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.

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[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-

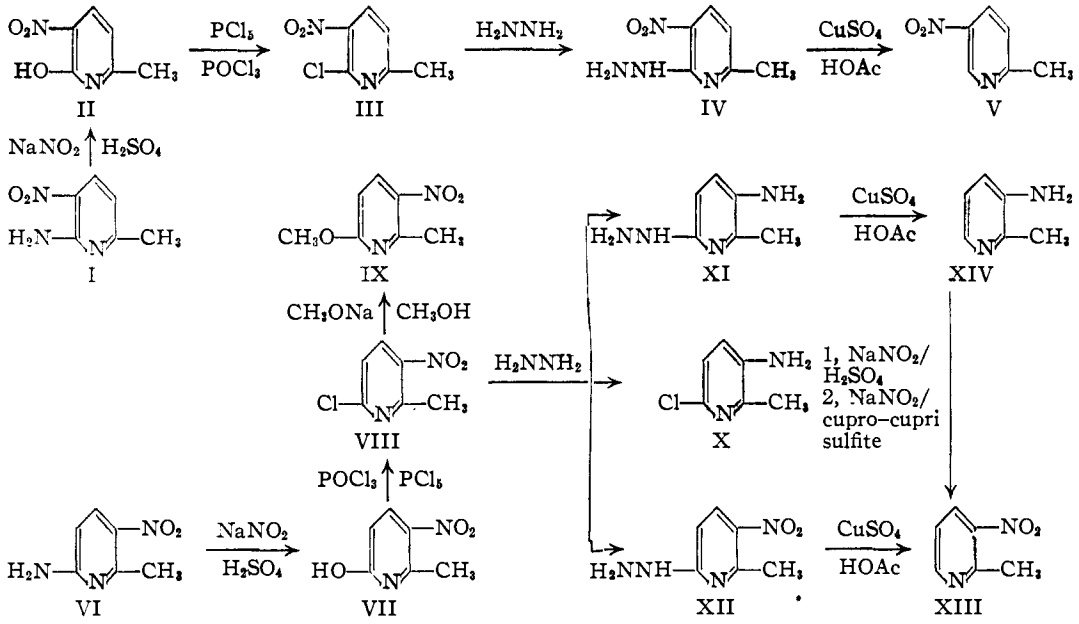
(1) E. Plazek, *Ber.*, **72B**, 577 (1939).

(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.



line (IX) was obtained. However, when III was treated in a similar manner, only decomposition products resulted. Apparently the more reactive halogen compound (III) reacted with itself to give a substance similar to Zincke's[6] 2,4-dinitrophenylpyridinium chloride which, on treatment with alkoxide, underwent ring cleavage to give colored decomposition products. 2-Nitro-5-chloropyridine[7] has been reported to behave similarly, and 4-chloro-3-nitropyridine[8] gave a low yield of the corresponding methoxy derivative accompanied by much decomposition.

When the more reactive compound III was treated with excess hydrazine hydrate in ethanolic solution, a spontaneous reaction resulted, giving a 90% yield of 6-hydrazino-5-nitro-2-picoline (IV). Under similar conditions VIII gave a very low yield of the corresponding hydrazino compound (XII) and, under forcing conditions, gave a mixture of substances from which XII could be isolated only with difficulty. Other components of the mixture were 3-amino-6-chloro-2-picoline (X) and possibly 3-amino-6-hydrazino-2-picoline (XI). The former was identified by comparison with an authentic specimen prepared by the procedure of Parker and Shive,[2] and the possible presence of the latter was inferred from the results of the oxidation of crude XII as described below. The presence of X and XI may be explained as resulting from the reduction of the 3-nitro groups of VIII and XII by the excess hydrazine present, the chlorine atom of X being then too unreactive to suffer replacement under the conditions used. Ultimately a 60% yield of XII was obtained by adding a solution of hydrazine hydrate (20% excess) and sodium acetate to a boiling ethanolic solution of VIII. Both IV and XII gave the corresponding hydrazones when treated with benzaldehyde.

Oxidation of IV with copper sulfate in dilute acetic acid solution gave a 30% yield of V. Similarly pure XII was converted into XIII in 20% yield. When an attempt was made to utilize crude XII in the oxidation, a colorless solid was obtained along with the expected liquid, XIII. Comparison of this solid with an authentic specimen of 3-amino-2-picoline (XIV), prepared according to the directions of Dornow,[9] showed the two substances to be identical. Apparently a small amount of XI present in the crude hydrazino compound was oxidized to give XIV.[10]

Replacement of the diazotized amino group of XIV by nitro was accomplished in 15% yield following the cupro–cupri sulfite procedure of Hodgson, Mahadevan and Ward,[11] this process affording a second route to XIII.

Experimental[12]

6-Amino-5-nitro-2-picoline (I) **and 6-amino-3-nitro-2-picoline** (VI) were prepared by the procedure of Parker and Shive[2] with the following modifications. After neutralization of the reaction mixture with sodium hydroxide, the resultant mixture was chilled in the refrigerator overnight. The precipitated solids were collected by suction filtration and extracted with ethanol, until the extracts became colorless. After evaporation of the ethanol, the residue was suspended in water and steam distilled as described by Parker and Shive.[2] The yield of 6-amino-5-nitro-2-picoline, m.p. 141°, was 33%; the yield of 6-amino-3-nitro-2-picoline, m.p. 188°, was 54%. Alternatively, the neutral mixture was filtered immediately after neutralization (*i.e.*, before much sodium sulfate could precipitate from solution) and the collected solids were steam distilled. The yields were somewhat lower by this procedure, but the operations were less time consuming.

6-Hydroxy-5-nitro-2-picoline (II).—A solution was prepared from 29.9 g. (0.195 mole) of 6-amino-5-nitro-2-picoline, 35 ml. of concentrated sulfuric acid and 500 ml. of water. About 150 g. of ice was added and a solution of 20 g. (0.29 mole) of sodium nitrite in 60 ml. of water was added slowly with stirring and cooling. The mixture was

(6) Reference 4, p. 425 ff.

(7) M. G. Bystritskaya and A. V. Kirsonov, *J. Gen. Chem.* (*U.S.S.R.*), **20**, 1101 (1940); *C. A.*, **35**, 4023 (1941).

(8) E. Koenigs and A. Fulde, *Ber.*, **60**, 2106 (1926).

(9) A. Dornow, *Ber.*, **73B**, 78 (1940).

(10) Although pure XII did not appear to give XIV on oxidation, the possibility that XIV was formed by self-oxidation and -reduction of XII cannot be excluded.

(11) H. H. Hodgson, A. P. Mahadevan and E. R. Ward, *J. Chem. Soc.*, 1392 (1947).

(12) All melting points are corrected, boiling points, uncorrected.

stirred for one hour at 10°. The precipitated solid was collected by filtration and washed with water, giving 23.5 g. (78%) of 6-hydroxy-5-nitro-2-picoline as elongated yellow prisms, m.p. 221–222°. Concentration of the filtrate yielded an additional 4.2 g. (14%).

6-Chloro-5-nitro-2-picoline (III).—A mixture of 27.5 g. (0.178 mole) of 6-hydroxy-5-nitro-2-picoline, 10 g. of phosphorus pentachloride and 5 ml. of phosphorus oxychloride was heated under reflux at 110–115° in an oil-bath for three hours. After cooling, 5 g. of phosphorus pentachloride and 5 ml. of phosphorus oxychloride were added and the mixture was refluxed for an additional hour. The cooled mixture was poured into a slush of 500 g. of ice and 1 l. of water. An oil separated which soon solidified on stirring to give a pale yellow solid, which was collected by filtration and washed with water. The yield of crude product was 27.7 g. (90%). The crude material was recrystallized from acetone, giving 26.5 g. (86%) of 6-chloro-5-nitro-2-picoline as pale yellow plates, m.p. 67–69°.

6-Hydrazino-5-nitro-2-picoline (IV).—To a solution of 4.0 g. (0.023 mole) of 6-chloro-5-nitro-2-picoline in the minimum amount of ethanol was added slowly with shaking 2.0 g. (0.04 mole) of hydrazine hydrate. The reaction mixture became warm and turned first brown then deep red. The mixture was allowed to stand until it had cooled to room temperature. Filtration of the product yielded 3.9 g. (98%) of deep red needles, m.p. 137–138°. The crude material was recrystallized by dissolving it in the minimum amount of ethanol (with little or no warming to prevent decomposition) and evaporating the solution to half volume under a gentle current of air. The fine bright red needles that formed at this point were collected for analysis. Further cautious evaporation gave a recovery of 90% of the 6-hydrazino-5-nitro-2-picoline, m.p. 138–139°. The product gave a negative Beilstein test for halogen.

Anal.[13] Calcd. for $C_6H_8N_4O_2$: C, 42.86; H, 4.79; N, 33.32. Found: C, 42.81; H, 4.81; N, 33.44.

To a solution of 0.5 g. of 6-hydrazino-5-nitro-2-picoline in 35 ml. of 40% acetic acid was added a solution of 1 g. of benzaldehyde in 40% acetic acid. An orange precipitate formed at once. The mixture was warmed on the hot-plate for 30 minutes, cooled in ice, and filtered. Recrystallization of the crude product from ethanol gave benzaldehyde (6-methyl-3-nitro-2-pyridyl)-hydrazone as fine orange crystals, m.p. 177–178°.

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72. Found: C, 60.65; H, 4.60.

5-Nitro-2-picoline (V).—A mixture of 0.63 g. (0.0038 mole) of 6-hydrazino-5-nitro-2-picoline, 20 ml. of water and 10 ml. of acetic acid was heated to boiling until the hydrazino compound dissolved. Then 15 ml. of 10% copper sulfate solution was added slowly dropwise. The solution turned violet then deep purple. The mixture was boiled for 15 minutes. The cooled mixture was made alkaline with 6 *N* sodium hydroxide (a dark precipitate formed) and was extracted with ether. Evaporation of the ether left a small amount of pale brown solid, which was picked up in petroleum ether and recovered by evaporation of the solvent. The crude yield of 5-nitro-2-picoline was 0.22 g. (43%), m.p. 104–105.5°. The crude product was recrystallized from petroleum ether (using a small amount of activated charcoal) for analysis, 85% of the material being recovered. The pure 5-nitro-2-picoline was obtained in the form of colorless flat needles, m.p. 107.5–108.5°.

Anal. Calcd. for $C_6H_6N_2O_2$: C, 52.18; H, 4.39; N, 20.30. Found: C, 52.70; H, 5.16; N, 20.37.

In other experiments the yield of crude 5-nitro-2-picoline varied from 30–43%.

6-Hydroxy-3-nitro-2-picoline (VII) was prepared by the procedure described above for 6-hydroxy-5-nitro-2-picoline. The product was obtained in 98% yield, after concentration of the filtrate, m.p. 230–232°.

6-Chloro-3-nitro-2-picoline (VIII) was prepared by the procedure described above for 6-chloro-5-nitro-2-picoline. The product was obtained in a crude yield of 87%, after recrystallization from ethanol, 80%, m.p. 52.5–54.5°.

6-Methoxy-3-nitro-2-picoline (IX).—To a solution of 2.0 g. (0.085 mole) of sodium in 30 ml. of methanol, cooled to room temperature, was added 8.6 g. (0.05 mole) of 6-chloro-3-nitro-2-picoline. The mixture was stirred for seven hours at room temperature, then heated at 75–85° for one hour, and, after cooling, poured into 500 ml. of cold water. The precipitate that formed was collected by filtration, washed well with water, and dried, giving 6.9 g. (82%) of 6-methoxy-3-nitro-2-picoline, m.p. 63–64°. The compound gave a negative Beilstein test for halogen. A sample was recrystallized from methanol for analysis, giving long white needles, m.p. 64–65°.

Anal. Calcd. for $C_7H_8N_2O_3$: N, 16.65. Found: N, 16.54.

6-Hydrazino-3-nitro-2-picoline (XII) could not be prepared satisfactorily by the procedure described above for 6-hydrazino-5-nitro-2-picoline. In general it was found necessary to apply external heat to the reaction mixture for at least 0.5 hour; however, occasionally under these conditions (large excess of hydrazine hydrate and heat) a greenish-brown solid was obtained, which could be separated into two main fractions by recrystallization from ethanol (using activated charcoal). The first compound to separate was a colorless solid (needles), m.p. 90–92°, giving a strong positive halogen test. Comparison of this solid with an authentic sample of 6-chloro-3-amino-2-picoline, m.p. 90–91°, prepared by the reduction of 6-chloro-3-nitro-2-picoline with tin and hydrochloric acid[2] showed the two to be identical, mixed m.p. 90–92°. Concentration of the filtrate yielded a yellow solid, m.p. 115–117°, subsequently shown to be the impure hydrazino compound. The reduction of the starting material by the excess hydrazine could be somewhat lessened by increasing the amount of ethanol used as solvent (to 30 ml. of ethanol per 1.73 g. of chloro compound), under which conditions the product was obtained by pouring the reaction mixture into water.

The most satisfactory procedure was as follows. To a boiling solution of 1.73 g. (0.01 mole) of 6-chloro-3-nitro-2-picoline in the minimum amount of ethanol was added slowly with shaking a solution of 0.65 g. (0.012 mole) of hydrazine hydrate and 0.7 g. (0.0085 mole) of sodium acetate in a small amount of ethanol. The mixture was boiled for 10 minutes on the hot-plate with occasional shaking, during which time some precipitate formed. The solution was allowed to cool to room temperature overnight and the precipitated product was collected as a yellow solid, crude yield 1.5 g. (88%). After recrystallization from ethanol, 1.0 g. (60%) of 6-hydrazino-3-nitro-2-picoline was obtained, m.p. 119–121°.

Anal.[13] Calcd. for $C_6H_6N_4O_2$: C, 42.86; H, 4.79; N, 33.32. Found: C, 42.71; H, 5.20; N, 33.27.

The benzaldehyde derivative, benzaldehyde (6-methyl-5-nitro-2-pyridyl)-hydrazone, was obtained, as described above for benzaldehyde (6-methyl-3-nitro-2-pyridyl)-hydrazone, as a bright yellow powder, m.p. 176–178°.

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72. Found: C, 60.97; H, 4.91.

3-Nitro-2-picoline (XIII) was prepared by the procedure described above for 5-nitro-2-picoline. In one experiment the product was isolated by steam distillation of the neutralized reaction mixture, followed by ether extraction of the steam distillate. The crude product was purified by distillation, giving 15–20% of 3-nitro-2-picoline, b.p. 99–100° (8 mm.), 110–112° (16 mm.), as a yellow oil, freezing in ice to a cluster of crystals and remelting on being warmed up to or near room temperature.

Anal. Calcd. for $C_6H_6N_2O_2$: C, 52.18; H, 4.38. Found: C, 52.01; H, 4.14.

For the nitrogen analysis a small amount of the product was converted into the solid hydrochloride by dissolving the oil in dry ether and passing dry hydrogen chloride into the solution until no more precipitate formed. The product, collected by filtration and washed with ether, was a white solid, m.p. 165–167°, slowly turning tan on standing.

Anal. Calcd. for $C_6H_7N_2O_2Cl$: N, 16.04. Found: N, 16.49.

Although the similar oxidation of 2-hydrazino-5-nitropyridine[14] has been reported to give yields of about 50% of 3-nitropyridine, a large number of experiments under varied conditions failed to give yields higher than those cited above. When crude 6-hydrazino-3-nitro-2-picoline was used in the

(13) Nitrogen analysis by Clark Microanalytical Laboratory, Urbana, Illinois.

(14) C. Räth, Swiss Patent 127,267, Aug. 8, 1928; *Chem. Zentr.*, **100**, II, 489 (1929).

above oxidation, the crude product (isolated by ether extraction of the neutralized reaction mixture) contained not only the liquid 3-nitro-2-picoline but also a solid which slowly crystallized out of the mixture. The solid was collected and recrystallized from benzene–petroleum ether yielding colorless halogen-free crystals, m.p. 112–114°; picrate, m.p. 232–234° (dec.), mixed m.p. with a sample of 3-amino-2-picoline, prepared by the method of Dornow,[9] was not depressed.

A second preparation of 3-nitro-2-picoline utilized the replacement of the 3-amino group of 3-amino-2-picoline[15] by the diazonium procedure of Hodgson, Mahadevan and Ward,[11] which was followed closely. Thus, when the bright orange diazonium sulfate (from 1.08 g. (0.01 mole) of 3-amino-2-picoline, 1.8 g. (0.025 mole) of sodium nitrite, 15 ml. of concentrated sulfuric acid, 20 ml. of glacial acetic acid and 140 ml. of ether) was added to a slurry of cupro–cupri sulfite (from 10 g. of sodium sulfite and 10 g. of copper sulfate) and sodium nitrite (20 g., 0.26 mole) in 80 ml. of water, the solution was neutralized with 6 *N* sodium hydroxide and steam distilled, and the product was extracted from the distillate with petroleum ether, 0.2 g. (15%) of 3-nitro-2-picoline was obtained. When the diazonium cobaltinitrile procedure of Hodgson and Marsden[16] was used with 3-amino-2-picoline, none of the desired 3-nitro-2-picoline could be isolated from the tarry reaction product.

(15) Although the 3-amino-2-picoline used in these experiments was prepared according to the directions of Dornow,[9] the compound may be prepared by the reduction of X in 37% yield.[2]

(16) H. H. Hodgson and E. Marsden, *J. Chem. Soc.*, 22 (1944).

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE][1]

2-, 3- and 4-(1-Methylpiperidyl)-carbinols and Derivatives

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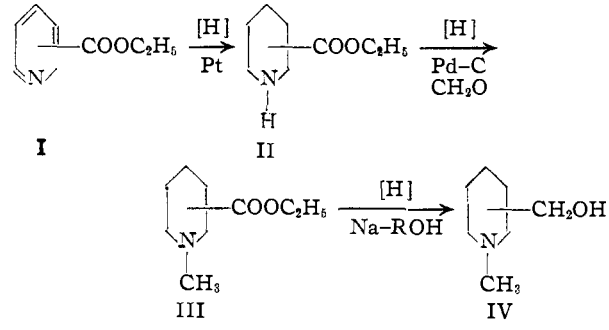
RECEIVED MARCH 18, 1952

As part of an extended program to find new antispasmodic agents, an investigation of the 2-, 3- and 4-(1-methylpiperidyl)-carbinols was undertaken. Of these, the 2- and 3-alcohols had previously been described but, when the physical data reported could not be confirmed, a new general synthesis was devised which gave excellent yields of hexahydropyridine derivatives and consistent physical data. From these new carbinols some of the reported derivatives were remade and the discrepancies described.

In our study of basic esters possessing spasmolytic properties, we became interested in 3-(1-methylpiperidyl)-carbinol which was first prepared by Sandborn and Marvel[3] in connection with their work on local anesthetics. Later Renshaw, *et al.*,[4] prepared the 2-(1-methylpiperidyl)-carbinol as well as the 3-carbinol by the same method, as intermediates in their study of heterocyclics analogous to acetylcholine. Ford-Moore and Ing[5] also prepared the 3-carbinol in their study of synthetic mydriatics. The 4-carbinol is apparently new although the unmethylated 4-piperidylcarbinol was described by Clemo and Metcalfe.[6] The method of synthesis employed by each of these workers, following the publication by Sandborn and Marvel, was essentially the same. Either ethyl isonicotinate, ethyl nicotinate or ethyl picolinate was reduced by a sodium–alcohol type reduction to the corresponding 2-, 3- or 4-piperidylcarbinols. This method appeared to be very advantageous because each paper reported that both the pyridine ring and the carboethoxy group were reduced simultaneously. Methylation was accomplished either by means of methyl iodide or with formaldehyde and formic acid.

Our primary concern was the preparation of the 3-carbinol which we first prepared by the original method. We were very disappointed with our yields but more so with our inability to either confirm the physical data of Sandborn and Marvel or repeat our own on various runs. Subsequent experiments led us to a general synthesis which applied equally well to each of the three homologs and gave good yields of the true piperidine products.



We started with the same pyridine esters (I) which we prepared in excellent yields from the corresponding acids by means of thionyl chloride and ethyl alcohol. These pyridine esters were readily reduced to their piperidine analogs by catalytic reduction with platinum in aqueous acetic solutions. Isolation of the piperidine derivatives (II) could be done at this stage but was not found to be necessary because N-methylation proceeded rapidly by exchanging the catalyst for palladium-on-charcoal and hydrogenating in the presence of a slight excess of aqueous formaldehyde. This latter step was most advantageous for two reasons. Whereas we were unable to methylate these esters by means of formic acid and formaldehyde, reductive methylation gave excellent yields. Also we found that all attempts to reduce the carboethoxy groups prior to N-methylation resulted in side reactions and very low yields.

The ethyl 1-methylpiperidylcarboxylates (III) were isolated and characterized as quaternary salts. Preparation of the carbinols (IV) from the piperidine esters was easily accomplished by means

(1) Preliminary work done at Frederick Stearns Scientific Laboratories, Detroit, Michigan.

(2) Present address: Smith–Dorsey, Lincoln, Nebraska.

(3) L. T. Sandborn and C. S. Marvel, THIS JOURNAL, **50**, 563 (1928).

(4) R. R. Renshaw, M. Ziff, B. B. Brodie and N. Kornblum, *ibid.*, **61**, 638 (1939).

(5) A. H. Ford-Moore and H. R. Ing, *J. Chem. Soc.*, 55 (1947).

(6) G. R. Clemo and T. P. Metcalfe, *ibid.*, 1523 (1937).