[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Nucleophilic Displacement Reactions of Hindered Ketimine Methiodides

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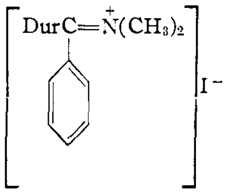
Mesitonitrile and duronitrile react with Grignard reagents to give the corresponding ketimines. The imines are very difficult to hydrolyze but yield acetyl derivatives readily. Treatment with methyl sulfate converts the imines to the corresponding N-methyl compounds which, in turn, combine with methyl iodide to yield methiodides. When the methiodide of N-methylduryl phenyl ketimine is treated with *t*-butylmagnesium chloride it undergoes *t*-butylation in the para position of the phenyl ring. The same product is obtained from the *p*-methoxyphenyl analog, the methoxyl group being displaced by the *t*-butyl group.

The vulnerability of pyridinium and quinolinium rings to attack by nucleophilic agents suggests that the phenomenon might prove to be general for conjugated systems terminated by a quaternized nitrogen atom. In a search for such compounds we have prepared hindered ketimines which might be expected to resemble their oxygen analogs in their behavior toward nucleophilic agents.

One of these, duryl phenyl ketimine, has been converted to the corresponding quaternary ammonium iodide I, which was found to undergo direct substitution when treated with *t*-butylmagnesium chloride. The product II was obtained also by indirect substitution, *i.e.*, by displacement of the methoxyl group from the corresponding *p*-methoxy methiodide III by the action of the *t*-butyl Grignard reagent. The successful displacement of the methoxyl group from the para position is the first example of its kind. In the ketone series such a displacement had proved to be possible until recently only if a second methoxyl group were placed in an adjacent position on the ring.[3] Now it is known that a lone methoxyl group may be replaced by the *t*-butyl Grignard reagent in the ketone series also.[4]

The behavior of the *o*-methoxyphenyl duryl compound IV toward Grignard reagents appeared to differ from that of the corresponding keto compound. Reaction occurred but no definite products could be isolated from the reaction mixture. In order to determine if a coördination complex involving the formation of a *quasi* six-membered ring is necessary for the displacement of the *o*-methoxyl group, the methiodide of duryl 2,3-dimethoxyphenyl ketimine (V) was prepared. The coördination complex suggested for the ketones[5] cannot form in the imine salt series, but coördination of the reagent between the adjacent methoxyl groups should provide an effective substitute. When the methiodide V was treated with phenylmagnesium bromide, results similar to those described for the *o*-methoxyimine were obtained.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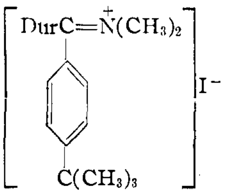
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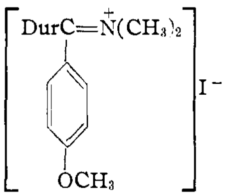
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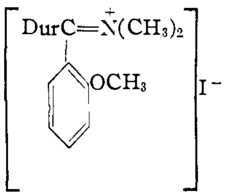
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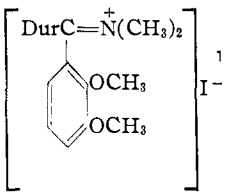
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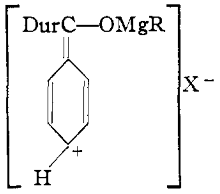
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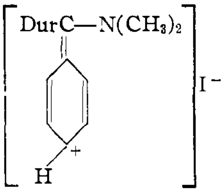
VII

The susceptibility of the aromatic nuclei of the methiodide I and its *p*-methoxy derivative III to nucleophilic attack may be interpreted as lending support to the concept that similar reactions in the ketone series proceed by way of a coördination complex involving the carbonyl oxygen atom and the magnesium atom of the Grignard reagent. The structure represented by formula VI, which corresponds to the type of reaction under consideration, is seen to be very similar to the corresponding structure of the methiodide VII.

The hindered imines described in this paper were prepared with one exception by treating mesitonitrile with Grignard reagents. That exception occurred in the preparation of duryl 2,3-dimethoxyphenyl ketimine where the nitrile was treated with 2,3-dimethoxyphenyllithium. This type of reaction of hindered nitriles, although to be expected on the basis of work by Kadesch[6] and others, had been realized previously only with 2,6-xylonitrile.[7]

We have condensed mesitonitrile with the benzyl and phenyl reagents and duronitrile with the ethyl, phenyl, *o*-methoxyphenyl and *p*-methoxyphenyl reagents.

The imines, isolated as the hydrochlorides, were

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[1] Rohm and Haas Fellow, 1949–1950; Socony-Vacuum Oil Company Fellow, 1950–1951.

[2] Atomic Energy Commission Predoctoral Fellow, 1951–1953.

[3] R. C. Fuson and R. Gaertner, *J. Org. Chem.*, **13**, 496 (1948).

[4] R. C. Fuson and W. S. Friedlander, THIS JOURNAL, **75**, in press (1953).

[5] R. Gaertner, *Chem. Revs.*, **45**, 493 (1949).

[6] R. G. Kadesch, THIS JOURNAL, **66**, 1207 (1944).

[7] J. B. Culbertson, *ibid.*, **73**, 4818 (1951).

acetylated and methylated successfully. An excess of methyl iodide produced the corresponding methiodides. These compounds are very resistant to hydrolysis and for this reason lend themselves to studies in which ordinary imino compounds would undergo solvolysis. Mesityl phenyl ketimine, for example, was hydrolyzed to the extend of only 5% when treated for 24 hours with boiling concentrated hydrochloric acid. This imine survived long heating with 20% potassium hydroxide.

Experimental

Duronitrile.—This nitrile was made by the Rosenmund–von Braun method as modified by Koelsch and Whitney.[8] A mixture of 106 g. of bromodurene, 53.7 g. of oven-dried cuprous cyanide, 60 ml. of dry pyridine and a few crystals of copper sulfate was heated at 220–230° under reflux for 6 hours. When the mixture had cooled to 100° it was poured, with vigorous stirring, into a mixture of 200 ml. of ammonium hydroxide and 100 ml. of water. The product, after being washed repeatedly with a dilute ammoniacal solution, was dried and dissolved in the minimum amount of 95% ethanol. The solution was filtered, treated with Darco and diluted with a small amount of water. The nitrile separated as shiny reddish needles, which, after repeated recrystallization from an ethanol-water mixture, became colorless; m.p. 77–78°, yield 60 g. (75%). This nitrile had been made earlier by Jacobsen[9] by distilling duroic acid with lead thiocyanate; he gave the melting point as 76–77°.

Mesitonitrile.—This nitrile was prepared in a yield of 80% by a modification of the method of Fuson and Denton.[10] It may be mentioned here that in other work it was discovered that this compound is formed also when mesitoyl chloride is heated with cuprous cyanide. A mixture of 96 g. of mesitoyl chloride and 62.1 g. of cuprous cyanide was heated at 220–230° for 90 minutes. The yield of mesitonitrile was 23.4 g. (31%). This apparently anomalous reaction was not studied further.

Duryl Phenyl Ketimine.—A solution of 32.8 g. (0.2 mole) of duronitrile in 150 ml. of dry benzene was added all at once to a solution of phenylmagnesium bromide made from 157 g. (1.0 mole) of bromobenzene. After being heated overnight, with stirring, the mixture was poured slowly into a mixture of ice and hydrochloric acid. The hydrochloride of the duryl phenyl ketimine, after being washed with water and ether, was suspended between water and ether in a separatory funnel and shaken with successive portions of saturated sodium carbonate solution. The ether layer was removed and filtered to remove magnesium hydroxide. The water layer was extracted with ether and the wash ether added to the original ether layer. After the ether had been dried over sodium sulfate, the solvent was evaporated. The imine, after being treated with Darco, was recrystallized from a mixture of ethanol and water. A second recrystallization yielded colorless needles, m.p. 119–120°, yield 26 g. (60%).

Anal.[11] Calcd. for $C_{17}H_{19}N$: C, 86.03; H, 8.07. Found: C, 85.92; H, 8.13.

The acetyl derivative was made by treating the imine with acetic anhydride and allowing the mixture to stand for 4 hours. The product, precipitated by pouring the reaction mixture into water, was recrystallized from methanol and water; m.p. 133–134°.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.69; H, 7.57. Found: C, 81.77; H, 7.72.

In an attempt to effect benzoylation of the durene nucleus as well as of the imino function, a mixture of 10 g. of duryl phenyl ketimine, 60 ml. of benzoyl chloride and 40 g. of polyphosphoric acid was heated at 150–160° for 90 minutes, cooled and poured into water. It was extracted with ether, and the extracts, after being washed with dilute sodium hydroxide solution and water, were dried. Evaporation yielded an orange oil that solidified when cooled. The white crystals, obtained by recrystallization of this solid from ethanol, proved to be the **N-benzoyl derivative** of duryl phenyl ketimine, m.p. 148–149°, yield 6.5 g. (45%).

Anal. Calcd. for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.63; H, 6.77; N, 3.90.

This compound had lost its basicity, and its infrared spectrum indicated that the N–H band was no longer present. There were bands indicating an imino function (1628 cm.$^{-1}$) and a conjugated amide carbonyl group (1639 cm.$^{-1}$, 1662 cm.$^{-1}$).

Duryl *o*-Methoxyphenyl Ketimine.—The method of preparation differed from that described in the preceding section only in the isolation step. The imine hydrochloride is soluble in water and, accordingly, the water layer was exhaustively extracted with ether, made basic with sodium hydroxide solution and then extracted with ether. The imine was recrystallized from ethanol and water; m.p. 160–161°, yield 40%.

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.84; H, 7.92; N, 5.25. Found: C, 80.63; H, 8.02; N, 5.32.

The acetyl derivative was crystallized from methanol and water; m.p. 135.5–137°.

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.63; H, 7.49. Found: C, 78.01; H, 7.54.

Duryl *p*-Methoxyphenyl Ketimine.—The methods of preparation, isolation and recrystallization were similar to those employed with the ortho isomer, m.p. 166–167°, yield 40%.

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.84; H, 7.92. Found: C, 80.91; H, 8.19.

The acetyl derivative was crystallized from methanol and water; m.p. 120–121°.

Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.63; H, 7.49. Found: C, 77.49; H, 7.40.

Duryl Ethyl Ketimine.—The hydrochloride of this imine, prepared by treating 7.3 g. of duronitrile with ethylmagnesium bromide, was recrystallized from a 1:1 mixture of ethanol and ethyl acetate; m.p. 226–228° dec.; yield 4.5 g. (40%).

Anal. Calcd. for $C_{13}H_{20}ClN$: C, 69.15; H, 8.93. Found: C, 69.07; H, 9.06.

Mesityl Phenyl Ketimine.—The hydrochloride of this imine, prepared by treating 2.5 g. of mesitonitrile with phenylmagnesium bromide, was recrystallized from a 1:1 mixture of ethanol and ethyl acetate; m.p. 215–224°, yield 2.4 g. (54%). This salt, after being heated under reflux for several hours with concentrated hydrochloric acid and then repeatedly recrystallized, melted at 260–265°. The melting point given by Gilman and co-workers is 261–264°.[12]

The imine was produced as an oil by shaking the hydrochloride with 5% sodium carbonate solution. Treatment with acetic anhydride converted it to the **acetyl derivative,** which was recrystallized from aqueous methanol; m.p. 93.5–94°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22. Found: C, 81.56; H, 7.16.

A solution of the imine hydrochloride (4 g.) in 35 ml. of hot concentrated hydrochloric acid was heated under reflux for 24 hours, cooled and diluted with water. The unchanged imine hydrochloride (3.5 g.) was removed by filtration and the filtrate extracted with ether. In this way 0.2 g. (5%) of benzoylmesitylene was obtained.

Benzyl Mesityl Ketimine.—As with the phenyl analog, the benzyl mesityl ketimine (obtained in 85% yield) failed to crystalliize. **Its acetyl derivative** was recrystallized from cyclohexane and then from ethanol; m.p. 198.5–201.5°.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.58. Found: C, 81.62; H, 6.88.

A mixture of 1 ml. of the imine, 1 ml. of benzoyl chloride, 20 ml. of benzene and 5 ml. of pyridine was heated for 30 minutes and poured into water. The benzene layer was washed with 5% sodium carbonate solution and water and dried over sodium sulfate. Evaporation of the solvent left an oil that crystallized from ethanol. **The benzoyl derivative** of the imine was recrystallized from aqueous ethanol; m.p. 132.5–133.5°.

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[8] C. F. Koelsch and A. G. Whitney, *J. Org. Chem.*, **6**, 795 (1941).

[9] O. Jacobsen, *Ber.*, **22**, 1215 (1889).

[10] R. C. Fuson and J. J. Denton, THIS JOURNAL, **63**, 654 (1941).

[11] Microanalyses by Miss Emily Davis, Mrs. Katherine Pih, Mrs. Jeanne Fortney, Mrs. Esther Fett and Mr. Joseph Nemeth.

[12] H. Gilman, E. L. St. John, N. B. St. John and M. Lichtenwalter *Rec. trav. chim.*, **55**, 577 (1936).

Anal. Calcd. for $C_{24}H_{24}NO$: C, 84.17; H, 7.06. Found: C, 84.48; H, 6.88.

Duryl 2,3-Dimethoxyphenyl Ketimine.—*n*-Butyllithium was prepared from 19.5 g. (0.2 mole) of *n*-butyl chloride, 3 g. of lithium and 100 ml. of ether. After this solution had been heated under reflux for 2 hours, 20.7 g. (0.15 mole) of veratrole in 75 ml. of ether was added. The reaction mixture was heated under reflux for 24 hours. A solution of 15.9 g. (0.1 mole) of duronitrile in 100 ml. of ether was then added; the solution turned bright yellow and heating was continued overnight. The reaction mixture was decomposed in the usual manner and the imine hydrochloride was collected; m.p. 100–102°, yield 21 g. (62%). An additional 5 g. of the hydrochloride was isolated from the water solution; total yield 26 g. (77%).

The imine was obtained as a bright yellow oily solid by shaking the hydrochloride with sodium carbonate solution. Treatment with acetic anhydride converted it to the **acetyl derivative,** which was recrystallized from ethanol; m.p. 124–125°.

Anal. Calcd. for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.41; H, 7.41; N, 4.17.

Duryl Phenyl N-Methylketimine Methiodide.—A mixture of 5 g. of duryl phenyl ketimine, 20 ml. of 5% sodium carbonate solution and 10 g. of methyl iodide was heated under reflux for 2 hours and cooled. The yellow crystals which separated proved to be insoluble in water but very soluble in ethanol. Treatment of the alcohol solution with silver nitrate solution gave an immediate precipitate. The methiodide was recrystallized from a mixture of ethanol and ethyl acetate in a 1:3 ratio, m.p. 232–234° dec., yield 6.2 g. (80%).

Anal. Calcd. for $C_{19}H_{26}NI$: C, 58.03; H, 6.15. Found: C, 57.94; H, 6.42.

The infrared spectrum[13] has a band (1628 cm.$^{-1}$) corresponding to the imine group, and the N–H band is absent.

Duryl Phenyl N-Methylketimine.—A mixture of 1 g. of duryl phenyl ketimine and 1 g. of redistilled methyl sulfate was allowed to stand until it became homogeneous. The process was accompanied by the evolution of heat. A solution of 4 g. of sodium bicarbonate in 25 ml. of water was added and the mixture was heated on a steam-bath for 15 minutes, cooled and extracted with ether. The imine was recrystallized repeatedly from a methanol–water mixture; m.p. 100–101°, yield 0.6 g. (60%).

Anal. Calcd. for $C_{18}H_{21}N$: C, 86.01; H, 8.42. Found: C, 86.26; H, 8.49.

Infrared analysis showed that the bond attributed to the N–H group had disappeared.

When the methylimine was treated with methyl iodide it was converted into the same methiodide that was obtained from the unmethylated imine.

Duryl *o*-Methoxyphenyl N-Methylketimine Methiodide.—This salt was obtained in a 50% yield by a procedure similar to the foregoing; m.p. 228–232°, dec.

Anal. Calcd. for $C_{20}H_{26}INO$ C, 56.75; H, 6.19; N, 3.31. Found: C, 56.87; H, 6.44; N, 3.41.

Duryl *p*-Methoxyphenyl N-Methylketimine Methiodide.—The yield of this iodide was 40%, m.p. 231–233° dec.

Anal. Calcd. for $C_{20}H_{26}INO$: C, 56.75; H, 6.19; N, 3.31. Found: C, 56.49; H, 6.11; N, 3.56.

Duryl 2,3-Dimethoxyphenyl N-Methylketimine Methiodide.—This iodide was obtained in a yield of 78%, m.p. 122–124° dec.

Anal. Calcd. for $C_{21}H_{28}INO_2$: C, 55.63; H, 6.23; N, 3.09. Found: C, 55.49; H, 6.46; N, 2.75.

Reaction of Duryl Phenyl N-Methylketimine Methiodide with *t*-Butylmagnesium Chloride.—The powdered methiodide (13 g.) was added to a Grignard reagent prepared from 19 ml. of *t*-butyl chloride. The mixture, which had become deep red in color, was heated under reflux overnight and decomposed with ice and hydrochloric acid. The light yellow product which appeared at the ether–water interface was washed with water and ether, dried and recrystallized from an ethanol–ethyl acetate mixture, m.p. 255–260° dec., yield 9 g. (62%)

Anal. Calcd. for $C_{23}H_{32}IN$: C, 61.47; H, 7.18; N, 3.11. Found: C, 61.41; H, 7.34; N, 3.31.

The infrared spectrum of this compound shows the presence of bands atrributable to the *t*-butyl (1377, 1388 cm.$^{-1}$), imino (1637 cm.$^{-1}$) and para substituted phenyl (850 cm.$^{-1}$) groups.

The same product was obtained by the interaction of duryl *p*-methoxyphenyl N-methylketimine methiodide with the *t*-butyl reagent.

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[13] The infrared spectra were observed and interpreted by Miss Elizabeth Petersen and Miss Helen Miklas.

[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE]

Acid-catalyzed Decarbobenzoxylation

BY NOEL F. ALBERTSON AND FRANK C. MCKAY

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In agreement with the recent publication of Ben-Ishai and Berger decarbobenzoxylation by means of phosphonium iodide has been recognized to be an acid-catalyzed reaction and not a reduction as generally assumed. As a consequence, a very rapid and simplified method of decarbobenzoxylation (using preferably hydrogen bromide in nitromethane) has been developed. Applications to peptide chemistry are discussed and examples are presented. Explanations are advanced for certain cases of diketopiperazine formation in acid solution and for the decomposition of carbalkoxyamino acids on heating.

In a recent contribution to urethan chemistry Ben-Ishai and Berger[1] point out that the removal of a carbobenzoxy group from an amine by means of the "phosphonium reduction" method of Harington and Mead[2] is actually an acid-catalyzed reaction. We had independently reached the same conclusion on the basis of published experimental data.[3] However, our application of this knowledge to peptide chemistry differs from that of Ben-Ishai and Berger.

When hydrogen bromide was bubbled into a solution of carbobenzoxy-DL-phenylalanine in nitromethane, the hydrobromide of DL-phenylalanine precipitated in a few minutes. Treatment of the

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[1] D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

[2] C. Harington and T. Mead, *Biochem. J.*, **29**, 1603 (1935).

[3] C. Stevens and R. Watanabe, THIS JOURNAL, **71**, 725 (1950). These authors found that whereas the carboallyloxy group behaved like the carbobenzoxy group in its cleavage by catalytic hydrogenation, sodium in liquid ammonia and phosphonium iodide, the carbopropyloxy group was cleaved only by phosphonium iodide. Incidentally, data in the original paper of Harington and Mead[2] indicate that the cleavage of a carbobenzoxy group by phosphonium iodide is not a reduction.

In an interesting paper published after the completion of our work, G. Anderson, J. Blodinger and A. Welcher, *ibid.*, **74**, 5309 (1952), report the removal of a carbobenzoxy group by hydrogen bromide in acetic acid. They state that their method was a development of the work of E. Waldschmidt-Leitz and K. Kuhn, *Ber.*, **84**, 381 (1951). The latter authors still referred to the phosphonium iodide method as a reduction.