[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF NEW HAMPSHIRE]

MOLECULAR REARRANGEMENTS. II. CLEAVAGE REACTIONS WITH BECKMANN REARRANGEMENT CONDITIONS

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The Beckmann rearrangement of 1-methyl-4-phenylpiperidyl-4-phenyl ketone oxime (I) should produce either 1-methyl-4-phenylisonipecotanilide (1-methyl-4-phenylpiperidine-4-carboxanilide) or N-(1-methyl-4-phenylpiperidyl-4)benzamide. Since both of these compounds are similar in structure to known pharmaceuticals, the interest in the chemistry of the heterocyclic ring system would be enhanced by the production of a potentially physiologically active type of compound.

In an effort to ascertain the course of the reaction, the rearrangement was first attempted using the cyclohexane analog of the piperidine compound. The pinacol rearrangement of 1-(1-hydroxycyclohexyl)diphenylcarbinol produces 1-phenylcyclohexyl phenyl ketone (1) from which the oxime (II) was prepared. On treatment with thionyl chloride as catalyst in the Beckmann rearrangement, II yielded only liquid products with no evidence of the expected amide. Distillation of the liquid gave two fractions, one of which was shown to be benzonitrile by its refractive index and by hydrolysis to benzoic acid. The second fraction was found to be a mixture of a small amount of an organic halide and an unsaturated compound. Dehydrohalogenation and distillation of this mixture gave an oil which was apparently 1-phenylcyclohexene-1 (III), although attempts to prepare the solid derivatives previously reported for the unsaturated compound failed (2, 3). It was found, moreover, that these reactions were unsatisfactory for identification of very small amounts of III.

In an attempt to find a satisfactory derivative for 1-phenylcyclohexene-1 (III), an extensive study of the reactions of an authentic sample of III was made. It was found that the peroxyacetic acid oxidation of III produced a solid (IV) in sufficient yield to be used as a derivative even for small amounts of III. The product IV showed a marked resemblance to 1-phenylcyclohexanediol-1,2 monoacetate (IV), reported as the product of the acetylation of 1-phenylcyclohexanediol-1,2 (V) (4). This identification was confirmed by the hydrolysis of IV to V in alcoholic potassium hydroxide and the rearrangement of IV to 2-phenylcyclohexanone (VI) using sulfuric acid or Lucas' reagent as catalyst. The merits of IV as a characterization derivative of 1-phenylcyclohexene-1 (III) are increased by the aforementioned reactions since both V and VI are solids which may be used as confirmatory derivatives.

No attempt was made to determine the structural or stereochemical nature of 1-phenylcyclohexanediol-1,2 monoacetate (IV); however, it is believed that the 2-hydroxyl group is acetylated. This assumption could be made by analogy to the monobenzoate of 1,1-diphenylethanediol-1,2 formed by the peroxyben-

zoic acid oxidation of 1,1-diphenylethylene (5). Furthermore, since this material results from the acetylation of V, it would be assumed that the secondary hydroxyl group was esterified rather than the tertiary.

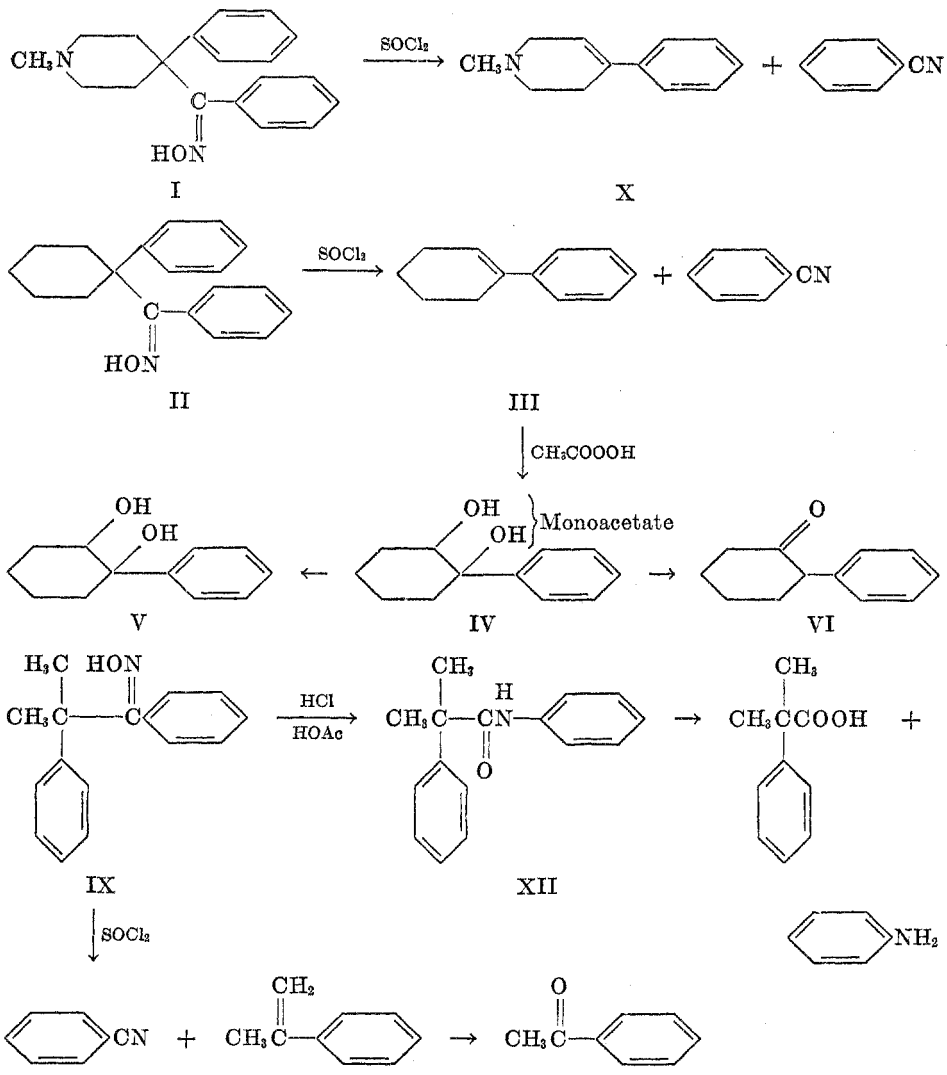
A repetition of the peroxyacetic acid oxidation and subsequent reactions on the unsaturated product of the attempted Beckmann rearrangement gave solids identical with those formed from III. This confirmed the cleavage of the oxime (II) to benzonitrile and 1-phenylcyclohexene-1 (III).

A search of the literature revealed that similar reactions had been observed with camphor oxime (6), pivalophenone oxime (VII) (7), benzopinacolone oxime (VIII) (8), and benzil monoöxime and benzoin oxime (9). In each case a tertiary ketone is involved and, omitting camphor oxime which may undergo cleavage as a result of the steric effects of the fused rings, each ketone is also aromatic.

In order to confirm that these structural features caused cleavage, α-phenylisobutyrophenone oxime (IX) was subjected to the Beckmann rearrangement with thionyl chloride. This compound was cleaved under these conditions forming benzonitrile, identified by hydrolysis to benzoic acid, and α-methylstyrene, identified by oxidation to acetophenone, which was isolated as the semicarbazone.

It seems evident, therefore, that the oxime of an aromatic tertiary ketone would be expected to undergo cleavage rather than a normal Beckmann rearrangement on treatment with such reagents as thionyl chloride, phosphorus pentachloride, etc. On the basis of the above information, it seemed likely that the heterocyclic ketone oxime (I) would not produce either of the anticipated amides. 1-Methyl-4-phenylpiperidyl-4 phenyl ketone was produced by the action of phenylmagnesium bromide on 1-methyl-4-cyano-4-phenylpiperidine by the method of Eisleb (10). The ketone produced the oxime (I) under stringent conditions (11). Reaction of the oxime (I) with thionyl chloride in dry benzene produced the predicted products, benzonitrile and 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (X). Benzonitrile was identified as above and X was identified by the preparation of the hydrochloride and hydrobromide salts (12).

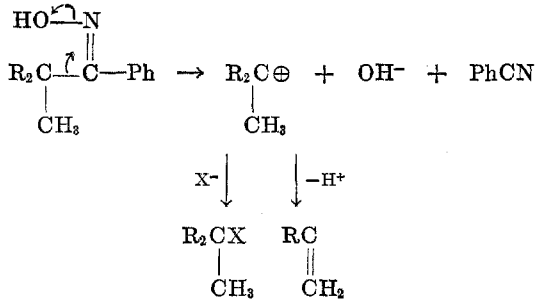
The Beckmann rearrangement of pivalophenone oxime (VII) was reported to occur on refluxing the oxime in a saturated solution of hydrogen chloride in acetic acid (7). The amide produced was the anilide (XI) of pivalic acid. These conditions were applied to IX and a normal rearrangement to an amide (XII) resulted with only small amounts of cleavage products being formed. The properties of the amide (XII) differed from those reported for N-α-phenylisopropylbenzamide (13), one of the amides which could be produced from the oxime (IX). In order to confirm the structure of XII, it was hydrolyzed with potassium hydroxide in diethylene glycol. Since α-phenylisobutyric acid was the only acid isolated and aniline, identified as the benzenesulfonamide, was the only amine fragment found, this would indicate that the only amide formed was α-phenylisobutyranilide (XII) and thus the most stable form of the oxime (IX) is *anti*-phenyl.



The rearrangement of 1-phenylcyclohexyl phenyl ketone oxime (II) was attempted using hydrogen chloride in acetic acid. Contrary to the previous examples, only cleavage occurred in this case. Variations in the length of reflux time gave either no reaction or cleavage. Using the most vigorous conditions, 1-methyl-4-phenylpiperidyl-4 phenyl ketone oxime (I) gave only a trace of cleavage and the remainder of the material was recovered unreacted.

Consideration of the structure of the amides (XI and XII) indicates that cleavage must occur before any rearrangement of the phenyl group results; otherwise, phenyl isocyanide should be one of the products as in the case of *beta*-benzoin oxime (9). This would indicate that with these sterically inhibited

ketones an electron shift, such as shown below, occurs in preference to the expected rearrangement.



EXPERIMENTAL

Reaction of 1-phenylcyclohexyl phenyl ketone oxime (II) *with thionyl chloride.* To a suspension of 2.8 g. (0.01 mole) of 1-phenylcyclohexyl phenyl ketone oxime (II) in 10 ml. of dry benzene in a 125-ml. Elrenmeyer flask there was added 2 ml. of thionyl chloride in 5 ml. of dry benzene. After standing for three hours, the reaction was apparently complete, for all of the solid had gone into solution. Water was added to decompose the excess thionyl chloride, and, after standing one hour, the benzene layer was separated and the aqueous layer extracted with two 25-ml. portions of ether. The solvents were removed by distillation and the residual oil was fractionally distilled. Two fractions were collected: I, 0.81 g., b.p. 79–89° at 15 mm., n_D^{25} 1.5285; and II, 1.25 g., b.p. 123–125° at 12 mm., n_D^{25} 1.5643. The properties of these fractions corresponded to those of benzonitrile, lit. b.p. 77° at 15 mm., n_D^{20} 1.5289 (14), and of 1-phenylcyclohexene-1 (III), lit. b.p. 126–128° at 16 mm., n_D^{20} 1.5670 (2), respectively.

The identity of the benzonitrile was confirmed by hydrolysis to benzoic acid using potassium hydroxide in diethylene glycol solution. The melting point of the hydrolysis product was 122–122.5°, and the mixture melting point with authentic benzoic acid was 121.5–122.3°.

1-Phenylcyclohexene-1 (III) was characterized by conversion to 1-phenylcyclohexanediol-1,2 monoacetate (IV) as described below, m.p. 114.5–116°; mixture melting point with authentic sample, 115–117°. Hydrolysis of the monoacetate (IV) gave 1-phenylcyclohexanediol-1,2 (V), m.p. 92.5–93°; mixture melting point with an authentic sample, 91.5–93°.

Oxidation of 1-phenylcyclohexene-1 (III) *with peroxyacetic acid.* To 10 g. (0.06 mole) of 1-phenylcyclohexene-1 (III) in 30 ml. of acetic acid there was added with cooling 16 g. of 40% peroxyacetic acid and 2 g. of anhydrous sodium acetate dissolved in 30 ml. of acetic acid. The mixture was allowed to stand for 5 days and was then poured into 100 ml. of water saturated with sodium chloride. After standing for several minutes, the water-insoluble oil crystallized and was removed by filtration, yielding 10.9 g. (78.2%) of crude material. Trituration with low-boiling petroleum ether and recrystallization from methanol gave 6 g. of pure 1-phenylcyclohexanediol-1,2 monoacetate (IV), m.p. 117–117.5°; lit. m.p. 118° (4).

Anal. Calc'd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74.

Found: C, 71.55; H, 7.85.

1-Phenylcyclohexanediol-1,2 (V). A solution of 1.88 g. (0.008 mole) of 1-phenylcyclohexanediol-1,2 monoacetate (IV) and 1.5 g. of potassium hydroxide in 15 ml. of methanol was refluxed for 4 hours. All but about 5 ml. of the solvent was removed by distillation and the remaining solution was poured into 15 ml. of water. The solid which precipitated was removed yielding 1.45 g. (94%) of crude 1-phenylcyclohexanediol-1,2 (V). After recrystallization from methanol and water, the solid melted at 91.8–92.5°; lit. m.p. 98.5° (4).

2-Phenylcyclohexanone. On dissolving 3.0 g. (0.015 mole) of pure 1-phenylcyclohexane-

diol-1,2 monoacetate (III) in 6 ml. of Lucas' reagent the mixture turned green. At the end of 7 minutes all of the solid was converted into a greenish-blue liquid. The mixture was then poured into water and seeded with 2-phenylcyclohexanone (VI). The water-insoluble oil slowly crystallized and was separated by filtration. Recrystallization from petroleum ether gave 1.66 g. (65.4%) of 2-phenylcyclohexanone (VI), m.p. 55–56°, b.p. 162–165° at 15 mm.; lit. m.p. 52.5–54.5°, b.p. 155–160° at 16 mm. (2).

Oxime and *semicarbazone* derivatives were prepared by conventional methods and, after recrystallization, melted at 170–171° and 179–181° respectively; lit. oxime m.p. 174–175° (15) and semicarbazone m.p. 189–190° (2).

α-Phenylisobutyrophenone. To a mixture of 24.2 g. (0.1 mole) of 2-methyl-1,1-diphenylpropanediol-1,2 and 13.5 g. of fused, pulverized zinc chloride there was added 120 ml. of acetic anhydride. Five minutes' heating on the steam-bath produced a dark green solution which was allowed to stand at room temperature for an hour. The solution was poured into a mixture of ice and 20 g. of potassium hydroxide and then extracted with five 50-ml. portions of ether. After the ethereal extracts were dried over sodium sulfate, the solution was fractionally distilled yielding 19.2 g. (85%) of α-phenylisobutyrophenone, b.p. 126–130° at 1 mm.; lit. b.p. 185–186° at 16 mm. (16).

The *oxime* (IX) was prepared and recrystallized from ethanol, m.p. 194–194.5°; lit. m.p. 192–193° (16).

Reaction of α-phenylisobutyrophenone oxime (IX) *with thionyl chloride.* To 6.0 g. (0.025 mole) of the oxime (IX) in 50 ml. of dry benzene there was added slowly 6 g. of thionyl chloride in 5 ml. of dry benzene. After all foaming ceased, the solution was allowed to stand 24 hours. The solvent was removed under reduced pressure and the oil was fractionally distilled at 50 mm. pressure producing three fractions: I, b.p. 68–75° (0.58 g.); II, b.p. 75–90° (1.21 g.); and III, b.p. 90–95° (2.73 g.). Redistillation of these fractions at atmospheric pressure yielded 1.02 g. of α-methylstyrene, b.p. 167–170°; lit. b.p. 165° (18). The structure was confirmed by oxidation in acetone with cold potassium permanganate to acetophenone which was identified as the semicarbazone. An intermediate fraction (1.13 g.) boiled at 170–175° and a third fraction, 1.77 g. of benzonitrile, distilled at 190–195°. The benzonitrile was identified by refractive index and hydrolytic conversion to benzoic acid.

Beckmann rearrangement of α-phenylisobutyrophenone oxime (IX) *using hydrogen chloride in acetic acid.* Dry hydrogen chloride was bubbled through a mixture of 6.0 g. (0.025 mole) of IX in 25 ml. of acetic acid for 30 minutes. After 10 minutes all the oxime had dissolved. The solution was refluxed for two hours and poured into water. The precipitated amide (XII) (4.85 g., 81%) was filtered off and recrystallized from alcohol-water, m.p. 100.5–101.5°.

Anal. Calc'd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54.

Found: C, 79.88; H, 7.59.

The filtrate was extracted with ether and the ether solution was treated with base to remove any possible acidic component. The extract was dried over sodium sulfate and distilled. The remaining oil was refluxed with 2 g. of potassium hydroxide in 15 ml. of diethylene glycol for one-half hour and poured into water. Acidification of the aqueous solution yielded 0.15 g. of benzoic acid, thus indicating the presence of a small amount of cleavage product in the reaction mixture.

Hydrolysis of α-phenylisobutyranilide (XII). A mixture of 1.4 g. (0.006 mole) of α-phenylisobutyranilide (XII) and 0.8 g. of potassium hydroxide in 10 ml. of diethylene glycol was refluxed for one-half hour and poured into water. The solution was extracted with ether and the ether extracted with dilute acid and then water. After drying the ether extract over sodium sulfate, removal of the ether yielded 0.44 g. of unchanged amide.

The acid solution was made basic with potassium hydroxide solution and extracted twice with ether. After the ether was dried and distilled, the remaining oil was treated with benzenesulfonyl chloride in basic solution. The product was identified as the benzenesulfonamide of aniline, and a yield of 0.3 g. (41% based on the recovery of unreacted XII) was obtained.

On acidification of the original water solution with dilute hydrochloric acid and extraction with ether, 0.54 g. (82% based on recovered XII) of α-phenylisobutyric acid was obtained. The acid was recrystallized from ethanol and melted at 75–76.2°; lit. m.p. 76–77° (17). The neutralization equivalent was determined and found to be 164 which agrees with the calculated value.

1-Methyl-4-phenylpiperidyl-4 phenyl ketone oxime (I). The ketone was prepared by the method of Eisleb (10) and the oxime (I) was prepared according to Bachmann and Barton (11). After recrystallization from methanol, it melted at 186–188°.

Anal. Calc'd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53.

Found: C, 76.98; H, 7.62.

Reaction of 1-methyl-4-phenylpiperidyl-4 phenyl ketone oxime (I) *with thionyl chloride.* A solution of 4 ml. of thionyl chloride in 5 ml. of carbon tetrachloride was added slowly to a suspension of 3.0 g. (0.01 mole) of the oxime (I) in 25 ml. of carbon tetrachloride. After the addition was complete, two oily layers separated and some material gradually crystallized. The mixture was allowed to stand for two days, and water was added which dissolved the solid. The carbon tetrachloride was separated and the water layer was extracted with 25 ml. of carbon tetrachloride. Removal of the solvent and distillation of the residual oil produced 0.56 g. (54%) of benzonitrile which distilled at 67° at 10 mm. The oil was hydrolyzed with 0.75 g. of potassium hydroxide in 5 ml. of diethylene glycol by refluxing for one hour yielding 0.42 g. of benzoic acid, identified by a mixture melting point with authentic benzoic acid.

The water layer was made basic with a solution of potassium hydroxide and the amine was extracted with three 40-ml. portions of ether. After being dried over sodium sulfate, the ether was removed and the residual oil was distilled yielding 0.83 g. of material boiling at 149–165° at 17 mm. Since the product was assumed to be 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (X), it was converted to known derivatives. From one-half of the material (free base), the hydrobromide was prepared, m.p. 213.8–215°; lit. m.p. 216–218° (12). The remainder was converted to the hydrochloride, m.p. 242–243.5°; lit. m.p. 248–250° (12).

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SUMMARY

1. The attempted Beckmann rearrangements of 1-methyl-4-phenylpiperidyl-4 phenyl ketone oxime, 1-phenylcyclohexyl phenyl ketone oxime, and α-phenylisobutyrophenone oxime with thionyl chloride lead to cleavage reactions producing benzonitrile and an unsaturated residue. These and previously reported examples indicate that aromatic, *alpha-tertiary* ketone oximes should be expected to give this type of reaction.

2. Some aspects of the mechanism are mentioned.

3. Rearrangement to the amide can be induced with certain of these compounds by using hydrogen chloride in acetic acid solution for the reaction.

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