Stereochemistry of the D-Seco-steroid Doisynolic Acid

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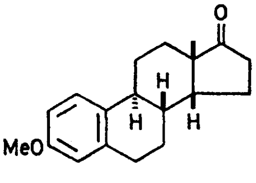
Summary The absolute configuration of (+)-*cis*-doisynolic acid is established by a stepwise conversion from oestrone 3-methyl ether.

ALTHOUGH known for almost forty years,[1] and in spite of a total synthesis of the racemate,[2] the stereochemistry of doisynolic acid has remained in doubt. In this work we assign the configuration at all centres by an unambiguous conversion of oestrone into (+)-*cis*-doisynolic acid 3-methyl ether.

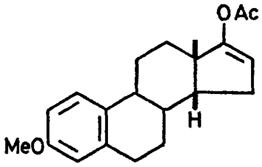
The osmium tetroxide oxidation of the enol acetate (**2**), m.p. 112—113°; $[\alpha]_D$ +163°,† prepared from 14β-oestrone 3-methyl ether (**1**),[3] provided 16α-hydroxy-14β-oestrone methyl ether (**3a**), m.p. 125—126°; $[\alpha]_D$ +130°, in 47% yield, easily acetylated into (**3b**), m.p. 128—129°; $[\alpha]_D$ +121°. Subsequent periodic oxidation of (**3a**) gave the lactol (**4**), m.p. 161—162°; $[\alpha]_D$ +129°, in 85% yield. Treatment of (**4**) with diazomethane furnished the D-seco-16-aldehydo-17-ester (**5a**), m.p. 113—115°, $[\alpha]_D$ + 97°, in 76% yield.

Electrochemical reduction[4] of the aldehyde (**5a**) afforded the methyl ester (**6a**), m.p. 93—94°; $[\alpha]_D$ + 109°; ν_{max} 1725 cm^{-1}, in 60% yield, also obtained by Raney nickel hydrogenolysis of the benzylthioacetal (**5b**) m.p. 104—105°; $[\alpha]_D$ + 25°, in 39% yield.

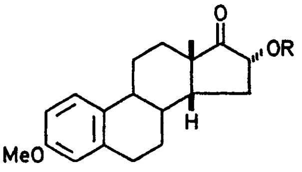
Hydrolysis of the ester (**6a**) with 10% sodium hydroxide in ethylene glycol at reflux temperature provided (+)-*cis*-doisynolic acid 3-methyl ether (**6b**), m.p. 174—175°; $[\alpha]_D$ +95°, in 80% yield. The physical properties of (**6b**) are in agreement with those reported[2] for the 3-methyl ether of (±)-*cis*-doisynolic acid, thus establishing unambiguously (+)-*cis*-doisynolic acid to present the natural 8βH,9αH configuration.



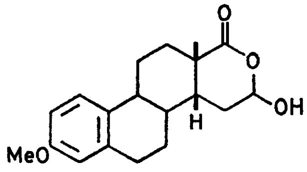
(1)



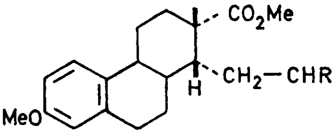
(2)



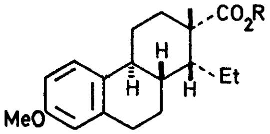
(3)
a; R = H
b; R = Ac



(4)



(5)
a; R = O
b; R = (SCH$_2$Ph)$_2$



(6)
a ; R = Me
b ; R = H

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† Satisfactory elemental analyses or mass spectra were obtained for all new compounds. N.m.r. and i.r. spectra were consistent with their formation.

[1] D. W. MacCorquodale, S. A. Thayer, and E. A. Doisy, *J. Biol. Chem.*, 1933, **99**, 327; D. W. MacCorquodale, L. Levin, S. A. Thayer, and E. A. Doisy, *ibid.*, p. 753.
[2] G. Anner and K. Miescher, *Helv. Chim. Acta*, 1947, **30**, 1422.
[3] P. Crabbé, A. Cruz, and J. Iriarte, *Canad. J. Chem.*, 1968, **46**, 349.
[4] L. Throop and L. Tökés, *J. Amer. Chem. Soc.*, 1967, **89**. 4789.