JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

VOLUME 65 MARCH 10, 1943 NUMBER 3

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

α,β-Unsaturated Aminoketones. VI.[1] The Mechanisms of the Reactions of Secondary Amines with α-Bromo-α,β-unsaturated Ketones

BY NORMAN H. CROMWELL AND DONALD J. CRAM

In the second paper[2] in this series, mechanisms were proposed for the reactions of secondary heterocyclic amines with bromine derivatives of benzalacetophenone. Other investigations[3] seemed to support this way of describing these complicated reactions. It was pointed out in this second paper that the proposed mechanism did not explain all of the then known experimental data. In all of these previous discussions the important bromo-amino ketones, which result from the primary addition of the amine to an α-bromo-α,β-unsaturated ketone, have been shown as α-bromo-α-amino ketones. It will be shown here that this structure must now be considered as highly improbable. Moreover, the present investigations showed that these reactions are even more complex than previously supposed.

Tetrahydroisoquinoline, for which a good method of preparation has been developed, has been found to be an unusually good base to use in these studies. As its structure indicates, this heterocyclic secondary amine would be expected to be a considerably stronger base than its isomer, tetrahydroquinoline, which has been used previously in these studies.[1] Tetrahydroisoquinoline is a strong base of about the same strength as morpholine and N-methylbenzylamine; indeed it may be thought of as an analog of this latter base.

With α-bromobenzalacetone, tetrahydroisoquinoline added rapidly and completely to give a bromo-amino ketone whose structure is now assigned as α-bromo-β-tetrahydroisoquinolinobenzylacetone (I) (see Discussion). This product reacted with sodium ethoxide to give α-tetrahydroisoquinolinobenzalacetone (II). With excess tetrahydroisoquinoline the bromo-amino ketone (I) gave a 75% yield of α,β-di-tetrahydroisoquinolinobenzylacetone (III) which was prepared directly from α,β-di-bromobenzylacetone in 63% yield.

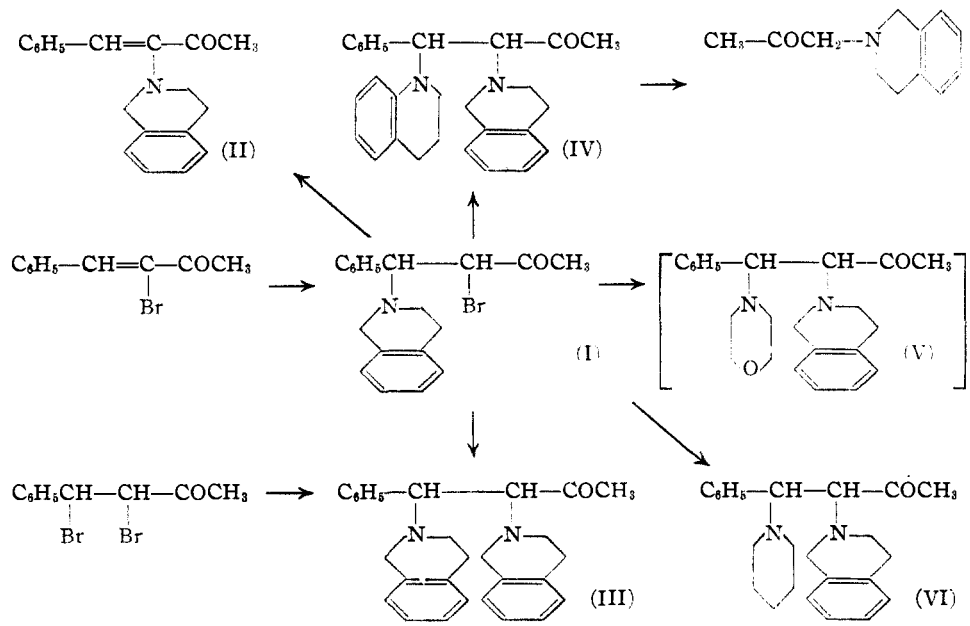
In either absolute alcohol or absolute ether the bromo-amino ketone (I) reacted readily with a much weaker base, tetrahydroquinoline, to give good yields of α-tetrahydroisoquinolino-β-tetrahydroquinolinobenzylacetone (IV). The structure of this diamino ketone was established by hydrolysis to give the expected α-tetrahydroisoquinolinoacetone.

When a base of almost equal or greater strength than tetrahydroisoquinoline was used in this reaction, a mixture of products resulted. With morpholine in alcohol solution the main product from the reaction with (I) was (III). It was not possible to obtain a pure sample of α-tetrahydroisoquinolino-β-morpholinobenzylacetone (V), although data are presented to indicate that it was present in the mixture. With piperidine, the bromo-amino ketone (I) gave a low yield of α-tetrahydroisoquinolino-β-piperidinobenzylacetone (VI) in absolute ether, while in absolute alcohol only (III) could be isolated.

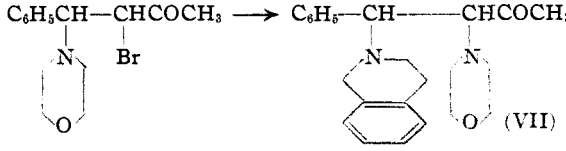
(1) For paper V in this series see Cromwell, THIS JOURNAL, **63**, 2984 (1941).

(2) Cromwell, *ibid.*, **62**, 2897 (1940).

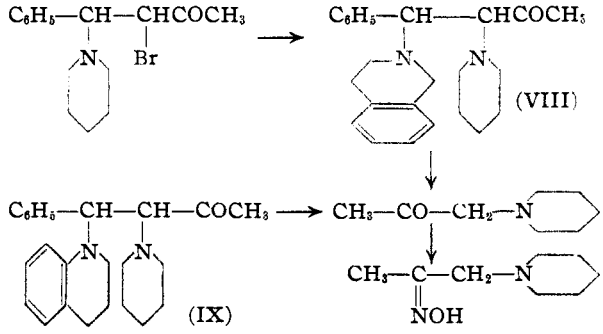
(3) (a) Cromwell, *ibid.*, **62**, 3470 (1940); (b) **63**, 837 (1941).



In an attempt to prepare the position isomer of (V), α-bromo-β-morpholinobenzylacetone[3a] was treated with tetrahydroisoquinoline in both alcohol and ether solutions. From the reaction carried out in ether a small amount of α-morpholino-β-tetrahydroisoquinolinobenzylacetone (VII) was isolated. Only the diamino ketone (III) could be isolated from the reaction carried out in alcohol solution.



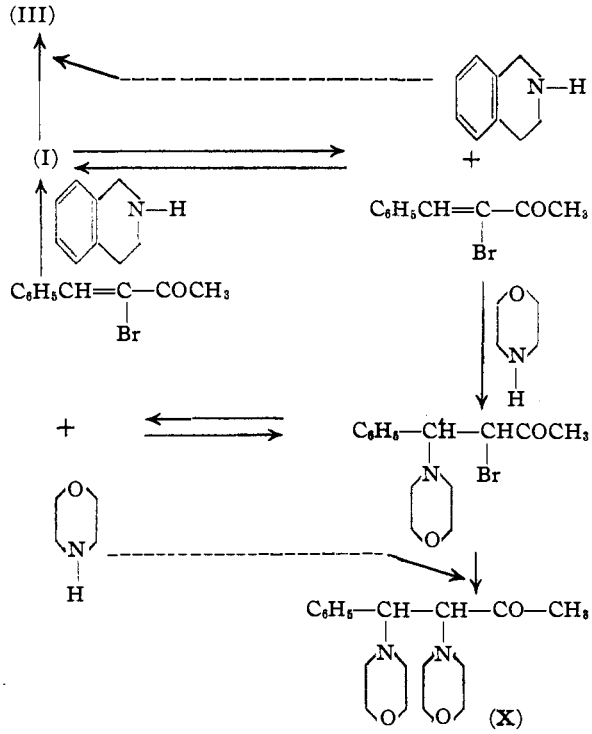
The position isomer of (VI) was prepared in good yield in both alcohol and ether by treating α-bromo-β-piperidinobenzylacetone[4] with tetrahydroisoquinoline to give α-piperidino-β-tetrahydroisoquinolinobenzylacetone (VIII). Mixtures of (VI) and (VIII) melted over a range of temperature that was considerably below the melting point of either (VI) or (VIII). Hydrolysis of (VIII) gave the expected α-piperidinoacetone which was isolated as its oxime.



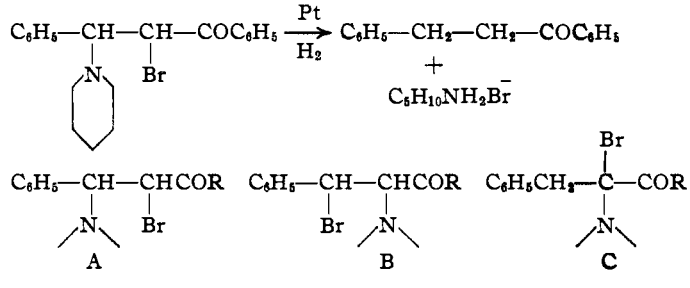
α-Piperidino-β-tetrahydroquinolinobenzylacetone (IX) was prepared in good yields in alcohol solution and in lesser amounts in ether solution from α-bromo-β-piperidinobenzylacetone. The structure of (IX) was established by hydrolysis.

It has been pointed out above that it was possible to obtain the diamino ketone (III) from the reactions in alcohol solutions of (I) with morpholine or piperidine and also from α-bromo-β-morpholinobenzylacetone and tetrahydroisoquinoline. This suggested that these bromo-amino ketones were unstable in solution, decomposing to give the starting materials. This supposition was established for both (I) and α-bromo-β-morpholinobenzylacetone. When either of these two bromo-amino ketones was allowed to stand in absolute alcohol solution, the corresponding diamino ketone (III) or (X)[3a] was formed. Addition of the other heterocyclic secondary amine to the filtrates gave the corresponding diamino ketones (X) and (III). These latter reactions were undoubtedly due to the presence in these filtrates of α-bromobenzalacetone. It was established that such decomposition was not appreciable in ether medium. These results are shown diagrammatically below.

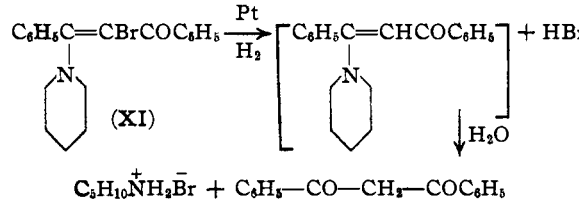
(4) Cromwell and Witt, THIS JOURNAL, **65**, 308 (1943).



In an attempt to prove the structure of these primary addition products from the reaction of α-bromo-α,β-unsaturated ketones with secondary amines, one of them, α-bromo-β-piperidinobenzylacetophenone,[5] was subjected to the mildest of reducing conditions. The reaction proceeded to give benzylacetophenone and piperidine hydrobromide. It had been hoped that only the bromine atom would be replaced. However, this was evidence for the structure A that has been assigned to these bromo-amino ketones, and evidence against structure B or C. It has been shown[6] that β-amino ketones are unstable to catalytic reduction, as compared with α-amino ketones.



Another attempt at proof of structure of these addition products was carried out by reducing the known α-bromo-β-piperidinobenzalacetophenone[7] (XI). Unfortunately the bromine is labile even with catalytic hydrogen. It had been shown by Dufraisse[7] that the bromine in these unusual compounds could be replaced by hydrogen without reducing the double bond when they were treated with acidic potassium iodide solutions. It was hoped that (XI) could be reduced to give A. However, the bromine was replaced by hydrogen and the resulting β-piperidinobenzalacetophenone apparently hydrolyzed to give the product isolated in good yields, dibenzoylmethane.



It was also found that it was not possible to isolate a bromo-amino ketone of structure B or C when α-piperidinobenzalacetophenone[5] was treated with dry hydrogen bromide.

The complexity of these interesting reactions plus the fact that all attempts at an unequivocal proof of the structure of the primary addition product from the reaction of an α-bromo-α,β-unsaturated ketone have failed, makes it difficult to assign with certainty a mechanism. It becomes readily apparent that if this mechanism that is now offered is the actual picture of these reactions it might indeed be difficult to establish the structure A. This product A can probably be isolated only because of its great insolubility in the reaction medium in which it is prepared. In solution the structure A might be expected to undergo more than one type of change, including decomposition to its starting materials and reaction with itself, functioning as a base.

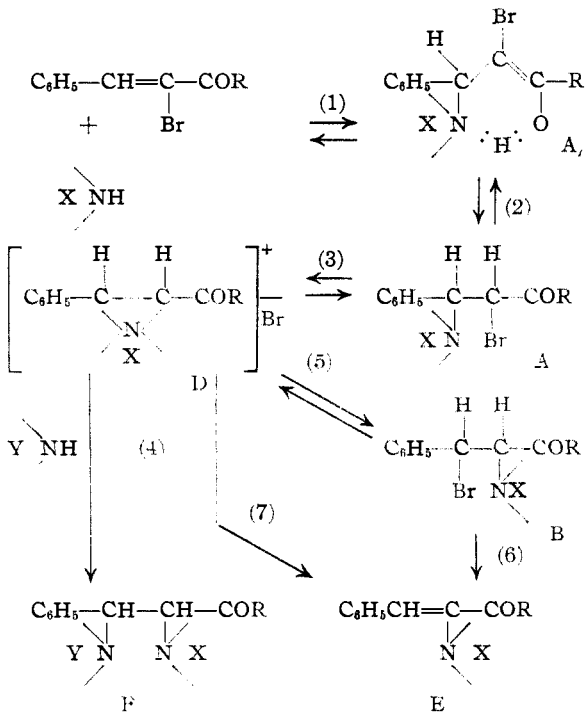
Discussion

In step (1) the amine X  adds to the conjugated system in the normal way as does hydrogen bromide (see experimental). The chelated structure A′ probably is instantly changed in ether solution (2) to the structure A which precipitates from the reaction medium at the low temperatures at which the reaction is carried out. It is to be remembered that compounds of type

(5) Dufraisse and Moureu, *Bull. soc. chim.*, [4] **41**, 457–472 (1927).

(6) Cromwell, Wiles and Schroeder, THIS JOURNAL, **64**, 2432 (1942).

(7) Dufraisse and Netter, *Bull. soc. chim.*, [4] **51**, 550–562 (1932).



A have been isolated only when X N—H is an amine of considerable strength and of particular molecular structure (diethylamine, tetrahydroquinoline, etc., give no isolable addition products). When A is allowed to remain in solution it may decompose to give the starting materials, reversing (2) and (1) and allowing "abnormal" reactions to take place. Also A may rearrange (3) to give a highly reactive quaternary ammonium salt D which may be isolable in some cases. The fact that these bromo-amino ketones react much more slowly with alcoholic silver nitrate when they have been dissolved in dilute nitric acid and alcohol than they do when dissolved in alcohol alone before adding nitric acid is evidence for the rearrangement in neutral or basic solutions of A to give D. The initial presence of nitric acid involves the unshared electrons of the amino nitrogen and prevents the formation of D.

Structure D is the most important of the intermediates in these reactions. Now the α-carbon atom in D would be expected to have the greater attraction for the amino group, X N— and consequently the bond to the β-carbon atom would be the most readily cleaved by a second base Y N—H. Thus a base, Y N—H (tetrahydroquinoline), weaker than base X N—H (piperidine) will react smoothly (4) to give good yields of F and only (7) small amounts of E. If base Y N—H (piperidine) is stronger than base X N—H (tetrahydroisoquinoline) then mixed products are obtained. This is also true when Y N—H and X N—H are of about equal strength. Undoubtedly steric factors enter in if there are wide differences in the structures of the two bases.

It seems unlikely that mixed diamino ketones of type F result from A by a reversal of (2) and (1) followed by reaction of the α-bromo-α,β-unsaturated ketone with the second base Y N—H to give a new A which then is substituted directly by the first base X N—H. This has been shown to be impossible when X N—H is tetrahydroisoquinoline and Y N—H is tetrahydroquinoline. Tetrahydroquinoline will not react with α-bromo-α,β-unsaturated ketones under these conditions.

In most cases the addition product is formed so rapidly that it seems improbable that structure B represents its structure. It is not beyond possibility, however, that under certain conditions, with certain bases X N—H the addition product may be actually B. It would certainly be difficult to decide between these two structures, A and B, since in solution they might be in equilibrium with each other. B could, of course, give (6) E readily and possibly F.

This mechanism, as it is here outlined, seems to explain in a logical and modern way all of the known experimental facts. It is broad enough to give a working basis for further investigations which are now being carried out. Although the structure C for the bromo-amino ketones, as assigned by Dufraisse[5] and accepted by Crom-

well,[1,2,3] readily explained the formation of unsaturated amino ketones, E, it did not explain the formation of mixed diamino ketones of type F. It has never been possible in any of these studies to add any amine to an unsaturated amino ketone E.

From a consideration of the factors of relative amine strength, temperature, solvent, and product solubilities, as outlined here and in other papers in this series, it is possible to use these reactions to prepare a wide variety of interesting and possibly valuable unsaturated amino ketones and diamino ketones. Future publications will deal with the reactions and interesting properties of these two types of products.

Experimental[8]

α-Bromobenzalacetone.—A mixture of 60 g. (0.731 mole) of anhydrous sodium acetate and 200 g. (0.653 mole) of α,β-di-bromobenzylacetone in 500 ml. of 95% alcohol (not denatured) was heated under reflux for four hours. The solvent was evaporated under reduced pressure and the resulting oil extracted with ether. The ether solution was washed six times with saturated sodium chloride solution, twice with 5% sodium bicarbonate solution, and finally twice with water. The ether layer was dried, evaporated, and the residual, light-yellow oil distilled, wt. 108 g., b. p. 114–117° (1 mm.).[3a] This oil was crystallized by cooling to 0°, m. p. 30–31°. This product is more stable in the solid form.

Anal. Calcd. for $C_{10}H_9OBr$: C, 53.34; H, 4.03. Found: C, 53.25; H, 4.18.

Tetrahydroisoquinoline.—In the bomb of a high pressure hydrogenator were placed 150 g. (1.162 moles) of isoquinoline, 15 g. of copper chromite catalyst[9] and 300 ml. of absolute alcohol. This mixture was reduced under a pressure of 1800 lb./sq. in. and a temperature of 180°, the theoretical amount of hydrogen being absorbed in fifteen minutes. The product was purified by distillation, 142 g. (1.069 moles) or a 92% yield being obtained, b. p. 234–236°; d^{25}_4 1.059; n_{22D} 1.5749.[10] The benzenesulfonamide derivative was prepared, m. p. 154°.[11]

α-Bromo-β-tetrahydroisoquinolinobenzylacetone.—In 20 ml. of a 50% ether–petroleum ether (b. p. 35°) solution, was dissolved 10 g. (0.0444 mole) of α-bromobenzalacetone and the solution cooled to −15°. Tetrahydroisoquinoline (6 g. (0.0451 mole)) was dissolved in 10 ml. of a 50% ether–petroleum ether mixture and added. In about an hour and a half 14.5 g. (0.0405 mole) of product had precipitated. This was filtered and washed with petroleum ether, m. p. 102–103°, yield 91%.

Anal. Calcd. for $C_{19}H_{20}NOBr$: C, 63.72; H, 5.63. Found: C, 63.95; H, 5.81.

This product was slightly soluble in benzene and in absolute alcohol, but insoluble in water. A sample of this bromo-amino ketone was dissolved in dilute nitric acid and then about four times this volume of absolute alcohol added. This solution gave a very slow reaction with alcoholic silver nitrate at room temperature. A second sample of this bromo-amino ketone was then dissolved in absolute alcohol and after five minutes a little dilute nitric acid added. This clear, colorless, acid solution gave an immediate precipitate of silver bromide with alcoholic silver nitrate.

α-Tetrahydroisoquinolinobenzalacetone.—To a solution of 0.33 g. (0.0143 mole) of sodium dissolved in 7 ml. of absolute alcohol was added 3.1 g. (0.00866 mole) of α-bromo-β-tetrahydroisoquinolinobenzylacetone and the resulting mixture refluxed on a water-bath for fifteen minutes. On the addition of water a brown precipitate appeared which after several recrystallizations from alcohol and water gave 2.2 g. (0.00746 mole) of yellow needles, m. p. 90–91°, yield 92%.

Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.26; H, 6.93; N, 5.05. Found: C, 82.20; H, 6.81; N, 4.99.

This compound gave no reaction with tetrahydroisoquinoline in alcohol solution.

α,β-Di-tetrahydroisoquinolinobenzylacetone.—This diamino ketone was prepared in two ways. (1) To 5 g. (0.014 mole) of α-bromo-β-tetrahydroisoquinolinobenzylacetone dissolved in 10 ml. of absolute alcohol was added 3.72 g. (0.028 mole) of tetrahydroisoquinoline. The reaction took place with the evolution of heat and was complete in an hour at room temperature. Purification of the precipitate by recrystallization from chloroform and alcohol gave 4.3 g. (0.0105 mole) of product, m. p. 169–170°, yield 75%.

Anal. Calcd. for $C_{28}H_{30}N_2O$: C, 81.91; H, 7.37; N, 6.83. Found: C, 81.92; H, 7.35; N, 6.89.

(2) In 60 ml. of absolute alcohol was dissolved 20 g. (0.0653 mole) of α,β-di-bromobenzylacetone and the solution cooled to 0°. Tetrahydroisoquinoline, 35 g. (0.263 mole), was added with stirring. The reaction, which took place with the evolution of heat, was complete in twenty minutes giving a finely divided yellow solid. This gave after three crystallizations from a chloroform–alcohol mixture 17 g. (0.0415 mole) of white crystalline product, m. p. 169–170°, yield 63.4%. A mixed melting point experiment with α,β-ditetrahydroisoquinolinobenzylacetone as prepared by (1) above, gave m. p. 169–170°.

This compound was almost completely insoluble in even absolute alcohol, but 0.1 g. dissolved readily in 1.5 ml. of 95% alcohol containing 0.013 g. of hydrogen chloride to give a yellow solution. It was very soluble in chloroform but only slightly soluble in dilute hydrochloric acid.

Tetrahydroquinoline gave no appreciable reaction with either the unsaturated bromide or the dibromide.

α-Tetrahydroisoquinolino-β-tetrahydroquinolinobenzylacetone.—To 25 ml. of absolute alcohol were added 12 g. (0.0335 mole) of α-bromo-β-tetrahydroisoquinolinobenzylacetone and 8.91 g. (0.0670 mole) of tetrahydroquinoline. The reaction took place over a period of four days at room temperature and at the end of this time the precipitate was filtered and purified by recrystallization from chloroform and alcohol. Soft white needles, 6 g. (0.01463 mole), were

(8) Micro Dumas analyses for nitrogen and semi-micro carbon-hydrogen analyses were performed in the analytical laboratory of the University of Nebraska, under the direction of H. Armin Pagel.

(9) "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., **19**, 31 (1939).

(10) Heilbron, "Dictionary of Organic Compounds," Vol. III, p. 695–696.

(11) von Braun, *Ber.*, **57B**, 908 (1924).

thus obtained, m. p. 107–109°, yield 43.7%. A mixed melting point of this compound with α,β-ditetrahydroisoquinolinobenzylacetone gave 93–130°.

Anal. Calcd. for $C_{28}H_{30}N_2O$: C, 81.91; H, 7.37; N, 6.83. Found: C, 81.97; H, 7.55; N, 7.01.

This experiment was repeated in ether solution giving a yield of 30.5%, m. p. 106–109°. A mixed melting point of the products from the two runs gave 107–109°.

This compound proved slightly soluble in ether and alcohol and fairly soluble in dilute hydrochloric acid solution.

Hydrolysis of this diamino ketone (4 g.) was carried out by boiling with 50 ml. of 15% sulfuric acid for thirty minutes. The cooled mixture was extracted with ether and the acid layer neutralized with sodium hydroxide. The precipitated oil was extracted with ether and the ether extract evaporated to give an oil which was shaken with an alkaline solution of benzenesulfonyl chloride. This reaction mixture was extracted with ether and the ether solution extracted with dilute hydrochloric acid. Neutralization of this acid solution gave an oil which was extracted with ether. Dry hydrogen chloride was passed into the ether solution to give an oily precipitate which after several recrystallizations from alcohol and ether gave a white crystalline solid (0.6 g.), m. p. 213–215°.

Anal. Calcd. for $C_{12}H_{16}NOCl$: C, 63.85; H, 7.14; Cl, 15.71. Found: C, 63.44; H, 7.17; Cl, 15.40.

This product was identical with a sample of the hydrochloride of α-tetrahydroisoquinolinoacetone prepared from chloroacetone in the usual way.

Reaction of Morpholine with α-Bromo-β-tetrahydroisoquinolinobenzylacetone.—With 50 ml. of absolute alcohol were mixed 25 g. (0.0700 mole) of α-bromo-β-tetrahydroisoquinolinobenzylacetone and 12.16 g. (0.140 mole) of morpholine. This mixture was placed in an ice-box for two days at the end of which time the precipitate was filtered and washed first with a 50% alcohol solution and then with water. The dry crude product amounted to 16 g. Five recrystallizations from a mixture of chloroform and alcohol gave 8 g. (0.0195 mole) of pure product, m. p. 169–170°. A mixed melting point experiment with α,β-ditetrahydroisoquinolinobenzylacetone gave m. p. 169–170°. The yield based on the amount of available bromo-amino ketone amounted to 27.9%.

The filtrate from the reaction mixture gave a second crop of crystals upon the addition of a little water, the crude dry product weighing 1.98 g. A series of fractional recrystallizations from alcohol gave a small amount of product m. p. 117–125°. It was found impossible to purify this compound. A series of mixed melting point experiments indicated this product to be a mixture of α-tetrahydroisoquinolino-β-morpholinobenzylacetone and α,β-ditetrahydroisoquinolinobenzylacetone and possibly some α,β-di-morpholinobenzylacetone.[3a]

Anal. Calcd. for $C_{28}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.69. Found: C, 74.21; H, 8.12; N, 7.71.

This reaction was repeated in dry ether solution, the product again turning out to be a mixture.

Hydrolysis of this mixed product gave only α-tetrahydroisoquinolinoacetone isolated as its hydrochloride, m. p. 213–214°.

α-Tetrahydroisoquinolino-β-piperidinobenzylacetone.—To 5 ml. of anhydrous ether were added 1.5 g. (0.0042 mole) of α-bromo-β-tetrahydroisoquinolinobenzylacetone and 0.714 g. (0.0084 mole) of piperidine. The mixture was tightly corked and heated to 60° for fifteen minutes and allowed to stand at room temperature for two days. At the end of this time it was filtered and the precipitate tested for water solubility. As it proved to be all piperidine hydrobromide the filtrate was well washed with water, dried, evaporated under reduced pressure, and the resulting oil taken up in alcohol and a little water added. Over a period of a day a yellow solid came out, which upon four recrystallizations from alcohol and water gave 0.08 g. (0.00022 mole) of white product; m. p. 150–151°; yield 5.3%.

Anal. Calcd. for $C_{24}H_{30}N_2O$: C, 79.51; H, 8.34; N, 7.73. Found: C, 79.67; H, 8.25; N, 7.81.

This reaction was also run in alcohol solution, a 19% yield of α,β-ditetrahydroisoquinolinobenzylacetone based on the amount of available bromo-amino ketone being obtained as well as a product which could not be purified.

α-Morpholino-β-tetrahydroisoquinolinobenzylacetone.—To 10 ml. of dry ether were added 5 g. (0.016 mole) of α-bromo-β-morpholinobenzylacetone[3a] and 4.26 g. (0.032 mole) of tetrahydroisoquinoline and the mixture placed in the ice-box for two days. The precipitate which had formed proved water soluble so the filtrate was evaporated and the resulting oil taken up in alcohol. A precipitate came out which after four recrystallizations from chloroform and alcohol gave 0.3 g. of a white product, m. p. 168–170°. A mixed melting point experiment with α,β-ditetrahydroisoquinolinobenzylacetone gave m. p. 168–170°.

The combined filtrates were concentrated and a small amount of solid obtained. Two recrystallizations from alcohol and water gave a small amount of white crystalline product, m. p. 134–135°. A mixed melting point with α,β-di-tetrahydroisoquinolinobenzylacetone gave 119–140° and with the impure α-tetrahydroisoquinolino-β-morpholinobenzylacetone, 106–122°.

Anal. Calcd. for $C_{23}H_{28}N_2O_2$: N, 7.69. Found: N, 7.65.

This reaction was also carried out in alcohol solution and a 5.9% yield, based on the amount of bromo-aminoketone, of α,β-di-tetrahydroisoquinolinobenzylacetone was obtained.

α-Piperidino-β-tetrahydroisoquinolinobenzylacetone.—To 50 ml. of anhydrous ether were added 23 g. (0.0757 mole) of α-bromo-β-piperidinobenzylacetone[4] and 20 g. (0.150 mole) of tetrahydroisoquinoline and the mixture kept at 0°. Much heat was given off and the reaction was complete in about ten minutes but it was allowed to stand for four hours before the precipitate was filtered. Two recrystallizations from chloroform and alcohol gave 10 g. (0.0276 mole) of white crystalline product, m. p. 147–148°, yield, 36.4%. A mixed melting point experiment with α-tetrahydroisoquinolino-β-piperidinobenzylacetone gave m. p. 122–134°.

Anal. Calcd. for $C_{24}H_{30}N_2O$: C, 79.51; H, 8.34; N, 7.73. Found: C, 79.26; H, 8.39; N, 7.78.

This reaction was also carried out in alcohol, a 40.3% yield being obtained, m. p. 146–148°. A mixed melting point with that made in ether gave 146–148°.

This compound was shown to be very soluble in dilute hydrochloric acid but almost completely insoluble in alcohol.

Hydrolysis of α-piperidino-β-tetrahydroisoquinolinobenzylacetone (5.0 g.) was effected by heating on a steam-bath with 25 ml. of 15% sulfuric acid for thirty minutes. The precipitated oil was removed by ether extraction and shown to be benzaldehyde along with a small amount of benzyl methyl diketone.[3a] The acid layer was made strongly basic with solid sodium hydroxide and extracted with ether. The ether solution was then extracted with water and the water layer made strongly basic with solid sodium hydroxide. The precipitated oil from this operation was then dissolved in a small amount of water and treated with a mixture of 3.8 g. of hydroxylamine hydrochloride and 3.3 g. of sodium hydroxide in 25 ml. of water and 5 ml. of methyl alcohol. After standing for twenty hours this solution was concentrated under vacuum and almost neutralized (just basic) with hydrochloric acid. White crystals precipitated from the solution (1.05 g.), m. p. 120–123°. Recrystallization from benzene and petroleum ether raised the melting point to 122–123°. This product was soluble in both dilute hydrochloric acid and sodium hydroxide solutions. It was also somewhat soluble in water.[12]

Anal. Calcd. for $C_8H_{16}N_2O$: C, 61.50; H, 10.32; N, 17.93. Found: C, 61.81; H, 10.12; N, 17.73.

α-Piperidino-β-tetrahydroquinolinobenzylacetone.—To 34 ml. of absolute alcohol were added 34 g. (0.110 mole) of α-bromo-β-piperidinobenzylacetone[4] and 29 g. (0.218 mole) of tetrahydroquinoline dissolved in 28 ml. of absolute alcohol. The reaction took place with evolution of heat and was complete in about two hours, at the end of which time the precipitate was filtered. This was purified by four recrystallizations from chloroform and alcohol giving 20 g. (0.0534 mole) of white crystalline product, m. p. 126–127°, 48.5% yield.

Anal. Calcd. for $C_{24}H_{30}N_2O$: C, 79.51; H, 8.34; N, 7.73. Found: C, 79.58; H, 8.37; N, 7.67.

This reaction was also carried out in ether giving a product, m. p. 126–127°, 12.7% yield. A mixed melting point experiment with this compound made in alcohol gave m. p. 126–127°.

Hydrolysis of this diamino ketone was carried out in the same manner as described above for α-piperidino-β-tetrahydroisoquinolinobenzylacetone. The oxime of α-piperidinoacetone was isolated as in the previous case in good yield, m. p. 122–123°.

Decomposition of α-Bromo-β-tetrahydroisoquinolinobenzylacetone in Alcohol.—In 10 ml. of absolute alcohol was placed 5.5 g. (0.0154 mole) of α-bromo-β-tetrahydroisoquinolinobenzylacetone and the mixture was allowed to stand at room temperature for one day. It was then placed in an ice-box for three hours, filtered, and the precipitate washed well with water. This was recrystallized from chloroform and alcohol, m. p. 168–170°. A mixed melting point experiment with α,β-di-tetrahydroisoquinolinobenzylacetone gave m. p. 169–170°. The yield was 1.65 g. (0.00402 mole) or 78.4% based on the possible theoretical amount, and a 26% yield based on the original amount of bromo-amino ketone.

To the reaction mixture filtrate was added 2.66 g. (0.0306 mole) of morpholine and the solution allowed to stand at room temperature for two days. It was then placed in an ice-box for two hours and filtered. The precipitate was washed well with water and recrystallized from chloroform and alcohol, m. p. 159–160°. A mixed melting point experiment with α,β-di-morpholinobenzylacetone[3a] gave m. p. 159–160°. The yield was 0.27 g. (0.00085 mole) or 8.29% based on the possible theoretical amount, and a 5.5% yield based on the original amount of bromo-amino ketone.

No appreciable decomposition of this bromo-amino ketone in absolute ether was noted when suspensions were kept at room temperature for two days. Over 95% of the unchanged bromo-amino ketone was recovered.

Decomposition of α-Bromo-β-morpholinobenzylacetone in Alcohol.—To 10 ml. of absolute alcohol was added 4.5 g. (0.0144 mole) of α-bromo-β-morpholinobenzylacetone,[3a] the mixture was allowed to stand at room temperature for one day, and then placed in an ice-box for two hours. The precipitate was filtered and washed with a 50% alcohol solution and finally with water, m. p. 158–160°. Further purification did not change this melting point. A mixed melting point experiment with α,β-di-morpholinobenzylacetone[3a] gave m. p. 158–160°. The yield was 0.7 g. (0.0022 mole) or a 45.8% yield based on the theoretically possible amount, and a 15.3% yield based on original amount of bromo-amino ketone.

To the reaction mixture filtrate was added 3.83 g. (0.0288 mole) of tetrahydroisoquinoline. Heat was evolved and the reaction was complete after standing at room temperature for four hours. At the end of this time it was placed in the ice-box for one hour and filtered. The precipitate was washed with a 50% alcohol solution and finally with water. It was recrystallized from chloroform and alcohol, m. p. 169–170°. A mixed melting point experiment with α,β-di-tetrahydroisoquinolinobenzylacetone gave m. p. 169–170°. The yield was 1.85 g. (0.00452 mole) or a 47.1% yield based on the theoretically possible amount, and a 31.4% yield based on original amount of bromo-amino ketone.

Reduction of α-Bromo-β-piperidinobenzylacetophenone[5] with Hydrogen and Platinum.—A mixture of 0.1 g. of platinum oxide catalyst and 1 g. (0.00269 mole) of α-bromo-β-piperidinobenzylacetophenone[5] dissolved in 10 ml. of dry benzene was reduced under a pressure of 1.2 atmospheres of hydrogen and at 28°. The theoretical amount of hydrogen was taken up in five minutes, the mixture was filtered, and the white precipitate (0.36 g.) shown to be piperidine hydrobromide. The filtrate was evaporated and the resulting oil taken up in alcohol. A brown crystalline product came out which gave a red-violet test with ferric chloride and which gave after two recrystallizations from alcohol, 0.4 g. (0.0019 mole) of white plates, m. p. 71–72°, yield 71%. A mixed melting point experiment with benzylacetophenone gave m. p. 70–72°. This relatively pure compound gave a negative test with ferric chloride.

Since it was discovered that these bromo-amino ketones readily release iodine from acid solutions of potassium

(12) An oxime of α-piperidinoacetone has been prepared and reported as melting at 104° by Stoermer, *Ber.*, **28**, 1251 (1895).

iodide, it was hoped that in this way these substances might be reduced to β-amino ketones. Unfortunately, only complicated condensation products containing neither halogen nor nitrogen resulted from such experiments.

Reduction of α-Bromo-β-piperidinobenzalacetophenone.[7]—A mixture of 0.1 g. of platinum oxide catalyst and 1 g. (0.0027 mole) of α-bromo-β-piperidinobenzalacetophenone[7] dissolved in 10 ml. of dry benzene was reduced under 1.2 atmospheres of hydrogen at about 28°. The theoretical amount of hydrogen was taken up in about five minutes at the end of which time the reaction mixture was filtered. The filtrate was concentrated and petroleum ether was added and an oil came out which defied attempts at crystallization from either benzene or ether. However, when taken up in alcohol and water a brown solid came out which upon two recrystallizations from alcohol and water gave 0.5 g. (0.00223 mole) of product, m. p. 74–76°. This compound gave a red-violet coloration with ferric chloride and a mixed melting point experiment with dibenzoylmethane gave m. p. 74–76°. The yield amounted to 82.7%.

Addition of Hydrogen Bromide to α-Bromobenzalacetophenone.—α-Bromobenzalacetophenone[2] (4 g.) was dissolved in 15 ml. of ether and dry hydrogen bromide passed into the solution at −5° for twenty minutes. After standing for two hours the white precipitate (5.55 g.) was removed, m. p. 156–158°. A mixture of this product with α,β-di-bromobenzylacetophenone prepared from benzalacetophenone melted at 156–158°.

Addition of Hydrogen Bromide to α-Piperidinobenzalacetophenone.[5]—Dry hydrogen bromide was passed into a dry benzene solution of α-piperidinobenzalacetophenone at 0°. The solution first turned colorless and then red again, indicating decomposition of the addition products. The only product that could be obtained from this reaction was piperidine hydrobromide, which precipitated from the original reaction mixture on standing for two days in the ice-chest.

Summary

1. Tetrahydroisoquinoline, for which a good method of preparation is described, has been found to react with α,β-di-bromobenzylacetone and α-bromobenzalacetone in a manner analogous to that of other strongly basic, heterocyclic, secondary amines.

2. The reactions of tetrahydroisoquinoline, tetrahydroquinoline, morpholine, and piperidine with α-bromo-β-tetrahydroisoquinolinobenzylacetone are discussed.

3. The reactions of tetrahydroisoquinoline with α-bromo-β-piperidinobenzylacetone and with α-bromo-β-morpholinobenzylacetone were investigated.

4. The effects of solvent medium and the relative basic strengths of the secondary amines used in these reactions are discussed with regard to the course of these reactions.

5. Further information is presented with regard to the structure of the addition products from the reaction of α-bromo-α,β-unsaturated ketones and secondary amines. Mechanisms for these reactions have been outlined.

LINCOLN, NEBRASKA RECEIVED SEPTEMBER 29, 1942

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

α,β-Unsaturated Aminoketones. VII.[1] Reaction of Piperidine and N-Methylbenzylamine with Bromine Derivatives of Benzalacetone and Benzalacetophenone

BY NORMAN H. CROMWELL AND IVAN H. WITT

In the first paper[2] in this series, it was reported that diethylamine reacted with α,β-dibromobenzylacetophenone to give only α-N-diethylaminobenzalacetophenone. Subsequent investigations[3] have shown that strong heterocyclic secondary amines such as morpholine, piperidine, pyrrolidine, etc., not only give the unsaturated amino ketone but also an α,β-diamino ketone in these reactions. Also these bases were found to add to the corresponding α-bromo-α,β-unsaturated ketone to give quite active bromo amino ketones. It has not been possible to isolate these addition products using diethylamine.

The present study was carried out in order to check this difference in reaction of open-chain secondary amines as compared with heterocyclic secondary amines.

For comparative purposes, 1-phenyl-3-piperidinobutene-2-one-1 (I) was prepared in the usual way from benzoylacetone. Piperidine was found to add readily to α-bromobenzalacetone to give an addition product whose structure has been assigned[1] as α-bromo-β-piperidinobenzylacetone (II). This addition product, which was quite unstable, reacted with sodium ethoxide to give

(1) For paper VI of this series, see Cromwell and Cram, THIS JOURNAL, **65**, 301 (1943).
(2) Cromwell, *ibid.*, **62**, 1672 (1940).
(3) Cromwell, *ibid.*, **62**, 2897, 3470 (1940); **63**, 837, 2984 (1941).