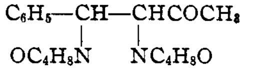
[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

α,β-Unsaturated Aminoketones. III. α- and β-Morpholinobenzalacetones

BY NORMAN H. CROMWELL

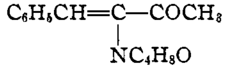
The type of study reported in the second paper in this series[1] with morpholino derivatives of benzalacetophenone has been extended to derivatives of benzalacetone.

Benzalacetone dibromide was found to react rapidly with morpholine to give mainly α,β-dimorpholinobenzalacetone I, with small amounts of α-morpholinobenzalacetone II.



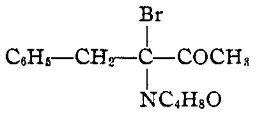
$C_6H_5-\underset{OC_4H_8N}{\underset{|}{CH}}-\underset{NC_4H_8O}{\underset{|}{CH}}COCH_3$

I



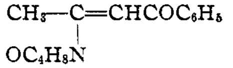
$C_6H_5CH{=}\underset{NC_4H_8O}{\underset{|}{C}}-COCH_3$

II



$C_6H_5-CH_2-\overset{Br}{\overset{|}{\underset{NC_4H_8O}{\underset{|}{C}}}}-COCH_3$

III



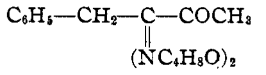
$CH_3-\underset{OC_4H_8N}{\underset{|}{C}}{=}CHCOC_6H_5$

IV

Under special conditions α-bromobenzalacetone reacted with morpholine to give α-bromo-α-morpholinobenzylacetone III. Compound III reacted slowly with morpholine to give mainly I and traces of II. When III was treated with sodium ethoxide a good yield of the light yellow compound II resulted. Compound II could not be made to add a second molecule of morpholine to give I.[1]

The structure of II was shown by its acid hydrolysis to benzyl methyl diketone. The structure of III is apparent from its properties and method of formation.

The hydrolysis of I was not clean-cut. About equal amounts of benzaldehyde and benzyl methyl diketone resulted, but it was not possible to identify ω-morpholinoacetone in the reaction mixture.[1] This may have been due to the probable water solubility of such a product.[2] Structure I should give these products, but structure A would be expected to give only benzyl methyl diketone on hydrolysis.[1]

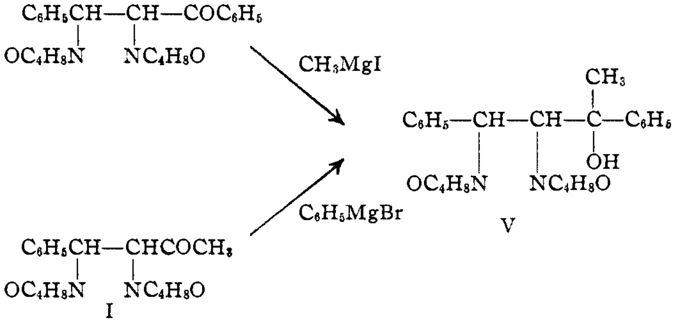


$C_6H_5-CH_2-\underset{(NC_4H_8O)_2}{\underset{\|}{C}}-COCH_3$

A

The diamino ketone I was found to react readily with phenylmagnesium bromide to give carbinol V. Carbinol V was also obtained in small amounts by treating α,β-dimorpholinobenzalacetophenone[1] with methylmagnesium iodide. Both of these additions, particularly the latter, seem to be accompanied by considerable cleavage reactions. A detailed study of the reaction of Grignard reagents with compounds of type I is being undertaken.

Carbinol V was a very stable substance, resisting hydrolysis even on long boiling with dilute acid or alcoholic–alkali solutions. Oxidation experiments with carbinol V gave only acetophenone and small amounts of unidentified substances. The study of these carbinols is also being continued, although only complicated mixtures are to be expected from the amino end of the chain in V, on oxidative cleavage. These experiments further substantiate structure I.



$C_6H_5CH-\underset{OC_4H_8N\ \ NC_4H_8O}{CH-COC_6H_5} \xrightarrow{CH_3MgI} C_6H_5-\underset{OC_4H_8N}{\underset{|}{CH}}-\underset{NC_4H_8O}{\underset{|}{CH}}-\overset{CH_3}{\overset{|}{\underset{OH}{\underset{|}{C}}}}-C_6H_5 \xleftarrow{C_6H_5MgBr} C_6H_5\underset{OC_4H_8N}{\underset{|}{CH}}-\underset{NC_4H_8O}{\underset{|}{CH}}COCH_3$

V

I

It is to be noted that compounds containing the structure $\underset{|}{-N}-\overset{|}{\underset{|}{C}}-\underset{|}{N-}$ are readily hydrolyzed to the carbonyl compounds, $-\underset{\underset{O}{\|}}{C}-$.[3] Thus it seems improbable that either the ketone I or carbinol V, contain the grouping, $\underset{|}{-N}-\overset{|}{\underset{|}{C}}-\underset{|}{N-}$. The formation of I and II from benzalacetone dibromide seems to proceed by the mechanisms outlined in the second paper in this series.[1]

1-Phenyl-3-morpholinobutene-2-one-1, IV, was prepared from benzoylacetone and morpholine in the usual way.

The study of the reactions of 1,2-dibromoketones and of the corresponding α-bromo-α,β-unsatu-

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[1] Cromwell, THIS JOURNAL, **62**, 2897 (1940).

[2] Note properties of ω-piperidinoacetone as described by Stoermer, *Ber.*, **28**, 1250 (1895).

[3] Craig, THIS JOURNAL, **55**, 3723 (1933); Graymore, *J. Chem. Soc.*, 1311 (1938).

rated ketones with various amines is being continued.

Experimental[4]

Benzalacetone Dibromide.[5]—A solution of 50 g. of benzalacetone dissolved in 125 ml. of carbon tetrachloride was cooled to 10° and treated dropwise with 54.8 g. of bromine in 15 ml. of carbon tetrachloride. The mixture was stirred vigorously during the addition of the bromine solution.

The white precipitate was filtered off and washed twice with warm dilute alcohol (70 ml. of 75% solution), and dried *in vacuo*, 74 g., m. p. 114–116°. Recrystallization from boiling methanol (500 ml.) gave white needles (69 g.) of m. p. 124–126°.[6]

α-Bromobenzalacetone.[5]—This unsaturated bromo ketone was prepared in a manner similar to that used to prepare α-bromobenzalacetophenone.[1] Benzalacetone dibromide (50 g., 0.163 mole) was heated (four hours) under reflux with sodium acetate (15 g., 0.183 mole) in an alcohol solution (125 ml., 95%). The solvent was evaporated under reduced pressure and the residue taken up in dry ether. The precipitated sodium bromide was filtered off and the ether solution washed several times with water and dried over anhydrous sodium sulfate. The product (29 g.) was a light yellow oil, b. p. 119–121° (1 mm.).[7,8]

Reaction of Benzalacetone Dibromide with Morpholine.—To an absolute ethyl alcohol (40 ml.) suspension of benzalacetone dibromide (10.0 g.), morpholine (11.3 g., a three mole excess) was added slowly (two minutes) with stirring. The dibromide dissolved and the solution turned a pale yellow, evolving considerable heat, and necessitating cooling in cold water. Colorless crystals soon separated from the solution. After standing at room temperature for twenty-four hours, the colorless precipitate was filtered off. Solvent was evaporated to give further quantities of white precipitate. The combined products were water washed several times to remove morpholine hydrobromide, and dried, giving a white crystalline product I (7.5 g.), m. p. 151–155°. Recrystallization from absolute alcohol and ethyl acetate, or benzene and low-boiling petroleum ether gave colorless cubes (6.5 g.), m. p. 159–160°.

Anal. Calcd. for $C_{18}H_{26}N_2O_3$: N, 8.79. Found: N, 8.82.

The rest of the solvent was evaporated from the reaction mixture and the residue dissolved in ether. This was washed with water several times and dried over anhydrous sodium sulfate. On adding low-boiling petroleum ether and seeding with α-morpholinobenzalacetone II, light yellow crystals (0.5 g.), m. p. 74–76° were obtained. This product was identical with the α-morpholinobenzalacetone prepared from α-bromo-α-morpholinobenzylacetone III as outlined below.

The diamino ketone I did not decolorize an alcoholic potassium permanganate solution in two minutes, but decolorized a carbon tetrachloride solution of bromine immediately to give a yellow precipitate, evolving *no* hydrogen bromide.

Hydrolysis of I.—The diamino ketone I (4.0 g.) was dissolved in dilute sulfuric acid (10 ml., 10%) and heated under reflux for thirty minutes. The condenser was equipped with a trap to catch any acetaldehyde that might be formed (none was noted). A yellow oil was extracted with ether from the cooled solution. The ether layer was extracted several times with dilute sodium hydroxide. The ether solution gave benzaldehyde (0.57 g.) identified as the phenylhydrazone. The alkali solution on neutralization gave benzyl methyl diketone (0.50 g.) identified as the osazone, m. p. 170–172°,[9] and small amounts of unidentified acids. In order to obtain good yields of this osazone the diketone must be heated (five minutes) with a two mole excess of phenylhydrazine in an alcohol solution (95%) containing a drop of acetic acid.

The acid residue of the hydrolysis solution was made basic with sodium carbonate to give a small amount (0.10 g.) of the starting material I. Possibly this acid solution contained ω-morpholinoacetone but this could not be obtained free from morpholine in this mixture due to the water solubility of such a compound.[2]

(III) α-Bromo-α-morpholinobenzylacetone.—α-Bromobenzalacetone (10.0 g.) was dissolved in a mixture of dry ether (9 ml.) and low-boiling petroleum ether (9 ml.) and the solution cooled (−5 to −10°). Morpholine (3.87 g., one mole) dissolved in 7 ml. of 50% dry ether–petroleum ether was added slowly to the cooled mixture over a period of five minutes. The mixture was then allowed to stand at −5° for two hours. The white precipitate (12.0 g.) was filtered off and washed two times with a cold mixture of dry ether (5 ml.) and low-boiling petroleum ether (10 ml.). This product was dried *in vacuo* for twenty-four hours, m. p. 100–101°, dec. (instantaneous).

Anal. Calcd. for $C_{14}H_{18}NO_2Br$: N, 4.48. Found: N, 4.50.

This bromide gave no reaction with aqueous silver nitrate, but with alcoholic silver nitrate an almost quantitative precipitation of silver bromide was noted. This compound is much less stable than the corresponding α-bromo-α-morpholinobenzylacetophenone.[1] Even in well stoppered containers it completely decomposes to a red oil in forty-eight hours.

(II) α-Morpholinobenzalacetone.—Freshly prepared III (5.0 g.) was dropped into a cool solution of sodium ethoxide (0.55 g. of sodium in 12 ml. of absolute alcohol). The mixture gave off heat and turned brown, precipitating sodium bromide. The mixture was then heated under reflux for fifteen minutes. Water was added to dissolve the sodium bromide and eventually a brown oil was precipitated. This oil was crystallized after some difficulty from alcohol and water to give a tan product (2.88 g.), m. p. 67–69°. Two recrystallizations from alcohol and water gave light yellow rods, m. p. 74–76°.

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[4] Analyses for nitrogen were determined by the Kjeldahl method by Mr. Clifford Hollenbeck of the Graduate College of the University of Nebraska, and micro C-H analyses by Mr. Edw. Renfrew of the University of Minnesota.

[5] Methods leading to good yields of pure benzalacetone dibromide and the corresponding α-bromobenzalacetone were developed by Mr. Ormond Schroeder of the Department of Chemistry of the University of Nebraska.

[6] Claisen, *Ber.*, **14**, 2463 (1881).

[7] Watson, *J. Chem. Soc.*, **85**, 464 (1904).

[8] This product is an extreme skin irritant, causing the formation of red spots which, after several days, form large red blisters that are very painful and take about ten days to heal.

[9] Müller and Pechmann, *Ber.*, **22**, 2133 (1889).

Anal. Calcd. for $C_{14}H_{17}NO_2$: N, 6.05. Found: N, 6.00.

It has not been possible to add a second molecule of morpholine to this unsaturated amino ketone II. This product II decomposes to a red oil, on contact with air, in about five days.

Hydrolysis of II.—The unsaturated amino ketone (0.30 g.) was heated on the steam-bath for twenty-five minutes with dilute sulfuric acid (15 ml., 10%). The precipitated oil was extracted with ether to give a pale yellow semi-solid (0.17 g.) which on treating with an excess of phenylhydrazine (see above) gave an osazone (0.186 g.) m. p. 169–171°, identical with the osazone of benzyl methyl diketone.[9]

Reaction of α-Bromo-α-morpholinobenzylacetone with Morpholine.—Freshly prepared III (3.0 g.) was mixed with absolute alcohol (10 ml.) and treated with morpholine (1.68 g., one mole excess). Only a small amount of heat was given off and the solution gradually turned yellow. After standing for twenty hours a white crystalline precipitate was filtered off, washed with water and dried, m. p. 150–157°. Recrystallization from benzene and petroleum ether gave product I (2.2 g.), m. p. 158–160°.

Further evaporation of the reaction mixture and seeding with α-morpholinobenzalacetone, gave the light yellow product II (0.05 g.), m. p. 74–76°.

(IV) 1-Phenyl-3-morpholino-butene-2-one-1.—A mixture of benzoylacetone (10 g.), morpholine (10.8 g., a one mole excess), and one drop of concd. hydrochloric acid was boiled under reflux for ten hours, and then allowed to stand at room temperature for two days. The dark red solution was mixed with sufficient ether to dissolve it and shaken with several portions of water to remove excess morpholine. Most of the unreacted benzoylacetone was removed as the morpholino salt in this process. Evaporation of the ether and addition of low boiling petroleum ether gave white cubes (5.0 g.), m. p. 144–146°. Recrystallization from benzene and low boiling petroleum ether did not raise the melting point. Longer reaction times decreased the yields.

Anal. Calcd. for $C_{14}H_{17}NO_2$: N, 6.05. Found: N, 6.02.

This compound gave clear solutions with dilute mineral acids, but these clouded almost immediately. The compound decolorized an alcoholic solution of potassium permanganate in one minute. This product IV gave a semi-solid hydrochloride with dry hydrogen chloride in dry ether, which decomposed quite rapidly.

Hydrolysis of (IV).—The amino ketone (IV) (0.3 g.) was dissolved in dilute hydrochloric acid (25 ml., 10%) and warmed (50°) for five minutes. A white precipitate (0.19 g.) deposited which was found to be identical with benzoylacetone.

Reaction of I with Phenylmagnesium Bromide.—This experiment was carried out in a manner similar to that of Kohler and Bruce with α-piperidinobenzylacetophenone.[10] The diamino ketone I (5.9 g.) dissolved in dry benzene (75 ml.) was added (five minutes) with stirring to an ether solution of phenylmagnesium bromide prepared from 1.79 g. of magnesium. Although a white precipitate came down during addition, the mixture was refluxed for one hour and then decomposed in an ice and ammonium chloride mixture.

On evaporation of the benzene–ether layer a white crystalline precipitate V (3.6 g.), m. p. 194–199°, was deposited. This on recrystallization from benzene and petroleum ether gave a colorless product, m. p. 201–202°.

Anal. Calcd. for $C_{24}H_{32}N_2O_3$: N, 7.06; C, 72.69; H, 8.12. Found: N, 7.07; C, 72.52; H, 8.09.

Some (1.4 g.) starting material I was recovered. This carbinol V dissolved in dilute sulfuric acid solutions (10 to 15%). On warming these solutions the diacid salt precipitated. When the carbinol was boiled for four hours under reflux with dilute sulfuric acid (6%) no change took place and all of the carbinol was recovered.

An alcoholic solution of potassium hydroxide (four equiv.) and the carbinol V were boiled under reflux for twenty hours. No hydrolysis or other degradation reactions took place.

Oxidation of Carbinol V.—This oxidation was carried out in the manner outlined by Stevens[11] with 1,1,3-triphenyl-2-N-dimethylaminopropanol-1. Carbinol V (2.0 g.) was dissolved in dilute sulfuric acid (60 ml. of 2%; 2 equiv.). This solution was then treated dropwise (one hour) with a dilute solution of ammonium persulfate (130 ml. of 1%; one equiv. plus a slight excess). During the addition of the oxidizing agent the mixture was distilled. The only product obtained from the slightly cloudy distillate was acetophenone (0.48 g.) identified as the phenylhydrazone. Small amounts of other substances that were present in this distillate (water soluble acids and aldehydes) could not be identified. Some starting material (0.4 g.) was recovered from the acid residuum.

Reaction of α,β-Dimorpholinobenzalacetophenone with Methylmagnesium Iodide.—The α,β-dimorpholinobenzalacetophenone[1] (1.97 g.), dissolved in dry benzene (30 ml.) was added rapidly to an ether solution of methylmagnesium iodide prepared from 0.50 g. of magnesium. A white precipitate came down during addition. The mixture was refluxed for five minutes and then decomposed as before. On evaporation the benzene layer gave a white crystalline product which was recrystallized from benzene and petroleum ether. This product (0.05 g.) was identical with carbinol V obtained from I, m. p. 199–200°, mixed with carbinol V as prepared above, m. p. 199–201°.

The major product from this reaction was an oil that has resisted attempts at purification and identification.

Summary

1. The reactions of morpholine with benzalacetone dibromide and with α-bromobenzalacetone have been shown to follow the same course as the corresponding benzalacetophenone dibromide and α-bromobenzalacetophenone, respectively.[1]

2. One new α-amino-α,β-unsaturated ketone and an isomeric β-amino-α,β-unsaturated ketone have been prepared.

3. Compounds having the grouping,

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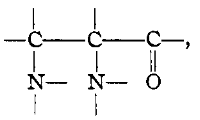
[10] Kohler and Bruce, This Journal, 53, 1994 (1931).

[11] Stevens and Hems, *J. Chem. Soc.*, 856 (1937).



$-\underset{\substack{|\\ \text{N}-\\ |}}{\overset{|}{\text{C}}}-\underset{\substack{|\\ \text{N}-\\ |}}{\overset{|}{\text{C}}}-\underset{\substack{\|\\ \text{O}}}{\text{C}}-$, have been found to add Grignard reagents to give varying amounts of the expected tertiary carbinol.

LINCOLN, NEBRASKA RECEIVED SEPTEMBER 3, 1940

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Mechanism of Ketone Formation from trans Indene Glycol and Halohydrins

BY C. M. SUTER AND H. BAYARD MILNE

It was reported by Bartlett and co-workers[1] that refluxing *cis*-1,2-dimethylcyclohexanediol-1,2 with 20% sulfuric acid gave 2,2-dimethylcyclohexanone whereas the *trans* isomer undergoes conversion to 1-acetyl-1-methylcyclopentane.[2]

Similarly, *cis*-1,2-dimethylcyclopentanediol-1,2 gave the dimethylcyclopentanone and the *trans* compound a resinous material, presumably from the intermediate diene. It was pointed out[1] that in these pinacolic rearrangements the group that migrates is closest to that face of the adjacent carbon atom which is opposite the hydroxyl being replaced, and hence the reaction probably occurs with Walden inversion. More recently it has been shown by Meerwein[3] that if the *cis*-dimethylcyclohexanediol is heated with 2% sulfuric acid at 150–160°, a 70% yield of 1-methyl-1-acetylcyclopentane results and that an appreciable amount of dimethylcyclopentanone can be obtained from the *trans* cyclopentanediol. Furthermore Criegee and Plate[4] have reported that both the *cis* and *trans* diphenylacenaphthenediols readily rearrange to the ketone in the presence of an acid catalyst. These results raise the question as to how generally applicable is the Walden inversion mechanism of pinacolic rearrangement and suggest further investigations on the behavior of a variety of cyclic glycols.

It has been known for some time[5] that both *cis* and *trans* indene glycols upon boiling with dilute acid yield 2-indanone. A clue to the mechanism whereby *trans* indene glycol rearranges was found in the observation of Hermans[6] that the *cis* and *trans* glycols are interconvertible in dilute acid solution. This suggested that the *trans* glycol did not go directly to the ketone but was first isomerized to the *cis* compound which in turn underwent rearrangement. The adequacy of this mechanism has been verified by studying the kinetics of ketone formation from the two glycols in acid solution. By plotting the rates of ketone formation for the two glycols (Figs. 1, 2) it at once became evident that the *trans* glycol yielded little or no ketone and that interconversion of the glycols was rapid compared with the rate of ketone formation. Reaction mixtures containing initially either glycol soon reached a steady state where the rates of ketone formation were the same. Both glycols were isolated from a typical reaction mixture when the starting material was the *trans* isomer, confirming the data on reaction rates.

The theoretical relationship between the concentrations of the two glycols and the ketone may be derived readily, assuming all reactions are first order where the hydrogen ion activity is constant.

$$\textit{trans}\text{ glycol } \underset{k_2}{\overset{k_1}{\rightleftarrows}} \textit{ cis}\text{ glycol } \xrightarrow{k'} \text{ ketone}$$

Let x, z and y be the concentrations of *cis* and *trans* glycols and ketone, respectively; the sum of these is the constant a. Then

$$dx/dt = k_1z - k_2x - k'x$$

$$dy/dt = k'x$$

$$\frac{d^2y}{dt^2} - k'\frac{dx}{dt} = 0 \text{ and}$$

$$dz/dt = k_2x - k_1z$$

Solving for y

$$\frac{d^2y}{dt^2} + (k_1 + k_2 + k')\frac{dy}{dt} + k'k_1y = k'k_1a \text{ or}$$

$$y = c_1e^{rt} + c_2e^{st} + a \qquad (1)^7$$

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[1] Bartlett and Pöckel, THIS JOURNAL, **59**, 820 (1937); Bartlett and Bavley, *ibid.*, **60**, 2416 (1938).

[2] Nametkin and Delektorsky, *Ber.*, **57**, 583 (1924).

[3] Meerwein, *Ann.*, **542**, 123 (1939).

[4] Criegee and Plate, *Ber.*, **72B**, 178 (1939).

[5] Böeseken and van Loon, *Proc. Acad. Sci. Amsterdam*, **20**, 1186 (1918).

[6] Hermans, *Z. physik. Chem.*, **113**, 337 (1924).

[7] An expression similar to (1) was developed by Esson [*Phil. Trans.*, **156**, 220 (1866)] to account for the rate of oxidation of oxalic acid by permanganate. In this, however, it was assumed that a substance was converted into a final product by two paths; one of these was a one-step and the other a two-step process. None of the three changes was considered to be reversible. Esson's mechanism for the oxalic acid oxidation is therefore not closely related chemically to the indene glycol behavior although the same type of exponential equation describes both phenomena.