Attempted Preparation of *exo-syn*-Bicyclo[3.2.1]octyl-2,8-*p*-nitrobenzylidine Acetal.—To a solution of 0.220 g. (1.45 mmoles) of *p*-nitrobenzaldehyde in 2.5 ml. of dry benzene was added 0.200 g. (1.40 mmoles) of diol **6a** and a catalytic amount of *p*-toluenesulfonic acid. The solution was heated at reflux for 8 hr., and then the solvent was removed *in vacuo*. The resulting yellow semicrystalline mass was triturated with ether until most of the yellow color was removed. The residual solid was recrystallized from ethanol–ether, affording 0.175 g. (88%) of starting diol **6a**, m.p. 265–268°.

The Mannich Reaction with 2-Methylcyclopentanone and 2-Methylcyclohexanone[1a]

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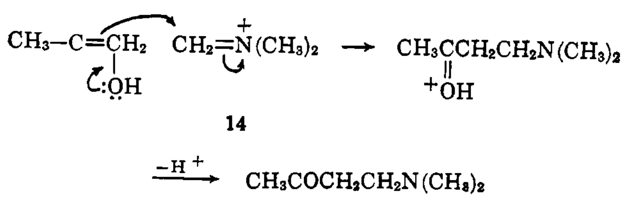
Received November 19, 1963

The Mannich reaction of dimethylamine and formaldehyde with 2-methylcyclopentanone yields 2-dimethylaminomethyl-2-methylcyclopentanone (**15**). The corresponding reaction with 2-methylcyclohexanone yields a mixture of structurally isomeric amino ketones **5** and **16** in which 2-dimethylaminomethyl-2-methylcyclohexanone (**16**) is the predominant product. These orientations are contrary to what has previously been reported for the Mannich condensation with these ketones.

As part of a study of the Michael reaction we wished to prepare an authentic sample of 2-(2-carboxyethyl)-5-methylcyclopentanone (**12**) and elected to follow a synthetic path (see Chart I) analogous to that previously employed[2] for the corresponding cyclohexanone derivative **13**. Both of these preparative procedures were intended to make use of the reported[3] Mannich condensations of 2-methylcyclopentanone (**1**) and 2-methylcyclohexanone (**2**) at the less highly substituted position to form Mannich bases **4** and **6**. Although the reported orientation in these two Mannich condensations has been widely accepted as correct,[2,4] the current view that Mannich reactions in slightly acidic media involve an electrophilic attack of an imminium salt such as **14** on the enol form of the ketone[5] is difficult to reconcile with the reported[3] orientation since the



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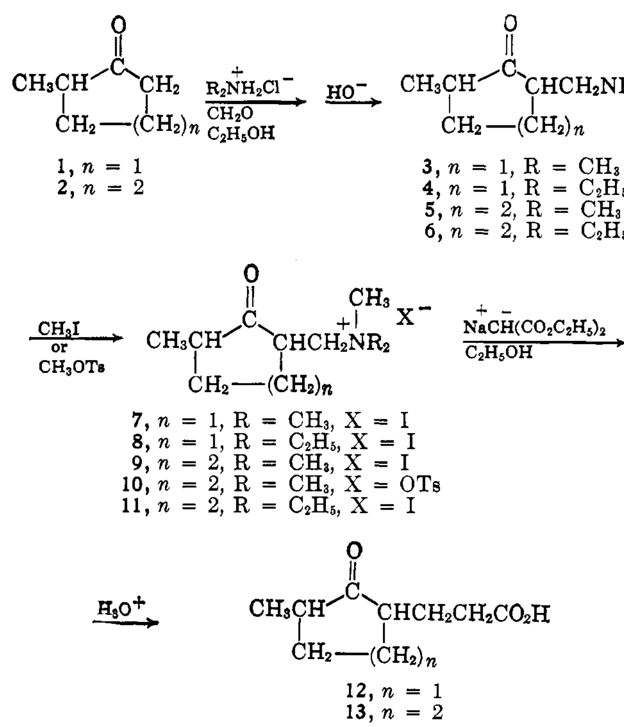
more highly substituted enols of 2-methylcyclopentanone and 2-methylcyclohexanone are expected to be the more stable.[6]

Our initial attempt to prepare acid **12** utilized the previously described[3] Mannich base derived from 2-methylcyclopentanone (**1**), diethylamine hydrochloride, and formaldehyde. Neither the previous investigators nor we were able to obtain the base (reported to be **4**) or its methiodide (reported to be **8**) as crystalline solids. From the reaction of this crude methiodide with diethyl sodiomalonate as previously described,[2] we were unable to isolate any of the desired keto acid

CHART I



1, $n = 1$
2, $n = 2$

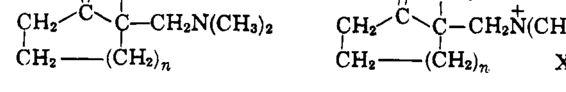
3, $n = 1$, R = CH_3
4, $n = 1$, R = C_2H_5
5, $n = 2$, R = CH_3
6, $n = 2$, R = C_2H_5

7, $n = 1$, R = CH_3, X = I
8, $n = 1$, R = C_2H_5, X = I
9, $n = 2$, R = CH_3, X = I
10, $n = 2$, R = CH_3, X = OTs
11, $n = 2$, R = C_2H_5, X = I

12, $n = 1$
13, $n = 2$

12, only a small amount of methylmalonic acid being recovered.

The Mannich reaction was, therefore, repeated with dimethylamine hydrobromide to form a Mannich base which readily yielded a crystalline methiodide in an over-all yield of 89%. However, the n.m.r. spectrum (see Experimental) of this crystalline product left no doubt that it was not the methiodide **7** but rather had structure **17**. The n.m.r. spectrum of the original



15, $n = 1$
16, $n = 2$

17, $n = 1$, X = I
18, $n = 2$, X = I
19, $n = 2$, X = TsO

Mannich base indicated that at least 80% of this material had structure **15** and not **3**. Thus, our earlier failure to prepare the keto acid **12** was not surprising.

(1) (a) This research has been supported in part by Grant No. RG-8761 from the National Institutes of Health; (b) National Science Foundation Predoctoral Fellow, 1963–1964.

(2) (a) R. L. Frank and R. C. Pierle, *J. Am. Chem. Soc.*, **73**, 724 (1951); (b) H. O. House and M. Schellenbaum, *J. Org. Chem.*, **28**, 34 (1963).

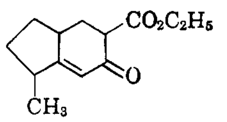
(3) E. C. duFeu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937).

(4) (a) F. F. Blicke, *Org. Reactions*, **1**, 303 (1942); (b) B. Reichert, "Die Mannich Reaktion," Springer-Verlag, Berlin, 1959; (c) R. Jacquier, M. Mousseron, and S. Boyer, *Bull. soc. chim. France*, 1653 (1956).

(5) (a) H. Hellmann and G. Opitz, *Angew. Chem.*, **68**, 265 (1956); (b) T. F. Cummings and J. R. Shelton, *J. Org. Chem.*, **25**, 419 (1960).

(6) H. O. House and V. Kramar, *ibid.*, **28**, 3362 (1963).

The previous experimental data[3] which had led to the assignment of structure **4** to the Mannich condensation product consisted of the conversion of the crude methiodide (reported to be **8**) to a liquid product, thought to be **20**, in 18% yield. Further transformation



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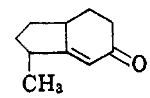

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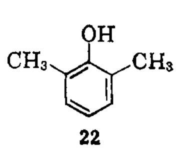
of this liquid product led to a mixture of materials from which a crystalline semicarbazone and a crystalline 2,4-dinitrophenylhydrazone were isolated in unstated yield. These crystalline materials were believed to be derivatives of the unsaturated ketone **21**. Thus, even if one accepts the fact that the liquid product was pure and had structure **20**, these earlier data require that 18% of the Mannich base have the assigned structure **4**.

This finding made the corresponding report[3] that the Mannich condensation of methylcyclohexanone (**2**) with diethylamine and formaldehyde yields **6** open to suspicion in spite of the fact that this report has been accepted by others.[2,4] Repetition of this reaction with dimethylamine hydrochloride produced, in 58% yield, a Mannich base whose n.m.r. spectrum (see Experimental) indicates the presence of approximately 30% of the Mannich base **5** and 70% of the Mannich base **16**. In previous studies[2] the crude methiodide or methotosylate of this Mannich base had been used for the preparation of keto acid **13**; the yield of the crude ester (a mixture of the ethyl ester of keto acid **13** and the corresponding malonic ester) corresponded to a yield of less than 42%.[2a] Partial separation of the mixture of methiodides obtained from the Mannich base afforded fractions, m.p. 190–192° dec. and 160–163° dec., which were thought[2b] to be the crude diastereoisomers of structure **9**. We have now measured the n.m.r. spectra of these samples and find the fraction, m.p. 190–192° dec., to be the pure methiodide **18** while the fraction, m.p. 160–163° dec., is a mixture of methiodide **9** and **18**. The crude Mannich base from 2-methylcyclohexanone (**2**) had also been converted[2b] to a mixture of crude methotosylates from which a small sample of a pure isomer, m.p. 141–142°, thought to be one of the diastereoisomers of structure **10** was isolated. The n.m.r. spectrum (see Experimental) of this material has established that this sample has structure **19**.

The experimental evidence[3] which had previously led to the assignments of structures **6** and **11** to the Mannich base and the corresponding methiodide derived from 2-methylcyclohexanone (**2**) consisted of the conversion of the crude Mannich base to 2,6-dimethylphenol (**22**) in unstated yield and the conversion of the crude methiodide to a liquid product, assigned structure



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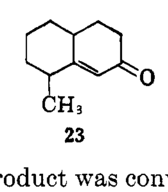

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23, in 60% yield. This liquid product was converted to several crystalline derivatives, but again no yields were stated. Consequently, no data permitting a reliable estimate of the homogeneity of this initial liquid product **23** are available.

Since the mechanism of the Mannich reaction has been suggested[5b] to change for reactions carried out in neutral or basic solution rather than the usual acidic conditions, we have also examined the reaction of 2-methylcyclohexanone with formaldehyde and free dimethylamine. The n.m.r. spectrum of the resulting Mannich base indicates the presence of about 65% of **16** and 35% of **5**. Thus, at least for ketone **2**, the proportion of structurally isomeric bases obtained in the Mannich reaction do not differ appreciably when the free amine is employed rather than the amine hydrochloride.

Consequently, we conclude that both 2-methylcyclohexanone (**2**) and 2-methylcyclopentanone (**1**) undergo predominant Mannich condensation at the most highly substituted position, contrary to previous claims in the literature, but in accord with the result to be expected on mechanistic grounds. It is also appropriate to note that 3-methyl-2-butanone (**24**), contrary to an

$$\underset{\mathbf{24}}{CH_3COCH(CH_3)_2} \xrightarrow[\substack{CH_2O \\ C_2H_5OH}]{(CH_3)_2\overset{+}{N}H_2\overset{-}{Cl}} \xrightarrow{OH^-} \underset{\mathbf{25}}{CH_3COC(CH_3)_2CH_2N(CH_3)_2}$$

earlier report,[4c] has also been found[7] to yield primarily, if not exclusively, the more highly substituted Mannich base **25**. These results suggest that certain previous reports[4] that Mannich reactions with unsymmetrical ketones occur at the less highly substituted position should be viewed with suspicion until rigorous structural evidence is provided.

Experimental[8]

Mannich Reaction of 2-Methylcyclopentanone (**1**).—A mixture of 7.89 g. (0.0805 mole) of 2-methylcyclopentanone, 3.22 g. (0.107 mole of formaldehyde) of paraformaldehyde, 10.00 g. (0.0795 mole) of dimethylamine hydrobromide, and 5 ml. of ethanol was heated on a steam bath overnight and then cooled. The resulting semisolid mixture was made basic by the addition of cold (0°) aqueous sodium hydroxide and then extracted with ether. After the ethereal solution had been dried and concentrated, 11.12 g. (90%) of the crude Mannich base **15** remained as a yellow liquid. To a solution of 9.72 g. (0.063 mole) of this crude amino ketone in 50 ml. of benzene was added, dropwise and with stirring, 9.50 g. (0.067 mole) of methyl iodide. After the resulting mixture had been allowed to stand in the refrigerator for 3 days, the crude methiodide **17** was collected and recrystallized from an ethanol–petroleum ether mixture to separate 18.2 g. (89% based on the starting dimethylamine) of the pure methiodide **17** as white needles, m.p. 196–196.5° dec. The product has infrared absorption[9] at 1730 cm.$^{-1}$ (cyclopentanone C=O) and n.m.r.[10] singlets at δ 3.74 (2H, CCH_2N^+), 3.36 (9H, CH_3N^+), and 1.30 (3H, CH_3C), as well as complex absorption attributable to three methylene groups in the region δ 2.1–3.1.

Anal. Calcd. for $C_{10}H_{20}INO$: C, 40.40; H, 6.79; I, 42.73. Found: C, 40.25; H, 6.72; I, 42.74.

(7) M. Brown and W. S. Johnson, *J. Org. Chem.*, **27**, 4706 (1962).

(8) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with either a Baird, Model B, or a Perkin-Elmer, Model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The n.m.r. spectra were determined at 60 Mc. with a Varian, Model A-60, n.m.r. spectrometer. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(9) Determined as a suspension in a potassium bromide pellet.

(10) Determined as a solution in deuterium oxide.

From a comparable reaction employing 3.99 g. (0.041 mole) of 2-methylcyclopentanone, 1.61 g. (0.054 mole of formaldehyde) of paraformaldehyde, 5.00 g. (0.040 mole) of dimethylamine hydrobromide, and 5 ml. of ethanol, distillation of the crude basic product separated 4.5 g. (73%) of the Mannich base **15**, b.p. 43–45° (0.3 mm.), $n^{23}D$ 1.4562. The mass spectrum of the product exhibits a molecular ion peak at *m/e* 155; the sample has infrared absorption[11] at 1730 cm.$^{-1}$ (cyclopentanone C═O). The n.m.r. spectrum[11] of this sample has a singlet at δ 2.13 (NCH_3) superimposed on a complex series of peaks in the region δ 1.5–2.5 and a singlet at δ 0.83 (CH_3C). A broadening at the base of the last mentioned singlet and several very small peaks in the region of δ 0.9–1.2 suggests that the major product **15** may be contaminated by a small amount (less than 20%) of one or both of the stereoisomeric Mannich bases **3**, containing a CH_3CH< function, whose n.m.r. C-methyl signals could appear as a pair of doublets. A solution of the Mannich base **15** in deuterium oxide containing 20% deuterium chloride exhibited n.m.r. peaks at δ 3.39 (2H singlet, CCH_2N^+D<) and 1.22 (3H singlet, CH_3C) with complex absorption in the region δ 1.6–2.8 and two peaks at δ 2.92 and 2.98 (6H, CH_3N^+D<). The presence of two peaks for the N-methyl signal in the salt suggests that the dimethylammonium grouping exists in a preferred conformation with respect to the asymmetric C-2 position of the cyclopentanone ring. As was the case for the n.m.r. spectrum of free base **15**, the n.m.r. singlet at δ 1.22 attributable to the C-methyl group has a slight broadening at the base suggesting the presence of a small amount of the salt of either one or both of the amino ketones **3**.

Mannich Reaction of 2-Methylcyclohexanone (2). A. With Dimethylamine Hydrochloride.—A mixture of 9.0 g. (0.080 mole) of 2-methylcyclohexanone, 3.42 g. of an aqueous solution containing 37% (0.040 mole) of formaldehyde, and 3.26 g. (0.040 mole) of dimethylamine hydrochloride was refluxed for 15 min. and then diluted with water and saturated with sodium chloride. After the resulting mixture had been extracted with ether, it was made basic with potassium hydroxide and extracted with ether. The resulting basic extract was dried, concentrated, and distilled to separate 3.95 g. (59%) of the Mannich base (a mixture of **5** and **16**), b.p. 48–50° (0.15 mm.), $n^{23}D$ 1.4638 [lit. 71° (1.3 mm.),[2a] 62–63° (0.7 mm.),[2b] $n^{20}D$ 1.4650,[2a] $n^{25}D$ 1.4639[2b]]. The mass spectrum of the product exhibits a molecular ion peak at *m/e* 169; the material has infrared absorption[11] at 1710 cm.$^{-1}$ (C═O). The n.m.r. spectrum of a solution of this Mannich base in deuterium oxide containing 20% deuterium chloride exhibits, apart from complex absorption in the region δ 1.7–2.7, a singlet at δ 3.33 CCH_2N^+D), a singlet at δ 2.98 (CH_3N^+D), and a singlet at δ 1.39 (CH_3C) attributable to the salt of the amino ketone **16**. In addition there is a small peak at δ 2.87 (CH_3N^+D<) and two doublets centered at δ 0.98 (J = 6.5 c.p.s.) and 1.22 (J = 7 c.p.s.) corresponding to the C-methyl signal from the CH_3CH< grouping in the two stereoisomeric salts derived from the amino ketones **5**. From the relative areas under these C-methyl peaks, we estimate the Mannich base to contain approximately 70% of the amino ketone **16** and 30% of the amino ketones **5**. The n.m.r. spectrum[11] of the free base has single peaks at δ 2.36 (CCH_2N<), 2.13 (CH_3N<), and 0.97 (CH_3C). In the n.m.r. spectrum of the free base, the singlet C-methyl peak at δ 0.97 partially obscures the small C-methyl doublets in the region δ 0.85–1.0.

B. With Dimethylamine.—Into a mixture of 6.0 g. (0.053 mole) of 2-methylcyclohexanone and 2.16 g. of an aqueous solution containing 37% (0.027 mole) of formaldehyde was distilled 1.22 g. (0.027 mole) of dimethylamine. An exothermic reaction occurred as the amine was added. The resulting mixture was refluxed for 10 min. and then cooled, poured into dilute aqueous hydrochloric acid, and extracted with ether. The aqueous layer was made basic with potassium hydroxide and again extracted with ether. After the basic, ethereal extract had been dried and concentrated, distillation of the residue separated 2.7 g. (59%) of the Mannich base (a mixture of **5** and **16**), b.p. 50–52° (0.2 mm.), $n^{26}D$ 1.4645. This sample, which has infrared absorption practically identical with the infrared absorption of the previous sample, has comparable n.m.r. absorption except that the C-methyl doublets are slightly more intense. From the areas under the C-methyl peaks we estimate that the sample contains about 35% of **5** and 65% of **16**.

N.m.r. Spectra of the Quaternary Salts Derived from the Mannich Base of 2-Methylcyclohexanone.—The previously described[2] methiodide, m.p. 190–192°,[2b] exhibits three n.m.r.[12] singlets at δ 3.81 (2H, CCH_2N^+), 3.22 (9H, CH_3N^+), and 1.42 (3H, CH_3C) as well as complex absorption in the region δ 1.7–2.9 and should be assigned structure **18** rather than the previously[2] assigned structure **9**. The methiodide sample, m.p. 160–163°,[2b] is apparently a mixture of approximately equal amounts of **18** and one of the diastereoisomers of structure **9**, since the n.m.r.[12] C-methyl absorption consists of a singlet at δ 1.42 and a doublet (J = 6.5 c.p.s.) centered δ 0.99. The previously described[2b] crude methotosylate, m.p. 120–145°, has C-methyl peaks in the n.m.r.[12] indicating the presence of **19** (about 65%, singlet at δ 1.32) and one of the diastereoisomers of **10** (about 35%, doublet, J = 6.5 c.p.s., centered at δ 0.97). The one pure isomer, m.p. 141–142°,[2b] isolated from the mixture has the structure **19** rather than the previously assigned structure **10**. The n.m.r. spectrum[12] has two doublets (J = 9 c.p.s. for each) centered at δ 7.37 and 7.74 (4H, aryl CH) as well as singlets at δ 3.69 (2H, CCH_2N^+), 3.12 (9H, CH_3N^+), 2.38 (3H, aryl CH_3), and 1.32 (3H, CH_3C), and complex absorption in the region δ 1.5–2.8.

(11) Determined as a solution in carbon tetrachloride.

(12) Determined as a solution in deuterium oxide.

Preparation of Perhydronaphthalene-1,8-dione from 1,4,4aβ,5,8,8aβ-Hexahydronaphthalen-5α-ol-1,4-dione Acetate

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Received July 2, 1963

Perhydro(4aβ,8aβ)naphthalene-1α,4β,5α-triol 5-acetate (**5a**) was prepared by a two-step reduction from 1,4,4aβ,5,8,8aβ-hexahydronaphthalen-5α-ol-1,4-dione acetate (**1**). The triol monoacetate (**5a**) was selectively tosylated in the 1-position and the tosyl group was eliminated with base. The 1,2,3,5,6,7,8,8aβ-octahydronaphthalene-1β,8α-diol (**8**) formed was hydrogenated and then oxidized to perhydronaphthalene-1,8-dione (**10a**). A new synthesis of 2-*n*-butyrylcyclohexanone (**14a**) is described wherein the diketone was prepared from 2-(1-hydroxy-*n*-butyl)cyclohexanone (**11a**). The n.m.r. spectra of these 1,3-diketones indicate that the decalindione (**10a**) is completely enolized in chloroform solution at room temperature, while its flexible monocyclic analog (**14a**) is only 77% enolized. Intermediate between these two values is the enolization (87%) of the bicyclic analog, perhydroindane-1,7-dione (**15a**).

Interest in this laboratory has been focused recently on the preparation of β-diketones which can give rise only to *cis* enols and in which the distance between the carbonyl groups is fixed and determined by the geometry of the molecule. In a previous communication[2] two methods were described for the preparation of a

(1) National Science Foundation Undergraduate Research Participant, 1961-1962.

(2) I. A. Kaye and R. S. Matthews, *J. Org. Chem.*, **28**, 325 (1963).