but it seems unlikely that forms of double- and triple-chain-length will transform reversibly one into the other, whether one is alpha and the other sub-alpha or both are sub-alpha as for the rather individualistic OSP which exhibits no alpha at all.

Only 2-oleyl glycerides show intermediate melting forms from the melt—both beta prime-2 and beta prime-3 for POS as compared with sub-beta prime-2 and beta prime-3 for POP and sub-beta-3 for SOS.

It has not been possible up to this time to develop a simple system to account for all the diverse polymorphic behavior of these glycerides.

Because of the considerable degree of individuality it should be possible to use the information now available to establish in many cases the identity of predominant oleyl-disaturated glycerides in such fats as lard, cacao butter and tallow, for example.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SYRACUSE UNIVERSITY]

The Mannich Reaction Involving Optically Active Substituted Mandelic Acids and Nitroalkanes[1,2]

BY GERALD F. GRILLOT AND RAYMOND I. BASHFORD, JR.[3]

The reaction of d- and l-o-nitromandelic acids with formaldehyde and piperidine gave Mannich bases as products whose rotations were higher than the rotation of the starting optically active mandelic acids. These results contradict the suggestion of Alexander and Underhill that enolization is a step in the mechanism that they suggested applied to the Mannich condensation of compounds having a methynyl group on a carboxyl group. The reaction of d-2-nitrobutane with formaldehyde and isopropylamine gave a Mannich base with but a slight rotation. The best explanation of this observation is that although the isopropylamine catalyzes the rapid racemization of much of the d-2-nitrobutane before the Mannich reaction occurs, some small amount does react in the unracemized state to give an optically active Mannich base.

On the basis of the fact that acetophenone will undergo the Mannich reaction, while the somewhat hindered α-methylbutyrophenone did not undergo this reaction, we are suggesting an S_N2 mechanism for the Mannich reaction rather than an ionization followed by a rapid union of the resulting carbanion with the alkylaminomethyl group.

This paper reports the results of a study of the stereochemical changes involved in the Mannich reaction when the reactive hydrogen of one of the reactants is attached to an asymmetric carbon atom. The cases examined are the condensation of d- and l-o-nitromandelic acids with formaldehyde and piperidine and of d-2-nitrobutane with formaldehyde and isopropylamine. The latter condensation using d,l-2-nitrobutane has previously been studied by Johnson.[4]

The condensation of d-o-nitromandelic acid $[\alpha]^{22}D$ +346° with formaldehyde and piperidine gave an optically active Mannich base with a rotation of $[\alpha]^{20}D$ +439°, while the l- acid, $[\alpha]^{20}D$ −320°, gave an isomer with a rotation of $[\alpha]^{20}D$ −449°. An equimolar mixture of these two Mannich bases gave a product that was identical with that obtained from d,l-o-nitromandelic acid.

If it is true that enolization involving an asymmetric center causes racemization, it is difficult to postulate an enolization step in the Mannich reaction involving o-nitromandelic acid with formaldehyde and piperidine. These results contradict the generalized statement made by Alexander and Underhill[5] that their mechanism (which involved an enolization) should hold for all compounds having a methynyl group.

It was hoped that rate studies on the reaction of d- and l-o-nitromandelic acid with formaldehyde

and piperidine could be made by observing the change of rotation as the reaction proceeded. However, the reaction occurs so rapidly that this project had to be abandoned.

The condensation of d-2-nitrobutane, $[\alpha]^{20}D$ +5.07°, with formaldehyde and isopropylamine gave a Mannich base with an observed rotation of +0.03 ± 0.02°.

It was at first inferred that the Mannich reaction involving d-2-nitrobutane, formaldehyde and isopropylamine produced complete racemization. However, the observed rotation 0.03 ± 0.02° is too large to assume experimental error from a zero reading. It was then called to our attention that very small amounts of piperidine produce a rapid mutarotation of nitrocamphor.[6] Lowry and Magson suspected that this was due to a change from the nitro to the aci-nitro isomer, but Bell and Sherred postulate that this involves a change to a diastereoisomer. Since isopropylamine should be about as basic as piperidine, we have reinterpreted our data to indicate that two simultaneous reactions are occurring. The first involves a very rapid racemization of the d-2-nitrobutane by the isopropylamine to give the dl-2-nitrobutane which then reacts with the isopropylaminomethanol to give the racemic Mannich base. A second and very much slower reaction involves the condensation of d-2-nitrobutane with isopropylaminomethanol to give an optically active Mannich base. The latter is responsible for the small rotation that we observed in the resulting product.

The yield study was made to determine optimum

(1) Taken from the Ph.D. Dissertation of Raymond I. Bashford, Jr., Syracuse University, 1950.

(2) Presented before the Organic Division of the A.C.S., Chicago Meeting, September 6, 1950.

(3) Syracuse University Fellow 1948-1949; Allied Chemical and Dye Fellow, 1949-1950.

(4) H. Johnson, THIS JOURNAL, **68**, 12 (1946).

(5) E. Alexander and E. Underhill, ibid., **71**, 4014 (1949).

(6) Lowry and Magson, J. Chem. Soc., **93**, 107 (1908); Taylor and Baker, Sidgwick's "The Organic Chemistry of Nitrogen," Oxford Press, 1945, p. 234; Bell and Sherred, J. Chem. Soc., 1202 (1940).

pH conditions for the condensation reaction of 2-nitrobutane with formaldehyde and isopropylamine. The mechanism of the reaction using 2-nitropropane should be essentially the same as the mechanism that applies to the 2-nitrobutane.

The ionization of a hydrogen atom from the methynyl group followed by the very rapid introduction of the alkylaminomethyl group before the resulting carbanion can assume a planar structure may explain the retention of activity by the Mannich bases. However, although we do not have sufficient evidence to make a definite pronouncement, we suggest that the Mannich reaction involves an S_N2 mechanism and if the carbon containing the active hydrogen replaced is asymmetric a Walden inversion will occur. Although acetophenone undergoes the Mannich reaction, the fact that we were unable to effect a reaction with α-methylbutyrophenone gives some support to the conjecture that in this compound, steric hindrance prevents the approach of an entering group from the opposite side of the hydrogen atom. Further Snyder and Brewster[7] found that isobutyrophenone would enter into this reaction only when very vigorous conditions were used and then in a yield of only 19%. We are planning some new studies that will further test these suggestions that the Mannich reaction involves the S_N2 type of mechanism.

Experimental

I. o-Nitromandelic Acid. o-Nitrobenzaldehyde.—This compound was obtained in a yield of 18% by the method of Tsang, Wood and Johnson.[8]

o-Nitromandelonitrile.—A procedure described by Heller and Fritsch[9] for the conversion of p-nitrobenzaldehyde to p-nitromandelonitrile was employed in the preparation of the ortho isomer. The 40 g. of crude material obtained gave, after recrystallization from benzene, 35 g. of o-nitromandelonitrile (m.p. 93–95°) in a yield of 84%. Melting point obtained by Heller and Amberger[10] was 95°.

o-Nitromandelic Acid.—A mixture of 35 g. (0.2 mole) of o-nitromandelonitrile and 560 ml. of concentrated hydrochloric acid, was heated for 24 hours at 70–80°, at the end of which time the solution was evaporated to dryness under slightly reduced pressure. The solid residue was dissolved in 75 ml. of acetone, heated to boiling and decolorized with activated charcoal. After filtration the acetone solution was evaporated to a sirupy consistency and hot chloroform was added with stirring until a cloudiness appeared. This cloudy solution was cooled in an ice-bath, and the solid was filtered and air-dried. There was obtained 14 g. of o-nitromandelic acid (m.p. 137–138°) which represented a yield of 36.2% of the theoretical. Engler and Zielke[11] obtained a melting point of 140° for this acid.

d- and l-o-Nitromandelic Acid.—The procedure described by McKenzie and Stewart[12] for the resolution of this compound was followed.

There was obtained d-o-nitromandelic acid $[\alpha]^{20}$D +346°, ethanol (m.p. 100–101°) and l-o-nitromandelic acid $[\alpha]^{20}$D −320°, ethanol.

Mannich Reaction of d- and l-o-Nitromandelic Acid with Formaldehyde and Piperidine.[13]—To 1.0 g. of d-o-nitromandelic acid $[\alpha]^{20}$D +346° was added 2 ml. of water in which the solid dissolved after very gentle warming. Piperidine was added to this solution drop by drop until the mixture was just alkaline to litmus paper. During this addition the piperidine salt separated from solution. Upon the addition

of 0.5 ml. of formalin with stirring, the solid material redissolved. After standing for one hour at room temperature, the solid material which crystallized from solution while standing was filtered and twice recrystallized from small quantities of hot water. There was obtained 0.4 g. of the d-Mannich base, m.p. 154–161° (with decomposition), $[\alpha]^{20}$D +439° (ethanol). A similar reaction with l-o-nitromandelic acid, $[\alpha]^{20}$D −320°, gave the corresponding l-Mannich base, $[\alpha]^{20}$D −449°, m.p. 154–157° (with decomposition).

Formation of the Racemate of the Mannich Bases by Mixing the Optically Active Antipodes.—A solution of 0.145 g. of the Mannich base of d-o-nitromandelic acid (+439°) and 0.150 g. of the Mannich base of l-o-nitromandelic acid (−449°) in a few ml. of warm water, when concentrated to incipient crystallization and then chilled, yielded the racemate, which after two crystallizations from water melted at 107–108° and had a zero rotation. The racemate gave no depression of the melting point when mixed with the racemate prepared from d,l-o-nitromandelic acid.

Attempted Kinetic Studies of the Reaction between d-o-Nitromandelic Acid, Formaldehyde and Piperidine.—Reactions run in a polarimeter tube were performed with the hope of observing the rate of change of rotation with time as the reaction progressed. It was observed that the reaction occurred too rapidly to be of any value in a kinetic study. The results of reactions run at 1° were virtually identical with the results obtained at 20°. Changes in pH also had no observable effect on the rate as long as the medium was alkaline. Reactions were performed at pH values of 7.2, 8.5 and 9.3 without any noticeable variation in the rate, while when the reaction was attempted at a pH of 3.1 (piperidine hydrochloride), it failed to occur.

II. 2-Nitrobutane.—The synthesis of d-2-nitrobutane described by Kuhn and Albrecht[14] and modified by Kornblum[15] Patton and Nordmann was followed as closely as possible. There was obtained 3.5 g. of d-2-nitrobutane, $[\alpha]^{20}$D +5.07°.

Mannich Reaction of d-2-Nitrobutane with Formaldehyde and Isopropylamine.—This reaction was conducted similarly to the reaction performed by Johnson,[4] who used the racemic nitro-alkane. Using 3.5 g. of d-2-nitrobutane, there was obtained after fractional distillation approximately 1 g. of the Mannich base whose observed rotation was +0.03 ± 0.02°.

Yield Studies with Variations in pH for the Reaction of 2-Nitropropane with Formaldehyde and Isopropylamine.[16]—In a 200-ml. flask was placed 30 g. (0.5 mole) of isopropylamine. The flask was immersed in a running water-bath whose temperature was 15°. To the flask was added 42 ml. of formalin at such a rate that the temperature of the mixture never exceeded 25°. After the addition of the formalin, the mixture was stirred without further cooling for five minutes. To the mixture was then added 50 ml. of water and 45 g. (0.5 mole) of 2-nitropropane, and the mixture was stirred for one minute. The pH of this mixture was 9.6. The mixture was stirred one hour at room temperature, at the end of which time the pH had not changed. Ten grams of sodium sulfate was then added and the stirring was continued for two minutes. The upper oily layer was separated, dried over magnesium sulfate, filtered and distilled, yielding considerable low boiling material and then the Mannich base (5.5 g., 6.8%) of b.p. 82–84° (10 mm.).

Using exactly the same procedure, three experiments were performed using buffer solutions of such pH range that the reaction medium after the addition of the 2-nitropropane had pH values of 7.4, 5.8 and 11.3, respectively. The results are summarized in Table I.

TABLE I

Expt.	Mole of reag.	pH	Product, g.	Yield, %
1	0.5	5.8	0.2	Less than 1
2	.5	7.4	1.4	1.7
3	.5	9.6	5.5	6.8
4	.5	11.3	1.7	2.1

(7) Snyder and Brewster, THIS JOURNAL, 71, 1061 (1949).

(8) S. Tsang, E. Wood and J. Johnson, Org. Syntheses, 24, 75 (1944).

(9) G. Heller and O. Fritsch, Ber., 46, 285 (1913).

(10) G. Heller and K. Amberger, ibid., 37, 948 (1904).

(11) C. Engler and O. Zielke, ibid., 22, 207 (1889).

(12) A. McKenzie and P. Stewart, J. Chem. Soc., 104 (1935).

(13) Mannich and Stein, Ber., 58, 2662 (1925).

(14) R. Kuhn and H. Albrecht, ibid., 60, 1297 (1927).

(15) N. Kornblum, J. Patton and J. Nordmann, THIS JOURNAL, 70, 746 (1948).

(16) The conduct of 2-nitropropane in a Mannich condensation should be similar to that for 2-nitrobutane. The 2-nitropropane was used instead of 2-nitrobutane because of its availability.

III. α-Methylbutyrophenone.—This was synthesized in the following steps: (a) s-butyl bromide by the method of Kamm and Marvel,[17] (b) dl-ethylmethylacetic acid by the carbonation of the Grignard reagent of s-butyl bromide,[18] conversion of this acid to the acid chloride by the method of H. C. Brown,[19] and (c), the preparation of α-methylbutyrophenone in a yield of 65% from the acid chloride using the Friedel–Crafts reaction.

The 2,4-dinitrophenylhydrazone was prepared according to the method described by Shriner and Fuson[20] and melted at 128–129°.

(17) Gilman and Blatt, "Organic Syntheses," Coll. Vol. I, second edition, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 29.

(18) Ibid., p. 361.

(19) H. C. Brown, THIS JOURNAL, 60, 1325 (1938).

(20) Shriner and Fuson, "Identification of Organic Compounds," second ed., John Wiley and Sons, New York, N. Y., 1940, p. 143.

Anal. Calcd. for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30. Found: C, 59.65; H, 5.32.

Attempted Mannich Reactions with α-Methylbutyrophenone. A.—To 21 g. (0.13 mole) of α-methylbutyrophenone was added 9.1 g. (0.13 mole) of piperidine, 10.8 ml. of formalin and 45 ml. of 95% alcohol. The solution was refluxed on a steam-bath for 48 hr. After removal of low boiling materials, the only material recovered was 19.5 g. of α-methylbutyrophenone.

B.—The above experiment was repeated substituting 15.7 g. (0.13 mole) of piperidine hydrochloride for the piperidine. Upon distillation of the reaction mixture, there was recovered 19.0 g. of α-methylbutyrophenone.
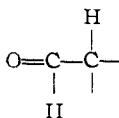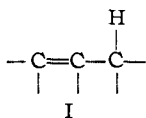

Autoxidation of Ketones. I. Diisopropyl Ketone[1]

BY DEXTER B. SHARP,[2a] LEO W. PATTON,[2a] AND STUART E. WHITCOMB[2b]

Liquid diisopropyl ketone has been oxidized by molecular oxygen in the absence of added inorganic catalysts to the primary oxidation product 2-(2,4-dimethylpentanone-3-yl) hydroperoxide, an α-hydroperoxide of the ketone. Acetone and isobutyric acid were obtained as secondary oxidation products and as decompositio ' products of the hydroperoxide. The progress of an oxidation was followed by chemical analysis. Infrared spectroscopic data were obtained during the oxidations. Mechanisms are suggested for the oxidation process.

Introduction

The susceptibility to attack by molecular oxygen of a position alpha to a carbon–carbon double bond was established when the α-hydroperoxides of cyclohexene,[3] 1-methylcyclohexene[4] and 1,2-dimethylcyclohexene[4] were shown to be primary autoxidation products of these cycloölefins. A similar α-position activation by an aromatic ring system was demonstrated when α-ac-tetralyl hydroperoxide[5] and α,α-dimethylbenzyl hydroperoxide[6] were isolated from the autoxidized hydrocarbons. Farmer[7] has pointed out that the α-position of the olefinic system (I) was the preferential point of attack by

$$
\begin{array}{cc}
\overset{\displaystyle H}{\underset{\displaystyle |}{}} & \overset{\displaystyle H}{\underset{\displaystyle |}{}} \\
-\text{C}=\text{C}-\text{C}- & \text{O}=\text{C}-\text{C}- \\
|\ \ |\ \ | & |\ \ | \\
\text{I} & \text{II}
\end{array}
$$

free radicals. The similarity in bond structure of I and the α-carbon–carbonyl system (II) suggested that the α-positions of ketones also might be susceptible to attack by free radicals, and particularly by oxygen in autoxidative reactions. Two literature reports which substantiated this postulate were those of Jenkins[8] and Paquot.[9] Jenkins did

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(2) (a) Dept. of Chemistry; (b) Dept. of Physics.

(3) R. Criegee, H. Pilz and H. Flygare, Ber., 72, 1799 (1939).

(4) E. H. Farmer and A. Sundralingam, J. Chem. Soc., 121 (1942).

(5) H. Hock and W. Susemihl, Ber., 66, 61 (1933).

(6) H. Hock and S. Lang, ibid., 77B, 257 (1944).

(7) E. H. Farmer, Trans. Faraday Soc., 38, 340, 348, 356 (1942); J. Soc. Chem. Ind., 66, 86 (1947).

(8) S. S. Jenkins, THIS JOURNAL, 57, 2733 (1935).

(9) C. Paquot, Bull. soc. chim., 12, 450 (1945).

not report any subsequent extensions of his results, and Paquot employed catalysts which are known to accelerate autoxidation processes. Fuson and Jackson[10] recently reported the formation of an α-hydroperoxide of β,β-dimesitylpropiophenone by action of molecular oxygen on the ketone. This ketone is similar to those for which Kohler and Thompson[11] earlier reported facile peroxide formation.

In order to follow the progress of oxidation, to detect all products formed and to provide foundations for postulates of mechanisms, a multiple attack upon the problem was employed. Chemical analyses were carried out during the course of autoxidation. Infrared spectroscopic analyses were made during the reaction and such data were compared with the chemical data. Efforts were directed toward complete separation and unequivocal identification of the final products. Inorganic oxidation catalysts were excluded insofar as possible from the reaction mixtures in order to minimize acceleration or other effects which might alter the reaction or destroy sensitive intermediate products. This paper reports the results obtained in the study of the autoxidation of diisopropyl ketone (III).

Experimental

Apparatus.—The oxidations were conducted in the all-glass apparatus constructed according to the diagram shown in Fig. 1. A Chromel ribbon-wound Pyrex tube and outer Pyrex jacket (F) were concentric with the inner Pyrex oxidation chamber (E) (20 mm. i.d.). This chamber (E) was fused to a sintered disk (D) which dispersed the oxygen entering at (A) through stopcock (C). Final reaction mixtures were drained through the opening at (B). A condenser (G) and Dry Ice-cooled trap (H) were connected in series at the top of the apparatus. The sample withdrawal unit

(10) R. C. Fuson and H. L. Jackson, THIS JOURNAL, 72, 1637 (1950).

(11) E. P. Kohler and R. B. Thompson, ibid., 59, 887 (1937).