enediamine. Therefore, the variation of acetylene obtained upon hydrolysis of a given material with respect to lithium before and after this decomposition treatment is a direct measure of the monolithium acetylide·ethylenediamine content. Definitions follow.

A = moles acetylene initially per mole of lithium
A_f = moles acetylene present after decomposition per mole of lithium
L = moles lithium present in initial sample
L_f = moles lithium present in decomposed sample
a = moles dilithium acetylide per mole of lithium
b = moles monolithium acetylide·ethylenediamine per mole of lithium

$$A/L = a + b \qquad b = 2(A/L - A_f/L_f)$$

$$A_f/L_f = a + \frac{b}{2} \qquad a = (A/L - b)$$

B. Procedure.—The apparatus employed was the same as that used in the N-lithioethylenediamine determination. After thoroughly flushing the apparatus with argon, water (15 ml.), which had been previously saturated with acetylene, was placed in the reactor and allowed to equilibrate. A sample (about 0.35 g. in a gelatin capsule) was hydrolyzed and the volume increase (v), room temperature (t), and atmospheric pressure (p) were noted.

$$\text{moles acetylene} = \frac{v}{22{,}030} \cdot \frac{(p - p')}{760} \cdot \frac{273}{263 + t}$$

Ethylenediamine and total lithium were determined on the aforementioned solution as described under procedure for N-lithioethylenediamine.

$$\text{moles ethylenediamine} = E = \frac{(\text{ml. NaOH} - B_E)}{2000} \times \frac{(\text{normality NaOH})}{(\text{normality HCl})}$$

$$\text{total moles lithium} = L = \frac{(\text{ml. HCl} - B_h)}{1000}(\text{normality HCl}) - E$$

A sample was decomposed in a vacuum desiccator at 125° for 24 hr. at 1 mm. Samples (0.14 g.) of the resulting material were taken and analyzed as before for moles acetylene, A_f, and moles lithium, L_f.

$$\%\ \text{monolithium acetylide·ethylenediamine} = \frac{9207\,bL}{W}$$

$$\%\ \text{dilithium acetylide} = \frac{3800\,aL}{W}$$

$$\%\ \text{N-lithioethylenediamine} = \frac{6604\,(L - 2aL - bL - L_h)}{W}$$

$$\%\ \text{ethylenediamine} = \frac{6010\,[E - (L - 2aL - L_h)]}{W}$$

where L_h = moles lithium hydroxide
E = moles ethylenediamine

Lithium hydroxide was determined independently by the same method used for its determination in N-lithioethylenediamine.

Acknowledgment.—The authors wish to thank Dr. H. G. Kuivila of the University of New Hampshire for many stimulating discussions during the course of this work.

Amine Exchange Reactions. Mannich Bases from Primary Aliphatic Amines and from Amino Acids[1]

J. CYMERMAN CRAIG, S. R. JOHNS,[2] AND M. MOYLE

Department of Pharmaceutical Chemistry, University of California, San Francisco 22, California

Received April 8, 1963

The exchange reaction between tertiary Mannich bases (I) and primary alkylamines has been shown to give the monosubstituted secondary Mannich bases (II), and the nonavailability of the latter by the normal Mannich reaction is accounted for by their instability to base, including the basic group in the same molecule. The exchange reaction has been further extended by the use of amino acids as the primary alkylamines and makes readily available the amino acid Mannich bases of type V, of possible application for N-terminal labeling of peptides.

The Mannich condensation between ketones, formaldehyde, and secondary alkylamines affords tertiary Mannich bases of type I.[3]

The reaction using primary alkylamines is more complicated since the first-formed product (II) can react further with the ketone and formaldehyde to give a bis-Mannich base (III). Considerable disagreement exists in the literature with regard to the actual products obtained in the reaction between ketones, formaldehyde, and primary alkylamines. Mannich and Heilner[4] report the preparation of bis(β-benzoylethyl)methylamine (IIIa) ,as well as β-methylaminopropiophenone (IIa) from the condensation between acetophenone, formaldehyde, and methylamine hydrochloride in the molar ratio 2:2:1. Blicke and Burckhalter[5] obtained the same products (IIIa and IIa) using equivalent amounts of the three reagents. Mannich and Heilner[4] found that steam distillation converted IIIa to IIa, while treatment of IIa with alkali[5] led to IIIa, also formed by reaction of phenyl vinyl ketone with methylamine. Warnat[6] reported yet a third product, N-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (IVa); this work was confirmed by Mannich and Hieronimus.[7] Plati and Wenner[8] have shown that the product isolated and assumed by Blicke and Burckhalter[5] to be the bis-Mannich base (IIIa) was in fact the substituted piperidine (IVa) obtained by Warnat. Plati and Wenner[8] suggest that this piperidine derivative is not a primary product of the Mannich reaction, but is formed from the bis-Mannich base (IIIa) *via* an internal Claisen reaction brought about by the action of alkali used in the isolation procedure by the previous

(1) This work was partially supported by a grant (HE-5881) from the National Institutes of Health, U. S. Public Health Service, and by the N.S.W. Cancer Council.

(2) Department of Organic Chemistry, University of Sydney, Sydney, Australia.

(3) (a) F. F. Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 303; (b) Houben-Weyl, "Methoden der Organischen Chemie," Georg Thieme Verlag, Stuttgart, 1957, p. 731; (c) B. Reichert, "Die Mannich Reaktion," Springer Verlag, Berlin, 1960.

(4) C. Mannich and G. Heilner, *Ber.*, **55**, 356 (1922).

(5) F. F. Blicke and J. H. Burckhalter, *J. Am. Chem. Soc.*, **64**, 451 (1942).

(6) W. Warnat, "Festschrift Emil Barell," Hoffman-LaRoche Inc., Basle, 1936, p. 255.

(7) C. Mannich and O. Hieronimus, *Ber.*, **75**, 49 (1942).

(8) J. T. Plati and W. Wenner, *J. Org. Chem.*, **14**, 543 (1949).

workers. When the methylamine hydrochloride was replaced by other primary alkylamine salts, *viz.* ethylamine and *n*-butylamine hydrochlorides, Plati, Schmidt, and Wenner[9] again obtained the substituted piperidines IVb and IVc, respectively, with only low yields of the monosubstituted Mannich bases (II).

The Mannich reaction using primary alkylamines is obviously not a satisfactory method for the preparation of monosubstituted secondary Mannich bases (II). These bases have now been obtained in good yields by the use of amine exchange reactions between primary alkylamines and Mannich bases derived from secondary alkylamines. Both β-diethylaminopropiophenone (Ib) and β-dimethylaminopropiophenone (Ia) were used as the original tertiary Mannich bases.

When equimolar quantities of cyclohexylamine and β-diethylaminopropiophenone (Ib) hydrochloride were refluxed in ethanol for one hour, treatment of the reaction mixture with base and preparation of the hydrochloride afforded a crystalline solid of constant melting point with analysis for a mixture of the hydrochlorides of β-cyclohexylaminopropiophenone (IId) and bis(β-benzoylethyl)cyclohexylamine (IIId). Double decomposition of this hydrochloride mixture with lithium picrate invariably gave N-cyclohexyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (IVd) picrate, all attempts to isolate β-cyclohexylaminopropiophenone picrate being unsuccessful. The identity of the product as the substituted piperidine and not the isomeric bis-Mannich base was shown by infrared spectroscopy. The product possessed strong hydroxyl absorption at 3400 cm.$^{-1}$ as well as the 1675-cm.$^{-1}$ (PhCO–) absorption band.

When the reaction was carried out at room temperature, N-cyclohexyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (IVd) crystallized from the reaction mixture in 98% yield. The presumed first-formed monoderivative (IId) had evidently reacted further with the starting material (Ib) to give the bis-Mannich base (III), which under the basic conditions of the reaction cyclized to the piperidine (IV).

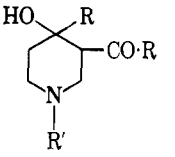
$$Ph\cdot CO\cdot CH_2CH_2\overset{+}{\underset{H}{N}}Et_2 + C_6H_{11}NH_2 \longrightarrow PhCOCH_2CH_2NHC_6H_{11} + Et_2NH_2^+$$

$$PhCOCH_2CH_2\overset{+}{\underset{H}{N}}HEt_2 + PhCOCH_2CH_2NHC_6H_{11} \rightleftharpoons (PhCOCH_2CH_2)_2N\cdot C_6H_{11} + Et_2\overset{+}{\underset{H}{N}}H_2$$

The higher yields of piperidine derivative obtained at the lower temperature suggest that the exchange reaction is an equilibrium which is forced to the piperidine derivative at room temperature by the low solubility of this product in the solvent and its removal from the reaction by precipitation. The formation of the bis-Mannich base (III), which in turn is converted to the piperidine derivative, depends upon the reaction between the first-formed secondary Mannich base and the original tertiary Mannich base. To undergo exchange with the tertiary base, this secondary Mannich base must compete with the cyclohexylamine present. The presence of excess cyclohexylamine should suppress this reaction with an expected increase in yield of the secondary monosubstituted base (IId). The reaction using a fivefold excess of cyclohexylamine, however, afforded the substituted piperidine almost quantitatively. The addition of the free tertiary Mannich base to an ice-cold solution of cyclohexylamine hydrochloride in ethanol, thus assuring a large excess of cyclohexylamine, again afforded the piperidine as the only product. When β-dimethylaminopropiophenone (Ia) hydrochloride was used in place of the diethyl derivative, the exchange with cyclohexylamine again proceeded smoothly with the formation of the substituted piperidine (IVd).

$R\cdot COCH_2CH_2\cdot NR'_2$ (I) $\quad$ $R\cdot COCH_2CH_2\cdot NHR'$ (II)

$(R\cdot COCH_2CH_2)_2NR'$ (III)



IV

$R\cdot COCH_2CH_2\cdot NHCHR'COOH$ (V)

$(R\cdot COCH_2CH_2)_2NCHR'COOH$ (VIII)

(a) R = Ph, R′ = Me
(b) R = Ph, R′ = Et
(c) R = Ph, R′ = *n*-Bu
(d) R = Ph, R′ = cyclohexyl
(e) R = Ph, R′ = H
(f) R = Ph, R′ = CH_2COOH
(g) R = Ph, R′ = CH_2Ph
(h) R = Ph, R′ = CH_2CONH_2
(i) R = Ph, R′ = CH_2CH_2COOH
(j) R = Me, R′ = Et
(k) R = Me, R′ = CH_2Ph

However, the desired β-cyclohexylaminopropiophenone (IId) was finally obtained in 92% yield when β-diethylaminopropiophenone base and excess cyclohexylamine were allowed to stand at room temperature for fifty hours, or when heated at 100° for two hours. During these reactions, diethylamine was liberated from the reaction mixture. The monosubstituted secondary Mannich base (IId) was isolated from the reaction mixture as its hydrochloride or picrate by removal of the excess of cyclohexylamine under reduced pressure and direct precipitation of the salt from an ethereal solution. No analytically pure sample of the free base could be prepared since distillation under high vacuum yielded a colorless liquid which could not be completely freed of cyclohexylamine. Chromatography of the pure picrate on alumina afforded not the expected free secondary Mannich base (IId), but the N-cyclohexylpiperidine derivative (IVd), and the alumina had clearly converted the monosubstituted secondary amine to the bis-Mannich base which in turn cyclized to the more stable piperidine derivative. The same problem was encountered when an attempt was made to obtain the pure free base (IId) from the hydrochloride. Dissolution of the hydrochloride in ethanol and addition of an equivalent of sodium hydroxide solution resulted in the crystallization of the piperidine derivative. However, treatment of an aqueous solution of the hydrochloride with ice-cold aqueous alkali followed by *immediate* ether extraction and preparation of the hydrochloride or picrate afforded the salts of the monosubstituted product. Treatment of the hydrochloride of IId with base and immediate

(9) J. T. Plati, R. A. Schmidt, and W. Wenner, *J. Org. Chem.*, **14**, 873 (1949).

treatment with benzenesulfonyl chloride in the cold similarly led to the isolation of N-benzenesulfonyl-β-cyclohexylaminopropiophenone whereas if, after addition of base, the reaction mixture was allowed to stand overnight, preparation of the benzenesulfonamide gave only N-cyclohexylbenzenesulfonamide and N-cyclohexyl - 3 - benzoyl - 4 - hydroxy - 4 - phenylpiperidine (IVd). The ease of conversion of the first-formed secondary amine (IId) to the piperidine derivative (IVd) under basic conditions was further exemplified by the slow conversion of the free base to the piperidine on standing alone. The secondary base can thus act as its own basic reagent, the replaced cyclohexylamine being slowly lost by evaporation at room temperature.

β-*n*-Butylaminopropiophenone (IIc) was similarly prepared by warming β-diethylaminopropiophenone base and excess *n*-butylamine on the water bath under distillation conditions. Diethylamine distilled from the reaction mixture leaving an oil which was characterized as β-*n*-butylaminopropiophenone (IIc) by preparation of the oxalate salt which had physical properties identical with that obtained by Plati, Schmidt, and Wenner.[9] The reaction between β-diethylaminopropiophenone hydrochloride and *n*-butylamine in 50% aqueous ethanol at room temperature resulted in the isolation of N-butyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (IVc), distinguished, as before, from the isomeric bis-Mannich base (IIIc) by the strong infrared absorption bands at 3310 cm.$^{-1}$ (OH) and 1650 cm.$^{-1}$ (PhCO). Attempts to isolate the picrate of the monosubstituted product by double decomposition of the oily hydrochloride with lithium picrate afforded the picrate of the cyclized N-butylpiperidine derivative (IVc).

Amine exchange reactions in Mannich bases may take place either by an elimination–addition mechanism to give the α,β-unsaturated ketone which undergoes a Michael addition with the second nucleophilic reagent to yield the product of exchange[10] or by an ionic mechanism when the absence of a β-hydrogen atom does not permit the formation of a vinyl ketone,[11] and the possible mechanisms are discussed in two excellent reviews.[12,13] While it is not possible to distinguish whether this reaction takes place by the elimination–addition or by the exchange mechanism, the reaction of equimolar quantities of phenyl vinyl ketone and cyclohexylamine, allowed to stand at room temperature for sixteen hours, afforded N-cyclohexyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (IVd) in good yield, indicating that if elimination is possible under such mild conditions, the addition and subsequent cyclization would occur readily.

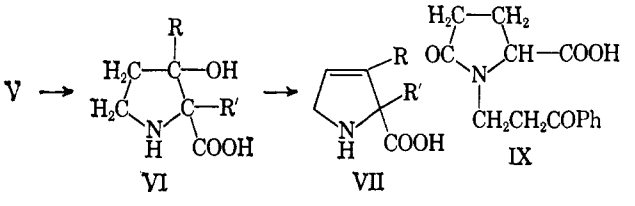
(10) (a) C. Mannich, W. Koch, and F. Borkowsky, *Ber.*, **70**, 355 (1937); (b) E. C. duFeu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937); (c) B. Reichert and H. Posemann, *Arch. Pharm.*, **275**, 67 (1937); (d) H. R. Snyder and J. H. Brewster, *J. Am. Chem. Soc.*, **70**, 4230 (1948); (e) N. H. Cromwell and D. J. Cram, *ibid.*, **65**, 301 (1943).

(11) (a) H. R. Snyder, C. W. Smith, and J. M. Stewart, *ibid.*, **66**, 200 (1944); (b) H. R. Snyder and E. L. Eliel, *ibid.*, **70**, 4233 (1948); (c) H. R. Snyder and J. H. Brewster, *ibid.*, **71**, 291 (1949); (d) H. R. Snyder and J. H. Brewster, *ibid.*, **71**, 1061 (1949); (e) H. R. Snyder and W. E. Hamlin, *ibid.*, **72**, 5082 (1950).

(12) J. H. Brewster and E. L. Eliel, "Organic Reactions," Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 99.

(13) H. Hellmann, *Angew. Chem.*, **65**, 473 (1953); H. Hellmann and G. Opitz, *ibid.*, **68**, 265 (1956); H. Hellmann and G. Opitz, "α-Aminoalkylierung," Verlag Chemie, Weinheim, 1960.

The exchange reaction between primary alkylamines and tertiary Mannich bases (I) may thus be used for the preparation of the monosubstituted secondary Mannich bases (II), and the nonavailability of the latter by the normal Mannich reaction is accounted for by their instability to base, including the basic group present in the same molecule. The ease with which tertiary Mannich bases (I) undergo amine exchange reactions suggested that amino acids could be used in place of the primary alkylamines previously described, to give amino acid Mannich bases of type V. No reference is made in the literature to the preparation of such compounds by direct reaction between a ketone, formaldehyde, and an amino acid. Since Mannich bases of type V should, moreover, readily undergo a base-catalyzed cyclization to hydroxypyrrolidines (VI) followed by dehydration to the pyrroline derivatives (VII), this reaction offers a potential method of N-terminal labeling for peptides by an amine exchange reaction between the N-terminal group of the peptide and a tertiary Mannich base with the formation of a product which on hydrolysis would give the pyrroline (VII) corresponding to the N-terminal amino acid in the original peptide.



Reaction of equimolar quantities of glycine and β-diethylaminopropiophenone (Ib) hydrochloride gave precipitation of N,N-bis(β-benzoylethyl)glycine (VIIIe) in 35% yield, and the use of two moles of Ib hydrochloride to one of glycine increased the yield of VIIIe to 55%. When one mole of glycine was made to react with only 0.5 mole of the Mannich base salt, the same material (VIIIe) was obtained in 21% yield. It was shown to be the bis-Mannich base, and not the piperidine (IVf), by formation of the bis-semicarbazone derivative, proving the presence of two free carbonyl groups. None of the monosubstituted product (Ve) was isolated. However, with α-alanine, reaction of equimolar quantities of Ib hydrochloride and the amino acid occurred normally and afforded an 82% yield of the required monosubstitution product (Va); none of the bis product (VIII) was obtained even when a molar excess of the Mannich base hydrochloride was used. Similar monosubstituted amino acid Mannich bases were readily formed from β-phenylalanine (Vg, 78%), aspartic acid (Vf, 72%), and asparagine (Vh, 85%). In several cases these products were converted to the corresponding methyl esters, the infrared spectra of which showed the presence of a keto group, indicating that they had not cyclized to the isomeric hydroxypyrrolidines (VI).

The expected product (Vi) from glutamic acid was not isolated, but cyclized to a compound identified as the lactam (IX) rather than the pyrroline (VIIi), by its infrared spectrum and the preparation of a 2,4-dinitrophenylhydrazone derivative, showing the presence of a free carbonyl group. The anomalous formation of the bis product (VIIIe) from glycine is probably

due to the high solubility of glycine and its derivatives, causing the first-formed substance (Ve) to remain in solution where it undergoes further reaction with Ia to give the insoluble bis derivative (VIIIe), the precipitation of which forces the equilibrium wholly in that direction. In the case of amino acids of higher molecular weight, the first-formed products (V) are evidently sufficiently insoluble to precipitate, and the reaction goes no further.

The amine exchange reaction with amino acids is equally applicable when tertiary aliphatic Mannich bases such as 1-diethylamino-3-butanone (Ij) are used, as shown by its reaction with β-phenylalanine to give the monosubstituted amino acid Mannich base (Vk, 81%).

The determination of molecular weights proved helpful in distinguishing between products of types V and VIII, and equivalent weight determinations were carried out by titration with perchloric acid in acetic acid solution,[14] using crystal violet as an indicator.

Since this work was completed, a publication[15] has appeared supporting our proposed route to the pyrrolines (VII). The condensation of N-tosylglycine ethyl ester with methyl vinyl ketone, or with 1-piperidino-3-butanone methiodide, gave 2-carboethoxy-3-hydroxy-3-methyl-N-tosylpyrrolidine which was readily dehydrated to 2-carboethoxy-3-methyl-N-tosyl-Δ^3-pyrroline. In view of this successful reaction, further work to complete the conversion of the similarly constituted amino acid Mannich bases (V) to the corresponding pyrrolines (VII), and the application of our amine exchange reaction to the N-terminal labeling of peptides, seems unnecessary.

Experimental[16]

N-Cyclohexyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (IVd). (**A**).—A solution of 12.05 g. of β-diethylaminopropiophenone hydrochloride and 5.0 g. of cyclohexylamine in 50 ml. of 50% aqueous ethanol was refluxed on the water bath for 1 hr., during which time a pale yellow oil separated. After cooling, diluting with water, and treating with dilute sodium hydroxide solution, the oil which separated was extracted with ether and the extract dried over anhydrous sodium sulfate. After removal of the solvent, the residual oil (7.5 g.) was converted to the hydrochloride, giving colorless prisms, m.p. 170–176°, after repeated recrystallization from acetone–ether.

Anal. Calcd. for $C_{15}H_{22}ClNO$: C, 67.3; H, 8.2; N, 5.2. Calcd. for $C_{24}H_{30}ClNO_2$: C, 72.1; H, 7.6; N, 3.5. Found: C, 70.0; H, 8.2; N, 4.7.

This constant-melting solid appears to be a mixture of the hydrochlorides of β-cyclohexylaminopropiophenone (IId) and the N-cyclohexylpiperidine derivative (IVd). N-Cyclohexyl-3-benzoyl-4-hydroxy-4-phenylpiperidine picrate separated when this hydrochloride was treated in ethanol with a saturated aqueous lithium picrate solution to give yellow prisms from ethanol, m.p. 165–167°; ν_{max} 3380 (OH), 1650 cm.$^{-1}$ (PhCO).

Anal. Calcd. for $C_{30}H_{32}N_4O_9$: C, 60.8; H, 5.4. Found: C, 60.8; H, 5.1.

(**B**).—A solution of 2.41 g. of the Mannich base (Ib) hydrochloride and 1.0 g. of cyclohexylamine in 50% aqueous ethanol was allowed to stand at room temperature. A white solid began to separate after a few minutes and after 16 hr. filtration gave 1.8 g. (98%) of N-cyclohexyl-3-benzoyl-4-hydroxy-4-phenylpiperidine as colorless needles from aqueous ethanol, m.p. 136–137°; ν_{max} 3400 (OH), 1675 cm.$^{-1}$ (PhCO).

Anal. Calcd. for $C_{24}H_{29}NO_2$: C, 79.0; H, 8.0; N, 3.85. Found: C, 79.2; H, 8.0; N, 3.6.

Picrate, yellow prisms from ethanol, had m.p. and mixture m.p. with picrate from A 165–166°. Hydrochloride, colorless plates from ethanol, had m.p. 204–205°; ν_{max} 3400 (OH), 2400 (R_3NH^+), and 1600 cm.$^{-1}$ (PhCO).

Anal. Calcd. for $C_{24}H_{30}ClNO_2$: C, 72.1; H, 7.6; N, 3.5. Found: C, 72.3; H, 7.6; N, 3.6.

(**C**).—Using a fivefold excess of cyclohexylamine and adding an alcoholic solution of the Mannich base (Ib) hydrochloride at room temperature again resulted in the isolation (in 94% yield) of N-cyclohexyl-3-benzoyl-4-hydroxy-4-phenylpiperidine, m.p. and mixture m.p. 135–136°; picrate had m.p. and mixture m.p. 165°.

(**D**).—The dropwise addition of an alcoholic solution of the free Mannich base (Ib) to an ice-cold, fivefold excess of cyclohexylamine hydrochloride in ethanol also gave the N-cyclohexylpiperidine derivative (IVd) in 95% yield.

(**E**).—Using 2.13 g. of β-dimethylaminopropiophenone (Ia) hydrochloride and 1.0 g. of cyclohexylamine in 50% aqueous ethanol at room temperature, 1.66 g. (91%) of N-cyclohexyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (IVd) crystallized from the reaction mixture as colorless needles from aqueous ethanol, m.p. and mixture m.p. 135–136°. The picrate and hydrochloride were identical with the salts from the diethylamine Mannich base reaction (A).

β-Cyclohexylaminopropiophenone (IId). (**A**).—A mixture of 2.05 g. of β-diethylaminopropiophenone and 5.0 g. of cyclohexylamine was heated on the water bath under distillation conditions for 2 hr. during which time diethylamine distilled. The excess of cyclohexylamine was removed by vacuum distillation, the temperature being kept below 60°, and 2.14 g. (92%) of a yellow oil remained. Distillation of a sample under reduced pressure gave a colorless liquid, b.p. 120–122° (10^{-4} mm.), $n^{24}D$ 1.5585.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.8; H, 9.2. Found: C, 75.6; H, 9.8.

These analytical figures suggest that a small amount of cyclohexylamine contaminates the distilled product. The hydrochloride, colorless plates from ethanol–ether, prepared by bubbling dry hydrogen chloride gas through an ice-cold ethereal solution of the undistilled base, had m.p. 175–176°.

Anal. Calcd. for $C_{15}H_{22}ClNO$: C, 67.3; H, 8.2; N, 5.2. Found: C, 67.6; H, 8.3; N, 4.9.

The picrate was prepared using an ethereal solution of picric acid, and crystallized from aqueous ethanol as yellow prisms, m.p. 136–137°.

Anal. Calcd. for $C_{21}H_{24}N_4O_8$: C, 54.8; H, 5.3; N, 12.2. Found: C, 54.9; H, 5.3; N, 11.8.

The benzenesulfonamide, prepared by the Schotten–Baumann reaction, formed colorless crystals from ethanol, m.p. 134–135°.

Anal. Calcd. for $C_{21}H_{25}NO_3S$: C, 67.9; H, 6.8; N, 3.8. Found: C, 67.8; H, 6.7; N, 3.4.

(**B**).—The Mannich base (Ib) and excess cyclohexylamine were allowed to stand at room temperature for 50 hr., the reaction mixture being open to the atmosphere to allow evaporation of the produced diethylamine. The excess of cyclohexylamine was removed and the hydrochloride (colorless plates from ethanol–ether) prepared from the resulting oil had m.p. and mixture m.p. identical with authentic β-cyclohexylaminopropiophenone hydrochloride from A, m.p. 175–176°; picrate, yellow prisms from aqueous ethanol, m.p. and mixture m.p. 136–137°. The picrate was adsorbed on activated alumina with benzene–petroleum ether and eluted with petroleum ether affording a white solid, colorless needles from aqueous ethanol, m.p. and mixture m.p. 136°, with authentic N-cyclohexyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (IVd); picrate, m.p. and mixture m.p. 165–166°.

Addition of Base to β-Cyclohexylaminopropiophenone Hydrochloride. (**A**).—A solution of 0.21 g. of the hydrochloride in 4 ml. of ethanol was treated with 4 ml. of 0.2 *N* sodium hydroxide solution. The resulting solution was diluted with water until it became cloudy and then allowed to stand. A precipitate of 0.3 g. (91.5%) of N-cyclohexyl-3-benzoyl-4-hydroxy-4-phenylpiperidine was deposited, recrystallizing as colorless needles from aqueous ethanol, m.p. and mixture m.p. 136°; picrate, m.p. 165–167°.

(**B**).—A solution of 2.5 g. of the hydrochloride in 5 ml. of water was treated with 3 *N* sodium hydroxide solution. Three milliliters of benzenesulfonyl chloride was added and the mixture shaken for 5 min., yielding a yellow semisolid. Attempts to extract with ether resulted in solidification to a solid floating at

(14) G. F. Nadeau and L. E. Branchen, *J. Am. Chem. Soc.*, **57**, 1363 (1935).

(15) A. H. Jackson, G. W. Kenner, and W. G. Terry, *Tetrahedron Letters*, 921 (1962).

(16) Melting points were taken on a Kofler block.

the interface of the ethereal and aqueous layers. Recrystallization of the solid from ethanol gave 2.2 g. of N-cyclohexylaminopropiophenone benzenesulfonamide, m.p. and mixture m.p. 132–134° (insoluble in 3 *N* hydrochloric acid). Acidification of the aqueous layer gave no sulfonamide, indicating that no piperidine derivative and hence no cyclohexylamine had been produced by the addition of base.

(**C**). A solution of 1.8 g. of the hydrochloride in 5 ml. of water was treated with 3 *N* sodium hydroxide as before. The reaction mixture was allowed to stand overnight, during which time the first-formed oil partially solidified. Benzenesulfonyl chloride (1.5 g.) was added and the mixture shaken for 5 min. Acidification of the resulting mixture with 3 *N* hydrochloric acid resulted in the dissolution of the oil and precipitation of 0.11 g. of cyclohexylbenzenesulfonamide as white crystals from ethanol, m.p. and mixture m.p. with authentic sample 88–89°. Addition of base to the acidic extract and ether extraction gave 0.65 g. of N-cyclohexyl-3-benzoyl-4-hydroxy-4-phenylpiperidine, m.p. and mixture m.p. 136°.

(**D**).—β-Cyclohexylaminopropiophenone, on standing at room temperature in an open flask, slowly solidified to N-cyclohexyl-3-benzoyl-4-hydroxy-4-phenylpiperidine, m.p. 136° after recrystallization from ethanol.

β-*n*-Butylaminopropiophenone (IIc).—A mixture of 4.1 g. of β-diethylaminopropiophenone and 7.3 g. of *n*-butylamine was warmed on the water bath under distillation conditions for 1 hr. during which time diethylamine was evolved. The excess of *n*-butylamine was removed under vacuum, the temperature being kept below 60° during this process. The resulting oil could not be induced to crystallize. The oxalate, prepared by addition of an ethereal solution of oxalic acid to the base in ether, crystallized as colorless plates from ethanol, m.p. 177–179°.

Anal. Calcd. for $C_{15}H_{21}NO_5$: C, 61.0; H, 7.2. Found: C, 60.9; H, 6.8. Lit.[9] reports oxalate, m.p. 177–179°.

Dry hydrogen chloride gas was bubbled through an ethereal solution of the base resulting in a hygroscopic hydrochloride. Double decomposition of this hydrochloride with lithium picrate gave N-*n*-butyl-3-benzoyl-4-hydroxy-4-phenylpiperidine picrate as yellow prisms from ethanol, m.p. 176–177°; ν_{max} 3450 (OH), 1670 cm.$^{-1}$ (PhCO).

Anal. Calcd. for $C_{28}H_{30}N_4O_9$: C, 59.4; H, 5.3; N, 9.9. Found: C, 59.3; H, 5.4; N, 9.8.

N-*n*-Butyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (IVc).—A solution of 2.4 g. of β-diethylaminopropiophenone hydrochloride and 0.73 g. of *n*-butylamine in 10 ml. of 50% aqueous ethanol was allowed to stand at room temperature for 16 hr. A thin oil separated which on cooling and scratching afforded 1.91 g. (93%) of the substituted piperidine (IVc) as colorless plates from aqueous ethanol, m.p. 98–100° (lit.[9] m.p. 98°); ν_{max} 3430 (OH), 1600 cm.$^{-1}$ (PhCO).

Anal. Calcd. for $C_{22}H_{27}NO_2$: C, 78.3; H, 8.1; N, 4.15. Found: C, 77.7; H, 8.2; N, 4.2.

The picrate formed yellow rectangular prisms from ethanol, m.p. and mixture m.p. 176–177°; infrared spectrum was identical with picrate from previous experiment.

Reaction between Phenyl Vinyl Ketone and Cyclohexylamine.—A solution of 1.32 g. of phenyl vinyl ketone[5] in 50 ml. of ethanol was treated with 0.99 g. of cyclohexylamine in ethanol and the mixture allowed to stand at room temperature for 16 hr. Dilution with water and recrystallization of the precipitated solid from aqueous ethanol gave 1.28 g. of N-cyclohexyl-3-benzoyl-4-hydroxy-4-phenylpiperidine, m.p. and mixture m.p. 136–137°.

N,N-Bis(β-benzoylethyl)glycine (VIIIe). (**A**).—A solution of 2.4 g. (0.01 mole) of β-diethylaminopropiophenone hydrochloride and 0.75 g. (0.01 mole) of glycine in 10 ml. of water was heated on the steam bath. The mixture was initially homogeneous, but solid began to separate after 10 min. After 2 hr. the product was filtered and purified by crystallization from water, and 1.27 g. (35%) of N,N-bis(β-benzoylethyl)glycine (VIIIe), m.p. 161–163° dec., was obtained.

Anal. Calcd. for $C_{20}H_{21}NO_4 \cdot H_2O$: C, 67.2; H, 6.5; N, 3.9; equiv. wt., 357. Found: C, 67.3; H, 6.3; N, 4.2; equiv. wt. 356.

The bissemicarbazone, crystallized from water, had m.p. 219–220°.

Anal. Calcd. for $C_{22}H_{27}N_7O_4 \cdot 3H_2O$: C, 52.0; H, 6.5. Found after drying at 100° at 0.01 mm: C, 52.1; H, 6.2.

(**B**).—A mixture of 1.5 g. (0.02 mole) of glycine and 2.4 g. (0.01 mole) of β-diethylaminopropiophenone hydrochloride, treated as in A, gave 0.75 g. (21%) of N,N-bis(β-benzoylethyl)-glycine, m.p. and mixture m.p. 161–163° dec.

(**C**).—Reaction of 0.75 g. (0.01 mole) of glycine and 4.8 g. (0.02 mole) of β-diethylaminopropiophenone hydrochloride as in (A) gave 1.96 g. (55%) of N,N-bis(β-benzoylethyl)glycine, m.p. and mixture m.p. 161–163° dec.

N-(β-Benzoylethyl)-α-alanine (Va). (**A**).—A solution of 4.5 g. (0.05 mole) of DL-α-alanine and 12.0 g. (0.05 mole) of β-diethylaminopropiophenone in 50 ml. of water was heated on the steam bath. Solid began to separate after a few minutes, and after 2 hr. 9.0 g. (82%) of N-(β-benzoylethyl)-α-alanine (Va), needles from water, m.p. 216–217° dec., was obtained.

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.1; H, 6.8; N, 6.3. Found: C, 64.6; H, 6.9; N, 6.1.

(**B**).—A solution of 0.89 g. (0.01 mole) of DL-α-alanine and 4.8 g. (0.02 mole) of β-diethylaminopropiophenone hydrochloride in 15 ml. of water was heated on the steam bath for 2 hr. The product was 1.96 g. (86%) of N-(β-benzoylethyl)-α-alanine, m.p. and mixture m.p. 216–217° dec.

N-(β-Benzoylethyl)-β-phenylalanine (Vg).—A solution of 2.4 g. (0.01 mole) of β-diethylaminopropiophenone hydrochloride and 1.6 g. (0.01 mole) of DL-β-phenylalanine in 20 ml. of water was heated on the steam bath for 2 hr. The product was 2.9 g. (78%) of N-(β-benzoylethyl)-β-phenylalanine (Vg), needles from water, m.p. 188–190° dec.

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.7; H, 6.4; N, 4.7. Found: C, 72.5; H, 6.5; N, 4.5.

N-(β-Benzoylethyl)aspartic Acid (Vf).—To a hot solution of 1.53 g. (0.01 mole) of DL-aspartic acid in 20 ml. of water was added 2.4 g. (0.01 mole) of β-diethylaminopropiophenone. Solid material began to separate from the initially homogeneous reaction mixture, and after 2 hr. on the steam bath, the mixture was filtered while still hot. The precipitate was 0.92 g. of unchanged aspartic acid, m.p. and mixture m.p. 237–239°. The filtrate gave, on cooling, 0.72 g. of N-(β-benzoylethyl)aspartic acid (Vf), needles from water, m.p. 169–170°.

Anal. Calcd. for $C_{13}H_{15}NO_5 \cdot 0.5H_2O$: C, 56.9; H, 5.9; N, 5.1; equiv. wt., 273. Found: C, 57.0; H, 5.9; N, 5.2; equiv. wt., 270.

N-(β-Benzoylethyl)asparagine (Vh).—To a solution of 1.1 g. (0.01 mole) of L-asparagine in 17 ml. of hot water was added 2.4 g. (0.01 mole) of β-diethylaminopropiophenone hydrochloride. The mixture was heated on the steam bath for 6 hr. and gave on cooling 1.3 g. (85%) of N-(β-benzoylethyl)asparagine (Vh), needles from water, m.p. 200–201° dec.

Anal. Calcd. for $C_{13}H_{16}N_2O_4 \cdot H_2O$: C, 55.3; H, 6.4. Found: C, 55.3; H, 6.6.

N-(β-Acetylethyl)-β-phenylalanine (Vk).—A mixture of 5.5 g. (0.033 mole) of DL-β-phenylalanine, 4.8 g. (0.033 mole) of 1-diethylamino-3-butanone, 75 ml. of water, and 3.3 ml. of 10 *N* hydrochloric acid was heated on the steam bath. Solid began to separate after about 30 min. and after 3 hr. the mixture was filtered while hot, and 6.3 g. (81%) of N-(β-acetylethyl)-β-phenylalanine (Vk), needles from water, m.p. 212° dec., was obtained.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.35; H, 7.3; N, 5.95. Found: C, 66.45; H, 7.2; N, 5.65.

N-(β-Benzoylethyl)-5-oxopyrrolidine-2-carboxylic Acid (IX).—A mixture of 7.4 g. (0.05 mole) of L-glutamic acid, 10.3 g. (0.05 mole) of β-diethylaminopropiophenone, 5 ml. of 10 *N* hydrochloric acid, and 75 ml. of water was heated on the steam bath for 12 hr. On cooling, the pH was brought to 4 by the addition of dilute sodium hydroxide, when a waxy solid separated. Crystallization from water gave 5.5 g. (44%) of N-(β-benzoylethyl)-5-oxopyrrolidine-2-carboxylic acid as needles, m.p. 152–153°.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.8. Found: C, 64.3; H, 5.8.

The 2,4-dinitrophenylhydrazone had m.p. 217° (prepared by F. W. Donovan).

Anal. Calcd. for $C_{20}H_{19}N_5O_7$: C, 54.4; H, 4.3; N, 15.8. Found: C, 54.0; H, 4.5; N, 15.7.