

THE TOTAL SYNTHESIS OF (±)-WIDDROL

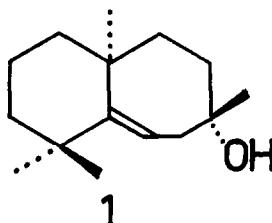
C. Enzell

Organisk-kemiska Institutionen, Kungl. Tekniska Högskolan, Stockholm

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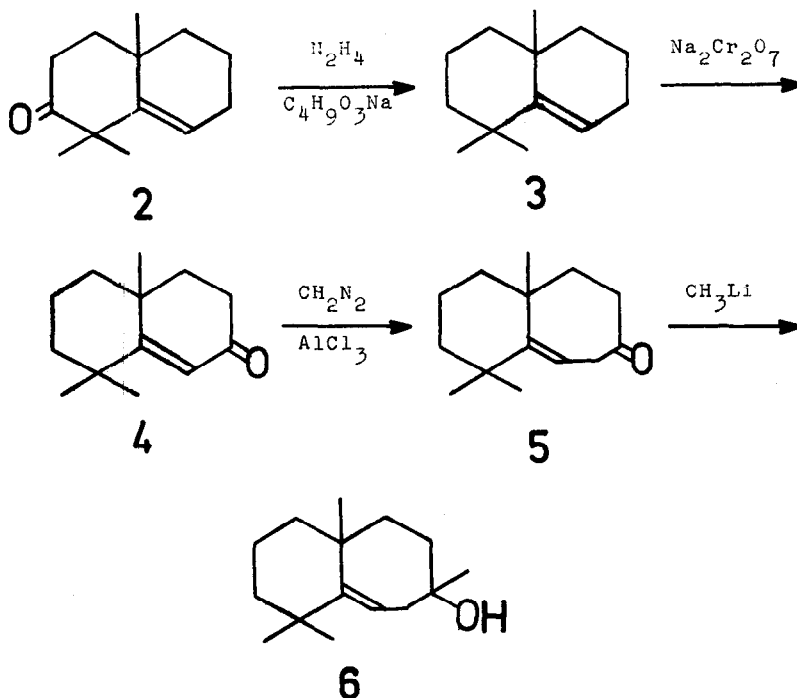
WIDDROL was first isolated from the heartwood of several Widdringtonia species by Erdtman and Thomas¹. It has since been encountered in the heartwood of a number of other conifers belonging to the natural order Cupressales and frequently together with the sesquiterpenes cuparene, cedrol and thujopsene.²

The structure of widdrol, as well as the orientation of its angular methyl group, has recently been reported³ and a full description⁴ on its absolute configuration, as shown in formula (1), will be published elsewhere.



(±)-Widdrol was synthesized as indicated in the following scheme:

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- ¹ H. Erdtman and B.R. Thomas, Acta Chem. Scand. 12, 267 (1958).
 - ² H. Erdtman, 4th Intern. Congr. Biochem. Vol. II, Biochemistry of Wood (1958).
 - ³ C. Enzell, Acta Chem. Scand. 15, 1191 (1961).
 - ⁴ C. Enzell, Acta Chem. Scand. 16, in press (1962).



A synthesis of the starting material, the trimethyl octalone (2) has recently been described by Mukherjee and Dutta⁵. It was obtained in 35% overall yield from 2-chloroethyl ethyl ketone and 2-methylcyclohexanone and methylation of the product with methyl iodide and potassium t-pentyl-oxide.

The ketone (2), sodium diethyleneglycolate and anhydrous hydrazine in diethyleneglycol were heated at 200-205° for 20 hr. The product was fractionally distilled at reduced pressure through a spinning band column to give the trimethyl octalin (3) in 65% yield. (n_D^{25} 1.4971; $\nu_{\text{max}}^{\text{CCl}_4}$ 795, 1640 cm^{-1}).

⁵ S.L. Mukherjee and P.C. Dutta, J. Chem. Soc. 67 (1960).

The octalin was oxidized with sodium dichromate (1.4 mole equivalents) in acetic acid at 20° overnight and then at 100° for 2.5 hr. Chromatography on alumina furnished the trimethyl octalone (4) in 70% yield. (n_D^{25} 1.5142; $\lambda_{\max}^{\text{EtOH}}$ 240 m μ , ϵ 13.000; $\nu_{\max}^{\text{CCl}_4}$ 1670, 1597 cm⁻¹.) It gave a deep red 2,4-dinitrophenylhydrazone m.p. 204-205°.

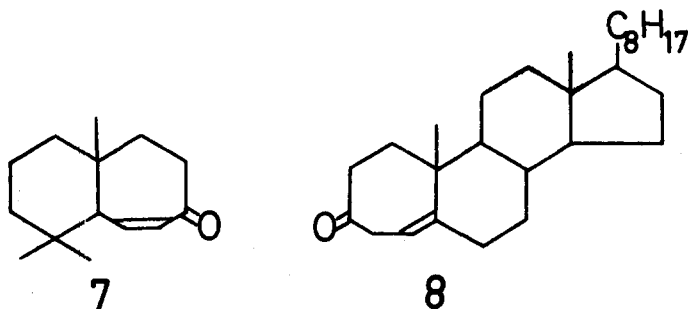
The expansion of ring B of the ketone (4) was accomplished at room temperature with excess diazomethane (1.6 mole equivalents) in ether in the presence of catalytic amounts of deactivated aluminium chloride* (0.08 mole equivalents). The product, a complex mixture of ketones, was chromatographed on silica gel and each fraction analysed by means of vapour phase chromatography (V.P.C.) and mass spectrometry. The ketone (5), possessing the required infra-red ($\nu_{\max}^{\text{CCl}_4}$ 1712 cm⁻¹) and mass spectrometric (m/e 206, molecule-ion) data, was obtained in 15% yield according to V.P.C. and furnished an orange 2,4-dinitrophenylhydrazone, m.p. 161-162° ($\lambda_{\max}^{\text{EtOH}}$ 255 m μ , ϵ 16.000, 370 m μ , ϵ 27.000) It was not obtained in higher purity than 90% and was contaminated with an α,β -unsaturated ketone, possibly (7). The reaction product was also found to contain starting material (20%) and non-conjugated ketones of higher molecular weight (220, 234, 248, 262) as shown by infra-red and mass spectrometry.

The previously reported⁶ ring expansion of cyclic, α,β -unsaturated ketones with diazomethane was carried out in methylene chloride with fluoboric acid as catalyst and led, in the case of 4-cholestene-3-one, to the production of A-homo-4a-cholestene-3-one (8). This catalyst, in methylene chloride or ether, had no effect in the present case and only starting material was recovered. Fully active aluminium chloride was also

* The aluminium chloride, from the residual contents of a stock bottle, was ground in a mortar without protection from moisture.

⁶ W.S. Johnson, M. Neeman and S.P. Birkeland, Tetrahedron Letters No. 5, 1 (1960), compare E. Müller, M. Bauer and W. Rundel, Ibid. 136 (1961).

found to be less satisfactory since it gave rise to larger amounts of compounds of higher molecular weight.



The ketone (5) was treated with an excess of methyl lithium in ether at reflux temperature for 1 hr. The product was chromatographed on alumina to give (\pm)-widdrol (6), m.p. 86-87^o, in 25% yield. The synthetic specimen gave infra-red and mass spectra identical with those of natural widdrol and its melting point was not depressed on admixture with this compound.

All new compounds gave correct analysis or correct molecular weights according to mass spectrometric measurements.

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