[Contribution from the Department of Chemistry, Columbia University]

THE REACTION OF 2-METHYLDIHYDRORESORCINOL WITH THE MANNICH BASE FROM METHOXYPROPANONE-2

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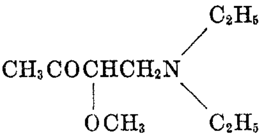
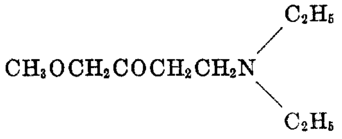
The factors determining the course of the Mannich and the Robinson-Mannich base reactions are not well understood (1, 2). The site of greatest reactivity cannot be predicted on the basis of the anionoid character alone, because methyl ethyl ketone reacts with dimethylamine hydrochloride and formaldehyde on the substituted carbon (3), while 2-methylcyclohexanone affords, with diethylamine hydrochloride and formaldehyde, 2-methyl-6-diethylaminomethylcyclohexanone (4). On the other hand, various *ortho* derivatives of cyclohexanone react exclusively on the substituted carbon in the Robinson-Mannich base reaction (5). With menthone the Mannich reaction is reported (6) to give a mixture of isomers and very likely this is generally the result of the Mannich reaction with simple unsymmetrical ketones.

We have now demonstrated that the reaction of methoxypropanone-2 with diethylamine hydrochloride and formaldehyde gives rise to a mixture of two products, 1-diethylamino-2-methoxybutanone-3 (I) and 1-methoxy-4-diethylaminobutanone-2 (II).



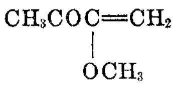
$CH_3COCH(OCH_3)CH_2N(C_2H_5)_2$

I



$CH_3OCH_2COCH_2CH_2N(C_2H_5)_2$

II



$CH_3COC(OCH_3){=}CH_2$

III

It was found that I was present to the extent of at least 61.5%, as shown by subjecting the mixture of I and II as the methiodides to a β-elimination reaction with silver oxide in aqueous methanol. In this way I was converted to 2-methoxybuten-1-one-3 (III) and then hydrolyzed to diacetyl, which was determined as nickel dimethylglyoxime.

The ultraviolet spectrum of III was determined in the crude methanolic reaction solution, and a maximum at 248 mμ was obtained. It would appear, therefore, that the bathochromic shift due to the methoxyl is 38 mμ[2], as compared to methyl vinyl ketone, λ_{max} 210 mμ (7).

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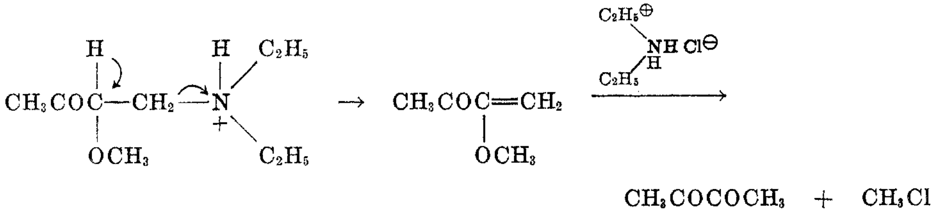
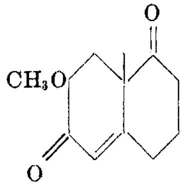
[1] This work was carried out during the tenure of a Syntex fellowship. Present address: The Upjohn Company, Kalamazoo, Michigan.

[2] It is interesting to compare the bathochromic shift caused by the α-hydroxy substituent in a monocyclic α,β-unsaturated ketone system. Thus, it is shown (8, 9) that Δ^2-2-hydroxy-3-methylcyclohexenone absorbs at λ_{max} 268.5 mμ as compared to λ_{max} 235 mμ for Δ^2-3-methylcyclohexenone (10).

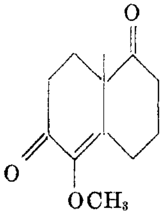
During the Mannich base condensation 6% of methoxypropanone-2 is converted to diacetyl, probably by the following process:



The mixture of I and II was subjected to a Robinson-Mannich base condensation with 2-methyldihydroresorcinol in boiling benzene containing pyridine (11) and afforded a small yield of an oily product along with 63% of recovered starting diketone. The oily product on separation by chromatography yielded Δ^4-2-methoxy-9-methyloctalin-3,8-dione (IV) (m.p. 83–84°, λ_{max} 244 mμ), and Δ^4-4-methoxy-9-methyloctalin-3,8-dione,[3] (V) (m.p. 67°, λ_{max} 258 mμ).



IV



V

The structures of these compounds are assigned on the basis of the ultraviolet and infrared spectra.

Acknowledgment. I wish to thank Professor Gilbert Stork for his interest in this problem.

EXPERIMENTAL

All melting points are uncorrected. Ultraviolet spectra were measured in 95% ethanol with a Cary Recording Spectrophotometer Model II. Infrared spectra were measured in chloroform solution with a Baird Spectrophotometer.

Methoxypropanone-2 (13, 14) was prepared by oxidation of methoxypropanol-2 according to Mariella and Leech. The yield was improved to 50% by increasing the amount of water. Thus, 750 g. of sodium dichromate in 600 ml. of water, 404 g. of methoxypropanol-2, and 490 ml. of concentrated sulfuric acid in 230 ml. of water were used. The addition of acid was accomplished in five hours with ice-cooling. After standing overnight, 200 ml. of water was added and the mixture was extracted as usual.

Mannich-base condensation. The conditions described by Wilds (15) for acetone were used. A mixture of methoxypropanone-2 (85.5 g., 0.97 mole), diethylamine hydrochloride (26 g., 0.237 mole), paraformaldehyde (10 g., 0.332 mole), and 47 ml. of absolute ethanol (dried over magnesium ethoxide) was refluxed for 16 hours. A clear yellow solution resulted and the characteristic odor of diacetyl was very noticeable. The solution was distilled *in*

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[3] Methyl enol ether of an α-diketone is also a characteristic feature of sinomenine, an alkaloid of the morphine group (12).

vacuo on the steam-bath until a suspension (A) appeared in the reaction flask while the clear yellow distillate (B) was collected in a receiver cooled in ice. Then 50 ml. of water was added to the suspension (A), the resulting solution was extracted twice with ether, and the yellowish ethereal extracts were discarded. A solution of 27 g. of potassium hydroxide in 30 ml. of water was added to the cold aqueous layer. The oil which formed was separated and the aqueous layer was extracted four times with ether. The oil was added to the combined ethereal extracts and the resulting solution was washed twice with a saturated sodium chloride solution and dried over sodium sulfate. Distillation at 10 mm. gave a small forerun (2.9 g.) and then the mixture of Mannich bases I and II, b.p. 70–85° (20.5 g.). The residue amounted to 2.6 g. Redistillation of the main fraction afforded 17.5 g. (42.6% yield based on diethylamine hydrochloride), b.p. 75–82° (10 mm.).

Anal. Calc'd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.09; OCH_3, 17.91.
Found: C, 62.51; H, 10.84; N, 8.11; OCH_3, 17.82.

The yellow distillate (B) was fractionated through a glass-helix packed column (17 x 2 cm.) to give: (a) 50 ml., b.p. 65–82° (mainly 78°); (b) 7.3 g., b.p. 82–112°; (c) 43.8 g. of methoxypropanone-2, b.p. 112–114° (51% recovery). The content of diacetyl in the first fraction was determined by the nickel dimethylglyoxime method on a 5-ml. aliquot. The precipitate amounted to 0.880 g., which corresponds to a total of 5.24 g. of diacetyl (6.25% yield based on methoxypropanone-2) in the first fraction. The ultraviolet spectrum of diacetyl (16, 17) was identical with that reported by Holmann, *et al.*

β-Elimination reaction (*cf.* 18). The Mannich base mixture (1.73 g.) was converted to the methiodide with 2 g. of methyl iodide by swirling for one-half hour while cooling in an ice-bath. Then an additional 0.5 ml. of methyl iodide was added, and the mixture was kept in the cold for one half-hour with only occasional swirling. It was then allowed to stand at room temperature for one-half hour, during which time the oily methiodide crystallized. The product was kept *in vacuo* (10 mm.) for 15 minutes, dissolved in 30 ml. of methanol and 7 ml. of water, and stirred vigorously with silver oxide (freshly prepared from 7.5 g. of silver nitrate) for 15 hours. The mixture was filtered and the inorganic precipitate was washed with methanol. The volume of the dark yellow filtrate amounted to 66 ml. One ml. of this solution was diluted to 250 ml. with methanol, and the resulting solution gave λ_{max} 248 mμ (D = 2.25). The nickel dimethylglyoxime obtained using 10 ml. of the above filtrate amounted to 0.134 g. (or 0.528 in 66 ml. of solution). The total content of I in the Mannich-base mixture was, therefore, at least 61.5%.

Robinson-Mannich base condensation. The conditions of Friedmann and Robinson (11) were followed. A mixture of 2-methyldihydroresorcinol (3.8 g., 0.03 mole), dry pyridine (2.54 ml., 0.0315 mole), dry benzene (42 ml.), and the Mannich base mixture (6.25 g., 0.036 mole) was refluxed for 16 hours under anhydrous conditions. The clear yellow solution was then evaporated slowly during a one-half hour period until 12 ml. of distillate was collected. The remaining solution was cooled to room temperature, allowed to crystallize, and the precipitate was washed with benzene to give 2.4 g. of crude 2-methyldihydroresorcinol (m.p. 180–200°, 63% recovery). The filtrate was washed three times with a total of 100 ml. of hydrochloric acid (7.5%), once with water, three times with 30-ml. portions of saturated sodium bicarbonate solution, and then washed three times with water until neutral, dried over sodium sulfate, and evaporated. Distillation at 0.001 mm. afforded 0.7 g. of a pale yellow oil (Bath temp., 140–155°), λ_{max} 253 mμ, ε7900. The oil was dissolved in benzene and chromatographed on 30 g. of acid-washed alumina (Merck). Elution with benzene (100 ml.) gave a trace of oil. An additional 150 ml. of benzene afforded crystals which melted at 66–67° after washing with petroleum-ether (30–60°). Recrystallization from ether-petroleum ether (30–60°) gave V as well defined prisms, m.p. 66–67° (0.06 g.); λ_{max} 258 mμ, ε11,500.

Anal. Calc'd for $C_{12}H_{16}O_3$: C, 69.20; H, 7.75; OCH_3, 14.90.
Found: C, 69.49; H, 7.88; OCH_3 14.73.

The elution was continued with 75 ml. of benzene, 150 ml. of ether-benzene (1:10), 300 ml. of ether-benzene (1:4), and 100 ml. of ether-benzene (1:1). On evaporation these fractions yielded crystalline residues which melted over a range of 66–76°. Further elution with

500 ml. of ether gave crystals, m.p. 75–81°, which on recrystallization from ether-petroleum ether (30–60°) afforded pure IV as prisms, m.p. 83–84° (0.14 g.); λ_{max} 244 mμ, ϵ10,200.

Anal. Calc'd for $C_{12}H_{16}O_3$: C, 69.20; H, 7.75; OCH_3, 14.90.

Found: C, 69.35; H, 7.80; OCH_3, 14.75.

The infrared spectra of IV and V showed typical peaks for saturated and unsaturated carbonyl groups.

SUMMARY

1. It has been shown that methoxypropanone-2 reacts with diethylamine hydrochloride and formaldehyde to give a mixture of two Mannich bases.

2. The condensation of this Mannich base mixture with 2-methyldihydroresorcinol affords two isomers, for which structures are proposed.

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