readily soluble in water, ethyl and methyl alcohol; difficultly soluble in cold acetone; but insoluble in chloroform and ether. In order to prove the above material to be a methiodide of formula $C_{66}H_{43}NO_3 \cdot CH_3I$, it was transformed into the addition compound of *peimine methochloride* with platinic chloride, $(C_{26}H_{43}NO_3 \cdot CH_3Cl)_2 \cdot PtCl_4$, as follows.

The above solid residue was repeatedly washed with ether to remove any organic impurities and dissolved in 2 cc. of water, and the solution filtered. The filtrate was then treated with freshly prepared silver chloride and heated in a boiling water-bath for one hour. After the mixture of silver chloride and bromide was filtered off, 2% aqueous H_2PtCl_6 was added to the filtrate, whereupon the orange platinum salt separated at once. It was dissolved in dilute hydrochloric acid, from which the pure salt finally separated after concentration of the solution in a vacuum desiccator. This salt softened at 230° and melted at 240° with decomposition.

Anal. Calcd. for $(C_{26}H_{43}NO_3 \cdot CH_3Cl)_2 \cdot PtCl_4$: Pt, 15.34. Found: Pt, 15.45, 14.96.

Amorphous Alkaloids.—The chloroform extract (described in our previous communication),[3] after removing the solvent, weighed 45 g., which represented about 0.042% of the total quantity of the crude drug. Various methods have been tried to obtain some crystalline alkaloid or its crystalline salts from this fraction, but all attempts have thus far been unsuccessful.

Summary

Peiminine has finally been obtained in a very pure condition and showed the following properties: it sintered at 140°, melted at 147–148°, solidified at 157°, and remelted at 212–213° to a brown oil. Its specific rotation is $[\alpha]^{13}D$ −65.8°. Its formula is $C_{26}H_{43}NO_3$ instead of $C_{18}H_{28}NO_2$, which was assigned to it by Chou. The present formula is substantiated by the results of analysis of the methiodide and several of its salts, namely, the hydrochloride, hydrobromide, hydriodide, acid sulfate, nitrate and platinichloride.

SHANGHAI, CHINA RECEIVED AUGUST 7, 1940

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

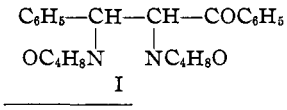
α,β-Unsaturated Aminoketones. II. α- and β-Morpholinobenzalacetophenones*

BY NORMAN H. CROMWELL

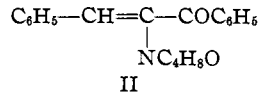
In the first paper of this series[1] two known reactions were extended to the preparation of α- and β-N-diethylamino-α,β-unsaturated ketones. One of these, the reaction of amines with 1,2-dibromoketones, has been studied extensively by Dufraisse, *et al.*[2] These workers studied the action of piperidine on several 1,2-dibromoketones, and with the corresponding α-bromo-α,β-unsaturated ketones.

Since the results obtained using diethylamine in the first paper in this series[1] were somewhat different from those experienced by Dufraisse, it seemed important to reinvestigate these reactions using morpholine in place of piperidine.

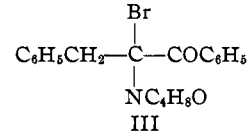
The rapid reaction of benzalacetophenone dibromide with morpholine has been found to give mostly α,β-dimorpholinobenzalacetophenone I, with small amounts of α-morpholinobenzalacetophenone II.



I



II



III

When α-bromobenzalacetophenone was treated with morpholine in the cold, the intermediate, α-bromo-α-morpholinobenzylacetophenone, III, was obtained. This compound III was found to give a slow reaction with morpholine, resulting in the formation of approximately equal amounts of I and II. However, when III was treated with a stronger base, sodium ethoxide, a 96% yield of II was obtained. It was not possible to convert II into I by heating II with an excess of morpholine, although this might have been expected in view of the work of Pollard,[3] in which it was shown that morpholine adds quite readily to benzalacetophenone.

The structure of I seems evident since hydrolysis gave a 70% yield of ω-morpholinoacetophenone, which has been prepared recently by Rubin,[4] and of benzaldehyde. Only traces of benzylphenyl diketone were noted. Reactions (1) and (2) seem to be likely ways to account for these results.

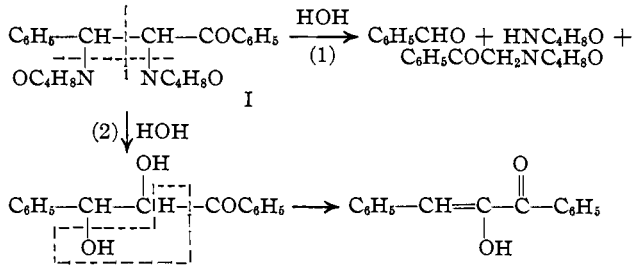
* Presented before the Division of Organic Chemistry, American Chemical Society, Detroit, Mich., September 12, 1940.

(1) Cromwell, THIS JOURNAL, **62**, 1672 (1940).

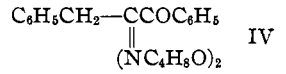
(2) Dufraisse and Moureu, *Bull. soc. chim.*, (4°) **41**, 457, 850, 1370 (1927); Dufraisse and Netter, *ibid.*, (4°) **51**, 550 (1932).

(3) Stewart and Pollard, THIS JOURNAL, **59**, 2702 (1937).

(4) Rubin and Day, *J. Org. Chem.*, **5**, 54 (1940).



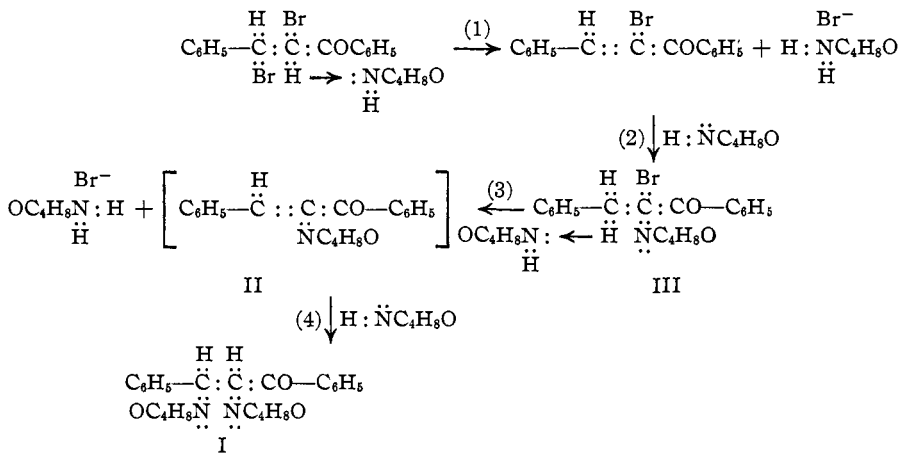
It would be expected that the isomeric structure IV



would give only benzylphenyl diketone on hydrolysis.

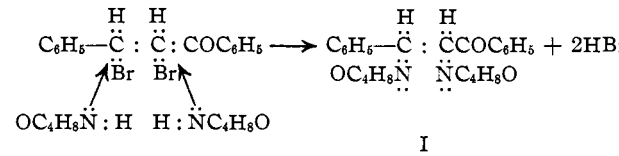
The two forms of I that were noted (form A, m. p. 173–175°, form B, m. p. 154–156°) are probably the two racemic mixtures or compounds, a possibility which is under investigation at present.

A possible mechanism to account for the formation of products I and II can now be written.



Discussion of Mechanism.—Step (1) involves the removal of hydrogen bromide[5] from the dibromide. Since the addition (2) has been shown to take place with great ease, even at very low temperatures, the olefin arising in step (1) would not be expected to exist long in this reaction medium. The α-carbon atom in this olefin must have the greater attraction for the unpaired electrons of the aminonitrogen, since there seems to be no doubt as to the structure of compounds of the type III.[2] Step (3) of the mechanism involves the removal of a second molecule of hydrogen bromide from III. This possibly takes place by the primary removal of a proton from the β-carbon atom, followed by an ionization of the α-bromine and subsequent reorientation of the electrons about the α- and β-carbon atoms to give the olefin II. The β-carbon atom in II must have the greater attraction for the unpaired electrons of the amino nitrogen in this case.

Experiments carried out thus far have failed to show any addition of morpholine either to the isolated unsaturated amino ketone II or to its isomer, V. These experiments are being continued. It is not possible to decide whether the formation of I from II in the reaction of the dibromide with morpholine is the result of addition to some momentarily existing reactive form of II or because of the high energy of reaction steps (1) and (2). Thus II has been written in brackets in the mechanism equations. It is to be noted that the reaction of morpholine with benzalacetophenone dibromide proceeds with great vigor to give mainly product I with small amounts of II, as compared with the much slower reaction of α-bromo-α-morpholinobenzylacetophenone III with morpholine to give about equal quantities of products I and II. This might be interpreted as indicating the possibility of a parallel mechanism for the formation of I from the dibromide, involving operations directly at the carbon atoms holding the bromine atoms.

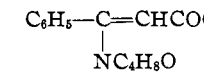


It was not surprising that aniline gave no reaction with benzalacetophenone dibromide at ordinary temperatures since steps (1) and (3) require a strong base. The failure of diethylamine to give a diamino ketone[1] probably can be explained by the relative unstability of such a product.[6]

(5) Foreman and McElvain, THIS JOURNAL, **62**, 1435, 1438 (1940).

(6) It has not been possible to add diethylamine to benzalacetophenone in preliminary experiments in this Laboratory.

The preparation of β-morpholinobenzalacetophenone V from dibenzoylmethane was carried out in the usual way.[1] The high boiling point of



V

the morpholine facilitated this condensation. It was not surprising that this product V failed to add a second molecule of morpholine to give I.

These reactions have been repeated with benzalacetone in another investigation, the results of which will be submitted soon.

Experimental[7]

Reaction of Benzalacetophenonedibromide with Morpholine.—To an absolute ethyl alcohol (50 ml.) suspension of benzalacetophenone dibromide (10 g.), morpholine (9.5 g., a three mol excess) was added rapidly with stirring. The dibromide dissolved and the solution turned first yellow then orange, evolving some heat. Yellow needles soon separated from the orange solution. After standing at room temperature for twenty-four hours the yellow precipitate was filtered off. Solvent was evaporated to give further quantities of yellow precipitate. The combined products were water washed several times to remove morpholine hydrobromide and dried, giving a pale yellow product I (7.2 g.), m. p. 155–165°. Continued recrystallizations of this substance from benzene and low-boiling petroleum ether gave two products, mainly A, hair-like yellow needles, m. p. 173–175° dec., and small amounts of B, yellow needles, m. p. 154–156° dec. A mixture of equal amounts of A and B gave m. p. 153–169° dec.

Anal. Calcd. for $C_{23}H_{28}N_2O_3$: N, 7.36. Found: for A, N, 7.30; for B, N, 7.40.

Evaporation of more of the solvent from the reaction mixture and the addition of water gave, on cooling and seeding with α-morpholinobenzalacetophenone II, orange crystals (1.0 g.), m. p. 85–91°. Several recrystallizations from alcohol and water gave orange plates, m. p. 93–95°. This product was identical with the α-morpholinobenzalacetophenone prepared from α-bromo-α-morpholinobenzylacetophenone as outlined below.

Study of $C_{23}H_{28}N_2O_3$, A and B.—Both A and B were completely soluble in dilute mineral acids. Neither decolorized alcoholic potassium permanganate solution in two minutes, but both decolorized a carbon tetrachloride solution of bromine immediately to give a yellow precipitate, evolving *no* hydrogen bromide.

Hydrolysis of I.—Form A (3.0 g.), m. p. 173–175°, was dissolved in dilute sulfuric acid (30 ml., 15%) and heated under reflux for twenty-five minutes. A strong odor of benzaldehyde was soon noted and an oil precipitated out. The mixture was then extracted with ether. The ether layer was extracted with dilute alkali. The ether solution gave only benzaldehyde (0.63 g.) and the alkali solution on neutralization gave traces of benzylphenyl diketone. These two products were identified by their reaction with phenylhydrazine and phenylenediamine, respectively.

The acid residue of the hydrolysis solution was made basic with sodium carbonate to give a colorless oil which was extracted with ether. The ether solution was washed several times with water and dried. On passing in dry hydrogen chloride, a white crystalline precipitate (1.3 g.), came down, m. p. 219–223°. Recrystallization from absolute alcohol and dry ether gave white crystals, m. p. 221–223°.

Anal. Calcd. for $C_{12}H_{16}NO_2Cl$: Cl, 14.68. Found: Cl, 14.62.

This product was identical with the hydrochloride of ω-morpholinoacetophenone prepared according to the method recently outlined by Rubin.[4] Form B, m. p. 154–156°, gave the same results as Form A on acid hydrolysis.

In benzene solution, (25 ml.) the reaction of morpholine (1.45 g., a two mol excess) with benzalacetophenone dibromide (2.0 g.) required heating on the steam-bath for one-half hour. The precipitated morpholine hydrobromide (1.4 g.)[8] was filtered off and the yellow solution washed with water. Evaporation of the benzene and addition of low boiling petroleum ether gave yellow crystals I (0.8 g.), m. p. 150–165°. Recrystallization of this product gave mainly the product A, m. p. 172–174°. Evaporation of the reaction mixture gave small amounts of α-morpholinobenzalacetophenone II, m. p. 93–95°.

α-Bromobenzalacetophenone.—This compound was prepared according to the method outlined by Wislicenus.[9] Benzalacetophenone dibromide (50 g.) was heated (four hours) under reflux with sodium acetate (13 g.) in an alcohol solution (200 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 product distilled under reduced pressure. The product (30 g.) was a yellow oil, b. p. 165-169° (1 mm.).

(III) α-Bromo-α-morpholinobenzylacetophenone.—The type of procedure outlined by Dufraisse[10] for the preparation of α-bromo-α-piperidinobenzylacetophenone was used. α-Bromobenzalacetophenone (10 g.) was dissolved in dry ether (25 ml.) and the solution cooled (−5°). Morpholine (3.03 g., one mol) was added slowly to the cooled mixture with shaking over a period of fifteen minutes. The mixture was then allowed to stand for two hours at −5°. The white precipitate (10 g.) was filtered off and washed three times with cold dry ether (10 ml. portions), and dried *in vacuo* for twenty hours, m. p. 138–139°, dec. (instantaneous).

Anal. Calcd. for $C_{19}H_{20}NO_2Br$: N, 3.74. Found: N, 3.70.

This bromide III gave no reaction with aqueous silver nitrate, but with alcoholic silver nitrate an almost quantitative precipitation of silver bromide was noted. This compound is reasonably stable in air.

(II) α-Morpholinobenzalacetophenone.—A procedure similar to that outlined by Dufraisse[10] for the preparation

(7) Analyses for nitrogen were determined by the Kjeldahl method by Mr. Clifford Hollenbeck of the Graduate College of the University of Nebraska.

(8) This hydrobromide was identical with an analyzed sample prepared by W. P. Utermohlen, Ph.D. Thesis, University of Nebraska, May, 1940.

(9) Wislicenus, *Ann.*, **308**, 226 (1899).

(10) Dufraisse and Moureu, *Bull. soc. chim.*, [4°] **41**, 466-469 (1927).

of α-piperidinobenzalacetophenone was used for this preparation. Freshly prepared α-bromo-α-morpholinobenzylacetophenone (5.0 g.) was dropped into a boiling absolute ethyl alcohol solution (13 ml.) of sodium ethoxide (0.46 g. sodium, 1.5 mol). The mixture turned orange immediately and a white precipitate settled out. The heating, under reflux, was continued for twenty minutes. The mixture was then cooled to 0° and water added slowly. The white precipitate (sodium bromide) dissolved and orange plates (3.8 g.) separated out, m. p. 85–92°. Several recrystallizations from alcohol and water gave orange plates, m. p. 94–96°.

Anal. Calcd. for $C_{19}H_{19}NO_2$: N, 4.77. Found: N, 4.65.

This unsaturated amino ketone (1.0 g.) was not soluble in sulfuric acid (10 ml., 15%), but reacted immediately to give a good yield (77%) of the enol form of benzylphenyl diketone, m. p. 60–63°, as indicated by its reaction with phenylenediamine to give the quinoxaline (0.77 g.), mentioned in paper I of this series, m. p. 98–99°.[1]

Even long heating of II with a one mol excess of morpholine in an absolute alcohol solution containing a few crystals of morpholine hydrobromide gave none of the dimorpholino compound I, $C_{23}H_{28}N_2O_3$. Long heating (ten hours) of II with morpholine in *n*-heptane likewise gave no addition.

Reaction of α-Bromo-α-morpholinobenzylacetophenone with Morpholine.—Freshly prepared α-bromo-α-morpholinobenzylacetophenone (3.5 g.) was mixed with absolute alcohol (10 ml.) and treated with morpholine (1.63 g., 1 mol excess). A slow reaction set in, the mixture gradually turning yellow. After standing for twenty hours, the then orange solution contained a yellow precipitate. This product was filtered off, washed several times with water and dried *in vacuo*, wt. 1.4 g., m. p. 158–172°. Recrystallization from benzene and low boiling petroleum ether gave mainly yellow needles, m. p. 171–173°, identical with the A form of I, $C_{23}H_{28}N_2O_3$, obtained above.

Evaporation of the reaction mixture and seeding, with α-morpholinobenzalacetophenone, gave orange plates (1.1 g.), m. p. 90–93°. This product was identical with α-morpholinobenzalacetophenone II prepared as outlined above.

(V) **β-Morpholinobenzalacetophenone.**—A mixture of dibenzoylmethane (10 g.), morpholine (7.8 g., a one mol excess), and one drop of concd. hydrochloric acid was heated under reflux for ten hours, and then allowed to stand at room temperature for two days. The dark red solution was dissolved in ether and shaken with several portions of water to remove excess morpholine. Much of the unreacted dibenzoylmethane was removed as the morpholino-salt in this process. Evaporation of the ether solution gave first, dibenzoylmethane, and finally, after adding low boiling petroleum ether, pale yellow crystals (5.0 g.), m. p. 91–95°. Several recrystallizations of this product from benzene and low boiling petroleum ether gave pale yellow prisms, m. p. 96–97°. The total amount of unreacted dibenzoylmethane recovered was 5.0 g.

Anal. Calcd. for $C_{19}H_{19}NO_2$: N, 4.77. Found: N, 4.60.

This compound reacted with mineral acids to give a white precipitate. An unstable hydrochloride was formed on passing dry hydrogen chloride into an ether solution of the compound. This unsaturated amino ketone decolorized dilute alcoholic potassium permanganate in less than one minute.

No trace of a dimorpholino compound, $C_{23}H_{28}N_2O_3$, was noted.

Hydrolysis of β-Morpholinobenzalacetophenone.—The unsaturated amino ketone (0.5 g.), was dissolved in dilute sulfuric acid (20 ml., 15%). The solution was allowed to stand at room temperature for eight hours. A white solid (0.37 g.) precipitated which was found to be identical with dibenzoylmethane.

Summary

1. The reactions of morpholine with a 1,2-dibromo ketone and with the corresponding α-bromo-α,β-unsaturated ketone have been studied and possible mechanisms of these reactions discussed.

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

LINCOLN, NEBRASKA RECEIVED JULY 12, 1940