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DEPARTMENT OF CHEMISTRY
UNIVERSITY OF LOUISVILLE
LOUISVILLE, KENTUCKY

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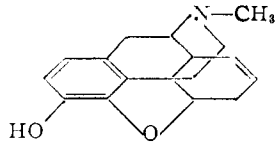
Δ^7-Desoxymorphine

BY HENRY RAPOPORT AND ROBERT M. BONNER

The ready availability of Δ^7-desoxycodeine[1] led us to examine the possibility of preparing the morphine analog, Δ^7-desoxymorphine (I), by ether-cleavage.



Although the cleaving agents commonly employed in the morphine series, such as hydrogen bromide in glacial acetic acid, proved too drastic, heating with pyridine hydrochloride[2] gave good yields of the morphine compound. That no other change had taken place in the molecule was shown by re-etherification to Δ^7-desoxycodeine with diazomethane.

Preliminary testing of Δ^7-desoxymorphine was kindly carried out by Dr. Nathan B. Eddy[3] who reported "the LD_{50} is 90, the analgesic dose is 0.2, the onset of effect is very rapid (about five minutes), and the duration of effect is short (about 53 minutes). The comparable values for morphine are LD_{50} 539; analgesic dose, 1.70; onset of effect, 15 minutes; and duration of effect, 144 minutes."

Experimental

Δ^7-Desoxymorphine.—A mixture of 2.0 g. of Δ^7-desoxycodeine[1] and 6 g. of pyridine hydrochloride was placed in a bath at 220° and heated for six minutes in a nitrogen atmosphere, after which the reaction mixture was immediately cooled and treated with 25 ml. of water. Non-phenolic material was removed by ether extraction after the solution had been made alkaline with sodium hydroxide, and the ether extract was washed with water, dried over magnesium sulfate, and evaporated to give 1.2 g. (60%) of recovered Δ^7-desoxycodeine. The aqueous phase was adjusted to *p*H 8 by addition of hydrochloric acid, and the mixture was extracted with methylene chloride. Evaporation of the methylene chloride left 0.7 g. (37% yield based on original Δ^7-desoxycodeine or 92% yield based on unrecovered starting material) of phenolic material which was crystallized from benzene (0.1 g. in *ca.* 2 ml. of benzene). In order to free the compound from benzene which it retains tenaciously, it was slowly heated to 125° and sublimed at this temperature at 0.05 mm. Pure Δ^7-desoxymorphine (0.47 g., 62%) was thus obtained, m.p. 143–144°; $[\alpha]^{25}D$ −67.2° (*c* 1.31, ethanol).

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.8; H, 7.1. Found: C, 75.8; H, 7.0.

A sample dissolved in methanol was converted to Δ^7-desoxycodeine by treatment with ethereal diazomethane.

DEPARTMENT OF CHEMISTRY AND RADIATION LABORATORY
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA

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(1) H. Rapoport and R. M. Bonner, THIS JOURNAL, **73**, 2872 (1951).
(2) V. Prey, *Ber.*, **74**, 1219 (1941).
(3) National Institutes of Health, Bethesda 14, Maryland. Doses are expressed in milligrams of base per kilogram of body weight for subcutaneous administration to mice.

A Solvent Extraction Procedure for Purifying Streptomycin

BY H. W. RHODEHAMEL, JR., W. B. FORTUNE AND S. L. MCCORMICK, JR.

The insolubility of streptomycin base and of mineral-acid salts of streptomycin in common organic solvents immiscible with water has precluded isolation or purification of streptomycin by simple solvent extraction procedures. Several solvent extraction systems have been reported[1,2] in which streptomycin has been solubilized in organic solvents by the formation of salts of streptomycin with non-polar organic acids. Other basic organic impurities are likewise solubilized, however, and, in consequence, little purification is achieved.

It has been found that water-immiscible, primary liquid alkyl or aralkyl amines have the ability to extract streptomycin from water solutions in satisfactory yields with a high degree of selectivity and with considerable purification. Reactions postulated for this selective extraction are the formation of an amine soluble combination of a Schiff base, or alcohol–ammoniate type linkage between the carbonyl group of the streptomycin molecule and the primary amine group. Such postulations gain support by the facts that dihydrostreptomycin is not extracted by this system, and that secondary and tertiary amines are ineffective in extracting streptomycin.

With suitable amines, streptomycin activity has been extracted efficiently from aqueous streptomycin solution of virtually any degree of purity, including filtered fermentation broths. The streptomycin solution must be on the basic side of neutrality for the extraction to take place. Except in cases of buffered solutions, the amine itself will raise the *p*H sufficiently. For efficient single-stage extraction, a high inorganic salt concentration in the streptomycin water phase is necessary. Since certain initial isolation steps for streptomycin tend to give concentrates of streptomycin high in salt content, for example, eluates of streptomycin activity from ion-exchange resins, this requirement for a high salt concentration in the aqueous phase is not necessarily undesirable.

The streptomycin may be recovered from the amine phase by extracting the latter with water and a water-immiscible solvent in which the amine used is soluble. For satisfactory recovery, it is necessary to have a streptomycin concentration in the amine phase equivalent to 150–300 mg. of streptomycin base per ml. This may be accomplished either in the original extraction by using suitable volumes of the amine phase or by concentration of the amine phase after extraction of and separation from the aqueous phase. Chloroform and amyl acetate have been found effective as the water-immiscible solvent to be used in conjunction with water to recover the streptomycin from the amine phase. The aqueous phase resulting from the mixture of chloroform (or amyl acetate), amine and water will contain substantially all the streptomycin originally present in the amine phase.

(1) E. Titus and J. Fried, *J. Biol. Chem.*, **168**, 393 (1947).
(2) U. S. Patents 2,537,933 (Jan. 9, 1951) and 2,537,934 (Jan. 9, (1951).