MICROCHEMICAL DIFFERENTIATION BETWEEN OPTICAL ISOMERS OF *N*-METHYLMORPHINAN ANALGESICS

By E. G. C. Clarke

*From the Department of Physiology, Royal Veterinary College, London, N.W.*1

Received July 1, 1958

A simple method for differentiating between microgram quantities of optical isomers is described.

The analgesic drug 3-hydroxy-*N*-methylmorphinan was brought into use in its racemic form in 1951 under the name of Dromoran. Subsequently, when it had been shown that the analgesic activity was associated with the *laevo* isomer only[1–3] manufacture of the racemic form was discontinued, and the *laevo* form was supplied under the same trade name. The three isomers were given the approved names of levorphanol, racemorphan, and dextrorphan, the three corresponding methyl ethers (3-methoxy-*N*-methylmorphinan) being designated levomethorphan, racemethorphan, and dextromethorphan. As these drugs were habit forming, they were placed under international control, and, in Great Britain, became subject to the provisions of the Dangerous Drugs Regulations. Both (+)-isomers were removed from control in 1954, when it was shown that they did not produce addiction. Since then, dextromethorphan has come into clinical use as an antitussive agent under the name of Romilar.

We thus have two drugs, of which the *laevo* and racemic forms are proscribed narcotic drugs, while the corresponding *dextro* isomers are free of control. As there are considerable penalties attached to the misuse of substances on the list of Dangerous Drugs, it is essential to have some method that will distinguish clearly between these isomers. The obvious method of measuring the optical rotations can of course be applied if sufficient material is available, but even modern high precision methods[4] cannot operate on quantities much below 1 mg.

Numerous methods have been described for the identification of these compounds, including X-ray diffraction patterns[5,6], ultra-violet spectra[7], infra-red spectra[8], paper chromatography[9,10], and crystal and colour tests[11–16]. Although several of these methods serve to distinguish the racemic compound from the optically active forms, none of them is capable of differentiating these (+) and (−) forms from one another. It is the purpose of this note to describe an extremely simple method for distinguishing between μg. quantities of these isomers.

Experimental Procedure

The hanging microdrop technique developed by Clarke and Williams[17] is used. When a microdrop of a 5 per cent solution of sodium carbonate is added to a similar drop of a solution of 1 part of racemorphan in 100–500 parts of 1 per cent hydrochloric acid, crystals in the form of bunches of small plates appear, usually within half an hour. Under similar conditions, the (+) and (−) isomers give only amorphous precipitates, which do not crystallise even after standing for 48 hours.

To distinguish between the (+) and (−) forms the following procedure is adopted: place a microdrop of the test solution on a cover slip; add a microdrop of a 1 per cent solution of, say, the (−) isomer, made up from a known sample; then add a microdrop of a 5 per cent sodium carbonate solution. Seal, invert, and examine under the microscope in the usual way. If the test solution is the (−) isomer, the addition of further (−) isomer will not affect it, and the precipitate formed will be amorphous. If, however, it is the (+) isomer, the solution will now contain both the (+) and (−) forms, and crystals typical of the racemic compound will be formed.

The same method is used to distinguish between dextromethorphan and levomethorphan, except that in this case the reagent employed is a saturated solution of trinitrobenzoic acid. With this reagent racemethorphan forms rosettes of crystals, feathery or dense in appearance according to the concentration. These usually form within a quarter of an hour. Dextromethorphan and levomethorphan give oily amorphous precipitates which do not crystallise.

As the volume of a microdrop is 0·1 μl., the sensitivity of this test is about 0·2 μg.

Discussion

Although the racemic form of an alkaloid will often give crystals that are different in form from those of the optical isomers, a fact that has long been used to distinguish atropine from hyoscyamine, the alkaloidal reagents normally used yield identical crystals with both (+) and (−) isomers. An alkaloidal precipitating agent which was itself optically active might be expected to give rise to different forms of crystal with each isomer, but up to now no such reagent has been described. Substances such as tartaric acid which are used to resolve racemic bases cannot be made to give satisfactory crystals on the microscale.

The method described above is of general application, and can be used for differentiating between the optical isomers of any alkaloid, provided that there can be found a precipitating agent that will give crystals with the racemic form and not with the (+) and (−) isomers, and that a pure sample of one of these isomers is available for cross-testing. In the case of the *N*-methylmorphinan analgesics there is no difficulty on the latter score, as both levorphanol and dextromethorphan are obtainable commercially.

Acknowledgements. I wish to express my thanks to Dr. J. Marks, and to the officials of the Dangerous Drugs branch of the Home Office, for the help they have given to me. I acknowledge most gratefully gifts of drugs from Roche Products, Ltd. I am also much indebted to Mrs. A. Williams for technical assistance.

References

1. Randall and Lehman, *J. Pharmacol.*, 1950, **99**, 163.
2. Isbell and Fraser, *ibid.*, 1951, **103**, 348.
3. Isbell and Fraser, *ibid.*, 1953, **107**, 524.
4. Gillham, *J. Sci. Inst.*, 1957, **34**, 435.

5. Barnes and Sheppard, *Bull. Narcotics*, 1954, **6** (1), 20.
6. Barnes, *ibid.*, 1954, **6** (2), 27.
7. Oestreicher, Farmilo and Levi, *ibid.*, 1954, **6** (3–4), 42.
8. Levi, Hubley and Hinge, *ibid.*, 1955, **7** (1), 42.
9. Vidic, *Arzneimitt.-Forsch.*, 1955, **5**, 291.
10. Goldbaum and Kazyak, *J. analyt. Chem.*, 1956, **28**, 1289.
11. Farmilo, Levi, Oestreicher and Ross, *Bull. Narcotics*, 1952, **4** (4), 16.
12. Levi, *ibid.*, 1955, **7** (3–4), 43.
13. Farmilo and Levi, *Canad. J. Chem.*, 1952, **30**, 782.
14. Brandstatter, *Arzneimitt.-Forsch.*, 1953, **3**, 33.
15. Vidic, *ibid.*, 1953, **3**, 34.
16. Breinlich, *ibid.*, 1953, **3**, 93.
17. Clarke and Williams, *J. Pharm. Pharmacol.*, 1955, **7**, 255.