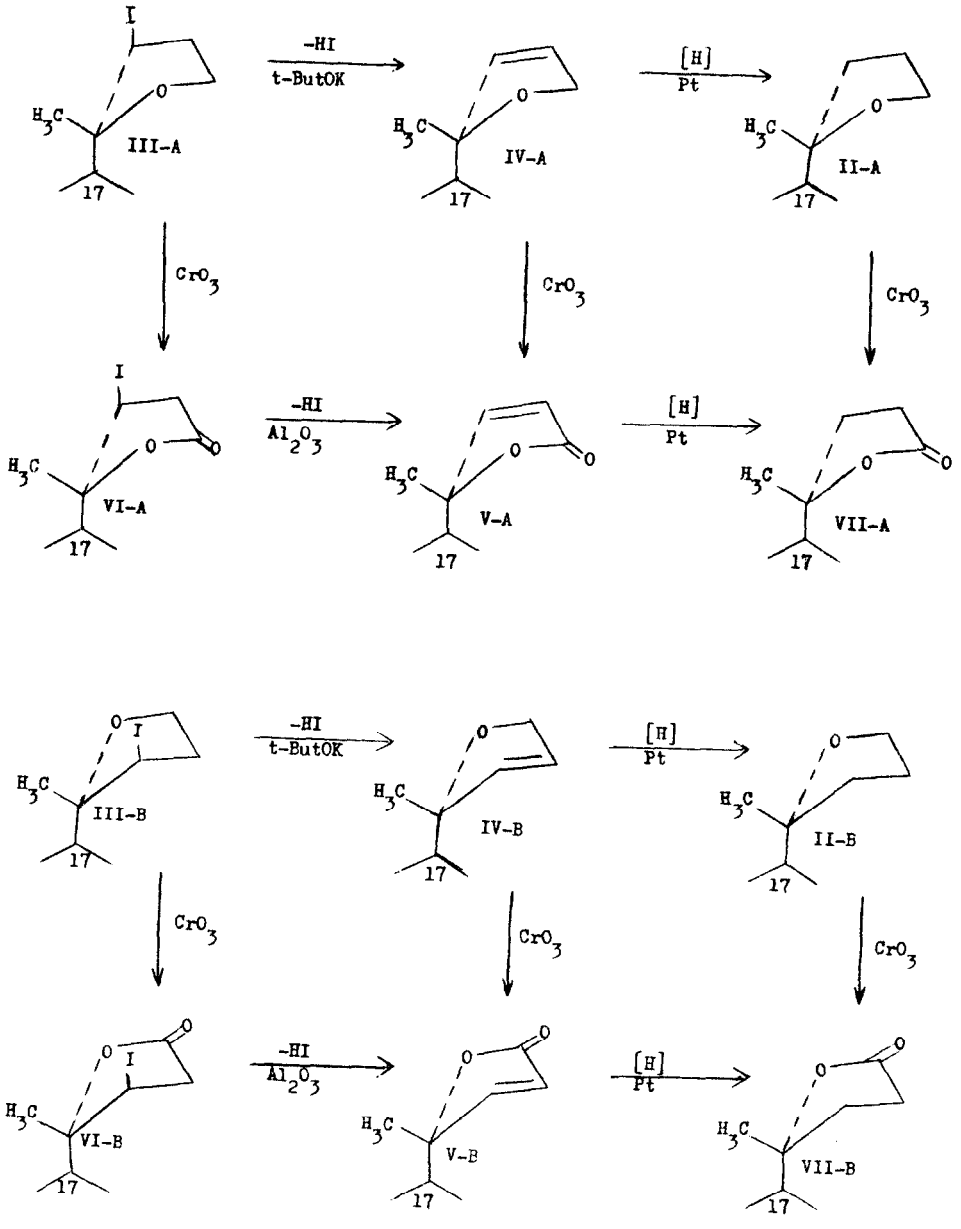
The two iodo-oxidocholanes analyzed as $C_{24}H_{39}IO$ compounds, both showing a molecular-ion peak at m/e 470 in the mass spectra, but otherwise they differ in their physical properties (see Table 1).

Crystallographic studies (2) show that the high melting isomer III-A is monoclinic with a = 7.69, b = 11.54, c = 12.45Å, β = 97.7°, and space group $P2_1$. The low melting isomer III-B is orthorhombic with a = 10.71, b = 26.82, c = 7.52Å, and a space group $P2_12_12$ or $P2_12_12_1$.

From the difference in the chemical shifts of the C-21 methyl group protons, which appear as singlets in the nmr spectra (see Table 2), it is possible to relate III-B to the 20β-OH series since its C-21 protons are more shielded than the respective protons in the isomer III-A, which should belong to the 20α-OH series (1).

The most striking difference between the two isomers is reflected in the signs of their optical rotations. It is positive for III-A, and negative and of similar magnitude for III-B. Furthermore, the circular dichroism curves of the two isomers are of the mirror image type (see Table 3). The mirror image type for the iodine absorption bands at 260 mμ in the CD studies indicates that the relative geometry of the iodine is enantiomeric in the two isomers. Nmr analysis shows that the iodine atom is on the tetrahydrofuran ring, located on C-22, which is also borne out from the degradative work described below. This implies that the iodine substituent in the two isomers must be either above or below the hetero-ring. That in both isomers the iodine is above the hetero-ring, can be deduced from

CHART I


I
-HI
t-ButOK
[H]
Pt
III-A
IV-A
II-A
17
CrO_3
VI-A
V-A
VII-A
Al_2O_3
III-B
IV-B
II-B
VI-B
V-B
VII-B

analysis of their $[M]_D$ values. From the literature it is known that the β-isomers in 22-hydroxycholesterol (3) and 24-hydroxycholesterol (4) are more levorotatory than the α-epimers (5). Indeed, the $[M]_D$ value is negative in III-B, but positive in III-A, thus allowing the assignment of β-configuration to C-22 in III-B, and vice-versa α-configuration to C-22 in III-A (6). Thus, the absolute configurations around C-20 and C-22 must be (R) and (S) in III-A, and (S) and (R) in III-B, respectively (7). We assign, therefore, the 22α-iodo-20α,24-oxidocholane structure for III-A and the 22β-iodo-20β-24-oxidocholane structure for III-B (6).

The chemical transformations portrayed in Chart 1 were performed with the objective of establishing the relationship of III-A to II-A and that of III-B to II-B and the position of the iodine substituent on carbon-22.

That III-A and III-B are true iodo derivatives of II-A and II-B, respectively, is evidenced from their initial dehydroiodination to the corresponding 20,24-oxidochol-22-enes, IV, followed by catalytic reduction (PtO_2 in ethanol) to yield II-A and II-B, respectively. The latter were identical in all respects with the respective 20,24-oxidocholanes described in the preceding paper.

The III-A ⟶ IV-A, III-B ⟶ IV-B conversions were effected at best by means of potassium t-butoxide in dimethyl sulfoxide at 50-60°. The position of the iodine substituent in the two isomers is inferred from the reaction sequences III ⟶ VI ⟶ V ⟶ VII. Chromic acid oxidations of III-A and III-B in acetic acid at 50-60° afforded the respective thermally labile iodolactones, VI-A ($\tilde{\nu}_{KBr}$ 1795 cm^{-1}) and VI-B ($\tilde{\nu}_{KBr}$ 1785 cm^{-1}). The latter underwent ready dehydroiodination either by passing through alumina G column or on short treatment with hot pyridine to yield the corresponding butenolides (V-A, $\tilde{\nu}_{KBr}$ 1765 cm^{-1}; λ_{max}^{EtOH} 212-214 mμ, ε 10800) and (V-B, $\tilde{\nu}_{KBr}$ 1750 cm^{-1}; λ_{max}^{EtOH} 215.5 mμ, ε 9100). They were further correlated with the corresponding saturated lactones, VII-A and VII-B, described in the preceding paper, by their catalytic reduction (PtO_2 in ethanol), the products of which were shown to be identical.

Of particular interest are the observed tendencies of 20α,24-oxido-chol-22-ene (IV-A) and of 20β,24-oxidochol-22-ene (IV-B) to undergo selective oxidations in high yields to the corresponding butenolides, V-A and V-B, by the action of chromic acid in acetic acid at room temperature.

CD studies show that the placement of an iodine substituent on the hetero-ring in II and VII brings about an inversion in the sign and also enhances the magnitude of $[\theta]_{max}$ probably because of conformational differences.

TABLE 1. ISOMERS OF 22-IODO-20,24-OXIDOCHOLANE (III), 20,24-OXIDOCHOL-22-ENE (IV), 20-HYDROXYCHOL-22-ENOIC ACID LACTONE (V), AND 22-IODO-20-HYDROXYCHOLANOIC ACID LACTONE (VI).

Compound	M.P. °C	$[M]_D^{27}$	C. in $CHCl_3$	Rf[a]	FORMULA	ANAL. C	ANAL. H	FOUND I
III-A	127-128[b]	+ 76	1.9	0.81	$C_{24}H_{39}IO$	61.2	8.1	26.9
III-B	112-113[b]	- 70	5.3	0.75	$C_{24}H_{39}IO$	61.3	8.3	27.1
IV-A	102-104	+ 20	3.0	0.64	$C_{24}H_{38}O$	84.0	11.3	-
IV-B	90-91	+ 146	1.8	0.56	$C_{24}H_{38}O$	84.3	11.0	-
V-A	155-156	- 51	3.2	0.21	$C_{24}H_{36}O_2$	80.6	9.9	-
V-B	193-194	+ 315	2.3	0.18	$C_{24}H_{36}O_2$	80.7	10.1	-
VI-A	133[b]	+ 307	1.4	0.47	$C_{24}H_{37}IO_2$	59.4	7.8	25.9
VI-B	146-148[b]	- 74	1.2	0.49	$C_{24}H_{37}IO_2$	59.5	7.6	26.3

a) Determined by TLC, Kieselgel G, benzene as eluent; b) Decomposed.

TABLE 2. NMR DATA ON ISOMERS OF III, IV, V AND VI IN $CDCl_3$ (δ AND J IN CPS)

Compound	C-18	C-21	C-22 δ	C-22 J	C-23 δ	C-23 J	C-24 δ	C-24 J
III-A	48	84	-	-	-	-	225[t]	9
III-B	45	78	248[t]	9	147[t]	7	220[t]	7
IV-A	45	71	337[s]	-	337[s]	-	274[s]	-
IV-B	40	75	342[s]	-	342[s]	-	271[s]	-
V-A	46	90	440[d]	5	350[d]	5	-	-
V-B	38	84	442[d]	5	352[d]	5	-	-
VI-A	49	92	261[d] 251[d]	9	172 162	- -	-	-
VI-B	41	94	281[d] 271[d]	9 9	181[s] 171[d]	- 3	-	-

s-singlet; d-doublet; t-triplet.

TABLE 3. CIRCULAR DICHROISM DATA ON ISOMERS OF III, V AND VI.

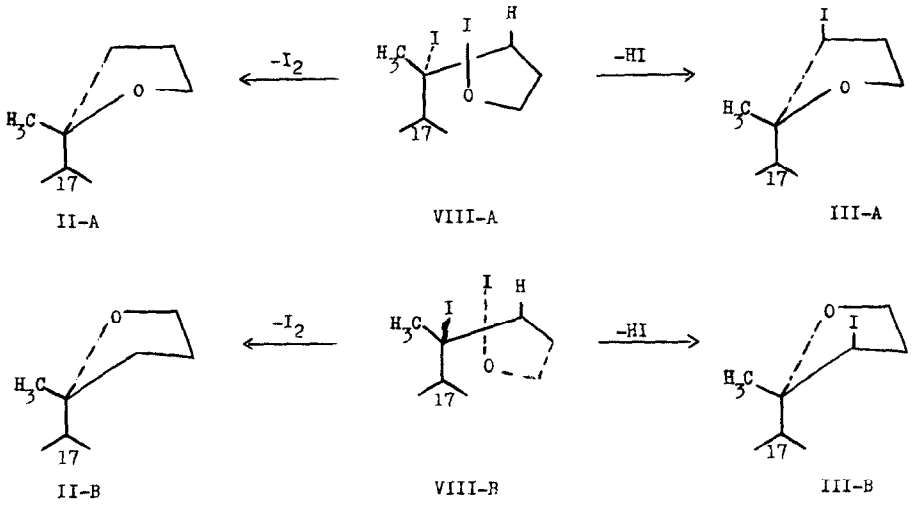
Compound		Conc. g./l	$\lambda_{m\mu}^{max}$	$\Delta\varepsilon$	$10^{-2}[\theta]_{max}$
22-Iodo-20α,24-oxidocholane	(III-A)[a]	1.96	195 260	- 2.0 + 0.143	- 66.0 + 4.7
22-Iodo-20β,24-oxidocholane	(III-B)[a]	1.56	198 260	+ 0.56 - 0.158	+ 18.5 - 5.2
20α-Hydroxychol-22-enoic acid lactone	(V-A)[b]	2.6	249-251 212-218	- 1.14 - 3.27	- 37.6 - 107.9
20β-Hydroxychol-22-enoic acid lactone	(V-B)[b]	2.1	255 248-250	+ 0.77 + 0.81	+ 25.4 + 26.7
22-Iodo-20α-hydroxy-cholanoic acid lactone	(VI-A)[b]	0.65	220-222	+ 7.1	+ 234.3
22-Iodo-20β-hydroxy-cholanoic acid lactone	(VI-B)[b]	0.62	220	- 3.83	- 126.4

a) In iso-Octane; b) In Dioxane.

From the foregoing it is clear that a) the functionalization of C-20 by means of lead tetracetate-iodine [Hypoiodite Reaction (8)] occurs in a non-stereospecific manner; b) the iodination at neighboring C-22, by contrast, is stereospecific; the iodine substituent is placed above the hetero-ring, and c) olefinic or C-21 or C-17 iodo-20,24-oxidocholanes which can be expected from the mechanism formulated by Heusler and Kalvoda (8) could not yet be found in the reaction product.

Although the formation of II-A and II-B from the Hypoiodite Reaction of I is evident from the mechanism described by Heusler and Kalvoda, that of the two 22-Iodo-20,24-oxidocholanes (III-A and III-B) is at variance with this mechanistic pattern. The free-radical substitution at the tertiary carbon-20 apparently invokes additional routes which are hitherto unknown (9).

To rationalize the new data presented here we suggest that the intermediate VIII, which according to the prevailing mechanism pattern can yield II-A and II-B on elimination of I_2, could also undergo a hitherto unknown elimination of hydrogen iodide to give III-A and III-B as depicted below. This entails that the iodination at C-22 results from C-20 to C-22 iodine shift (10) invoked by a free-radical hydrogen abstraction from C-22 caused by the hypoiodite group at C-24 concurrently with the oxy-radical attack from the back-side on C-20. It is most likely that these bond-ruptures and bond-formations occur in a concerted fashion. Detailed discussion of this mechanistic route will be given in the full paper.



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10. Compare, P.S.Skell and R.R.Pavlis, J.Amer.Chem.Soc., 86, 2956 (1964); P.S.Skell in "Organic Reaction Mechanisms", The Chemical Society, Special Publication No.19, 1965, p.131.