CONDENSATION OF ALDEHYDES AND KETONES

XVIII. The Aminomethylation of Methylene- and Benzylidenediacetophenones*

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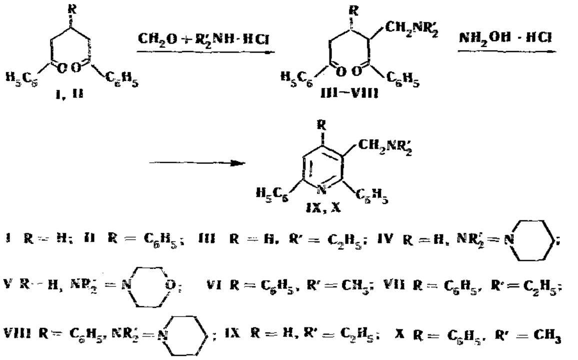
The Mannich reaction with methylene- and benzylidenediacetophenones has given: 1,3-dibenzoyl-4-piperidinobutane, 1,3-dibenzoyl-4-morpholinobutane, 1,3-dibenzoyl-4-diethylamino-2-phenylbutane, 1,3-dibenzoyl-2-phenyl-4-piperidinobutane, 1,3-dibenzoyl-4-diethylaminobutane, and 1,3-dibenzoyl-4-dimethylamino-2-phenylbutane. From the latter two compounds, 3-diethylaminomethyl-2,6-diphenylpyridine and 3-dimethylaminomethyl-2,4,6-triphenylpyridine have been obtained.

Continuing previous work [1], we have effected the condensation of methylenediacetophenone (I) and benzylidenediacetophenone (II) with formaldehyde and a series of secondary amines. As a result, we have obtained the amino diketones III–VIII. The keto bases III and VI have been converted by the Stobbe reaction into the pyridines IX and X.



In the diketones I and II, only one of the two α-CH_2 groups underwent aminomethylation. Judging from Bailey's data, this circumstance is also characteristic of the diketones of the 1,2-dibenzoylethane series, which can be regarded as homologs of the 1,3-dibenzoylpropane series (I).

In ethanol, only the diketone I took part in this reaction, while the diketone II was recovered unchanged. The reaction could be carried out successfully with the diketone II in acetic acid.

EXPERIMENTAL

Methylenediacetophenone (I) was obtained by a previously-described method [4], somewhat modified. A flask fitted with a stirrer, a thermometer, and a reflux condenser was charged with 1200 g of freshly-distilled acetophenone and, at 70° C, 50 ml of a 2 N solution of sodium methoxide in methanol was added, followed by 50 g of paraformaldehyde over 2 hr. The mixture was heated for another 30 min, cooled, and neutralized with dilute hydrochloric acid. The alcohol, water, and acetophenone were driven off in vacuum with heating by a water bath, and from the residue at 195°–200° C (0.02 mm) 93 g (21.7%) of distillate was collected which crystallized completely. It gave colorless plates, mp 65° C, when crystallized from methanol. According to the literature [4], mp 65°–67° C.

Benzylidenediacetophenone (II) was obtained by the method of Kostanecki and Rassbach [5]. It gave colorless crystals, mp 83° C, when crystallized from methanol. According to the literature [5], mp 85° C.

Method of preparing the keto bases III, IV, and V. A mixture of 0.1 mole of the diketone I, 0.11 mole of an amine hydrochloride, 0.15 mole of paraformaldehyde, 70 ml of ethanol, and 1 ml of concentrated hydrochloric acid was heated in the boiling water bath for 6 hr. Another 0.15 mole of paraformaldehyde was added and heating was continued (6 hr). Then the alcohol was distilled off in vacuum and the residue was diluted with water. The unchanged diketone I was separated off, washed with water, and dried. The filtrate from the elimination of the diketone was made alkaline with saturated sodium carbonate solution, and the liberated amine was extracted with ether. The dry ethereal solution of the keto base was saturated with hydrogen chloride. The hydrochloride formed was separated off and purified by crystallization. The free base was isolated by making an aqueous solution of the salt alkaline.

1,3-Dibenzoyl-4-diethylaminobutane (III). Yield 45%, liquid, n_D^{20} 1.5550; decomposes on distillation. Found, %: C 78.36, 77.59; H 8.19, 8.16. Calculated for $C_{22}H_{27}NO_2$ %: C 78.33; H 8.01. **Hydrochloride**, colorless crystals, mp 124°–125° C (from acetone). Found, %: Cl 9.53, 9.56. Calculated for $C_{22}H_{27}NO_2 \cdot HCl$, %: Cl 9.50. **Picrate**, yellow rhombs, mp 119°–120° C (from ethanol). Found, % N 9.85, 10.13. Calculated for $C_{22}H_{27}NO_2 \cdot C_6H_3N_3O_7$, %: N 9.89.

1,3-Dibenzoyl-4-piperidinobutane (IV). Yield 72.2%. Colorless crystals, mp 61°–62° C (from methanol). Found, %: C 78.75, 78.77; H 7.84, 7.95; N 3.88, 4.33. Calculated for $C_{23}H_{27}NO_2$, %: C 79.09; H 7.79; N 4.01. **Hydrochloride**, colorless crystals, mp 166°–167° C (from ethanol). Found, %: Cl 8.68, 8.70. Calculated for $C_{23}H_{27}NO_2$; HCl, %: Cl 9.20 **Picrate**, yellow crystals, mp 177°–180° C (decomp., from ethanol). Found, %: N 10.21, 10.19. Calculated for $C_{23}H_{27}NO_2 \cdot C_6H_3N_3O_7$, %: N 9.67.

1,3-Dibenzoyl-4-morpholinobutane (V). Yield 40%. Colorless crystals, mp 93°–95° C (from methanol). Found, %: C 75.11, 74.78; H 7.26, 7.11; N 4.57, 4.15. Calculated for $C_{22}H_{25}NO_3$, %: C 75.21; H 7.12; N 3.93. **Hydrochloride**, colorless crystals, mp 174°–175° C (from ethanol). Found, %: Cl 8.86, 9.00. Calculated for $C_{22}H_{25}NO_3 \cdot HCl$, %: Cl 9.13. **Picrate**, yellow needles, mp 179° C (decomp., from ethanol). Found, %: N 10.22, 10.11. Calculated for $C_{22}H_{25}NO_3 \cdot C_6H_3N_3O_7$, %: N 10.03.

1,3-Dibenzoyl-4-dimethylamino-2-phenylbutane (VI). A mixture of 24 g of the diketone II, 6 g of dimethylamine hydrochloride, 3 g of paraformaldehyde, and 100 ml of 98% acetic acid was heated in the boiling water bath. After 4 hr 30 min, another 3 g of paraformaldehyde was added and heating was continued for another 2 hr 30 min. Then the acetic acid was distilled off in vacuum and the residue was treated with a mixture of 300 ml of water and 150 ml of ether. The ethereal solution was separated off, washed with water, and dried over $MgSO_4$. Distillation of the ether yielded 16 g of the initial diketone. The aqueous layer was evaporated to half bulk. On cooling, it deposited a white crystalline precipitate of the salt of the base VI. Weight 10.6 g, mp 190°–195° C. The filtrate

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*For part XVII, see [7].

was made alkaline with a saturated solution of sodium carbonate. The amine liberated was extracted with ether. After saturation of the dry ethereal extract with hydrogen chloride, another 2.7 g of salt was obtained. The total yield of the hydrochloride of the reaction product was 13.3 g (52%). The free base was liberated by making an aqueous solution of the salt alkaline. It gave colorless needle-like crystals, mp 122° C when crystallized from methanol. Found, %: C 80.87, 81.00; H 7.15, 6.96; N 3.46, 3.42. Calculated for $C_{26}H_{27}NO_2$, %: C 81.03; H 7.01; N 3.63. The **hydrochloride**, gave colorless plates, mp 195° C when crystallized from ethanol. Found, %: Cl 8.55, 8.47. Calculated for $C_{26}H_{27}NO_2 \cdot HCl$, %: Cl 8.42. The **methiodide** was obtained by a published method [6]. It gave colorless rods, mp 214°-215° C when crystallized from ethanol. Found, %: I 23.70, 23.78. Calculated for $C_{27}H_{30}INO_2$, %: I 24.09. The **ethiodide** was obtained by a published method [6] as colorless crystals, mp 186° C. Found, %. I 23.81, 23.93. Calculated for $C_{28}H_{32}INO_2$, %: I 23.47. The **picrate** occured as yellow crystals, mp 163°-165° C when crystallized from ethanol. Found, %: N 9.46, 9.13. Calculated for $C_{26}H_{27}NO_2 \cdot C_6H_3N_3O_7$, %: N 9.12.

The bases **VII** and **VIII** were obtained in a similar manner to **VI.**

1,3-Dibenzoyl-4-diethylamino-2-phenylbutane (VII). Yield 45%. Occuring colorless crystals, mp 95°-96° C when crystalized from methanol. Found, %: C 80.54, 80.89; H 0.08, 8.06; N 3.87, 3.79. Calculated for $C_{28}H_{31}NO_2$, %: C 81.35; H 7.50; N 3.39; The **methiodide** occured as colorless plates, mp 192°-193° C when crystallized from absolute ethanol. Found, %: I 22.78, 22.27; N 2.51, 2.56. Calculated for $C_{29}H_{34}INO_2$, %: I 22.88; N 2.52. The **picrate** occured as yellow plates, mp 192°-193° C when crystallized from ethanol. Found, %: N 9.21, 9.11. Calculated for $C_{28}H_{31}NO_2 \cdot C_6H_3N_3O_7$, %: N 8.71.

1,3-Dibenzoyl-2-phenyl-4-piperidinobutane (VIII). Yield 43%. Occuring as colorless needles, mp 137°-140° C when crystallized from ethanol. Found, %: C 81.41, 81.39; H 7.67, 7.64; N 3.57, 3.45. Calculated for $C_{29}H_{31}NO_2$, %: C 81.88; H 7.29; N 3.29. The **picrate** occured as yellow plates, mp 174°-176° C when crystallized from ethanol. Found, %: N 8.80, 8.78. Calculated for $C_{29}H_{31}NO_2 \cdot C_6H_3N_3O_7$. %: N 8.56.

The transformation into the pyridines **IX** and **X** was carried out as described previously [1].

3-Diethylaminomethyl-2,6-diphenylpyridine (IX). Yield 80%. It is a light yellow viscous oil, bp 180°C (0.15 mm); n_D^{20} 1.6132. Found, %: N 8.91, 9.05. Calculated for $C_{22}H_{24}N_2$, %: N 8.86.

3-Dimethylaminomethyl-2,4,6-triphenylpyridine (X). Yield 84.5%. Occuring as colorless crystals, mp 143°-145° C when crystallized from methanol. Found, %: C 85.63, 85.67; H 6.87, 6.81; N 7.80, 7.55; Calculated for $C_{26}H_{24}N_2$, %: C 85.71; H 6.59; N 7.65. The **methiodide** occurs as colorless crystals when crystallized from ethanol mp 209°-210° C (decomp.). Found, %: I 24.99, 24.73. Calculated for $C_{27}H_{27}IN_2$, %: I 25.09.

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