

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

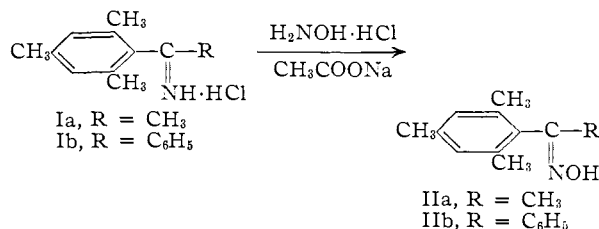
Formation of Certain Mesityl Ketoximes from Ketimines. Beckmann Rearrangements¹

BY CHARLES R. HAUSER AND DAVID S. HOFFENBERG

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Mesityl methyl and mesityl phenyl ketoximes have been prepared from the corresponding ketimine hydrochlorides and hydroxylamine hydrochloride in the presence of sodium acetate, but dimesityl ketimine or its *N,N*-dimethyl derivative failed to react. The Beckmann rearrangements of the ketoximes were effected by means of boron fluoride. Dimesityl ketimine was converted to the Beckmann rearrangement product of the corresponding ketoxime by means of peracetic acid. The significance of an electronic *versus* steric factor is indicated.

It has been observed previously that certain ketoximes may be prepared more readily from ketimines than from the corresponding ketones.² The method consists in treating the ketimine hydrochlorides with hydroxylamine hydrochloride in the presence of sodium or potassium acetate. It therefore seemed possible to prepare certain mesityl ketoximes from appropriate ketimines even though they apparently have not been obtained from the corresponding mesityl ketones such as acetomesitylene.^{3,4} This was accomplished for ketoximes IIa and IIb which were synthesized from ketimine hydrochlorides Ia and Ib in yields of 94 and 72%, respectively. The ketimine hydrochlorides were prepared readily from the appropriate nitriles and Grignard reagents, followed by treatment with hydrochloric acid.



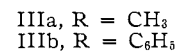
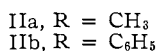
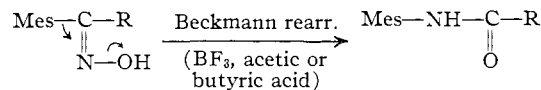
Oximes IIa and IIb were acetylated with acetic anhydride to form corresponding acetates and were rearranged (Beckmann) by means of boron fluoride to give amides IIIa and IIIb, respectively. These rearrangements of the oximes, which established their configurations, were realized in excellent yields (86–94%) by heating their boron fluoride coordination complexes with acetic or butyric acid. Only an impure product was obtained from oxime IIb with phosphorus pentachloride. The products were identified as amides IIIa and IIIb by independent syntheses from mesidine and acetic anhydride and benzoyl chloride, respectively.

(1) Supported by the Office of Ordnance Research, U. S. Army.

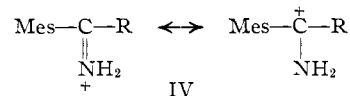
(2) Mme. Bruzau, *Ann. Chem.*, [11] 1, 332 (1934); A. E. Brodhag and C. R. Hauser, *THIS JOURNAL*, **77**, 3024 (1955).

(3) See E. P. Kohler and R. Baltzly, *ibid.*, **54**, 4015 (1932). Recently D. E. Pearson and F. Greer (*ibid.*, **77**, 1294 (1955)) have prepared the 2,4-dinitrophenylhydrazone of acetomesitylene and they suggest that the oxime might be obtained similarly.

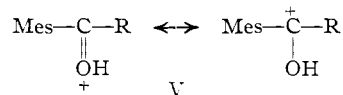
(4) A medium that is weakly acidic or strongly basic has been shown to favor oxime formation; see L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 334. Yet we have recovered acetomesitylene after treatment with hydroxylamine in weakly acidic medium (using hydroxylamine hydrochloride and sodium acetate), and in strongly basic medium employing potassium methoxide in refluxing methanol, or potassium amide in refluxing ether. However, E. Feith and S. H. Davies (ref. 11) have obtained the Beckmann rearrangement product on heating acetomesitylene with hydroxylamine hydrochloride in a sealed tube at 160°.



The success of the reaction of the ketimines with hydroxylamine in the weakly acidic medium (*pH* 5–6) presumably is dependent on the presence of an appreciable concentration of the immonium ion IV in equilibrium with the acetate ion, the carbonium resonance form of IV being regarded as the active intermediate. In agreement with this, the reaction failed when sodium hydroxide was employed instead of sodium acetate, under which conditions the immonium ion IV presumably was converted largely to the free ketimine.



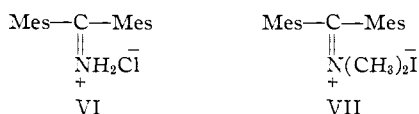
Since these ketimines are of comparable size and complexity to the corresponding ketones, the failure of oxime formation with the latter under similar conditions hardly can be due solely to a steric factor as often has been assumed. Rather, the failure with the ketones appears to be ascribable to the lack of a sufficient concentration of the oxonium ion V, this being associated with an electronic factor. Certainly the concentration of V would be less than that of IV since the ketone is a weaker base than the ketimine.⁵ Presumably, the contribution of the carbonium ion resonance form to the structure of the ion would be at least as great with V as with IV.



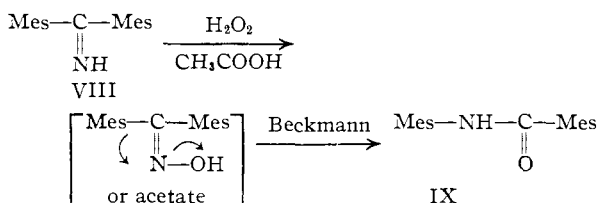
However, dimesityl ketimine hydrochloride (VI) failed to react with hydroxylamine under the conditions employed with ketimine hydrochlorides Ia and Ib or under more drastic conditions. Moreover, the *N,N*-dimethyl derivative VII failed to react with hydroxylamine under similar conditions even though it would retain a full positive charge in the presence of sodium acetate. Also, VII failed to

(5) Although increasing the acidity of the medium would increase the concentration of the oxonium ion V, it would at the same time decrease the concentration of free hydroxylamine with which the carbonium ion reacts. This is presumably the reason why strongly acidic media do not favor oxime formation; see A. Ölander, *Z. physik. Chem.*, **129**, 1 (1927). Also see J. B. Conant and P. D. Bartlett *THIS JOURNAL*, **54**, 2888 (1932).

yield the ketoxime in the presence of sodium hydroxide.



Although dimesityl ketimine hydrochloride (VI) failed to form the ketoxime with hydroxylamine, the free ketimine VIII was converted by hydrogen peroxide in acetic acid (peracetic acid) to mesitylmesidide (IX) which is the Beckmann rearrangement product of the corresponding oxime. Apparently the oxidizing agent produced the N-oxide of the ketimine which isomerized to the ketoxime, since N-oxides of primary and secondary amines are known to isomerize to the corresponding hydroxylamines.⁶ It is possible that the acetate of the oxime was formed as an intermediate. Attempts to oxidize the ketimine to the oxime in basic medium, in which the Beckmann rearrangement should not be expected, were unsuccessful.



Experimental⁷

Mesityl Methyl Ketimine Hydrochloride (Ia).—To a stirred solution of methylmagnesium iodide in 100 ml. of anhydrous ether was added 13.8 g. (0.095 mole) of mesitronitrile⁸ in 100 ml. of anhydrous benzene. Most of the ether was removed by distillation and the resulting benzene solution was refluxed for 12 hours. The reaction mixture was decomposed with iced hydrochloric acid and the aqueous layer, to which was added aqueous extracts of the benzene layer, was made basic with 20% sodium hydroxide. The liberated ketimine was taken up in ether, and the ether solution refluxed with animal charcoal, dried over drierite, and filtered. Dry hydrogen chloride was passed into the etheral solution to precipitate the ketimine hydrochloride Ia as a white solid which was collected on a funnel and dried. The yield was 12.1 g. (67%) melting at 228–231°. A sample, recrystallized from a mixture of ethanol and ethyl acetate, melted at 235–237°.

Anal. Calcd. for $\text{C}_{11}\text{H}_{16}\text{NCl}$: Cl, 17.93. Found: Cl, 17.85.

Mesityl Methyl Ketoxime (IIa).—A solution of 5.6 g. (0.03 mole) of mesityl methyl ketimine hydrochloride (Ia), 3.1 g. (0.045 mole) of hydroxylamine hydrochloride and 5.4 g. (0.075 mole) of sodium acetate in 100 ml. of 70% ethanol was refluxed for 10 hours and then stored in a refrigerator for 8 hours more. Water (100 ml.) was added to precipitate 4.7 g. (94%) of oxime IIa as a white solid melting at 98–99°. Recrystallization of the compound from a minimum of acetone and an equal volume of methanol, water being added to produce cloudiness,⁹ yielded fine white needles but did not raise the melting point.

Anal. Calcd. for $\text{C}_{11}\text{H}_{15}\text{NO}$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.71; H, 8.32; N, 7.95.

A sample of the oxime IIa was treated with acetic anhydride to give, after recrystallization from acetone-methanol-water, white needles of the oxime acetate melting at 68°.

(6) See T. W. A. Taylor and W. Baker, Sidgwick's "Organic Chemistry of Nitrogen," Oxford University Press, London, 1937, p. 26.

(7) Melting points are uncorrected. Analyses by Galbraith Laboratories, Knoxville, Tenn.

(8) R. C. Fuson and J. J. Denton, *THIS JOURNAL*, **63**, 655 (1941).

(9) See C. R. Hauser and C. T. Sullivan, *ibid.*, **56**, 4611 (1933).

Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{NO}_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.36; H, 7.73; N, 6.24.

Beckmann Rearrangement of Oxime IIa.—A solution of 2.0 g. of the oxime in 250 ml. of dry thiophene-free benzene was saturated with gaseous boron fluoride (as evidenced by the copious evolution of dense white fumes¹⁰), and sufficient petroleum ether added to precipitate the boron fluoride complex of the oxime. The white complex was collected on a funnel, dried, and a solution of it in 50 ml. of glacial acetic acid refluxed for 10 minutes. After cooling, water was added to precipitate acetylmesidide (IIIa) which was collected on a funnel and dried. The yield was 1.7 g. (86%) melting at 215–216°, lit. m.p. 216°, 210–212°. There was no depression in melting point on admixture with an authentic sample of acetylmesidide prepared from mesidine and acetic anhydride.¹³

Mesityl Phenyl Ketimine Hydrochloride (Ib).—This salt was prepared by addition of 30.9 g. (0.3 mole) of benzonitrile in 100 ml. of dry benzene to mesitylmagnesium bromide (obtained from 0.1 mole of bromomesitylene and 0.35 g. atom of magnesium turnings employing the entrainment method with 0.2 mole of ethyl bromide). Most of the ether was removed, and the mixture refluxed for 12 hours. Decomposition with iced hydrochloric acid precipitated the imine hydrochloride Ib as a tan solid which was collected on a funnel and dried. The yield was 22.7 g. (88%) melting at 255–260°, and at 267–269° (white powder) after treatment with dilute (2 M) sodium hydroxide, extraction with ether, and reprecipitation with dry hydrogen chloride. Reported melting points are 261–264°¹⁴ and 260–265°.¹⁵

Mesityl Phenyl Ketoxime (IIb).—This oxime was prepared essentially as described for oxime IIa employing 15.0 g. (0.057 mole) of mesityl phenyl ketimine hydrochloride (Ia), 6.3 g. (0.09 mole) of hydroxylamine hydrochloride, 12.6 g. (0.15 mole) of sodium acetate and 200 ml. of 70% ethanol. The solution was refluxed for 10 hours and allowed to stand in the refrigerator for 24 hours more. The precipitated oxime IIb was collected on a funnel, washed with petroleum ether, and dried. A second crop was obtained by the addition of water to the alcoholic filtrate; total yield 9.9 g. (72%), melting at 140–142°. Recrystallization from a mixture of acetone-methanol-water gave small white needles melting at 150°.

Anal. Calcd. for $\text{C}_{18}\text{H}_{17}\text{NO}$: C, 80.30; H, 7.16; N, 5.58. Found: C, 80.17; H, 7.03; N, 5.83.

A sample of the oxime IIb gave, on treatment with acetic anhydride cooled to 0°, white needles of the oxime acetate which, after recrystallization from acetone-methanol-water, melted at 137°.

Anal. Calcd. for $\text{C}_{18}\text{H}_{19}\text{NO}_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.74; H, 6.81; N, 5.00.

When the ketimine hydrochloride Ib was treated with hydroxylamine hydrochloride under the conditions described above employing sodium hydroxide instead of sodium acetate, the oxime IIb failed to form, and 90% of the imine was recovered as its hydrochloride.

Beckmann Rearrangement of Oxime IIb.—The boron fluoride complex of this oxime (3.0 g.) was prepared as described for oxime IIa. A mixture of this complex and 25 ml. of butyric acid was refluxed (154°) for 10 minutes producing a red solution. After cooling, water was added to precipitate 2.8 g. (94%) of benzoylmesidide (IIIb), melting at 202–204°. Recrystallization from 95% ethanol gave fine white needles melting at 204° (lit. m.p. 204°).¹⁶ There was no depression in melting point on admixture with an authentic sample of benzoylmesidide prepared from mesidine and benzoyl chloride.

When the Beckmann rearrangement of the boron fluoride complex was carried out in acetic acid as described for oxime IIa the amide was difficult to purify.

When the rearrangement of oxime IIb was effected with

(10) See C. R. Hauser and J. T. Adams, *ibid.*, **66**, 345 (1944).

(11) E. Feith and S. H. Davies, *Ber.*, **24**, 3546 (1891).

(12) C. K. Ingold and H. A. Piggot, *J. Chem. Soc.*, **125**, 173 (1924).

(13) See H. E. Dadswell and J. Kenner, *ibid.*, 1104 (1927).

(14) H. Gilman, E. L. St. John, N. B. St. John and N. Lichtenwalter, *Rec. trav. chim.*, **56**, 579 (1936).

(15) R. C. Fuson, W. D. Emmons and J. P. Freeman, *THIS JOURNAL*, **75**, 5322 (1953).

(16) H. Huber, *Ber.*, **10**, 1711 (1877).

phosphorus pentachloride a still more impure product was obtained.

Dimesityl Ketimine Hydrochloride (VI).—To a stirred solution of mesitylmagnesium bromide (prepared on a 0.1-mole scale as described by Barnes¹⁷) was added 14.3 g. (0.10 mole) of mesitonitrile in 100 ml. of toluene. After distillation of the ether, the reaction mixture was refluxed for 12 hours, and then decomposed with iced hydrochloric acid. The precipitate was collected on a funnel and dried to give 22.8 g. (76%) of dimesityl ketimine hydrochloride (light tan) melting at 257–263°. A sample, recrystallized from a mixture of ethanol and ethyl acetate, melted at 264–267°.

Anal. Calcd. for $C_{19}H_{24}NCl$: N, 4.64; Cl, 11.75. Found: N, 4.73; Cl, 12.22.

The free dimesityl ketimine VIII was obtained by treatment of the hydrochloride VI with 10% sodium hydroxide; after recrystallization from 95% ethanol, it melted at 130°.

Anal. Calcd. for $C_{19}H_{23}N$: N, 5.28. Found: N, 5.27.

Treatment of 10.0 g. (0.033 mole) of dimesityl ketimine hydrochloride with 3.5 g. (0.05 mole) of hydroxylamine hydrochloride and 6.7 g. (0.083 mole) of sodium acetate in 140 ml. of 70% ethanol (refluxed for 9 days) failed to produce the oxime, 96% of dimesityl ketimine (m.p. 122–124°) being recovered on adding water.

Heating a solution of 3.0 g. of dimesityl ketimine hydrochloride, 1.5 g. of hydroxylamine hydrochloride and 2.0 g. of sodium acetate in 30 ml. of 70% ethanol in a sealed Carius tube at 170° for 24 hours failed to give the oxime, 55% of the ketimine (m.p. 123–124°) being recovered.

Dimesityl Ketimine N,N-Dimethyl Iodide (VII).—This compound was prepared in 92% yield from 2.8 g. (0.011 mole) of dimesityl ketimine, 10.0 g. (0.07 mole) of methyl iodide and 20 ml. of 5% sodium bicarbonate employing the procedure described by Fuson¹⁸ for the preparation of duryl phenyl N-methyl ketimine methiodide. The product (VII) melted at 256–259° dec.

Anal. Calcd. for $C_{21}H_{28}NI$: N, 3.33. Found: N, 3.14.

(17) R. P. Barnes, *Org. Syntheses*, **21**, 77 (1941).

Treatment of quaternary salt VII with hydroxylamine hydrochloride and sodium acetate in 70% ethanol failed to give the ketoxime after 12 hours of refluxing or after 24 hours in a sealed tube at 185°, 92–94% of VII being recovered.

Refluxing VII with hydroxylamine and excess sodium hydroxide in ethanol for 10 hours failed to yield the oxime, dimesityl ketone (5%), m.p. 135–136° (reported 136–137°),¹⁸ being the only product isolated.

Conversion of Dimesityl Ketimine (VIII) to Mesitoylmesidide (IX) by Peracetic Acid.—In a small flask fitted with a condenser was placed 5.0 g. (0.019 mole) of dimesityl ketimine (m.p. 128–129°), 25 ml. of glacial acetic acid and 3.0 ml. of 30% hydrogen peroxide.¹⁹ The mixture was heated to 80° for 6 hours, 3.0 ml. more of hydrogen peroxide was then added, and the heating continued for 9 hours longer. After cooling, 15 ml. of water was added. The resulting white precipitate was collected on a funnel and washed with water and sodium bicarbonate solution, and again with water. After drying, the solid weighed 3.5 g. and melted at 190–195°. On recrystallization from 95% ethanol it gave 2.5 g. (50%) of mesitoylmesidide melting at 207°.

Anal. Calcd. for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.05; H, 8.32; N, 5.05.

This substance did not depress the melting point of a sample of mesitoylmesidide prepared by the general Scotten-Baumann procedure from mesidine and mesitoyl chloride.

In another experiment, employing somewhat impure ketimine hydrochloride (m.p. 122–124°), the yield of mesitoylmesidide (VII), m.p. 207°, was only 17%.

In a blank experiment, employing water instead of hydrogen peroxide, dimesityl ketimine failed to react, and 91% of it was recovered.

Treatment of dimesityl ketimine with hydrogen peroxide in methanolic sodium hydroxide or with potassium permanganate in alkaline acetone–water resulted in the recovery of most of the imine. Treatment with potassium periodate and sodium hydroxide in aqueous dioxane produced tars.

(18) E. P. Kohler and R. Baltzly, *THIS JOURNAL*, **54**, 4023 (1932).

(19) See E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

DURHAM, N. C.

[CONTRIBUTION FROM THE BIOLOGY DIVISION, OAK RIDGE NATIONAL LABORATORY]

The Hydrolysis of Carbon-Carbon Bonds by α -Chymotrypsin

BY DAVID G. DOHERTY^{1,2}

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The enzymic hydrolysis of ethyl 5-(*p*-hydroxyphenyl)-3-ketovalerate by α -chymotrypsin to yield *p*-hydroxyphenyl-propionic acid has been established. The effect of pH, substrate concentration and enzyme concentration have been investigated and K_s and k_3 for the system evaluated. The K_s and k_3 for the system 5-(*p*-hydroxyphenyl)-3-ketovaleric acid- α -chymotrypsin have also been determined. Procedures are given for the synthesis of these substrates.

Introduction

The investigation of the nature of enzyme-substrate or inhibitor complex formation under equilibrium conditions has yielded apparent thermodynamic functions for several substrate and competitive inhibitor systems.³ Examinations of these functions reveal increasingly negative ΔS and ΔH values for systems catalytically bound at the active center in contrast to the small positive values obtained for those in which no catalytic activity may be demonstrated. The results were explained³ by the assumption that (1) the active center of the enzyme consisted of an attractive

center determining the specificity and orientation and responsible for the high intrinsic binding forces evinced by the large negative ΔH , and (2) a repulsive charge center, activating the labile bond and responsible for the entropy loss that was found experimentally. In the 5-(*p*-hydroxyphenyl)-3-acetaminobutanone-2- α -chymotrypsin system, the above properties are found and the compound is a competitive inhibitor since the carbonyl-methyl bond is relatively unpolarized and not within the activation energy range of the enzyme. However, if the carbonyl-methyl bond could be sufficiently polarized by the addition of electrophilic groups, its activation energy might be lowered to the extent that the enzyme could bring about the scission of the carbonyl to carbon linkage. Polarization of this bond could be effected by the addition of a carboxy group to form a β -keto

(1) This work was performed for the Atomic Energy Commission under Contract No. W-4705-eng-28.

(2) Presented in part at the Federation of American Societies for Experimental Biology, Atlantic City, N. J., April 12–16 (1954).

(3) D. G. Doherty and F. Vaslow, *THIS JOURNAL*, **74**, 931 (1952); F. Vaslow and D. G. Doherty, *ibid.*, **75**, 928 (1953).