naphthoquinones and naphthohydroquinones,[1] we had for some time been engaged in the preparation of 1,4-dihydroxy-2-naphthyl hydroxymethyl ketone.[2] This compound represented a suggested structure for bacterial luciferin.[3]

In the course of the work we arrived at a method for the preparation of the compound by a route which differs slightly from that of Spruit[1] and which offers some advantages in terms of the stability of the intermediate compounds.

It was found that 1-hydroxy-4-acetoxy-2-naphthyl methyl ketone[4] can be conveniently brominated to form 1-hydroxy-4-acetoxy-2-naphthyl bromomethyl ketone in satisfactory yield. This compound can be acetylated to form Spruit's 1,4-diacetoxynaphthyl bromomethyl ketone. The indirect hydrolysis of this diacetate to form 1,4-dihydroxy-2-naphthyl hydroxymethyl ketone is best carried out according to Spruit.[1]

Experimental

1-Hydroxy-4-acetoxy-2-naphthyl Bromomethyl Ketone.—To an illuminated solution of 0.655 g. of resublimed 1-hydroxy-4-acetoxy-2-naphthyl methyl ketone in 7 cc. of purified glacial acetic acid[5] was added at room temperature 2.56 cc. of a freshly titrated solution of bromine (2.1 *N*) in the same solvent. Final warming in a warm water-bath completed the reaction in one-half hour (solution negative to wet KI–starch paper).

The reaction mixture on being poured into water deposited a yellow oil which crystallized on the addition of alcohol. The product was recrystallized from 95% ethanol and sublimed (0.1 mm., 120°); m.p. 172° dec. micro. cor.

Anal.[6] Calcd. for $C_{14}H_{11}O_4Br$: C, 52.03; H, 3.43; Br, 24.73. Found: C, 51.94, 52.15; H, 3.78, 3.73; Br, 24.29, 24.58.

1,4-Diacetoxy-2-naphthyl bromomethyl ketone prepared by acetylation of the 1-hydroxy compound with acetic anhydride and zinc chloride and crystallized from absolute ethanol, was identical with the product described by Spruit.[1] The 1-acetoxy group is easily lost by hydrolysis in a work-up involving water.

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(1) C. P. J. Spruit, *Rec. trav. chim.*, **67**, 285 (1948).

(2) F. H. Johnson, D. R. Rexford and E. N. Harvey, *J. Cellular Comp. Physiol.*, **33**, No. 1, 133 (1949).

(3) C. P. J. Spruit, Thesis, "Naphthothinonen en Bioluminescentie," Drukker ij Fa. Schotanus & Jens, Utrecht, 1946.

(4) C. P. J. Spruit, *Rec. trav. chim.*, **66**, 655 (1947).

(5) Fractionated from acetic anhydride. Several other solvents were tried. Specially purified acetic acid appeared to yield the purest product.

(6) Analyses by Joseph F. Alicino, P. O. Box 267, Metuchen, N. J.

FRICK CHEMICAL LABORATORY
PRINCETON UNIVERSITY
PRINCETON, N. Y.

RECEIVED JUNE 6, 1951

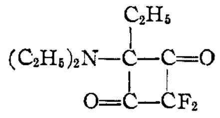
Reactions of Polyfluoro Olefins. IV.[1] Reaction with Triethylamine[2]

BY KARL E. RAPP

Reaction between triethylamine and chlorotrifluoroethylene was undetectable when this amine was used as an alkaline catalyst in the anionic addition of thiols to the polyfluoro olefin.[3]

When triethylamine was used to catalyze the addition of 1-butanethiol to hexafluorocyclobutene, however, an interesting and unexpected side reaction involving the tertiary amine occurred. This reaction was shown to take place independently of the addition reactions reported by Rapp, *et al.*[3] The product of the reaction was an extremely hygroscopic crystalline solid which reacted readily with water, moist air or absolute methanol with the evolution of heat and hydrogen fluoride. Because of this reactivity, the extent to which purification for analysis could be carried was somewhat limited. On the other hand, the white crystalline solid resulting from hydrolysis was so stable that it could be employed as a calibration reference in the development of an analytical procedure for the determination of organic fluoride.[4]

Elemental analysis of the stable hydrolyzed compound and determination of its molecular weight strongly indicated a molecular composition of $C_{10}H_{15}NO_2F_2$. Although attempts to prepare an oxime or *p*-nitrophenylhydrazone were unsuccessful, a possible diketone structure



$$\begin{array}{ccccc} & & C_2H_5 & & \\ & & | & & \\ (C_2H_5)_2N & - & C & - & C=O \\ & & | & & | \\ & O= & C & - & CF_2 \end{array}$$

satisfying both composition and valence requirements might be expected to possess the low water-solubility responsible for the initial precipitation of the compound when the amine-catalyzed butanethiol reaction mixture was washed with water. Consideration of a means by which a structure of this type might be attained would initially involve the formation of a quaternary ammonium fluoride by a fluorine substitution reaction in contrast to the addition mechanism followed by primary and secondary amines.[5] Analysis of the somewhat impure reactive product agreed fairly well with the composition, $C_{10}H_{15}NF_6$. Existence of such a quaternary salt was further substantiated by the reaction with absolute methanol to form an active methoxy derivative which was extremely soluble in methanol and was converted to the stable hydrolysis product immediately by dilution of its methanol solution with water or within a few hours when exposed in the solid form to normally moist air. Acceptance of the suggested diketone structure would require a shift of an ethyl radical from nitrogen to the adjacent carbon of the ring during the removal of hydrogen fluoride by hydrolysis of either the quaternary fluoride or its methoxy derivative.

Experimental

Reaction in the Presence of 1-Butanethiol.—As described in a previous report[3] the closed cylinder was charged with 1-butanethiol, hexafluorocyclobutene and triethylamine in a molar ratio of 1:1.1:1.1. The reactants were shaken at a temperature of 46° for 48 hr. although there was evidence of heat-evolution at the Dry Ice charging temperature. At the end of this period the reaction mixture was transferred to a separatory funnel and acidified with concentrated hydrochloric acid. At the time, the relatively small amount of

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(1) The previous paper in this series is: J. T. Barr, K. E. Rapp, R. L. Pruett, C. T. Bahner, J. D. Gibson and R. H. Lafferty, Jr., THIS JOURNAL, **72**, 4480 (1950).

(2) This document is based on work performed for the Atomic Energy Commission by Carbide and Carbon Chemicals Company a Division of Union Carbide and Carbon Corporation, at Oak Ridge, Tennessee.

(3) K. E. Rapp, R. L. Pruett, J. T. Barr, C. T. Bahner, J. D. Gibson and R. H. Lafferty, Jr., THIS JOURNAL, **72**, 3642 (1950).

(4) R. R. Rickard, F. L. Ball and W. W. Harris, *Anal. Chem.*, **23**, 919 (1951).

(5) R. L. Pruett, J. T. Barr, K. E. Rapp, C. T. Bahner, J. D. Gibson and R. H. Lafferty, Jr., THIS JOURNAL, **72**, 3646 (1950).

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.

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

RESEARCH LABORATORIES, K-25 PLANT
CARBIDE AND CARBON CHEMICALS COMPANY
OAK RIDGE, TENNESSEE

RECEIVED APRIL 30, 1951

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 $C_{35}H_{53}N_3O_6S \cdot H_2O$: 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.

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(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.

THE LILLY RESEARCH LABORATORIES
INDIANAPOLIS, INDIANA

RECEIVED DECEMBER 18, 1950

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

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(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).