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

Reactions of β-Dimethylaminopivalophenone and its Methiodide

BY H. R. SNYDER AND JAMES H. BREWSTER[1]

Ketonic Mannich bases and their quaternary salts alkylate active methylene compounds[2,3] by a process of amine replacement and react with secondary amines by amine exchange.[4] Amine replacement also occurs in the reaction of sodium cyanide with the hydrochlorides of ketonic Mannich bases.[5]

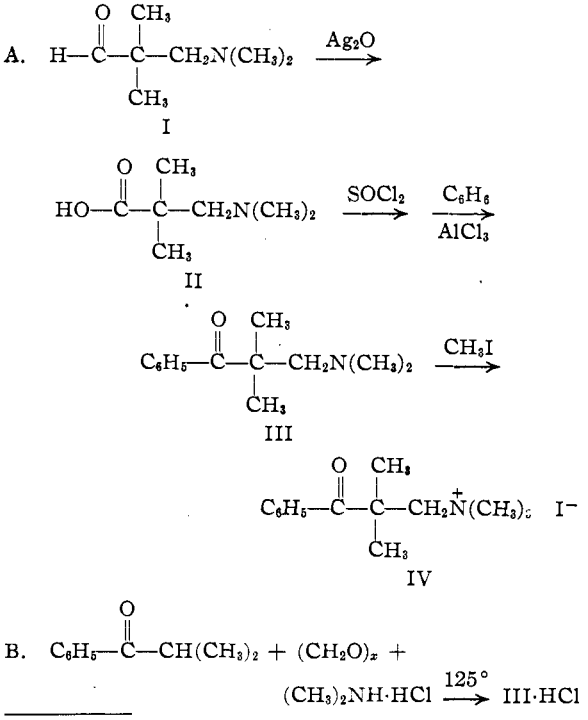
The ease with which vinyl ketones can be prepared from β-aminoketones[6,7] has suggested that amine elimination is the first step in amine replacement[2,3] and exchange[4] reactions. Nisbet has presented evidence that amine elimination precedes ring closure in the formation of pyrazolines from the phenylhydrazones of ketonic Mannich bases.[8]

In connection with studies of the reactions of Mannich bases which cannot suffer amine elimination,[9,10] β-dimethylaminopivalophenone (III) and its methiodide (IV) were prepared and subjected to the conditions of amine replacement and exchange reactions. These compounds (III and IV) would be expected to be extremely unreactive in such processes; not only is amine elimination impossible, but also S_N2 amine displacements[11] are prevented by the steric hindrance offered by the α-methyl groups,[12] and S_N1 amine replacements[11] are hindered because no resonance-stabilized "carbonium ion" (or its solvated equivalent)[13] can be formed as an intermediate.

Although isobutyraldehyde readily undergoes the Mannich reaction to form β-dimethylaminopivaldehyde (I),[14] isobutyrophenone (V) is not attacked under the conditions generally employed for this process.[15] The ketonic Mannich base (III) could, however, be prepared in low yield by the reaction of isobutyrophenone with dimethylamine hydrochloride and an excess of molten paraformaldehyde (eqn. B). The β-aminoketone so formed was identical with that prepared from β-dimethylaminopivalic acid (II) by the method of Dalmer, Diehl and Pieper[16] (eqn. A).

The β-aminoketone (III) failed to react with alcoholic alkali, morpholine or malonic ester. Although III apparently formed a phenylhydrazone, this derivative could not be crystallized, nor could it be cyclized to a pyrazoline, in contrast to the phenylhydrazone of the dimethylamino Mannich base of acetophenone.[17] When heated with aqueous-alcoholic sodium cyanide, III formed isobutyrophenone in 67% yield. A similar reverse Mannich reaction occurred readily when a dilute hydrochloric acid solution of III was distilled. A possible mechanism for this reaction is indicated in equation C.

The methiodide (IV) formed no appreciable amounts of neutral or acidic products when heated with aqueous sodium cyanide or sodiomalonic ester in diethyl carbitol. When an aqueous solution of IV and sodium cyanide was distilled to dryness, III was formed by demethylation of the quaternary salt. Hot aqueous alkali slowly converted IV to benzoic acid, trimethylamine and, perhaps, isobutylene, possibly by the mechanism shown in equation D.



(1) Present address: Department of Chemistry, University of Chicago, Chicago, Illinois.

(2) Mannich, Koch and Borkowsky, *Ber.*, **70**, 355 (1937).

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(6) Blicke, in "Organic Reactions," Vol. I, John Wiley and Sons Inc., New York, N. Y., 1942, p. 303.

(7) Cromwell, *Chem. Rev.*, **38**, 83 (1946).

(8) Nisbet, *J. Chem. Soc.*, 126 (1945).

(9) Snyder and Eliel, THIS JOURNAL, **70**, 1703, 1857 (1948).

(10) Snyder and Brewster, *ibid.*, **71**, 1058 (1949).

(11) Hughes, Ingold and Patel, *J. Chem. Soc.*, 526 (1933).

(12) Dostrovsky, Hughes and Ingold, *ibid.*, 173 (1946).

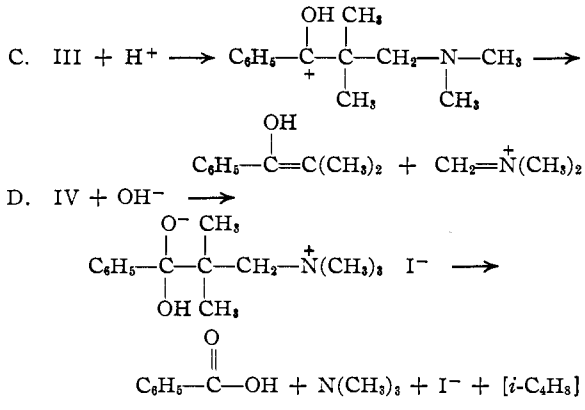
(13) Swain, THIS JOURNAL, **70**, 1119 (1948).

(14) Mannich, Lesser and Silten, *Ber.*, **65**, 378 (1932).

(15) Winstein, Jacobs, Seymour and Linden, *J. Org. Chem.*, **11**, 215 (1946).

(16) Dalmer, Diehl and Pieper, German Patent 606,349; *Frdl.*, **21**, 622 (1937); German Patent 629,054; *Frdl.*, **23**, 584 (1940).

(17) Jacob and Madinaveitia, *J. Chem. Soc.*, 1929 (1937).



Experimental[18,19]

β-Dimethylaminopivalophenone (III). 1. By the Friedel-Crafts Reaction.—β-Dimethylaminopivaldehyde[14] (I, 14.8 g.) was added dropwise to a stirred suspension of thoroughly washed silver oxide (prepared from 39.2 g. of silver nitrate) in 150 ml. of water. The oxidation was completed by heating the mixture on the steam-bath for two hours. The crude amino acid (II), obtained by evaporation (at 25 mm.) of the filtered aqueous solution, was dissolved in a mixture of 200 ml. of acetone and 5 ml. of water, and the filtered hot solution was placed in the ice-chest. After twelve hours pure II was collected as glistening white needles melting at 98–99° (lit.[16] 100°); yield, 12.2 g. (74%). The amino acid was converted to the ketone (III) as previously described[16]; the ketone (III) was obtained as a nearly odorless, water-white liquid, b.p. 103–105° (2.5 mm.), $n^{20}D$ 1.5128; the yield of III from II was 32%.

2. By the Mannich Reaction of Isobutyrophenone.—In a 300-ml. Kjeldahl flask fitted with an air-cooled condenser a mixture of 7.4 g. of isobutyrophenone, 8.2 g. of dimethylamine hydrochloride and 7.5 g. of paraformaldehyde was heated for two hours at 140–150° (oil-bath temperature). The cooled mixture was diluted with 150 ml. of water, filtered and washed with ether. The aqueous layer was made alkaline and extracted with ether. Distillation of the residue from evaporation of the dried ether extracts gave 2.03 g. (19%) of III, b.p. 83–84° (1 mm.), $n^{20}D$ 1.5130.

Anal. Calcd. for $C_{13}H_{19}ON$: C, 76.05; H, 9.34; N, 6.82. Found: C, 76.03; H, 9.48; N, 6.88.

The hydrochloride[16] melted at 143–144°, alone or mixed with the hydrochloride prepared from the product of the first synthesis.

The methiodide (IV) formed when III was allowed to stand with a fivefold excess of methyl iodide for twelve hours or longer; it separated as a dark oil which crystallized when the mixture was diluted with ether. The salt could be recrystallized by the slow addition of dry ether to an absolute ethanol solution. It melted at 122–122.5°; samples prepared from the two lots of II were identical.

Anal. Calcd. for $C_{14}H_{22}ONI$: C, 48.42; H, 6.39. Found: C, 48.64; H, 6.49.

Attempted Amine Exchange Reaction with β-Dimethylaminopivalophenone.—β - Dimethylaminopivalophenone (III) (0.41 g.) and morpholine (4.35 g.) were refluxed for forty-eight hours under nitrogen. The solution was cooled and 20 ml. of water was added. The cloudy mixture was extracted with three 5-ml. portions of ether. The combined ether extract was distilled, finally under vacuum (water pump), to remove the morpholine that had been extracted along with the aminoketone. A large excess of methyl iodide was added to the residue; the methiodide of β-dimethylaminopivalophenone (IV), m.p. 122–123°, identical with that previously prepared, was obtained; yield, 0.45 g. (65%).

Attempted Alkylation of Malonic Ester with β-Dimethylaminopivalophenone.—To a solution of β-dimethylaminopivalophenone (III) (0.41 g.) and malonic ester (1.00 g.) in 5 ml. of xylene was added a small amount of powdered sodium hydroxide. The mixture was refluxed under nitrogen for forty-eight hours. No amine evolution was observed. The solution was cooled and extracted with three 5-ml. portions of 10% hydrochloric acid. The combined acid extract was made strongly alkaline and the oil which separated was taken up in ether; the ether was evaporated and the residue was treated with an excess of methyl iodide. The methiodide of the Mannich base was obtained; yield, 0.43 g. (62%), m.p. 122–123°.

Reverse Mannich Reaction of Isobutyrophenone Mannich Base.—β-Dimethylaminopivalophenone (2.05 g.) and sodium cyanide (1.00 g.) were heated together in 30 ml. of 50% ethanol for four days. A volatile amine was evolved. Water (70 ml.) was added to the cooled solution, which was then extracted with 20-ml. portions of ether. The combined ether extract was distilled, finally under reduced pressure. Isobutyrophenone, (1 g., 67.5%) b.p. 56° (1 mm.), $n^{20}D$ 1.5189 (lit.[20] $n^{20}D$ 1.5190), was the sole product obtained. The 2,4-dinitrophenylhydrazone melted at 162–162.5°.[20]

A similar reverse Mannich reaction occurred when the Mannich base was heated in acid medium.

β-Dimethylaminopivalophenone (1.00 g.) was dissolved in a mixture of 2 ml. of 37% hydrochloric acid and 10 ml. of water. The solution was slowly distilled almost to dryness from an oil-bath maintained at 130–140°. When no further distillation occurred more water was added and the distillation was resumed. This process was continued until only a clear distillate was obtained; there was a small amount of tarry residue.

The acidic, cloudy distillate (20 ml.) was extracted with ether. The ether was evaporated, and the residue, dissolved in 95% ethanol, was treated with 1 g. of 2,4-dinitrophenylhydrazine. The solution was brought to boiling, and, after it had been cooled slightly, 37% hydrochloric acid (1.3 ml.) was added. The acid solution was heated under reflux for one hour; the crude 2,4-dinitrophenylhydrazone of isobutyrophenone, m.p. 153–155°, 1.34 g. (81.8%), crystallized from the solution when it was chilled in ice. The reddish crystals were digested with ethanol to give 1.02 g. (62.3% from the Mannich base) of the pure derivative, m.p. 162.5–163°.[20]

β-Dimethylaminopivalophenone (1.0 g.) was heated with a solution of sodium hydroxide (2 g.) in 75% ethanol (20 ml.) for two days. No appreciable evolution of basic gases occurred. The flask was cooled and water (30 ml.) was added. The oil which separated was collected in ether and extracted with 10% hydrochloric acid. The ether solution left no residue on evaporation. The acid solution was made strongly basic and 0.75 g. (75%) of the unchanged Mannich base, b.p. 90° (1 mm.), $n^{20}D$ 1.5125 was recovered.

Reaction of the Methiodide of β-Dimethylaminopivalophenone with Sodium Cyanide.—A solution of the methiodide of β-dimethylaminopivalophenone (IV) (1.74 g.) and sodium cyanide (0.50 g.) in water (5 ml.) was distilled to dryness at atmospheric pressure in a flask with a low-set wide side-arm. The bulb of the flask was set in a Wood's metal-bath, and, while the pressure inside the flask was maintained at about 35 mm., the bath temperature was raised slowly to 180°. A liquid formed in the bulb of the flask but did not distil. After half an hour the mixture was allowed to cool somewhat and was distilled at 1.5 mm. pressure yielding a fraction of b.p. 100–120° (1.5 mm.).

The solid residue in the distillation flask was extracted with ether, and this ethereal solution was used in an extraction of the first (aqueous) distillate and was then added to the volatile material from the final distillation. The ether solution was extracted with 10% sodium hydroxide

(18) Microanalyses by Misses Theta Spoor and Betty Snyder.

(19) All melting points corrected.

(20) Evans, *J. Chem. Soc.*, 788 (1936).

solution and then with 10% hydrochloric acid. The neutral and base-soluble fractions contained only traces of material. The acid-soluble fraction was recovered and treated with methyl iodide to give 0.87 g. (50%) of the methiodide of β-dimethylaminopivalophenone; m. p. 122–123°. No melting point depression occurred on admixture of authentic IV to this salt.

Reaction of Methiodide of β-Dimethylaminopivalophenone with Sodium Hydroxide.—The methiodide (IV) (1.04 g.) was heated under reflux with 8 ml. of 5% sodium hydroxide for forty-eight hours. A basic gas was evolved rapidly during the first few hours. The cooled solution was filtered, the filtrate acidified, and the precipitated benzoic acid was collected in benzene; m.p. (and mixed m.p.) 122–122.5°, after recrystallization from water; yield 0.21 g. (57%).

Summary

β-Dimethylaminopivalophenone has been prepared by the Mannich reaction of isobutyrophenone. This β-aminoketone cannot suffer amine elimination, is sterically hindered to amine displacement, and cannot form a resonance-stabilized "carbonium ion." It failed to undergo amine exchange and replacement reactions; it was stable to strong base, but it readily underwent the reverse Mannich reaction in weakly basic or acidic medium.

The methiodide of this Mannich base reacted with sodium cyanide by demethylation rather than by amine replacement. Hot aqueous alkali caused cleavage of the methiodide to benzoic acid.

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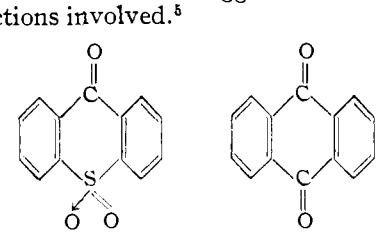
[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA AND SWARTHMORE COLLEGE]

The Thiaxanthone Dioxide–Thiaxanthenol Dioxide–Thiaxanthene Dioxide Oxidation–Reduction System: A Sulfone Series Analog of the Anthraquinone–Anthrahydroquinone–Anthrone System[1]

BY EDWARD A. FEHNEL[2]

Several investigators have called attention to the peculiar color reactions of thiaxanthone-5-dioxide and substituted thiaxanthone-5-dioxides in the presence of zinc dust and alkali,[3] but no detailed study of these reactions has previously been reported and the nature of the chromogen has remained a subject for speculation.[3] Our interest in the physico-chemical properties of the sulfone function[4] led us to investigate the color reactions of thiaxanthone-5-dioxide in some detail, and we are now able to report the isolation and characterization of the substance responsible for color formation and to suggest a mechanism for the reactions involved.[5]



I II

On treatment with zinc dust or sodium hydrosulfite and alkali, alcoholic solutions of thiaxanthone-5-dioxide (I) give an intense blue color, which is discharged on shaking with air. The striking similarity of this behavior to that shown by anthraquinone[6] (II) under the same conditions immediately suggests that the color is to be attributed to the formation of a sulfone anion analogous to the deeply colored, readily oxidizable anthrahydroquinone anion formed in the familiar vatting reaction.[7] Our data on the oxidation–reduction reactions in the thiaxanthone dioxide series are in accord with this interpretation. The demonstration of a close parallelism in the reactions of the thiaxanthone dioxide and anthraquinone series of compounds is of particular interest in view of the fact that the formulation of a sulfone oxidation–reduction system analogous to the anthraquinone–anthrahydroquinone system requires

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(2) American Chemical Society Postdoctoral Fellow at the University of Pennsylvania, 1946–1948. Present address: Department of Chemistry, Swarthmore College, Swarthmore, Pa.

(3) (a) Graebe and Schulthess, *Ann.*, **263**, 1 (1891); (b) Ullmann and Lehner, *Ber.*, **38**, 729 (1905); (c) Ullmann and Glenck, *ibid.*, **49**, 2487 (1916); (d) Amstutz, Fehnel and Hunsberger, THIS JOURNAL, **70**, 133 (1948).

(4) Fehnel and Carmack, *ibid.*, **71**, 231 (1949).

(5) NOTE ADDED IN PROOF.—While the present paper was in press, Heymann [*ibid.*, **71**, 260 (1949)] reported a closely related study of the thiaxanthone dioxide–thiaxanthenol dioxide oxidation–reduction system, in which essentially the same conclusions were reached with regard to the reaction mechanism.

(6) For a detailed discussion of the chemistry of anthraquinone and its reduction products, see Houben and Fischer, "Das Anthracen und die Anthrachinone," Georg Thieme, Leipzig, 1929, esp. pp. 143-172 and 197-206. An excellent concise summary of the more important oxidation-reduction reactions has been given by Fieser and Fieser, "Organic Chemistry," D. C. Heath, Boston, 1944, pp. 798-802.

(7) NOTE ADDED IN PROOF.—Strictly speaking, it is not entirely accurate to attribute the color to the simple ion, since the colored species is undoubtedly the semiquinone ion-radical which results from the loss of one electron by the doubly-charged anion (*cf.* Heymann, ref. in footnote 5). This idea is, of course, implicit in the present discussion of the thiaxanthone-enol dioxide oxidation–reduction system, since it follows from the analogy with the anthraquinone–anthrahydroquinone system, in which the blood-red color of the "anthrahydroquinone anion" is almost certainly due to the presence of the corresponding semiquinone ion-radical (see, however, Dufraisse and Priou, *Bull. soc. chim.*, [5] **6**, 1649 (1939), who postulate a biradical anion).