New Pathways towards Bufadienolides. Synthesis of 5β,14α-Bufa-20,22-dienolide from Cholanic Acid

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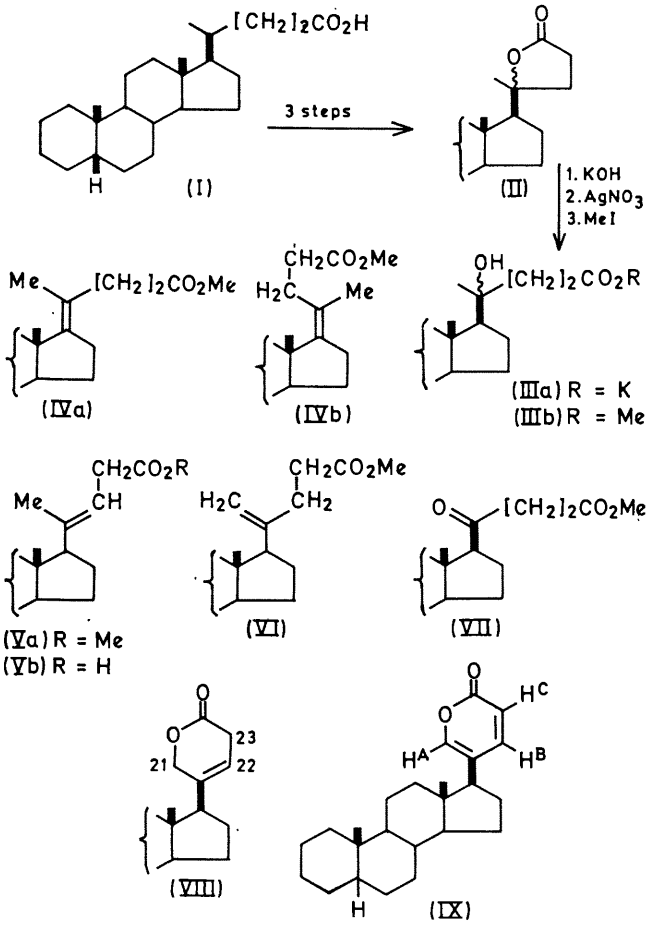
Summary A new route to steroidal bufadienolide systems is illustrated by stepwise functionalization of the cholanic acid side-chain, following the sequence (I) → (II) → (IIIb) → (Vb) → (VIII) → (IX).

THE several known syntheses of 17-steroidal α-pyrones[1] consist of the construction of the α-pyrone system from the C_2 side-chain of a suitable pregnane derivative, the additional three carbons being added in two steps. For the synthesis of bufadienolide system, a C_1 unit (C-22) is first attached at C-20, and then a C_2 unit is added to provide C-23 and C-24 of the system.[2] In a similar manner, isobufadienolides can be obtained if the operation is started at C-21.[3]



The synthesis of the hitherto unknown 5β,14α-bufa-20,22-dienolide represents an alternative synthetic pattern for the α-pyrone system from a cholanic acid side-chain (I) which already contains the required carbon chain.

Conversion of (I) into (IX) entails, formally, both the removal of six hydrogen atoms from the saturated side-chain and its ring-closure. This was achieved by stepwise functionalization, first of C-20, and then of C-22, of C-21, and finally of C-23, following the route (I) → (III) → (V) → (VIII) → (IX).

Lactone (II) was prepared in a three-step synthesis from (I) by the method previously described,[4] and then converted in 75% yield into the methyl 20-hydroxycholanate (III).

The epimeric mixture of (III) could not be induced to crystallize. Its n.m.r. and i.r. spectra were in accord with structure assigned.

The dehydration of (IIIa) by means of thionyl chloride–pyridine, followed by esterification with methanol led predominantly (80%) to a mixture of (IVa) and (IVb),[5] whereas, if (IIIb) (6 g) is exposed to the action of $POCl_3$ (15 ml) in dry pyridine (30 ml)[6] for 24 hr. at room temperature, the product consists of a mixture of (Va) (*cis* and *trans*, 70%), 22% of (IVa–IVb) and 8% of (VI). This was inferred from (i) analysis of the n.m.r. spectrum; and (ii) estimation and identification of ketonic products resulting from ruthenium tetroxide oxidation in CCl_4 (1 hr.)[7] (isolated by preparative t.l.c.).

The predominant ketonic product was identified as 5β-pregnan-20-one,[8] R_F 0·77†, m.p. 115—116° $[\alpha]_D^{27}$ +1·03° (2·6%, $CHCl_3$), i.r.: 1705 cm^{-1}. The minor ketonic products were identified as 5β-androstan-17-one,[9] R_F 0·65,† m.p. 101°, $[\alpha]_D^{27}$ + 75° (1%, $CHCl_3$), i.r.: 1740 cm^{-1}; and (VII), hitherto unknown, R_F 0·55,† m.p. 74—76°, $[\alpha]_D^{27}$ +84° (0·5%, $CHCl_3$), i.r.: 1738 (ester), 1705 (20-ketone).

We found that the oxidative cyclisation step (V → VIII) could best be achieved by applying the *N*-bromosuccinimide (NBS) reaction to the chol-20(22)-enic acid (Vb) rather than to its ester (Va). The entire dehydration product was first hydrolysed by base, and then exposed to the action of NBS in CCl_4 for 48 hr. at room temperature. Preparative t.l.c. afforded (57% yield) the hitherto unknown 5β,14α-bufa-20(22)-enolide (VIII), m.p. 179—180° (from C_6H_{12}), $[\alpha]_D^{27}$ −11·7° (6·7%, $CHCl_3$); i.r.: 1740, 1635, and 1225 cm^{-1}; u.v. (EtOH): 215 nm (ε 2000).

The 60 MHz n.m.r. (downfield from Me_4Si) of (VIII) in $CDCl_3$ exhibits resonances at τ 4·45, a sextet [collapsing to a sharp t (1H, *J* 5 Hz, 22-H) on irradiation at τ 5·4, appearing as singlet on irradiation at τ 7·05 (centre of 23-H_2)], 5·40 [2H, q, 21-H_2; collapsing to d with *J* 1 Hz on irradiation at τ 4·45], 7·07 [2H, double q, 23-H_2; collapsing to an A_2B_2 q on irradiation at τ 5·40, which collapses to d with *J* 1·5 Hz on irradiation at τ 4·45], 9·09 (3H, s, 19-H_3), 9·47 (3H, s, 18-H_3).

In the following communication[10] we show that the quinone-mediated dehydrogenation of (VIII) favours the removal of 17-H and 23-H to yield the isomeric bufa-17(20),-22-dienolide. Fortunately, if (VIII) (0·2 g) is exposed to the action of 2,3-dichloro-5,6-dicyanoquinone (DDQ, 0·2 g) in boiling dioxan (50 ml) containing 50 mg of toluene-*p*-sulphonic acid (20 hr.), the dehydrogenation is specific at

† Determined by t.l.c., Kieselgel G, chloroform–benzene (1 : 9) as eluant.

C-21 and C-23, providing 5β,14α-bufa-20,22-dienolide (IX), m.p. 194—196° (C_6H_6–petrol), $[\alpha]_D^{27}$ + 17° (3·3%, $CHCl_3$), in almost quantitative yield.

The peak at 300 nm (ε 5630) in the u.v. spectrum (EtOH), and the low-field resonances at τ 2·85 (1H, s, H^A), 2·95 (1H, dd, *J* 10 Hz, H^B), and 3·95 (1H, d, *J* 10 Hz, H^C) in the 100 MHz n.m.r. spectrum (CCl_4) are in agreement with formulation (IX).

Although the splitting characteristics of α-pyrone protons in (IX) are similar to those in 14β-hydroxybufa-20,22-dienolides (toad poisons),[11] the corresponding proton resonances in the two systems exhibit differences pertaining both to field location and τ values. Whereas in (IX) the resonances of 21-H and 22-H occur at higher fields, and, 21-H is more deshielded than 22-H, the respective resonances in the n.m.r. spectra of 14β-hydroxybufa-20,22-dienolides occur at lower fields, and the protons at C-22 are more deshielded by 14β-oxygen than those at C-21. This is probably due to conformational factors.

(*Received, October 31st,* 1969; *Com.* 1647.)

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