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SYNTHETIC STUDIES IN STEROIDAL SAPOGENINS AND ALKALOIDS—VI

SYNTHESIS OF ISONARTHOGENIN

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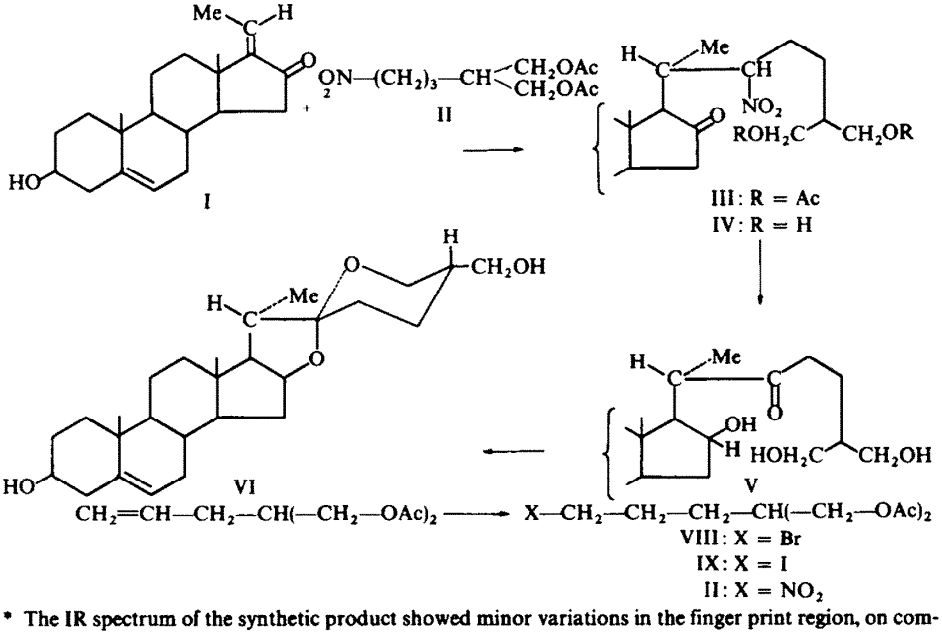
Abstract—Michael adduct of 5-nitro-2-hydroxymethylpentanol-1 diacetate and *cis*-5,17(20)-pregnadien-3β-ol-16-one gives, on reduction with sodium borohydride, 25*R*-spirost-5-ene-3β, 27-diol which has been shown to be identical with isonarthogenin.

RECENTLY Minato and Shimaoka[1] have isolated a new steroidal sapogenin, isonarthogenin, from the epigeous part of *M. luteoviride*. On the basis of degradative and correlative work this compound was assigned 25*R*-spirost-5-ene-3β, 27-diol (III) structure which is now confirmed by an unambiguous synthesis.

Michael addition of 5-nitro-2-hydroxymethylpentanol-1 diacetate (II) to *cis*-5,17(20)-pregnadien-3β-ol-16-one (I) furnished an oily product. By chromatography a solid corresponding to structure IV could be isolated from this material in low yield. The crude oil, however, on reaction with sodium borohydride in boiling ethanol furnished a product identical with natural isonarthogenin by mixed m.p., IR spectrum,* specific rotation and TLC. The postulated intermediate, tetraol V,



* The IR spectrum of the synthetic product showed minor variations in the finger print region, on comparison with the natural sample. This was traced to difference in solvent of crystallization. The spectra were completely superimposable when both the products were crystallized from acetone. We are grateful to Prof. Minato for a sample of isonarthogenin and for the later IR comparison.

was expected to spiroketalize in such a manner as to place the C-27 hydroxymethyl group in stable equatorial position.

The nitro compound II was prepared from 2-hydroxymethyl-4-pentenol-1 diacetate (VII) *via* peroxide catalysed hydrogen bromide addition. In reaction of halides VIII and IX with sodium or silver nitrite the product was contaminated with an impurity which was difficult to eliminate. As this may be due to formation of secondary halide during hydrogen bromide addition,[2] reduction of diethyl 3-bromopropylmalonate with LAH in presence of anhydrous aluminium chloride was attempted. The desired diol, however, could not be obtained by this reaction.

The present work constitutes first formal total synthesis of a steroidal sapogenin with an additional function in ring F, and illustrates the versatility of this route.[2]

EXPERIMENTAL

5-Bromo-2-hydroxymethyl-1-pentanol diacetate (VIII). Dry HBr was bubbled through a mixture of VII[3] (5 g), pet. ether (15 ml, 80–100°), benzoyl peroxide (100 mg) and a drop of water. Every 15 min the supply of gas was discontinued and air passed through the reaction mixture for 1 min. After 3 hr water was added and the aqueous layer extracted with ether. The combined organic layer was washed free of acid and dried. The solvent was removed and the residue fractionated to collect VIII as colourless oil (5·5 g), b.p. 120–122°/0·5 mm, n_D 1·4728. (Found: C, 42·58; H, 5·80. $C_{10}H_{17}O_4Br$ requires: C, 42·70; H, 6·05%.)

5-Iodo-2-hydroxymethyl-1-pentanol diacetate (IX). The bromoacetate VIII (19 g) was refluxed with NaI (17·8 g) in acetone (125 ml) for 2 hr. After removal of acetone, the residue was diluted with water and extracted with ether. The ethereal soln was washed with $Na_2S_2O_3$ aq and water, dried and the solvent removed. The residue distilled with decomposition with liberation of I_2 (19·4 g), b.p. 132–133°/0·5 mm, n_D^{27} 1·506. The coloured distillate was used as such in the next reaction.

5-Nitro-2-hydroxymethyl-1-pentanol diacetate (II). A soln of the above iodo compound (19 g) in dry ether (100 ml) was added in the dark, dropwise with stirring, to a cold (0°) suspension of $AgNO_2$ (13·7 g) in ether (100 ml). Stirring was continued for 24 hr at 0° and for 36 hr at room temp. The suspended solid was removed and washed with ether. Solvent was stripped off from the combined ethereal soln and the residue distilled to collect 3 fractions: (a) b.p. 70–135°/1 mm (1 g); (b) b.p. 139–142°/1 mm (8 g); ν_{max} 5·75 (s), 6·1 (s), 6·45 (s), 8·1 (s) μ; (c) b.p. 142–145°/1 mm (3 g), ν_{max} 5·75 (s), 6·1 (ω), 6·45 (s), 8·1 (s) μ. The material (b) was resolved into 2 fractions by distillation. The higher boiling portion was combined with (c) and the whole refractionated to collect a light pale liquid (3 g), b.p. 143–144°/1 mm, ν_{max} 5·75, 6·45, 8·1 μ, n_D^{27} 1·5765. (Found: C, 48·40; H, 6·70; N, 6·09. $C_{10}H_{17}NO_6$ requires: C, 48·58; H, 6·88; N, 5·66%.)

A reaction of VIII with $NaNO_2$ in DMF gave similar results.

Michael addition of II *to* cis-5,17(20)-*pregnadien*-3β-*ol*-16-*one* (I). A soln of the potassium salt of II (from II, 700 mg and K metal, 62 mg) in t-butyl alcohol (3 ml) was added to a soln of *cis*-ketone I (500 mg) in the same solvent (3 ml). The reaction mixture was allowed to stand at room temp for 10 days, when on addition of 10% AcOH (2 ml) an oil separated. Excess water was added, the organic material was taken up in CH_2Cl_2, washed with $NaHCO_3$ aq, water and dried. Evaporation of solvent left an oil which was triturated with two 3 ml portions of ether–pet. ether (40–60°) mixture (1:1). The residual gum (600 mg), ν_{max} 5·75, 6·45 μ (film) could not be induced to crystallize. Half of it was chromatographed on alumina (20 g). Most of the fractions were oily, and only from EtOH fraction a solid (15 mg) was obtained. It was crystallized from benzene, m.p. 175–177°, ν_{max} 5·75, 6·45 μ (KBr). (Found: N, 3·26. $C_{27}H_{43}NO_6$ requires: N, 2·93%.)

Isonarthogenin (VI). A soln of the above gum (84 mg) in EtOH (24 ml) was refluxed with $NaBH_4$ (700 mg) for 4 hr. The mixture was decomposed by addition of 4% HCl (80 ml). A solid slowly separated which was collected after 4 hr, washed with water and dried (40 mg), m.p. 217–212°. It was crystallized from MeOH, m.p. 236–238°, $[\alpha]_D$ −110°. It had superimposable IR (Chf), identical R_f value and mixed m.p. (236–238°) with the natural sample.

Diacetate was obtained in the usual manner, m.p. 151–153°. No depression in m.p. was observed on admixture with the diacetate from the natural sample and their IR spectra were superimposable.

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