Synthesis of Bufalin[1]

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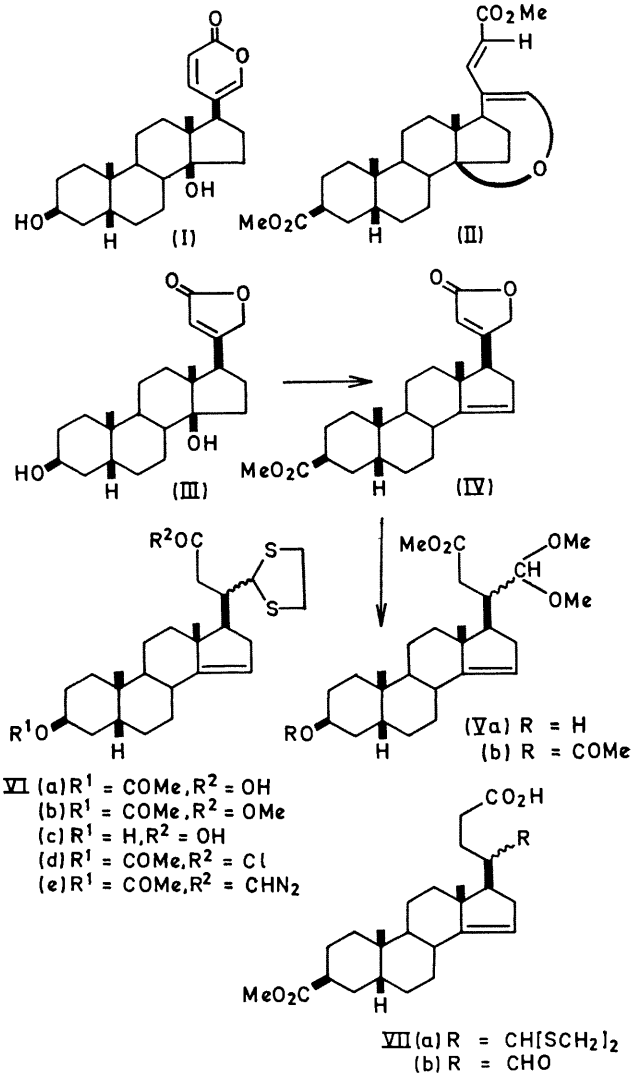
Summary A new total synthesis of resibufogenin and bufalin using digitoxigenin, represents the first chemical transformation of a cardenolide to a bufadienolide.

STEROIDS of the bufadienolide type are important components of toad venoms. Bufalin, a constituent of *e.g. Bufo bufo gargarizans* venom was initially isolated[2] from the Chinese drug, Ch'an Su (Japanese Sen-so) in 1939. Subsequent chemical studies[3] led to structure (I) and a total synthesis was recently reported.†,[4] We have summarized[5] the conversion of bufalin into 3β-acetoxyisobufalin methyl ester (II) and total synthesis[6] of the latter proceeding from digitoxigenin (III). We now report a synthesis of 3β-acetoxy-14-dehydrobufalin (IX). In turn, this constitutes a new total synthesis of bufalin (I).

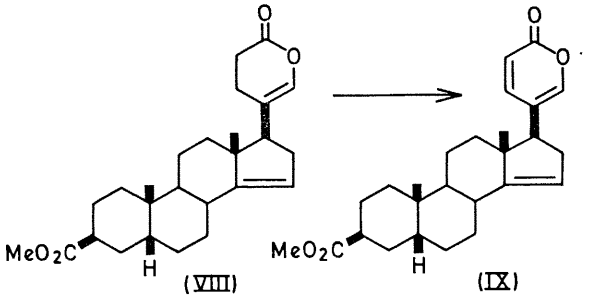
Digitoxigenin (III) was acetylated and dehydrated[7] to yield 3β-acetoxy-14-dehydrodigitoxigenin (IV). Lactone (IV) was suspended in dry methanol and treated (3·5 hr. room temperature) with 5% sodium methoxide in methanol. The intermediate lactol was heated (3·5 hr.) in refluxing methanol containing toluene-*p*-sulphonic acid to afford acetal (Va) (88%).‡ The oily acetal (Va) epimeric mixture was acetylated (acetic anhydride–pyridine) and the product (Vb) allowed to react (2 hr. at 25°) with ethanedithiol containing 70% perchloric acid. Acid (VIa) m.p. 126—129° was obtained (63%) directly from this reaction by washing the ethereal solution with 2N-sodium hydroxide, whereupon the sodium salt of (VIa) was precipitated. The yield of (VIa) was further enhanced (89% overall) by saponification (2N-sodium hydroxide, methanol reflux 2 hr.) of the expected thioacetal (VIb) to give carboxylic acid (VIc), which was then reacetylated (acetic anhydride–pyridine, 18 hr.). Homologation of acid (VIa) was achieved using the following Arndt–Eistert sequence: acid chloride [(VId), oxalyl chloride in benzene at reflux, 2 hr.], diazo-ketone [(VIe), diazomethane in diethyl ether, 18 hr., 54%], and Wolff rearrangement (silver oxide, sodium thiosulphate, dioxan 60°, 2 hr.) to carboxylic acid (VIIa) (m.p. 176–180°, 81% yield). Cleavage of the thioacetal group (mercuric chloride–mercuric oxide–acetic acid–water) yielded (80%) aldehyde (VIIb). Non-crystalline epimeric mixtures of compounds (Va, b), (VIb—e),



† Consult ref. 4b for a synthesis of the related bufadienolide scillarenin.

‡ Intermediates from lactone (IV) to bufadienolide (IX) are new substances and the structure assigned each has been confirmed by an appropriate combination of mass, ^{1}H n.m.r., i.r., and u.v. spectral data. Also, the purity of each was substantiated by preparative layer and thin-layer chromatography.

and (VIIb) were employed in each instance. Enol lactone (VIII) (20%, by preparative layer chromatography, m.p. 165—167°) was obtained by warming (18 hr.) aldehyde (VIIb) in benzene containing toluene-*p*-sulphonic acid. Heating (210°, 25 min.) an intimate mixture of enol lactone



(VIII) and sulphur[8] readily afforded (28% by preparative layer chromatography) 3β-acetoxy-14-dehydrobufalin [(IX), m.p. 170—172°], identical with an authentic specimen (m.p. 171—173°) prepared from bufalin. Completion of the remaining three steps from bufadienolide (IX) to bufalin was reported by Sondheimer and his colleagues[4a] and has also been accomplished in our laboratory.

The synthetic approach to resibufogenin and bufalin now reported also represents the first chemical transformation of a cardenolide to a bufadienolide. Interconversion of certain cardiac aglycones to their otherwise difficultly accessible toad poison counterparts now appears practical.

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