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THE DEHYDROCHLORINATION OF 3β-CHLORO-5β-CHOLESTANE. NEW SYNTHESES OF 5β-CHOLEST-2-ENE AND 5β-CHOLEST-3-ENE[°]

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Although most cholestenes of the 5α series have been throughly investigated,[1] only few informations can be found in the literature about the analogous 5β-derivatives. It has been reported, for instance, that 5β-cholestan-3β-ol tosylate is transformed by alumina into 5β-cholest-2-ene,[2] and that the dehydrochlorination of 3α- and 3β-chloro-5β-cholestane, as well as the pyrolysis of the benzoates of 5β-cholestane-3α- and -3β-ol also leads to the 2-olefin, m.p. 47-48°.[3] On the other hand the monobromination of 5β-cholestan-3-one gives the 4β-bromoderivative,[4] a fact which is indicative for the preferential enolization towards the 4 position.[°°] As the dehydrobromination of 3α- and 3β-bromo-5α-cholestane gives 5α-cholest-2-ene,[5] in accordance with the known tendency to enolization towards the 2 position of 5α-cholestane-3-one, the formation of the 3-ene in the 5β series would appear more likely, in contrast with the

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[°] Dedicated to Prof.Remo de Fazi, on his 75th birthday.

[°°] The recent report [L.Mamlok, Bull.Soc.Chim.France, 3466(1965)] about the isolation of the 2-bromoketone along with the 4-bromoketone, in a ratio of 1:4, in the bromination of 17β-hydroxy-5β-androstan-3-one indicates that in the 5β series the direction of enolization may not be as univocal as in the 5α series.

literature data given above. We therefore thought it worth while to check again the elimination reactions in 3-substituted 5β-cholestanes, with the aid of that excellent analytical tool, which is GLC.

It was found that, in contrast with the previous data,[3] the quinoline dehydrochlorination of 3β-chloro-5β-cholestane (I), m.p. 122-124°, does not give 5β-cholest-2-ene (II) as the only, and not even as the main product. GLC[°°°] showed that the product consisted of two hydrocarbons in the ratio of 55:45, which were identified respectively as 5β-cholest-3-ene (III) and 5β-cholest--2-ene (II); retention times relative to 5α-cholestane: II, 1.06; III, 0.94. Chromatography of the mixture over silica gel-silver nitrate[6] allowed to separate pure (GLC) III, which was eluted more rapidly with petroleum ether, while only very little pure II was thus obtained. In order to get samples of II and III for comparison, they were prepared by the following methods.

III was obtained by applying a method which had been used before for the synthesis of methyl 3-cholenate.[7] Reduction of 4β-bromo-5β-cholestan-3-one[4] (IV), m.p. 110-112°, with $NaBH_4$ in absolute ethanol at 25° gave a mixture of 3-epimeric bromohydrins (V), which was transformed by reflux with zinc in acetic acid into pure III, m.p. 48-49° (from ethyl acetate-methanol), $[\alpha]_D^{23}$ + 19.2° (c 1.583, $CHCl_3$); lit.[8], m.p. 50-50.5°, $[\alpha]_D$ + 19°; dibromoderivative (3α,4β-dibromo-5β-cholestane), m.p. 98.5-100°; lit.[8], m.p. 99-100°.

For the preparation of II, 2α-acetoxycholest-4-en-3-one (VII), obtained through the abnormal opening of 4β,5-epoxy-5β-cho-

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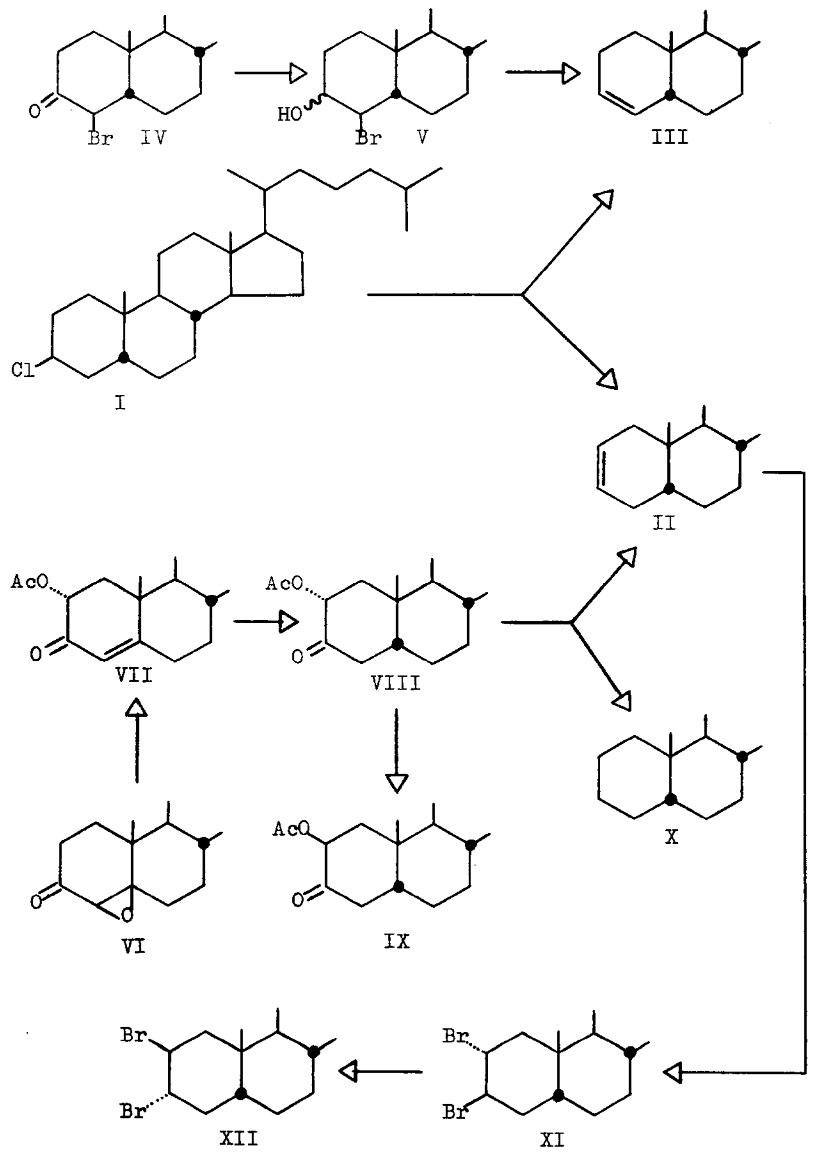
[°°°] GLC analysis was carried out at 190° on a Perkin-Elmer, Mod F20 gas-chromatograph, with 2 m x 4 mm - glass columns containing 1% NGS on silanized Chromosorb W, 80/100 mesh.


O
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IV
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XI

lestan-3-one (VI) with H_2SO_4-acetone, followed by acetylation,[9] was hydrogenated over 10% palladium on charcoal in methanol-dioxane saturated with $NaHCO_3$ to yield 65% of 2α-acetoxy-5β-cholestan-3-one (VIII), m.p. 137-139° (from petroleum ether), $[\alpha]_D^{28}$ + 0.5°. The α (axial) configuration of the acetoxy group in VIII was confirmed by its easy epimerization in acetic acid-hydrobromic acid to the more stable 2β-acetoxy-5β-cholestan-3-one (IX), m.p. 150.5-152° (petroleum ether), $[\alpha]_D^{27}$ - 4°, in accordance with the behaviour of the corresponding 5α-derivatives.[10]

It is well known[11] that the Wolff-Kishner reaction on α-hydroxy- or α-acetoxyketones leads to olefins through reduction-elimination. Accordingly, VIII gave under Huang-Minlon conditions, the olefin II, accompanied by about 30% (GLC) 5β-cholestane (X), m.p. 70-71°. The formation of saturated hydrocarbon, which had been observed before for similar reactions,[12] may be due to the intermediate formation of the osazone, because of the presence of a large excess of hydrazine. In fact, when the reaction was carried out with an equimolar amount of hydrazine, the hydrocarbon fraction which was obtained, even if in low yield, consisted of II practically free from X. The separation of II from X was carried out by bromination of the mixture in CCl_4 at 18°, followed by heating at 180-200° under nitrogen,[13] to isomerize the dibromide of II to the more stable form (see below), and by chromatography on silica: petroleum ether eluted first X, then a dibromide, m.p. 165-167° (from acetone), $[\alpha]_D^{27}$ + 71.4° (c 1.060, $CHCl_3$). Reflux of the latter with zinc in acetic acid gave pure (GLC) II, m.p. 47.5-48° (acetone), $[\alpha]_D^{28}$ + 19.9° (c 1.720, $CHCl_3$).

The bromination of pure II, under the conditions specified above, gave a dibromide, m.p. 74-76° (from acetone), which was isomerized to the dibromide, m.p. 165-167°, referred to above. Although a more through study of these reactions remains to be done, it is most likely, in consideration of the similar reactions in the 5α-series,[13] that the lower-melting dibromide is the diaxial 2α,3β-dibromo-5β-cholestane (XI), which isomerizes to the diequatorial 2β,3α-dibromo derivative (XII).

The incorrect report on the exclusive formation of 5β-cholest-2-ene (II) from 3β-chloro-5β-cholestane was probably due to the fact that II and III have very similar physical properties, that their mixtures have rather sharp melting points, with very little depression, and that they are difficult to separate by conventional techniques, such as fractional crystallization. It would therefore be advisable and interesting to study again all those elimination reactions which can lead to II or III, a task which is now easy with the aid of GLC analysis.

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REFERENCES

1) L.F.Fieser and M.Fieser, "Steroids", Reinhold Publ.Corp., New York (1959), p.251; G.M.L.Cragg, C.W.Davey, D.N.Hall, G.D.Meakins, E.E.Richards and T.L.Whateley, J.Chem.Soc.(C), 1966,1266.

2) D.D.Evans and C.W.Shoppee, J.Chem.Soc., 1953,540.
3) R.J.Bridgewater and C.W.Shoppee, J.Chem.Soc., 1953,1709.
4) C.W.Shoppee, A.B.Devine and R.E.Lack, J.Chem.Soc., 1965,6458.
5) A.Fürst and Pl.A.Plattner, Helv.Chim.Acta, 32,275(1949).
6) A.S.Gupta and Sukh Dev, J.Chromatog., 12,189(1963).
7) L.F.Fieser and R.Ettorre, J.Am.Chem.Soc., 75,1700(1953).
8) A.Nickon, N.Schwartz, J.B.Di Giorgio and D.A.Widdowson, J.Org.Chem., 30,1711(1965).
9) M.Tomoeda, M.Ishizaki, H.Kobayashi, S.Kanatomo, T.Koga, M. Inuzuka and T.Furuta, Tetrahedron, 21,733(1965).
10) K.L.Williamson and W.S.Johnson, J.Org.Chem., 26,4563(1961).
11) D.H.R.Barton and C.H.Robinson, J.Chem.Soc., 1954,3045; N.J. Leonard and S.Gelfand, J.Am.Chem.Soc., 77,3272(1955).
12) D.H.R.Barton, N.J.Holness and W.Klyne, J.Chem.Soc., 1949,2456; L.Ruzicka, Pl.A.Plattner and M.Furrer, Helv.Chim.Acta, 27, 727(1944).
13) G.H.Alt and D.H.R.Barton, J.Chem.Soc., 1954,4284.