

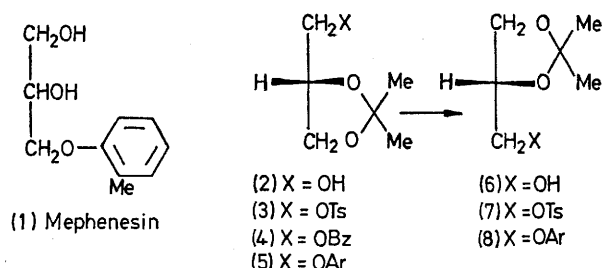
## Absolute Configuration of 3-Aryloxypropane-1,2-diols and Derivatives: Mephenesin Isomers

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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.<sup>1</sup> Demonstration of these significant differences is dependent upon finding methods to obtain materials of known absolute stereochemistry and high optical purity.



We report the preparation of the optical isomers of 3-*o*-tolylxypropane-1,2-diol, mephenesin, (1),<sup>2</sup> 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,<sup>†</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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, (0.5*N* aq. HCl; 70°; 2 h) to afford respectively 2*R*-mephenesin, m.p. 89–90° (H<sub>2</sub>O) (70% yield), and 2*S*-mephenesin, m.p. 89–90° (H<sub>2</sub>O) (65% yield). The i.r. spectra (KBr) are not significantly different than that recorded for mephenesin, m.p. 70–72°.<sup>5</sup> High-resolution mass spectral fragmentation were essentially identical with the spectrum of *rac*-mephenesin.

† 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 cm<sup>2</sup>/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 [0.01*M*-Cu<sup>2+</sup> dissolved in 0.34*M*-NH<sub>3</sub> (H<sub>2</sub>O-EtOH)].<sup>6</sup>

Optical rotations, Na<sub>D</sub> 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,<sup>‡§</sup> and provided data consistent with the known absolute configurations based on synthesis.

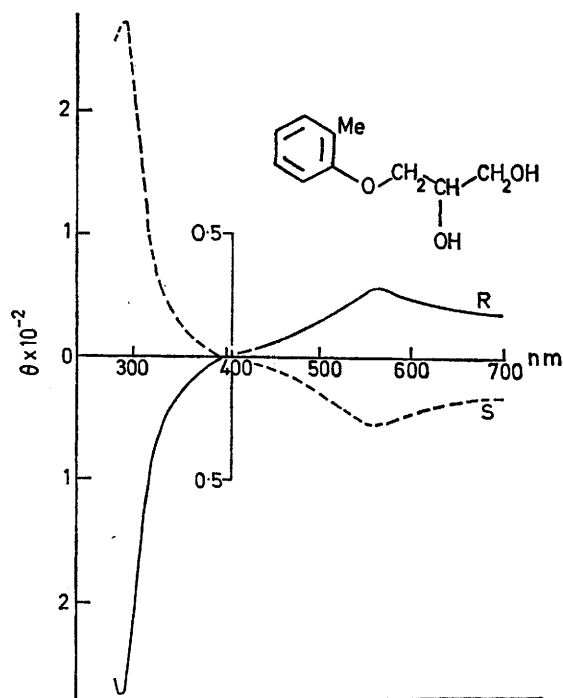
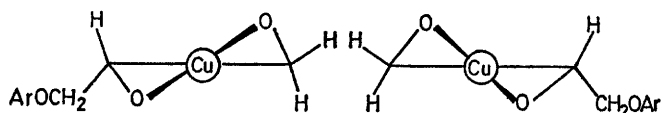


FIGURE. C.d. spectra of mephenesin isomers in Cupra A solution.

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) [ $\theta$ ]<sub>560</sub> 30°, [ $\theta$ ]<sub>380</sub> 0°, [ $\theta$ ]<sub>290</sub> -275°; (*c* 0.232 Cupra A) [ $\theta$ ]<sub>565</sub> -30°, [ $\theta$ ]<sub>380</sub> 0°, [ $\theta$ ]<sub>290</sub> 270°.

The Cotton effects are similar to those consistently observed for the chloramphenicol isomers, and assigned to the chiral centre at C-1.<sup>7</sup> The signs of the bands in the



$\lambda$  2S-Mephesisin  
Ar = *o*-Tolyl

$\delta$  2R-Mephesisin  
Ar = *o*-Tolyl

400—700 nm region are consistent with stereochemistry assigned from Cupra A spectra of other 1,2-glycols,<sup>8</sup> and to the chiral phenylethane-1,2-diols.<sup>9</sup> Conformations of  $\delta$  and  $\lambda$ <sup>8,10</sup> are, therefore, assigned to the diol-Cupra A complexes of 2R- and 2S-mephesisin, respectively.

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<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> E. Baer, *Biochem. Prep.*, 1952, **2**, 31; E. Baer and Fischer, *J. Amer. Chem. Soc.*, 1955, **67**, 944, 2031.

<sup>4</sup> O. T. Schmidt and W. Blank, *Chem. Ber.*, 1956, **89**, 283; J. S. Brimacombe, A. B. Foster, and A. H. Haines, *J. Chem. Soc.*, 1960, 2582; B. Belleau and J. Puranen, *J. Medicin. Chem.*, 1963, **6**, 325; D. Triggie and B. Belleau, *Canad. J. Chem.*, 1962, **40**, 1201.

<sup>5</sup> E. C. G. Clarke, 'Isolation and Identification of Drugs,' Pharmaceutical Press, London, 1969, p. 744.

<sup>6</sup> R. E. Reeves, *Methods Carbohydrate Chem.*, 1965, **5**, 203; R. E. Reeves, *Adv. Carbohydrate Chem.*, 1957, **6**, 107.

<sup>7</sup> L. A. Mitscher, P. W. Howison, and T. D. Sokolowski, *J. Medicin. Chem.*, 1973, **16**, 98.

<sup>8</sup> S. T. K. Bukhari, R. D. Guthrie, A. I. Scott, and A. D. Wrixon, *Tetrahedron*, 1969, **26**, 3653.

<sup>9</sup> L. A. Mitscher, G. Clark, and M. S. Bathala, unpublished results.

<sup>10</sup> J. I. Legg and B. E. Douglas, *J. Amer. Chem. Soc.*, 1966, **88**, 2697; *IUPAC Information Bulletin*, 1968, **33**, 68.