analogous to the formation of a nitrile acid chloride from camphoric imide, observed by Bredt and Iwanoff. It was identified by conversion into the amide and the free acid.

The tetrachlorodiethyldihydropyrimidine readily undergoes hydrolysis to diethylmalononitrile. It is suggested that this reaction occurs by way of an enolic tautomer of barbital.

Reduction of the tetrachloro derivative with zinc dust yields a stable dichlorodiethyldihydropyrimidine which does not easily undergo further reduction.

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

STUDIES IN THE DIPHENYL ETHER SERIES. III. DERIVATIVES OF THE LOCAL ANESTHETIC TYPE[1]

BY C. M. SUTER AND ELMER OBERG

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The purpose of this work was to study some derivatives of diphenyl ether which differ from the commonly used esters of *p*-aminobenzoic acid mainly in that the amino and ester groups are not attached to the same benzene ring. By a comparison of the local anesthetic action of these compounds with isomers containing both groups in the same ring it is hoped some conclusions may be drawn concerning the mutual effect of these two atomic complexes. The derivatives here reported upon are esters of 4-(4-aminophenoxy)-benzoic acid.

There are several methods which might be used in synthesizing the 4-(4-nitrophenoxy)-benzoic acid necessary for preparing the desired esters. It has been previously[2] obtained in small amounts by the action of the dipotassium salt of *p*-hydroxybenzoic acid upon *p*-chloronitrobenzene. Since the potassium salt of *p*-hydroxybenzaldehyde undergoes this type of reaction very readily, giving an aldehyde which may be oxidized to the desired 4-(4-nitrophenoxy)-benzoic acid, this latter method was used instead of the original one. When this work was practically completed, another feasible method was found in the acetylation of 4-nitrodiphenyl ether and the subsequent oxidation of the 4-(4-nitrophenoxy)-acetophenone.

The 4-(4-nitrophenoxy)-benzoic acid was converted into the acid chloride by the use of thionyl chloride. This was reacted with ethyl, *n*-butyl and β-diethylaminoethyl alcohols to give the nitro esters, which were catalytically reduced[3] to the desired compounds.

[1] Presented before the Organic Division of the American Chemical Society at the Cincinnati Meeting, September, 1930.

[2] Haeussermann and Bauer, *Ber.*, **29**, 2083 (1896).

[3] Adams, Cohen and Rees, THIS JOURNAL, **49**, 1093 (1927).

Preliminary experiments[4] indicate that the ethyl and butyl ester hydrochlorides show a slight local anesthetic action although they are too insoluble in water to be tested adequately. The β-diethylaminoethyl ester monohydrochloride has an activity approximately equal to that of borocaine or procaine, but it is considerably more toxic than these. Although its solubility in water is too small to give the 2% solution generally used, addition of the amount of hydrochloric acid necessary to form the dihydrochloride renders it sufficiently soluble.

Throughout the experimental work, Fischer short-stemmed thermometers were used in obtaining the melting points.

Experimental

4-(4-Nitrophenoxy)-benzaldehyde.—A solution of 45 g. of potassium hydroxide in 25 cc. of hot water was added with stirring to 97 g. of crude *p*-hydroxybenzaldehyde in 200 cc. of absolute ethyl alcohol. By cooling in ice there was obtained 116 g. or 91% of the theoretical of the potassium salt. The material so obtained was dark red in color but was satisfactory for the following reaction.

To 200 g. (1.27 moles) of *p*-chloronitrobenzene kept at 165–170° was added in small portions with stirring during one hour 93 g. (0.58 mole) of the dry potassium salt. The mixture was then maintained at 190–200° for six hours, cooled and steam distilled to remove the excess *p*-chloronitrobenzene. One crystallization from dilute acetic acid gave 106 g., 75% of the theoretical, of a brownish product which, after treatment with bone-black in alcohol, was obtained as colorless needles melting at 104–105°.

Anal. Calcd. for $C_{13}H_9O_4N$: N, 5.76. Found: N, 5.60, 5.62.

4-(2-Nitrophenoxy)-benzaldehyde.—This was prepared similarly to the preceding by the reaction of the potassium salt of *p*-hydroxybenzaldehyde with *o*-chloronitrobenzene. It was obtained as a white powder melting at 84–85°.

Anal. Calcd. for $C_{13}H_9O_4N$: N, 5.76. Found: N, 5.90, 5.84.

4-(4-Nitrophenoxy)-acetophenone.[5]—To a solution of 10.8 g. (0.05 mole) of 4-nitrodiphenyl ether and 13.3 g. (0.1 mole) of anhydrous aluminum chloride in 100 cc. of carbon disulfide was added during ten minutes 5 g. (0.06 mole) of acetyl chloride. After refluxing the mixture for fifteen minutes, the solvent was removed by distillation and the residue heated for half an hour longer on the steam-bath. Water was added and the product crystallized from 95% alcohol. The yield was 7 g., 55% of the theoretical, of a colorless product melting at 80–81°.

Anal. Calcd. for $C_{14}H_{11}O_4N$: N, 5.45. Found: N, 5.49, 5.38.

4-(4-Nitrophenoxy)-benzoic Acid.—A mixture of 60 g. of sodium dichromate in 100 cc. of water and 49 g. of the crude aldehyde was warmed until the aldehyde melted; then 43 cc. of concentrated sulfuric acid was added to the stirred mixture during half an hour. After an hour, the mixture was cooled, diluted with water and the insoluble residue extracted several times with hot dilute sodium hydroxide solution. Acidifying this alkaline solution gave 41 g., 79% of the theoretical, of the acid melting at 235–236°. Haeussermann and Bauer[2] report 236–237° for the acid prepared in a different way.

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[4] Our thanks are due Mr. Leonard Fosdick of the Northwestern Dental School for this report.

[5] Dilthey, Bach, Grütering and Hausdörfer, *J. prakt. Chem.*, **117**, 361 (1927).

The same acid was obtained in 76% yield by oxidation of 4-(4-nitrophenoxy)-acetophenone with bleaching powder by warming in water solution. This indicates the structure of this compound to be that assigned to it.

4-(4-Nitrophenoxy)-benzoyl Chloride.—A mixture of 10 g. of the acid and 50 g. of thionyl chloride was refluxed for an hour, the excess thionyl chloride distilled off and the residue extracted several times with petroleum ether (60–90°). There was obtained 9 g., 84% of the theoretical, of a slightly colored product which upon recrystallizing again from the same solvent gave long colorless needles which melted at 79–80°. It is slightly soluble in ether and readily soluble in benzene.

Anal. Calcd. for $C_{13}H_8O_4NCl$: N, 5.04. Found: N, 5.00, 5.05.

The amide was obtained by passing ammonia into a benzene solution of the acid chloride. It melts at 167–168°.

Anal. Calcd. for $C_{13}H_{10}O_4N_2$: N, 10.86. Found: N, 10.94, 10.93.

Ethyl 4-(4-Nitrophenoxy)-benzoate.—A solution of 24 g. of the acid chloride in 125 cc. of absolute ethyl alcohol was warmed on the steam-bath for an hour. Upon cooling, the ester separated as a white powder in nearly quantitative yield. Upon recrystallizing from alcohol, it melted at 74–75°.

Anal. Calcd. for $C_{15}H_{13}O_5N$: N, 4.88. Found: N, 4.74, 4.94.

Ethyl 4-(4-Aminophenoxy)-benzoate.—A solution of 17.3 g. (0.06 mole) of the nitro ester in 230 cc. of 95% alcohol was reduced with hydrogen in the presence of 0.2 g. of platinum oxide[6] catalyst. Upon removing the solvent, a viscous, slightly colored oil remained which did not crystallize. The hydrochloride was obtained as a white powder by passing hydrogen chloride through a benzene solution of the amine. It had no definite melting point but decomposed at about 165°. It is very slightly soluble in water.

Anal. Calcd. for $C_{15}H_{16}O_3NCl$: N, 4.77. Found: N, 4.76, 4.63.

The acetyl derivative separated from 95% alcohol as colorless crystals melting at 122–123°.

Anal. Calcd. for $C_{17}H_{17}O_4N$: N, 4.68. Found: N, 4.70, 4.53.

Butyl 4-(4-Nitrophenoxy)-benzoate.—This was obtained from 4-(4-nitrophenoxy)-benzoyl chloride and *n*-butyl alcohol as a thick yellow oil which distilled at 250–255° at 5 mm.

Anal. Calcd. for $C_{17}H_{17}O_5N$: N, 4.44. Found: N, 4.50, 4.58.

Butyl 4-(4-Aminophenoxy)-benzoate.—This was obtained similarly to the ethyl homolog by reduction of the nitro ester. It was obtained as a jelly-like material which did not crystallize. It was converted into the hydrochloride, which is practically insoluble in water and upon heating decomposes at 155–160°.

Anal. Calcd. for $C_{17}H_{20}O_3NCl$: N, 4.35. Found: N, 4.35, 4.38.

The acetyl derivative separated from 95% alcohol as a white flocculent material which melted at 98–99°.

Anal. Calcd. for $C_{19}H_{21}O_4N$: N, 4.29. Found: N, 4.33, 4.41.

β-Diethylaminoethyl 4-(4-Nitrophenoxy)-benzoate Hydrochloride.—A solution of 17 g. of the acid chloride in 100 cc. of benzene was treated with 6 g. (0.05 mole) of β-diethylaminoethyl alcohol in 15 cc. of benzene. The mixture was heated on the steam-bath for an hour, cooled and filtered. There was obtained 18 g. or 90% of the theoretical of material which decomposed at 100–110°.

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[6] Adams, Voorhees and Shriner, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1928, Vol. VIII, p. 92.

Anal. Calcd. for $C_{19}H_{23}O_5N_2Cl$: N, 7.09. Found: N, 7.05, 7.08.

β-Diethylaminoethyl 4-(4-Aminophenoxy)-benzoate Hydrochloride.—This was obtained, by reduction of the nitro compound described in the preceding preparation, as a jelly-like material which is insoluble in ether and benzene, but dissolves in warm water and separates upon cooling in an amorphous condition.

Anal. Calcd. for $C_{19}H_{25}O_3N_2Cl$: N, 7.68. Found: N, 7.33, 7.36.

Summary

A number of local anesthetic type derivatives of diphenyl ether have been prepared in which the carboxy and amino groups are not attached to the same benzene ring.

Although these derivatives show considerable anesthetic action, they are too toxic to be of practical value.

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THE OXIMES OF ORTHO HYDROXY BENZOPHENONE

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The oximes of *o*-hydroxy benzophenone have acquired a certain importance in connection with the interpretation of the Beckmann rearrangement. One of the two possible oximes was first made by Cohn,[1] who described a product melting at 134°. Meisenheimer and Meis[2] recently repeated the work under somewhat different conditions, but likewise obtained only a single oxime (135°). Like *o*-chloro benzophenone and *o*-bromo benzophenone, therefore, *o*-hydroxy benzophenone appeared to be capable of forming but one oxime that was sufficiently stable for isolation, and it seemed probable that the known oximes of these three ketones had the same configuration.

Since alkalies convert the known oximes of *o*-chloro and *o*-bromo benzophenone into a cyclicc ompound—phenyl indoxazene—Meisenheimer and Meis concluded that these were probably *syn* oximes. They subsequently verified[3] this conclusion beyond all doubt by preparing the much more reactive dinitro *o*-chloro benzophenone oxime and showing that it forms the corresponding indoxazene under conditions under which isomerization of the oxime need not be feared. The configuration of these three oximes can therefore be regarded as established by their relation to cyclic compounds. When they were subjected to a Beckmann rearrangement, all three gave products which were in accord with Meisenheimer's interpretation of this rearrangement.

[1] Cohn, *Monatsh.*, **17**, 102 (1896).

[2] Meisenheimer and Meis, *Ber.*, **57**, 289 (1924).

[3] Meisenheimer, Zimmermann and v. Kummer, *Ann.*, **446**, 208 (1926).