Isobufadienolides†

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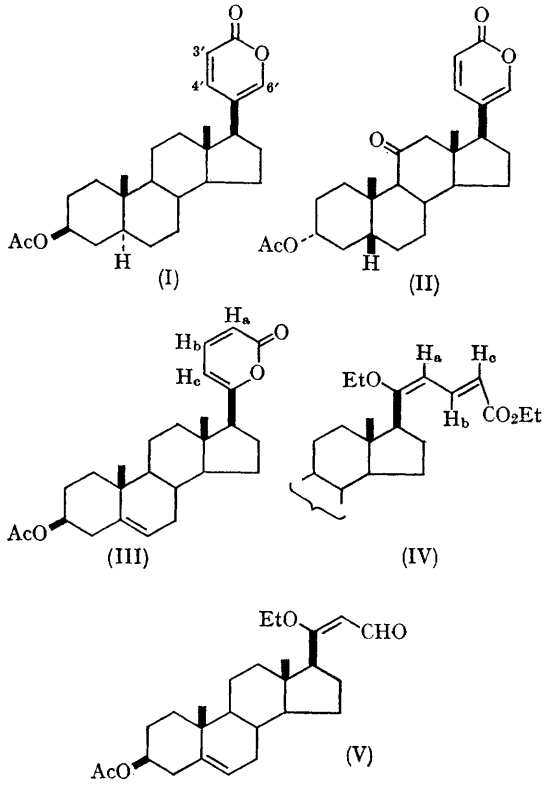
A COMMON structural feature of certain physiologically active steroids is an unsaturated δ-lactone ring, which may be the 2-pyrone system typical of bufadienolides (I), or a dihydro-2-pyrone ring as in the anti-tumour agent withaferin A[2] and related compounds.[3]

Several 2-pyrones have been prepared in which the lactone ring is part[4] of, or fused[5] to, a steroid nucleus, and conversion of the eburicoic acid side-chain into a 2-pyrone group has been described.[6] Although routes to the 5′-substituted 2-pyrones (I) and (II) have been reported,[7,8] the natural

† For the previous contribution in this series, see ref. 1. This investigation was supported by Public Health Service Research Grants from the National Cancer Institute and in part by a grant from CIBA, Summit, New Jersey.

bufadienolides have defied all attempts at synthesis; this is a problem that has assumed increasing importance since the demonstration that compounds of the bufadienolide type also exhibit anti-tumour properties.[9]

With the object of evaluating anti-neoplastic activity and general biological characteristics of bufadienolides, we have undertaken investigation of steroids in which the 2-pyrone ring is linked at C-17 in one of the three possible alternative positions (3′, 4′, and 6′). We now report the first synthesis of a steroidal 6′-substituted 2-pyrone (III). The reaction sequence employed is currently under evaluation as a new and general route to 6-substituted 2-pyrones.



To illustrate, diene (IV) was prepared by treatment of unsaturated aldehyde[10] (V) with the carbanion generated from triethyl phosphonoacetate.[11] A single isomer (IV),‡ the *trans–trans*-form, was isolated, m.p. 153—155°, $[\alpha]_D$ −283° (*c* 1·46); λ_{max} 305 mμ (ε 27,570). The n.m.r. spectrum showed signals at 5·53 (H_a, d., J_{ab} = 12 c./sec.); 5·68 (H_c, d., J_{cb} = 15 c./sec.), and 7·66 (H_b, qu., J_{ab} = 12; J_{bc} = 15 c./sec.) δ. Ester (IV) was converted into pyrone (III) by successive treatment with: (*a*) perchloric acid in diethyl ether to remove the vinyl ether group; (*b*) 2·5% methanolic potassium hydroxide to saponify the ester group; and (*c*) 0·001M-perchloric acid and 1M-acetic anhydride in ethyl acetate[12] to cyclize the resulting keto-acid. The sequence was carried out without isolation of intermediate products, and 2-pyrone (III) was purified by chromatography on silica. Recrystallization from diethyl ether gave needles m.p. 213—216°, $[\alpha]_D$ −67° (*c* 0·82); λ_{max} 305 mμ (ε 6270). The n.m.r. spectrum (100 Mc./sec.) showed signals at 6·005 (H_a or H_c, d., J_{ab} = 6·5 c./sec., with allylic splitting, J_{ac} = 0·75 c./sec.); 6·125 δ (H_c or H_a, d., J_{bc} = 9, J_{ac} (allylic) = 0·75 c./sec.); and 7·27 (H_b, qu., J_{ab} = 6·5; J_{bc} = 9 c./sec.) δ. The elemental analyses and mass spectrum were also consistent with formula (III). Later, the pyrone (III) was obtained (reasonable yields) in one step from the aldehyde (V) by the use of malonic acid in warm pyridine–morpholine solution.

Other lactones of related structure are currently being prepared for biological evaluation.

(*Received, March 13th*, 1967; *Com.* 242.)

‡ All new compounds gave satisfactory elemental analyses. Optical rotations were measured in $CHCl_3$ and u.v. spectra in 95% ethanol solution. ^1H n.m.r. spectra at 60 Mc./sec. were obtained with a Varian A–60 spectrometer ($CDCl_3$ as solvent and tetramethylsilane as internal standard) and a Varian HR–100 was employed for the 100 Mc./sec. measurements. We are grateful to Dr. J. Kutney for the 100 Mc./sec. spectra.

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