[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

DERIVATIVES OF PARA-HYDROXYMETHYL-BENZOIC ACID II. ETHER ESTERS[1]

BY FRANCIS H. CASE[2]

RECEIVED JULY 22, 1925 PUBLISHED DECEMBER 12, 1925

The esterification of *p*-hydroxymethylbenzoic acid and its attendant difficulties were described in a previous paper.[3] It was pointed out that the author's inability to obtain an acid chloride of this acid greatly complicated the preparation of certain esters of pharmacological importance, such as the β-diethylamino-ethyl ester.

The acid, *p*-ethoxymethyl-benzoic acid, $C_2H_5OCH_2C_6H_4COOH$, has been prepared by Hill and Johnson.[4] It was felt that the esters of this acid, which might be readily prepared from its acid chloride, should possess most of the pharmacological properties of the esters of *p*-hydroxymethylbenzoic acid.

Accordingly, the benzyl, the carbethoxybenzyl, and the β-diethylaminoethyl esters of *p*-ethoxymethyl-benzoic acid have been prepared. The hydrochloride of the last named ester, which is readily soluble in water, causes a distinct numbness when applied to the tip of the tongue, a crude criterion of local anesthesia.

In the course of the work involving *p*-cyanobenzyl bromide and chloride, a study was made of the optimum conditions for converting these nitriles into their corresponding acids and into *p*-hydroxymethyl-benzoic acid. The literature records but two methods for preparing *p*-chloromethylbenzoic acid: (1) by hydrolysis of *p*-chloromethyl-benzamide with concd. hydrochloric acid,[5] and (2) by chlorination of toluyl chloride, and hydrolysis of the acid chloride.[6] Both these methods were found by the author to give low yields. By merely hydrolyzing *p*-cyanobenzyl chloride with concd. hydrochloric acid and recrystallizing the product from alcohol, a yield of 78% of chloro acid was obtainable. On the other hand, when the hydrolytic product was boiled with water until it dissolved and then was recrystallized from that solvent, a yield of 73% of *p*-hydroxymethylbenzoic acid was obtainable. *p*-Chloromethyl-benzoic acid was also prepared by hydrolyzing *p*-cyanobenzyl bromide as before, when the bromine is replaced by chlorine.

The reverse of this process, that is, the preparation of *p*-bromomethyl-

[1] Presented before the Organic Section at the 68th meeting of the American Chemical Society, Ithaca, N. Y., September, 1924.

[2] National Research Fellow.

[3] Case, THIS JOURNAL, **47,** 1143 (1925).

[4] Hill and Johnson, unpublished thesis.

[5] Mellinghoff, *Ber.,* **22,** 3207 (1889).

[6] Ger. pat. 240,835 (1911).

benzoic acid by hydrolysis of *p*-cyanobenzyl chloride with hydrobromic acid has recently been reported.[7] This acid has also been prepared by bromination of toluic acid in bromoform. We were able to obtain a 73% yield of it by boiling *p*-cyanobenzyl bromide with constant-boiling hydrobromic acid.

Experimental Part

Preparation of *p*-Chloromethyl-benzoic Acid, $ClCH_2C_6H_4COOH$.—Twenty-five g. of *p*-cyanobenzyl chloride was refluxed on the steam-bath for ten hours with 500 cc. of concd. hydrochloric acid; the mixture was cooled and filtered. The precipitated acid was dissolved in ammonium hydroxide, filtered, reprecipitated with concd. hydrochloric acid and recrystallized from alcohol; yield of acid (m. p., 201–202°), 22. g. or 78%. This melted unchanged when mixed with a sample prepared by the method of Mellinghoff.[5] This acid was also obtained equally readily by hydrolyzing *p*-cyanobenzyl bromide in the same way.

Preparation of *p*-Hydroxymethyl-benzoic Acid, $HOCH_2C_6H_4COOH$.—The crude hydrolytic product obtained as described above was boiled with water until it dissolved, and crystallized from the cold solution; yield of hydroxy acid (m. p., 179–181°), 73%.

Preparation of *p*-Bromomethyl-benzoic Acid, $BrCH_2C_6H_4COOH$.—A mixture of 15 g. of *p*-cyanobenzyl bromide and 400 cc. of constant-boiling hydrobromic acid was kept at the boiling point for five hours, cooled and filtered. The precipitated acid was crystallized from alcohol; m. p., 223–224°; yield, 12 g., or 73%.

Anal. Calcd. for $C_8H_7O_2Br$: Br, 37.19. Found: 37.10.

Preparation of *p*-Ethoxymethyl-benzoic Acid, $C_2H_5OCH_2C_6H_4COOH$.—The method of Hill and Johnson[4] was used.

***p*-Ethoxymethyl-benzoyl Chloride, $C_2H_5OCH_2C_6H_4COCl$.**—Fifteen g. of *p*-ethoxymethyl-benzoic acid was refluxed for two hours with 15 g. of thionyl chloride. After evaporation of the thionyl chloride, the acid chloride was distilled in a vacuum; b. p., 136–138° (8 mm.); yield, 14 g., or 85%.

Anal. Calcd. for $C_{10}H_{11}O_2Cl$: Cl, 17.87. Found: 17.71.

Benzyl *p*-Ethoxymethyl-benzoate, $C_2H_5OCH_2C_6H_4COOCH_2C_6H_5$.—Eight g. of *p*-ethoxymethyl-benzoyl chloride was warmed on the steam-bath with 9 g. of benzyl alcohol. After evolution of hydrogen chloride had ceased, the mixture was dissolved in ether, the solution washed with 5% sodium carbonate solution and dried. After removal of the ether, it distilled at 198–201° (5 mm.) as a colorless oil; yield, 3.5 g., or 32%.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.56; H, 6.67. Found: C, 75.21; H, 6.76.

***p*-Carbethoxybenzyl *p*-Ethoxymethyl-benzoate, $C_2H_5OCH_2C_6H_4COOCH_2C_6H_4COOC_2H_5$.**—Ten g. of *p*-ethoxymethyl-benzoyl chloride was heated on the steam-bath with 9 g. of ethyl *p*-hydroxymethyl-benzoate. After completion of the reaction the mixture was treated as before. The ester distilled as a colorless oil at 243–244° (3 mm.); m. p., 36–37°. It is a white solid, insoluble in water, but soluble in alcohol; yield, 10 g., or 58%.

Anal. Calcd. for $C_{19}H_{22}O_5$: C, 70.18; H, 6.43. Found: C, 70.15; H, 6.12.

β-Diethylamino-ethyl *p*-Ethoxymethyl-benzoate, $C_2H_5OCH_2C_6H_4COOCH_2CH_2N(C_2H_5)_2$.—Twelve g. of *p*-ethoxymethyl-benzoyl chloride was dissolved in 20 g. of benzene; 14 g. of β-diethylamino-ethyl alcohol was gradually added to the solution, which

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[7] Swiss pat. 93,500 (1924).

[8] Salkind, *J. Russ. Phys.-Chem. Soc.*, **46**, 512 (1914).

was then warmed on the steam-bath for four hours. The mixture was treated with 5% sodium carbonate solution, extracted with ether and dried. After removal of the ether the base distilled as a colorless oil; b. p., 183–185° (5 mm.); yield, 10 g., or 59%.

Anal. Calcd. for $C_{16}H_{25}O_3N$: C, 68.82; H, 8.96. Found: C, 68.39; H, 9.10.

Hydrochloride.—Hydrogen chloride was passed into a solution of the base in dry ether. The precipitated solid was filtered off and recrystallized from ethyl acetate; m. p., 122–123°. It is soluble in water and alcohol.

Anal. Calcd. for $C_{16}H_{26}O_3NCl$: Cl, 11.24. Found: 11.55.

Summary

1. A few esters of *p*-ethoxymethyl-benzoic acid of possible value as local anesthetics have been prepared.

2. Simple methods for preparing chloro-, bromo- and hydroxymethyl-benzoic acids are described.

Cambridge 38, Massachusetts

[Contribution from the Chemical Laboratory of Harvard University]

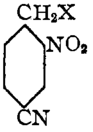
DERIVATIVES OF PARA-HYDROXYMETHYL-BENZOIC ACID
III. AMINO ESTERS[1]

By Francis H. Case[2]

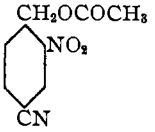
Received July 22, 1925 Published December 12, 1925

In a previous paper[3] was described the preparation of some esters of *p*-hydroxymethyl-benzoic acid which were expected to exhibit anesthetic properties. Physiological tests on these compounds by Dr. Hirschfelder indicate that the butyl ester does possess to some extent the desired properties.

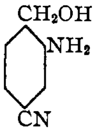
The nitration of *p*-cyanobenzyl chloride and bromide to form 4-halogen-methyl-3-nitrobenzonitrile (I) is described by Banse,[4] but in the case of the bromide no yield is given. Whereas the writer was able to obtain a 69% yield of chloro compound, he could obtain only a 28% yield of bromo derivative.



I



II



III

From the chloro compound Banse obtained the acetate (II), and by reduction with tin and concd. hydrochloric acid, 4-hydroxymethyl-3-aminobenzontrile (III). Due to the difficulty involved in preparing

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[1] Presented before the Organic Section at the 70th meeting of the American Chemical Society, Los Angeles, California, August, 1925.

[2] National Research Fellow.

[3] Case, This Journal, **47**, 1143 (1925).

[4] Banse, *Ber.*, **27**, 2161 (1894).