Acknowledgment.—We are indebted to Dr. V. Toome for the ultraviolet spectra, to Dr. T. Williams for the nmr spectra, to Dr. F. Vane for the mass spectra, to Mr. S. Traiman for the infrared spectra, and to Dr. A. Steyermark and Dr. F. Scheidl for the microanalyses.

The Condensation of *o*-Benzoylbenzaldehyde with Aliphatic Diamines

W. METLESICS, T. ANTON, M. CHAYKOVSKY, V. TOOME, AND L. H. STERNBACH

Chemical Research Department, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110

Received March 6, 1968

The reaction of *o*-benzoylbenzaldehyde (II) with aliphatic diamines gave condensation products of type V which could readily be oxidized *via* peroxides of type VI to the carbinolamine derivatives of type IXa. The equilibrium between the tautomeric imidazoline derivatives IXa and IXb was investigated.

The reaction of aromatic *o*-dialdehydes with aromatic *o*-diamines gives derivatives containing the imidazo[2,1-*a*]isoindole[1] ring system rather than eight-membered heterocyclic compounds claimed in some cases.[2] This reaction has recently been reinvestigated and Thiele's original assignment was confirmed.[3] A similar problem had arisen concerning the structure of the products obtained by condensation of *o*-benzoylbenzoic acid with ethylenediamine.[4] This led us to study the condensation of *o*-benzoylbenzaldehyde with aliphatic diamines.

The *o*-benzoylbenzaldehyde, compound II, was obtained in over 50% yield by the oxidation of the benzhydrol derivative I (Scheme I). On reaction with ethylenediamine in aqueous ethanolic solution the known phthalimidine derivative III[4b] was formed. This result is analogous to the formation of N-phenylphthalimidine on reaction of *o*-phthalaldehyde with aniline.[5]

When the condensation of *o*-benzoylbenzaldehyde with ethylenediamine was performed under anhydrous conditions, a product was obtained[6] to which we assigned structure V in analogy to the results obtained with phthalaldehyde and *o*-phenylenediamine.[1] Proof for this structure was supplied by preparing the same compound by cyclization of the phthalimidine derivative III using titanium tetrachloride as condensing agent. Compound III was not cyclized to V in boiling ethylenediamine and, therefore, is not an intermediate in the reaction II → V.

The free base V was rapidly oxidized by exposing it in various solvents to air or, more conveniently, by using hydrogen peroxide as the oxidant. The primary reaction product was the peroxide VI which could be isolated by chromatographic separation. The crude oxidation product always contained compound IX, which is most likely formed by a reduction of the intermediate peroxide VI. This peroxide liberated iodine from an acidified potassium iodide solution and was readily reduced to compound IX which on mild hydrolysis yielded the known 3-hydroxyphthalimidine derivative XIII.[4b] Confronted with the problem of deciding between structure a and b for IX, we found that infrared absorption at 1660 $\mathrm{cm^{-1}}$ could not be accepted as proof for the presence of a carbonyl function since compounds V and VI also showed strong absorption at 1660 $\mathrm{cm^{-1}}$ obviously due to C=N stretching. Near-infrared spectra[7] were measured in chloroform and the overtones of OH and NH absorption at 1.4 and 1.5 μ, respectively, were found to be of equal intensity, indicating the presence of a 1:1 mixture of the forms IXa and b. As expected, this equilibrium proved to be pH dependent as shown by the ultraviolet spectra. On acidification a maximum at 251 mμ (ϵ 13,600) appeared which was attributed to the benzophenone chromophor and allowed the determination of a p*K* 8.6.[8] This constant describes the equilibrium between the carbinolamine base IXa and the protonated keto form IXb. To remove all remaining doubt about the structure of IX, its hydrobromide was subjected to single crystal X-ray structure analysis[9] which showed that compound IX in its protonated form has the keto structure b. The formation of the ether XII observed on treatment of IX with methanol is a reaction typical for carbinolamines and proves the presence of the tautomer IXa in the equilibrium.

We propose that the equilibrium of IXa with IXb is determined by the competition between the intermolecular association of the amidine functions[10] and the intramolecular interaction of amine and carbonyl groups.

Ring homologs of IX were prepared by condensation of *o*-benzoylbenzaldehyde with the appropriate diamines and subsequent oxidation. As indicated by ultraviolet and near-infrared spectra, the increased size of the heterocyclic ring changes the character of the amidine functions sufficiently to force the expected equilibrium to the side of the carbinolamine structures (VII and VIII).

Another route for the preparation of compound IX was found by treating the condensation product of phthaldehydic acid and ethylenediamine (X) with phenyllithium. This reaction which presumably proceeds *via* the hypothetical intermediate d gave only a poor yield of IX. We, therefore, oxidized X with

---

[1] J. Thiele and K. Falk, *Ann.*, **347**, 112 (1906).

[2] (a) M. Betrabet and G. Chakravarti, *J. Indian Chem. Soc.*, **7**, 495 (1930). (b) W. Ried and H. Bodem, *Chem. Ber.*, **89**, 708 (1956); W. Ried and E. Torinus, *ibid.*, **92**, 2902 (1959).

[3] (a) D. Amos and R. Gillis, *Aust. J. Chem.*, **17**, 1440 (1964); (b) H. Perlmutter and P. Knapp, *J. Org. Chem.*, **32**, 2350 (1967).

[4] (a) T. Sulkowski, M. Wille, A. Mascitti, and J. Diebold, *ibid.*, **32**, 2180 (1967); (b) W. Metlesics, T. Anton, and L. H. Sternbach, *ibid.*, **32**, 2185 (1967).

[5] J. Thiele and J. Schneider, *Ann.*, **369**, 287 (1909).

[6] The sulfate of this compound was isolated since the base was found to be unstable in air (*vide infra*).

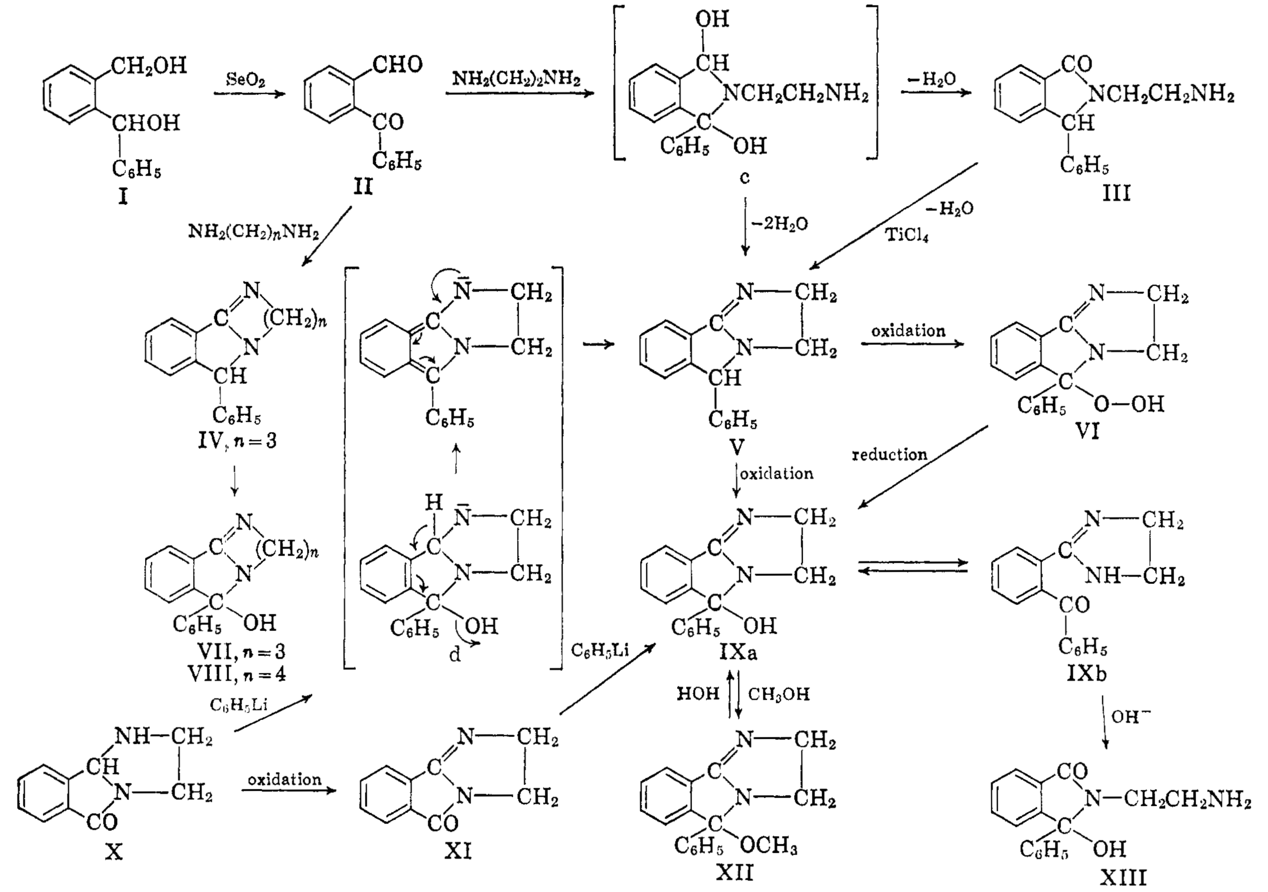
[7] R. Goddu and D. Delker, *Anal. Chem.*, **32**, 140 (1960).

[8] A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen and Co. Ltd., London, 1962, p 72.

[9] J. S. McKechnie and I. C. Paul, paper in preparation.

[10] L. Hunter and J. A. Marriott, *J. Chem. Soc.*, 777 (1941).

SCHEME I



diethyl azodicarboxylate to compound XI (mp 139–141°)[11] which on treatment with phenyllithium afforded IX in 49% yield.

Experimental Section[12]

o-Benzoylbenzaldehyde (II).—A suspension of 41.7 g (0.376 mol) of selenium dioxide in 147 ml of acetic acid and 294 ml of xylene was refluxed for 15 min and any water present was removed in a Dean–Stark receiver. To this mixture was added dropwise a solution of 64.2 g (0.3 mol) of o-hydroxymethylbenzhydrol (I)[13] in 86 ml of acetic acid and 258 ml of xylene in the course of 1 hr. During this time 25 ml of an aqueous phase was removed by cooling the distilling trap. During continued refluxing another 50–70 ml of an aqueous phase was removed. After 20 hr the solution was cooled and filtered from selenium. The filtrate was poured into ice water, basified with sodium hydroxide, and extracted with ether. Concentration of the extract yielded a yellow oil which on addition of petroleum ether (bp 30–60°) gave 33.5 g (53%) of white prisms melting at 64–67°: uv max (2-propanol) 226–227 mμ (ε 15,750), 251–252 (18,500), infl 294 (2600); ir ($CHCl_3$) 1665 (PhCOPh) and 1705 cm^{-1} (CH=O).

Anal. Calcd for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79. Found: C, 80.00; H, 4.68.

2-(2-Aminoethyl)-3-phenylphthalimidine (III).—A solution of 4.2 g (0.02 mol) of II in 85 ml of ethanol, 50 ml of water, and 6.8 ml (0.1 mol) of ethylenediamine was refluxed for 18 hr. The solution was concentrated to remove the alcohol and diluted with 160 ml of water. A solid product was collected on a filter and dried. A maleate was prepared in a mixture of methylene chloride, methanol, and ether. After recrystallization from a mixture of methanol and ether 2.6 g of a maleate melting at 184–187° dec was obtained. This salt was suspended in water and after basification gave 1.2 g (24%) of III melting at 88–91° (lit.[4b] mp 90–93°).

2,3,4,6-Tetrahydro-6-phenylpyrimido[2,1-a]isoindole Sulfate ($IV \cdot H_2SO_4$).—A solution of 10.5 g (0.05 mol) of II in 22 ml (0.26 mol) of 1,3-propanediamine in 125 ml of toluene was refluxed for 3 hr. During this time 3.2 ml of an aqueous phase had separated in a Dean–Stark receiver. The solution was cooled, washed with water, and concentrated *in vacuo*. The residue crystallized, was collected on a filter, and washed with a small amount of ethyl acetate. This crop was dissolved in 100 ml of ethanol and a solution of 3 ml of concentrated sulfuric acid in 50 ml of ethanol was added. On addition of ethyl acetate a solid was obtained which after recrystallization from a mixture of ethanol and petroleum ether gave 12.7 g (73%) of white prisms melting at 170–172° dec: uv max (2-propanol) 238 mμ (ε 18,200), infl 246 (16,000), 265 (5600), 276 (3400), 285 (2100); ir (KBr) 1675 cm^{-1} (C=N); nmr (DMSO) δ 2.1 (m, 2, C—CH_2—C), 3.0–4.0 (m, 4, 2N—CH_2), 6.23 [s, 1, $(Ph)_2C$—H], 7.1–8.3 (m, 9).

Anal. Calcd for $C_{17}H_{16}N_2 \cdot H_2SO_4$: C, 58.94; H, 5.24. Found: C, 58.62; H, 5.49.

2,3-Dihydro-5-phenyl-5H-imidazo[2,1-a]isoindole Sulfate ($V \cdot H_2SO_4$). A. From II.—A solution of 10.5 g (0.05 mol) of II in 125 ml of toluene and 17 ml (0.25 mol) of ethylenediamine was refluxed for 18 hr. During this time 4.5 ml of an aqueous phase was separated in a Dean–Stark receiver. The reaction mixture was cooled, washed with water, and concentrated *in vacuo* to an orange oil which was dissolved in a mixture of 35 ml of ethanol and 50 ml of ethyl acetate. A solution of 2.5 ml of concentrated sulfuric acid in 50 ml of ethanol was added and a crystalline precipitate was collected which after recrystallization from a mixture of methanol and ethyl acetate gave 7.2 g (43%) of white prisms melting at 221–223° dec. A sample was recrystallized again for analytical purposes and melted at

---

[11] A compound with structure XI had been described in the literature,[2a] mp 229–230°. In agreement with a previous investigation,[3a] we were also unable to reproduce this result and have to conclude that the compound previously described has a different structure.

[12] The melting points were determined with a Mettler FP-1 melting point apparatus by raising the temperature 2°/min from 10° below the melting or decomposition point. Ultraviolet and near-infrared spectra were determined with a Cary 14 spectrophotometer, infrared spectra using a Beckman IR-9 spectrophotometer, and nmr spectra on a Varian A-60 spectrometer at 60 Mc/sec [$(CH_3)_4Si$ internal standard]. The purity of compounds was established by thin layer chromatography. The identity of compounds was proved by comparison of spectral properties and mixture melting point.

[13] W. A. Bonner, *J. Amer. Chem. Soc.*, **85**, 439 (1963).

226–229° dec: uv max (2-propanol) 240 mμ (ε 15,000), 276 (5400); ir (KBr) 1660 cm^{-1} (C=N).

Anal. Calcd for $C_{16}H_{14}N_2 \cdot H_2SO_4$: C, 57.82; H, 4.85; N, 8.43. Found: C, 57.61; H, 4.81; N, 8.73.

The hydrochloride was prepared from the corresponding base with aqueous 1 *N* hydrochloric acid. On recrystallization from a mixture of methanol and toluene, white prisms melting at 226–228° dec were obtained: nmr (DMSO) δ 3.6–4.6 (m, 4 -CH_2—CH_2), 6.13 (s, 1, CH), 7.3–7.9 (m, 9); mass spectrum (70 eV), *m/e* 234 ($C_{16}H_{14}N_2$).

Anal. Calcd for $C_{16}H_{14}N_2 \cdot HCl$: Cl, 13.09. Found: Cl, 13.22.

B. From III.—A solution of 1.2 ml of titanium tetrachloride in 30 ml of xylene was added at 25° to a stirred solution of 2.5 g of III in 150 ml of xylene. The mixture was refluxed for 18 hr, cooled, and washed with an aqueous solution of sodium carbonate. The xylene solution was extracted with 2 *N* hydrochloric acid. The acidic extract was poured on ice and made alkaline with sodium hydroxide. The solution was extracted with ethyl acetate and the extract was concentrated. Addition of a solution of sulfuric acid in a mixture of ethanol and tetrahydrofuran and further dilution with ethyl acetate gave a crystalline precipitate. Recrystallization from a mixture of methanol and ethyl acetate gave 0.5 g (15%) of white prisms melting at 225–228° dec ($V \cdot H_2SO_4$).

2,3-Dihydro-5-hydroperoxy-5-phenyl-5H-imidazo[2,1-*a*]isoindole (VI).—The crude base liberated from 16.6 g (0.05 mol) of $V \cdot H_2SO_4$ was dissolved in 50 ml of ethanol and 11 ml of a 30% aqueous solution of hydrogen peroxide was added. The mixture was stirred at 25° for 40 hr. A crystalline crop (8.6 g) was collected and placed on a column containing 250 g of silica gel. Elution with a mixture of one part of methanol and one part of chloroform gave fractions from which on concentration a crystalline residue was obtained. Recrystallization from a mixture of methanol and chloroform gave 2.3 g of white prisms melting at 165–167° dec: uv infl (2-propanol) 232 mμ (ε 14,000), 290 (2600), max 269 (4000), 275 (4400); ir (KBr) 1665 cm^{-1} (C=N).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.09; H, 5.39; N, 10.22.

Hydrochloride of VI.—This compound was prepared with methanolic hydrogen chloride and after recrystallization from a mixture of methanol and ether gave white platelets melting at 165–168° dec: uv max (2-propanol) 245 mμ (ε 14,800), 278 (5200); ir (KBr) 1680 cm^{-1} (C=N).

Anal. Calcd for $C_{16}H_{14}N_2O_2 \cdot HCl$: C, 63.47; H, 4.99; Cl, 11.71. Found: C, 63.63; H, 4.83; Cl, 11.79.

2,3,4,6-Tetrahydro-6-phenylpyrimido[2,1-*a*]isoindol-6-ol (VII).—A solution of 10 g of $IV \cdot H_2SO_4$ in water was basified with 2 *N* sodium hydroxide and extracted with methylene chloride. The extract was concentrated and the residue was dissolved in 50 ml of ethanol and 3 ml of 30% hydrogen peroxide. The solution was stirred at 25° for 12 hr and diluted with ether. A precipitate was collected and suspended in a refluxing mixture of 35 ml of methanol, 3.5 g of sodium sulfite heptahydrate, and 15 ml of water. After 15 min the suspension was cooled and diluted with water. The solid was collected and after recrystallization from a mixture of methylene chloride and methanol gave 2.2 g (29%) of white prisms melting at 227–230° dec: uv infl (2-propanol) 230 mμ (ε 15,000), 262 (4400) max 266 (4600), 271 (4800), infl 279 (3200), 285 (2400); uv max (0.1 *N* HCl) 239 mμ (ε 15,200), infl 266 (4500); near-ir ($CHCl_3$) max 1.43 μ (ε *ca.* 1) (OH); ir (KBr) 1655 cm^{-1} (C=N).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10. Found: C, 77.38; H, 6.15.

2,3,4,5-Tetrahydro-7-phenyl-7H-diazepino[2,1-*a*]isoindol-7-ol (VIII).—A solution of 10.5 g of II and 28.5 ml of 1,4-diaminobutane in 125 ml of toluene was refluxed for 2.5 hr, during which 3 ml of an aqueous phase had separated in a Dean-Stark receiver. The solution was cooled, washed with sodium chloride solution, and concentrated *in vacuo*. The residue was an orange oil which was dissolved in 150 ml of ethanol and 5 ml of 30% hydrogen peroxide was added. The solution was stirred at 25° for 18 hr. A solid precipitate was collected, washed with a mixture of ether and ethanol, and suspended in 25 ml of methanol. The mixture was refluxed and a solution of 5 g of sodium sulfite heptahydrate in 15 ml of water was added. After refluxing for 15 min the mixture was cooled, diluted with 30 ml of water, and filtered. The solid crop was washed with water, dried, and recrystallized from a mixture of chloroform and ether to give 4.5 g (32%) of white prisms melting at 216–218° dec: uv max (2-propanol) 258 mμ (ε 5000), 265 (5100), 273 (4800), infl 230 (15,000) 290 (2400); near-ir ($CHCl_3$) max 1.43 μ (ε *ca.* 1) (OH); ir (KBr) at 1650 cm^{-1} (C=N); nmr (DMSO) δ 1.84 (broad, 4), 3.12 (broad, 2), 3.70 (broad, 2), 6.75 (1), 7.1–7.8 (m, 9).

Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; O, 5.75. Found: C, 77.64; H, 6.75; O, 5.64.

2,3-Dihydro-5-phenyl-5H-imidazo[2,1-*a*]isoindol-5-ol and/or 2-(2-Imidazolin-2-yl)benzophenone (IX). A. From V.—To a suspension of 3 g of $V \cdot H_2SO_4$ in water was added 2 *N* aqueous sodium hydroxide. Extraction with methylene chloride and concentration gave an orange oil (2 g) which was dissolved in 20 ml of ethanol. To this solution was added 1 ml of 30% hydrogen peroxide. After stirring at 25° for 18 hr 1.3 g of a precipitate was collected. This crop was refluxed in 5 ml of methanol and a solution of 1.2 g of sodium sulfite heptahydrate in 5 ml of water was added. After 15 min the mixture was cooled, diluted with 10 ml of water, and filtered. The collected solid was recrystallized from methanol to give 0.8 g (35%) of white prisms melting at 194–196° dec: uv infl (2-propanol) 225 mμ (ε 15,500), 290 (2250), max 269 mμ (ε 4100), 275 (4250); near-ir ($CHCl_3$) max 1.40 (ε *ca.* 0.5), 1.42 (*ca.* 0.5) (OH), and 1.48 μ (*ca.* 0.4) (NH); ir (KBr) 1660 cm^{-1}; nmr (CF_3CO_2H) δ 4.12 (s, 4, —CH_2CH_2—), 7.35–8.0 (m, 9), 8.31 [2, $(NH^+)_2$].

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 56.4; N, 11.19. Found: C, 76.42; H, 5.79; N, 11.13.

B. From VI.—A solution of 0.7 g of sodium sulfite heptahydrate in 3 ml of water was added to 0.5 g of VI in 7 ml of dimethylformamide. The solution was heated to 100° for 15 min. On cooling and addition of 20 ml of water 0.3 g (45%) of IX was obtained.

C. From VI.—A solution of 0.1 g of VI and 0.33 g of triethylphosphite in 20 ml of ethanol was kept on a steam bath for 5 min, then 18 hr at 25°. The solution was concentrated *in vacuo*, and on addition of water 0.07 g (75%) of IX was obtained.

D. From X.—To a solution of 1.75 g of X in a mixture of 50 ml of benzene and 50 ml of ether was added 25 ml of a 2 *N* solution of phenyllithium in a mixture of benzene and ether (7:3). After stirring at 25° for 18 hr the solution was poured into ice water and extracted with ether. This extract was dried and concentrated and the residue was dissolved in a mixture of benzene and ethanol (1:1). A stream of air was bubbled through the solution for 60 hr. The solution was concentrated and the crystalline residue was collected and washed with methylene chloride and ether. Recrystallization from a mixture of methylene chloride and methanol gave 0.2 g (10%) of IX melting at 192–196° dec.

E. From XI.—To a solution of 0.85 g (0.005 mol) of XI in 15 ml of benzene cooled to 5–10° was added 12 ml (0.024 mol) of a 2 *N* solution of phenyllithium in a mixture of seven parts of benzene and three parts of ether. The mixture was stirred at 20° for 1 hr and poured into ice water. Extraction with methylene chloride gave a crystalline crop which after recrystallization from a mixture of methanol and methylene chloride gave 0.6 g (49%) of white prisms of IX melting at 194–196° dec.

Hydrochloride of IX.—To a suspension of IX in methanol was added a solution of hydrogen chloride in methanol. Ether was added and the crystalline precipitate was collected. Recrystallization from a mixture of methanol and ether gave white prisms melting at 173–175° dec: uv max (2-propanol) 251 mμ (ε 13,600); ir (KBr) 1665 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{14}N_2O \cdot HCl$: Cl, 12.36. Found: Cl, 12.22.

On prolonged heating in methanol this salt is transformed into the salt of the carbinolamine ether XII.

Hydrobromide of IX.—To a suspension of IX in ethanol was added an aqueous solution of hydrobromic acid. Addition of ether gave a precipitate which after recrystallization from a mixture of ethanol and ether gave white platelets melting at 184–186° dec.

Anal. Calcd for $C_{16}H_{14}N_2O \cdot HBr$: Br, 24.13. Found: Br, 24.15.

This product was submitted for X-ray structure analysis.[9]

1,2,3,9b-Tetrahydro-5H-imidazo[2,1-*a*]isoindol-5-one (X).—A solution of 100 g (0.67 mol) of phthalaldehydic acid in 1200 ml of methanol and 225 ml of ethylenediamine was refluxed for 17 hr. The solution was concentrated *in vacuo* and the residual oil was dissolved in 1000 ml of chloroform. This solution was washed successively with concentrated aqueous solutions of potassium carbonate and sodium chloride, dried, and concentrated. The residual yellow oil was dissolved in ethanol, a solution of 37 g of maleic acid in ethanol was added, and on addition of ether a crystalline crop of a maleate was obtained which after recrystallization from a mixture of methanol and ether gave 43 g of white prisms. This product was suspended in an ice-cold aqueous solution of potassium carbonate. Extraction with methylene chloride gave a product which after recrystallization from a mixture of benzene and petroleum ether yielded 20.1 g (17%) of white needles melting at 130–132°: uv max (2-propanol) 223 mμ (ε 9300), infl 245 (4500), shoulder 278 (1300); ir ($CHCl_3$) 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.17; H, 5.76; N, 15.99.

2,3-Dihydro-5H-imidazo[2,1-*a*]isoindol-5-one (XI).—From a solution of 17.4 g (0.1 mol) of X in 350 ml of benzene 25 ml of solvent was removed by distillation. After cooling 25 g (0.14 mol) of diethylazodicarboxylate was added and the solution was refluxed for 65 hr. The mixture was chilled and the hydrazo ester was removed by filtration. The orange filtrate was concentrated *in vacuo* and the residue was recrystallized from a mixture of tetrahydrofuran and petroleum ether to give 10.6 g (62%) of white needles melting at 139–141°: uv max (2-propanol) 215 mμ (ε 37,000), 218 (36,900), 252 (12,500), 303 (4300), infl 246 (11,500), 260 (9500); ir ($CHCl_3$) 1670 (C=N) and 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.49; H, 4.54; N, 15.98.

2,3-Dihydro-5-methoxy-5-phenyl-5H-imidazo[2,1-*a*]isoindole Hydrochloride (XII·HCl).—A solution of 5 g of IX hydrochloride in 50 ml of methanol was refluxed for 18 hr. The solution was concentrated *in vacuo* dissolved in 20 ml of methanol and 60 ml of ether was added. Crystals (0.5 g) precipitated and were identified as starting material. The mother liquor was concentrated and the residue was recrystallized from a mixture of methanol, methylene chloride and ether to give 3.1 g (59%) of white prisms melting at 139–141° dec: uv max (2-propanol) 244 mμ (ε 14,400), 278 (5100); ir (KBr) 1670 cm^{-1} (C=N).

Anal. Calcd for $C_{17}H_{16}N_2O \cdot HCl$: C, 67.83; H, 5.70; OCH_3, 10.32. Found: C, 67.84; H, 5.63; OCH_3, 10.44.

The corresponding base was obtained as a colorless oil on treatment with alkali: uv infl (0.1 *N* KOH) 230 mμ (ε 14,600), 290 (2700), max 269 (4200), 275 (4600); ir (smear) 1660 cm^{-1} (C=N); nmr ($CDCl_3$) δ 3.12 (s, 3, OCH_3), 2.6–3.5 (m, 2, —N—CH_2), 4.2–4.5 (m, 2, =N—CH_2), 7.1–8.0 (m, 9).

Hydrolysis of XII·HCl to IX.—A solution of 0.2 g of XII·HCl in 10 ml of water was kept at 25° for 48 hr. The solution was basified with 2 *N* aqueous sodium hydroxide and the precipitate (0.14 g, 84%) was collected and identified as IX.

2-(2-Aminoethyl)-3-hydroxy-4-phenylphthalimidine (XIII).—A solution of 0.5 g of IX in 50 ml of tetrahydrofuran, 10 ml of methanol and 5 ml of aqueous 2 *N* sodium hydroxide was refluxed for 48 hr. The yellow solution was concentrated, diluted with water, and extracted with methylene chloride. The extract was dried and concentrated to give 0.35 g (65%) of white prisms which after washing with ether melted at 172–176° (lit.[4b] mp 175–176°).

Registry No.—II, 16780-82-8; IV·H_2SO_4, 16780-83-9; V·H_2SO_4, 16780-84-0; V·HCl, 16780-85-1; VI, 16780-86-2; VI·HCl, 16780-87-3; VII, 16780-98-6; VIII, 16780-97-5; IXa, 16780-88-4; IXa·HCl, 16780-89-5; IXa·HBr, 16797-48-1; IXb, 16780-90-8; IXb·HCl, 16780-91-9; IXb·HBr, 16780-92-0; X, 16780-93-1; XI, 16780-94-2; XII, 16780-95-3; XII·HCl, 16780-96-4.

Acknowledgment.—We are indebted to Mr. S. Traiman, Dr. F. Vane, and Dr. T. Williams for spectroscopic data and interpretations and to Dr. Al Steyermark and Dr. F. Scheidel for microanalytical data. We wish to thank Professor G. Büchi for valuable advice and stimulating discussions.

The Reaction of Active Methylene Compounds with Carbon Disulfide in the Presence of Ammonia. II. The Reaction of Acetone and Methyl Ethyl Ketone

TATSUO TAKESHIMA,[1a,b] TSUNEO IMAMOTO,[1c] MASATAKA YOKOYAMA,[1a] KIYOKO YAMAMOTO,[1b]
AND MAKIKO AKANO[1b]

The Second Laboratory of Organic Chemistry, The Institute of Physical and Chemical Research, Honkomagome, Bunkyo-ku, Tokyo, Japan

Received October 18, 1967

The title reaction was extended to acetone and methyl ethyl ketone as the active methylene compound. Acetone, in the presence of ammonia, reacted with carbon disulfide to give a series of thiazine and diazine compounds. The most stable compound obtained was 3,4-dihydro-4,4,6-trimethyl-2(1H)-pyrimidinethione (V). Methyl ethyl ketone yielded 2-ethyldihydro-2,5,6-trimethyl-4H-3,1-thiazine-4-thione (X) and 4-ethyl-3,4-dihydro-4,5,6-trimethyl-2(1H)-pyrimidinethione (XI). A dithiole (XII) also was isolated from the reaction products of methyl ethyl ketone. The structures of these new compounds were proposed. The interrelation of a series of compounds which were obtained from the reaction product of acetone was described.

In previous research,[2] it was found that cyclohexanone, in the presence of ammonia and treated with carbon disulfide, gives 4(1H)-thiono-5,6,7,8-tetrahydro-2H-3,1-benzothiazine-2-spirocyclohexane and the related compounds. The reaction has now been extended to acetone and methyl ethyl ketone as the active methylene compound.

First, it was found that acetone, in contrast with cyclohexanone, did not give the corresponding thiazine derivative. Instead, a series of thiazine and diazine compounds of a different type was isolated. For example, when a mixture of acetone, carbon disulfide, and aqueous ammonia was shaken at room temperature for 20 hr, 6-hydroxy-4,4,6-trimethyltetrahydro-2H-1,3-thiazine-2-thione (I), 6-amino-4,4,6-trimethyltetrahydro-2H-1,3-thiazine-2-thione (II), 6-amino-4,4,6-trimethyltetrahydro-2(1H)-pyrimidinethione (III), and 3,4-dihydro-4,4,6-trimethyl-2(1H)-pyrimidinethione (V) were isolated from the reaction mixture.

Among these compounds, V was the most stable and thus could be most easily obtained from the reaction mixture. Compound I proved to be identical with the compound which was synthesized by Jansen and Mathes[3] from diacetonamine and carbon disulfide or from 2-methyl-2-isothiocyano-4-pentanone and dithiocarbamic acid. Compound II also was obtained from the reaction of diacetone alcohol or mesityl oxide.

[1] (a) Chiba University. (b) The Institute of Physical and Chemical Research, Honkomagome, Bunkyo-ku, Tokyo, Japan. (c) Shizuoka University.

[2] T. Takeskima, T. Hayashi, M. Muraoka, and T. Matsuoka, *J. Org. Chem.*, **32**, 980 (1967).

[3] J. E. Jansen and R. A. Mathes, *J. Amer. Chem. Soc.*, **77**, 5431 (1955).