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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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

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.

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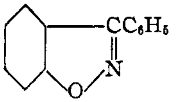
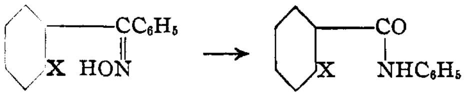
[1] Cohn, *Monatsh.*, **17**, 102 (1896).

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

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

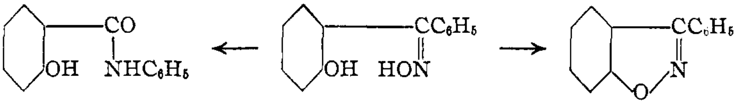


II



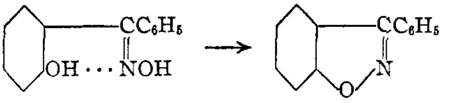
I III

By analogy with these halogen compounds, the known oxime of *o*-hydroxy benzophenone would be expected to yield salicylanilide on rearrangement and phenyl indoxazene on dehydration. Meisenheimer and Meis found that it is readily rearranged by phosphorus pentachloride and that the principal product is salicylanilide, but they also found that it resisted all their efforts to convert it into the cyclic compound.

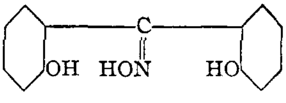


IV V II

In order to account for this unexpected resistance to dehydration, they resorted to the same auxiliary hypothesis that Meisenheimer had adopted to explain why the γ-dioxime of benzil, which according to Meisenheimer's interpretation is the *amphi* form, loses water more readily than any of its isomers.[4] Accordingly, they assumed that for the elimination of water, the interplay of residual valences was decisive, and they predicted that the indoxazene derivative would be readily formed from the *anti* form.



VI II



VII

This prediction lost much of its probability when Auwers and Jordan[5] showed that it was impossible to transform the oxime of *o*,*o*'-dihydroxy benzophenone (VII) into an indoxazene derivative. As a matter of fact the prediction is wrong; we have prepared both of the oximes of *o*-hydroxy benzophenone, and have found that neither of them can be dehydrated. It is impossible, therefore, to establish the configuration of these oximes by relating them to phenyl indoxazene.

Surprisingly enough, in view of the fact that isomeric oximes of ortho substituted benzophenones have so seldom been obtained,[6] both of the oximes of *o*-hydroxy benzophenone are relatively stable substances. They differ little in solubility and melting point but they are readily distinguished by their crystalline form, the *h*-oxime (143°) crystallizing from benzene

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[4] Meisenheimer and Lamparter, *Ber.*, **57**, 276 (1924).

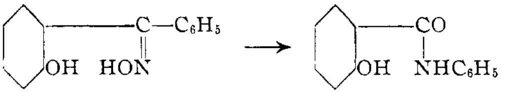
[5] Auwers and Jordan, *ibid.*, **58**, 26 (1925).

[6] (a) A. W. Smith, *ibid.*, **24**, 4057 (1891); (b) A. Hantzsch, *ibid.*, **25**, 2164 (1892); (c) Auwers and Myenburg, *ibid.*, **24**, 2383 (1891); **29**, 1264 (1896); (d) Auwers and Jordan, *ibid.*, **57**, 800 (1924).

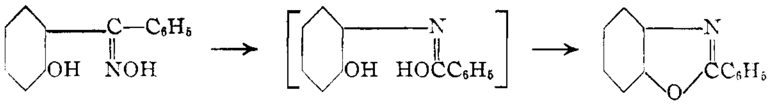
in plates while the *n* form (141°) appears in needles. Neither passes into the other in boiling solvents or at the melting point. At higher temperatures the *h*-form sublimes unchanged, while the *n*-form is changed to its isomer, but even at 185–200° the process is exceedingly slow.

Although both oximes can be obtained in alkaline solutions of hydroxylamine, and Cohn, as well as Meisenheimer and Meis, doubtless had mixtures of the two, the needles must be regarded as the "alkali-stable" form because boiling alkalies slowly convert the plates into this form. Formic acid, on the other hand, changes the *n*- to the *h*-form; this may, therefore, be regarded as the "acid-stable" oxime, but the term is misleading because formic acid also very readily brings about a Beckmann rearrangement.

With phosphorus pentachloride in ether each oxime yields a single rearrangement product, the *n*-oxime being converted into salicylanilide and the *h*-oxime into 2-phenyl benzoxazole (VIII). As usual the process is accompanied by side reactions but no salicylanilide is formed from the *h*-oxime and no phenyl benzoxazole from the isomer. Since Meisenheimer's interpretation of the Beckmann rearrangement has proved to be correct in every case in which an oxime has been obtained from a cyclic compound, we regard the *n*-form as the *syn* and the *h*-form as the *anti* oxime.



V IV



VI VIII

From the foregoing account it is evident that the isomeric oximes of *o*-hydroxy benzophenone do not furnish any independent evidence with respect to the proper interpretation of the Beckmann rearrangement. Their behavior, however, serves to dispel some of the doubts raised by Auwers and Seyfried[7] concerning the use of this rearrangement for determining configurations. These authors point out that not infrequently a single oxime gives two rearrangement products and that while, as is generally assumed, these products may be due to isomerization of part of the oxime, antecedent to rearrangement, this is not certain because they may also be due to different modes of rearrangement of the same oxime. In the absence of evidence to the contrary, this is doubtless true. We have found, however, that in the case of the *n*-oxime, which is exceedingly sensitive to acids, it is possible to get a single rearrangement product by operating with phosphorus pentachloride in absolute ether, at a low temperature; and we also found that while formic acid very readily transforms this oxime into the

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[7] Auwers and Seyfried, *Ann.*, **484**, 178 (1930).

rearrangement product of its isomer, it is possible to isolate the *h*-oxime as an intermediate in the process. We therefore believe that even when but one isomer is known, the Beckmann rearrangement is useful if it is employed with sufficient care.

Experimental Part

Both of the oximes of *o*-hydroxy benzophenone can be obtained directly from the ketone by treating it with hydroxylamine in an alkaline medium. The result of this treatment depends mainly, at any rate, upon the temperature. At the ordinary temperature the product is almost pure *h*-oxime, which crystallizes in plates. In boiling solutions the product is a mixture in which the quantity of *n*-oxime increases with the time that the solution is boiled. From mixtures which are composed mainly of either isomer it is comparatively easy to get pure substances by recrystallization from benzene and petroleum ether, but it is not feasible to separate mixtures containing considerable quantities of both components in this manner.

The h-oxime is most readily obtained by operating at the ordinary temperature. Thus 0.5 g. of the ketone was added to 4 cc. of 40% aqueous potassium hydroxide. The ketone dissolved with the characteristic yellow coloration and a yellow solid soon precipitated from the solution. To this mixture was added 0.5 g. of hydroxylamine hydrochloride. The temperature rose, the yellow solid soon dissolved and the intense yellow color disappeared within fifteen minutes. The solution was then acidified with hydrochloric acid; it deposited a white precipitate which was collected on a funnel, washed with a little 50% methyl alcohol and dried. The crude product weighed 0.45 g. and melted at 128–130°. Recrystallization from benzene and a little petroleum ether gave 0.35 g. of pure oxime, crystallizing in thin plates and melting at 142–143°. The pure oxime crystallizes well from dilute methyl alcohol in large thick plates but it is very difficult to separate a mixture of the oximes by crystallization from this solvent.

Anal. Calcd. for $C_{13}H_{11}O_2N$: C, 73.2; H, 5.1. Found: C, 72.9; H, 5.2.

The n-oxime is probably obtained most readily by heating the *h*-oxime with strong alkalies. Thus a solution of 0.5 g. of the *h*-oxime in 20 cc. of 20% aqueous sodium hydroxide was boiled vigorously for two hours, during which it became slightly yellow (possibly because some of the hydroxy ketone was regenerated). On acidification the solution deposited a solid contaminated with a small quantity of red oil. Recrystallization from benzene and petroleum ether yielded 0.3 g. of a pure product crystallizing in needles and melting at 141–142°. A mixture of the two forms melted at 115–120°.

Anal. Calcd. for $C_{13}H_{11}O_2N$: C, 73.2; H, 5.1; N, 6.6. Found: C, 73.5; H, 5.4; N, 7.0.

Separation of Mixtures.—To a solution of 5 g. of *o*-hydroxy benzophenone and 5 g. of hydroxylamine hydrochloride in 50 cc. of methyl alcohol was added a solution of 8 g. of potassium hydroxide in 8 cc. of water. The mixture was boiled for two hours, then poured into 150 cc. of water. A slight gummy precipitate was removed by filtration, and then the clear filtrate was partially neutralized with 3 cc. of glacial acetic acid; it deposited 1.34 g. of a colorless solid which was collected on a filter, washed and dried. One recrystallization of this first crop from 4 cc. of benzene gave the pure *h*-oxime melting at 143°.

From the filtrate from the first fraction 1 cc. of glacial acetic acid precipitated 1.08 g. of a pale yellow solid which melted at 128–135° and which proved to be a mixture of the two isomers, separable most readily by a repetition of the operation. Final acidification with 3 cc. of glacial acetic and 3 cc. of concentrated hydrochloric acids resulted in

0.8 g. of a colorless precipitate which after one recrystallization from benzene and petroleum ether was pure *n*-oxime.

The Action of Alkalies on the Oximes.—It has been shown that the isomerization of the *h*-oxime by alkalies is accompanied by secondary reactions that lead to the development of color. The *n*-oxime appears to be much more stable in boiling alkalies, for when a solution of 0.5 g. of the substance in 20 cc. of 20% aqueous sodium hydroxide was boiled for two hours it remained colorless and 0.45 g. of the pure oxime was recovered when the solution was acidified.

The Action of Heat on the Oximes.—A small quantity (0.24 g.) of the *h*-oxime was heated under 25 mm. to 175–180° for half an hour during which most of it (0.15 g.) sublimed to the upper part of the flask. The sublimate was unchanged oxime. The residue was dissolved in a little methyl alcohol in which the dehydration product, phenyl indoxazene, is sparingly soluble, but nothing except unchanged *h*-oxime could be detected in the solution. Two-tenths of a gram of the *n*-oxime was heated in a similar manner to 180–200° and a part of the material sublimed in plates. Solid residue and sublimate dissolved completely in 2 cc. of methyl alcohol and inoculation of this solution with phenyl indoxazene had no effect. The solution, on cautious dilution with water, deposited 0.15 g. of the *h*-oxime, and further dilution gave 0.05 g. more or less pure material (137–140°). At elevated temperatures, therefore, the *n*-oxime does not undergo dehydration but is changed to the *h*-isomer.

The Action of Phosphorus Pentachloride on the Oximes.—To a solution of 1 g. of the *n*-oxime in 30 cc. of absolute ether was added 1.9 g. of phosphorus pentachloride. The cloudy solution was allowed to remain at 20° for fifteen minutes, then mixed with 20 g. of ice. The ethereal layer was washed with hydrochloric acid and with water, dried and evaporated. It left a gummy residue which was completely soluble in alkalies, therefore contained no phenyl benzoxazole. From the alkaline solution carbon dioxide precipitated 0.45 g. of salicylanilide melting at 132–133°.

In a similar manner 1 g. of the *h*-oxime was treated with 1.5 g. of phosphorus pentachloride. The washed and dried ethereal solution on evaporation left a gummy residue of which all but 0.42 g. was soluble in alkali. The insoluble portion was identified as 2-phenyl benzoxazole melting at 102–103°. From the alkaline solution carbon dioxide precipitated a solid which after recrystallization melted at 164–167°. Only a small amount of this substance was obtained in fairly pure state; it had the properties of *o*-aminophenol, a cleavage product of the compound resulting from the initial rearrangement.

The Action of Hydrogen Chloride on the Oximes.—Attempts to dehydrate one or other of the oximes with dry hydrogen chloride met with no success. From ethereal solutions of *h*-oxime dry hydrogen chloride precipitated a yellow hydrochloride that melted at 118–120° when freshly prepared but which rapidly deteriorated when kept in a vacuum desiccator. When an alcoholic solution of this chloride was immediately diluted with water, the *h*-form was recovered, practically quantitatively, and when the chloride was dissolved in chloroform, hydrogen chloride was given off and again the *h*-form was recovered. But when the chloride was heated to 140–145° it decomposed freely, and moisture condensed on the cool part of the tube. From the residue alkali extracted *o*-hydroxy benzophenone and left 2-phenyl benzoxazole, which was identified by a mixed melting point.

The *n*-form likewise gave a solid hydrochloride. This melted at 132–134° and regenerated the *n*-oxime when it was dissolved in hot chloroform or when its solution in alcohol was diluted with water. When it was heated to 145° this oxime likewise gave 2-phenyl benzoxazole. Under these conditions, therefore, neither of the oximes can be dehydrated.

The Action of Formic Acid on the Oximes.—Preliminary experiments showed that neither cold concentrated sulfuric nor glacial acetic acid has any action on the oximes. We therefore turned to formic acid, which is known[6d] to be much more effective. Both oximes gave, along with a small quantity of yellow oil which was doubtless the hydroxy ketone due to hydrolysis, mainly phenyl benzoxazole. This result was to be expected in the case of the *h*-oxime because the oxazole derivative is obtained from the normal Beckmann rearrangement product of this oxime. But in the case of the *n*-oxime the formation of this product involves either an abnormal rearrangement or a combination of isomerization and rearrangement.

In order to decide between these alternatives we repeated the experiment with the *n*-oxime with much greater care. To this end a solution of 0.25 g. of the oxime in 2 cc. of formic acid (sp. gr. 1.20) was heated without delay to 100° for five minutes. The yellow solution was then cooled and diluted with 10 cc. of water. A gummy yellow precipitate separated. Excess of sodium carbonate was added and the mixture was left to itself for several hours, during which the precipitate became solid and nearly white. It was collected on a sintered glass filter and digested for fifteen to twenty minutes with sodium bicarbonate solution. After this had been sucked off, a clean receiver was placed under the filter and the solid was stirred with 5 cc. of 10% sodium hydroxide. A partial solution occurred. The insoluble part was washed with alkali, water and dilute methyl alcohol (about 50%), and dried. It weighed 0.05 g. and melted at 97–100°. The mixed melting point with 2-phenyl benzoxazole gave no depression.

To the faintly turbid alkaline filtrate was added drop by drop with shaking 5% acetic acid until a more pronounced permanent turbidity just became evident. The solution stood overnight and the small brown plates which formed were filtered off. They weighed 0.04 g. and melted at 134–137°. On crystallization from benzene and petroleum ether a solid melting at 140–141° was secured. The mixed melting point with the plate form oxime was 141–143°, and with the needle form 110–115°. It is important not to add more than the specified amount of acid in precipitating this portion since a slight excess will precipitate the *n*-form also, and separation of a mixture of the isomers by crystallization is practically impossible unless one form is very largely in excess.

Acidification of the faintly alkaline filtrate gave 0.12 g. of white unchanged *n*-oxime melting at 138–140°, mixed melting point with the original *n*-oxime, 139–141°. This procedure was carried out twice with the same result.

Summary

The stereoisomeric oximes of *o*-hydroxy benzophenone have been prepared. Neither of them can be dehydrated to a cyclic compound. Their behavior, therefore, contributes no independent evidence with respect to the proper interpretation of the Beckmann rearrangement, but indicates that this rearrangement is reliable when it is employed with sufficient care.

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