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Preparation of noratropine by oxidative *n*-demethylation of atropine

M. J. VAN DER MEER, H. K. L. HUNDT*, *Department of Pharmacology, University of the Orange Free State, Bloemfontein, Republic of South Africa.*

Phillipson et al (1976) reported good yields (48%) of noratropine by oxidative *N*-demethylation of atropine in aqueous solution with potassium permanganate, (pH 7·5–8·0, 30 °C, 1 h). In our hands this method gave poor and inconsistent yields. The following procedure proved reproducible.

To atropine sulphate (5 g) spiked with [^{3}H]atropine sulphate (500 ng: 3·6 Ci mmol^{-1}) in water (200 ml at 4 °C), potassium permanganate (5 g) was added and the mixture stirred (10 min) without temperature or pH control. Precipitated MnO_2 was filtered off and the filtrate treated again with a further 5 g portion of permanganate. After removal of MnO_2, the alkaloids were extracted from the filtrate with chloroform (4 × 50 ml). The dried extract was evaporated and the residue in absolute ethanol (2 ml) was treated dropwise with aqueous oxalic acid (10% w/v) to yield noratropine oxalate (425 mg).

The manganese dioxide suspended in water was reduced with sodium metabisulphite until a clear solution was obtained, the pH was adjusted to 9·2 with concentrated ammonia solution and the alkaloids extracted with chloroform. Noratropine oxalate was precipitated as described above; yield 370 mg. Total yield: 795 mg (16.8%). Noratropine oxalate was recrystallized from absolute ethanol and water (2:1): m.p. 258–264 °C. Phillipson et al (1976) give 260–262 °C; Carr & Reynolds (1912) give 247–248 °C. M.s. of the oxalate *m/z* 275 (molecular ion of base 7%) 111 (21), 110 (100), 109 (13), 103 (14), 91 (13), 82 (21), 81 (23), 80 (40), 77 (10), 69 (11), 68 (37), 67 (29).

* Correspondence.

The free base obtained by ether extraction of an alkalinized aqueous solution of the oxalate was dried overnight (0·05 torr, 51 °C): mp 111–113 °C. Carr & Reynolds (1912) give 113–114 °C. N.m.r. δ 7·24–7·37 (5H, m; aromatics) 5·07 (1H, t; H-3), 4·17 (1H dt; benzylic), 3·80 (2H, m; CH_2-O-), 3·37 (2H, dm; H-1 and H-5), 1·23–2·04 (8H, mm; H-4, H-6, H-7).

Identification of the products formed in this oxidation reaction was achieved by h.p.l.c. analysis by the method of Fell et al (1979) (20 mM tetrabutyl ammonium hydrogen sulphate being used instead of 10 mM)). From 100 µl of the filtrate after oxidation the eluate was collected in 10 drop fractions which were examined for radioactivity (Packard 3385 Scintillation Spectrometer) after addition of 10 ml scintillation fluid (Instagel, Packard Instruments). Three radioactive components were detected representing, in order of increasing retention volume, tropine (26%), noratropine (55%) and tropic acid (19%). Their identity was established from their retention volumes using authentic specimens as markers: this was confirmed by t.l.c.

Although the yield of noratropine is low, this is amply compensated for by the extreme simplicity with which small amounts of it can be prepared when required.

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