

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)-hydroxymethylimidazole 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).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA, LOS ANGELES 7, CALIF.]

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-

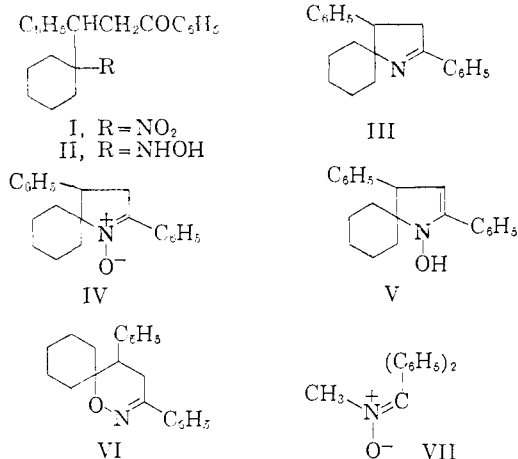
(5) R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland and Sir A. Todd, *J. Chem. Soc.*, 2094 (1959).

(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).

meric hydroxylamine V, and the 1,2-oxazine VI. The latter may be considered a rearrangement product of nitron IV. Analogous N-alkyl to O-alkyl rearrangements have been reported to occur under a variety of conditions.⁹



Structure V and isomeric hydroxypyrroline structures are not consistent with the chemical and spectral properties of this oxygen-containing compound. The substance was insoluble in 5% aqueous hydrochloric acid and in 20% aqueous sodium hydroxide, either at 25 or 60°, and it did not reduce Fehling solution. A proton resonance spectrum¹⁰ showed no trace of resonance in the region typical of a proton on a doubly bonded carbon atom. Finally no O-H absorption band appears in the 3 μ region of the infrared spectrum.

Spectral characterization of the N-O link in oximes and their derivatives is somewhat tenuous.¹¹ However, to the extent that the oxygen-containing reduction product failed to exhibit the strong absorption in the 10.3–10.8 μ region which is characteristic of certain ketoximes and their ethers,¹² structure VI appears unlikely.

The infrared spectrum of compound C₂₁H₂₃NO exhibits an absorption band at 6.47 μ , which is strongly enhanced in chloroform solution. This band, which is not present in the spectrum of III, also has been observed in the spectra of benzophenone oxime methyl nitron (VII),¹³ benzofuraxans^{14,15} and phenazine N-oxide,¹⁶ and appears

(9) J. Meisenheimer, *Ber.*, **52**, 1667 (1919); P. Grammaticakis, *Compt. rend.*, **205**, 60 (1937); A. C. Cope and P. H. Towle, *J. Am. Chem. Soc.*, **71**, 3423 (1939); A. H. Blatt, *J. Org. Chem.*, **15**, 869 (1950).

(10) We are indebted to Dr. James N. Shoolery of Varian Associates, Palo Alto, Calif., who kindly determined and interpreted this spectrum.

(11) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1954, p. 249.

(12) J. F. Brown, Jr., *J. Am. Chem. Soc.*, **77**, 6341 (1955).

(13) H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangle, "Infrared Determination of Organic Structures," Van Nostrand Co., Inc., New York, N. Y., 1949, p. 5. We have confirmed the presence of bands at 5.81, 6.41 and 7.42 μ in the spectrum of this compound, prepared according to the procedure of L. Semper and L. Lichtenstadt, *Ber.*, **51**, 928 (1918). Our sample separated from ethanol or petroleum ether in colorless needles, m.p. 108–109°, and gave excellent analytical data.

(14) J. H. Boyer, D. I. McCane, W. J. McCarville and A. T. Tweedie, *J. Am. Chem. Soc.*, **75**, 5298 (1953).

(15) R. J. Gaughran, J. P. Picard and J. V. R. Kaufman, *ibid.*, **76**, 2233 (1954).

(16) This spectrum, which shows bands at 6.43 and 7.44 μ , was kindly determined by R. Bruce Scott, Parke, Davis and Co., Detroit,

to coincide with the asymmetric stretching frequency of the NO₂ group.^{11–13,17,18}

The aforementioned spectral evidence cannot be correlated readily either with structure V or structure VI and strongly suggests that the oxygen-containing reduction product, C₂₁H₂₃NO, is 2,4-diphenyl-1-azaspiro[4,5]-1-decene (IV).

The formation of pyrroline IX by high pressure hydrogenation of 4-methyl-4-nitro-3-phenyl-1-(3-pyridyl)-1-pentanone (VIII) at 100° was reported in a previous paper of this series.³ However, the present study has disclosed that an oxygenated pyrroline derivative is the principal product from reduction of VIII under milder conditions. For example, when hydrogenation of VIII was effected with Raney nickel at low pressure, the yield of IX was only 13–39% and an oxygenated compound of composition C₁₇H₁₈N₂O was obtained in 45–71% yield. The ratio of products depended upon the age of the catalyst employed. Reduction of VIII with zinc dust and aqueous ammonium chloride gave a 64% yield of the compound C₁₇H₁₈N₂O. However, reduction with hydrazine⁸ and Raney nickel afforded the best yield (75%) of the oxygen-containing compound.

The infrared spectral characteristics of this reduction product are similar to those of IV. There is no evidence of O-H absorption. Characteristic absorption occurs at 6.47 μ and is strongly enhanced and shifted slightly toward shorter wave lengths in chloroform solution. The compound does not reduce Fehling solution nor does it react with phenyl isothiocyanate. The absence of active hydrogen was confirmed by means of a Zerewitinoff analysis. Although the compound added 1 mole of methylmagnesium iodide at 100°, essentially no Grignard reagent was consumed at 25°. These observations rule out the possibility of a structure analogous to V for the oxygen-containing reduction product from VIII.

The view that this substance is actually the nitron X, analogous to IV, is strengthened by successful reduction of the compound to an hydroxylamine (XI) with lithium aluminum hydride²⁰ and to pyrroline IX with zinc dust. However, an attempt to oxidize IX and X to the same dioxide proved unsuccessful. Treatment of X with perbenzoic acid in chloroform resulted in the introduction of one oxygen atom to give C₁₇H₁₈N₂O₂, m.p. 216–217°. Monoperphthalic acid converted IX to an isomer of C₁₇H₁₈N₂O₂, m.p. 173–173.5°. This result is perhaps not surprising in view of the ease with which imines are oxidized to oxaziranes.^{20,21}

As expected,⁶ hydroxylamine XI was readily

Mich., on a Nujol mull of the compound, employing a Beckman IR-2T spectrophotometer equipped with a sodium chloride prism.

(17) J. S. Belew, C. E. Grabel and L. B. Clapp, *J. Am. Chem. Soc.*, **77**, 1110 (1955).

(18) Compound C₂₁H₂₃NO exhibits additional absorption bands at 7.23, 7.37, 7.46 and 7.62 μ , in a region where benzophenone oxime methyl nitron,¹³ nitro compounds,^{11,12,17} and amine oxides^{16,19} also absorb. However, the presence of bands at 7.34 and 7.51 μ in the spectrum of III renders the assignment of bands in this region of doubtful significance for compound C₂₁H₂₃NO.

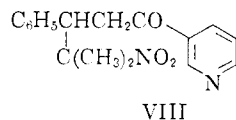
(19) G. R. Clemo and A. F. Daghish, *J. Chem. Soc.*, 1481 (1950).

(20) Compare W. D. Emmons, *J. Am. Chem. Soc.*, **78**, 6208 (1956).

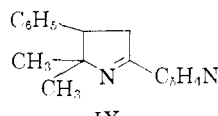
(21) L. Horner and E. Jürgens, *Chem. Ber.*, **90**, 2184 (1957).

reconverted to nitrone X by oxidation with mercuric oxide in hot chloroform.

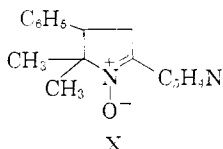
Oxidative degradation of nitrone X with nitric acid yielded nicotinic acid. This behavior ruled out the possibility that the oxygen-containing compound might be the 1,2-oxazoline isomer resulting from a conceivable cyclization of X by attack of the nitrone oxygen upon the α -position of the pyridine nucleus.



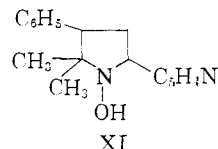
VIII



IX



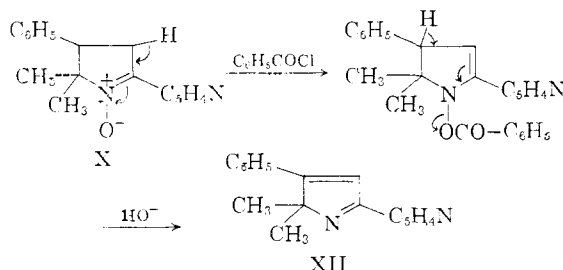
X



XI

With acetic anhydride, X did not undergo the Beckmann rearrangement which is characteristic of some nitrones^{5,22} but instead yielded a dehydration product $C_{17}H_{16}N_2$. The same product resulted from treatment of X with benzoyl chloride and aqueous sodium hydroxide.²³ This dehydration product which formed a stable monopicrate and an easily dissociated dipicrate showed imine absorption²⁴ at 6.22μ but no absorption in the 3μ region of the spectrum. A Zerewitinoff analysis demonstrated the absence of active hydrogen and showed addition of one mole equivalent of methylmagnesium iodide both at 25° and at 100° . On the basis of this evidence, $C_{17}H_{16}N_2$ has been tentatively assigned the pyrrolenine structure XII. It is of interest that this same substance is formed when pyrroline IX is dehydrogenated by heating with sulfur.

The conversion of X to XII by means of acetic anhydride or benzoyl chloride and alkali formally resembles the aromatization of certain oximes in the hydrothiophene series²⁵ by means of acid, or the conversion of 3,4,5-triphenylisoxazoline oxide to 3,4,5-triphenylisoxazole²⁶ by means of alkali, respectively. In our case, however, alkali is not directly responsible for conversion of X to XII, for X is recovered unchanged after treatment with alkali alone. The dehydration of X therefore may be formulated as



- (22) O. L. Brady and F. P. Dunn, *J. Chem. Soc.*, 2411 (1926).
 (23) Contrast the behavior of 2,4,4-trimethyl- Δ^1 -pyrroline 1-oxide.⁵
 (24) Compare spectrum of IX.³
 (25) L. C. Cheney and J. R. Piening, *J. Am. Chem. Soc.*, **67**, 729 (1945).
 (26) E. P. Kohler and G. R. Barrett, *ibid.*, **46**, 2105 (1924).

Dehydration of X was effected also by phosphorus trichloride but in this instance pyrroline IX was formed in addition to XII. Kohler and Barrett found that 3,4,5-triphenylisoxazoline oxide behaved in an analogous manner upon treatment with phosphorus pentachloride.

The oxide X forms a hydrochloride and a monopicrate (from either of which the base can be liberated unchanged) as well as a monomethiodide and a molecular complex with hydroquinone. The failure of X to undergo various other addition reactions which have been described^{5,6} for more reactive nitrones, such as with potassium cyanide, hydrogen cyanide, sodium iodide or water, may be attributable to the steric hindrance afforded by the concentration of substituents in this molecule as well as to the stabilization which results from conjugation of the imino linkage with the aromatic pyridine nucleus.

Acknowledgment.—The authors are indebted to Parke, Davis and Co., Detroit, Mich., for generous financial aid which made part of this study possible.

Experimental²⁷

1,3-Diphenyl-3-(1-nitrocyclohexyl)-1-propanone (I).—A solution of benzalacetophenone (62 g.), nitrocyclohexane²⁸ (58 g.) and diethylamine (3.3 g.) in methanol (156 ml.) was allowed to stand at room temperature for 6 weeks. The adduct which had separated was recrystallized from methanol; yield 97 g. (96%), m.p. $166-167^\circ$.

Anal. Calcd. for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.53; H, 6.82; N, 4.30.

Reduction of 1,3-Diphenyl-3-(1-nitrocyclohexyl)-1-propanone (I).—Six-gram portions of zinc dust were added every 15 minutes to a mechanically stirred slurry of I (23.4 g.), ammonium chloride (24 g.), water (80 ml.) and methanol (400 ml.), maintained at $5-10^\circ$, until a total of 96 g. of zinc had been added. Stirring was then continued for 16 hours while the reaction mixture gradually warmed from 5 to 20° . Inorganic solids were filtered and washed with 200 ml. of methanol.²⁹ The combined filtrates were concentrated under reduced pressure to a volume of 350 ml. and treated with gaseous hydrogen sulfide for 5 minutes. After removal of precipitated sulfide by centrifugation and filtration, the solution was diluted with 500 ml. of water, made basic with sodium hydroxide and extracted with four 300-ml. portions of ether. Evaporation of the water-washed ether extract under reduced pressure yielded 13.6 g. of colorless solid, m.p. $70-85^\circ$. Fractional crystallization from ether gave 720 mg. (3%) of unchanged nitro ketone I, 5.9 g. (28%) of nitrone IV, m.p. $120-127^\circ$, and 4.6 g. (23%) of pyrroline III, m.p. $80-85^\circ$.

2,4-Diphenyl-1-azaspiro[4,5]-1-decene 1-oxide (IV), recrystallized from ether and finally from ethyl acetate, formed colorless needles, m.p. $134-135^\circ$. It did not dissolve at 60° in 20% aqueous sodium hydroxide or in 5% hydrochloric acid, nor did it reduce Fehling solution even

(27) Melting points are uncorrected. Microanalyses are by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, Calif., and by Mr. Joseph Pirie and Mr. William J. Schenck, formerly of the University of Southern California. Except where otherwise indicated, infrared spectra were determined by W. J. Schenck, employing a Perkin-Elmer model 13 double beam spectrophotometer equipped with sodium chloride prism.

(28) Courtesy of E. I. du Pont de Nemours and Co., Inc., Wilmington, Del.

(29) Further extraction of the inorganic material with methanol yielded 676 mg. of an unidentified substance which separated from ethanol or benzene in colorless needles, m.p. $194.5-195.5^\circ$. The compound did not decolorize a 2% acetone solution of potassium permanganate. An infrared spectrum (Nujol mull) showed absorption maxima at 3.05(s), 5.93(s), 6.11(s), 6.26(w), 6.34(m), 6.51(s), 6.71(m), 7.41(m), 7.53(w), 7.60(m) and 7.77(m) μ .

Anal. Calcd. for $C_{41}H_{42}N_2O_5$: C, 76.63; H, 6.54; N, 4.36. Found: C, 76.68; H, 6.52; N, 4.35; mol. wt. (Rast), 245.

after prolonged heating at 90°. A proton resonance spectrum¹⁰ of this substance showed no trace of resonance in the region typical of a proton on a doubly bonded carbon atom. An infrared spectrum of IV in Nujol mull showed absorption maxima at 6.38(w), 6.47(m), 7.64(m), 8.20(m), 8.58(m) and 8.67(m) μ . In chloroform solution IV absorbed at 6.25(w), 6.34(m), 6.42(s), 6.68(s), 6.88(s), 7.23(s), 7.37(m), 7.46(m), 7.62(m), 7.80(m), 8.61(m), 8.97(w), 9.14(m) and 9.33(m) μ .

Anal. Calcd. for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.42; H, 7.73; N, 4.50.

2,4-Diphenyl-1-azaspiro[4,5]-1-decene (III), recrystallized from petroleum ether and finally from ether or ethyl acetate, formed colorless hexagonal plates, m.p. 87–88°. It did not decolorize potassium permanganate in acetone. An infrared spectrum of III in Nujol mull showed absorption maxima at 6.22(m), 6.36(m), 6.70(m), 7.34(s) and 7.51(m) μ .

Anal. Calcd. for $C_{21}H_{23}N$: C, 87.15; H, 8.01; N, 4.84. Found: C, 87.21; H, 8.08; N, 4.96.

Treatment of pyrroline III with dry hydrogen chloride in anhydrous ether afforded a crystalline hygroscopic hydrochloride, m.p. 100–105°. The perchlorate of III was prepared in isopropyl alcohol and melted at 153.5–155° after recrystallization from a mixture of isopropyl alcohol and ether.

Anal. Calcd. for $C_{21}H_{23}ClNO$: Cl, 9.09. Found: Cl, 9.16.

Reductive Cyclization of 4-Methyl-4-nitro-3-phenyl-1-(3-pyridyl)-1-pentanone (VIII). (a) **Low Pressure Hydrogenation over Raney Nickel**.³⁰—A mixture of 20 g. of nitro ketone VIII,³ 180 ml. of 95% ethanol and 8 g. of Raney nickel (2–4 months old), was subjected to hydrogenation at an initial pressure of 50 p.s.i. until absorption of hydrogen had ceased (12 hr.). Evaporation of solvent under reduced pressure left a semi-solid residue, of which the ether-insoluble portion (8.1 g., or 45%, m.p. 138–140°) was **5,5-dimethyl-4-phenyl-2-(3-pyridyl)- Δ^1 -pyrroline 1-oxide (X)**. The ether-soluble portion consisted of 300 mg. of unreduced VIII and 6.5 g. (39%) of **5,5-dimethyl-4-phenyl-2-(3-pyridyl)- Δ^1 -pyrroline (IX)**,³ b.p. 155–170° at 1–2 mm.

When catalyst less than 1 month old was employed, the yields of IX and X were 13 and 71%, respectively.

(b) **With Zinc Dust and Aqueous Ammonium Chloride**.—A mixture of nitro ketone VIII (5 g.), ammonium chloride (6 g.), methanol (100 ml.) and water (20 ml.) was stirred mechanically for 2 hrs. Zinc dust (24 g.) was added in portions during this period and the temperature was maintained at 10–15°. After filtration from zinc and zinc oxide, the solution was evaporated and the residue was dissolved in dilute hydrochloric acid. The clarified solution was made basic with 10% sodium hydroxide solution and was then extracted with ether. Upon standing, the aqueous layer deposited 400 mg. (9% yield) of nitrone X, m.p. 140–141°. The residue from evaporation of the ether layer was dissolved in anhydrous ethanol and dry hydrogen chloride was passed into the solution. Almost immediately there was precipitated 2.8 g. (55%) of the hydrochloride of X in colorless needles, m.p. 221–222°, from which the nitrone X was liberated readily by treatment with 10% aqueous sodium hydroxide.

(c) **With Hydrazine and Raney Nickel**.—Hydrazine (2 ml. of 64% solution or an equivalent amount of 85% solution) was added dropwise to a mechanically stirred mixture of VIII (3 g.), methanol (30 ml.) and Raney nickel (1 g.) maintained below 55°. Stirring was continued for 2 hr. and the filtered solution then was allowed to evaporate. Crystallization of the residue from petroleum ether (b.p. 65–70°) yielded nitrone X in 75% yield when freshly prepared catalyst (1 day old) was employed, or 70% when aged catalyst (2–4 months old) was employed.

5,5-Dimethyl-4-phenyl-2-(3-pyridyl)- Δ^1 -pyrroline 1-oxide (X) separated from aqueous ethanol or from ethyl acetate in colorless needles, m.p. 143–144°. An infrared absorption spectrum of X in Nujol mull showed absorption maxima at 6.29(w), 6.47(m), 7.11(m), 7.50(m) and 7.62(m) μ ; in chloroform solution, 6.24(w), 6.27(m), 6.40(s), 6.80(m), 6.85(m), 7.31(s), 7.50(m) and 7.57(m) μ .

(30) Raney nickel employed in this investigation was prepared according to R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.74; H, 6.90; N, 10.40.

Zerewitinoff determinations³¹ in anisole or in *n*-butyl ether showed addition of 0.03 mole of methylmagnesium iodide and no methane evolution at 25°. At 100°, in a mixture of *n*-butyl ether and xylene, there was addition of 0.95 mole of methylmagnesium iodide but no evolution of methane.

The picrate of X separated from 95% ethanol in yellow needles, m.p. 187–187.5°.

Anal. Calcd. for $C_{23}H_{21}N_5O_8$: 55.75; H, 4.27; N, 14.14. Found: C, 55.80; H, 4.54; N, 14.37.

The methiodide of X separated almost immediately when X was dissolved in excess methyl iodide and formed yellow plates from 95% ethanol, m.p. 215–216°.

Anal. Calcd. for $C_{18}H_{21}IN_2O$: C, 52.94; H, 5.18. Found: C, 53.08; H, 5.17.

When a warm solution of X (1 g.) and hydroquinone (250 mg.) in 95% ethanol (5 ml.) and water (5 ml.) was allowed to cool, an addition compound (900 mg.) separated as colorless crystals, m.p. 162–163°.

Anal. Calcd. for $C_6H_6O_2 \cdot 2C_{17}H_{18}N_2O$: C, 74.74; H, 6.59. Found: C, 75.00; H, 6.23.

When this addition compound was dissolved in 95% ethanol containing an equivalent amount of picric acid, the picrate of X, m.p. 187–188°, was obtained.

Oxidative Degradation of Nitrone X.—A mixture of 6 g. of nitrone X and 90 ml. of concentrated c.p. nitric acid (sp. gr. 1.42)³² was warmed to 70° on a steam-bath and reaction then was allowed to continue spontaneously without further heating. After 1 hr. the mixture was again heated (for 12 hr.) on a steam-bath and then was evaporated to dryness. The residue was washed with ether, and the remaining gummy solid was dissolved in hot water. The clarified (decolorizing charcoal), filtered and cooled solution deposited 3.4 g. of the nitrate of nicotinic acid, m.p. 189–191°.

The nitrate (3 g.) was decomposed by being heated for 12 hr. with 30 ml. of concentrated hydrochloric acid (sp. gr. 1.19). Removal of solvent under reduced pressure left 2.5 g. of the hydrochloride of nicotinic acid,³³ m.p. 255–260°. Crystallization of the salt from 80% ethanol yielded 2.3 g. of purified hydrochloride, m.p. 262–263°, which did not depress the m.p. of an authentic sample, m.p. 263–264°.

The hydrochloride (2 g.) was dissolved in the minimum volume of hot water and 30% aqueous sodium carbonate was added slowly until precipitation of nicotinic acid was complete (1.4 g. of dried solid, m.p. 220–225°). Recrystallization from ethanol yielded 1.2 g. of pure acid, m.p. 229–231°, which did not depress the m.p. of an authentic sample.

Oxidation of Nitrone X with Perbenzoic Acid.—A mixture of nitrone X (1 g.), perbenzoic acid (560 mg.) and chloroform (10 ml.) was allowed to stand at room temperature for 5 days. After being washed successively with 0.1 *N* aqueous sodium thiosulfate, 10% aqueous sodium bicarbonate and water, the dried chloroform solution was evaporated under reduced pressure. The residue (813 mg., m.p. 199–211°) was crystallized from ethyl acetate and then from a mixture of chloroform and ether; m.p. 216–217°.

Anal. Calcd. for $C_{17}H_{18}N_2O_9$: C, 72.32; H, 6.42. Found: C, 72.06; H, 6.16.

Pyrroline IX (400 mg.) in ether (55 ml.) was oxidized similarly with monoperphthalic acid (928 mg.). There was obtained 280 mg. of solid, m.p. 168–171°, which melted at 173–173.5° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{17}H_{18}N_2O_9$: C, 72.32; H, 6.42; N, 9.92. Found: C, 72.34; H, 6.39; N, 9.70.

Reduction of Nitrone X. (a) **With Zinc Dust**.—A mixture of X (5 g.) and zinc dust (5 g.) was distilled at 280–300° under 20 mm. pressure. The distillate was separated with the aid of ether to give 1.7 g. of relatively insoluble nitrone X and a soluble fraction. The latter yielded 1.3 g. of the dipicrate of pyrroline IX, m.p. 177–178°, which did not depress the m.p. of an authentic sample.³

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(b) **With Lithium Aluminum Hydride.**—A suspension of 180 mg. of lithium aluminum hydride in 150 ml. of dry ether was added in portions, over a period of 20 minutes, to a warm stirred solution of 1.2 g. of nitrone X in 300 ml. of dry ether and the mixture was then heated to reflux for 17 hr. After dropwise addition of water, the ether layer was dried and evaporated under reduced pressure. The residual 1-hydroxy-2,2-dimethyl-3-phenyl-5-(3-pyridyl)-tetrahydropyrrole (XI, 1.05 g., m.p. 214–217°) was recrystallized from ethanol; m.p. 216–217°.

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 76.04; H, 7.53; N, 10.50.

The hydroxylamine gave a positive Fehling test and a slow positive Tollens test. A Zerewitinoff determination in xylene at 100° showed evolution of 0.88 mole of hydrogen.

When the hydroxylamine (800 mg.) was heated to reflux for 5 hr. with mercuric oxide (870 mg.) and chloroform (4 ml.) the solution became first yellow, then colorless, and a gray precipitate appeared. The residue from evaporation of the filtered solution under reduced pressure was crystallized from a mixture of ethanol and petroleum ether (b.p. 60–70°) and afforded 500 mg. of nitrone X, m.p. 141–143°, which did not depress the m.p. of a sample of X obtained from reductive cyclization of VIII.

Dehydration of Nitrone X. (a) With Acetic Anhydride.—A solution of nitrone X (1 g.) in acetic anhydride (10 ml.) was heated on a steam-bath for 30 min. and then was diluted with water (100 ml.); 10% sodium hydroxide solution (100 ml.) was added, and the organic product was extracted with ether. Evaporation of the dried ether layer under reduced pressure yielded a residue that was converted to a picrate by being heated to boiling in 95% ethanol with picric acid (1 g.); yield 1.2 g. (63%) of the monopicate of 2,2-dimethyl-3-phenyl-5-(3-pyridyl)-2H-pyrroline (XII), m.p. 208–209°, in yellow needles from 95% ethanol.

Anal. Calcd. for $C_{23}H_{19}N_3O_7$: C, 57.85; H, 4.01; N, 14.67. Found: C, 57.94; H, 4.34; N, 14.52.

When a hot solution of 200 mg. of this monopicate and 200 mg. of picric acid in ethanol was allowed to cool, 300 mg. of a dipicate of XII separated in yellow needles, m.p. 186–187°. Attempts to recrystallize this compound resulted in regeneration of the monopicate.

2,2-Dimethyl-3-phenyl-5-(3-pyridyl)-2H-pyrroline (XII) was obtained by shaking the picrate with 2% aqueous ethanolamine and ether. Evaporation of the ether under reduced pressure yielded an oil that solidified on standing and separated from heptane in pale yellow crystals, m.p. 93–94°. An infrared spectrum³⁴ of XII in Nujol mull

(34) Kindly determined by R. Bruce Scott, Research Department, Parke, Davis and Co., Detroit, Mich.

showed absorption maxima at 6.22(m), 6.38(ms), 6.70(ms) and 7.38(s) μ . Zerewitinoff determinations³¹ in *n*-butyl ether showed no evolution of methane at 25 or 100°; there was addition of 1.09 and 1.05 moles of methylmagnesium iodide at 25 and 100°, respectively.

Anal. Calcd. for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.43; H, 6.76; N, 11.24.

(b) **Dehydration of Nitrone X with Benzoyl Chloride and Alkali.**—A mixture of nitrone X (1 g.), benzoyl chloride (1 g.) and 10% aqueous sodium hydroxide (10 ml.) was shaken until excess benzoyl chloride was hydrolyzed. Evaporation of an ether extract of the reaction mixture and treatment of the resulting oil with picric acid in 95% ethanol as described previously yielded 1.4 g. of crude picrate. Recrystallization from 95% ethanol afforded 700 mg. of pure picrate of XII, m.p. 208–209°, which did not depress the m.p. of the picrate obtained from dehydration of the nitrone with acetic anhydride.

When 100 mg. of nitrone X was shaken for 2 hr. with 2 ml. of ethanol and 1 ml. of 11 *M* aqueous sodium hydroxide, 79% of the nitrone was recovered unchanged as the picrate, m.p. 186.5–187.5°.

(c) **Dehydration and Reduction of Nitrone X with Phosphorus Trichloride.**—Phosphorus trichloride (13.74 g.) was added, over a period of 5 min., to a mechanically stirred solution of nitrone X (1.08 g.) in anhydrous benzene (40 ml.) under an atmosphere of dry nitrogen. After 1 hr. at room temperature the mixture was stirred for 2 hr. at reflux temperature and the solvent was removed by distillation. Ice and water (30 g.) were added to the semi-solid residue, followed by 6.5 *N* aqueous potassium hydroxide (22 ml.). The mixture was extracted several times with ether and the combined ethereal extracts were washed with water and then evaporated. The residual oil and 1.25 g. of picric acid were dissolved in hot ethanol. On cooling, the solution deposited 1.97 g. of a mixture of crystalline picrates. Fractional crystallization from ethanol afforded 875 mg. of the less soluble picrate of pyrroline XII, m.p. 207–208°, and 474 mg. of the dipicate of pyrroline IX, m.p. 178–179°. Mixed m.p.'s with authentic picrates showed no depression.

Dehydrogenation of 5,5-Dimethyl-4-phenyl-2-(3-pyridyl)- Δ^1 -pyrroline (IX).—When 500 mg. of pyrroline IX was heated with 64 mg. of sulfur, evolution of hydrogen sulfide began at 200° and was completed by brief heating to 290°. The cooled product, together with 500 mg. of picric acid, was dissolved in boiling ethanol. On cooling, the solution deposited 400 mg. of the picrate of pyrroline XII, m.p. 207–208° after one crystallization from ethanol, which did not depress the m.p. of an authentic sample.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY 4, CALIF.]

Cyclization of Dialdehydes with Nitromethane. VI.¹ Preparation of 3-Amino-1,6-anhydro-3-deoxy- β -D-gulose, - β -D-altrose and - β -D-idose Derivatives and their Characterization by Means of Inversion of Mesyloxy Groups

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Cyclization of the dialdehyde, obtained by periodate oxidation of levoglucosan, with nitromethane has afforded a method leading to 3-amino-1,6-anhydro-3-deoxy derivatives of *D*-gulose, *D*-altrose and *D*-idose. Structural assignment of these compounds was accomplished by converting each to the 3-acetamido-1,6-anhydro-3-deoxy-2,4-di-*O*-mesyl derivative. Inversion of the mesyloxy groups which were *trans* to the acetamido group, with sodium acetate in β -methoxyethanol, led in each case to *D*-allose derivatives. Each of these inverted products was then characterized by conversion to the same di-*O*-mesyl derivative.

The first successful application of the well-known aldehyde-nitromethane condensation reaction to

the field of carbohydrate chemistry was accomplished by Sowden,^{4,5} who condensed aldoses with nitromethane. The resulting 1-deoxy-1-nitro-polymers have proved to be of considerable use as inter-

(1) Part V published as a preliminary communication, A. C. Richardson and H. O. L. Fischer, *Proc. Chem. Soc.*, 341 (1960).

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(4) J. C. Sowden and H. O. L. Fischer, *J. Am. Chem. Soc.*, **66**, 1312 (1944).

(5) J. C. Sowden, *Adv. Carbohydrate Chem.*, **6**, 291 (1951).