

solid obtained was recrystallized from hot water yielding 76 g. (92%) of quinolinic acid, which decomposed at 190.0–191.2° into a black solid (nicotinic acid), which remelted at 229.2–230.4°. The melting point was not depressed when the product was mixed with an authentic sample of quinolinic acid. If small amounts of water were present some quinolinic acid precipitated during the ozonization.

**Ozonization of Quinoline.**—The ozonization was conducted as described above. The solvent was removed under vacuum and the resulting product refluxed in turn with water, concentrated sodium hydroxide solution, concentrated hydrochloric acid, glacial acetic acid and zinc, stannous chloride and hydrochloric acid, 30% hydrogen peroxide and concentrated nitric acid. Traces of quinolinic acid were isolated only in the last two cases as well as upon low pressure catalytic hydrogenation with 5% palladium on charcoal and subsequent treatment with 30% hydrogen peroxide. The addition compound, upon steam distillation in a basic solution, did not produce any unreacted quinoline. Attempts to distill the compound under low pressures failed, the majority of the material forming a tar, while, to a lesser extent, quinoline and ozone were regenerated. The ozone was detected by the formation of a sodium hydroxide ozonate,<sup>13</sup> which results from the action of ozone on solid sodium hydroxide and which liberates oxygen when placed in an acid solution.

**Ozonization of Isoquinoline.**—A solution of 20.0 g. (0.155 mole) of isoquinoline in 200 ml. of glacial acetic acid was ozonized as previously described. Best results

(13) A study of sodium hydroxide ozonates is being conducted in this Laboratory by Mr. Thomas Whaley.

were obtained if a small amount of water was added to the solvent; cinchomeronic acid (11.4 g., 44.5%), m. p. 259–260°, then precipitated from solution during the ozonization. The solid material was separated by filtration and the filtrate refluxed with 35 g. of 30% hydrogen peroxide for two hours. Evaporation to dryness (or continuous ether extraction) of the resulting solution yielded 12.8 g. (49.5%) of phthalic acid, melting at 204–205°, and small amounts of cinchomeronic acid. The yield of cinchomeronic acid was lowered to 10% when the ozonization time was reduced to twelve hours.

**Ozonization of Other Quinolines.**—6-Amino-, 6-fluoro-8-amino-, 6-fluoro- and 6-nitroquinoline yielded 65, 44, 15 and 6%, respectively, of quinolinic acid when ozonized as previously described. Tarry oxidation products were also formed and, in the last two cases, almost half of the quinolines were recovered unchanged.

### Summary

1. Preparation of quinolinic acid in 90–95% yield and of cinchomeronic acid in 45% yield by ozone oxidation of 8-hydroxyquinoline and isoquinoline, respectively, is described.

2. Studies on the oxidation by ozone of quinoline, 6-aminoquinoline, 6-fluoroquinoline, 6-nitroquinoline, and 6-fluoro-8-aminoquinoline are also reported.

LAWRENCE, KANSAS

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## The Chemical Effects Accompanying Hydrogen Bonding. II. Alkylation of the Oximes of 2-Hydroxy-5-methylbenzophenone

BY A. H. BLATT AND S. ARCHER<sup>1</sup>

The chemical effects of hydrogen bonding were examined in a study of the acyl derivatives of the oximes of 2-hydroxy-5-methylbenzophenone where it was shown that the isomeric bonded (I) and non-bonded (II) oximes behaved similarly on acylation, but that their acyl derivatives showed striking differences in behavior.<sup>2</sup> We have examined the alkylation of these same oximes and find that the differences in behavior show up in the alkylation reaction rather than in the chemistry of the alkylation products.

The generalization in the chemical literature which describes the alkylation of ketoximes in alkaline solution with alkyl halides or dimethyl sulfate is that mixtures of O- and N-alkyl derivatives are formed.<sup>3</sup> The generalization is not applicable to the alkylation of the oximes I and II. The bonded oxime I in normal sodium methoxide solution with methyl iodide (ratios of oxime, alkyl halide, base = 1, 1.5, 1) furnishes the O-methyl ether III in 77–83% yield.<sup>4</sup> None of the

N-methyl ether V is obtained. The non-bonded oxime II under the same conditions furnishes the N-methyl ether VI in 83–90% yield. None of the isomeric O-methyl ether IV is obtained. The course of the alkylation is completely controlled by the presence or absence of bonding and it seems reasonable to suggest that the bonding operates by freezing the configuration shown in I and thus preventing the rear-ward approach to the nitrogen atom which would lead to the N-ether V. A scale model of the oxime I shows this clearly. A similar model of the isomeric oxime shows that the oximino group cannot be accommodated to the atomic dimensions involved in IIa and that some rotation about the bond between the substituted phenyl group and the carbon atom of the C=N group is necessary to accommodate the oximino group. In arrangements such as II in which this rotation has taken place the nitrogen atom is relatively accessible to rear-ward approach.

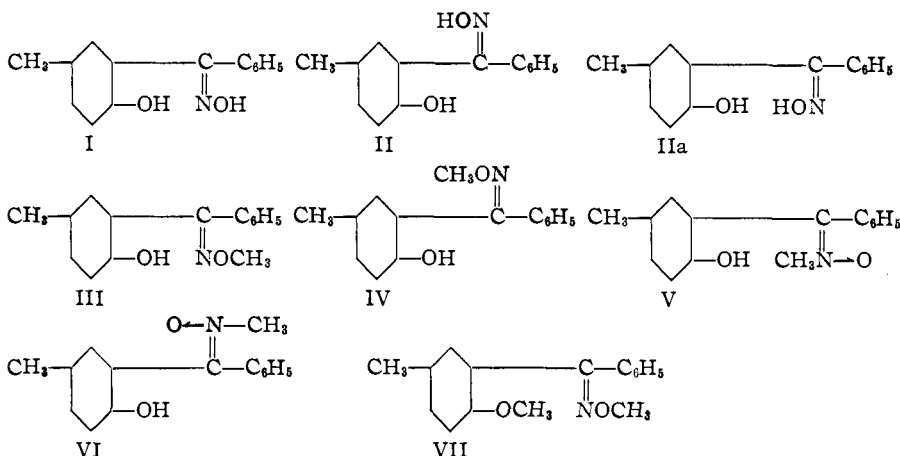
In the alkylation of the non-bonded oxime II, variations in the ratio of oxime to base and to alkylating agent as well as variations in the concentration of the base were without effect. The only product obtained was the N-ether VI. In the alkylation of the bonded oxime I, by con-

(1) Present address: Sterling-Winthrop Research Institute, Rensselaer, New York.

(2) Blatt, *THIS JOURNAL*, **60**, 205 (1938).

(3) Freudenberg, "Stereochemie," Franz Deuticke, Leipzig, 1932, Vol. 3, p. 1035.

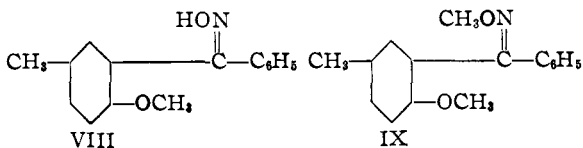
(4) The evidence for the configuration and structure of the alkylation products is to be found in the experimental section.



trast comparable variations in the concentration and molar ratios of the reactants did determine the nature of the alkylation product. The principal product was usually the O-ether III. If, however, a large excess of base and alkylating agent was used, the O-ether III was accompanied by the dimethyl ether VII. The dimethyl ether presumably results from further alkylation of the monomethyl ether III; in fact, the most convenient method of preparing VII is by alkylation of the monomethyl ether III with methyl iodide and sodium methoxide. When the concentration of the sodium methoxide was increased from 1 to 2 *N*, the monomethyl ether III and the dimethyl ether VII were again formed, but the principal product was the N-methyl ether V. This seems to be the result of the formation of the phenoxide ion which would destroy the bonding in I; then the oxime behaves in normal fashion to yield a mixture of N-methyl and O-methyl derivatives.

### Experimental

In addition to the alkylations, a number of experiments were run in order to establish the structure and configuration of the alkylation products; and to prepare the reference compounds VIII and IX which were not obtained by alkylation. These experiments are described first and are followed by a description of the alkylation reactions.



***syn*-Phenyl 2-Hydroxy-5-methylphenyl Ketoxime O-Methyl Ether (III).**—This ether is most conveniently prepared from the ketone and methoxyamine. When 6.7 ml. of concd. hydrochloric acid diluted to 15 ml. with water was added to a solution of 10.6 g. of 2-hydroxy-5-methylbenzophenone and 3.7 g. of methoxyamine in 50 ml. of alcohol and the reaction mixture was boiled for four hours, an oil separated. The oil was redissolved by the addition of hot alcohol. On cooling, 7.5 g. of the ether crystallized; yield, 62%. The ether crystallizes from methyl alcohol in stout plates which melt at 94–95°.

*Anal.* Calcd. for  $C_{15}H_{15}NO_2$ :  $OCH_3$ , 12.9. Found:  $OCH_3$ , 13.1.

The ether is sparingly soluble in methyl and ethyl alcohols, moderately soluble in ligroin and very soluble in acetone, benzene, chloroform and ether. The structure of the compound is established by its method of preparation; the configuration follows from the fact that the material shows no hydroxyl group absorption in the infrared. We are indebted to Dr. Oliver Wulf for examining the infrared absorption spectrum.

The ether does not form an acetyl derivative when its solution in acetic anhydride is warmed for ten minutes. It undergoes no shift of configuration and is recovered unchanged after treatment at room temperature or at the boiling point with aqueous potassium hydroxide solutions ranging in concentration from 10 to 40% of potassium hydroxide. Similarly, the ether was recovered unchanged after 1.3 g. in 13 ml. of 3 *N* sodium methoxide was kept at room temperature for fourteen days.

***syn*-Phenyl 2-Methoxy-5-methylphenyl Ketoxime O-Methyl Ether (VII).**—To a solution of 0.23 g. of sodium in 10 ml. of methanol, was added 1.2 g. of *syn*-phenyl 2-hydroxy-5-methyl ketoxime O-methyl ether (III) and 1 ml. of methyl iodide. After twenty-four hours at room temperature, the precipitate of dimethyl ether (VII) was filtered; 1.05 g., 80%. The filtrate on dilution with water furnished a mixture of starting material and dimethyl derivative—see below.

The dimethyl ether (VII) crystallizes from methanol or ligroin in hemispherical clusters of fine needles which melt at 91–92°.

*Anal.* Calcd. for  $C_{16}H_{17}NO_2$ : C, 75.3; H, 6.7;  $OCH_3$ , 24.3. Found: C, 74.8; H, 6.4;  $OCH_3$ , 23.7.

An equimolar mixture of the dimethyl ether (VII) and monomethyl ether III melts fairly sharply at 67–68°. (*Anal.* Calcd. for a mixture of  $C_{15}H_{15}NO_2$  (III) and  $C_{16}H_{17}NO_2$  (VII):  $OCH_3$ , 18.6. Found:  $OCH_3$ , 18.5.) This mixture often crystallizes from solutions containing both ethers. The mixture can be separated into its components by careful crystallization from methyl alcohol. The first crop consists of the characteristic plates of the monomethyl ether III. After they have been separated, the filtrate is evaporated to dryness and the residue taken up in ligroin. From this solvent the dimethyl ether VII crystallizes first.

The structure of the dimethyl ether follows from its method of preparation. It has been assigned the same configuration as the monomethyl ether III because that ether undergoes no change in configuration in sodium methoxide solution.

***anti*-Phenyl 2-Methoxy-5-methylphenyl Ketoxime (VII).**—To prepare this oxime 4.5 g. of 2-methoxy-5-methylbenzophenone was dissolved in 20 ml. of alcohol and 2.0 g. of hydroxylamine hydrochloride in 5 ml. of water was added. The solution was boiled for two hours and diluted with 10 ml. of water. The crude oxime, which crystallized as the solution cooled, weighed 4 g., 83%. In a parallel experiment using hydroxylamine hydrochloride and excess sodium hydroxide the yield of crude oxime was 93%. For analysis the oxime was crystallized from ethanol. The pure product melts at 162–163°.

*Anal.* Calcd. for  $C_{15}H_{15}NO_2$ :  $OCH_3$ , 12.9. Found:  $OCH_3$ , 13.2.

The structure and configuration of the oxime were established by a Beckmann rearrangement. When 1.7 g. of

the oxime suspended in 30 ml. of absolute ether was treated with an equal weight of phosphorus pentachloride, the oxime dissolved to furnish a yellow solution. After an hour and a half the reaction mixture was poured onto ice and water and left until the ether had evaporated. The yield of crude product was quantitative. For analysis the material was crystallized from ethanol. It was obtained as stout matted needles which melted at 90.5–91.5°.

*Anal.* Calcd. for  $C_{15}H_{15}NO_2$ :  $OCH_3$ , 12.9. Found:  $OCH_3$ , 13.1.

The rearrangement product to be expected from the oxime VIII is 2-methoxy-5-methylbenzanilide, described as melting at 96°. We prepared a sample of this anilide by methylating 2-hydroxy-5-methylbenzanilide with sodium methoxide and methyl iodide. The synthetic product melted at 93–94° and a mixture of the synthetic product and rearrangement product melted at 92.5–93.5°.

The oxime VIII does not furnish a copper derivative when its ethereal solution is shaken with aqueous copper acetate. When it is warmed with acetic anhydride, the oxime furnishes an acetate which melts at 104–105° after recrystallization from ethanol.

*Anal.* Calcd. for  $C_{17}H_{17}NO_3$ :  $OCH_3$ , 10.95. Found:  $OCH_3$ , 10.75.

**anti-Phenyl 2-Methoxy-5-methylphenyl Ketoxime O-Methyl Ether (IX).**—A solution of 2.5 g. of methoxyamine hydrochloride in 5 ml. of water was added to 4.5 g. of 2-methoxy-5-methylbenzophenone in 20 ml. of ethanol. The reaction mixture was boiled for two and one-half hours during which time an oil separated. Water was added and the reaction mixture was left in the ice-chest overnight. The solid thus obtained was crystallized from methanol and furnished 3.3 g. of the dimethyl ether IX which melted at 67–68°; yield, 66%.

*Anal.* Calcd. for  $C_{18}H_{17}NO_2$ :  $OCH_3$ , 24.3. Found:  $OCH_3$ , 24.6.

The dimethyl ether is related configurationally to the oxime VIII by its preparation from that oxime. When 1.2 g. of the oxime VIII in 10 ml. of methanol containing 0.23 g. of sodium was treated with 1 ml. of methyl iodide, the reaction mixture furnished, after twenty-four hours, 0.8 g. of the dimethyl ether IX; yield, 63%.

**Alkylation of the Oximes I and II.**—The alkylations were run unless otherwise specified on 4.5 g. (0.02 mole) quantities of oxime. The oxime was dissolved in sodium methoxide solution, the alkylating agent added and the reaction mixture left stoppered for eighteen to twenty-four hours at room temperature. Any solid was removed by filtration, then water was added to the filtrate and the organic material extracted with ether. In experiments where an excess of base was used the reaction mixtures were acidified.

When 1 mole of the bonded oxime I was treated with 1 mole of 1 or 1.3 *N* sodium methoxide and 1.5 to 2 moles of methyl iodide, the product obtained in 77–83% yield was the oxime O-methyl ether III. From 1 mole of oxime, 2 moles of 1 *N* sodium methoxide and 1 mole of methyl iodide, the principal product was the non-bonded oxime II; 70% of the oxime I which was not converted into its stereoisomer II appeared as the monomethyl ether III. From 1 mole of oxime, 3 moles of 1 *N* sodium methoxide and 4 moles of methyl iodide, the yield of crude alkylation product was very satisfactory; but the product was a mixture of the ether III and the dimethyl ether VII and more than half of the material was lost in the fractional crystallization, so that the yields of III and VII were 30 and 5%, respectively. When the concentration of the base was increased to 2 *N*, the *N*-methyl ether V appeared as a product. From 1 mole of oxime, 4 moles of sodium methoxide and 3 moles of methyl iodide, the yield of *N*-

methyl ether was 50%; the filtrates furnished a mixture of the monomethyl ether III and the dimethyl ether VII.

*syn*-Phenyl 2-hydroxy-5-methylphenyl ketoxime *N*-methyl ether (V) is obtained as small cubes by recrystallization from methyl or ethyl alcohol. It is almost insoluble in ether. The melting point of the material, 180–181°, varies with the rate of heating.

*Anal.* Calcd. for  $C_{15}H_{15}NO_2$ : C, 74.65; H, 6.3. Found: C, 74.6; H, 6.1; methoxyl, negative.

The structure of the *N*-ether was established by its ready hydrolysis. Boiling with methyl alcohol and hydrochloric acid for twenty minutes brought about complete hydrolysis to 2-hydroxy-5-methylbenzophenone.

The experiments with methyl *p*-toluenesulfonate paralleled those with methyl iodide and need not be described in detail. The ester is so readily hydrolyzed, however, that in the runs using 1 mole of ester and 2 to 4 moles of sodium methoxide only unreacted oxime was obtained. In a single run using diazomethane the only product obtained was unchanged oxime.

The non-bonded oxime on alkylation furnished only the *N*-methyl derivative VI. This material, *anti*-phenyl 2-hydroxy-5-methylphenyl ketoxime *N*-methyl ether, crystallizes from methyl or ethyl alcohol in splendid yellow cubes which melt at 142–143°.

*Anal.* Calcd. for  $C_{15}H_{15}NO_2$ : C, 74.65; H, 6.3. Found: C, 74.9; H, 6.2; methoxyl, negative.

The *N*-methyl derivative turns purple on exposure to light. It is hydrolyzed by twenty minutes of boiling in a solution of 7 parts of methanol and 1 part of concd. hydrochloric acid to 2-hydroxy-5-methylbenzophenone (85% yield) and *N*-methylhydroxylamine hydrochloride.

From 1 mole of the non-bonded oxime II, 1 mole of sodium methoxide and 1.5 or 2 moles of methyl iodide the yield of *N*-ether VI was 83–90%. The same ether, VI, was the only product isolated from 1 mole of oxime, 2 moles of 1 *N* sodium methoxide and 1 mole of methyl iodide, and from 1 mole of oxime, 4 moles of 1 *N* sodium methoxide and 2.5 moles of methyl iodide. In these experiments the yields were not so good and oily products were also formed.

Alkylation of the non-bonded oxime with methyl *p*-toluenesulfonate and sodium methoxide and with diazomethane also furnished only the *N*-methyl ether VI.

### Summary

The behavior on alkylation of the bonded and non-bonded oximes of 2-hydroxy-5-methylbenzophenone was studied. The non-bonded oxime furnished only the *N*-ether, *anti*-phenyl 2-hydroxy-5-methylbenzophenone ketoxime *N*-methyl ether, regardless of the ratios of oxime to alkylating agent and base. On the other hand, the nature of the products formed when the bonded oxime was alkylated did depend on the concentrations of the reactants. When one mole of base and two moles of iodide were used only *syn*-phenyl 2-hydroxy-5-methylphenyl ketoxime O-methyl ether was obtained. Increasing the quantities of base and methyl iodide resulted in the appearance of the dimethyl ether, *syn*-phenyl 2-methoxy-5-methylphenyl ketoxime O-methyl ether. With a very large excess of base and alkylating agent another product, namely, *syn*-phenyl 2-hydroxy-5-methylphenyl ketoxime *N*-methyl ether was encountered also.

(5) Leuckart, *J. prakt. Chem.*, [2] 41, 315 (1890).