

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, THE JOHNS HOPKINS SCHOOL OF MEDICINE, BALTIMORE, MD.]

A Facile Base-catalyzed Ester Hydrolysis Involving Alkyl-Oxygen Cleavage. The Mechanism of Hydrolysis of Esters of 4(5)-Hydroxymethylimidazole¹

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O-Acetyl- and O-succinyl-4-hydroxymethylimidazole were found to undergo hydroxide ion-catalyzed hydrolysis about 10⁶ faster than expected of an aliphatic ester. These esters were found to be very labile to O-alkyl scission and the hydrolysis was shown to be general base catalyzed. The proposed mechanism of hydrolysis involves the concerted elimination of acetate anion from the neutral ester on proton abstraction by base (eq. 4) or the kinetically equivalent slow formation of the anion followed by a rapid elimination of acetate anion.

Introduction

The study of the hydrolysis of esters of 4-hydroxymethylimidazole (Ia,b) is of interest be-

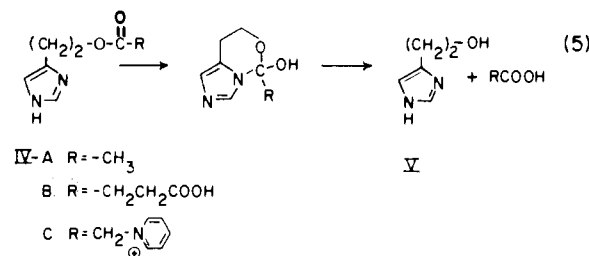
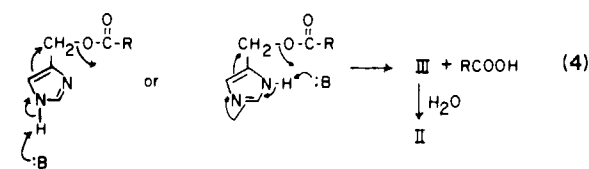
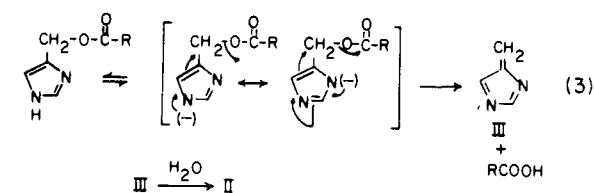
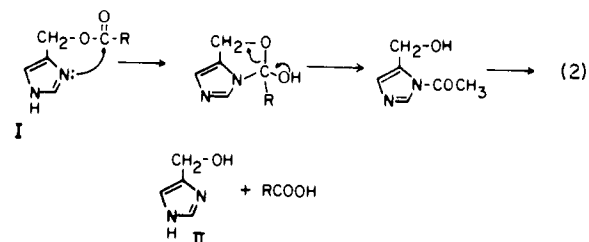
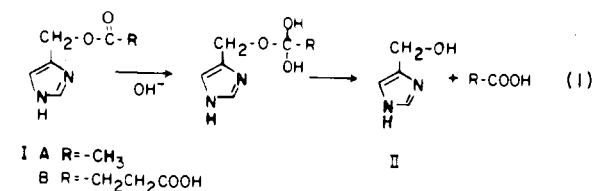


CHART I

cause of the various possible modes of base catalysis possible (Chart I). These include the normal B_{AC}2 mechanism (1), anchimeric catalysis (2) and elimination of carboxylic acid anion in a B_{AL}2 mechanism proceeding *via* specific (3) or general (4) base catalysis.

Reaction 1 is of course the ordinary mechanism by which most esters undergo base-catalyzed hydrolysis.⁴ Anchimeric catalysis (2) has been found in the hydrolysis of the esters of 4-(2'-hydroxyethyl)-imidazole (IVa,b,c).^{5,6} This process might also have been anticipated in Ia,b since, though the bicyclic transition state in 2 would be more strained than that in 5, it is known that in intramolecular nucleophilic catalysis five-membered cyclic transition states are greatly favored^{7,8} over six. Some justification for the expectation of the involvement of mechanisms 3 and 4 arises from certain observations on 3-substituted indoles. Thus, Mannich bases of the gramine (VI) type⁹ or 3-cyanomethylindoles¹⁰ serve as alkylating agents (Chart II) forming,

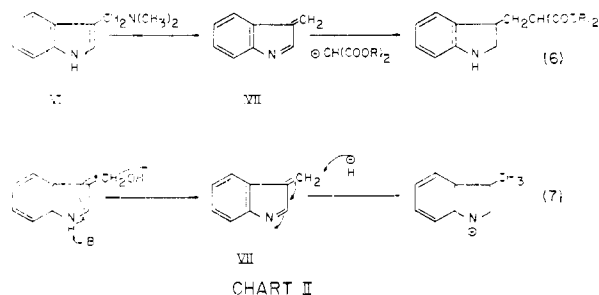


CHART II

as an intermediate, 3-methylene-3H-pseudoin-dole (VII). Base catalysis of an elimination reaction, as in 3 and 4, has been proposed to account for the ready LiAlH₄ reduction of 3- as compared to 2-hydroxymethylindole (eq. 7).¹¹

(1) Part VIII in the series "Imidazole Catalysis"; for previous papers see ref. 6.

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(4) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Chapt. XIV.

(5) T. C. Bruce and J. M. Sturtevant, *THIS JOURNAL*, **81**, 2860 (1959).

(6) U. K. Pandit and T. C. Bruce, *ibid.*, **82**, 3386 (1960).

(7) T. C. Bruce and U. K. Pandit, *Proc. Natl. Acad. Sci. (U. S.)*, **46**, 402 (1960).

(8) T. C. Bruce and U. K. Pandit, *THIS JOURNAL*, **82**, 5858 (1960).

(9) J. D. Albright and H. R. Snyder, *ibid.*, **81**, 2239 (1959).

(10) P. N. James and H. R. Snyder, *ibid.*, **82**, 589 (1960).

(11) E. Leete, *ibid.*, **81**, 6023 (1959).

The formation of a 1,3-diazafulvene intermediate in 3 and 4 has precedence in the indole chemistry discussed and in the proposed contribution of this structure to the resonance of imidazole-4-aldehyde.¹²

Results and Discussion

Apparent Specific Base Catalysis.—The *pH*-rate profile for the hydrolysis of Ia and for comparative purposes that for the labile ester, *p*-nitrophenylacetate (*p*-NPA), are given in Fig. 1. At the temperature employed (78°) and between *pH* 5.5 and 7.5 the experimentally determined first-order hydrolysis constants (k_{obs}) for Ia and *p*-NPA fit the theoretical linear plots of slope 1.1 (K_w at 78° = $10^{-12.5}$)¹³ expected from eq. 6. The

$$-d(E_T)/dt = k_{OH}(K_w/a_H) \quad (6)$$

value of k_{OH} calculated from the plots of Fig. 1 are 8.95×10^4 l. mole⁻¹min.⁻¹ for Ia and 1.0×10^4 l. mole⁻¹min.⁻¹ for *p*-NPA. Since the value of k_{OH} for the B_{AC}2 hydrolysis of *p*-NPA exceeds that for methyl acetate by 10^4 ,¹⁴ it is apparent that the value of k_{OH} associated with the hydrolysis of Ia is about 10^5 greater than that for a normal aliphatic ester.

The unusually large value of k_{OH} for Ia indicates a mechanism in which the imidazolyl ring partakes (as in 2, 3 or 4). In order that the reaction involve nucleophilic catalysis (2) and the kinetics follow that of 6 the imidazolyl anion would have to be the intramolecular nucleophile. Therefore, both reactions 2 and 3 should follow the kinetic expressions of 7.

$$\frac{-dE_T}{dt} = k_r(E^-) = k_r(E_T) \left[\frac{K_2 K_1}{K_2 K_1 + K_1 a_H + a_{H_2}} \right]$$

Where

$$K_1 = \frac{(EH)(a_H)}{(EH_2^+)}; K_2 = \frac{(E^-)(a_H)}{(EH)} \quad (7)$$

- a_H = hydrogen ion activity as measured by the glass electrode
 E_T = $EH_2^+ + EH + E^-$ = total ester
 EH_2^+ = acid form of ester
 EH = neutral form of ester
 E^- = ester anion

In the *pH* range employed (5.5 to 7.5) eq. 7 reduces to 8, since K_2 for 4(5)-alkyl substituted imidazoles are comparable to K_w for water.¹⁵

$$\frac{dE_T}{dt} = \frac{k_r(E_T)K_2}{a_H} \left[\frac{K_1}{K_1 + a_H} \right] \quad (8)$$

The value of K_1 in eq. 8 cannot be determined at the temperature of the experiments of Fig. 1 (78°) because of the hydrolytic lability of the ester. However, by titration at 20°, pK_1' for Ia was found to be 6.2. At 20° and 78° the pK_1' for IVa was found to be 7.5 and 6.48, respectively. With the reasonable assumption that the heat of ionization of Ia and IVa are comparable, one can calculate a pK_1' value of 5.2 for Ia at 78°. Therefore, between *pH* 5.5 and 7.5 the kinetics of Ia solvolysis

(12) R. A. Turner, *THIS JOURNAL*, **71**, 3472 (1949).

(13) Extrapolated from the data in "International Critical Tables," Vol. VI, p. 152.

(14) "Tables of Chemical Kinetics of Homogeneous Reactions," Natl. Bur. Stand. Circular 510 (1951).

(15) H. Walba and R. W. Isensee, *THIS JOURNAL*, **77**, 5488 (1955); *J. Org. Chem.*, **21**, 702 (1956).

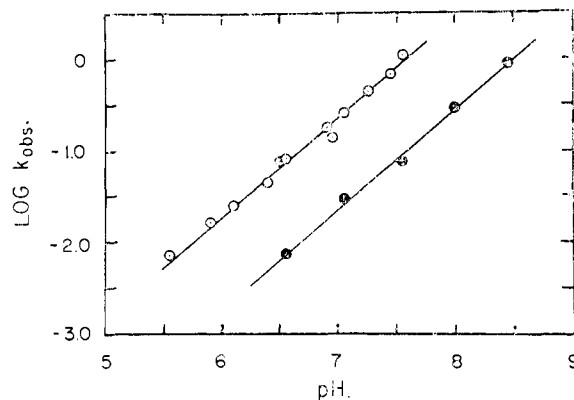


Fig. 1.—Plot of the logarithm of the observed first-order hydrolysis constants ($\log k_{obs}$) obtained at 78°; $\mu = 1.0 M$ vs. *pH* for O-acetyl-4-hydroxymethylimidazole (Ia, O) and *p*-nitrophenyl acetate (*p*-NPA, ●).

reduce to apparent hydroxide ion catalysis

$$k_{obs} = \frac{k_r K_2}{a_H} \left[\frac{K_1}{K_1 + a_H} \right] \cong k_{OH} \left(\frac{K_w}{a_H} \right) \quad (9)$$

$$k_r = k_{OH}(K_w/K_2)$$

Attempts to follow the hydrolysis of Ia titrimetrically at *pH* values below 5.5 were not successful because: (a) The shift in pK_a' of the imidazolyl group of Ia to a higher value in the hydrolysis product removes protons from solution; (b) the carboxylic acid produced is not completely ionized; (c) the combination of the first two factors requires the use of high concentrations of Ia which has the disadvantage of increasing the buffer capacity of the system so that the *pH*-Stat is insensitive; and (d) the validity of results obtained with a high concentration of E_T would be doubtful due to the danger of self-catalysis *via* a general base mechanism (*cf.* discussion of general base catalysis).

In Fig 2 is presented the *pH*-rate profile for the hydrolysis of Ib. Unlike the profile for Ia, that of Ib is not a linear function of *pH* over the entire range investigated. The reason for this would appear to be the greater value of pK_1' for Ib (6.4) as compared to Ia (5.2) at 78°. Thus, the importance of the term $K_1/(K_1 + a_H)$ in eq. 8 is reflected in the kinetic results, and for Ib eq. 8 and 9 are not equivalent in the *pH* range employed.

In preliminary experiments of a qualitative nature it was found that Ia reacted with hydroxylamine at *pH* 7.0 to give acetylhydroxamic acid¹⁶ only under those conditions required of an aliphatic ester and that the yield of acetylhydroxamate, determined colorimetrically, was quite small (20%). On the other hand, the more slowly hydrolyzed *p*-NPA reacted with hydroxylamine very rapidly at room temperature to give quantitative yields of acetylhydroxamic acid. Thus, from the low yield of acetyl hydroxamate and the conditions necessary for its production we must conclude that Ia is no more subject to acyl-oxygen scission with hydroxylamine than an ordinary aliphatic ester and that another mechanism of hydrolysis must account for its disappearance from the hydroxylamine solution. This conclu-

(16) F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **159**, 21 (1945).

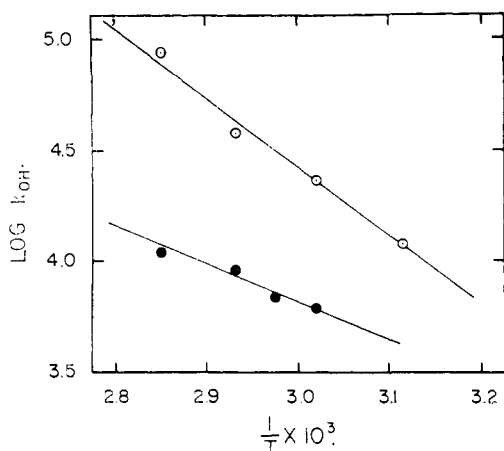


Fig. 3.—Plots of the logarithm of the second-order rate constants ($l. \text{ mole}^{-1} \text{ min.}^{-1}$) for hydroxide ion catalysis of the hydrolysis of Ia and *p*-NPA vs. $1/T$. The values of k_{OH} were obtained from k_{obs} constants at *pH* values of 7.45 for Ia and 8.40 for *p*-NPA taking into account the variation of K_w with temperature.

values established the catalytic species in each case to be the base. The apparent second-order rate constants (k_2') are obtained as the slopes of Fig. 3 and the true second-order rate constant (k_2) is obtained after correcting for the fraction of reagent in the base form. The calculated constants are given in Table II.

TABLE II
SECOND-ORDER RATE CONSTANTS FOR THE GENERAL BASE-CATALYZED HYDROLYSIS OF Ia

Base	pK_a' (78°)	<i>pH</i>	k_2' $l. \text{ mole}^{-1}$	k_2 min.^{-1}
CH_3COO^-	4.75	6.7	0.194	0.194
$\text{C}_6\text{H}_5\text{N}$	5.05	6.42	1.04	1.08
Imidazole	6.4	6.45	12.5	23.7

Self-catalysis in the hydrolysis of Ia,b was shown not to be of importance at the concentrations employed since at *pH* 6.3 solutions 0.002 to 0.02 *M* gave the same value of k_{obs} .

These investigations are presently being extended to esters of other vinylogous carbinol amines.

Experimental

Kinetics.—All the rate constants reported herein were determined on a *pH*-Stat. The assembly consisted of a Radiometer T 111a autotitrator and a Radiometer Titrigraph equipped with an automatic drive for a Hamilton microliter syringe which led to a three-neck \ddagger Metrohm Microtitration cell by way of a glass capillary which extended to just above a small bar-magnet stirrer. The Metrohm Microtitration assembly was fitted with a \ddagger Metrohm type X glass electrode and an external calomel electrode. The problem of rapid flow of KCl from the salt bridge at 78° was circumvented by fusion of a Beckman calomel electrode tip to its end. The microtitration vessel was maintained at constant temperature by circulation of water through the water jacket from a Blue M Magni Whirl Bath ($\pm 0.2^\circ$). For best results separate electrodes were used at the various temperatures and were kept at constant temperature during the entire investigation.

Samples employed were of 2.0 to 1.5 ml. in volume and the volume of base (*ca.* 0.10 *M* KOH) delivered from the microburet did not exceed 0.04 ml. during the course of any run giving only a small dilution error (2–3%) in the bimolecular reactions. The use of an inert atmosphere after initial flushing with prehumidified nitrogen was found to be unessential since the microtitration cell, as assembled, was

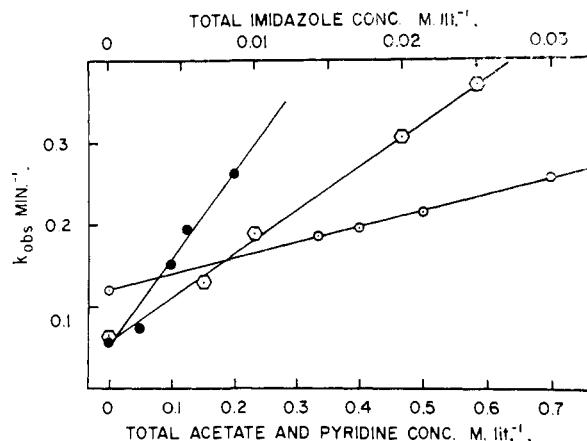


Fig. 4.—Plots showing the catalysis of Ia hydrolysis by imidazole ($\langle \circ \rangle$), pyridine (\bullet) and acetate anion (\circ). In the diagram the values of k_{obs} have been plotted vs. the total concentration of reagent employed. The values of k_{obs} determined in the presence of each reagent were obtained at constant *pH* values (Table II).

air-tight. The latter factor also minimized evaporation. All runs were made in 1.0 *M* KCl, to maintain constant ionic strength, and were followed to completion. The pseudo first-order rate constants were calculated by the method of Guggenheim.²¹

pK_a' determinations were carried out with the same apparatus employed for the determination of rate constants. The values of pK_a' were calculated by fitting the entire experimental curves, after correction for water titration, to theoretical dissociation curves.

Compounds: Mono-2-(4'-imidazolyl)-ethyl succinate hydrochloride (IVB) was that of a previous study.⁶ Mono-4-imidazolylmethyl succinate hydrochloride (IB) was prepared by the same procedure. After recrystallization from an absolute ethanol-ether mixture (% yield 50%), m.p. 144–146°.

Anal. Calcd. for $\text{C}_8\text{H}_{11}\text{N}_2\text{O}_4\text{Cl}$: C, 40.94; H, 4.69; N, 11.94; Cl, 15.14. Found: C, 40.83; H, 4.98; N, 12.10; Cl, 15.12.

4-Imidazolylmethyl Acetate Hydrochloride (Ia).—To a round-bottomed flask containing 1.5 g. (0.01 mole) of 4-hydroxymethylimidazole hydrochloride²² covered with ethyl acetate was added 30 ml. of acetic anhydride. The mixture was refluxed for 1 hour and taken to dryness by flash evaporation. To the oily residue was added 20 ml. of water containing 1.26 g. of sodium bicarbonate (0.015 mole). The solution was allowed to stand 15–20 min. at 0°, acidified with hydrochloric acid and flash evaporated to dryness. The residue was taken up in absolute ethanol and filtered. The filtrate was concentrated and chloroform added. Upon the addition of anhydrous carbon tetrachloride material precipitated which crystallized on standing. After several recrystallizations from an abs. ethanol, chloroform and carbon tetrachloride mixture there was obtained 0.61 g., 35%, of product melting at 137.5–139°.

Anal. Calcd. for $\text{C}_6\text{H}_9\text{N}_2\text{O}_2\text{Cl}$: C, 40.79; H, 5.10; N, 15.95; Cl, 20.22. Found: C, 40.80; H, 5.39; N, 15.88; Cl, 19.94.

Reaction of Ia,b with Sodium Methoxide.—The procedure given here for Ib also was employed for Ia. In a 100-ml. round-bottomed flask there was placed 25 ml. of absolute methanol which had been dried by refluxing over magnesium and distilling. Metallic sodium (0.22 g., 0.0096 mole) was added. When all the sodium had dissolved the succinate ester hydrochloride (0.76 g., 0.0032 mole) dissolved in a small volume of abs. methanol was added. The reaction mixture, protected against moisture and CO_2 with an Ascarite drying tube, was stirred for 3 hours, anhydrous ether added, and the precipitated salt collected on a sintered

(21) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

(22) J. R. Totter and W. J. Darby, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 460.

glass funnel. In this manner there was obtained 0.70 g. of salt (98.6%, calculated as 1 equiv. of NaCl and 1 equiv. of disodium succinate). The salt was titrated at 35° (see pK_a' determination). The titration curve obtained after correction for a water blank was identical (pH 2.3 to 7.5) with that obtained on titration of an authentic sample of disodium succinate.

In a similar manner a 75% yield of sodium acetate was obtained from Ia and identified titrimetrically (pK_a 4.5).

Reaction of Mono-4-imidazolymethyl Succinate Hydrochloride (Ib) with Sodium Hydroxide.—In a 200-ml. round-bottomed flask was placed 1.0 g. (0.0043 mole) of mono-4-imidazolymethyl succinate hydrochloride. To this was added 50 ml. of water. The solution was heated to 75° by means of a water-bath and 0.73 g. (0.013 mole) of potassium hydroxide dissolved in 10 ml. of water was added. The mixture was heated for 45 minutes. The solution was evaporated to dryness by flash evaporation and ethanol added to the residue. The mixture then was filtered. The filtrate was evaporated to dryness and the residue taken up in water. The solution was made acid with dilute hy-

drochloric acid, charcoaled, filtered, and evaporated to dryness by flash evaporation. The residue was dissolved in a small volume of ethanol and filtered. Addition of ether to the filtrate resulted in a precipitate which appeared semi-crystalline but which became quite oily when the solvent was removed. The material was chromatographed for 9.5 hr. on Whatman #1 paper using as solvent a 3:1 mixture of *n*-propyl alcohol and 1.0 *N* acetic acid.²³ The chromatogram was developed, after air-drying, by the Pauli spray, as given by Ames and Mitchell.²³ A compound capable of coupling with diazotized sulfanilic acid and possessing the same R_f (0.77) as a standard of 4(5)-hydroxy-methylimidazole hydrochloride was identified as a major component.

Acknowledgments.—This work was supported by grants from The Institute of Arthritis and Metabolic Diseases, National Institutes of Health, and from The National Science Foundation.

(23) B. N. Ames and H. K. Mitchell. *THIS JOURNAL*, **74**, 252 (1952).

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Heterocyclic Compounds. IX. Oxygenated Pyrrolines from Reductive Cyclization of Aliphatic γ -Nitro Ketones¹

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Partial reduction of 1,3-diphenyl-3-(1-nitrocyclohexyl)-1-propanone (I) and 4-methyl-4-nitro-3-phenyl-1-(3-pyridyl)-1-pentanone (VIII) under a variety of conditions yielded oxygen-containing pyrroline derivatives. Spectral and chemical properties appear to be best explained by the assumption of nitron structures IV and X for these products. Treatment of 5,5-dimethyl-4-phenyl-2-(3-pyridyl)- Δ^1 -pyrroline 1-oxide (X) with phosphorus trichloride, acetic anhydride or a mixture of benzoyl chloride and aqueous alkali yielded a dehydration product which is probably the pyrrolenine XII.

The paucity of recorded instances² in which oxygen-containing compounds have been obtained from reduction of aliphatic γ -nitro ketones prompted us to investigate the reduction of the nitro ketones I and VIII, which possess structural features likely to promote formation of a nitron (such as IV) or a hydroxylamine (such as V). Such oxygenated derivatives might be expected if cyclization of the presumed intermediate hydroxylamine II could be made to proceed more rapidly than its reduction to an amine. Since geminal substitution frequently has been observed to facilitate ring closure,³ it was anticipated that the presence of *gem*-methyl groups in VIII and the corresponding pentamethylene group in I would have this desired effect.⁴

(1) Abstracted from portions of the Ph.D. dissertations of Francis L. Chubb, Ramsis Gobran and Jack L. Pinkus.

(2) Previously discussed by M. C. Kloetzel and J. L. Pinkus, *J. Am. Chem. Soc.*, **80**, 2332 (1958).

(3) References to this phenomenon have been cited previously; see M. C. Kloetzel, F. L. Chubb and J. L. Pinkus, *ibid.*, **80**, 5773 (1958).

(4) In some measure, our choice of nitro ketone I was influenced by the report of G. D. Buckley and T. J. Elliott, *J. Chem. Soc.*, 1508 (1947), who obtained several nitrones, including 5-amino-2,2-pentamethylenepyrroline N-oxide, by reductive cyclization of γ -nitro nitriles. After our work had been completed, R. F. C. Brown, V. M. Clark and A. Todd, *Proc. Chem. Soc.*, 97 (1957), also reported the preparation of two nitrones by reductive cyclization. These workers⁵ confirmed our report² that 3-(3,4-methylenedioxyphenyl)-4-nitro-1-phenyl-1-butanone is reduced to 4-(3,4-methylenedioxyphenyl)-2-phenyl- Δ^1 -pyrroline by zinc dust and aqueous methanolic ammonium chloride at room temperature. Under milder conditions, and employing aqueous tetrahydrofuran, they were able to obtain 4-(3,4-methylenedioxyphenyl)-2-phenyl- Δ^1 -pyrroline 1-oxide, thereby confirming the report of Kohler and Drake, *J. Am. Chem. Soc.*, **45**, 2144 (1923), that an oxygenated pyrroline could be obtained.

A general method for preparation of nitrones involves the condensation of an N-alkyl- or N-arylhydroxylamine with an aldehyde or ketone.⁶ Since reduction with zinc dust and aqueous ammonium chloride is a specific method for obtaining hydroxylamines from nitro compounds,⁷ this method was chosen for effecting the reduction of nitro ketone I.

The reaction afforded two major products; an oxygen-containing compound, $C_{21}H_{23}NO$, melting at 134–135°, and a base, $C_{21}H_{23}N$, melting at 87–88°. A small amount of an unidentified compound melting at 194.5–195.5° also was isolated.

The compound melting at 87–88° formed salts with hydrogen chloride and perchloric acid. It did not decolorize potassium permanganate in acetone and its infrared spectrum showed no N–H absorption in the 3μ region. In other respects, including the appearance of C=N absorption at 6.22μ , the infrared spectrum of this base resembled the spectra of Δ^1 -pyrrolines which we have obtained previously by reduction of γ -nitro ketones.^{2,3,8} Accordingly, this substance is presumed to be 2,4-diphenyl-1-azaspiro[4,5]-1-decene (III).

The three most probable structures to be considered for the reduction product of composition $C_{21}H_{23}NO$ are those of the nitron IV, the tauto-

(5) R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland and Sir A. Todd, *J. Chem. Soc.*, 2094 (1959).

(6) L. I. Smith, *Chem. Revs.*, **23**, 193 (1938).

(7) W. J. Hickinbottom, "Reactions of Organic Compounds," 2nd edition, Longmans, Green and Co., New York, N. Y., 1948, p. 343.

(8) M. C. Kloetzel, J. L. Pinkus and R. M. Washburn, *J. Am. Chem. Soc.*, **79**, 4222 (1957).