Tetrahedron Letters No.20, pp. 1533-1536, 1969. Pergamon Press. Printed in Great Britain.

THE LEAD TETRAACETATE-IODINE REACTION OF NORCHOLANOL. ASSIGNMENT OF CONFIGURATION IN 17,23-OXIDONORCHOLANE AND IN 22-IODO-17,23-OXIDONORCHOLANE

Yehuda Yanuka, Shalom Sarel* and Moshe Beckermann

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

(Received in UK 10 March 1969; accepted for publication 27 March 1969)

Previously [1,2], we have shown that the lead tetraacetate-iodine reaction of cholanol results in functionalization of both the δ and the γ carbons (C-20 and C-22, respectively), providing two epimers of 20,24-oxidocholanes and two 22-iodo-20,24-oxidocholanes of mirror image types.

We deemed it of interest to establish whether the lead tetraacetate-iodine reaction of the lower homolog, norcholanol (I), in which the δ and the γ positions, C-17 and C-20, both containing asymmetric tertiary carbons of known configuration, would pursue a reaction course similar to that of cholanol.

Norcholanol was prepared in excellent yield by way of sodium borohydride reduction of norcholanal [3], m.p. 151°, $[M]_D^{27}$ + 92 (1% in $CHCl_3$), (reported [4] m.p. 159.5°), showing a single spot in the TLC. Its NMR spectrum exhibited a singlet at 40 cps (C-18 methyl), a doublet at 54 and 60 cps (C-21 methyl), a multiplet centered at 222 cps (C-23 methylene) and a signal at 93 cps (OH).

A mixture of I (10 mmoles), lead tetraacetate (18 gr.) and iodine (10 mmoles) in 250 ml. carbon disulfide was agitated for 25 hrs. at room temperature. The TLC chromatogram of the reaction product exhibited about seven spots, four of which correspond to IV (25%), II (40%), V (5-6%) and III (10%) in increasing order of Rf values. Data on physical properties of pure forms of II, III and IV, obtained by means of preparative TLC, are given in Table 1, and the NMR data in Table 2.

The assignment of 17β,24-oxidonorcholane structure (II) for the main product (Rf 0.43) is inferred from (i) its elemental analysis; (ii) the absorption band at 1085 cm^{-1} in the IR spectrum (tetrahydrofuran); (iii) the C-21 methyl protons in the NMR spectrum which appear as a doublet (J = 6 cps) and which give rise to a singlet (61 cps) after irradiation of the C-20 proton at 120 cps. The spin-spin decoupled C-20 proton similarly appears as a singlet as the result of irradiation of the C-21 methyl protons; (iv) the conversion of II into the corresponding γ-lactone (IV) by the chromic acid oxidation in glacial

*To whom inquiries should be sent.

Table 1. 17β,23-Oxidonorcholane (II), 22α-Iodo-17β,23-oxidonorcholane (III) and 17β-Hydroxynorcholanoic acid lactone (IV)

Compound	M.P. °C	$[M]_D^{27}$ [a]	Rf [b]	cm^{-1}	Formula	Anal. Found C	H
II	130	- 98	0.43	1085	$C_{23}H_{38}O$	83.6	11.2
III	142 d.	- 158	0.90	1080	$C_{23}H_{37}IO$	61.0	7.8
IV	218	- 51	0.07	1760 1200	$C_{23}H_{36}O_2 \cdot \frac{1}{2}H_2O$	78.2	10.6

a) In ca. 1% $CHCl_3$; b) Determined by TLC, Kieselgel G, benzen-cyclohexane (1:1); c) In KBr.

Table 2. NMR Data of II, III and IV (δ and J in cps)

Compound	C-18	C-20	C-21 δ	C-21 J	C-22	C-23
II [a]	48^s	120^m	61^d	6	-	214^m
III [b]	52.5^s	141^m	70^d	6	270^m	234^m
IV [a]	55.5^s	-	68^d	6	153^m	-

s-singlet; d-doublet; m-multiplet; a) In $CDCl_3$; b) In CCl_4

acetic acid at room temperature, the IR and NMR spectra [5] of which are consistent with the assigned structure; and (v) from the negative values of the molecular rotations in II and IV.

From the literature it is known that both in 5α- and 5β-pregnanes the 17β orientation of the sidechain imparts positive sign to the steroid rotation whereas the 17α-epimers are levorotatory [6,7]. In C_{29}-stanols [8] and norcholanic acids the 20βH-epimers are consistently more levorotatory than the 20αH-epimers [9]. Moreover, in 17-hydroxypregnanes and cholestanes, the 3-OH epimers are considerably more levorotatory than the α-OH epimers [10]. Indeed, analysis of the molecular rotation shows that the observed value of $[M]_D^{27}$ - 98 is consistent with 17β orientation for the heteroatom in II. This implies an α-orientation for the C-21 methyl group in II, due to an inversion in the side-chain position which acquires the α-orientation. It must be therefore, of (17R),(20R)-configuration.

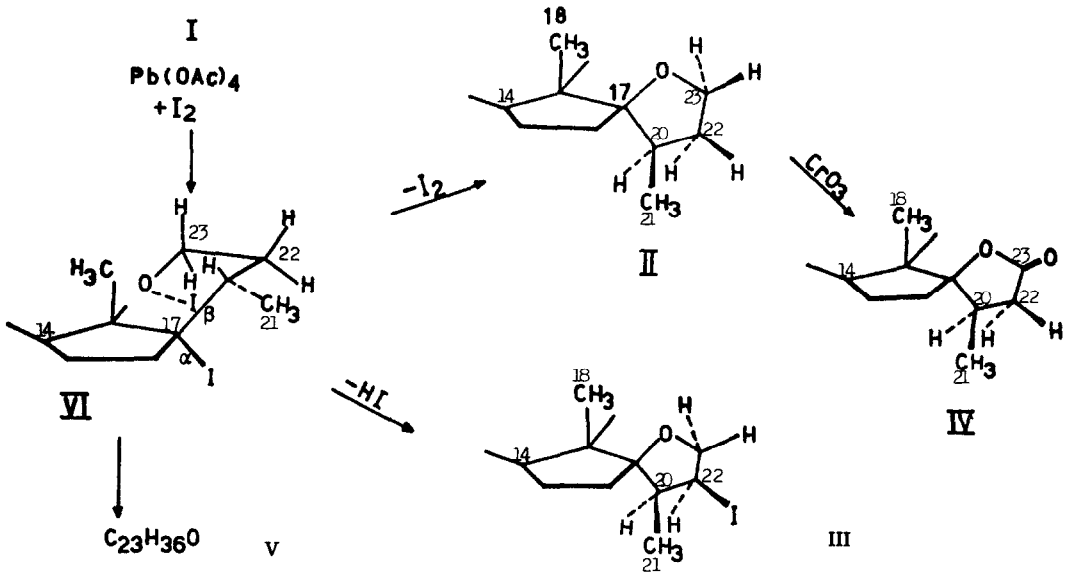
A 22α-iodo-17β,24-oxidocholane structure (III) was assigned to the iodo-compound on the basis of its (i) elemental analysis; (ii) its strongly negative $[M]_D$ value; (iii) the absorption band at 1080 cm^{-1} in the infrared spectrum; and (iv) from the analysis of its NMR spectrum.

The C-21 methyl protons in III appear as a doublet which collapses to a singlet (70 cps) when irradiated at 141 cps (center of C-20 proton multiplet). The spin-spin decoupled resonance of the C-20 proton appears as a doublet with J = 1 cps, after irradiation of the C-21 methyl protons. The C-23 methylene gives rise to a double doublet centered at 234 cps.

The iodine substituent must be on carbon-22 since integration shows the presence of one proton on C-22, appearing as a multiplet which is collapsed to a double doublet (centered at 270 cps) when irradiated at 70 cps (C-21 methyl group signal). That the C-20 and C-22 protons assume a cis relationship is inferred from the splitting of the C-20 proton decoupled resonance, J = 1 cps [11]. As a consequence, the C-21 methyl and the iodine substituent at C-22 should reside on the same side of the heteroring, pointing away from the C-18 methyl group. Therefore, III must be of (17R),(20R),(22S)-configuration. The minor product, V, analyzed as a $C_{23}H_{36}O$ compound, giving absorption at 1072 cm^{-1} (tetrahydrofurane), 882 cm^{-1} (double bond). More work on its detailed structure is currently in progress.

We have not so far observed the presence of isomers either of II or III in the reaction products. The functionalization of both C-17 and C-22 seemingly occur in a stereospecific manner. Unlike cholanol, the oxido-bridge formation in I ⟶ II conversion takes place predominantly by way of oxy-radical attack from the β-side with an inversion of the side-chain at C-17.

The position and the orientation of the iodine substituent in III could not be envisioned from the prevailing concepts in intramolecular free-radical substitutions of oxy-radicals [12]. Like in cholanol, the placement of the iodine substituent, in the course of hypoiodite reaction of norcholanol, occurs on the heteroring, at C-22, adopting a cis relationship with the adjacent C-21 methyl group. However, in contrast to cholanol, in which the iodination occurs at γ position to the oxygen atom, in the case of norcholanol it occurs unexpectedly at the β position. This suggests that the intermediate [VI], which according to Sarel, Shalon and Yanuka [2], can yield II on elimination of I_2, could also undergo a hitherto unknown elimination of hydrogen iodide to give III as outlined below. This requires the assumption that the iodination at C-22 results from C-20 to C-22 iodine shift caused by a free-radical hydrogen abstraction from C-22 invoked by the hypoiodite group at C-23 concurrently with the oxy-radical attack from the back-side on C-20. Here again, the bond-ruptures and bond-formations should occur by a



concerted mechanism.

A study of the lead tetraacetate reaction of (I) and of lead tetraacetate-iodine reaction of bis-nor-cholanol are currently in progress. It was undertaken with a purpose to shed more light on reaction mechanism patterns.

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