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THE PREPARATION OF CODEINE-AND MORPHINE-N-METHYL-C^{14}

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no successful application of this reaction to codeine itself has been reported. The usual ether-cleaving reagents (concentrated hydrogen iodide and hydrogen bromide, in aqueous solution or in glacial acetic acid) appear to be too drastic. However, pyridine hydrochloride, which has been used recently to prepare desoxymorphines from desoxycodeines,[4] under carefully controlled conditions effected the cleavage of codeine to morphine in a reasonable yield (22%), and hence was applied to the preparation of morphine-N-methyl-C^{14} from codeine-N-methyl-C^{14}.

Experimental[5]

Norcodeine. - Acetylcodeine (m.p. 132-133°)[6] was prepared in 95% yield by heating a solution of codeine in acetic anhydride under reflux for twenty hours. Following the procedure of von Braun,[3] this was converted by reaction with cyanogen bromide to N-cyanoacetylnorcodeine (m.p. 183-184°) and then hydrolyzed stepwise to N-cyanonorcodeine (m.p. 259-261°) and norcodeine (m.p. 184-185°) [reported (3) m.p. 184°]. The over-all yield from codeine to norcodeine was 46%.

Codeine-N-methyl-C^{14}. - Alkylation was carried out as described by von Braun[3] using 5.23 g. (18.4 millimoles) of norcodeine and 1.30 g. (9.2 millimoles) of methyl iodide containing 4.72 mc. of C^{14}. The crude codeine was crystallized from benzene and sublimed to give 940 mg. of codeine-N-methyl-C^{14}, m.p. 154-155°, specific activity, 1.78 μc/mg. The yield was 35% based on methyl iodide.

Morphine-N-methyl-C^{14}. - Cleavage of 1.00 g. of codeine-N-methyl-C^{14} (specific activity 3.56 μc/mg.) was effected by heating with pyridine hydrochloride in the manner previously described for Δ^7-desoxycodeine.[4b] The reaction mixture was dissolved in 20 ml. of water, basified with 10 ml. of 4N sodium hydroxide, and the non-phenolic material was removed by extraction with four 15 ml. portions of chloroform. The combined chloroform

extracts were washed with 10 ml. of 0.5N sodium hydroxide and 10 ml. of water, and the aqueous phase, after adding the washings, was adjusted to pH 9 and cooled thoroughly to precipitate phenolic material. After filtering and drying, this phenolic material was digested with 75 ml. of methanol, the mixture was filtered hot, and the filtrate was chromatographed on an alumina (Merck) column (120 x 11 mm.) using 700 ml. of methanol as eluent. The residue after evaporation of the methanol was dissolved in 10 ml. of 0.2N sodium hydroxide, filtered, and the filtrate was adjusted to pH 9, precipitating the crude morphine. After drying, this crude morphine was sublimed (180-190°/0.1 mm.), and the sublimate was crystallized from absolute ethanol. There was thus obtained a total of 210 mg. (22%) of morphine-N-methyl-C^{14}, m.p. 254-255°, specific activity, 3.75 μc/mg.

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References

(1) F. N. Chang, J. F. Oneto, P. T. Sah, B. M. Tolbert, and H. Rapoport, J. Org. Chem., 15, 634 (1950).

(2) T. K. Adler and M. E. Latham, Proc. Soc. Exptl. Biol. Med., 73, 401 (1950); M. E. Latham and H. W. Elliott, J. Pharmacol. Exptl. Therap., 101, 259 (1951).

(3) J. von Braun, Ber., 47, 2312 (1914).

(4) (a) H. Rapoport and R. M. Bonner, J. Am. Chem. Soc., 73, 2872 (1951);
(b) H. Rapoport and R. M. Bonner, ibid., 73, 0000 (1951).

(5) All melting points are corrected.

(6) M. Tiffeneau, Bull. soc. chim. France, [4] 17, 109 (1915).