acid required was noticeable. When water was added to remove the expected amine salt an emulsion formed which precipitated later as finely divided, white crystals. Repeated recrystallization of this product from hot methanol gave well defined, colorless, orthorhombic crystals melting at 167.0–167.5°. An average of twelve molecular weight determinations made in absolute ethanol by the boiling point elevation method gave 210 ± 10 (calcd. 219).

Anal.[6] Calcd. for $C_{10}H_{15}NO_2F_2$: C, 54.79; H, 6.90; N, 6.39. Found: C, 54.95; H, 6.87; N, 6.59.

Independent Reaction with Hexafluorocyclobutene.—The reaction cylinder was charged at Dry Ice temperature with equimolar quantities of triethylamine (86 g.) and hexafluorocyclobutene (138 g.). After standing at room temperature for 6 hr. the cylinder was shaken at 40° for 16 hr. The liquid portion of the reaction mixture was removed leaving approximately 75 g. of yellow, crystalline solid which reacted vigorously with water with the evolution of heat and hydrogen fluoride to form a product precipitating as white crystals. Recrystallization from methanol gave a compound identical with the one analyzed above.

The reactive crystalline product obtained initially was soluble in benzene but separated, upon the addition of *n*-heptane, as a red oil from which crystals precipitated when cooled below 0°. After centrifugation, the liquid was decanted from the solid which was then washed twice with heptane and finally recovered by suction filtration upon fritted glass under an atmosphere of dry nitrogen in an effort to remove the occluded heptane. The solid was transferred to a drying tube and the residual heptane was removed by evacuation for 16 hr. at room temperature and 4 hr. at 50°. Retention of susceptibility to hydrolysis was established but the spongy consistency of the product prevented determination of a reliable melting point.

Anal. Calcd. for $C_{10}H_{15}NF_6$: C, 45.63; H, 5.74; N, 5.32. Found: C, 45.72; H, 6.05; N, 6.35.

Methanolysis of the Quaternary Salt.—Solution of approximately 1 g. of the reactive quaternary salt in 5 ml. of absolute methanol liberated small amounts of hydrogen fluoride and heat. The product did not precipitate at Dry Ice temperature nor upon standing overnight in a closed container. After aeration of the warmed solution with dry nitrogen until the volume was reduced by approximately one-half, the solution became quite viscous and precipitation occurred. The crystals, recovered by filtration under an atmosphere of nitrogen and washed twice with anhydrous ether, initially melted at 131–134°. Hydrogen fluoride slowly evolved upon continued exposure to air. Finally, a compound was obtained which melted at 156° and gave a mixed melting point of 163° with the recrystallized diketone.

(6) Organic fluoride reported (*cf.* ref. 4) was 17.20 av. (calcd. 17.33).

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Organic Salts of Benzylpenicillin. II. Local Anesthetic Amines

BY H. W. RHODEHAMEL, JR.

A number of amines possessing local anesthetic activity have been tested for their ability to form salts with benzylpenicillin. Emphasis has been placed on finding relatively water-insoluble combinations.

For this study, the ability of various local anesthetic amines to form relatively water-insoluble salts was tested as follows: the amine hydrochloride was dissolved in approximately the minimum amount of water necessary for solution at room temperature. This solution was then added to a water solution of potassium or sodium penicillin at a concentration of about 50,000 Oxford units per ml., using a slight stoichiometric excess of penicillin. In several cases, relatively water-insoluble crystalline salts formed immediately; in other cases, amorphous combinations formed which could be caused to crystallize by scratching and chilling; in many cases, no insoluble product resulted or an amorphous material formed which could not readily be made to crystallize. Only relatively water-insoluble crystalline combinations are reported here.

In cases where water-insoluble products did not result, attempts were made to form water-soluble derivatives following the procedure as outlined for the preparation of certain aliphatic amine vasoconstrictor salts of penicillin.[1] Such water-soluble combinations will be reported elsewhere.

The β-Diethylaminoethyl-2-chloro-4-aminobenzoate Salt of Benzylpenicillin.—White, needle-like crystals with a theoretical penicillin potency of 953 Oxford units per mg. and a water solubility of approximately 0.3% (25°), $[\alpha]^{25}D$ +172° (*c* 0.1 in water). *Anal.* Calcd. for $C_{29}H_{37}O_6N_4ClS \cdot H_2O$: C, 55.89; H, 6.31; N, 8.99; Cl, 5.69. Found: C, 55.98; H, 6.56; N, 8.97; Cl, 6.17.

The β-Diethylaminoethyl-2-methyl-4-aminobenzoate Salt of Benzylpenicillin.—White, needle-like crystals with a theoretical penicillin potency of 985 Oxford units per mg. and a water solubility of approximately 0.3% (25°), $[\alpha]^{25}D$ +169° (*c* 0.1 in water). *Anal.* Calcd. for $C_{30}H_{40}O_6N_4S \cdot H_2O$: C, 59.77; H, 7.02; N, 9.30. Found: C, 59.06; H, 7.41; N, 9.48.

The N,N′-Bis-*p*-ethoxyphenylacetamidine[2] Salt of Benzylpenicillin.—White, irregularly shaped crystals tending to form a gum on exposure to air at room temperature with a theoretical penicillin potency of 915 Oxford units per mg. and a water solubility of about 0.37% (25°), $[\alpha]^{25}D$ +157° (*c* 0.1 in water). *Anal.* Calcd. for $C_{34}H_{40}O_6N_4S \cdot H_2O$: C, 62.74; H, 6.51; N, 8.61. Found: C, 62.89; H, 6.46; N, 8.91.

The β-Diethylaminoethyl Ester of 4-Amino-1-naphthoic Acid[3] Salt of Benzylpenicillin.—Yellow, long, thin needle-like crystals with a theoretical penicillin potency of 931 Oxford units per mg. and a water solubility of approximately 0.65% (25°), $[\alpha]^{25}D$ +154° (*c* 0.1 in water). *Anal.* Calcd. for $C_{33}H_{40}N_4O_6S \cdot H_2O$: C, 62.04; H, 6.63; N, 8.77. Found: C, 61.96; H, 6.77; N, 9.48.

The β-Diethylaminoethyl-1-cyclohexylcyclohexanecarboxylate[4] Salt of Benzylpenicillin.—White, needle-like crystals with a theoretical penicillin potency of 896 Oxford units per mg. and a water solubility of about 0.3% (25°), $[\alpha]^{25}D$ +159° (*c* 0.1 in water). *Anal.* Calcd. for $C_{35}H_{52}N_3O_6S \cdot H_2O$: C, 63.46; H, 8.38; N, 6.35. Found: C, 62.95; H, 8.35; N, 6.56.

The author is indebted to Mr. W. L. Brown for microanalyses and to Miss Mary Stieff for technical assistance.

(1) H. W. Rhodehamel, Jr., THIS JOURNAL, **72**, 3302 (1950).

(2) Available as the hydrochloride from Winthrop-Stearns, Inc., under the trade name of Holocaine Hydrochloride.

(3) Available as the hydrochloride from Parke, Davis and Company under the trade name of Naphthocaine Hydrochloride.

(4) Available as the hydrochloride from the Wm. S. Merrell Company under the trade name of Bentyl Hydrochloride.

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The Preparation of 5-Chloro-2-thenyl Chloride

BY NORMAN A. ROSENTHAL[1]

The value of 5-chloro-2-thenyl chloride in the synthesis of antihistamines,[2] as well as the recent interest displayed in chloromethylation studies of

(1) Nestle Le Mur Co., New York, N. Y.

(2) L. P. Kyrides, F. C. Meyer, F. B. Zienty, J. Harvey and L. W. Bannister, THIS JOURNAL, **72**, 745 (1950).