The Reduction of 22,26-Oxido-$\Delta^{17(20)}$-cholestene-3β,22-diol-16-one with Lithium Aluminum Hydride

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In 1952, Nussbaum, *et al.*,[2] converted 5,6-dihydrokryptogenin diacetate through a series of reactions to 22,26-oxido-$\Delta^{17(20)}$-cholestene-3β,22-diol-16-one (Ia). Reduction of Ia with lithium aluminum hydride was reported[2] to yield IVa. Compound IVa appeared to us to be an appropriate starting material for the partial synthesis of 5,6-dihydropennogenin of structure V, proposed by Marker and associates.[3] An alternate formulation VI has been sugested by Heusler and Wettstein.[4]

We attempted to prepare IVa from 5,6-dihydrokryptogenin by carrying out the sequence of reactions as previously reported.[2] The intermediates leading to IVa were in regard to physical properties and yields in complete agreement with the published data.[2] While the physical properties of the final product, supposed to be the IVa, were also in full agreement with those reported, the analytical data of IIa and its derivatives, particularly of the acyl derivatives showed clearly that in the reduction of Ia a dialcohol of the structure of 22,26-oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol (IIa)[5] had been formed. Esterification gave readily diesters (acetate, dinitrobenzoate). Oxidation of IIa with chromic acid led to the diketone III. Its ultraviolet spectrum showed a band at 237 mμ practically identical with that of Ia. The strong bands at 1706 and 1666 cm.$^{-1}$ also indicated α,β-unsaturated carbonyl. The 3- and 16-ketone absorption bands overlap because of the shift of the 16-ketone band to lower frequency (conjugation with the C-$^{17(20)}$-double bond). Compound III gave a crystalline monooxime which exhibited strong bands at 1706 and 1666 cm.$^{-1}$ indicating that only the 3-ketone was involved in oxime formation.[6] Lithium aluminum hydride reduction of III gave IIa in a yield of 60%.

An analogous sequence of reactions was carried out in the Δ^{5}-series starting from kryptogenin.[7] The results were entirely analogous.

Experimental[8]

22,26-Oxido-$\Delta^{17(20)}$-cholestene-3β,22-diol-16-one (Ia).—The isomerization of 5,6-dihydrokryptogen diacetate (10.0 g.) with refluxing acetic anhydride containing a small amount of *p*-toluenesulfonic acid proceeded as described.[2] Three recrystallizations from methanol gave 6.0 g of $\Delta^{16,20(22)}$-allofurostadiene-3β,26-diol 3β,26-diacetate, m.p. 94–96°, $[\alpha]^{20}\text{D}$ +10°, $\lambda_{\max}$ 226 mμ(ϵ 10,500)[lit.,[2] m.p. 96–98°, $[\alpha]^{20}\text{D}$ +10°, $\lambda_{\max}$ 226 mμ (log ϵ 4.05)]. The free diol, m.p. 187–189°, $[\alpha]^{20}\text{D}$ + 30°, $\lambda_{\max}$ 228 mμ(ϵ 10,100)[lit.,[2] m.p. 189–191°, $[\alpha]^{20}\text{D}$ +31°, $\lambda_{\max}$ 227 mμ (log ϵ 4.03)].

We observed that the pseudokryptogenins and their derivatives exhibit two bands of moderate intensity in chloroform solution at 1623 and 1572 cm.$^{-1}$. The presence of these bands may be used for the detection of a $\Delta^{16,20(22)}$-furostadiene system.

The $\Delta^{16,20(22)}$-allofurostadiene-3β,26-diol 3β,26-diacetate (5.0 g.) was oxidized with an excess of chromic acid in acetic acid at room temperature and the mixture worked up as reported.[2] The crude oily product, $\lambda_{\max}$ 246 mμ (ϵ 11,000), was immediately saponified by refluxing for 1 hr. with 2% methanolic potassium hydroxide solution and extracting with a large volume of ether. The product crystallized from the dried ether extracted in a yield of 3.0 g.; spears m.p. 204–206°. Recrystallization from ethyl acetate gave 2.8 g. of Ia as rods, m.p. 205–206°, $[\alpha]^{20}\text{D}$ −106°, $\lambda_{\max}$ 237 mμ (ϵ 13,300) $\nu_{\max}^{\text{Nujol}}$ 3390, 1712, and 1672 cm.$^{-1}$ [lit.,[2] m.p. 205–206°, $[\alpha]^{20}\text{D}$ −105°, $\lambda_{\max}$ 237 mμ (log ϵ 4.19)].

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.30; H, 9.83. Found: C, 75.18; H, 9.79.

22,26-Oxido-$\Delta^{5,17(20)}$-cholestadiene-3β,22-diol-16-one (Ib).—This product was obtained from kryptogenin diacetate by repeating the sequence of reactions used in the preparation of Ia.[7]

The intermediate $\Delta^{5,16,20(22)}$-furostatriene-3β,26-diol 3β,26-diacetate was obtained in a yield of 60%, m.p. 94–95°, $[\alpha]^{20}\text{D}$ −44°, $\lambda_{\max}$ 226 mμ (ϵ 12,000)[lit.,[7] m.p. 94–95°, $[\alpha]^{20}\text{D}$ −44°, $\lambda_{\max}$ 226 (log ϵ 4.16)]. Oxidation of 5.0 g. of the $\Delta^{5,16,20(22)}$-furostatriene-3β,26-diol 3β,26-diacetate and immediate saponification of the oxidized product with 2% methanolic potassium hydroxide solution gave after isolation and purification 3.1 g. of Ib, m.p. 220–223°, $[\alpha]^{20}\text{D}$ −178°, $\lambda_{\max}$ 237 mμ (ϵ 13,100), $\nu_{\max}^{\text{Nujol}}$ 3367, 1706, and 1669 cm.$^{-1}$ [lit.,[7] m.p. 225–226°, $[\alpha]^{20}\text{D}$ −173°, $\lambda_{\max}$ 236 mμ (log ϵ 4.17)].

22,26-Oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol (IIa).—A solution of 2.0 g. of 22,26-oxido-$\Delta^{17(20)}$-cholestene-3β,22-diol-16-one (Ia), 1.5 g. of lithium aluminum hydride, and 150 ml. of tetrahydrofuran was refluxed for 1 hr. Decomposition of the excess reagent with ethyl acetate, followed by addition of water and dilute sulfuric acid, filtration of the precipitate, and recrystallization from methanol gave 1.2 g. of elongated needles, m.p. 228–230°, $[\alpha]^{20}\text{D}$ −11°, no selective absorption

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(5) The configuration at C-22 as shown in the structural formulas Ia, IIa, and III is arbitrary.

(6) A compound of similar structure to III was observed to exhibit considerable hindrance at C-16, I. Scheer, M. J. Thompson, and E. Mosettig, *J. Am. Chem. Soc.*, **79**, 3218 (1957).

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(8) All melting points were determined on Kofler block. Rotations were determined in approximately 1% solutions in chloroform and ultraviolet spectra in absolute ethanol with a Cary Model 11 recording spectrophotometer. Infrared spectra were obtained with a Perkin-Elmer Model 21 double beam spectrophotometer with sodium chloride prism and cells. Microanalyses are by the Analytical Service Laboratory of this Institute under the direction of Dr. William C. Alford. Infrared spectra were determined by Mr. H. K. Miller and ultraviolet spectra by Mrs. A. Wright of this laboratory.

in the ultraviolet, free hydroxyl in the infrared but no carbonyl (lit.,[2,9a] m.p. 226–228° $[\alpha]^{20}\text{D}$ −12°).

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.64; H, 10.38.

The diacetate (acetic anhydride–pyridine, steam bath, 2 hr.) was obtained as plates from methanol, m.p. 218–220°, $[\alpha]^{20}\text{D}$ −9°, acetate but no free hydroxyl bands in the infrared (lit.,[2,9b] m.p. 223–225°, $[\alpha]^{20}\text{D}$ −8°.

Anal. Calcd. for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66; acetyl, 17.1. Found: C, 74.29; H, 9.56; acetyl, 16.3

The bis-3,5-dinitrobenzoate (3,5-dinitrobenzoyl chloride–pyridine, 3 hr., steam bath) was obtained as plates from acetone–methanol, m.p. 186–187°, $[\alpha]^{20}\text{D}$ +35°.

Anal. Calcd. for $C_{41}H_{48}O_{13}N_4$: C, 61.18; H, 6.01; N, 6.96. Found: C, 61.29; H, 6.14; N, 6.85.

22,26-Oxido-$\Delta^{5,17(20)}$-cholestadiene-3β,16ξ-diol (IIb).—The lithium aluminum hydride reduction of 22,26-oxido-$\Delta^{5,17(20)}$-cholestadiene-3β,22-diol-16-one (Ib) carried out exactly as in the preparation of IIa gave IIb in a yield of 65% as needles after recrystallization from methanol, m.p. 236–237°, $[\alpha]^{20}\text{D}$ −80° (lit.,[7,9c] m.p. 236–237°, $[\alpha]^{20}\text{D}$ −81.3°).

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.28; H, 10.10.

The diacetate (acetic anhydride–pyridine, 2 hr., steam bath) was obtained as rectangular plates from chloroform–methanol, m.p. 258–260°, $[\alpha]^{20}\text{D}$ −71° (lit.,[7,9d] m.p. 260–262° $[\alpha]^{20}\text{D}$ −70.7°).

Anal. Calcd. for $C_{31}H_{46}O_5$: C, 74.66; H, 9.29; acetyl, 17.3. Found: C, 74.53; H, 8.99; acetyl, 17.1.

The bis-3,5-dinitrobenzoate (3,5-dinitrobenzoyl chloride–pyridine 3 hr., steam bath) was obtained as thin plates from acetone–methanol, m.p. 206–207°, $[\alpha]^{20}\text{D}$ −1°.

Anal. Calcd. for $C_{41}H_{46}O_{13}N_4$: C, 61.34; H, 5.77; N, 6.97. Found: C, 61.52; H, 5.72; N, 6.77.

22,26-Oxido-$\Delta^{17(20)}$-cholestene-3,16-dione (III).—To a stirred solution of 300 mg of 22,26-oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol (IIa) in 200 ml. of acetone at 20°, was added dropwise, an 8 *N* solution of chromic acid in dilute sulfuric acid (*ca.* 40%) until a persistent orange-brown coloration indicated oxidation was complete. The mixture was diluted with water and the crystalline precipitate was collected, washed with water, and dried to yield 280 mg. of III, m.p. 182–188°. Recrystallization from ethanol raised the melting point to 195–197°, $[\alpha]^{20}\text{D}$ −78°, λ_{max} 236 (ε 10,400), ν^{CHCl_3} 1706 cm.$^{-1}$ strong (3-ketone and 16-ketone) and 1666 cm.$^{-1}$, strong (double bond in conjugation with a carbonyl).

Anal. Calcd. for $C_{27}H_{40}O_3$: C, 78.59; H, 9.77. Found: C, 78.82; H, 9.54.

The monoöxime (hydroxylamine hydrochloride, methanol–pyridine, water, steam bath, 2 hr.) was obtained as plates from ethanol, m.p. 234–237°, with slight decomposition.

Anal. Calcd. for $C_{27}H_{41}O_3N$: C, 75.83; H, 9.67, N, 3.28. Found: C, 75.70; H, 9.50; N, 3.33.

Reduction of III with lithium aluminum hydride gave the original diol IIa in a yield of 60%.

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(9) (a) Considered previously to be IVa; (b) acetate of IVa; (c) considered previously to be IVb; (d) acetate of IVb.

Furazan Oxides. II. Evidence for Equilibria of Benzofurazan Oxides with *o*-Dinitrosobenzenes[1]

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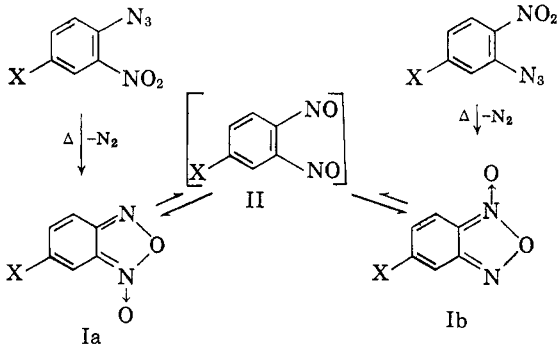
The fact that the pyrolysis of either of the substituted nitroazides of the type shown below yields a single compound X—$C_6H_3N_2O_2$ rather than two separate isomeric benzofurazan oxides such as Ia and Ib was originally thought[2] to indicate a symmetrical configuration of the N_2O_2 grouping. However, recent n.m.r.[3,4] and X-ray[5] results have demonstrated the validity of the unsymmetrical *N*-oxide formulation I for this class of compound. These results require the existence of an equilibration Ia ⇌ Ib such that only the more stable isomer is isolated. This type of equilibration was originally postulated by Hammick[6] and has recently been demonstrated by n.m.r. studies.[3,4] For example, the proton resonance pattern of the parent benzofurazan oxide (I with X = H) is a complicated ABCD type at low temperatures but changes to a symmetrical A_2B_2 pattern at higher temperatures when the rate of the Ia ⇌ Ib interconversion is sufficiently rapid that only the average proton environments are detected. Similarly, the two peaks of the 0^{17} n.m.r. spectrum of I (X = H) at room temperature coalesce to a single peak above 45°.[4]



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