Steroid Ring-C Aromatization with Side-chain Configurational Inversion

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Summary A derivative of the bile acid, cholic acid, undergoes a molecular rearrangement yielding a 12-methyl-18-nor-C-benzenoid steroid with inversion of configuration of the side-chain.

THE fungal metabolite, viridin,[1] is the first reported example of a naturally occurring ring-C benzenoid steroid. The conversion of the sterol, ergosterol[2,3] and the bile acid, cholic acid,[4] to 12-methyl ring-C benzenoid steroids by molecular rearrangement has been demonstrated and three independent total syntheses of ring-C aromatic steroids have been reported.[5] We now report a novel pathway by which cholic acid is readily converted into 3α-hydroxy-12-methyl-18-nor-5β,17α-chola-8,11,13-trien-24-oic acid (**2c**).

When hydrogen chloride was passed through a methanolic solution of the 12-epimeric alcohols (**1**), readily obtained[6] by sodium borohydride reduction of methyl 3α,7α-diacetoxy-12-oxochol-9(11)-enate, there was obtained in 80—90% yield a product for which we suggest the constitution (**2a**) in which the original 3-acetoxy-group has been hydrolysed, the 7-acetoxy- and 12-hydroxy-groups have been eliminated, the angular methyl group (C-18) has migrated from C-13 to C-12, and the 17β-configuration of the side-chain has been inverted. The n.m.r. spectrum of (**2a**), $C_{25}H_{36}O_3$, non-crystalline,† $[\alpha]_D$ + 64°, has signals attributable to a

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† Difficulties in obtaining 12-methyl-18-nor-C-benzenoid steroids crystalline have been previously noted.[2] Consistent n.m.r., mass, i.r., and (where informative) u.v. spectra have been recorded for all compounds reported.

highly shielded secondary methyl group (δ0·59 d., J 6 Hz, C-21), a tertiary methyl group (δ1·17 s., C-19), a benzylic methyl group (δ2·23 s, C-18), a methoxycarbonyl group (δ3·68 s), a carbinol proton (δ3·67 m, 3β-H), an aromatic proton (δ6·94 s, 11-H), and an OH group (δ1·79, exchanged by D_2O, 3α-OH). Compound (**2a**) was characterized by formation of the crystalline acetate (**2b**) [$C_{27}H_{38}O_4$, m.p. 124—126°] and by alkaline hydrolysis to the crystalline hydroxy-acid (**2c**), $C_{24}H_{34}O_3$, m.p. 81—84°.

Chemical evidence regarding the configuration of the side-chain was sought as follows. Oxidation of the hydroxy-acid (**2c**) to the keto-acid (**3a**), $C_{24}H_{32}O_3$, $[\alpha]_D$ + 61°, followed by bromination to the 4β-bromo keto-acid (**3b**), $C_{24}H_{31}O_3Br$, $[\alpha]_D$ + 107°, and dehydrobromination with lithium chloride yielded the conjugated ketone (**4**), $C_{24}H_{30}O_3$, $[\alpha]_D$ + 199°. Reduction of (**4**) with lithium–ammonia gave the ring A/B-trans hydroxy-acid (**5a**), $C_{24}H_{34}O_3$, m.p. 200—203°, whose acetate (**5b**) underwent oxidative decarboxylation with lead tetra-acetate to give the olefin (**6**), $C_{25}H_{34}O_2$, $[\alpha]_D$ + 41°. Hydroxylation of (**6**) with osmium tetroxide–hydrogen peroxide, followed by periodate cleavage yielded an aldehyde (**7**), $C_{22}H_{30}O_2$, $[\alpha]_D$ + 112·5°, characterized as its 2,4-dinitrophenylhydrazone (m.p. 172—174°). Since this differed from the aldehyde (**8**) obtained from the ergosterol-derived ring-C benzenoid steroid (**9**) with known 17β-configuration, we considered that (**2a**) probably possessed the inverted 17α-side-chain.

This has been fully confirmed by a crystal structure analysis of the iodoacetate derivative (**2d**), $C_{27}H_{37}O_4I$, m.p. 77—78°. The crystals are monoclinic, space group $P2_1$ with 2 molecules per unit cell. The cell dimensions are $a = 11{\cdot}236 \pm 0{\cdot}01$, $b = 14{\cdot}35 \pm 0{\cdot}01$, $c = 8{\cdot}117 \pm 0{\cdot}008$ Å, $\beta = 90{\cdot}59 \pm 0{\cdot}2°$. The structure was solved with 608 non-zero independent reflections collected using Cu-K_α X-rays on a Picker full-circle manual diffractometer with scintillation counter and pulse-height analyser. The heavy-atom method revealed the structure although many electron-density maps were necessary because of the centrosymmetric arrangement of iodine atoms. Oxygen atoms were distinguished from carbon atoms solely on chemical grounds. Refinement was accomplished by full-matrix least-squares calculation. In the final cycles, anisotropic temperature factors were allowed to vary for iodine while carbon and oxygen were refined isotropically. The final value of $R = \Sigma|(|F_o| - |F_c|)|/\Sigma|F_o| = 0{\cdot}07$.

It may be further concluded that the ring-C benzenoid steroid previously obtained from cholic acid by a more circuitous pathway,[4] and differing from (**2**), principally in having a much less shielded 20-methyl group (C-21) (δ 0·99) has the normal 17β-side-chain configuration.

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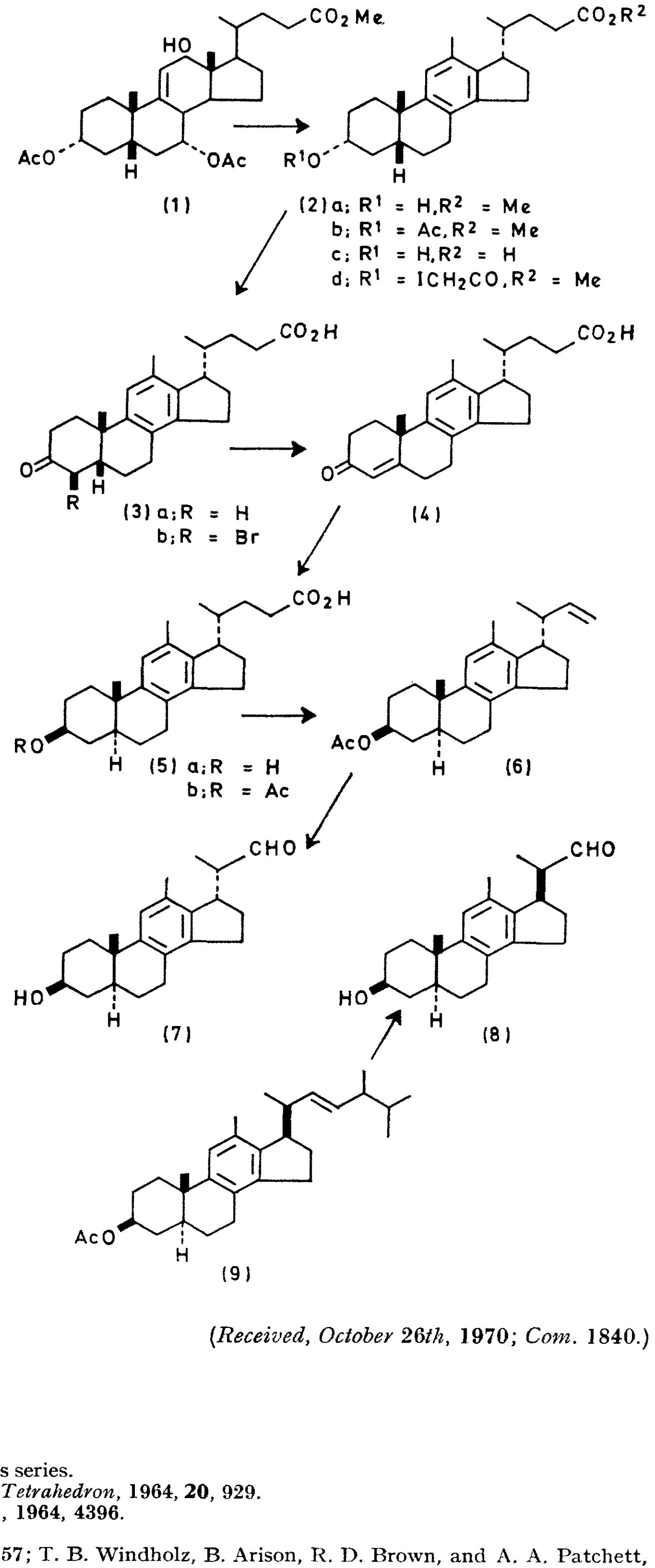

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