Absolute Configuration of 3-Aryloxypropane-1,2-diols and Derivatives: Mephenesin Isomers

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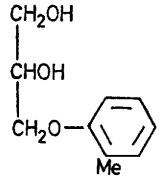
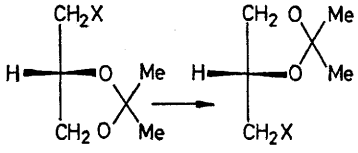
Summary The optical isomers of mephenesin (3-*o*-tolylpropane-1,2-diol) were prepared from 2*R*- and 2*S*-3-tosyloxypropane-1,2-diol acetonide by reaction with *o*-cresol (NaOH) and the configurations confirmed on the basis of c.d. spectra in Cupra A Solution.

MANY important drugs demonstrate stereospecificity in their pharmacological actions and/or metabolism, sometimes showing enantiomeric potency differences of several hundred-fold, or even different pharmacological effects.[1] Demonstration of these significant differences is dependent upon finding methods to obtain materials of known absolute stereochemistry and high optical purity.



(1) Mephenesin



(2) X = OH
(3) X = OTs
(4) X = OBz
(5) X = OAr

(6) X = OH
(7) X = OTs
(8) X = OAr

We report the preparation of the optical isomers of 3-*o*-tolyloxypropane-1,2-diol, mephenesin, (**1**),[2] suitable for study of muscle relaxants of known absolute configuration, and an intermediate suitable for obtaining the optical isomers of 1-alkylamino-3-aryloxypropan-2-ols,† important selective adrenergic agonists and antagonists. The acetonide (**2**) was prepared by the method of Baer from (+)-2*R*,3*R*,4*R*,5*R*-mannitol.[3] 2*S*-Glycerol-2,3-acetonide (**2**) was converted into the 2*S*-tosylate ester (**7**), by formation of the benzyl ether, hydrolysis of the acetal, tosylate ester formation, hydrogenolysis and subsequent reformation of the acetonide acetal.[4] The respective tosylates, (**3**) and (**7**), were converted into aryl ethers (**5**) and (**8**) respectively using sodium *o*-cresolate [MeOH; 110° (sealed bomb); 30 h] followed by hydrolysis, (0·5N aq. HCl; 70°; 2 h) to afford respectively 2*R*-mephenesin, m.p. 89—90° (H_2O) (70% yield), and 2*S*-mephenesin, m.p. 89—90° (H_2O) (65% yield). The i.r. spectra (KBr) are not significantly different than that recorded for mephenesin, m.p. 70—72°.[5] High-resolution mass spectral fragmentation were essentially identical with the spectrum of *rac*-mephenesin.

Optical rotations, Na_D line, were small and not useful. Differentiation between isomers using o.r.d. spectra or n.m.r. spectra in asymmetric solvents failed. The c.d. spectra, in Cupra A solution (Figure), provided clear distinction between optical isomers,‡§ and provided data consistent with the known absolute configurations based on synthesis.

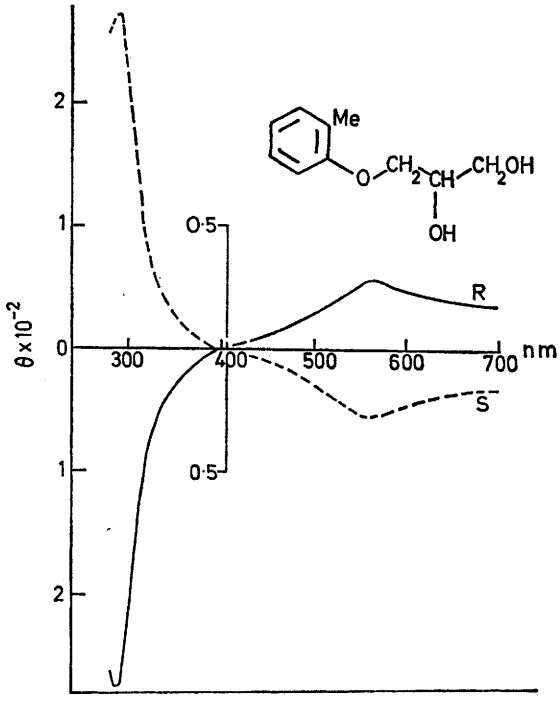


FIGURE. C.d. spectra of mephenesin isomers in Cupra A solution.

The c.d. spectra of 2*R*- and 2*S*-mephenesin show positive and negative bands respectively in the 600 nm region and Cotton effects of opposite sign in the 300 nm region consistent with their absolute configurations:¶ 2*R* (*c* 0·220 Cupra A) $[\theta]_{560}$ 30°, $[\theta]_{380}$ 0°, $[\theta]_{290}$ −275°; (*c* 0·232 Cupra A) $[\theta]_{565}$ −30°, $[\theta]_{380}$ 0°, $[\theta]_{290}$ 270°.

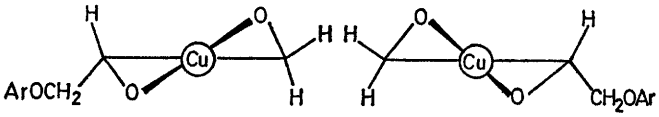
† Following completion of this work a report appeared using a related derivative in the synthesis of an isomer of practalol, thus establishing its absolute configuration: J. C. Danilewicz and J. E. G. Kemp, *J. Medicin. Chem.*, **1973**, **16**, 168. Similar results have been obtained in this laboratory.

‡ We thank Dr. L. A. Mitscher and Mr. M. S. Bathala, Ohio State University, for these spectra.

§ Incomplete separation of the half-acid phthalates of mephenesin has been reported, although no assignments of absolute stereochemistry were made: K. A. Thaker and S. H. Patel, *J. Sci. Ind. Res., India*, 1961, **20B**, 327.

¶ C.d. measurements (in deg cm²/mol) were recorded on a JASCO UV/ORD/5 instrument with a c.d. attachment (Sproul Instrument Corporation, Model SS20-2). Intensities are not absolute since the reaction between glycols and Cupra A is an equilibrium process. Solutions were prepared in Cupra A solution [0·01M-Cu^{2+} dissolved in 0·34M-NH_3 (H_2O–EtOH)].[6]

The Cotton effects are similar to those consistently observed for the chloramphenicol isomers, and assigned to the chiral centre at C-1.[7] The signs of the bands in the 400—700 nm region are consistent with stereochemistry assigned from Cupra A spectra of other 1,2-glycols,[8] and to the chiral phenylethane-1,2-diols.[9] Conformations of δ and λ[8,10] are, therefore, assigned to the diol-Cupra A complexes of 2*R*- and 2*S*-mephenesin, respectively.



λ 2*S*-Mephenesin
Ar = *o*-Tolyl

δ 2*R*-Mephenesin
Ar = *o*-Tolyl

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[1] For recent reviews, see A. F. Casy, "Medicinal Chemistry,' 3rd edn., ed. A. Burger, Wiley, New York, 1970, pp. 81—107; W. L. Alworth, 'Stereochemistry and Its Applications in Biochemistry—The Relations Between Symmetry and Biological Stereospecificity,' Wiley-Interscience, New York, 1972.

[2] The glycol muscle relaxants have been reviewed: H. B. Donahoe and K. K. Kimura, 'Drugs Affecting the Central Nervous System,' Medicinal Research Series, vol. 2, ed. A. Burger, Dekker, New York, 1968, pp. 265—326; E. L. Engelhart and C. A. Stone, 'Medicinal Chemistry,' 3rd edn., ed. A. Burger, Wiley, New York, 1970, pp. 1525—1537.

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