Reaction of the Mixed Anhydride D with Aniline.—A solution of 0.252 g. of the mixed anhydride D and 0.093 g. of aniline in 15 ml. of benzene was warmed briefly to 60° and then allowed to stand at room temperature overnight, during which time 0.071 g. of 2-methoxy-4-carboxytropone separated out. The filtered solution was washed with 10% sodium bicarbonate, followed by water, dried and evaporated. The residual oil deposited 0.08 g. of white solid (m.p. 148–150°) when triturated with warm heptane. Two recrystallizations from benzene–heptane gave the analytical sample of 2-methoxy-4-carboxytropone anilide which melted at 153–153.5°.

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.66; H, 5.29; N, 5.52.

Di-*t*-butyl 2-Amino-3,4,5-trimethoxybenzylmalonate (H-2).—Di-*t*-butyl 2-nitro-3,4,5-trimethoxybenzylmalonate was reduced to the amine (H-2) in 82% yield in hot (70–80°) benzene solution upon shaking with Adams catalyst under 2 atmospheres of hydrogen for 13 hr. The amine was recrystallized from pentane and melted at 74–75°.

Anal. Calcd. for $C_{21}H_{33}NO_7$: C, 61.29; H, 8.08. Found: C, 61.00; H, 7.89.

Treatment of the amine H-2 with acetic anhydride in pyridine gave the amide H-3, m.p. 135.5–136° (from heptane).

Anal. Calcd. for $C_{23}H_{35}NO_8$: C, 60.91; H, 7.78. Found: C, 61.01; H, 7.89.

Similar treatment of the amine H-2 with *m*-methoxybenzoyl chloride in pyridine gave the N-*m*-methoxybenzoyl derivative H-4, m.p. 110–110.5° (from heptane).

Anal. Calcd. for $C_{29}H_{39}NO_9$: C, 63.83; H, 7.21. Found: C, 63.94; H. 7.52.

β-[2-N-*m*-Methoxybenzamido)-3,4,5-trimethoxyphenyl]-3'-methoxypropiophenone (M-2).—Acylation of the lithium salt of the amide H-3 (prepared with 2 equivalents of lithium amide) with 6 equivalents of *m*-methoxybenzoyl chloride gave, after decarbo-*t*-butoxylation. an oily ketone mixture which gave the 2,4-dinitrophenylhydrazone of M-2. Recrystallization from ethyl acetate–ethanol gave the analytical sample with m.p. 215.5–216°.

Anal. Calcd. for $C_{33}H_{33}N_5O_{10}$: C, 60.08; H, 5.04. Found: C, 60.55, 60.50; H, 5.13, 5.00.

ROCHESTER, N. Y.

Alkylhydrazines in the Mannich Reaction; a Convenient Synthesis of Δ³-Pyrazolines[1]

BY R. L. HINMAN,[2] RALPH D. ELLEFSON AND RICHARD D. CAMPBELL

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The behavior of a number of alkylhydrazines under the conditions of the Mannich reaction has been examined. With acetophenone and formaldehyde, trimethylhydrazine yielded β-trimethylhydrazinopropiophenone (I). Under similar conditions 1,2-dimethyl-, 1,2-diethyl- and 1,2-di-*n*-propylhydrazine yielded the corresponding 1,2-dialkyl-3-phenyl-Δ³-pyrazolines (III). This is the first simple, generally useful synthesis of Δ³-pyrazolines to be reported. The structure of the dimethyl member of the series was established by its ultraviolet and infrared spectra, by ozonolysis, and by hydrogenation to 1,2-dimethyl-3-phenylpyrazolidine (IV), which was also synthesized by reduction of 1,2-dimethyl-3-phenyl-5-pyrazolone with lithium aluminum hydride. The reaction of ethyl benzoylacetate with 1,2-dimethylhydrazine and formaldehyde produced a mixture of 1,2-dimethyl-3-phenyl-4-carbethoxy-Δ³-pyrazoline (VI) and IIIa. Saponification and decarboxylation converted VI to IIIa. With benzyl methyl ketone and formaldehyde, 1,2-dimethylhydrazine yielded a mixture of isomers, including 1,2-dimethyl-3-benzyl-Δ³-pyrazoline. No product was obtained from the reaction of methylhydrazine with paraformaldehyde and acetophenone, but 1-methyl-3-phenyl-Δ²-pyrazoline (XIII) was prepared by the reaction of methylhydrazine with the Mannich base, β-dimethylaminopropiophenone.
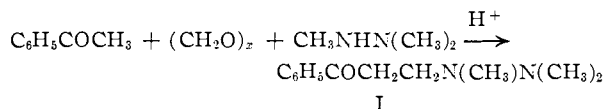
Although the Mannich reaction has been extended to a wide variety of amines, the use of hydrazines in this reaction has received little attention.[3] This paper describes the behavior of a number of alkylhydrazines under the conditions of the Mannich reaction.

Trimethylhydrazine.—When trimethylhydrazine, as the hydrochloride, was refluxed with acetophenone and paraformaldehyde in ethanol, an oil was obtained which decomposed when distillation was attempted. The undistilled oil was identified as β-trimethylhydrazinopropiophenone (I) by means of the analysis of its metho-*p*-toluenesulfonate, and the fact that its methiodide absorbed strongly in the carbonyl region of the infrared.

$$C_6H_5COCH_3 + (CH_2O)_x + CH_3NHN(CH_3)_2 \xrightarrow{H^+}$$
$$C_6H_5COCH_2CH_2N(CH_3)N(CH_3)_2$$
$$I$$

1,2-Dialkylhydrazines.—In the hope that both nitrogens of the hydrazine might undergo the Mannich reaction, molar ratios of 1:2:2 of 1,2-dimethylhydrazine dihydrochloride, acetophenone and paraformaldehyde were chosen. The product, however, contained no oxygen. Its composition was that of 1,2-dimethyl-3-phenyl-Δ³-pyrazoline (IIIa), presumably formed by acid-catalyzed ring closure of the Mannich base formed initially.

$$
\begin{array}{c}
C_6H_5COCH_3 \\
+ \\
(CH_2O)_x \\
+ \\
RNHNHR \cdot 2HCl
\end{array}
\longrightarrow
(C_6H_5COCH_2CH_2NRNHR)
$$

II

IIIa, R = CH_3
b, R = C_2H_5
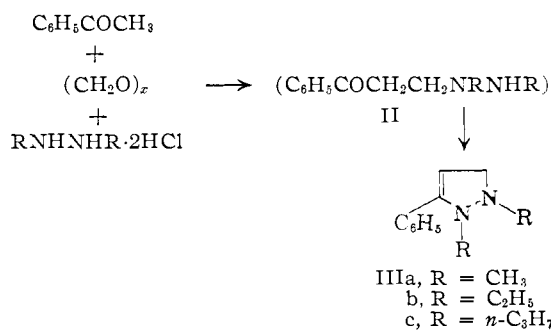c, R = $n\text{-}C_3H_7$

(1) Abstracted from the Ph.D. thesis of R. D. Ellefson, State University of Iowa, August, 1958. Presented before the Organic Division of the American Chemical Society at the Atlantic City Meeting, September 15, 1959.

(2) To whom inquiries should be addressed: Union Carbide Research Institute, 32 Depot Plaza, White Plains, N. Y.

(3) (a) W. Ried and K. Wesselborg (*Ann.*, **611**, 71 (1958)) have recently reported the use of hydrazine and some 1,2-dialkylhydrazines in the Mannich reaction with antipyrene and formaldehyde. Both nitrogens of the hydrazines underwent condensation to yield products of the type YCH₂NRNRCH₂Y, where Y is the group derived from antipyrene. (b) An intramolecular Mannich reaction between benzaldehyde and 1-phenyl-1-skatylhydrazine has been reported (J. Thesing and C. H. Willersinn, *Ber.*, **89**, 1195 (1956)).

The skeletal structure of IIIa was established by low pressure hydrogenation[4] which produced 1,2-dimethyl-3-phenylpyrazolidine (IV). The latter was also synthesized by reduction of 1,2-dimethyl-3-phenyl-5-pyrazolone (isoantipyrene, V) with lithium aluminum hydride.[5]

$$\text{IIIa} \xrightarrow[\text{HOAc}]{\text{H}_2,\ \text{Pd-C}} \quad \text{IV} \quad \xleftarrow{\text{LiAlH}_4} \quad \text{V}$$
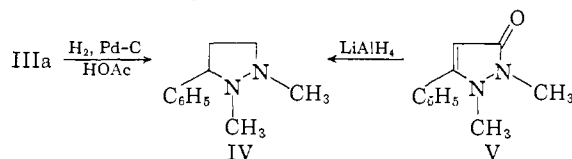
The position of the double bond in the pyrazoline IIIa was deduced from its ultraviolet and infrared spectra and confirmed by ozonolysis, from which benzoic acid was obtained. The ultraviolet spectrum (Fig. 1), which resembles that of α-(N-methylanilino)-styrene,[6] shows λ_{max} 228, 277 mμ (log ϵ_{max} 4.03, 3.60). The peak at longer wave lengths could have arisen only if the double bond were conjugated with the aromatic ring. This also accounts for the absorption at 1580 cm.$^{-1}$ in the infrared,[7] which becomes a shoulder in the pyrazolidine IV.[8]

The synthesis of 1,2-dialkyl-Δ^3-pyrazolines was extended to the 1,2-diethyl (IIIb) and 1,2-di-n-propyl (IIIc) derivatives by the use of 1,2-diethylhydrazine and 1,2-di-n-propylhydrazine, respectively. These pyrazolines were identified by their elementary analyses and by their ultraviolet and infrared spectra which had the same principal features as those of IIIa.

The yields of pyrazolines were: IIIa, 40%; IIIb, 50%; IIIc, 26%. Taken together with the fact that no pyrazoline was obtained when 1,2-diisopropylhydrazine was used in the reaction, these figures indicate the existence of steric hindrance at some stage of the reaction, probably in the ring closure where the alkyl and phenyl groups are in close proximity.[9]

(4) Reduction of IIIa with lithium in diethylamine, which has been used to reduce styrene to ethylbenzene (K. Ziegler, L. Jacob, H. Wollthan and A. Wenz, *Ann.*, **511**, 64 (1934)), or with lithium aluminum hydride (see below) could not be achieved.

(5) A. Uffer and E. Schlittler (*Helv. Chim. Acta*, **31**, 1397 (1948)) have reported the reduction of an α,β-unsaturated amide to a saturated amine by an excess of lithium aluminum hydride (*cf.* N. G. Gaylord, "Reductions with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p. 591). To determine whether the pyrazoline IIIa might have been an intermediate in the reduction of isoantipyrene (V), a sample of IIIa was treated with an excess of hydride, but only unchanged IIIa was isolated.

(6) P. Ramart-Lucas and M. J. Hoch, *Bull. soc. chim. France*, [5] **3**, 918 (1936). The spectrum of α-(N-methylanilino)-styrene shows λ_{max} 242, 285 mμ (log ϵ_{max} 4.20, 3.60), while the spectrum of β-(N-methylanilino)-styrene has a shoulder at 295 mμ (log ϵ 4.25) and λ_{max} 360 mμ (log ϵ_{max} 3.95).

(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Second Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 72.

(8) A number of unsuccessful attempts were made to synthesize IIIa directly. The reaction of 1,2-dimethylhydrazine with cinnamaldehyde was carried out under a variety of conditions from acidic to mildly basic, but no identifiable product was isolated. The reaction of phenylacetylene, paraformaldehyde and 1,2-dimethylhydrazine dihydrochloride yielded only unidentified oils. When isoantipyrene (V) was treated with sufficient lithium aluminum hydride for reduction of the carbonyl group only, the pyrazolidine IV and unchanged pyrazolone V were isolated, but no pyrazoline IIIa was found.

(9) If ring closure were blocked in the experiment with 1,2-diisopropylhydrazine, a Mannich base of type II would be the product of the reaction. A water-insoluble basic liquid was obtained from the reaction, but it could not be purified sufficiently for identification.
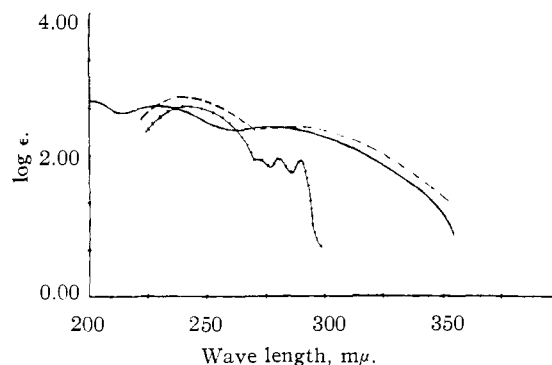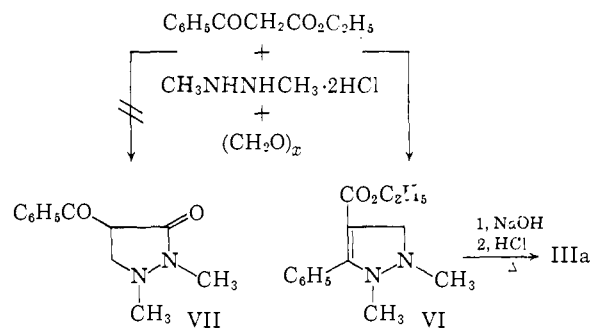

Fig. 1.—Ultraviolet spectra: 1,2-dimethyl-3-phenyl-Δ^3-pyrazoline, ——; α-(N-methylanilino)-styrene, – – – –; styrene, + + + +.
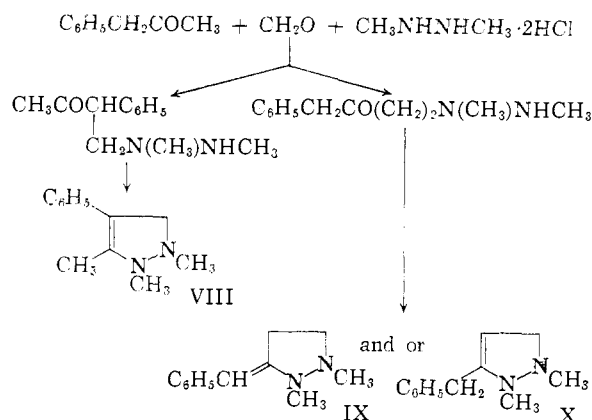
We turned our attention next to the reactions of 1,2-dimethylhydrazine with other compounds containing active hydrogens. Ethyl benzoylacetate was chosen because it might yield either a pyrazoline (VI) or a pyrazolidone (VII) if cyclization occurred.

$$C_6H_5COCH_2CO_2C_2H_5 \quad + \quad CH_3NHNHCH_3 \cdot 2HCl \quad + \quad (CH_2O)_x$$

VII   VI $\xrightarrow[2,\ HCl]{1,\ NaOH}$ IIIa

As actually carried out, the reaction yielded two liquid products. The lower boiling of these substances was IIIa. The higher-boiling fraction was mainly 1,2-dimethyl-3-phenyl-4-carbethoxy-Δ^3-pyrazoline (VI). Although not obtained in sufficiently pure form for a satisfactory analysis, the structure of VI was established by its ultraviolet spectrum (λ_{max} 238, 327 mμ) which resembled that of IIIa, but shifted to longer wave lengths, as would be expected, and by its conversion to IIIa by saponification and subsequent decarboxylation. It is not known whether the product IIIa, isolated from the original reaction mixture, was formed from VI by hydrolysis and decarboxylation or from acetophenone produced by degradation of the keto ester. No pyrazolidone was found in the reaction mixture, indicating that pyrazoline formation is the preferred direction of ring closure.

The Mannich reaction of 1,2-dimethylhydrazine, formaldehyde and benzyl methyl ketone was also investigated. On the assumption that Mannich base formation is the first step in pyrazoline formation, the product (or products) actually formed in the reaction would depend on whether the Mannich base is formed at the methylene group or at the methyl group of benzyl methyl ketone, or both. The three most probable products are VIII, IX and X.
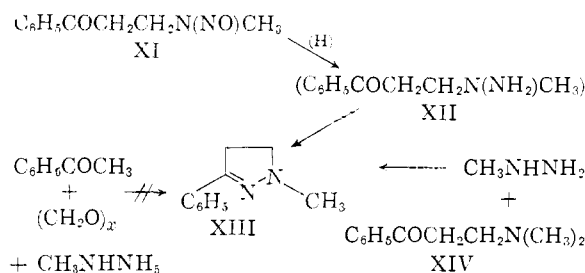
The ultraviolet spectrum of the liquid product isolated from the reaction had λ_{max} 297 mμ (ϵ_{max}

$C_6H_5CH_2COCH_3 + CH_2O + CH_3NHNHCH_3 \cdot 2HCl$

$CH_3COCHC_6H_5$ $C_6H_5CH_2CO(CH_2)_2N(CH_3)NHCH_3$
|
$CH_2N(CH_3)NHCH_3$

VIII

and or

IX   X

5900) and a shoulder at 217 mμ (ε 7800). The maximum at 297 mμ is consistent only with structures VIII and IX.[10] However, ozonolysis of the product produced phenylacetic acid in 35% yield, indicating the presence of X among the products. Structure VIII would probably yield an α-hydrazinoacetophenone on ozonolysis, while IX would give rise to benzaldehyde and a pyrazolone. If these products were formed, they were lost in the workup of the ozonolysis. On the basis of the information at hand, therefore, we conclude that the Mannich reaction of benzyl methyl ketone, formaldehyde and 1,2-dimethylhydrazine yields a mixture of 1,2-dimethyl-3-benzyl-Δ^3-pyrazoline (X), and either or both 1,2,3-trimethyl-4-phenyl-Δ^3-pyrazoline (VIII) and 1,2-dimethyl-3-benzylidene-pyrazolidine (IX).

The reactions described above[11] represent the first generally useful, simple synthesis of Δ^3-pyrazolines.

Methylhydrazine.—The reaction of methylhydrazine, formaldehyde and acetophenone was examined as a possible route to 1-methyl-3-phenyl-Δ^2-pyrazoline (XIII).[12] No identifiable product was obtained from the reaction in acidic ethanol nor

$C_6H_5COCH_2CH_2N(NO)CH_3$
XI
↘ [H]

$(C_6H_5COCH_2CH_2N(NH_2)CH_3)$
XII

$C_6H_5COCH_3$
+   ←——— CH_3NHNH_2
$(CH_2O)_x$ XIII   +
+ CH_3NHNH_2 $C_6H_5COCH_2CH_2N(CH_3)_2$
XIV

from a reaction in which acetophenone methylhydrazone was formed prior to addition of the paraformaldehyde.

The pyrazoline XIII was synthesized successfully by the related reaction of methylhydrazine with the Mannich base β-dimethylaminopropiophenone (XIV). This reaction is similar to the synthesis of 1,3-diphenyl-Δ^2-pyrazoline from XIV and phenylhydrazine.[13] The product XIII was identified by comparison with an authentic specimen prepared by the method of Mannich (XI → XIII).[12]

Experimental[14]

β-Trimethylhydrazinopropiophenone.—Dry hydrogen chloride was passed into a cooled solution of 7.4 g. (0.1 mole) of trimethylhydrazine[15] in 100 ml. of absolute ethanol until the solution was acidic to moist congo red paper. To this solution were added 7.5 g. of paraformaldehyde (0.25 mole of formaldehyde) and 12 g. (0.10 mole) of acetophenone. The mixture was heated under reflux for 3 hours and then poured into about 400 ml. of water. The excess acetophenone was extracted with ether. Sodium carbonate was added to the aqueous solution until it became basic to litmus. The basic product was then extracted from the aqueous mixture with five 100-ml. portions of ether. The combined ether portions were dried over anhydrous potassium carbonate, and the ether was then distilled. The residue was dissolved in 50 ml. of petroleum ether (b.p. 60–70°), with just enough ethyl ether added to effect complete solution, and then adsorbed on a column of activated alumina. The column was developed with petroleum ether (b.p. 60–70°). Elution of the column was begun with petroleum ether (b.p. 60–70°), and the elution solvent was enriched in benzene by 10% with the collection of each 50 ml. of eluate. Following elution with pure benzene a 50% ethanol–benzene solution was added, and the concentration of ethanol was increased by 10% for every 20 ml. of eluate collected. After pure ethanol had been run through the column the final elution was made with pure methanol. Twenty-five fractions of eluate were collected. The petroleum ether–benzene fractions contained the main product. The ethanol–benzene fractions contained a very small amount of highly colored material and an unidentified basic product. On concentrating the petroleum ether–benzene fractions, 5.7 g. of oil was obtained (45% yield of the Mannich base). Attempts to distil this oil led only to thermal decomposition.

The product formed a white crystalline solid when treated with methyl iodide. This solid underwent decomposition in hot ethanol, but was purified somewhat by trituration with cold ethanol, although not sufficiently for an accurate combustion analysis. The methiodide obtained in this way melted at 195° dec. The infrared spectrum, determined in Nujol mull, contained a peak at 1665 cm.$^{-1}$ (C=O of aryl ketone).

With methyl p-toluenesulfonate in benzene the product formed a white crystalline solid which, after three triturations with cold ethanol, melted at 150–151° dec.

Anal. Calcd. for $C_{20}H_{28}N_2O_4S$: C, 61.20; H, 7.18. Found: C, 61.10; H, 6.74.

1,2-Dimethyl-3-phenyl-Δ^3-pyrazoline.—A solution of 13.3 g. (0.10 mole) of 1,2-dimethylhydrazine dihydrochloride,[16] 24 g. (0.20 mole) of acetophenone and 6.0 g. of paraformaldehyde (0.20 mole of formaldehyde) in 200 ml. of absolute ethanol was heated under reflux for 24 hours. The reaction mixture was then concentrated to about 50 ml. by evaporation under reduced pressure. The concentrate was poured into 600 ml. of water and the excess acetophenone was extracted with ether. The aqueous mixture was then made

(10) The ultraviolet spectra of pyrazolines of type III resemble closely the spectrum of α-(N-methylanilino)-styrene.[6] It might be expected therefore that the spectrum of VIII or IX would be similar to that of a β-aminostyrene. The increase in intensity compared to that of IIIa is in keeping with the comparison, but the shift to longer wave lengths in passing from IIIa to (VIII, IX) is much smaller than the corresponding shift in passing from an α-aminostyrene to a β-aminostyrene.[6]

(11) The reaction of acetylacetone with 1,2-dimethylhydrazine and formaldehyde was also investigated, but no identifiable product was obtained from the reaction mixture.

(12) Compound XIII has been prepared by reduction of β-(N-nitroso-N-methylamino)-propiophenone (XI), a reaction which may proceed via a Mannich base (XII) of the hydrazino type (C. Mannich and G. Heilner, *Ber.*, 55, 365 (1922)). If XII were formed in the Mannich reaction described in the present work, pyrazoline XIII might have formed also.

(13) A. Jacob and J. Madinaveitia, *J. Chem. Soc.*, 1929 (1937).

(14) Melting points and boiling points are uncorrected. Infrared spectra were obtained with a Perkin–Elmer model 21 double beam recording spectrophotometer, equipped with sodium chloride optics. Ultraviolet spectra were determined with a Cary model 11 recording spectrophotometer.

(15) J. B. Class, J. G. Ashton and T. S. Oakwood, This Journal, 75, 2937 (1953).

(16) R. L. Hinman, *ibid.*, 78 1648 (1956).

strongly alkaline by the addition of an excess of a 20% solution of sodium hydroxide, and the product was extracted with three 100-ml. portions of ether, which were combined and dried over anhydrous sodium sulfate. The ether was evaporated and the concentrate was distilled. The distillate collected at 83° (2 mm.) (71° (1.2 mm.)) weighed 7.0 g. (41% yield); $\lambda_{max}^{95\% \text{ EtOH}}$ 228, 277 mμ (ϵ_{max} 10800, 4000). The infrared spectrum of a film of the pure liquid showed bands at 1642 (C=C) and 1580 cm.$^{-1}$ (benzene ring conjugated with C=C).

Anal. Calcd. for $C_{11}H_{14}N_2$: C, 75.86; H, 8.05; N, 16.09. Found: C, 75.63; H, 8.09; N, 16.24.

1,2-Dimethyl-3-phenyl-Δ³-pyrazoline Picrate.—With picric acid in ether the pyrazoline formed a yellow crystalline solid. After two recrystallizations from absolute ethanol the product melted at 122° dec.

Anal. Calcd. for $C_{17}H_{17}N_5O_7$: C, 50.62; H, 4.22; N, 17.37. Found: C, 51.12; H, 4.41; N, 17.02.

1,2-Dimethyl-3-phenyl-Δ³-pyrazoline Methiodide.—With methyl iodide in ether the pyrazoline formed a white crystalline solid, which was purified by precipitation from chloroform by the addition of carbon tetrachloride. After three precipitations the methiodide melted at 150° dec.

Anal. Calcd. for $C_{12}H_{17}N_2I$: C, 45.57; H, 5.42; N, 8.81. Found: C, 45.45; H, 5.44; N, 8.56.

1,2-Diethyl-3-phenyl-Δ³-pyrazoline was prepared from 16.1 g. (0.10 mole) of 1,2-diethylhydrazine dihydrochloride,[17] 6.0 g. of paraformaldehyde (0.20 mole of formaldehyde) and 24 g. (0.20 mole) of acetophenone by the procedure used for the preparation of 1,2-dimethyl-3-phenyl-Δ³-pyrazoline. The product distilled at 94–95° (2 mm.). The yield was 10.1 g. (50%); $\lambda_{max}^{95\% \text{ EtOH}}$ 229, 288 mμ (ϵ_{max} 11,600, 4100).

Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.20; H, 8.97. Found: C, 76.47; H, 8.92.

When the product was added dropwise to a solution of picric acid in ether, a red oil formed. Attempts to obtain a solid picrate from this oil by crystallization from ethanol were unsuccessful. Treating this pyrazoline with methyl iodide resulted only in the formation of a reddish viscous oil.

1,2-Di n-propyl-3-phenyl-Δ³-pyrazoline was prepared from 18.9 g. (0.10 mole) of 1,2-di-n-propylhydrazine dihydrochloride,[17] 6.0 g. of paraformaldehyde (0.20 mole of formaldehyde) and 24.0 g. (0.20 mole) of acetophenone by the procedure used for the preparation of 1,2-dimethyl-3-phenyl-Δ³-pyrazoline. The yield was 3.0 g. (26%), b.p. 110° (1.5 mm.); $\lambda_{max}^{95\% \text{ EtOH}}$ 229, 289 mμ (ϵ_{max} 12000, 5300).

Anal. Calcd. for $C_{15}H_{22}N_2$: C, 78.21; H, 9.64. Found: C, 78.21; H, 9.63.

As in the case of 1,2-diethyl-3-phenyl-Δ³-pyrazoline, attempts to prepare a picrate and a methiodide from this compound were unsuccessful.

1,2-Dimethyl-3-phenylpyrazolidine. A. By Catalytic Hydrogenation of 1,2-Dimethyl-3-phenyl-Δ³-pyrazoline.—A 6.0-g. sample of 1,2-dimethyl-3-phenyl-Δ³-pyrazoline (0.034 mole) in about 50 ml. of glacial acetic acid was shaken in a 6-oz. bottle in the presence of 0.1 g. of 10% palladium-on-charcoal and a hydrogen atmosphere under an initial pressure of 40 p.s.i. The reaction mixture was heated to about 50° by an external heating coil. During a period of about four hours the pressure in the reaction vessel dropped to about 36.5 p.s.i. The catalyst was filtered, the acetic acid was neutralized with 20% sodium hydroxide, and the product was extracted with three 50-ml. portions of ether. The combined ether solutions were dried over anhydrous sodium sulfate. The ether was evaporated and the residue was distilled. The fraction collected at 72° (1.2 mm.), weighed 4.3 g. (73% yield), n^{21}D 1.5318.

Anal. Calcd. for $C_{11}H_{16}N_2$: N, 15.90. Found: N, 15.39.

The picrate was prepared by reaction with a solution of picric acid in 95% ethanol. It melted at 175–176° after two recrystallizations from 95% ethanol. The m.p. was not depressed when it was mixed with an authentic sample (see below). The infrared spectrum of the picrate was identical to that of a specimen prepared by method B below.

Anal. Calcd. for $C_{17}H_{19}N_5O_7$: N, 17.28. Found: N, 16.98.

A methiodide of the pyrazolidine was obtained by reaction with methyl iodide in ether. It melted at 178–179° dec.

after three recrystallizations from an ethanol–ether mixture. Satisfactory analytical values could not be obtained. The m.p. of the methiodide was not depressed when mixed with an authentic sample (see below).

B. By Reduction of 1,2-Dimethyl-3-phenyl-5-pyrazolone with Lithium Aluminum Hydride.—Reduction was carried out by a modification of the Soxhlet technique. A 500-ml. round-bottom flask was equipped with a mechanical stirrer and a reflux condenser at each side neck. In between one reflux condenser and the flask was interposed a separatory funnel containing a piece of fluted filter paper to serve as the extractor thimble. The flask was charged with 300 ml. of freshly distilled, dry tetrahydrofuran and 7.6 g. (0.20 mole) of finely ground lithium aluminum hydride. In the fluted filter paper was placed 18.8 g. (0.10 mole) of 1,2-dimethyl-3-phenyl-5-pyrazolone.[18] The stirred slurry was heated sufficiently to allow a moderate rate of reflux through the extractor. After all the pyrazolone had been added to the reaction mixture, heating was continued for about 24 hours. Water was added dropwise to the cooled reaction mixture until the evolution of hydrogen ceased. The inorganic precipitate was removed by filtration. Excess sodium chloride was added to the filtrate, and two layers appeared. The aqueous layer was discarded, and the organic layer was dried over anhydrous sodium sulfate. The tetrahydrofuran was removed by evaporation under reduced pressure, and the residue was distilled. The fraction collected at 72° (1.2 mm.) weighed 11.5 g. (65% yield), n^{21}D 1.5318; picrate, m.p. 175–176° after three recrystallizations from 95% ethanol.

Anal. Calcd. for $C_{17}H_{19}N_5O_7$: C, 50.37; H, 4.69. Found: C, 49.83; H, 4.60.

The infrared spectrum of this picrate agrees completely with that of the picrate obtained from the product of the catalytic hydrogenation of 1,2-dimethyl-3-phenyl-Δ³-pyrazoline.

Methiodide, m.p. 178–179° after recrystallization from 95% ethanol aided by the addition of ether. Satisfactory analytical values could not be obtained.

Ozonolysis of 1,2-Dimethyl-3-phenyl-Δ³-pyrazoline.—A stream of oxygen containing about 3% ozone was bubbled through a cooled (0°) solution of 6.0 g. (0.034 mole) of 1,2-dimethyl-3-phenyl-Δ³-pyrazoline in 70 ml. of absolute ethanol. The stream of oxygen leaving the reaction vessel was bubbled through a solution of potassium iodide (40%). The solution of the pyrazoline completely absorbed the ozone from the stream of gas for about 3.5 hours, when the solution of potassium iodide suddenly became colored. The stream of oxygen–ozone was bubbled through the reaction mixture at the same moderate rate during an additional half-hour. The reaction mixture was poured into a small flask and allowed to warm to room temperature. The solution was then concentrated to about 15 ml. under reduced pressure. The concentrate was poured into 50 ml. of 10% sodium hydroxide, gently heated, and finally refluxed for about an hour. After cooling, the mixture was acidified with concd. hydrochloric acid. The precipitate of benzoic acid was filtered, recrystallized from a mixture of ethanol and water, and dried. The yield was 2.1 g. (51%), m.p. 122°. Mixed melting point with an authentic sample was not depressed.

When a 5% solution of sodium hydroxide was added dropwise to the acid filtrate so that the solution very gradually was neutralized and finally made basic no further precipitation occurred. Extraction of the aqueous solution with chloroform at several acidic and basic pH values yielded no other product.

Reaction of 1,2-Dimethylhydrazine Dihydrochloride with Formaldehyde and Benzyl Methyl Ketone.—A solution of 13.3 g. (0.10 mole) of 1,2-dimethylhydrazine dihydrochloride, 3.0 g. of paraformaldehyde (0.10 mole of formaldehyde and 20 g. (0.15 mole) of benzyl methyl ketone in 250 ml. of ethanol was heated under reflux for 24 hours. The product was isolated by the procedure used in the preparation of 1,2-dimethyl-3-phenyl-Δ³-pyrazoline. Distillation of the crude product yielded 4.1 g. of a nearly colorless oil, b.p. 98° (1.7 mm.) (22% yield based on 1,2-dimethylhydrazine dihydrochloride). The product discolored rapidly after being exposed to air. The ultraviolet spectrum showed λ_{max} 297 mμ (ϵ_{max} 5900), and a shoulder at 217 mμ (ϵ 7800).

Methiodide.—After adding a few drops of the product to a solution of methyl iodide in ether a colorless crystalline pre-

(17) R. Renaud and L. C. Leitch, *Can. J. Chem.*, **32**, 545 (1954).

(18) A. Michaelis and H. Dorn, *Ann.*, **352**, 163 (1907).

cipitate formed. After three reprecipitations from ethanol induced by the addition of ether, the methiodide melted at 187–188° dec.

Anal. Calcd. for $C_{13}H_{19}N_2I$: C, 47.58; H, 5.76; N, 8.49. Found: C, 47.30; H, 5.53; N, 8.68.

Ozonolysis of the Product from the Reaction of 1,2-Dimethylhydrazine Dihydrochloride with Formaldehyde and Benzyl Methyl Ketone.—A stream of oxygen containing about 3% ozone was bubbled through a cooled solution (0°) of 1.0 g. of the product in 60 ml. of absolute ethanol. The stream of oxygen leaving the reaction vessel was bubbled through a 40% solution of potassium iodide. The ethanolic solution completely absorbed the ozone from the steam of gas for about 45 minutes, after which the solution of potassium iodide suddenly became colored. The stream of ozone and oxygen was bubbled through the reaction mixture for an additional half-hour at the same moderate rate. The solution was then concentrated to about 15 ml. by removing most of the ethanol under reduced pressure. The concentrate was heated under reflux for about an hour with 50 ml. of a 10% solution of sodium hydroxide. After cooling, the mixture was acidified with excess concd. hydrochloric acid. The product was extracted with three 30-ml. portions of ether. Evaporation of the ether left a residue of 0.25 g. of phenylacetic acid (35% yield based on 1,2-dimethyl-3-benzyl-Δ³-pyrazoline). After recrystallization from ethanol and water the melting point was 75–77°; mixed melting point with an authentic sample was unchanged.

Reaction of Ethyl Benzoylacetate with Formaldehyde and 1,2-Dimethylhydrazine Dihydrochloride.—A solution of 25.0 g. (0.13 mole) of ethyl benzoylacetate, 9.0 g. of paraformaldehyde (0.15 mole of formaldehyde) and 13.3 g. (0.10 mole) of 1,2-dimethylhydrazine dihydrochloride in 250 ml. of 95% ethanol was heated under reflux for 24 hours. The mixture was concentrated by evaporation under reduced pressure. The residual oil was poured into 300 ml. of water, and the excess ethyl benzoylacetate was extracted with ether. The aqueous mixture was made alkaline by the addition of an excess of sodium bicarbonate, and the product was then extracted with three 100-ml. portions of ether. The combined extracts were dried over anhydrous sodium sulfate, the ether was removed by evaporation under reduced pressure, and the residue was distilled. About 3 ml. of distillate was collected at 70–90° (1.2 mm.) and about 3 ml. at 120–140° (1.2 mm.).

(a) **Lower-boiling Fraction.**—From the ultraviolet spectrum (λ_{max} 229, 278 mμ) this appeared to be mostly 1,2-dimethyl-3-phenyl-Δ³-pyrazoline. The product formed a methiodide, m.p. 150°, and a picrate, m.p. 122°. Mixed elting points of the methiodide and picrate with authentic samples were unchanged.

(b) **Higher-boiling Fraction.**—From the ultraviolet spectrum (λ_{max} 238, 327 mμ) this appeared to contain 1,2-dimethyl-3-phenyl-4-carbethoxy-Δ³-pyrazoline.

Saponification and Decarboxylation.—The higher-boiling fraction was heated under reflux for 2 hours in 50 ml. of a solution of 10% sodium hydroxide in 50% ethanol. The reaction mixture was acidified with a slight excess of concd. hydrochloric acid and heated for an additional hour and then concentrated under reduced pressure. The residue was poured into about 200 ml. of water, and a small excess of a 20% solution of sodium hydroxide was added. The product was then extracted with three 75-ml. portions of ether, which were combined and dried over anhydrous sodium sulfate. The ether was removed by distillation under reduced pressure, and the residual oil was distilled. About 1.2 ml. of distillate was collected at 71° (1.2 mm.). The ultraviolet spectrum of this liquid resembled closely that of 1,2-dimethyl-3-phenyl-Δ³-pyrazoline. The distillate formed a methiodide, m.p. 150°, and a picrate, m.p. 122°, whose m.p.'s were not depressed when mixed with the corresponding derivatives from an authentic specimen of 1,2-dimethyl-3-phenyl-Δ³-pyrazoline.

Reaction of β-Dimethylaminopropiophenone with Methylhydrazine.—A solution of 32 g. (0.15 mole) of β-dimethylaminopropiophenone hydrochloride, 15 g. (0.33 mole) of methylhydrazine and 32 g. (0.39 mole) of sodium acetate in 300 ml. of 50% acetic acid was heated on a steam-bath for 48 hours. The cooled mixture was made basic with 20% sodium hydroxide. The product was then extracted with four 100-ml. portions of ether, which were combined and dried over anhydrous sodium sulfate. Dry hydrogen chloride was bubbled into the ether solution, and a crystalline solid precipitated. After three recrystallizations from a mixture of ethanol and ether the m.p. was 162°. Additional recrystallizations did not alter the m.p. Mixed melting point with an independently prepared sample of 1-methyl-3-phenyl-Δ²-pyrazoline hydrochloride[12] (m.p. 162°) was not raised or depressed.

Anal. Calcd. for $C_{10}H_{13}N_2Cl$: C, 61.01; H, 6.66; N, 14.25; Found: C, 58.60, 59.12; H, 6.72, 6.14; N, 14.24.

A sample of the hydrochloride was sublimed at 140° (1.2 mm.). The m.p. rose to 197°.

Anal. Found with sublimed sample: C, 60.94; H, 6.75; N, 14.00. (No analytical data were reported by Mannich and Heilner[12] for this hydrochloride; the melting point was reported as 162°.)

A sample of the hydrochloride was treated with a 5% solution of sodium hydroxide. The organic base was extracted with ether, and the ether was evaporated. The residue melted at 36–37°. Mixed m.p. with a sample of 1-methyl-3-phenyl-Δ²-pyrazoline prepared by the method of Mannich and Heilner[12] was not raised or depressed.

IOWA CITY, IOWA

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH OF G. D. SEARLE AND CO.]

Azasteroids. II[1,2]

BY ROBERT H. MAZUR

The degradation of hecogenin acetate lactam (I) to 3β-acetoxy-12a-aza-C-homo-5α-pregn-16-ene-12,20-dione (II) is described. Further transformations of II to various azasteroids are shown.

In the first paper of this series,[1] we described a scheme for the introduction of nitrogen into ring C of a steroid, specifically the conversion of hecogenin to 3β-acetoxy-12a-aza-C-homo-5α,22a-spirostan-12-one (I). We also suggested that compound I could be the precursor of modified steroid

hormones, and we now report some experiments along these lines.

It was found that Mueller's modification[3] of the sapogenin side-chain degradation worked satisfactorily with hecogenin acetate lactam I and yielded 3β-acetoxy-12a-aza-C-homo-5α-pregn-16-ene-12,20-dione (II). This product had the

(1) Part I, R. H. Mazur, THIS JOURNAL, 81, 1454 (1959).

(2) R. H. Mazur, U. S. Patent 2,806,029 (September 10, 1957).

(3) G. P. Mueller, *Nature*, 181, 771 (1958).