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THE STEREOSPECIFIC SYNTHESIS OF d,l-VERBENALOL

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Verbenalol (II) is the aglucone of verbenalin (I), a glycoside contained in Verbena officinalis L., the most plausible structure (I) of which was given by G. Büchi and R. E. Manning in 1960 (1).

Now, we wish to report the stereospecific synthesis of racemic verbenalol, which is one of the most possible biogenetic precursors of the indole alkaloids (2), and has a closely related structure to the components from Actinidia polygama Miq. and Boschniakia rossica Hult. (3).

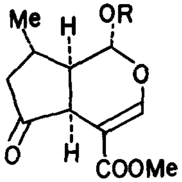
In order to suffice the stereochemistry of verbenalol (II), endo-tricyclo [5.2.1.$0^{2,6}$] decan-3,8-dien-5-one (III), the configuration of which was previously decided (4), was chosen as a starting material, and treated with the etheral solution of methylmagnesium bromide containing a small amounts of cuprous bromide. The reagent attacked the α,β-unsaturated carbonyl system in III from its exo-side for the steric reason and at its β-position by the effect of the cuprous salt (5) to give a methylated compound (IV), b.p. 78°/3 mm, ν_{max}^{oil} 3050, 1750, 1560 cm^{-1}, Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.52; H, 8.75, $\delta\, ppm_{TMS}^{CCl_4}$ a doublet centered at 1.08 (J=6c.p.s).

IV was reduced to the corresponding alcohol (V), b.p. 90-92°/4.5 mm, ν_{max}^{oil} 3400, 3080, 1580 cm^{-1}, Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.41; H, 9.55, which was acetylated with acetic anhydride-pyridine to the acetate (VI), b.p. 93-95°/3.5 mm, ν_{max}^{oil} 3080, 1745, 1570, 1240 cm^{-1}, Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.72; H, 8.81. The Lemieux oxidation (6) of the acetate (VI) successfully yielded the desired dicarboxylic acid (VII), m.p. 296-271°, ν_{max}^{nujol} 3400, 2700, 1745, 1680 cm^{-1}, Anal. Calcd. for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.75; H, 6.65.

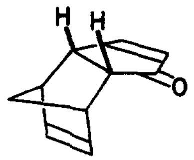
The dicarboxylic acid (VII) was easily converted to an acid anhydride (VIII), m.p. 98-100°, ν_{max}^{nujol} 1810, 1780, 1745 cm^{-1}, by refluxing in acetic anhydride for 2 hours. Both VII and VIII were lactonized in cold concentrated sulfuric acid (5°) to a lactone acid (IX), m.p. 196-197.5°, $\nu_{max}^{CHCl_3}$ 3500, 2700, 1765, 1745, 1710 cm^{-1}, Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.61; H, 6.89.

Oxidative decarboxylation of IX with lead tetraacetate in N,N-dimethylacetamide (7), afforded an olefinic lactone (XII), m.p. 31-32°, ν_{max}^{nujol} 3030, 1780, 1600, 1170 cm^{-1},

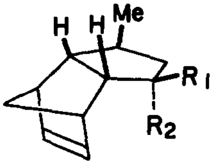
$\delta\ \mathrm{ppm}^{CCl_4}_{TMS}$ 5.80 (2H: olefinic protons), besides an acetoxylated product (XI), m.p. 65-67°, ν^{nujol}_{max} 1780, 1750, 1210, 1170 cm^{-1}, Anal. Calcd. for $C_{12}H_{16}O_4$: C, 75.69; H, 8.80. Found: C, 75.72; H, 8.81 in only 6 and 3 per cent yield, respectively.



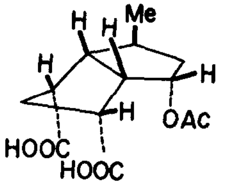
I : R = Glucose
II : R = H



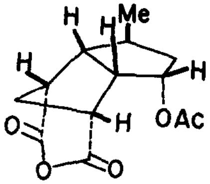
III



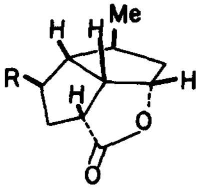
IV : R_1, R_2 = O
V : R_1 = H, R_2 = OH
VI : R_1 = H, R_2 = OAc



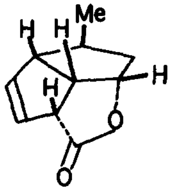
VII



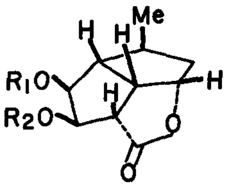
VIII



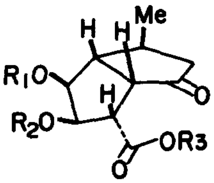
IX : R = COOH
X : R = OAc
XI : R = J



XII



XIII : $R_1 = R_2$ = H
XIV : $R_1 = R_2$ => CMe_2



XV : R_1, R_2 => CMe_2, R_3 = H
XVI : R_1, R_2 => CMe_2, R_3 = Me
XVII: R_1, R_2 = H , R_3 = Me

The yield of XII was improved by the alternative method, that is, IX was converted into the lactone (XI), m.p. 84°, by the Barton procedure (8) and its subsequent dehydroiodination by refluxing in pyridine for ten hours gave the olefinic lactone (XII) in 60% overall yield.

XII was oxidized to a dihydroxylactone (XIII), m.p. 103-104°, ν^{nujol}_{max} 3550, 3450, 1775, 1190 cm^{-1}, Anal. Calcd. for $C_{10}H_{12}O_4$: C, 60.59; H, 7.12. Found: C, 60.59; H, 7.19, with an equimolar amount of osmium tetraoxide in a quantitative yield.

XIII was led to the acetonide (XIV), m.p. 84-86° in a good yield, when allowed to stand with anhydrous cupric sulfate in acetone at room temperature for 24 hours. XIV was dissolved in aqueous sodium carbonate solution, and oxidized with ruthenium tetraoxide under cooling below 5° for 25 minutes, to the ketonic acid (XV), which was immediately methylated with an ethereal diazomethane solution to an oily keto ester (XVI) in a good yield. This keto ester (XVI) was hydrolyzed by warming with 20 % aqueous acetic acid at 70° for a few hours to a dihydroxy keto ester (XVII), m.p. 119-120°, $\nu_{max}^{CHCl_3}$ 3550, 3450, 1740, 1730 cm^{-1}, Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.72; H, 7.12.

The dihydroxy keto ester (XVII) was oxidized with lead tetraacetate in absolute benzene to verbenalol II, which was completely consistent with the natural verbenalol in both IR (chloroform), and UV (ethanol) spectra.

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