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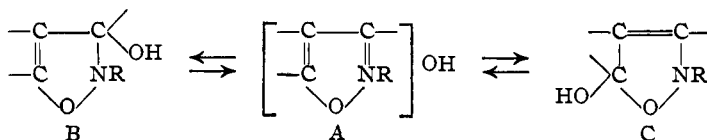
**PSEUDO BASES IN THE ISOXAZOLE SERIES. FOURTH PAPER**

BY E. P. KOHLER AND W. F. BRUCE

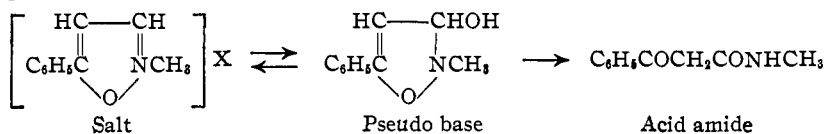
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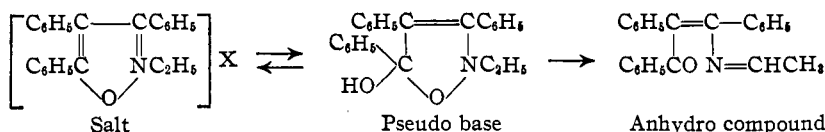
In earlier papers of this series it has been shown that when the salts which are obtained by alkylating various isoxazoles are treated with bases they give rise to a great variety of products. All these products can be traced to two fundamental reactions which differ in the positions assumed by the hydroxyl group in the rearrangement from the true to the pseudo bases



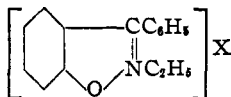
The rearrangement from A to B, in which the hydroxyl group ends in the 3-position, has heretofore been observed only when both the 3- and the 4-positions were occupied by hydrogen alone, as, for example<sup>1</sup>



In all other cases the hydroxyl group entered the 5-position and the sequence of reactions was as follows



Before concluding our studies in this series it was desirable to investigate a case in which the 3- and 4-positions are occupied by hydrocarbon residues but in which there is also a pronounced hindrance to the shift of linkage that is essential to a rearrangement from A into C. To this end we have alkylated 3-phenyl benzisoxazole and studied the behavior of the resulting salts

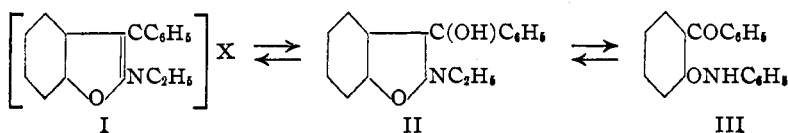


Except in their solubilities these salts differ but little from those obtained by ethylating triphenyl isoxazole. Even their behavior toward bases bears a certain superficial resemblance to that of the monocyclic salts, be-

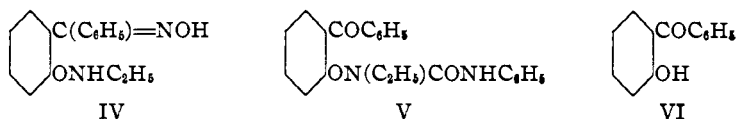
<sup>1</sup> Mumm and Münchmeyer, *Ber.*, **43**, 3340 (1910).

cause like these they yield, first, a pseudo base from which they can be regenerated, and finally an anhydro compound from which they cannot. Here, however, the resemblance ceases.

The pseudo base from the dicyclic salts reacts readily both with hydroxylamine and with phenyl isocyanate; it therefore behaves like an open-chained compound containing an active hydrogen atom and a carbonyl group. Such a substance manifestly can be formed only by a rearrangement of the type  $A \rightarrow B$ , and the relations must be represented as follows

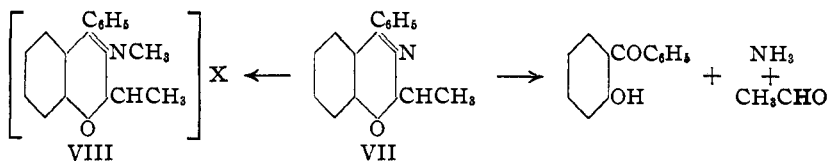


In acid solutions all transformations are toward the left, in alkaline solution they are toward the right; hence the ease with which the salts are regenerated and the inability to secure a methyl ether of II in the usual manner; hence also the ability to react with hydroxylamine and phenyl isocyanate and the readiness with which the pseudo base is oxidized to *o*-hydroxy benzophenone



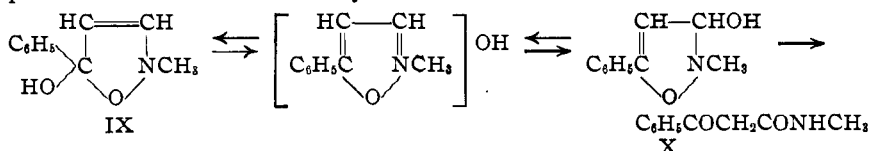
The formation of this open-chained pseudo base shows that when the hindrance to every other type of rearrangement is sufficiently great, isoxazolinium bases may rearrange to form 3-hydroxy isoxazolines even though the 3-position is occupied by a hydrocarbon residue and the lack of hydrogen in the 4-position prevents the usual adjustment to a stable acid amide. The open-chained formula, however, gives no clue to the structure of the anhydro compound. The pseudo base loses water rapidly when heated, and it even slowly passes into the anhydro compound when it is left to itself at the ordinary temperature. Despite the ease with which the process occurs, however, it must nevertheless represent a major change in structure because it cannot be reversed.

For determining the structure of the anhydro compound the following facts are available. The substance is a base, capable of forming salts that are isomeric with those derived from the pseudo base. It combines with dimethyl sulfate to form a salt in which one methyl group is in combination with nitrogen. And, finally, the anhydro compound is hydrolyzed, both by acids and by bases, to *o*-hydroxy benzophenone, acetaldehyde and ammonia. When these facts are assembled they lead to the metoxazine derivative VII



Doubtless there are a number of ways in which the metoxazine derivative might be formed from the pseudo base, but whatever the route, its formation demonstrates anew the instability of all pseudo bases in the isoxazole series. In view of this great instability, it seems doubtful whether these bases can serve the main purpose of this series of investigations, namely, to ascertain the factors which determine the mode of addition of an ion to the unsaturated nucleus.

As a result of the investigations, it is now possible to predict the outcome of a reaction between a base and any isoxazolinium salt which has no substituents other than hydrocarbon residues; but in nearly all cases, there is a measure of uncertainty about the structure of the intermediate pseudo bases. In most cases the structure, of necessity, is inferred from the nature of the products into which the pseudo bases pass by spontaneous rearrangement or degradation. Since the base and the pseudo base are connected by a reversible process, inferences drawn from subsequent products are not necessarily reliable, and the fact that the final products always represent the most stable substances that could be formed leads to a suspicion that the outcome of these reactions may depend more upon the stability of the final products than upon the mode of addition. Thus the pseudo base obtained from the alkylation product of 5-phenyl isoxazole might have the structure represented by formula IX even though the final product can be reconciled only with X.



### Experimental Part

Phenyl benzisoxazole was prepared as usual by converting *o*-chlorobenzophenone into its oxime and heating the oxime with bases, but it was found advantageous to combine the two steps into a single operation. The procedure was as follows.

A solution of 290 g. of hydroxylamine hydrochloride in 100 cc. of warm water was poured into a mixture of 350 g. of *o*-chlorobenzophenone and 300 cc. of alcohol contained in a two-liter flask. The flask was then connected with an inverted condenser and through the condenser a solution of 280 g. of sodium hydroxide in 300 cc. of water was added as rapidly as the refluxing permitted. The flask was heated for seven hours on a steam-bath and then most of the alcohol was removed by distillation. To the residue in the flask was added a solution of 220 g. of potassium hydroxide in 500 cc. of water.

The mixture was heated on a steam-bath for three days, then cooled to about 6° and shaken vigorously. It deposited a pale yellow solid which was thoroughly washed with water and recrystallized from methyl alcohol. It gave 220 g. of phenyl benzisoxazole, pure white in color, and melting at 81–82°—a yield of 70%.

**Ethylation.**—The isoxazole is ethylated less readily than those which have been studied heretofore. A mixture of 80 g. of the substance and 33 g. of freshly distilled diethyl sulfate was heated in an oil-bath at 130–140°. The liquid darkened somewhat and there was a slow evolution of sulfur dioxide. After it had been heated for fifteen hours the mixture was cooled, treated with 50 cc. of 6 *N* hydrochloric acid and heated on a steam-bath for two hours. On cooling it deposited 5 g. of unchanged isoxazole and a little more was obtained when the solution was thoroughly extracted with ether.

For the purpose of preparing the ferric chloride double salt the sirupy aqueous solution was treated with concentrated ferric chloride solution in excess. After two hours the light yellow precipitate was collected on a filter, washed with dilute hydrochloric acid and with ether, then recrystallized from 60–70 cc. of glacial acetic acid. The yield was 47 g. or 87%.

*Anal.* Calcd. for  $C_{16}H_{14}ONCl_4Fe$ : C, 42.7; H, 3.4. Found: C, 42.7; H, 3.3.

The ferric chloride double salt is readily soluble in water, very sparingly soluble in ether, ethyl bromide and cold acetic acid. It crystallizes in pale yellow platelets and melts at 134°.

**Other Salts.**—For the purpose of comparison with the isomeric salts derived from the metoxazine a few other salts were prepared. These were obtained most easily by forming the pseudo base from the ferric chloride salt and then converting the pseudo base into the new salt.

**The Chloride.**—An ethereal solution containing about 1 g. of the pseudo base was saturated with dry hydrogen chloride, whereupon it gradually separated into two clear liquid layers. The top layer was decanted, the bottom layer washed, by decantation, with dry ether, then placed in a vacuum over solid potassium hydroxide. It slowly solidified, first to a glassy, finally to an opaque solid. This was dissolved in chloroform. The chloroform solution, when cooled in a freezing mixture deposited colorless needles melting at 95–97°. The chloride is difficult to handle because it is very hygroscopic. With ferric chloride solution it forms the double chloride melting at 134°.

*Anal.* Calcd. for  $C_{16}H_{14}ONCl$ : Cl, 13.6. Found: Cl, 13.3.

**The Mercuric Chloride Salt.**—This salt was made both by adding excess of saturated mercuric solution directly to the ethylation product and by adding a similar solution to the pseudo base dissolved in hydrochloric acid. It is more soluble than the ferric chloride double salt. From glacial acetic acid it crystallizes in white fluffy needles melting at 119–120°.

*Anal.* Calcd. for  $C_{16}H_{14}ONCl_2Hg$ : Hg, 37.8. Found: Hg, 37.8.

With picric acid ethereal solutions of the pseudo base yielded a picrate crystallizing in yellow needles which melt at 132–133°, and with 60% perchloric acid similar solutions formed a perchlorate melting at 183–184°.

*Anal.* Calcd. for  $C_{21}H_{18}O_8N_4$ : C, 55.8; H, 3.6. Found: C, 55.6; H, 3.6.

**The Pseudo Base (III).**—The pseudo base was first obtained by the usual procedure of shaking the ferric chloride double salt with sodium hydroxide in the presence of ether but it is more easily prepared directly from the ethylation mixture. For this purpose the mixture is as usual digested with hydrochloric acid and thoroughly extracted with ether. Fresh ether is then stratified on top of the sirupy liquid, the mixture is cooled with ice and sodium hydroxide solution is slowly added in excess with constant shaking. The alkaline layer is drawn off and again extracted with ether.

The ethereal extracts are combined, washed with water, dried over sodium sulfate and evaporated by suction. It leaves a pale yellow oil. This oil is dissolved in low-boiling petroleum ether and the solution is cooled to 0°. The pseudo base has a tendency to separate as oil but vigorous rubbing of the walls of the vessel with a glass rod usually induces the formation of a granular precipitate. This is recrystallized by solution in benzene and addition of petroleum ether.

*Anal.* Calcd. for  $C_{15}H_{15}O_2N$ : C, 74.6; H, 6.3. Found: C, 74.8; H, 6.3.

The pseudo base crystallizes in small prisms and melts at 79–80°. It is soluble in the usual organic solvents except petroleum ether. All operations with it must be carried out at low temperatures and as rapidly as possible because in solution it soon changes into the anhydro compound. The solid base likewise changes into the anhydro compound. At the ordinary temperature the process is relatively slow but in the course of a month all preparations turn from colorless solids to yellow oils interspersed with small droplets of water. At  $-10^\circ$ , however, a sample which had been kept for a year had changed but slightly; it was pale yellow in color and its melting point had dropped two degrees.

**Attempts to Prepare a Methyl Ether.**—Since the ability to form methyl ethers in basic media is one of the most characteristic properties of pseudo bases of all sorts, we made many attempts to prepare such an ether. To this end we treated the ferric chloride double salt with methyl alcoholic sodium hydroxide, the chloride with sodium methylate and the pseudo base with various concentrations of alkali in methyl alcohol. All methods gave only pseudo base or, in case the experiments were too prolonged, the anhydro compound.

**The Oxime (IV).**—To a solution of 1.5 g. of the pseudo base in 10 cc. of methyl alcohol was added 1.5 g. of hydroxylamine hydrochloride and then 4 cc. of a 40% solution of potassium hydroxide. The mixture was left to itself for an hour, then poured into 80 cc. of water. The solid precipitate was washed with water, dried and recrystallized from benzene. It separated in long felted needles and melted with decomposition at  $135.6^\circ$ .

*Anal.* Calcd. for  $C_{15}H_{15}O_2N_2$ : C, 70.3; H, 6.3. Found: 70.4; H, 6.3.

The oxime is readily soluble in acetone, methyl alcohol and acetic acid, slightly soluble in benzene and in chloroform. To prove that it is really an oxime of the pseudo base, it was treated with dilute hydrochloric acid. It dissolved at once and when ferric chloride was added to the solution it precipitated the double salt melting at 133–134°.

**The Urea Derivative (V).**—To a solution of 2.4 g. of the pseudo base in 7 cc. of benzene was added 1.4 g. of phenyl isocyanate. The temperature of the solution rose rapidly to 55–60°. On cooling, the solution slowly deposited a crystalline solid. After three days the solid was recrystallized from methyl alcohol. It separated as a granular deposit which melted at  $128^\circ$ .

*Anal.* Calcd. for  $C_{22}H_{20}O_2N_2$ : C, 73.3; H, 5.6. Found: 73.6; H, 5.7.

**The Oxime of the Urea Derivative,  $C_6H_5$   $\left\{ \begin{array}{l} C(=NOH)C_6H_5 \\ ON(C_2H_5)CONHC_6H_5 \end{array} \right.$** —In order to distinguish between the two possible phenyl isocyanate addition products—the urethan and the urea derivative—the substance was treated with hydroxylamine. To this end 2.2 g. of the substance and an equal weight of hydroxylamine hydrochloride were dissolved in 100 cc. of hot methyl alcohol. To this solution was added gradually 6 g. of potassium hydroxide dissolved in 8 cc. of water. The light yellow mixture was immediately cooled under the tap and set aside for twenty-four hours.

A small quantity of unchanged material was removed by filtration. The solution was diluted with 300 cc. of water and filtered again to remove a small quantity of impure product. The filtrate on acidification deposited 2.0 g. of a colorless product which

was dried and recrystallized from benzene. It was thus obtained as long filmy needles resembling those of the oxime of the pseudo base. The substance melted with decomposition between 145 and 150°, depending upon the method of heating.

*Anal.* Calcd. for  $C_{22}H_{21}O_2N_3$ : C, 70.4; H, 5.6. Found: 70.5; H, 5.6.

**The Anhydro Compound: 2-Methyl-4-phenyl-5,6-benzometoxazine (VII).**—As has been stated, the pseudo base spontaneously loses water and passes into the metoxazine derivative. In solution the process is rapid, hence all filtrates from the pseudo base are rich in this derivative. For preparation from the pure pseudo base the substance was heated to 95° under diminished pressure. Under these conditions bubbles of water vapor began to appear at about 60° and became brisk as the temperature rose. The residue was purified either by vacuum distillation or by transforming it into its hydrochloride, which was readily purified, and then regenerated by treatment with bases.

*Anal.* Calcd. for  $C_{15}H_{13}ON$ : C, 80.7; H, 5.9. Found: C, 80.8; H, 5.9.

When perfectly pure, the metoxazine derivative crystallizes in colorless needles melting at 33–35°. It is, however, extremely difficult to obtain it in crystalline form. It is readily soluble in all organic solvents and can be crystallized only from petroleum ether at low temperatures. It distils at 175–177° under a pressure of 11 mm. The distillate is a viscous oil which partially solidifies when its solution in petroleum ether is cooled in a freezing mixture and inoculated with solid.

**The Hydrochloride.**—The hydrochloride can be made by dissolving the base in concentrated hydrochloric acid, but a better yield and a purer product are obtained by operating with dry hydrogen chloride in ether. Thus when dry hydrogen chloride was passed into a solution of 2 g. of the substance in 20 cc. of ether, a pale yellow precipitate began to form immediately. The solution was saturated, set aside for an hour, then filtered. The hydrochloride was washed thoroughly with ether, then dissolved in 4 cc. of methyl alcohol at 50° and this solution was very gradually diluted with ether to 120 cc. It deposited 2.2 g. of the hydrochloride in pale yellow needles.

*Anal.* Calcd. for  $C_{15}H_{14}ONCl$ : C, 69.3; H, 5.5; Cl, 13.6. Found: C, 69.2; H, 5.6; Cl, 13.6.

When it is heated rapidly the salt melts at 104°, but it decomposes slowly even at 110°. It is soluble in water but the solution soon becomes cloudy as it deposits the anhydro compound as a yellow oil. The metoxazine derivative itself is most easily obtained in a perfectly pure condition by adding sodium hydroxide to a solution of the hydrochloride and extracting the base with ether. The first crystals of the base were obtained by evaporating such an ethereal solution, dissolving the residual oils in petroleum ether, and keeping the mixture at -13° for several days.

**The Ferric Chloride Double Salt.**—Ferric chloride in excess was added to a clear solution of 3 g. of the chloride in 4 cc. of concentrated hydrochloric acid. The mixture was cooled to 6° for an hour during which it deposited the double salt in large, well-formed needles, darker in color than those of the corresponding salt of the pseudo base. The salt melted at 139–140°. When it was treated with sodium hydroxide it regenerated the metoxazine derivative.

*Anal.* Calcd. for  $C_{15}H_{14}ONCl_2Fe$ : C, 42.7; H, 3.4. Found: C, 42.7; H, 3.5.

**The Picrate.**—An ethereal solution of the anhydro compound was added, drop by drop, to a saturated ethereal solution of picric acid. A bright yellow solid appeared after the addition of the first few drops. After washing with ether the solid melted at 128–129°.

*Anal.* Calcd. for  $C_{21}H_{16}O_5N_4$ : C, 55.8; H, 3.6. Found: C, 55.5; H, 3.5.

**The Mercuric Chloride Double Salt.**—The salt was prepared like the preceding one and was purified by crystallization from acetone. It crystallized in yellow needles and melted at 180–181°.

*Anal.* Calcd. for  $C_{15}H_{14}ONCl_3Hg$ : Hg, 37.7. Found: Hg, 37.3.

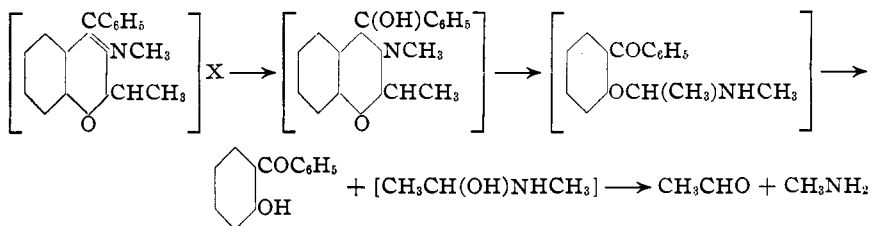
**Hydrolysis of the Metoxazine Derivative.**—In dilute acids the metoxazine derivative is slowly hydrolyzed. Thus when 1 g. of the substance was suspended in 25 cc of water containing one equivalent of hydrochloric acid, the color of the oil gradually became lighter and after two weeks an ethereal solution of it no longer gave a solid hydrochloride with dry hydrogen chloride. The aqueous solution, from which the oil had been removed, had a strong odor of acetaldehyde. A few drops were therefore added to a  $\beta$ -naphthol solution and condensed according to the directions of Mulliken.<sup>2</sup> A precipitate formed which melted at 169°. The remainder of the aqueous solution, when evaporated to dryness, left a residue of ammonium chloride.

These products—acetaldehyde and ammonium chloride—indicated that the oily hydrolysis product was probably ortho hydroxy benzophenone. The oil was therefore recovered and treated with 0.5 g. of hydroxylamine hydrochloride and 4 cc. of 40% potassium hydroxide. It turned yellow and deposited a yellow solid—a behavior which is characteristic of ortho hydroxy benzophenone.<sup>3</sup> The yellow color disappeared when the solution was acidified. The melting point of the crude product was 127–128°. After several recrystallizations from ether it had risen to 135°, the melting point of ortho hydroxy benzophenone oxime found by Meisenheimer and Meis.<sup>4</sup>

*Anal.* Calcd. for  $C_{13}H_{11}O_2N$ : C, 73.2; H, 5.1. Found: C, 73.5; H, 5.2.

**Cleavage with Phenylhydrazine.**—Although the metoxazine derivative is very resistant to the action of aqueous alkalis it is very easily cleaved with phenylhydrazine. A mixture of 2 g. of the substance and 1.1 cc. of phenylhydrazine was heated to 130–150° for half an hour. The gas which was given off had the odor of ammonia and was identified by conversion into the picrate and into ammonium chloride. The residue in the tube was dissolved in methyl alcohol and the solid obtained in this manner was recrystallized from the same solvent. It melted at 154–155° and was identified as the phenylhydrazone of ortho hydroxy benzophenone by comparison with a sample made from the ketone obtained by acid hydrolysis. It was observed incidentally that this phenylhydrazone like a number of others is phototropic,<sup>5</sup> turning orange in the light and reverting to yellow in the dark.

**Methylation.**—Since the metoxazine derivative is an unsaturated cyclic tertiary amine, it can be methylated in the usual manner. The resulting salts are, however, extremely unstable. Even the ferric chloride double salt is rapidly hydrolyzed by water at the ordinary temperature, and the process does not stop either with the formation of the base or that of the pseudo base. It involves the metoxazine ring and proceeds until the substances are completely degraded to ortho hydroxy benzophenone, acetaldehyde and methylamine.



<sup>2</sup> Mulliken, "Identification of Pure Organic Compounds," Vol. I, pp. 22–23.

<sup>3</sup> Cohn, *Monatsh.*, 17, 102 (1896).

<sup>4</sup> Meisenheimer and Meis, *Ber.*, 57, 289 (1924).

<sup>5</sup> Chalkley, *Chem. Reviews*, 6, 233 (1929).

**The Ferric Chloride Double Salt.**—A mixture of 5 g. of dimethyl sulfate, which had been freed from acid by thorough washing with sodium bicarbonate and then dried over sodium sulfate, and 4.7 g. of the metoxazine derivative was heated on a steam-bath for five minutes. The light brown solution was diluted with 10 cc. of concentrated hydrochloric acid and left to itself for fifteen minutes, during which time the two layers disappeared. To the clear homogeneous solution very concentrated ferric chloride was added in excess. A dark brown oil precipitated. After cooling the mixture to 6° for three hours the top layer was decanted, the oil washed rapidly with cold 6 *N* hydrochloric acid, and dried over solid potassium hydroxide in a vacuum desiccator. The residue was almost completely soluble in chloroform and the solution gradually deposited 8 g. of the solid salt in deep yellow hexagonal plates. The pure salt melted at 119–120°.

*Anal.* Calcd. for  $C_{16}H_{16}ONCl_4Fe$ : C, 44.1; H, 3.7. Found: C, 44.3; H, 3.8.

**Hydrolysis.**—When the salt is shaken with cold dilute sodium hydroxide, or even with water, the odor of acetaldehyde appears almost immediately. For the purpose of identifying all the products of hydrolysis, one gram of the salt was shaken with 15 cc. of water until the salt was completely disintegrated. After the precipitated ferric hydroxide had been dissolved by addition of a little dilute hydrochloric acid, there remained a clear aqueous solution and a pale yellow oil.

The aqueous layer was decanted into a distilling flask and distilled to two-thirds its volume. The distillate, when treated with a solution of  $\beta$ -naphthol in glacial acetic acid in the usual manner, gave a precipitate of ethylidene  $\beta$ -dinaphthyl oxide melting at 173–174°, and therefore contained acetaldehyde. The remainder of the aqueous solution was diluted with 10 cc. of water, treated with 3 cc. of 40% potassium hydroxide and cautiously heated. The distillate was collected in 6 *N* hydrochloric acid. On evaporation it left a hydrochloride which melted at 226–227° and when this was added to a 1% solution of picric acid it formed a flaky yellow picrate which melted at 208–211°. The aqueous solution therefore contained methylamine.

The pale yellow oil was dissolved in ether. The washed and dried ethereal solution contained ortho hydroxy benzophenone, which was identified by conversion into its hydrazone and oxime.

### Summary

When the salts that are obtained by alkylating 3-phenyl benzisoxazole are treated with bases they yield a pseudo base which readily loses water, and passes into an anhydro compound. The anhydro compound is a metoxazine derivative.

Since the anhydro compound can be formed only from a pseudo base which has the hydroxyl group in the 3-position, its formation shows that in the rearrangement from a base to a pseudo base the hydroxyl group may enter this position when the hindrance to every other type of rearrangement is sufficiently great.

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