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STEROIDS CCCXII.(1)

A NEW SYNTHETIC ROUTE TO BISDEHYDRODOISYNOLIC ACIDS.

W. R. J. Simpson,(2) D. Babbe, J. A. Edwards and J. H Fried

Institute of Steroid Chemistry
Syntex Research, Palo Alto, California

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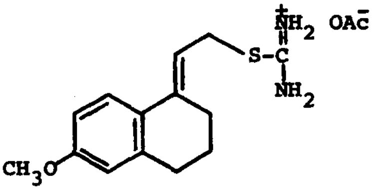
The *cis*-doisynolic acids constitute a unique class of ring D seco steroids in that these substances show hormonal activity similar to that of the natural estrogens.(3) Herein is described a novel and highly practical stereospecific synthesis of the methyl ester of (±)-cis-bisdehydrodoisynolic acid methyl ether (6) commencing with the readily available isothiuronium salt (1)(4) and α,γ-dimethyltetronic acid (2).(5)

The base catalyzed condensation of 1,2,3,4-tetrahydro-6-methoxy-1-vinyl-1-naphthol with 2-methylcyclopentane-1,3-dione yields the alkylated product (3, $X=CH_2$; R=H), a key intermediate in the total synthesis of estrogenic steroids.(6) It was later demonstrated that this reaction is acid-catalyzed although an external proton source is not essential since 2-methylcyclopentane-1,3-dione (pK_a 4.5) readily alkylates both the tetrahydrovinylnaphthol and the derived isothiuronium salt (1) in aqueous alcohol.(4)

It appeared likely that α,γ-dimethyltetronic acid (pK_a 4.0)(5) should alkylate (1) to afford the intermediate (3, X=O; $R=CH_3$) having all the carbon atoms of the doisynolic acid skeleton. Indeed, addition of the tetronic acid (2) to a solution of the salt (1) in aqueous ethanol resulted in precipitation of α-(6-methoxy-1,2,3,4-tetrahydronaphthylidenethyl)-α,γ-dimethyltetronic acid (3, X=O; $R=CH_3$) [m.p. 82-83°; λ_{max} 209, 266 mμ (log ε 4.29, 4.22); ν_{max} 1800, 1755, 1600, 1500 cm^{-1}; n.m.r. 1.33 (s., tert. CH_3), 1.45 (d., *J* 7 c.p.s., sec. CH_3), 3.77 (s., aromatic methoxyl), 4.59 (q., *J* 7 c.p.s., $CH_3\underline{CH}$), 5.70 p.p.m. (t., broadened by allylic coupling, *J* 7 c.p.s., olefinic-H). Found: C, 72.81; H, 7.12](7)(8) from the reaction mixture in 86% yield. Brief treatment of (3, X=O; $R=CH_3$) with *p*-toluenesulfonic acid in boiling benzene gave the tetracyclic enol lactone (4a) (93% yield) [m.p. 156-157°; λ_{max} 215, 232, 316 mμ (log ε 4.06, 3.99, 4.42); ν_{max} 1780, 1670, 1620, 1590, 1560 cm^{-1}; n.m.r. 1.21 (s., tert. CH_3), 2.16 (s., vinylic CH_3), 3.74 p.p.m. (s., aromatic methoxyl). Found: C, 76.58; H, 6.57] which was dehydrogenated by 5% palladized charcoal in boiling xylene to the naphthalene derivative (4b) (80% yield) [m.p. 117.5-119°; λ_{max} 259, 294, 305, 335, 350 mμ (log ε 4.60, 4.19, 4.17, 3.29, 3.29); ν_{max} 1800, 1675, 1620, 1600 cm^{-1}; n.m.r. 1.28 (s., tert. CH_3), 2.30 (s., vinylic CH_3), 3.90 p.p.m. (s., aromatic methoxyl). Found: C, 77.59; H, 6.08].



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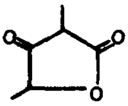

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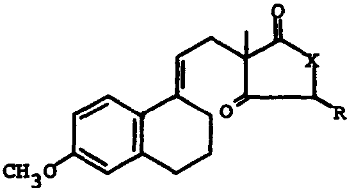

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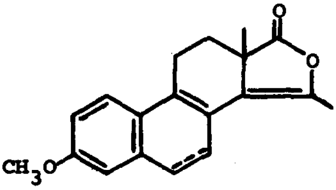
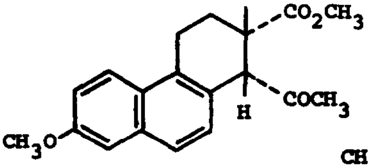


4a 6,7-dihydro
b 6,7-double bond



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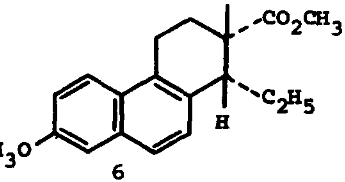

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Exposure of the latter product to dilute aqueous sodium hydroxide in ethanol gave in high yield an insoluble crystalline sodium salt which was converted into the (±)-*cis*-keto ester (5) (76% yield from 4b) [m.p. 156-157°; λ_{max} 235, 277, 322, 356 mμ (log ε 4.72, 3.70, 3.25, 3.22); ν_{max} 1710, 1625, 1600 cm^{-1}; n.m.r. 1.15 (s., tert. CH_3), 2.26 (s., $COCH_3$), 3.74 (s., CO_2CH_3), 3.91 (s., aromatic methoxyl)4.13 p.p.m. (s., H-C-$COCH_3$). Found: C, 73.71; H, 6.82] by treatment with methyliodide in dimethylacetamide. Electrochemical reduction(9) of (5) at a lead cathode (current density 0.01 amps./sq. cm.) in dioxane containing 20% sulfuric acid gave in 70% yield the methyl ester of (±)-*cis*-bisdehydrodoisynolic acid methyl ether (6) [m.p. 76.5-77° (lit.(10) reports 76-78°); λ_{max} 229, 266, 276, 288, 331, 335 mμ (log ε 4.73, 3.70, 3.70, 3.57, 3.34, 3.41); ν_{max} 1725, 1625, 1600 cm^{-1}; n.m.r. 0.94 (t., J 7.5 c.p.s., $CH_2C\underline{H}_3$), 1.16 (s., tert. CH_3), 3.76 (s., CO_2CH_3), 3.90 p.p.m. (s., aromatic methoxyl). Found: C, 77.31; H, 7.97] identical in all respects with an authentic sample(10) obtained by methylation of (±)-cis-bisdehydrodoisynolic acid methyl ether.

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7. All rotations are for chloroform solutions, ultraviolet spectra for 95% ethanol solutions and infrared spectra for KBr discs, unless otherwise specified. N.m.r. spectra were recorded for 5-10% solutions in deuteriochloroform containing tetramethylsilane as internal reference on Varian A-60 and H.R.-100 spectrometers. Chemical shifts are reported as p.p.m. on the δ scale (we wish to thank J. Murphy and J. Tremble for the n.m.r. determinations). In the presentation of data s. = singlet, d. = doublet, t. = triplet, q. = quartet (aromatic proton resonance frequencies are not reported).
8. The analogous condensation of 1,2,3,4-tetrahydro-6-methoxy-1-vinyl-1-naphthol with α-methyltetronic acid has been described recently by R. Pappo in U.S. Patent 3,309,383 (March 14, 1967).
9. A detailed account of this method will be the subject of a forthcoming publication by Dr. L. Throop and associates of this laboratory.
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