RESOLUTION OF (±)-ADRENALINE

By C. J. HAWKINS* and G. T. KLEASE*

[Manuscript received 30 May 1973]

Abstract

The resolution of (±)-adrenaline with ethylenediaminetetraacetatocobaltate(III) is described. Both isomers were obtained in an optically pure state in good yield with a high percentage recovery of the resolving agent.

The resolution of β-sympathomimetic amines is of considerable importance as the optical forms of the drugs have markedly different physiological activities.[1] The method which has been almost exclusively used for the resolution has utilized tartaric acid or one of its derivatives.[2–8] However, in most cases difficulties have been encountered in obtaining optically pure samples of the resolved product. Where pure isomers have been produced, several recrystallizations and recycling procedures were required throughout the resolution, which consequently resulted in very low yields. Similar difficulties in resolving phenolic amines have been described.[9]

In this paper, the resolution of adrenaline is reported by a method which gives high yields of both isomers in optically pure form with the resolving agent being recovered. The sulphate salt of the protonated compound is mixed with resolved barium ethylenediaminetetraacetatocobaltate(III), in a 2 : 1 adrenaline : $[Co(edta)]^-$ ratio and, after the barium sulphate is removed, a diastereoisomer is precipitated by adding ethanol. One isomer in a high degree of optical purity remains in solution and can be isolated and recrystallized. The diastereoisomer is decomposed by barium chloride which precipitates the barium salt of the resolving agent. Both isomers were obtained with over 70% yield and the recovery of the optically pure resolving agent was approximately 88%.

Experimental

Melting points were observed on a Büchi oil-bath melting point apparatus and optical rotations were measured with a Perkin–Elmer 141 automatic polarimeter.

* Department of Chemistry, University of Queensland, St. Lucia, Qld. 4067.

[1] Portoghese, P. S., *A. Rev. Pharmac.*, 1970, **10**, 51.
[2] Flächer, F., *Hoppe-Seyler's Z. physiol. Chem.*, 1908, **58**, 189.
[3] Gero, A., U.S. Pat., 2,650,938 (1953).
[4] Fabiam, F., Brit. Pat., 816,857 (1959).
[5] Tullar, B. F., *J. Am. chem. Soc.*, 1948, **70**, 2067.
[6] Lands, A. M., Luduena, F. P., and Tullar, B. F., *J. Pharmac.*, 1954, **111**, 469.
[7] Hartley, D., and Middlemiss, D., *J. mednl Chem.*, 1971, **14**, 895.
[8] Wetterlin, K., *J. mednl Chem.*, 1972, **15**, 1182.
[9] Brossi, A., O'Brien, J., and Teitel, S., *Helv. chim. Acta*, 1969, **52**, 678.

Resolution of 1-(3',4'-Dihydroxyphenyl)-2-methylaminoethanol (Adrenaline)

To a warm solution of (±)-adrenaline (Sigma) (1·41 g, 0·008 mol) in dilute sulphuric acid (8 ml) was added $(+)_{546}$-Ba[Co(edta)]$_2$,4H$_2$O (1·75 g, 0·002 mol), $[\alpha]_{546}$ +890° (*c*, 0·025 in water), which had been prepared from the resolved potassium salt.[10] The barium sulphate which precipitated was filtered. The filtrate was cooled in ice to yield crystals of diastereoisomer. Further diastereoisomer was obtained by the addition of ethanol and ether. The combined fractions of diastereoisomer (1·91 g) were washed with ethanol and ether and air dried.

(+)-*1-(3',4'-Dihydroxyphenyl)-2-methylaminoethanol*

The diastereoisomer (1·91 g) was dissolved in a minimum of warm water to which was added barium chloride (0·44 g). The barium salt of the resolving agent precipitated on cooling, and was completely removed from the filtrate by the careful addition of ethanol and ether; yield 1·54 g (88%). A few drops of sulphuric acid were added to the filtrate and the volume reduced under vacuum at about 40°C to approximately 10 ml. Concentrated aqueous ammonia was added with cooling to precipitate the free base, $[\alpha]_D^{20}$ +48° (*c*, 0·05 in 0·1M HCl), yield 0·59 g (85%). The amine was recrystallized from dilute sulphuric acid by the addition of aqueous ammonia, and the white product was washed with ethanol and ether, and air dried away from light, m.p. 213° (dec.) (lit.[11] 211–212° (dec.)), $[\alpha]_D^{20}$ +52° [*c*, 0·05 in 0·1M HCl (lit.[12] $[\alpha]_D^{20}$ +50° to +53° (*c*, 4 in 1M HCl)], yield 0·49 g (70%).

(−)-*1-(3',4'-Dihydroxyphenyl)-2-methylaminoethanol*

The filtrate remaining after the removal of the diastereoisomer was reduced in volume and the free base, (−)-adrenaline, was precipitated as previously outlined for the dextro isomer, $[\alpha]_D^{20}$ −44° (*c*, 0·05 in 0·1M HCl), yield 0·69 g (95%). After one recrystallization, a white powder was obtained, m.p. 213° (dec.) (lit.[11] 211–212° (dec.), $[\alpha]_D^{20}$ −50° [*c*, 0·05 in 0·1M HCl (lit.[12] $[\alpha]_D^{20}$ −50° to −53° (*c*, 4 in 1M HCl)], yield 0·59 g (85%). Both isomers successfully passed the tests outlined in the British Pharmacopoeia[12] for drug identification and purity.

Acknowledgments

The authors gratefully acknowledge financial support from the Asthma Foundation of Queensland and the Australian Research Grants Committee.

[10] Dwyer, F. P., and Garvan, F. L., *Inorg. Synth.*, 1960, Coll. Vol. VI, 195.
[11] Stecher, P. G., (Ed.) "The Merck Index," 8th Edn, p. 411 (Merck: Rahway, N.J., 1968).
[12] British Pharmacopoeia, p. 20 (The Pharmaceutical Press: London 1968).