An Abnormal Mannich Reaction

BY JERROLD MEINWALD AND FRANCIS BAIRD HUTTO, JR.

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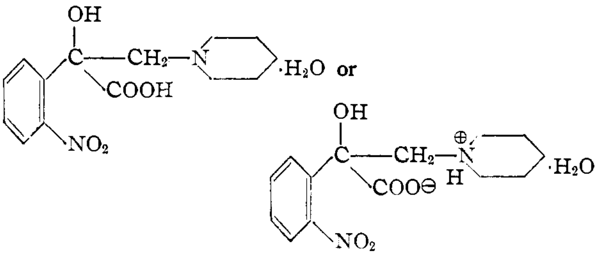
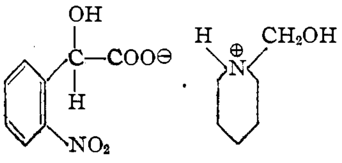
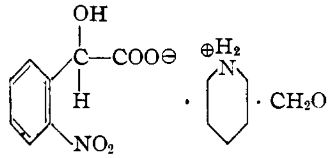
The condensation of an amine with formaldehyde and an active hydrogen component, known as the Mannich reaction,[1] has acquired enhanced interest with the growing realization that it may well be the characteristic step in alkaloid biogenesis.[2] The excellent kinetic study of Alexander and Underhill,[3] which culminated in the proposal of a mechanism involving the enol of the active hydrogen component, provided a generally satisfactory picture of this condensation. The recent report of Grillot and Bashford[4] in which the obtention of an optically active product upon treatment of resolved *o*-nitromandelic acid with formaldehyde and piperidine was cited as evidence against the participation of enolic intermediates, was, therefore, most surprising. This conclusion was based on the implicit assumptions that this product is accurately represented by structure I[5] and that the reaction under consideration is a *bona fide* Mannich reaction. In an attempt to resolve these apparently conflicting views, these assumptions have been reëxamined and seem to be unjustified.

An indirect indication that formula I does not represent the structure of this key reaction product was recorded by Grillot and Bashford, who found that "...the reaction occurred too rapidly to be of any value in a kinetic study."[4] This surprising observation suggests that the reaction under consideration is not the presumed condensation, which hardly would be expected to be so rapid under the relatively mild conditions employed, but rather simple salt formation. Two salts which could be imagined to form are represented by formulas II and III.[6]


I


II


III

In order to enable a choice from among the possible structures for this reaction product, several lines of approach have been followed. The infrared absorption spectrum of the solid material was found to be compatible with either I as zwitterion, or the true salt II. The broad band in the region of 4.2 μ may possibly be associated with vibrations of the N^+–H group, while the band at 6.20 μ may be assigned to the carboxylate anion.[7] The absence of the usual carbonyl absorption near 5.8 μ seems to exclude the presence of formaldehyde as such, and thus rules out III as an accurate representation of the solid.

Valuable chemical evidence was obtained from an experiment in which the acidification of an aqueous solution of the "Mannich base," followed by extraction with ether, led to the obtention of a nearly quantitative yield of *o*-nitromandelic acid. Since earlier work has indicated that the Mannich reaction would not be expected to reverse under these conditions,[3] this result clearly limits the choice to II and III.

Support for this conclusion was obtained in a series of experiments in which the apparent molecular weight of the "Mannich base" was determined by the measurement of freezing point depressions in aqueous solution. The true Mannich base (I) would be expected to show depressions compatible with a molecular weight of 304. In several experiments, however, the molecular weights calculated in the standard fashion from the observed depressions ranged from 104 to 118. Although the activity coefficients for the relevant species are not available, the gross incongruity between the experimental results and those predicted from the Mannich base structure (I) seems sufficiently large to exclude this structure from further consideration. It may thus be concluded that this product is best represented by structure II, and that in aqueous solution it is nearly completely dissociated into the original components from which it is obtained.

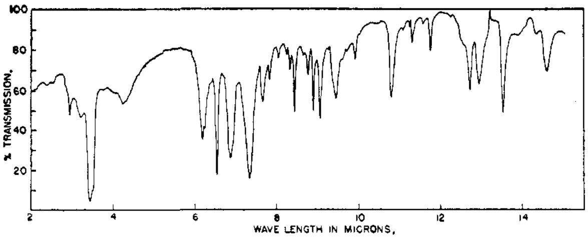


Fig. 1.—Spectrum of a Nujol mull of the abnormal Mannich reaction product as recorded by the Perkin-Elmer model 21 infrared spectrophotometer.

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(1) F. F. Blicke in R. Adams, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 303.

(2) R. Goutarel, M.-M. Janot, V. Prelog and W. I. Taylor, *Helv. Chim. Acta*, **33**, 150 (1950).

(3) E. Alexander and E. Underhill, THIS JOURNAL, **71**, 4014 (1949).

(4) G. F. Grillot and R. I. Bashford, Jr., *ibid.*, **73**, 5598 (1951).

(5) The additional mole of water is required by the analytical data obtained by C. Mannich and L. Stein, *Ber.*, **58**, 2662 (1925).

(6) The distinction between II and III probably has meaning only for the solid compound, since in solution both of these would undoubtedly be interconvertible as the result of simple equilibrium processes.

(7) T. Gaumann and Hs. H. Günthard, *Helv. Chim. Acta*, **35**, 53 (1952).

Experimental

o-Nitromandelic Acid.—A mixture of 7 g. of o-nitromandelonitrile and 110 ml. of concentrated hydrochloric acid was warmed to 70–80° under a reflux condenser for 20 hours. The resultant solution was then concentrated to a volume of 20 ml. under reduced pressure. The o-nitromandelic acid which had separated at this point was removed by filtration and the filtrate extracted twice with 30-ml. portions of ethyl acetate. The product obtained by filtration was dissolved in the ethyl acetate extracts, which were then dried over magnesium sulfate. Concentration and dilution of the hot solution with cyclohexane caused 5.1 g. of o-nitromandelic acid (64.5%), m.p. 137–138°, to be deposited as white crystals on cooling. Grillot and Bashford[4] report an identical melting point for this acid.

Reaction of o-Nitromandelic Acid with Formaldehyde and Piperidine.—This reaction was carried out exactly as described by Grillot and Bashford,[4] in order to ensure the identity of the product with that previously obtained. The once recrystallized material was dried over phosphorus pentoxide at reduced pressure and submitted for analysis, in order to confirm its empirical composition.

Anal. Calcd. for $C_{14}H_{20}O_6N_2$: C, 53.75; H, 6.40; N, 8.89. Found: C, 54.20; H, 6.33; N, 8.84.

The melting point of this product did not seem to be a reliable criterion of purity, since it was found to be strongly dependent on the rate of heating. Thus, using a Fisher melting point block, a high rate of heating caused the crystals to melt to a colorless liquid somewhere between 95–105°, whereas very slow heating resulted in some darkening with melting accompanied by decomposition occurring at 152–154°. It seems clear that the rapid heating gives the true melting point of the compound under consideration, while prolonged heating must result in some chemical change. It is perhaps worth noting in passing that repeated recrystallization led to the loss of some of the formaldehyde, with a resultant shift of the infrared spectrum toward that of piperidinium o-nitromandelate, and a parallel increase in apparent molecular weight.

Acid Treatment and Recovery of o-Nitromandelic Acid.—A 204-mg. sample of twice recrystallized "Mannich base" was dissolved in 5 ml. of water and the solution acidified with 3 drops of concentrated hydrochloric acid. The acidic solution was extracted rapidly with four 5-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate and evaporated. The residue consisted of 125 mg. (94.6%) of o-nitromandelic acid, identified by melting point, mixture melting point and a comparison of its infrared absorption spectrum with that of an authentic sample.

Molecular Weight.—The cryoscopic measurements were made using a cell similar to that described by Billings,[8] but using a Western Electric 14B thermistor[9,10] for measuring temperature instead of a Beckmann thermometer. The thermistor circuit was similar to that used by Zemany[11] but somewhat modified to attain the desired precision. The resistance of the thermistor was measured with a Wheatstone bridge, employing a G.E. Photoelectric Recorder for the galvanometer. The apparatus was calibrated against a platinum resistance thermometer and the slope of the curve (in this case 0.00343° per ohm) used in calculating ΔT. The apparatus and method will be discussed fully in a later paper.

Two runs were made, each time diluting to obtain a second concentration. The material for the two runs was obtained from two separate preparations. The results are given in Table I.

TABLE I

APPARENT MOLECULAR WEIGHT OF "MANNICH BASE"

Run	I	Ia	II	IIa
Wt. sample, g.	0.299	0.299	0.192	0.192
Wt. water, g.	19.9	29.9	19.9	29.9
F.p. water, ohms	6441.5	6441.5	6441.5	6441.5
F.p. solution, ohms	6520.0	6593.5	6487.0	6471.0
$\Delta\Omega$	78.5	52.0	45.5	29.5
Apparent mol. wt.	104	104	115	118

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(8) O. B. Billings, Ph.D. Thesis, Cornell University, 1942.

(9) A thermistor is a ceramic resistor having a 4% change in resistance per degree change in centigrade temperature.

(10) K. P. Dowell, Electrical Manufacturing, August, 1948.

(11) P. D. Zemany, *Anal. Chem.*, **24**, 348 (1952).

The Properties of Nickel Carbide

BY G. MEYER AND F. E. C. SCHEFFER

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Browning and Emmett have published[1] a series of equilibrium measurements of the system Ni–C–H_2 and described some properties of a nickel carbide.[1] In their opinion their results disagree with those mentioned in a recent publication.[2]

In the latter a carbide is described which is exothermic (forms from the elements with evolution of heat). Below 419° this carbide is stable, at 700° it decomposes into its elements.[3] The carbide found by Browning and Emmett has quite different properties being endothermic. This follows from the lines of equilibrium in the diagram log p *versus* $1/T$ for the reaction with carbide and the reaction with carbon. These lines intersect at approximately 510°. Thus their carbide is stable above 510°, below this temperature there will be decomposition in carbon and nickel, the compound being unstable. The foregoing is proved by the free energy calculations made by the authors. For the reaction of formation of nickel carbide they find 7127 cal. at 500°K. and 4655 cal. at 600°K. These values being positive the carbide is metastable at these temperatures. Above approximately 783°K. (510°) the value for the free energy of formation becomes zero, the carbide being stable at higher temperatures. So the experiments of Browning and Emmett prove the existence of another carbide, quite different from the carbide described by us 25 years ago. The chemical composition of each carbide is unknown. Bahr and Bahr[4] propose the formula Ni_3C; from their work it is impossible to say whether the carbide they have obtained is the endothermic or the exothermic compound.

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(1) L. C. Browning and P. H. Emmett, THIS JOURNAL, **74**, 1680 (1952).

(2) F. E. C. Scheffer, T. Dokkum and J. Al, *Rec. trav. chim.*, **45**, 803 (1926).

(3) G. Meyer and F. E. C. Scheffer, *ibid.*, **46**, 1 (1927).

(4) H. A. Bahr and Th. Bahr, *Ber.*, **61**, 2177 (1928).

LABORATORY FOR INORGANIC AND PHYSICAL CHEMISTRY
UNIVERSITY AT DELFT, HOLLAND

11-Oxygenated Steroids. III. The Preparation of 11β-Hydroxy Pregnanes[1]

BY EUGENE P. OLIVETO, TEMPLE CLAYTON AND E. B. HERSHBERG

RECEIVED AUGUST 11, 1952

The reported efficacy[2] of 17α-hydroxycorticosterone (Kendall's Compound F) in certain types of arthritis led us to prepare a series of 11β-hy-

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(1) For the previous paper in this series, *cf.* H. L. Herzog, M. A. Jevnik and E. B. Hershberg, THIS JOURNAL, **75**, 269 (1953).

(2) J. L. Hollander, *J. Am. Med. Assoc.*, **147**, 1629 (1951).