This resistance can be overcome by the use of digestion mixtures containing 20% alcohol. It is suggested that the effect of the alcohol may be due to an inhibition of antiproteases present in the serum.

2. Tryptic digestion of serum proceeded smoothly in concentrations of 10 to 30% alcohol for as long as two weeks, at which time approximately 70 to 80% of the potential amino groups had been liberated.

3. Concentrations of alcohol higher than 30% inhibited tryptic digestion of serum, but appreciable hydrolysis occurred even in 60% alcohol.

4. Efficient digestion of several other proteins (casein, lactalbumin, soy bean protein, egg albumin) was obtained in the presence of alcohol (20%).

5. Digestion at 60°, instead of the more usual 37°, was less rapid and complete when alcohol (20%) was present in the digestion mixture.

6. It is suggested that ethyl alcohol is a useful reagent for preventing putrefaction during tryptic digestion.

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

# $\alpha,\beta$-Diamino Ketones. II.[1] Reactions of Thalline and Open Chain Secondary Amines with $\alpha$-Bromo-$\beta$-aminoketones

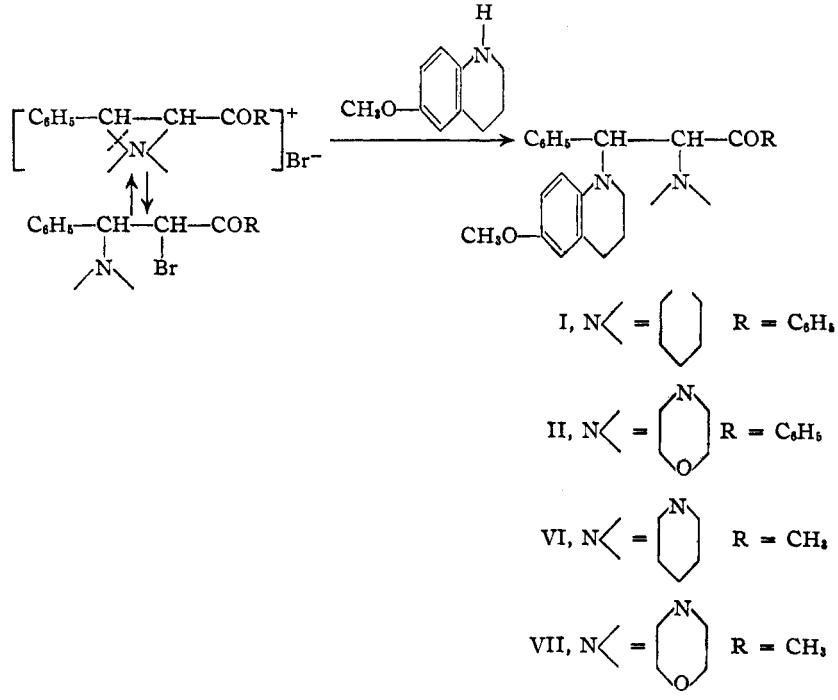
BY NORMAN H. CROMWELL, JOHN A. CAUGHLAN[2] AND GORDON F. GILBERT

A wide variety of mixed diamino ketones may be prepared from $\alpha$-bromo-$\alpha,\beta$-unsaturated ketones. Since tetrahydroquinoline had been shown to react with $\alpha$-bromo-$\beta$-aminoketones to give excellent yields of mixed diamino ketones[3] it seemed important to prepare for chemotherapeutic investigations the analogous tetrahydro-6-methoxyquinolino (thallino) compounds. Thalline for these investigations was prepared by a high pressure reduction of 6-methoxyquinoline using hydrogen and a copper chromite catalyst. The 6-methoxyquinoline was prepared by a modified Skraup reaction.

$\beta$-Piperidino- and $\beta$-morpholino - $\alpha$ - bromobenzylacetophenone and the corresponding benzylacetones reacted readily with thalline to give good yields of the mixed diamino ketones.

The only diamino ketone which had been prepared by treating an $\alpha$-bromo-$\beta$-amino ketone with an open chain type of secondary amine was $\alpha,\beta$-di-N-methylbenzylaminobenzylacetophenone.[4] Since this product was obtained in such low yields it seemed of interest to establish whether or not such low yields are to be expected generally when an open chain secondary amine is used in these reactions.

It was found that $\beta$-piperidino-$\alpha$-bromobenzylacetophenone and $\beta$-piperidino-$\alpha$-bromobenzylacetone reacted with N-methylbenzylamine, di-




benzylamine and N-methylethanolamine[5] to give from fair to poor yields, of the mixed diamino ketones.

It has been shown previously[3b] that these reactions give the best yields of the mixed diamino

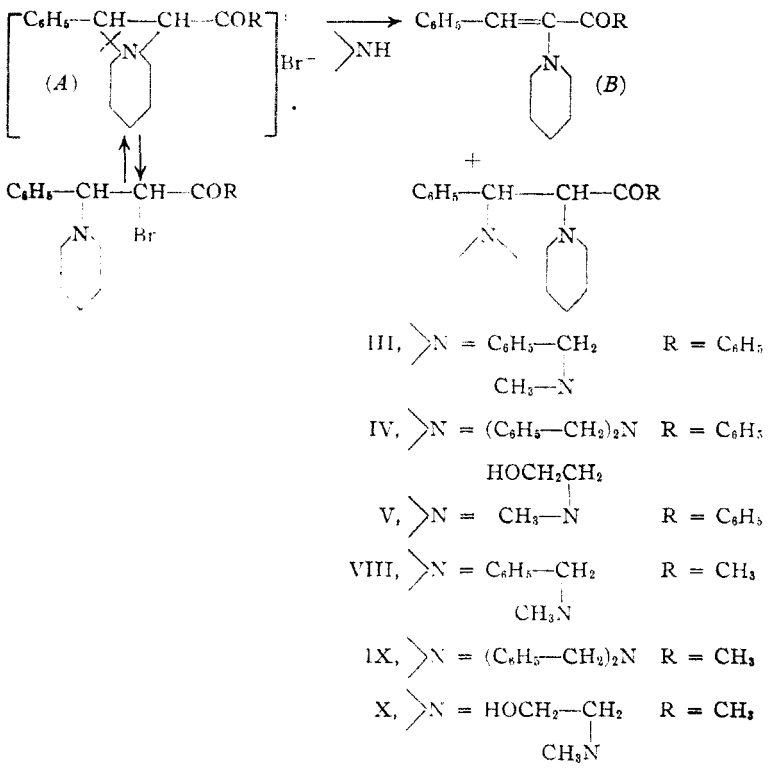
(1) For the previous paper in this series see: Cromwell, Harris and Cram, THIS JOURNAL, 66, 134 (1944).

(2) Eastman Kodak Co. Fellow, 1942–1943.

(3) (a) Cromwell, THIS JOURNAL, 63, 2984 (1941); (b) Cromwell and Cram, *ibid.*, 65, 301 (1943).

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

(5) The N-methylethanol amine for these experiments was generously furnished to us by the Carbide and Carbon Chemicals Corporation, New York, N. Y.




ketones when the amine used is a weaker base than the amine used to form the α-bromo-β-amino ketone. In all of these present cases this condition has been met, but a major portion of the reaction seems to have proceeded in such a manner as to form the colored α-piperidinobenzalacetophenone and α-piperidinobenzalacetone (B).

This difference in the nature of the reactions of α-bromo-β-aminoketones with heterocyclic secondary amines as compared with the reactions with open chain secondary amines can possibly be explained on the basis of the relative steric effects of these two types of amines on the relative rates of the two competing reactions. The formation of the mixed diamino ketones from the quaternary ammonium salt (A) comes about through an attack of the amine, >NH, at the β-carbon atom. Open chain secondary amines might be expected to be more hindered in their approach to the β-carbon atom than the heterocyclic secondary amines such as thalline, etc. Moreover, the α-piperidino-α,β-unsaturated ketones (B) are formed from (A) by loss of a proton from the α-carbon atom of (A) followed by rearrangement to the products (B). This latter reaction to form (B) is more dependent on the basic strength and less dependent on the structure of the amine, >NH, than the former reaction that leads to the mixed diamino ketone. Thus the rate of formation of the mixed diamino ketone is slowed so as to allow more of (A) to be converted into (B), when open chain secondary amines are used in these reactions. The very low yields of the mixed diamino ketones experienced when N-methylethanolamine was used were probably due to a combination of the steric factor and the considerable strength of this base.

TABLE I

PHYSICAL AND ANALYTICAL DATA

| Mixed diamino ketones | No. | M. p., °C., dec. | Yield, % | Formula | Percentage composition Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|
| Benzylacetophenones | | | | | | | | |
| α-Piperidino-β-thallino- | (I) | 160 | 85 | $C_{30}H_{34}N_2O_2$ | 79.26 | 7.54 | 79.06 | 7.82 |
| α-Morpholino-β-thallino- | (II) | 143 | 68 | $C_{29}H_{32}N_2O_3$ | 76.28 | 7.07 | 76.27 | 7.22 |
| α-Piperidino-β-N-methylbenzylamino- | (III) | 140 | 36 | $C_{28}H_{32}N_2O$ | 81.51 | 7.82 | 81.50 | 7.94 |
| α-Piperidino-β-dibenzylamino- | (IV) | 175 | 13 | $C_{34}H_{36}N_2O$ | 83.56 | 7.43 | 83.46 | 7.49 |
| α-Piperidino-β-N-methylethanolamino- | (V) | 108 | 10 | $C_{29}H_{30}N_2O_2$ | 75.37 | 8.25 | 75.48 | 8.32 |
| Benzylacetones | | | | | | | | |
| α-Piperidino-β-thallino- | (VI) | 124 | 39 | $C_{25}H_{32}N_2O_2$ | 76.49 | 8.17 | 76.35 | 8.43 |
| α-Morpholino-β-thallino- | (VII) | 126 | 40 | $C_{24}H_{30}N_2O_3$ | 73.06 | 7.69 | 72.96 | 7.78 |
| α-Piperidino-β-N-methylbenzylamino- | (VIII) | 111 | 14 | $C_{23}H_{30}N_2O$ | 78.81 | 8.63 | 78.67 | 8.59 |
| α-Piperidino-β-dibenzylamino- | (IX) | 160 | 4 | $C_{29}H_{34}N_2O$ | 81.65 | 8.03 | 81.41 | 8.08 |
| α-Piperidino-β-N-methylethanolamino- | (X) | 132 | 5 | $C_{18}H_{28}N_2O_2$ | 71.01 | 9.27 | 70.96 | 9.11 |

## Experimental[6]

**6-Methoxyquinoline.**—A modified Skraup reaction[7] was applied to this preparation. In a liter round-bottom flask were placed 14 g. of well-powdered ferrous sulfate, 50.6 g. (0.41 mole) of *p*-anisidine and 36.8 g. (0.24 mole) of *p*-nitroanisole. A solution of 25 g. of boric acid dis-

(6) All m. p.'s were obtained by placing the sample in the bath about 10° below the m. p. and heating at the rate of 3° per minute. Micro-Dumas analyses for nitrogen and semi-micro carbon-hydrogen analyses are by the Analytical Laboratory, Department of Chemistry, University of Nebraska, under supervision of H. Armin Pagel.

(7) E. W. Cohn, THIS JOURNAL, **52**, 3685 (1930).

solved in 150 g. (1.63 mole) of dry glycerol was then added and the flask contents thoroughly mixed. To this mixture was then slowly added 69.8 ml. of 95% sulfuric acid with good stirring. The mixture was refluxed over a direct flame for twenty hours. The reaction solution was then diluted with one half its volume of water and cooled to 0° to precipitate some unchanged *p*-nitroanisole which was filtered off.

The filtrate was steam distilled to remove the last traces of *p*-nitroanisole, cooled and made alkaline with strong sodium hydroxide. The mixture was again steam distilled until the distillate was clear. The distillate was extracted with benzene and the benzene extract evaporated to give an oil which was diazotized with saturated sodium nitrite solution in an acid mixture of 20 ml. of concd. sulfuric acid and 150 ml. of water. After allowing the diazotized mixture to stand for one hour at 0° it was steam distilled for about two hours. The residual solution was then made alkaline and the 6-methoxy-quinoline steam distilled, and extracted from the distillate with benzene. The product was distilled under reduced pressure to give 35 g. of a light yellow oil, b. p. 182–184° (34 mm.) (yield 53% based on *p*-anisidine). This product was quite pure, m. p. 18–20°.[8]

**Tetrahydro-6-methoxyquinoline (Thalline).**—A solution of 88.5 g. (0.555 mole) of 6-methoxyquinoline dissolved in 175 ml. of absolute alcohol, and 9 g. of copper chromite catalyst[9] were placed in the bomb of a high pressure hydrogenator. This mixture was reduced under a pressure of 1800 lb./sq. in., and at a temperature of 180°, the theoretical amount of hydrogen being absorbed in fifteen minutes. The product was purified by vacuum distillation to give 84.1 g. (93% yield) of a pale yellow oil, b. p. 127–130° (1 mm.). The oil solidified on cooling, m. p. 42–43°[8]; $n_{50}$, 1.5718. The bright yellow picrate, which is not very stable in air was prepared, m. p. 164–165°.[10]

### Mixed α,β-Diaminobenzylacetophenones and Mixed α,β-Diaminobenzylacetones

**α-Piperidino-β-thallinobenzylacetophenone (I).**—A suspension of 11.2 g. of α-bromo-β-piperidinobenzylacetophenone[11] in 18 ml. of absolute alcohol was treated with 9.7 g. of thalline. The mixture was warmed on a water-bath to 70° for one hour with frequent shaking. The clear orange solution was then cooled in the ice chest for five hours to give a yellow precipitate. The precipitated material was filtered, washed with 95% alcohol, water, then 95% alcohol and dried, to give 10.6 g. of a bright yellow solid, m. p. 151–153°. This crude product was recrystallized successively from chloroform and alcohol, and from benzene and petroleum ether and dried under vacuum at 90° for two hours, m. p. 159–160°.

The other new mixed diamino ketones prepared by essentially this same procedure were: (II) from α-bromo-β-morpholinobenzylacetophenone[12] and thalline; (VI) from α-bromo-β-piperidinobenzylacetone,[4] and thalline; and (VII) from α-bromo-β-morpholinobenzylacetone[13] and thalline.

**α-Piperidino-β-N-methylbenzylaminobenzylacetophenone (III).**—α-Bromo-β-piperidinobenzylacetophenone[11] (23.5 g., 0.063 mole) was made pasty with a 25% absolute alcohol–75% dry ether solution, and 15.3 g. (0.126 mole) of N-methylbenzylamine[14] added. After the mixture had stood at room temperature for twelve hours, it was placed in the ice chest for two days. The yellow precipitate was filtered off and purified in the previously described manner, to give 9.3 g. of light yellow needles, m. p. 138–140°.

The other new mixed diamino ketones prepared by essentially this same procedure were (V) from α-bromo-β-piperidinobenzylacetone[4] and N-methylethanolamine[5]; (VIII) from α-bromo-β-piperidinobenzylacetone and N-methylbenzylamine; and (X) from α-bromo-β-piperidinobenzylacetone and N-methylethanolamine, the product, however, was recrystallized from alcohol and water.

**Hydrolysis of (III).**—This diamino ketone (III) (5.0 g.) was heated on the steam-bath with 30 ml. of 15% sulfuric acid for two hours. The precipitated benzaldehyde was extracted with ether. Neutralization of the residual acid solution gave an oily precipitate which was removed by ether extraction. The ether extract was evaporated and the residual oil taken up in a small amount of methyl alcohol to which was added 8.5 g. of potassium hydroxide and 4.35 g. of hydroxylamine hydrochloride in 50 ml. of methyl alcohol and 9 ml. of water. After this reaction mixture had stood at room temperature for two days it was neutralized with dilute hydrochloric acid to give a white precipitate. Several recrystallizations of this product from alcohol and water gave 1.5 g. of white plates, m. p. 112–115°. This product was identical with a mixture of the high and low melting forms of the oxime of ω-piperidinoacetophenone, prepared from ω-piperidinoacetophenone.

*Anal.* Calcd. for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.69; H, 8.50; N, 12.59.

**α-Piperidino-β-dibenzylaminobenzylacetophenone (IV).**—Freshly prepared α-bromo-β-piperidinobenzylacetophenone[11] (6.0 g., 0.0161 mole) was suspended in 15 ml. of absolute alcohol, and 6.35 g. (0.0322 mole) of dibenzylamine added. After standing at room temperature for twelve hours, the mixture was cooled in the icebox for forty-eight hours. A bright yellow precipitate formed. The solution was filtered and the precipitate washed with chloroform. The insoluble amine hydrobromide remained. The chloroform was partially evaporated from the diamino ketone and alcohol was added. A yellow precipitate was obtained which weighed 1.0 g., m. p. 167–169°, dec. This was recrystallized from benzene and petroleum ether to give bright yellow needles, m. p. 173–175°, dec.

**α-Piperidino-β-dibenzylaminobenzylacetone (IX).**—Freshly prepared α-bromo-β-piperidinobenzylacetone[4] (23.0 g., 0.074 mole) was made pasty with a 37% absolute alcohol–63% dry ether solution, and 29.5 g. (0.150 mole) of dibenzylamine added. After standing at room temperature for thirty minutes the mixture was cooled in the ice chest for four days to give a white precipitate. The solution was filtered and the precipitate was suspended in warm chloroform and again filtered. The insoluble amine hydrobromide remained. The chloroform was evaporated from the diamino ketone and the resulting oil taken up in ether, washed with three 25-ml. portions of water and dried over anhydrous sodium sulfate. This was filtered and the ether partially evaporated and petroleum ether added. A white precipitate was obtained which weighed 1.2 g., m. p. 144–148°, dec. This was recrystallized from 95% alcohol to give white crystals, m. p. 158–160°, dec.

## Summary

1. A method of preparing tetrahydro-6-methoxyquinoline (thalline) has been described.

2. The preparation of ten new mixed diamino ketones has been outlined, and the general nature of the reaction of open chain secondary amines with α-bromo-β-amino ketones discussed.

LINCOLN, NEBRASKA RECEIVED OCTOBER 14, 1943

(8) Z. H. Skraup, *Monatsh.*, **6**, 760–784 (1885).

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

(10) Heilbron, "Dictionary of Organic Compounds," Vol. III, p. 740.

(11) Dufraisse and Moureu, *Bull. soc. chim.*, [IV] **41**, 466 (1927).

(12) Cromwell, THIS JOURNAL, **62**, 2897 (1940).

(13) Cromwell, *ibid.*, **62**, 3470 (1940).

(14) Cromwell, Babson and Harris, *ibid.*, **65**, 313 (1943).