tionation under reduced pressure gave 5.2 g. (33.5%) of pale yellow liquid which solidified to colorless plates. It was purified by vacuum sublimation, m.p. 82–83°.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.14; H, 7.14; N, 16.66. Found: C, 57.54; H, 7.28; N, 16.79.

This compound on decomposition with aqueous sodium hydroxide gave after extraction with chloroform 2-amino-6-methylpyridine identified as its picrate, m.p. 201–202°.

A similar treatment of 2-aminopyridine with peracetic acid resulted in an oil which did not solidify. On making this alkaline as described for the salt of the 2-amino-6-methylpyridine, 2-aminopyridine was obtained, picrate m.p. 216°.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Reaction of Hydrazine with Mannich Bases

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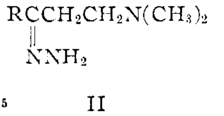
The following products have been obtained from the reaction of hydrazine and the Mannich base β-dimethylaminopropiophenone by varying the reaction conditions: the hydrazone II and azine IVa of β-dimethylaminopropiophenone, the pyrazolinoketone 1-(β-benzoylethyl)-3-phenyl-Δ²-pyrazoline (Va), and the azine of this ketone VI. Some reactions of β-dimethylamino-*p*-methoxypropiophenone and of β-dimethylamino-*p*-nitropropiophenone with hydrazine also have been investigated.

The reaction of hydrazine with a Mannich base, such as β-dimethylaminopropiophenone (Ia), could conceivably lead to the formation of a variety of products, the more obvious of which are the hydrazone II, the pyrazoline III and the azine IV. Recently, Beech and co-workers[2] reported the preparation of 3-phenyl-Δ^2-pyrazoline (IIIa) in 81% from the reaction of excess hydrazine with Ia in refluxing ethanol. Earlier Jacob and Madinaveitia[3] observed that the hydrochloride of Ia, sodium acetate and an excess of hydrazine when heated at 100° in 70% acetic acid, gave a yellow crystalline compound, m.p. 141°, whose analyses corresponded to the formula $(C_6H_6N)_n$. To date the isolation of the hydrazone II or an azine IV of a Mannich base has not been reported.

The present paper is concerned with the products formed in the reaction of some representative Mannich bases (Ia, b, c) with hydrazine. At 100° in aqueous sodium bicarbonate solution one equivalent of hydrazine reacts with two equivalents of Ia to form 1-(β-benzoylethyl)-3-phenyl-Δ^2-pyrazoline (Va) in 83% yield. This product was formed also from the reaction of Ia or its methiodide with 3-phenyl-Δ^2-pyrazoline (III). The structure of Va was shown by the formation of an oxime, its oxidation to the corresponding pyrazole with lead dioxide[4] and by its absorption spectra.[5] When Va was treated with excess hydrazine in dilute hydrochloric acid, it was converted to the azine VI, which proved to be identical with the product obtained by the procedure of Jacob and Madinaveitia.[3]

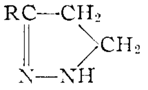
$RCOCH_2CH_2N(CH_3)_2$

Ia, R is C_6H_5
Ib, R is p-$CH_3OC_6H_5$
Ic, R is p-$NO_2C_6H_5$

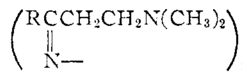


$$\underset{NNH_2}{\overset{\|}{RC}}CH_2CH_2N(CH_3)_2$$

II

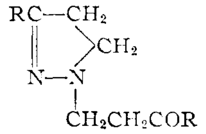


III, R is C_6H_5

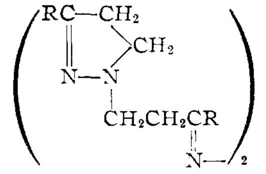


$$\left(\underset{N-}{\overset{\|}{RC}}CH_2CH_2N(CH_3)_2\right)_2$$

IVa, R is C_6H_5
IVb, R is p-$CH_3OC_6H_5$
IVc, R is p-$NO_2C_6H_5$



Va, R is C_6H_5
Vb, R is p-$CH_3OC_6H_5$



VI, R is C_6H_5

As the pyrazoline III is doubtless formed from an intermediate hydrazone II probably *via* the vinylhydrazone, so can the formation of the pyrazolinoketone V result from the addition of III to the phenyl vinyl ketone resulting from the elimination of dimethylamine from the Mannich base I. In the presence of an excess of hydrazine the secondary reaction of III with I is prevented by the complete conversion of I to III.

The Mannich base Ib was converted to Vb in 49% yield under the conditions used for the preparation of Va. Vb yielded an oxime and was converted by oxidation to the corresponding pyrazole.[4] In contrast to Ia and Ib, the nitro Mannich base Ic was converted with sodium bicarbonate solution at 100° into an acid-insoluble glass, which was doubtless a polymer of *p*-nitrophenyl vinyl ketone.

Under acidic conditions at 25° one equivalent of hydrazine reacts with two equivalents of the Mannich base Ia, b or c to yield the corresponding azines IV in a manner similar to the conversion of V (which is also a Mannich base) to the azine VI. It is apparent, therefore, that the nature of the reaction products from hydrazine and a Mannich base is dependent upon conditions of *p*H and temperature. The hydrazones II are probable intermediates in the formation of III, IV and V. It is well-

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[1] (a) Eli Lilly and Company, Indianapolis, Ind.; (b) Rohm and Haas Company, Philadelphia, Penna.

[2] S. G. Beech, J. H. Turnbull and W. Wilson, *J. Chem. Soc.*, 4686 (1952).

[3] A. Jacob and J. Madinaveitia, *ibid.*, 1929 (1937).

[4] *Cf.* K. v. Auwers and P. Heimke, *Ann.*, **458**, 199 (1927).

[5] The infrared spectrum of Va (solid in Stanolind oil) shows bands at 1670 cm.$^{-1}$ (ArCOR) and 1581 cm.$^{-1}$ (C=N in a ring). The first maximum in the ultraviolet spectrum occurs at 238 mμ, which lies between the 234 mμ maximum of acetophenone dimethylhydrazone and the 243 mμ maximum of acetophenone. A second maximum at 296 mμ falls between that of benzyl benzalhydrazone at 290 mμ and the 311 mμ maximum of acetophenone dimethylhydrazone.

known that hydrazones of simple aldehydes and ketones are transformed to azines simply by the addition of a drop of acid during recrystallization.[6–8] A mechanism for this transformation has been proposed.[7]

On the basis of the above observations, it would appear that the hydrazone of a Mannich base II could be formed at 25° and at a *p*H of approximately 7. In an attempt to prepare II the hydrochloride of Ia was treated with two equivalents of hydrazine in methanol. Removal of the solvent at room temperature left a residue of one equivalent of hydrazine hydrochloride and yellow oil. The ultraviolet absorption spectrum of this oil exhibited a maximum at 246 mμ, which is attributed to unreacted ketone, and an inflection point at 264 mμ, which is in the region where the hydrazone would be expected to absorb, since the hydrazone of acetophenone was found to have a single maximum at 263 mμ (Table I). There was no indication of the peaks at 276 and 298 mμ characteristic of the azine of this compound. When an ether solution of this oil was treated with an ethanolic solution of picric acid, the dipicrate of the azine of β-dimethylaminopropiophenone (IVa) precipitated in 66% yield.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA[a]

Compound	λ_{max}, mμ	E_{max}
1-(β-Benzoylethyl)-3-phenylpyrazoline	238	14,400
	296	12,000
Acetophenone[b]	243	12,600
	278	1,000
Acetophenone dimethylhydrazone[c]	234	11,100
	311	2,200
Benzyl benzalhydrazine[d]	290	16,600
Azine of 1-(β-benzoylethyl)-3-phenylpyrazoline	296	39,700
1-(β-Anisoylethyl)-3-anisylpyrazoline	283	28,150
1-(β-Anisoylethyl)-3-anisylpyrazole	265.5	35,900
	349	529
1-(β-Benzoylethyl)-3-phenylpyrazole	249	27,750
	337	1,250
Azine of β-dimethylaminopropiophenone hydrochloride (as the monohydrate)	276 298	17,400 18,000
Azine of β-dimethylamino-*p*-nitropropiophenone hydrochloride	321	23,800
Hydrazone of acetophenone[e]	263	10,400

[a] All ultraviolet absorption spectra were determined with a Beckman quartz spectrophotometer, using 95% ethanol as solvent. [b] R. A. Morton and Z. Sawires, *J. Chem. Soc.*, 1054 (1940). [c] G. H. Hildahl, Department of Chemistry, University of Wisconsin, B.S. Thesis, 1950, p. 24. [d] G. v. Fodor and P. Szarvas, *Ber.*, **76**, 334 (1943). [e] Prepared according to Th. Curtius and L. Pflug, *J. prakt. Chem.*, [2] **44**, 540 (1891); n^{25}_D 1.6072.

Acknowledgment.—One of the authors (M.S.) wishes to thank Dr. S. M. McElvain for his advice and assistance in the completion of this work. The infrared absorption spectra were determined and interpreted by Dr. Keith McCallum.

Experimental

Mannich Bases.—The hydrochlorides of the following Mannich bases used were prepared according to known methods: β-dimethylaminopropiophenone, m.p. 154.8–156.8° (lit.[9] 156°); β-dimethylamino-*p*-methoxypropiophenone, m.p. 181.5–182.5° (lit.[10] 181°); β-piperidylpropiophenone, m.p. 191–192° (lit.[10] 192–193°). β-Dimethylamino-*p*-nitropropiophenone hydrochloride was prepared by the following procedure: A solution of 12.00 g. (0.073 mole) of *p*-nitroacetophenone,[11] 6.32 g. (0.078 mole) of dimethylamine hydrochloride and 2.40 g. (0.080 mole) of paraformaldehyde in 30 ml. of glacial acetic acid was heated under reflux for three hours. The acetic acid was distilled off at reduced pressure, and the red oil which remained was dissolved in a minimum amount of glacial acetic acid. Upon the addition of ethyl acetate, 12.85 g. (68.3%) of fine tan-colored needles was obtained, m.p. 120–140° dec. Three recrystallizations from glacial acetic acid–ethyl acetate gave tan needles, m.p. 177–181° dec.

Anal. Calcd. for $C_{11}H_{15}O_3N_2Cl$: Cl, 13.71. Found: Cl, 13.93.

Treatment of the hydrochloride with a sodium bicarbonate solution at 100° resulted in the immediate separation of a tan-colored oil which cooled to form a glass. The latter was found to be insoluble in dilute hydrochloric acid and to become fluid at about 88–113°. It is apparently a polymer of *p*-nitrophenyl vinyl ketone.

1-(β-Benzoylethyl)-3-phenyl-Δ²-pyrazoline (Va). (a) From β-Dimethylaminopropiophenone and Hydrazine Hydrate.—To a solution of 12.00 g. (0.056 mole) of β-dimethylaminopropiophenone hydrochloride in 50 ml. of saturated aqueous sodium bicarbonate solution was added 1.66 g. (0.028 mole) of 85% hydrazine hydrate. A colorless precipitate formed. The reaction mixture was heated on a steam-bath under a reflux condenser for 45 minutes, during which time the solution and precipitate became pale green. The reaction mixture was cooled, the precipitate collected and dried; it weighed 7.27 g., m.p. 100–102°. After recrystallization from 95% ethanol, 6.52 g. (83.4%) of light green needles was obtained, m.p. 105.2–106.5°.

Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.66; H, 6.51; N, 10.06. Found: C, 77.53; H, 6.66; N, 9.99.

(b) From β-Piperidylpropiophenone and Hydrazine Hydrate.—The pyrazoline Va was also prepared by the reaction of 9.14 g. (0.036 mole) of β-piperidylpropiophenone hydrochloride and 1.15 g. (0.020 mole) of 85% hydrazine hydrate as in method a. After one recrystallization from 95% ethanol, 2.71 g. (54.1%), m.p. 105—106.4°, was obtained. The melting point was not depressed after admixture with material obtained in (a).

(c) From 3-Phenylpyrazoline and Trimethyl-β-benzoylethylammonium Iodide.—3-Phenylpyrazoline was prepared by the reaction of phenyl vinyl ketone and hydrazine hydrate in methanol solution, according to the method of von Auwers.[12] To 0.57 g. (0.004 mole) of 3-phenylpyrazoline was added a suspension of 0.48 g. (0.002 mole) of β-benzoylethyltrimethylammonium iodide in 10 ml. of saturated aqueous sodium bicarbonate solution. The mixture was heated on a steam-bath under a stream of nitrogen for 15 minutes, and was then allowed to stand at room temperature for 2 days. A pale yellow precipitate was collected by filtration. The crude product was 0.46 g., m.p. 89–96°. After recrystallization from absolute ethanol, the yield was 0.28 g. (67%) of product melting at 104.8–105.6°. This compound did not depress the melting point of the material obtained in (a).

(d) From β-Dimethylaminopropiophenone and 3-Phenylpyrazoline.—To a solution of 10.0 g. (0.068 mole) of 3-phenylpyrazoline[2] in 50 ml. of ethanol was added 12.1 g. (0.068 mole) of β-dimethylaminopropiophenone. The solution was boiled on a steam-bath for 15 minutes and then allowed to stand at room temperature for 5 days. The precipitated product was separated by filtration and washed with petroleum ether; it weighed 15.7 g. (82.4%), m.p. 105–106°. The melting point was not depressed on admixture with 1-(β-benzoylethyl)-3-phenyl-Δ²-pyrazoline prepared above.

Azine of 1-(β-Benzoylethyl)-3-phenyl-Δ²-pyrazoline (VI).—To a solution of 0.20 g. of 1-(β-benzoylethyl)-3-phenyl-Δ²-pyrazoline in 10 ml. of absolute ethanol was added 3 ml. of

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[6] W. J. Bruining, *Rec. trav. chim.*, **41**, 655 (1922).

[7] E. R. Blout and R. M. Gofstein, THIS JOURNAL, **67**, 13 (1945).

[8] H. H. Szmant and C. McGinnis, *ibid.*, **72**, 2890 (1950).

[9] C. Mannich and G. Heilner, *Ber.*, **55**, 359 (1922).

[10] C. Mannich and D. Lammering, *ibid.*, **55**, 3510 (1922).

[11] R. E. Bowman, *J. Chem. Soc.*, 322 (1950).

[12] K. v. Auwers and P. Heimke, *Ann.*, **458**, 207 (1927).

85% hydrazine hydrate and 3 ml. of water. The solution was acidified to litmus with hydrochloric acid and heated on a steam-bath for 15 minutes. The product was obtained as a yellow precipitate, 0.08 g. (40.2%), m.p. 134–137°. Repeated recrystallizations from absolute ethanol gave a sample melting at 139.6–140.8°.

Oxime of 1-(β-Benzoylethyl-3-phenyl-Δ^2-pyrazoline.—A solution of 0.25 g. (0.0036 mole) of hydroxylamine hydrochloride in 10% aqueous sodium hydroxide was added to 0.10 g. (0.0036 mole) of 1-(β-benzoylethyl)-3-phenyl-Δ^2-pyrazoline, m.p. 104–105.5°, dissolved in 95% ethanol. The mixture was heated on a steam-bath, sufficient 95% ethanol was added to form a clear solution, and heating was continued for 30 minutes. On cooling, the oxime precipitated as colorless prisms, 0.075 g. (71.4%), m.p. 113–116°. One recrystallization from a benzene–petroleum ether mixture, followed by two recrystallizations from 95% ethanol gave 0.0199 g., m.p. 117.5–118.8°.

Anal. Calcd. for $C_{18}H_{19}ON_3$: C, 73.69; H, 6.53. Found: C, 74.02; H, 6.42.

1-(β-Benzoylethyl)-3-phenylpyrazole.—To a solution of 0.5630 g. (0.002 mole) of 1-(β-benzoylethyl)-3-phenyl-Δ^2-pyrazoline in hot glacial acetic acid was added 0.60 g. (0.002 mole) of 90% lead dioxide in small amounts over a period of 15 minutes while the solution was heated on a steam-bath. The reaction mixture was cooled and filtered, and 15 ml. of water was added. The product separated as an amorphous yellow precipitate which was extracted with ether. The ether was evaporated and the residue was made alkaline with dilute sodium hydroxide and extracted with ether. The ethereal solution was dried over sodium sulfate and the ether was removed, giving 0.37 g. (66%) of light brown needles, m.p. 115.5–117.5°. The product was dissolved in ethanol and treated with Norit and Filter-Cel to remove the color. Another recrystallization from methanol gave colorless needles, m.p. 118–118.8°.

Anal. Calcd. for $C_{18}H_{16}ON_2$: C, 78.23; H, 5.84; N, 10.15. Found: C, 78.31; H, 5.89; N, 10.11.

The aqueous layer was saturated with hydrogen sulfide gas, precipitating 0.49 g. of lead sulfide, corresponding to the theoretical amount needed for the oxidation. No additional product was obtained from the filtrate after neutralization with dilute sodium hydroxide, extraction with ether and evaporation of the ether.

Azine and Hydrazone of β-Dimethylaminopropiophenone.—To a solution of 1.65 g. (0.028 mole) of 85% hydrazine hydrate in 10 ml. of absolute methanol was added 3.00 g. (0.014 mole) of β-dimethylaminopropiophenone hydrochloride in 50 ml. of absolute methanol. The solvent was removed at room temperature and reduced pressure and the residue extracted with anhydrous ether. The ether-insoluble material consisted of 1.00 g. of hydrazine monohydrochloride, as colorless needles, m.p. 85–89°.

To the ethereal extract was added a warm solution of 6.43 g. (0.028 mole) of picric acid in 150 ml. of absolute ethanol. A precipitate of 3.81 g. of yellow needles, m.p. 150–158°, separated at once, corresponding to a 66% yield of the dipicrate of β-dimethylaminopropiophenone azine monohydrate. After four recrystallizations from acetone the compound melted at 161–162.6° and did not depress the melting point of a sample made from the azine of β-dimethylaminopropiophenone hydrochloride monohydrate.

Anal. Calcd. for $C_{34}H_{38}O_{15}N_{10}$: C, 49.40; H, 4.63; N, 16.95. Found: C, 49.41; H, 5.00; N, 16.72.

In a duplicate experiment the ethereal extract was dried over anhydrous calcium sulfate and the ether was distilled off, leaving a residual oily yellow solid. The ultraviolet absorption spectrum of this material in 95% ethanol exhibited a maximum at 246 mμ and an inflection point at 264 mμ ($E_{\max}$ 7430).

1-(β-Anisoylethyl)-3-anisyl-Δ^2-pyrazoline (Vb).—The reaction of 5.00 g. of β-dimethylamino-*p*-methoxypropiophenone hydrochloride and 0.62 g. of 85% hydrazine hydrate was carried out as in method a for 1-(β-benzoylethyl)-3-phenylpyrazoline (Va). The yield was 3.40 g. (48.9%) of pale yellow crystals, m.p. 138–140.5°. One recrystallization from 95% ethanol gave 2.63 g. of colorless plates, m.p. 142.5–143.5°.

Anal. Calcd. for $C_{20}H_{22}O_3N_2$: C, 70.98; H, 6.55. Found: C, 71.21; H, 6.52.

The oxime of Vb was obtained in 93.8% yield as colorless needles, m.p. 118–122°. Repeated recrystallizations from ethanol gave material melting at 128–128.6°.

Anal. Calcd. for $C_{20}H_{23}O_3N_3$: C, 67.97; H, 6.56. Found: C, 67.65; H, 6.29.

1-(β-Anisoylethyl)-3-anisylpyrazole.—Oxidation of 0.452 g. of the pyrazoline Vb with lead dioxide gave 0.441 g. (98.2%) of an orange-red product, m.p. 142–146°. After decolorization with Norit and recrystallization from methanol, pale yellow plates were obtained, m.p. 142–142.7°. The melting point was depressed after admixture with the starting material.

Anal. Calcd. for $C_{20}H_{20}O_3N_2$: C, 71.40; H, 5.99. Found: C, 71.56; H, 5.82.

Azine of β-Dimethylaminopropiophenone Hydrochloride Monohydrate (IVa).—To a solution of 2.00 g. (0.009 mole) of β-dimethylaminopropiophenone hydrochloride in 10 ml. of water containing 0.30 g. of acetic acid was added 0.277 g. (0.005 mole) of 85% hydrazine hydrate. The solution was allowed to stand at room temperature for 24 hours. After removal of the solvent at 65° and reduced pressure 2.194 g. of fine yellow crystals remained, m.p. 120–132° dec. One recrystallization from absolute ethanol gave 1.076 g. (52% yield), m.p. 176–178° dec. with previous darkening at 168° when placed in the bath at 165°.

Anal. Calcd. for $C_{22}H_{34}N_4OCl_2$: Cl, 16.06. Found: Cl, 16.05.

Azine of β-Dimethylamino-*p*-methoxypropiophenone Hydrochloride Monohydrate (IVb).—The reaction was carried out as above, using 10.0 g. (0.04 mole) of β-dimethylamino-*p*-methoxypropiophenone hydrochloride and 1.21 g. (0.02 mole) of 85% hydrazine hydrate. Removal of the solvent left a residue of yellow needles. One recrystallization from methanol–ethyl acetate gave 6.3 g. (61%), m.p. 168–174° dec. Recrystallization from methanol gave material melting at 183–185° dec.

Anal. Calcd. for $C_{24}H_{38}O_3N_4Cl_2$: Cl, 14.14. Found: Cl, 14.23.

Azine of β-Dimethylamino-*p*-nitropropiophenone Hydrochloride (IVc).—To a solution of 2.097 g. (0.008 mole) of β-dimethylamino-*p*-nitropropiophenone hydrochloride in 7 ml. of water containing 0.5 g. of acetic acid was added 0.241 g. (0.004 mole) of 85% hydrazine hydrate. The reaction mixture was allowed to stand at room temperature for 15 hours. The solvent was then removed at 50° and reduced pressure, and the dark red oily solid which remained was dissolved in warm glacial acetic acid. On cooling, 0.612 g. (28.5% yield) of orange-colored crystals precipitated, m.p. 164–165° dec. with previous softening at 162°. After two recrystallizations from glacial acetic acid and drying to constant weight at 2 mm. pressure and room temperature, an analytical sample was obtained which melted at 179–180° dec. when placed in the bath at 165°. It was necessary to avoid overheating during the recrystallizations since the azine was thermally unstable.

Anal. Calcd. for $C_{22}H_{30}O_4N_6Cl_2$: Cl, 13.81. Found: Cl, 13.44.

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