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

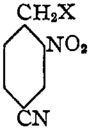
III. AMINO ESTERS[1]

BY FRANCIS H. CASE[2]

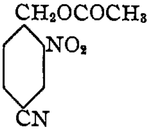
RECEIVED JULY 22, 1925 PUBLISHED DECEMBER 12, 1925

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



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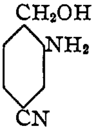

III

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.

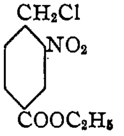
[2] National Research Fellow.

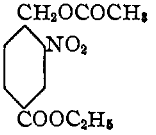
[3] Case, THIS JOURNAL, **47,** 1143 (1925).

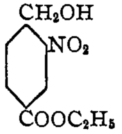
[4] Banse, *Ber.*, **27,** 2161 (1894).

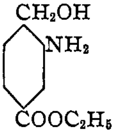
the latter compound, and its sensitivity toward acid and alkali it did not seem a desirable starting point for the preparation of esters of the corresponding acid.

By hydrolyzing 4-chloromethyl-3-nitrobenzonitrile with sulfuric acid in the presence of absolute alcohol, the corresponding ester (IV) was obtained. It was then converted into its acetate (V) with the idea of hydrolyzing the acetate group and reducing; but as the nitro ester was difficult to distil without complete decomposition and the acetate was very difficult to crystallize, a more feasible method of approach was sought.


IV


V


VI


VII

It was found that 4-acetoxymethyl-3-nitrobenzonitrile (II) on hydrolysis with alcohol saturated with hydrogen chloride yields ethyl 4-hydroxymethyl-3-nitrobenzoate (VI). This was confirmed by the preparation of a benzoate and a phenylurethan of the latter compound. The nitro ester may then be reduced by means of tin and hydrochloric acid to the desired amino ester (VII). Reduction by means of colloidal platinum was found to give better yields. In reductions carried out with the platinum oxide catalyst in the presence of ferric chloride, the product was found to be contaminated with undesirable by-products.

Ethyl and butyl 4-hydroxymethyl-3-aminobenzoates were prepared by this method. Their hydrochlorides are readily soluble in water. The results of pharmacological tests on these esters will be reported later.

Experimental Part

Preparation of 4-Chloromethyl-3-nitrobenzonitrile.—The procedure was the same as that of Banse;[4] yield, 69%.

Ethyl 4-Chloromethyl-3-nitrobenzoate, $C_6H_3(ClCH_2)(NO_2)(COOC_2H_5)$.—Twenty g. of 4-chloromethyl-3-nitrobenzonitrile was refluxed for four hours with a mixture of 150 cc. of absolute ethyl alcohol and 80 cc. of sulfuric acid. The reaction mixture was poured into water and extracted with ether. After the solution had been washed with sodium bicarbonate solution, dried and the ether removed, the residue distilled at 170–174° (4 mm.) as a heavy yellow oil; yield, 16.5 g., or 67%.

Anal. Calcd. for $C_{10}H_{10}O_4NCl$: C, 49.29; H, 4.11; Cl, 14.57. Found: C, 49.31; H, 3.87; Cl, 14.14.

Acetate of Ethyl 4-Hydroxymethyl-3-nitrobenzoate, $C_6H_3(CH_3COOCH_2)(NO_2)(COOC_2H_5)$.—Ethyl 4-chloromethyl-3-nitrobenzoate was refluxed with an alcoholic solution containing an excess of one molecular equivalent of anhydrous sodium acetate. The sodium chloride formed was filtered off, half of the alcohol evaporated from the filtrate and the residue poured into water. The resulting solid was filtered off and dried. It separated from a mixture of ether and petroleum ether in yellow crystals; m. p., 57–58°.

Anal. Calcd. for $C_{12}H_{13}O_6N$: C, 53.93; H, 4.87. Found: C, 53.71; H, 4.61.

Ethyl 4-Hydroxymethyl-3-nitrobenzoate, $C_6H_3(HOCH_2)(NO_2)(COOC_2H_5)$.—Thirty-nine g. of 4-acetoxymethyl-3-nitrobenzonitrile was dissolved in 300 cc. of absolute alcohol saturated with hydrogen chloride, and the solution refluxed for five hours on the steam-bath. The solution and precipitated ammonium chloride were poured into ice water, and the precipitated yellow solid was filtered off and dried. It was crystallized from a mixture of ethyl acetate and petroleum ether; m. p., 115–116°; yield, 27 g., or 67%.

Anal. Calcd. for $C_{10}H_{11}O_5N$: C, 53.33; H, 4.89. Found: C, 53.52; H, 5.03.

Benzoate of Ethyl 4-Hydroxymethyl-3-nitrobenzoate, $C_6H_3(C_6H_5COOCH_2)(NO_2)(COOC_2H_5)$.—Ethyl 4-hydroxymethyl-3-nitrobenzoate was dissolved in pyridine and treated with an excess of benzoyl chloride. After five minutes the mixture was poured into 1:2 hydrochloric acid, and the resulting precipitate was washed by decantation. It separated from alcohol in pale yellow crystals; m. p., 129–130°.

Anal. Calcd. for $C_{17}H_{15}O_6N$: C, 62.01; H, 4.56. Found: C, 61.95; H, 4.36.

Phenylurethan of Ethyl 4-Hydroxymethyl-3-nitrobenzoate, $C_6H_3(C_6H_5NHCOOCH_2)(NO_2)(COOC_2H_5)$.—Three g. of the ethyl ester described above was mixed with 1.7 g. of phenylisocyanate and the mixture warmed on the steam-bath for five hours. At the end of this time it had solidified to a yellow mass. On crystallization from alcohol the phenylurethan thus obtained melted at 125–126°; yield, 54%.

Anal. Calcd. for $C_{17}H_{16}O_6N_2$: C, 59.30; H, 4.65. Found: C, 59.76; H, 4.75.

Ethyl 4-Hydroxymethyl-3-aminobenzoate, $C_6H_3(HOCH_2)(NH_2)(COOC_2H_5)$. Tin Reduction Method.—Eleven g. of ethyl 4-hydroxymethyl-3-nitrobenzoate was dissolved in 300 cc. of 95% alcohol saturated with hydrogen chloride; 18 g. of tin was added gradually, while the temperature was kept below 40°. After the mixture had stood overnight, the tin had completely dissolved. The solution was dissolved in water and the tin removed by hydrogen sulfide. The slightly acid filtrate from the hydrogen sulfide was concentrated in a vacuum, made alkaline and extracted with ether. The residue from the ether was recrystallized from a mixture of benzene and petroleum ether. It is a white solid, insoluble in water but soluble in alcohol; m. p., 85–86°; yield, 5 g., or 53%.

Anal. Calcd. for $C_{10}H_{13}O_3N$: C, 61.54; H, 6.67. Found: C, 61.28; H, 6.55.

Reduction with Colloidal Platinum.[5]—Five g. of the nitro ester was dissolved in a mixture of 40 cc. of glacial acetic acid and 30 cc. of water. It was placed in a pressure bottle with 0.2 g. of colloidal platinum prepared by the method of Skita, subjected to about 2.5 atmospheres' pressure of hydrogen and shaken. After about two hours the absorption had practically ceased as indicated by the gage reading on the tank. The catalyst was then precipitated by means of acetone and filtered off. The filtrate was nearly neutralized with sodium hydroxide and extracted with ether. The ether was washed with sodium carbonate solution and dried. The residue from evaporation of the ether was recrystallized from benzene and petroleum ether; yield of base (m. p., 83–84°), 3.5 g., or 82%.

Reduction with Platinum Oxide Catalyst.—Ten g. of the nitro ester was dissolved in a mixture of 70 cc. of acetic acid and 40 cc. of water; 0.33 g. of platinum oxide catalyst prepared by the method of Voorhees and Adams,[6] and a few drops of ferric chloride solution were then added and the reduction was conducted as before. The absorption of hydrogen had practically ceased in three hours. The platinum was removed by filtration, and the filtrate treated as in the previous experiment. From the ether solution 7.5 g. of

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[5] Skita and Meyer, *Ber.*, **45**, 3579 (1912).

[6] Voorhees with Adams, THIS JOURNAL, **44**, 1397 (1922).

a crude solid was obtained, from which only 3.8 g. of pure base, m. p. 84–85°, was obtained; yield, 44%.

Hydrochloride of Ethyl 4-Hydroxymethyl-3-aminobenzoate.—Dry hydrogen chloride was passed into an ether solution of the amino ester. The resulting precipitate was recrystallized from a mixture of absolute alcohol and petroleum ether. When pure, the hydrochloride melts with decomposition at 129–130°. It is soluble in water. Very little pure product could be obtained, due to formation of resin, probably caused by a condensing action of hydrogen chloride on the alcohol and amino groups present.

Anal. Calcd. for $C_{10}H_{14}O_3NCl$: Cl, 15.32. Found: 15.71.

***n*-Butyl 4-Hydroxymethyl-3-nitrobenzoate,** $C_6H_3(HOCH_2)(NO_2)(COOC_4H_9)$.—This was prepared similarly to the corresponding ethyl ester, using absolute butyl alcohol saturated with hydrogen chloride instead of ethyl alcohol. After the reaction was complete, the ammonium chloride was filtered off, the excess of butyl alcohol was removed on the water pump and the residue distilled. The butyl ester distils as a heavy, yellow oil; b. p., 198–203° (3 mm.); yield, 66%.

Anal. Calcd. for $C_{12}H_{15}O_5N$: C, 56.92; H, 5.93. Found: C, 57.02; H, 5.73.

***n*-Butyl 4-Hydroxymethyl-3-aminobenzoate,** $C_6H_3(HOCH_2)(NH_2)(COOC_4H_9)$.—Ten g. of butyl nitro ester in 500 cc. of 50% alcohol and 5 cc. of concd. hydrochloric acid was reduced by means of colloidal platinum. The platinum was removed as before, the alcohol evaporated by means of the water pump, and the solution made alkaline and extracted with ether. Four g. of product, m. p. 73–74°, was obtained. The pure butyl ester is a white solid, m. p. 76–77°, soluble in dil. hydrochloric acid. Due to resinification, its hydrochloride could not be isolated.

Anal. Calcd. for $C_{12}H_{17}O_3N$: C, 64.57; H, 7.62. Found: C, 64.90; H, 7.30.

Summary

1. Ethyl and butyl 4-hydroxymethyl-3-aminobenzoates have been prepared, thus making available in soluble form the corresponding esters of *p*-hydroxymethyl-benzoic acid intended for use as local anesthetics.
2. A comparison of methods of reduction of ethyl 4-hydroxy-methyl-3-nitrobenzoate has been made.

CAMBRIDGE 38, MASSACHUSETTS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMICAL RESEARCH, PARKE, DAVIS AND COMPANY, NO. 34]

ETHYLHEXYLACETIC ACID AND ITS ESTERS

BY ARTHUR W. DOX

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The malonic ester synthesis has for many years been used for the preparation of fatty acids of the $C_nH_{2n+1}COOH$ series. The method is so well known and of such wide application that a discussion of the simple reactions involved would be superfluous. The present note merely describes the acid obtained from ethyl ethylhexylmalonate by saponification and expulsion of carbon dioxide, and the esters prepared from the acid by refluxing with methyl, ethyl, propyl and butyl alcohols, respectively, in the presence of a small amount of concd. sulfuric acid.