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DEPARTMENT OF CHEMISTRY
UNIVERSITY OF LOUISVILLE
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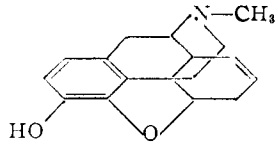
Δ^7-Desoxymorphine

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 RECEIVED JUNE 25, 1951

(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).

Removal of residual amine from this aqueous phase is necessary for the subsequent preparation of streptomycin suitable for clinical use. This may readily be accomplished by extracting the aqueous phase with a mixture of chloroform and acetone before any *p*H adjustments have been made. The *p*H of the aqueous phase is then adjusted to desirable limits for streptomycin stability with a suitable mineral acid and dried to give a purified streptomycin product.

Experimental

The streptomycin used in the following example of this procedure was obtained by the process essentially as described by Vander Brook, *et al.*,[3] for the preparation of streptomycin sulfate. All assays were conducted by the paper-disc plate method[4] using *B. subtilis* as a test organism. One unit is equivalent to one microgram of streptomycin base.

Purification of Streptomycin Sulfate by Solvent Extraction.—Forty grams of streptomycin sulfate, assaying 580 units per mg., was dissolved in water to give 925 ml. of solution testing 25,000 units per ml. The *p*H of this solution was adjusted to 12 with dilute NaOH, and 3 g. of NaCl was added per 10 ml. of resulting solution. 2-Aminoheptane (465 ml.) was added, the mixture stirred one-half hour, and the two phases separated. The water phase containing less than 6% of the starting activity was discarded. The amine phase was concentrated *in vacuo* to approximately one-third volume, and filtered. To the filtered amine phase were added an equal volume of water and three volumes of $CHCl_3$. After stirring one hour, the mixture was allowed to separate. The $CHCl_3$ was discarded.

The water phase, 370 ml. at 57,000 units per ml., contained 21,000,000 units or 91% of the starting activity. The water phase was extracted with one-half volume of acetone and one volume of $CHCl_3$. After separation, the *p*H of the water phase was adjusted to 5.5 with dilute H_2SO_4 and the resulting solution dried to give 27 g. of streptomycin sulfate testing 748 units per mg., $[\alpha]^{25}D$ −73.5° (*c* 1 in H_2O), and representing 87% of the original activity.

Acknowledgments.—The authors are indebted to Dr. J. J. Stefaniak for the microbiological assays and to Mrs. Ruth St. John and Mrs. Margaret Wilson for technical assistance.

(3) M. J. Vander Brook, A. N. Wick, W. H. DeVries, R. Harris and G. F. Cartland, *J. Biol. Chem.*, **165**, 463 (1946).

(4) Y. H. Loo, P. S. Skell, H. H. Thornberry, J. Ehrlich, J. M. McGuire, G. M. Savage and J. C. Sylvester, *J. Bact.*, **50**, 701 (1945).

THE LILLY RESEARCH LABORATORIES
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Propylgermanium Trichloride: The Question of Pyrolysis and Isomerization in the Direct Synthesis of Organogermanium Compounds

BY EUGENE G. ROCHOW, ROTISLAV DIDTSCHENKO AND ROBERT C. WEST, JR.

The action of methyl chloride[1] on elementary germanium intimately mixed with copper powder as catalyst results in dimethylgermanium dichloride as principal product, only one-tenth as much methylgermanium trichloride being formed. Under similar conditions ethyl chloride[2] yields principally diethylgermanium dichloride plus four-tenths as much ethylgermanium trichloride. If the alkyl groups are transferred first as copper alkyls and then as free radicals, as appears to be so in the reaction of methyl chloride with silicon,[3] larger alkyl groups may be expected to suffer some rearrangement and pyrolysis at the elevated temperatures necessary for the reaction. This in turn should place an upper limit on the size of the alkyl group that can successfully be transferred to germanium by the direct synthesis as ordinarily conducted.

To investigate these matters, the reaction of *n*-propyl chloride in the vapor phase with a contact mass of powdered metallic germanium and copper at 310 to 330° was studied. The only isolable product was found to be a propylgermanium trichloride. Pure isopropyl- and *n*-propylgermanium trichloride then were prepared by the Grignard reaction, since they had not previously been made, in order that the product of the direct reaction might be compared with these pure substances.

Experimental

The apparatus for the experiments with metallic germanium consisted of a glass reaction tube 2.5 cm. in diameter and 50 cm. long, fitted with standard taper joints to an inlet system for *n*-propyl chloride and hydrogen at one end, and a condensing trap and drying tube at the other. The inlet system consisted of a vertical elbow bearing a small dropping funnel for the *n*-propyl chloride (which was delivered through a capillary tube) and a sealed-in stopcock leading from the hydrogen drier. The reaction tube was mounted in an electric furnace tilted downward at an angle of 15°, so that the *n*-propyl chloride ran into the hot tube and was vaporized before it entered the charge of powdered germanium.

The reaction tube was charged with a finely-ground mixture of 11.5 g. of germanium and 2.5 g. of copper, supported on glass wool to provide maximum contact area. A thermometer was embedded in the contact mass in such a way that it was totally enclosed in the reaction system but protruded from the exit end of the furnace sufficiently to be read.

The reaction tube and its charge were brought to 300° with a slow stream of hydrogen passing through, in order to reduce any copper oxide. The temperature was then raised to 320°, the stream of hydrogen stopped and 50 ml. of *n*-propyl chloride admitted over a period of seven hours. During this time the temperature was maintained at 320 to 330°. High-boiling liquid was seen to condense after a lapse of 45 minutes, and was collected in the trap along with unchanged *n*-propyl chloride.

The condensate from the reaction was distilled, yielding 30 ml. of unchanged *n*-propyl chloride and 2 ml. of clear viscous liquid boiling above 145° with some decomposition. The high-boiling material from a second run, conducted at the somewhat reduced temperature of 310 to 320°, was combined with the distillate of the first run, and the mixture distilled at reduced pressure through a packed column 40 cm. long and 6 mm. in diameter. The main fraction of 3.5 ml. was collected at 43 to 45° at 12 mm. pressure. This was analyzed for carbon and hydrogen by combustion, and for chlorine by hydrolysis and titration.

Anal. Calcd. for $C_3H_7GeCl_3$: Cl, 47.8; C, 16.2; H, 3.2. Found: Cl, 47.5, 47.9; C, 16.7, 16.7; H, 3.3, 3.4.

Propylgermanium trichloride prepared this way is a colorless, viscous oil with a sharp, unpleasant odor. It hydrolyzes to a white gelatinous precipitate which dissolves in alkalies. The boiling point is 167° at 763 mm., 43 to 45° at 12 mm. and the density at 20° is 1.513.[4] The index of refraction at 20° is 1.4779 and at 25° is 1.4720.

Isopropylgermanium trichloride was prepared by the action of one equivalent of isopropylmagnesium chloride on germanium tetrachloride in anhydrous ether, and was purified by fractional distillation. Its boiling point was found to be 164.5 at 767 mm., and the refractive index was 1.4760 at 20° and 1.4700 at 25°.

n-Propylgermanium trichloride was prepared by the action of 1.5 equivalents of *n*-propylmagnesium chloride on germanium tetrachloride in ether. The purified product

(1) E. G. Rochow, THIS JOURNAL, **69**, 1729 (1947).

(2) E. G. Rochow, *ibid.*, **72**, 198 (1950).

(3) D. T. Hurd and E. G. Rochow, *ibid.*, **67**, 1057 (1945).

(4) The densities at 20° of the entire propyl series now are known:

n-Pr_4Ge	0.9539	*n*-Pr_3GeCl_3	1.227	$GeCl_4$	1.879
n-Pr_3GeCl	1.106	*n*-$PrGeCl_3$	1.513		