hydrous chloroform maintained at a temperature of −25° was added 4.04 g. (0.04 mole) of triethylamine in 40 ml. of chloroform over a period of 40 minutes with vigorous stirring. After completion of the addition, the temperature was maintained at −25° for 10 minutes (with continued stirring) and then slowly raised to 0° and held at that temperature for another 10 minutes. After a final holding period of 20 minutes at room temperature, the solvent was removed under reduced pressure, the residue was washed with cold water to remove the triethylamine hydrochloride, and the product was crystallized from water. The phthaloylglycylglycine methyl ester was obtained in the form of colorless needles, m.p. 203–204°, yield 5.10 g. (90%). The recorded[16] m.p. is 205°.

Phthaloylglycylglycine.[2]—Phthaloylglycylglycine methyl ester (2.76 g., 0.01 mole) was heated with 25 ml. of 2 *N* hydrochloric acid on a steam-cone for one hour; upon cooling, the crude phthaloylglycylglycine crystallized from the solution. The crude product was recrystallized from ethyl alcohol; 2.50 g. (95%) of colorless needles was obtained, m.p. 230–231°. Hydrazinolysis[2] afforded glycylglycine in 90% yield.

Phthaloyl-L-phenylalanylglycine Ethyl Ester.—To a solution of phthaloyl-L-phenylalanyl chloride (prepared from 1.48 g. (0.005 mole) of phthaloyl-L-phenylalanine and used without purification) in 20 ml. of dry methylene chloride there was added 0.70 g. (0.005 mole) of glycine ethyl ester hydrochloride. The solution was cooled in a bath at −45° and, with stirring, a solution of 2.10 ml. (0.015 mole) of triethylamine in 20 ml. of methylene chloride was added over a period of 20 minutes. The mixture was stirred further for 100 minutes as the bath came to room temperature, then stored overnight. After extraction with dilute aqueous bicarbonate solution, the organic layer was evaporated to dryness. Crystallization from 20 ml. of ethanol yielded two crops of colorless needles; 1.01 g., m.p. 160–161.5°, and 0.11 g., m.p. 154–157° (total yield 59% over-all), $[\alpha]^{29.5}D$ −146° (0.0320 g. in 3.00 ml. absolute ethanol).

A portion was twice crystallized from ethanol for analysis, m.p. 160.6–161.4°.

Anal. Calcd. for $C_{21}H_{20}O_5N_2$: C, 66.30; H, 5.30; N, 7.37. Found: C, 66.19; H, 5.30; N, 7.62.

(16) E. Drechsel, *J. prakt. Chem.*, [II] **27**, 418 (1883).

Phthaloyl-L-phenylalanylglycine.—To 4.6 g. (0.0121 mole) of phthaloyl-L-phenylalanylglycine ethyl ester was added a solution of 50 ml. of acetone, 35 ml. of water and 15 ml. of concentrated hydrochloric acid. After heating for 2 hours under reflux, the clear solution was evaporated to dryness under reduced pressure, and the residue was dissolved in 50 ml. of water containing 6 g. of potassium bicarbonate. The solution was filtered and acidified to congo red with concentrated hydrochloric acid. Ethanol (25 ml.) was added and solution was attained by heating. On cooling, very fine, colorless needles separated. The product was collected, and washed with 50 ml. of water; yield 3.55 g. (83%), m.p. 183–185°, $[\alpha]^{28}D$ −148.5° (0.0311 g. in 2.00 ml. of absolute ethanol).

Anal. Calcd. for $C_{19}H_{16}O_5N_2$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.71; H, 4.67; N, 7.94.

L-Phenylalanylglycine Monohydrate.—A solution of 3.52 g. (0.01 mole) of phthaloyl-L-phenylalanylglycine in 100 ml. of ethanol containing 3.0 ml. (0.06 mole) of hydrazine hydrate was heated under reflux for one hour. Water (50 ml.) was added to ensure continued solubility of the hydrazine salt of phthalhydrazide. The solvent was removed under reduced pressure. The residue was taken up in 50 ml. of water and the solution was acidified to *p*H 5 with glacial acetic acid. After one hour, the phthalhydrazide was removed by filtration and washed with 50 ml. of water. The combined filtrates were concentrated to dryness under reduced pressure. To the resulting sirup acetone (15 ml.) was added dropwise with swirling. After a short period a further quantity of acetone (35 ml.) was added to the mass of fine, colorless crystals. The product was collected by suction filtration, washed with 20 ml. of acetone, and dried for two hours in a vacuum desiccator at 70°; weight 2.37 g. (99%, calculated as a monohydrate), m.p. 259.5–260.5° with charring, $[\alpha]^{28}D$ +42° (0.0307 g. in 1.50 ml. of acetic acid, $[\alpha]^{28}D$ +84.4°)(0.0299 g. in 1.50 ml. of water). The reported[14] value is $[\alpha]^{20}D$ +54.2° in water.

A portion was recrystallized by the slow addition of acetone to the aqueous solution, m.p. 259.2–260.4°.

Anal. Calcd. for $C_{11}H_{16}O_4N_2$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.13; H, 6.58; N, 11.39.

CAMBRIDGE 39, MASSACHUSETTS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Synthesis of Teloidinone and 6-Hydroxytropinone

BY JOHN C. SHEEHAN AND BARRY M. BLOOM[1]

RECEIVED JANUARY 7, 1952

2,5-Dimethoxy-2,5-dihydrofuran (V) was converted by treatment with potassium permanganate to *cis*-3,4-dihydroxy-2,5-dimethoxytetrahydrofuran (VI), the cyclic acetal of *meso*-tartaraldehyde. Interaction of V with hypochlorous acid gave 3-chloro-4-hydroxy-2,5-dimethoxytetrahydrofuran (IX) which was converted by means of potassium hydroxide to 3,4-epoxy-2,5-dimethoxytetrahydrofuran (X), the cyclic acetal of epoxysuccinaldehyde. Reduction of the epoxyacetal X with lithium aluminum hydride gave 3-hydroxy-2,5-dimethoxytetrahydrofuran (XI), the cyclic acetal of malicaldehyde. *meso*-6,7-Dihydroxytropinone (teloidinone) and 6-hydroxytropinone were prepared by condensation of *meso*-tartaraldehyde and malicaldehyde (obtained by hydrolysis of the corresponding tetrahydrofuran derivatives VI and XI) with methylamine and acetonedicarboxylic acid.

The synthesis of tropinone by the effective method of Robinson,[2] as modified by Schöpf and Lehmann,[3] involves the condensation of a γ-dialdehyde with acetonedicarboxylic acid and methylamine hydrochloride to form the tropane skeleton. Because of its remarkable simplicity, this type of reaction has been utilized in a preponderance of the recorded attempts to synthesize various tropane alkaloids. From a practical point of view the major difficulty to be overcome in accomplishing the synthesis of the more complex tropane alkaloids lies with the prerequisite preparation of the appropriate dialdehyde.

Among the tropane alkaloids,[4] scopolamine (I), valeroidine (II) and meteoloidine (III) bear structural resemblance to one another in that they possess oxygen-bearing substituents on the pyrrolidine ring of the bicyclic tropane system, in addition to the acylated 3-hydroxyl group commonly found in this family. Because of these substituents the preparation of the substituted tropinones from which these naturally occurring bases are derived

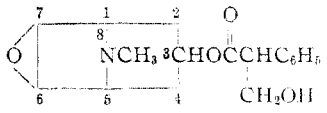
(1) F. J. Moore Fellow, 1950–1951.

(2) R. Robinson, *J. Chem. Soc.*, **111**, 762, 876 (1917).

(3) C. Schöpf and G. Lehmann, *Ann.*, **518**, 1 (1935).

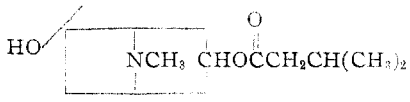
(4) For an excellent review of the chemistry of the tropane alkaloids, see: R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. I, Academic Press, Inc., New York, N. Y., 1950, p. 271.

presents an increasingly difficult problem of dialdehyde synthesis. The development of a method which makes practical the preparation of tropinones containing hydroxyl substituents in the 6- and 7-positions is described in this communication.



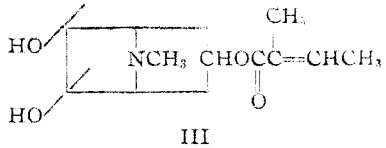
I

Scopolamine



II

Valeroidine

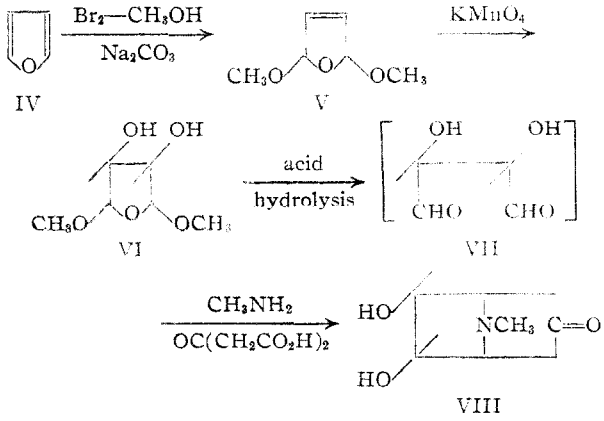


III

Meteloidine

Furan was brominated in a suspension of potassium carbonate in methanol to give 2,5-dimethoxy-2,5-dihydrofuran (V).[5] The olefinic linkage in V can be utilized for the introduction of substituent groups, yielding several compounds of interest as the cyclic acetals of substituted succinaldehydes. It was found that even mildly acidic reagents cause ring scission of V, but several successful additions to the double bond were carried out under non-acidic conditions.

The addition of bromine to V yielded a crystalline dibromide. The preparation of *meso*-tartaraldehyde in the stable form of its crystalline cyclic acetal, *cis*-3,4-dihydroxy-2,5-dimethoxytetrahydrofuran (VI), was accomplished by the oxidation of V with potassium permanganate in neutral solution. The acetal readily afforded the free aldehyde on hydrolysis with dilute acid. The action of hydrogen peroxide on V in the presence of osmium tetroxide gave poorer results. Such reagents as perbenzoic acid and the silver benzoate–iodine complex (Prévost reagent)[6] were without effect.



Teloidine, the basic moiety obtained upon alkaline hydrolysis of meteloidine (III), is optically inactive and cannot be resolved. It follows that the adjacent hydroxyl groups in the alkaloid molecule must possess the *cis*-glycol configuration. This led Schöpf and Arnold[7] to expect the condensation of *meso*-tartaraldehyde, acetonedicarboxylic acid and methylamine hydrochloride, when effected under "simulated physiological conditions," to yield teloidinone (VIII), the C-3 ketone from which teloidine is derived. The hypothesis was substantiated when these workers succeeded in isolating teloidinone from such a reaction mixture in excellent yield. No trace of the other possible isomer, also a *meso* form, was detected. The *meso*-tartaraldehyde employed in the synthesis was prepared from acetylene by the lengthy classical method of Wohl and Mylo.[8]

Utilizing *meso*-tartaraldehyde, conveniently prepared from furan, we have accomplished the synthesis of teloidinone in a similar manner. In view of the successful preparation of pure tropine by the reduction of tropinone in ethanol solution over Raney nickel,[9] it was hoped that teloidine, free from pseudoteloidine, could be prepared similarly. However, a mixture of isomers was obtained on reduction of teloidinone (VIII) in aqueous ethanol over Raney nickel W-4.

The preparation of 6-hydroxytropinone, from which valeroidine is derived, has not been attempted by previous investigators, probably because the malicaldehyde necessary to effect synthesis by the method of Robinson was unknown. The synthesis of the cyclic acetal of malicaldehyde has now been accomplished in three steps from 2,5-dimethoxy-2,5-dihydrofuran (V).

Reaction of the unsaturated cyclic acetal V in the cold with an aqueous solution of hypochlorous acid at *p*H 6.7 produced the corresponding chlorohydrin, 3-chloro-4-hydroxy-2,5-dimethoxytetrahydrofuran (IX). By treatment with a suspension of powdered potassium hydroxide in dry ether, IX was smoothly converted to the crystalline epoxide, 3,4-epoxy-2,5-dimethoxytetrahydrofuran (X), which is the cyclic acetal of the long sought-after[7,10] epoxysuccinaldehyde. The reduction of X in ether solution with lithium aluminum hydride gave 3-hydroxy-2,5-dimethoxytetrahydrofuran (XI), the cyclic acetal of the previously unknown malicaldehyde (XII).

An attempt was made to prepare XI from the chlorohydrin IX directly, eliminating the isolation of the intermediate epoxide X. The reaction was carried out by shaking a solution of the chlorohydrin and potassium hydroxide in methanol with Raney nickel W-4 under an atmosphere of hydrogen. Although the desired conversion of the

(5) J. Fakstorp, D. Raleigh and L. Schniepp, THIS JOURNAL, **72**, 869 (1950). Information concerning this preparation was made available to us prior to publication by Dr. Fakstorp. Furan was generously furnished by the Electrochemicals Department of E. I. du Pont de Nemours and Co.

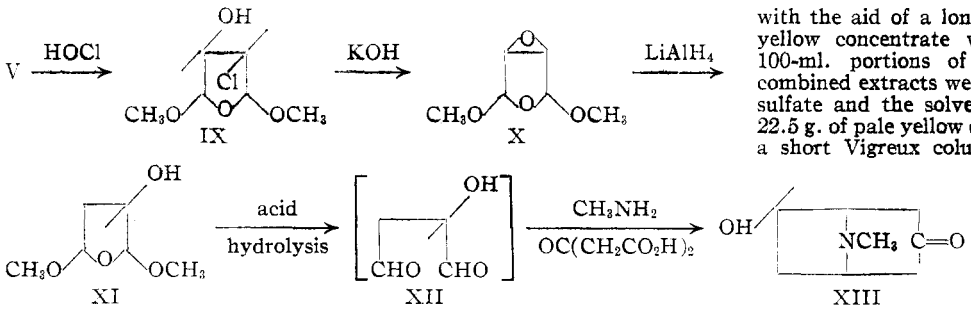
(6) C. Prévost, *Compt. rend.*, **196**, 1129 (1933), and succeeding papers.

(7) C. Schöpf and W. Arnold, *Ann.*, **558**, 109 (1947).

(8) A. Wohl and B. Mylo, *Ber.*, **45**, 322 (1912); A. Wohl and E. Bernreuther, *Ann.*, **481**, 1 (1930).

(9) J. Van de Kamp and M. Sletzinger, U. S. Patent 2,366,760 (January 9, 1945); *C. A.*, **39**, 2080 (1945).

(10) J. King, V. Hofmann and F. H. McMillan, *J. Org. Chem.*, **16**, 1100 (1951).



chlorohydrin grouping was effected, the reaction mixture was difficult to purify.

The condensation of malicaldehyde (XI) with methylamine hydrochloride and acetonedicarboxylic acid was carried out in the usual manner at *p*H 5, producing 6-hydroxytropinone (XIII) in 20% yield. The infrared absorption spectrum of XIII shows a broad band at 2.92 μ, attributable to an associated hydroxyl grouping and a strong carbonyl absorption at 5.85 μ, which indicates that the compound does not exist as a lactolide or internal hemiketal.

The condensation of the carbonyl compound resulting from the hydrolysis of X under mild conditions might be expected to yield scopinone, the C-3 ketone from which scopolamine is derived. A simple acid hydrolysis of the epoxide X followed by interaction of the resulting aqueous solution with methylamine hydrochloride and acetonedicarboxylic acid gave a crystalline product in reproducible, low yield. On the basis of the infrared absorption spectrum and analytical data the product does not appear to possess either the expected structure or that of the *trans*-glycol which would result from hydrolytic scission of the epoxide ring. The investigation of this reaction is being continued in this Laboratory.

Experimental[11]

3,4-Dibromo-2,5-dimethoxytetrahydrofuran.—Bromine (6.4 g., 0.04 mole) dissolved in 10 ml. of dry methylene chloride was added dropwise with stirring at −60° to a solution of 5.2 g. (0.04 mole) of 2,5-dimethoxy-2,5-dihydrofuran (V)[5] in 30 ml. of dry methylene chloride. Stirring was continued for 1 hour before the reaction mixture was allowed to warm up to room temperature. Removal of the solvent (35° bath) gave a red oil which was yellow after standing 24 hours at 5°. A sample was evaporatively distilled at 55° (0.3 mm.) to give colorless prisms, m.p. 63–65°. Three recrystallizations from ligroin raised the melting point to 88–89°.

Anal. Calcd. for $C_6H_{10}O_3Br_2$: C, 24.85; H, 3.48; Br, 55.12. Found: C, 25.14; H, 3.60; Br, 54.81.

cis-**3,4-Dihydroxy-2,5-dimethoxytetrahydrofuran (VI).**—A solution of 39.0 g. (0.30 mole) of V in 300 ml. of 95% ethanol was placed in a 2-l. beaker equipped with a stirrer, a dropping funnel and a thermometer and cooled to −5° with an ice–salt-bath. With vigorous stirring a solution of 31.6 g. (0.20 mole) of potassium permanganate and 45 g. (0.183 mole) of magnesium sulfate heptahydrate dissolved in 750 ml. of water was added dropwise over a 25-minute period together with 1 kg. of crushed ice. The temperature range of −5 to 0° was maintained throughout the addition. After stirring the resultant suspension for 4 hours at room temperature, the manganese dioxide was removed by filtration through a layer of Celite.

The filtrate was concentrated to a volume of about 90 ml. with the aid of a long-tube evaporator. The yellow concentrate was extracted with five 100-ml. portions of *n*-butyl alcohol. The combined extracts were dried over magnesium sulfate and the solvent was removed to give 22.5 g. of pale yellow oil. Distillation through a short Vigreux column gave 18.3 g. (37%) of colorless, viscous distillate boiling at 106–132° (2 mm.). A sample purified for analysis by distillation through a semi-micro fractionating column[12] possessed the following physical properties: b.p. 130° (2 mm.), $n^{25}D$ 1.4600.

Anal. Calcd. for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 44.04; H, 7.50.

After storage for 2 days at 25°, the analytical sample was completely crystalline, m.p. 65–67°.

Teloidinone (VIII).—The hydrolysis of VI (8.47 g., 0.052 mole) was accomplished by warming on a steam-cone with 50 ml. of *N* hydrochloric acid for 15 minutes. The methanol formed was removed by distillation under reduced pressure, and the resultant yellow, aqueous solution of *meso*-tartaraldehyde was adjusted to *p*H 5 by the addition of 6 *N* sodium hydroxide. The aldehyde solution was added to a buffer solution prepared from 62.7 g. of citric acid monohydrate and 612 ml. of 1 *N* sodium hydroxide. This was followed by the addition of a solution (adjusted to *p*H 5 with 6 *N* sodium hydroxide) of 19.5 g. (0.13 mole) of acetonedicarboxylic acid in 250 ml. of water. Finally, 5.4 g. (0.08 mole) of methylamine hydrochloride dissolved in 15 ml. of water was added. The acidity of the yellow reaction mixture was adjusted to *p*H 5.2 by the addition of 6 *N* sodium hydroxide, bringing the total volume to just over 1 liter. Vigorous carbon dioxide evolution commenced within 10 minutes, and the color of the solution darkened gradually.

After 64 hours, the reaction mixture (*p*H 5.6) was saturated with solid potassium carbonate to give a deep-red solution, which was extracted continuously with ether for 3 days. The crystalline teloidinone (1.58 g.), separated from the ether extract by filtration, melted at 188–189° with decomposition. Concentration of the ether solution yielded 0.96 g. of the same material. Further extraction of the reaction mixture gave an additional 1.22 g. of teloidinone (total yield, 42%). Several recrystallizations from ethanol gave stout prisms, m.p. 193–194° with decomposition. Schöpf and Arnold[7] reported a melting point of 192° with decomposition.

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.15; H, 7.66; N, 8.19. Found: C, 56.61; H, 7.71; N, 8.05.

3-Chloro-4-hydroxy-2,5-dimethoxytetrahydrofuran (IX).—Chlorine gas was bubbled into an ice-cold solution of 195 g. of sodium bicarbonate in 2 l. of water until the resulting solution no longer gave a precipitate with barium chloride. Sufficient sodium hydroxide solution to adjust the *p*H to 6.7 was then added. Titration showed the solution to be 0.70 *N* in hypochlorous acid.

A 124-g. portion (0.95 mole) of V was treated with 1960 ml. (1.37 moles) of the aforementioned freshly prepared hypochlorous acid solution. The mixture was thoroughly stirred, and then stored for 18 hours at 5°, after which time the solution showed practically no oxidizing power as tested by acidified starch–iodide paper. The solution was saturated with sodium chloride and extracted with five 300-ml. portions of ether. Removal of the solvent from the combined extracts, after drying over magnesium sulfate, afforded 144.1 g. of almost colorless oil. Distillation through a 15-cm. vacuum-jacketed Vigreux column gave 47.5 g. of unreacted V, b.p. 39–50° (0.8 mm.), and 62.6 g. of faintly yellow IX, b.p. 79–89° (0.4 mm.). This represents a 58% yield of chlorohydrin based on unrecovered starting material. The pure chlorohydrin was colorless and had a b.p. of 80° (0.4 mm.), $n^{25}D$ 1.4569.

Anal. Calcd. for $C_6H_{11}O_4Cl$: C, 39.46; H, 6.07; Cl, 19.42. Found: C, 39.55; H, 6.05; Cl, 19.49.

(11) All melting points are corrected and all boiling points are uncorrected. We are indebted to Dr. S. M. Nagy and his associates for the analyses and the infrared absorption measurements.

(12) C. W. Gould, G. Holtzmann and C. Niemann, *Ind. Eng. Chem., Anal. Ed.*, **20**, 361 (1948).

3,4-Epoxy-2,5-dimethoxytetrahydrofuran (X).—To a suspension of 60.7 g. (1.1 moles) of powdered potassium hydroxide in 250 ml. of dry ether was added slowly with stirring a solution of 62.5 g. (0.34 mole) of the chlorohydrin in 275 ml. of dry ether, whereupon an orange coloration rapidly developed. After the heat of reaction had subsided, the mixture was shaken mechanically for 9 hours. The precipitated salts were removed by filtration and washed thoroughly with ether. After drying the combined filtrates over magnesium sulfate, the solvent was removed and the crude epoxide (43.3 g.) was distilled through a 15-cm. vacuum-jacketed Vigreux column. The colorless distillate, b.p. 48–53° (0.5 mm.), 35.1 g. (70%), partially crystallized to yield 17.1 g. of needles, m.p. 42.5–45°. A sample was evaporatively distilled to give long needles, m.p. 43–45°.

Anal. Calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 48.99; H, 6.84.

The oil remaining after separation of crystalline (X) contained a small amount of impurity which prevented the further crystallization of the low-melting material. However, this oil was sufficiently pure for use in subsequent reactions.

3-Hydroxy-2,5-dimethoxytetrahydrofuran (XI).—A solution of 17.1 g. (0.117 mole) of X in 175 ml. of dry ether was added dropwise over a 40-minute period to a suspension of 2.24 g. (0.059 mole) of lithium aluminum hydride in 100 ml. of dry ether. During the addition period, the heat of reaction maintained the ether at reflux. Stirring was continued for 2 hours, and then the excess hydride was decomposed with 10 ml. of water followed by 30 ml. of 6 *N* sodium hydroxide solution. After separating the ether layer, the aqueous layer was extracted with three 200-ml. portions of ether, and the combined extracts were dried over magnesium sulfate. The ether was removed and the residue was distilled through a short Vigreux column. The yield of colorless 3-hydroxy-2,5-dimethoxytetrahydrofuran amounted to 15.0 g. (87%); b.p. 48–51° (0.9 mm.), $n^{25}D$ 1.4382.

Anal. Calcd. for $C_6H_{12}O_4$: C, 48.64; H, 8.17. Found: C, 48.73; H, 7.98.

6-Hydroxytropinone (XIV).—A solution of 15.0 g. (0.10 mole) of XI in 75 ml. of *N* hydrochloric acid was heated on a steam-cone for 8 minutes. The resulting orange solution was freed of methanol by concentration. Acetonedicarboxylic acid (29.2 g., 0.20 mole) and methylamine hydrochloride (8.78 g., 0.13 mole) were dissolved in 400 ml. of citrate buffer solution (*p*H 5). The aqueous solution of malicaldehyde was then added, and the acidity adjusted to *p*H 5.0 with 6 *N* sodium hydroxide solution The resultant orange solution (700 ml.) evolved carbon dioxide vigorously. After 32 hours the red-orange reaction mixture (*p*H 6.1) was saturated with potassium carbonate and continuously extracted with ether for 4 days. Removal of the ether gave 8.1 g. of a clear orange oil which partially crystallized on standing at room temperature. Trituration with ether containing a small amount of ethanol gave 1.67 g. of colorless needles, m.p. 121.5–123°. The residual oil, on similar treatment, yielded additional crops amounting to 1.45 g., bringing the total yield to 3.12 g. (20%). A sample sublimed at 70° (0.2 mm.) gave tiny prisms, m.p. 122.5–123.5°.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.12; H, 8.57; N, 8.91.

CAMBRIDGE 39, MASSACHUSETTS

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Synthesis of 3- and 5-Nitro-2-picoline and Derivatives

BY HENRY E. BAUMGARTEN AND HELEN CHIEN-FAN SU

RECEIVED FEBRUARY 25, 1952

6-Amino-5-nitro-2-picoline has been converted successively into 6-hydroxy-, 6-chloro- and 6-hydrazino-5-nitro-2-picoline and the latter has been oxidized to 5-nitro-2-picoline. By a similar sequence, 6-amino-3-nitro-2-picoline has been converted into 3-nitro-2-picoline. Several derivatives of the intermediate and final products have been prepared and characterized.

Investigations concerning the synthesis of polynuclear heterocyclic bases required the preparation of 5-nitro-2-picoline (V), 3-nitro-2-picoline (XIII), and some of their ring-substituted derivatives. Plazek[1] has reported the formation of V (and possibly XIII) in trace amounts through the direct nitration of 2-picoline, but the method was stated not to be of preparative value. The only other reported syntheses of derivatives of V and XIII are those of Parker and Shive,[2] who nitrated 6-amino-2-picoline to obtain the readily separable isomers, 6-amino-5-nitro-2-picoline (I) and 6-amino-3-nitro-2-picoline (VI), and converted these substances into a number of 2-picoline derivatives. This communication reports the preparation of V, XIII and several of their derivatives through the modification and extension of the procedures of Parker and Shive as outlined in the flow sheet.

Parker and Shive[2] converted I and VI directly into 6-chloro-5-nitro-2-picoline (III) and 6-chloro-3-nitro-2-picoline (VIII), respectively, by diazotization of the amino compounds with sodium nitrite and concentrated hydrochloric acid in sealed tubes. As is the usual experience in such procedures,[3] yields of less than 50% were obtained (38% for III and 29% for VIII) and a considerable portion of the product consisted of the corresponding 6-hydroxy compounds, II (30%) and VII (49%). A two-step conversion[4] of 2-amino-substituted pyridines to the 2-chloro compounds has given, in general, more satisfactory results. Thus, in this work I was converted into II in 92% yield by diazotization in cold sulfuric acid solution and then II was transformed into III in 86% yield by treatment with a mixture of phosphorus pentachloride and phosphorus oxychloride. Similarly, VI was converted successively into VII (98% yield) and VIII (80% yield).

In the work described below it became increasingly apparent that there was a pronounced difference in reactivity between the halogen atoms of compounds III and VIII, the compound with the chlorine atom and nitro group ortho to each other (III) being the more reactive. A similar comparison has been drawn previously between 4-chloro-3-nitropyridine and 2-chloro-5-nitropyridine,[5] the former being more reactive. Thus, when VIII was treated with a methanolic solution of sodium methoxide, an 82% yield of 6-methoxy-3-nitro-2-pico-

(1) E. Plazek, *Ber.*, **72B**, 577 (1939).

(2) E. D. Parker and W. Shive, THIS JOURNAL, **69**, 63 (1947).

(3) H. S. Mosher in R. C. Elderfield's "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 515.

(4) For a recent example of the utility of the two-step procedure, see: M. A. Phillips, *J. Chem. Soc.*, 9 (1941).

(5) H. Maier-Bode and J. Altpeter, "Das Pyridin und seine Derivate," Wilhelm Knapp, Halle, Saale, 1934, p. 119.