Anal. Calcd. for $C_8H_9NO_3$: N, 8.4. Found: N, 8.7.

When V was treated with lithium aluminum hydride using either ethyl ether or butyl ether as solvents it was not possible to isolate any VII.

3-Hydroxymethyl-6-methyl-2-pyridol (VII).—Since the reaction of lithium aluminum hydride in ethyl ether with IV was not successful, it was decided to use butyl ether. To a solution of 7.1 g. of IV in 500 ml. of dry butyl ether was added 4.5 g. of lithium aluminum hydride. Upon addition of the solid, a visible evolution of hydrogen occurred. The mixture was then refluxed for 16 hours, and then poured onto 500 g. of ice. Solid sodium bicarbonate was then added until a *p*H of 8 was attained. The mixture was then filtered, and the resulting two clear layers were separated. The water layer was extracted with various solvents, ethyl acetate, chloroform and benzene, using acidic and basic conditions, but all that was recovered was 3.1 g. of unreacted acid. The water layer was then brought to a *p*H of 8, and taken to complete dryness. The dry residue was extracted with three 100-ml. portions of ethyl acetate at room temperature. The combined extracts were evaporated, leaving 1.1 g. of a white solid, m.p. 150°. This was recrystallized several times from absolute ethanol, giving large crystals, m.p. 164–165°. These crystals gave a deep ferric chloride test.

Anal. Calcd. for $C_7H_9NO_2$: N, 10.1. Found: N, 10.2.

3-Cyano-6-methyl-2-methoxypyridine (III).—To a solution of 1 g. of sodium in 100 ml. of absolute methanol was added 1.4 g. of II,[5] and the mixture was refluxed for three hours. The cooled solution was then acidified with hydrochloric acid, and the precipitated sodium chloride filtered off. The filtrate was taken to dryness, and the residue was vacuum distilled at 184° and 5 mm. to yield white crystals, m.p. 81.5°, 0.8 g. (59%).

Anal. Calcd. for $C_8H_8N_2O$: N, 18.9. Found: N, 19.2.

3-Carboxy-6-methyl-5-nitro-2(1)-pyridone (IX).—A solution of 3 g. of VIII in 30 ml. of concentrated hydrochloric acid was refluxed for 24 hours. The cooled solution was brought to a *p*H of 8, and filtered. The filtrate was acidified, and the pink solid which formed was filtered, 2 g. (60%). Recrystallization from water gave a flesh-colored powder, m.p. 268°.

Anal. Calcd. for $C_7H_6N_2O_5$: N, 14.1. Found: N, 14.4.

3-Carboxy-2-chloro-6-methyl-5-nitropyridine (XI).—A solution of 3 g. of X[4] in 30 ml. of concentrated hydrochloric acid was refluxed for 24 hours. The resulting solution was cooled, and filtered, 2.2 g. (66%). The crude crystals were dissolved in a solution of sodium hydroxide and filtered, and the filtrate acidified to a *p*H of 4–5, and the pure acid precipitated. Recrystallization of these crystals from water gave a fine powder, m.p. 261–262°.

Anal. Calcd. for $C_7H_5ClN_2O_4$: N, 12.9. Found: N, 12.9.

Reaction of X and XII.—When 1 g. of XII[4] was refluxed in a solution of 0.5 g. of sodium in 50 ml. of methanol for two hours and the solution worked up as described in the formation of III, only unreacted XII could be isolated, m.p. 227°.

An attempt was made to prepare a Grignard reagent with XII, using magnesium in absolute ether, but no Grignard reagent could be obtained.

When X[4] was added to sodium methoxide in methanol, or sodium cyanide in water, the solution turned dark purple immediately. The workup of the solutions yielded a dark amorphous solid, which could not be crystallized from such solvents as ethanol, water, methanol, petroleum ether, and dioxane, and which could not be sublimed. It is interesting to note that VIII could be mixed with bases without any color formation.

EVANSTON, ILLINOIS RECEIVED NOVEMBER 5, 1951

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

α-Oxygenated Pyridines. III. The Reaction of N-Bromosuccinimide with Some Pyridine Derivatives[1]

BY RAYMOND P. MARIELLA[2] AND ELIZABETH P. BELCHER

The bromination of 4,6-dimethyl-2-pyridol, of 4,6-dimethyl-2-aminopyridine and of 2-acetamino-4,6-dimethylpyridine with N-bromosuccinimide has been investigated. The reaction even in the presence of benzoyl peroxide and ultraviolet light is predominantly nuclear. When a high concentration of benzoyl peroxide is used only 4,6-dimethyl-2-pyridol underwent both nuclear and side-chain bromination.

In conjunction with our work on compounds structurally related to pyridoxin,[3] we have investigated the reaction of various pyridine derivatives, 4,6-dimethyl-2-pyridol, 4,6-dimethyl-2-aminopyridine and 2-acetamino-4,6-dimethylpyridine with N-bromosuccinimide. It was expected that by carrying out this reaction in the presence of benzoyl peroxide and ultraviolet light bis-bromomethylpyridines might be prepared which on further reaction would lead to bis-hydroxymethylpyridols. These pyridols somewhat similar in structure to pyridoxin might be expected to have some vitamin or antivitamin activity.

There have been many reports in the recent literature on the reaction of N-bromosuccinimide with aromatic compounds. These include the benzenoid compounds and picolines discussed in the review by Djerassi,[4] the methylfurans studied by Buu-Hoï,[5] and the methylthiophenes studied by both Campaigne[6] and Dittmer.[7] In all cases it was shown that, in the absence of peroxides, the reaction occurs with the aromatic nucleus; in the presence of small percentages of peroxides the reaction is predominantly with the aliphatic side-chain. This latter reaction is particularly favored if the reaction is carried out in a quartz vessel under ultraviolet light.[4,6] The orientation of the reaction with aromatic compounds substituted with groups other than alkyl has not been widely studied. There is some work on substituted 4-pyrones[8] which showed that even in the absence of peroxides 2,6-dimethyl-4-pyrone will react with N-bromosuccinimide to form 2-bromomethyl-6-meth-

(1) Taken in part from the Ph.D. thesis of E. P. Belcher. Eli Lilly Fellow, 1949–1951.

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(3) (a) R. P. Mariella and J. L. Leech, THIS JOURNAL, **71**, 331 1949); (b) R. P. Mariella and E. P. Belcher, *ibid.*, **73**, 2616 (1951).

(4) C. Djerassi, *Chem. Revs.*, **43**, 271 (1948).

(5) Ng. Ph. Buu-Hoï, *Ann.*, **556**, 1 (1944).

(6) E. Campaigne and W. M. LeSuer, THIS JOURNAL, **70**, 1555 (1948).

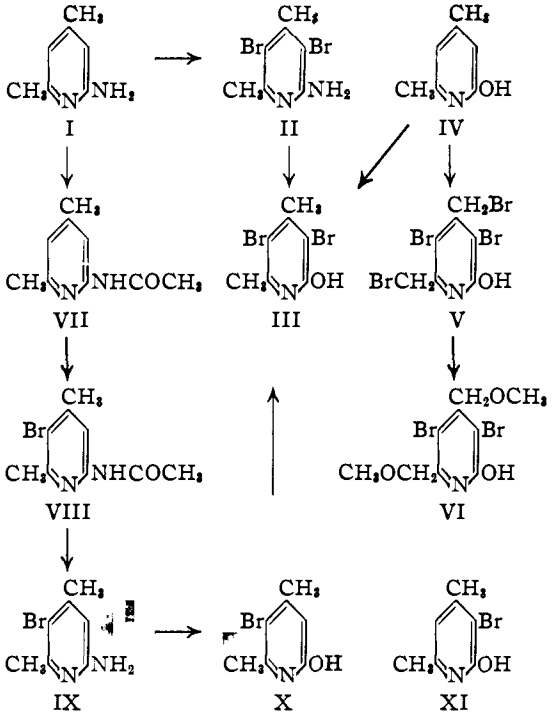
(7) K. Dittmer, R. P. Martin, W. Herz and S. J. Cristol, *ibid.*, **71**, 1201 (1949).

(8) J. LeCocq, *Ann. Chim.*, **3**, 62 (1948).

yl-4-pyrone. The dibromo derivative was not formed. The substituted coumarones have also been studied.[9-11] It was shown that if there is no alkyl group in the 3-position of a coumarone, bromination will occur there,[8,9] or also on an alkyl group located on the benzene ring.[9,10] If there is an alkyl group at the 3-position of the coumarone, bromination will occur at the α-position of this group.[9,11] These reactions were studied without any added peroxides and indicate that here at least the hetero atom has activated the pyrone ring in the 3-position.

Similarly we have found that N-bromosuccinimide will brominate the pyridine nucleus if there is either an hydroxyl, an amino, or an acetamino group in the α-position of the ring. This reaction occurs even in the presence of benzoyl peroxide and ultraviolet light. If the peroxide concentration is sufficiently high (10 mole per cent.) bromination will also occur on the alkyl groups of 4,6-dimethyl-2-pyridol; a similar high concentration has no effect on the reaction of 4,6-dimethyl-2-aminopyridine. Under no conditions was the reaction exclusively on the alkyl groups.

The compounds which were prepared in this study and their interrelationships are shown in the accompanying flow sheet.



Bromination of 4,6-dimethyl-2-aminopyridine (I) with free bromine in acetic acid gave the hydrobromide of 3,5-dibromo-4,6-dimethyl-2-aminopyridine (II). The free base of this compound was identical with the product of the reaction of I with N-bromosuccinimide in the presence of 2.5 mole per cent. benzoyl peroxide and under ultraviolet light. Diazotization of this compound yielded 3,5-dibromo-4,6-dimethyl-2-pyridol (III) which could also be prepared from 4,6-dimethyl-2-pyridol either by direct bromination[12] or by reaction with N-bromosuccinimide in the presence of 2.5 mole per cent. benzoyl peroxide. None of these compounds reacted with alcoholic silver nitrate, nor were they hydrolyzed on refluxing in aqueous solution or in a methanolic solution of silver nitrate, indicating that the bromine was on the aromatic ring.

By increasing to ten the mole percentage of benzoyl peroxide in the reaction mixture and again carrying out the reaction in a quartz vessel under ultraviolet light, 4,6-bis-bromomethyl-3,5-dibromo-2-pyridol (V) was prepared by the reaction of 4,6-dimethyl-2-pyridol with N-bromosuccinimide. This tetrabromide gave an immediate precipitate with alcoholic silver nitrate. Only two bromides were removed by hydrolysis with sodium hydroxide to give 4,6-bis-methoxymethyl-3,5-dibromo-2-pyridol (VI). VI did not react with silver nitrate. Bromination of 4,6-dimethyl-2-aminopyridine under the conditions which produced a tetrabromo derivative of IV yielded only II. Neither II nor III would react further with N-bromosuccinimide to form a tetrabromide.

These results made apparent the pronounced activation of the pyridine ring to N-bromosuccinimide by an α-amino or α-hydroxyl group. It was proposed that, as in the aniline–acetanilide relationship, acetylation of the amino group would decrease the activity of the ring thereby permitting side-chain reaction. To test this hypothesis 2-acetamino-4,6-dimethylpyridine (VII) was prepared. As anticipated, this compound was less reactive; but instead of reacting with N-bromosuccinimide to form bromomethyl derivatives, it reacted even in the presence of benzoyl peroxide and ultraviolet light, to form a monobromide, 2-acetamino-5-bromo-4,6-dimethylpyridine (VIII). The location of the bromine atom in this molecule was shown by unambiguous methods.

VIII was hydrolyzed to 2-amino-5-bromo-4,6-dimethylpyridine (IX) which on diazotization yielded 5-bromo-4,6-dimethyl-2-pyridol (X). Direct bromination of 3-cyano-4,6-dimethyl-2-pyridol in acetic acid gave 3-cyano-5-bromo-4,6-dimethyl-2-pyridol[13] which on hydrolysis and decarboxylation with 50% sulfuric acid gave a compound identical with X. The isomeric compound, 3-bromo-4,6-dimethyl-2-pyridol, was prepared by the reaction of bromine with the silver salt of 3-carboxy-4,6-dimethyl-2-pyridol. The product of this reaction melted twenty degrees below X; their mixed melting point showed a sharp depression. Kerp[14] has reported the preparation of 3-(or 5)-bromo-4,6-dimethyl-2-pyridol by the reaction of a monobromo-4,6-dimethyl-2-pyrone with ammonia in a sealed tube. The product of his reaction melted at 186–187°; as X melts at 241–242° and XI at 226–228°, the compound reported by Kerp was probably a mixture of the two isomers. Direct bromination of X gave III, indicating further the location of the bromine on the pyridine nucleus.

The various compounds prepared in this study have made possible an interesting study of the keto-

(9) D. Molho and C. Mentzer, *Compt. rend.*, **224**, 471 (1947).
(10) J. LeCocq and Ng. Ph. Buu-Hoï, *ibid.*, **224**, 937 (1947).
(11) D. Molho and C. Mentzer, *ibid.*, **223**, 1141 (1946).
(12) J. Moir, *J. Chem. Soc.*, **81**, 100 (1902).
(13) J. Guareschi, *Ber.*, **26**, 943 (1893).
(14) W. Kerp, *Ann.*, **274**, 267 (1893).

enol equilibrium in the 2-pyridols and of their basicity as indicated by their formation of picrates. The 4,6-dimethyl-2-pyridol gives an immediate strong color with ferric chloride and easily forms a picrate.[3b] The monobromopyridols (X and XI) and the dibromopyridols give only faint coloration to a solution of ferric chloride indicating that both exist largely in the 2(1)-pyridone structure. There is, however, an observable difference apparently due to a difference in basicity in their formation of picrates. A picrate is easily formed by X; V does not form one even on long standing in a saturated picric acid solution. However, application of this hypothesis to the aminopyridines shows such a conclusion to be unwarranted as IX, a monobromide, forms only a monopicrate, but II, a dibromide with a theoretically less basic ring nitrogen, easily forms a dipicrate. Similar irrationality in the formation of salts has been observed previously with 2-aminomethyl-4,6-dimethyl-2-methoxypyridine[3b] which easily forms a dihydrochloride, a diacetate, but only a monopicrate. Perhaps then the nature of the picrate isolated depends only on their relative insolubility. The results of the ferric chloride color test in these studies[3] have been more predictable; a strongly electronegative group in the β-position of an α-pyridol will favor the pyridone structure, *i.e.*, β-cyano-α-pyridols and β-carboxy-α-pyridols always give negative results. Reduction of the electronegativity of these groups by either reduction or esterification, respectively, forms compounds which exist largely as pyridols, giving positive ferric chloride color tests.

Experimental[15]

4,6-Dimethyl-2-aminopyridine (I).—The crude material obtained from Reilly Tar and Chemical Company was recrystallized from hexane to shiny white platelets, m.p. 69–70°.

The picrate was prepared, m.p. 205–207° (dec.).

Anal. Calcd. for $C_{19}H_{16}N_8O_{14}$: N, 19.3. Found: N, 19.4.

3,5-Dibromo-4,6-dimethyl-2-aminopyridine (II).—(a) To a solution of 2 g. of I in 50 ml. of glacial acetic acid and 10 ml. of water was added dropwise with stirring 6 g. of bromine in 10 ml. of glacial acetic acid. The amine hydrobromide crystallized out on standing (61% yield); it was recrystallized from 95% ethanol to pale yellow needles, m.p. 225–226°.

Addition of sodium bicarbonate solution to an aqueous suspension of these needles gave the free base which, after recrystallization from 80% ethanol, melted 136–136.5°. An alcoholic solution gave no precipitate with alcoholic silver nitrate.

Anal. Calcd. for $C_7H_8Br_2N_2$: N, 10.0. Found: N, 10.0.

The dipicrate was prepared, m.p. 200–201° (dec.).

Anal. Calcd. for $C_{19}H_{14}Br_2N_8O_{14}$: N, 15.2. Found: N, 15.5.

(b) II was also prepared by the reaction of I with N-bromosuccinimide. To a solution of 2 g. of I in 150 ml. of dry carbon tetrachloride was added 5.8 g. of N-bromosuccinimide[16] and 0.1 g. of benzoyl peroxide. The reaction mixture was refluxed in a quartz flask under ultraviolet light for five hours; during this time the solution gradually became a dark red-brown. The mixture was cooled, the succinimide removed by filtration, and the filtrate distilled to dryness under reduced pressure. The dark gummy residue, recrystallized from 80% ethanol, gave white needles, m.p. 136–137° (65% yield). It did not depress the melting point of II prepared by method (a).

The reaction of 3.0 g. of I with 15.0 g. of N-bromosuccinimide in the presence of 0.6 g. of benzoyl peroxide was carried out in the same manner. II was obtained in 80% yield.

II was recovered in 95% yield after refluxing 2 g. in 50 ml. of absolute methanol containing 0.2 g. of sodium for 24 hours followed by neutralization.

The starting material II was also recovered in 80% yield when 1.5 g. of II, 2.0 g. of N-bromosuccinimide and 0.1 g. of benzoyl peroxide were refluxed in 150 ml. of dry carbon tetrachloride in a quartz flask under ultraviolet light for six hours.

3,5-Dibromo-4,6-dimethyl-2-pyridol (III) (**a**) **From II.**—To a hot solution of 1 g. of II in 65 ml. of water and 10 ml. of concentrated hydrochloric acid was added with swirling 0.5 g. of sodium nitrite dissolved in 5 ml. of water. Fumes of oxides of nitrogen were evolved, and a white precipitate appeared immediately. This precipitate was recrystallized from glacial acetic acid, m.p. 236–237° (75% yield). It did not form a picrate; it gave no precipitate with alcoholic silver nitrate; it gave a faintly positive ferric chloride color test.

(**b**) From IV.—The dropwise addition of 0.4 g. of bromine in 20 ml. of glacial acetic acid to a solution of 0.5 g. of IV[3b] in 40 ml. of glacial acetic acid gave III, m.p. 236–237° (67% yield). Six recrystallizations from methanol–acetic acid did not raise the melting point although it has been reported as 236°[14] and 253°.[12]

4,6-Bis-bromomethyl-3,5-dibromo-2-pyridol (V).—A mixture of 1.5 g. of IV, 5.4 g. of N-bromosuccinimide and 0.2 g. of benzoyl peroxide in 150 ml. of dry carbon tetrachloride was refluxed for 30 minutes in a quartz flask under ultraviolet light. An additional 0.1 g. of benzoyl peroxide was added and refluxing continued for seven hours. The cooled solution was treated as above. Distillation of the filtrate and recrystallization of the oily residue from glacial acetic acid gave V in 29% yield, white needles, m.p. 154–156°. This gave a faintly positive ferric chloride color test and a heavy precipitate with alcoholic silver nitrate. It did not form a picrate.

Anal. Calcd. for $C_7H_5Br_4NO$: Br, 72.9. Found: Br, 72.8.

Digestion of the succinimide precipitate with 48% hydrobromic acid followed by filtration and neutralization gave III in 49% yield. The same reaction carried out in the absence of ultraviolet light and using only 0.1 g. *in toto* of benzoyl peroxide gave only III.

4,6-Bis-methoxymethyl-3,5-dibromo-2-pyridol (VI).—A solution of 1 g. of V in 25 ml. of absolute methanol containing 0.1 g. of freshly cut sodium was refluxed for 24 hours. Neutralization of the reaction mixture to *p*H 8 gave white needles, m.p. 189.5–191°. This compound gave a very weak ferric chloride color test.

Anal. Calcd. for $C_9H_{11}Br_2NO_3$: N, 4.1. Found: N, 4.5.

2-Acetamino-4,6-dimethylpyridine (VII).—A solution of 10 g. of I in 50 ml. of freshly distilled acetic anhydride containing 0.1 g. of fused sodium acetate was refluxed for three hours. The unreacted anhydride was decomposed by dropwise addition of water through the condenser. The solution was then neutralized with sodium bicarbonate and allowed to stand overnight. The acetylated material was removed by filtration (73% yield); recrystallized from water containing a little ethanol, it melted at 157–158°.

Anal. Calcd. for $C_9H_{12}N_2O$: N, 17.1. Found: N, 17.1.

The picrate melted at 171–172°.

Anal. Calcd. for $C_{15}H_{15}N_6O_8$: N, 17.8. Found: N, 18.0.

2-Acetamino-5-bromo-4,6-dimethylpyridine (VIII).—To a suspension of 2 g. of VII in 150 ml. of dry carbon tetrachloride in a quartz flask was added 4.2 g. of N-bromosuccinimide and 0.1 g of benzoyl peroxide. The mixture was refluxed under ultraviolet light for four hours; an additional 0.1 g. of benzoyl peroxide was added after the first ten minutes of reaction. At no time during the reaction was solution complete. The reaction mixture was cooled, filtered and the precipitate suspended in dilute (1:1) hydrochloric acid. Addition of excess sodium bicarbonate to this suspension decomposed the unreacted N-bromosuccinimide and dissolved the succinimide leaving VIII as precipitate. The

(15) Carbon, hydrogen and nitrogen analyses by Misses Sorensen and Brauer; bromine analysis by Micro-Tech Laboratories, Skokie, Illinois.

(16) K. Zeigler, A. Spaeth, E. Schaaf, W. Schumann and E. Winkelmann, *Ann.*, **551**, 80 (1942).

product was isolated in essentially 100% yield and, recrystallized from 50% ethanol, melted at 216–217°.

Anal. Calcd. for $C_9H_{11}BrN_2O$: N, 11.5. Found: N, 11.6.

The picrate was prepared, m.p. 166–167°.

Anal. Calcd. for $C_{15}H_{14}BrN_5O_8$: N, 14.8. Found: N, 14.7.

2-Amino-5-bromo-4,6-dimethylpyridine (IX).—A solution of 1.5 g. of VIII in 35 ml. of 15% sodium hydroxide was refluxed for two hours. The free base separated out on cooling as fluffy white crystals, m.p. 145–146°. A mixture of this with II melted at 90–95°.

Anal. Calcd. for $C_7H_9BrN_2$: N, 13.9. Found: N, 14.1.

The monopicrate was prepared, m.p. 226–228°.

Anal. Calcd. for $C_{13}H_{12}BrN_5O_7$: C, 36.29; H, 2.81; N, 16.3. Found: C, 36.73; H, 2.76; N, 16.3.

5-Bromo-4,6-dimethyl-2-pyridol (X) (a) From IX.—A solution of 0.5 g. of IX in 30 ml. water and 10 ml. of concd. hydrochloric acid was heated to boiling and filtered. To the clear hot filtrate was added with swirling a solution of 0.5 g. of sodium nitrite in 10 ml. of water. Fumes of oxides of nitrogen were evolved. On cooling, a white precipitate X was isolated in 78% yield. This was recrystallized from 95% ethanol, m.p. 240–241°. A mixture of this with III melted at 200–205°. It gave a weak ferric chloride color test and was not affected by boiling water nor boiling alcoholic silver nitrate.

Anal. Calcd. for C_7H_8BrNO: N, 6.9. Found: N, 6.7.

The picrate was prepared, m.p. 195–197°.

Anal. Calcd. for $C_{13}H_{11}BrN_4O_8$: N, 13.0. Found: N, 13.5.

The addition of an excess of bromine to an acetic acid solution of X in glacial acetic acid gave III, m.p. 235–236°. This sample of III did not depress the melting point of III prepared by the above methods.

(b) From **3-Cyano-4,6-dimethyl-2(1)-pyridone.**—The bromination of 3-cyano-4,6-dimethyl-2(1)-pyridone in glacial acetic acid gave 5-bromo-3-cyano-4,6-dimethyl-2(1)-pyridone in 80% yield even though neither the starting material nor the product are appreciably soluble in this solvent. Recrystallized from 70% ethanol, it melted at 259–260°. A solution of 1 g. of this compound in 22 ml. of sulfuric acid (50% by volume) was refluxed for five hours. The reaction mixture was poured into 100 ml. of a slurry of ice and water containing 17 g. of sodium hydroxide. The neutralization was completed with sodium bicarbonate. The insoluble product was isolated as fluffy white crystals (85% yield). Recrystallized from 95% ethanol it melted at 241–242° and did not depress the melting point of X prepared by method (a).

3-Bromo-4,6-dimethyl-2-pyridol (XI).—The silver salt of 3-carboxy-4,6-dimethyl-2-pyridol[3b] was prepared according to the method of Barnes and Prochaska.[17] To a suspension of 0.25 g. of the dry salt in 25 ml. of dry carbon tetrachloride was added an equivalent amount of dry bromine. The reaction mixture was refluxed on a steam-bath for five hours, cooled, and filtered. The filtrate was distilled to dryness under reduced pressure. The residue recrystallized from 95% ethanol gave white crystals, m.p. 228–229°. A mixture of this with X melted at 180–185°. It gave a weak ferric chloride color test.

Anal. Calcd. for C_7H_8BrNO: N, 6.9. Found: N, 7.2.

(17) R. A. Barnes and R. J. Prochaska, THIS JOURNAL, **72**, 3188 (1950).

EVANSTON, ILLINOIS RECEIVED NOVEMBER 5, 1951

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Antispasmodics. III. N-Methyl-2(4)-(ω-R-ω-phenylalkyl)-piperidines and 2-R-2-Phenyl-4(5)-(N-methyl-4-piperidyl)-alkanenitriles

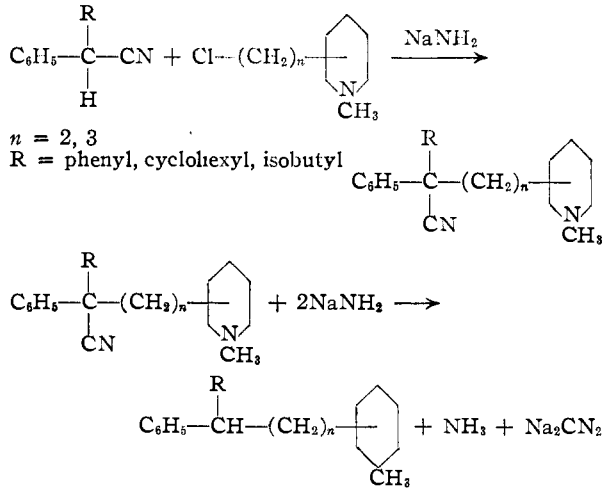
BY A. WAYNE RUDDY[1] AND HOWARD W. BISHOP

A series of amines has been synthesized to determine the effect on spasmolytic activity of moving various ω-substituted phenylalkyl groups from the nitrogen into the 2- and 4-positions of the piperidine ring. 2-R-2-Phenyl-4(5)-(N-methyl-2(4)-piperidyl)-alkanenitriles have been prepared where R is phenyl, cyclohexyl and isobutyl. The corresponding N-methyl-2(4)-(ω-R-ω-phenylalkyl)-piperidines were obtained from these nitriles by treatment with excess sodamide. The most active compound in the series was 2-(3,3-diphenylpropyl)-N-methylpiperidine methiodide.

In continuing work in these laboratories on spasmolytics it was believed that the availability of the 2- and 4-pyridylethanols and propanols offered an excellent opportunity to study the effect on spasmolytic activity of moving various ω-substituted phenylalkyl groups from the 1-position[2] into the 2- and 4-positions of the piperidine ring.

Although a number of phenylalkylpiperidines have been reported, a literature search revealed only one substituted phenylalkylpiperidine, N-methyl-3-benzhydrylpiperidine[3] and no N-methyl-2(4)-(ω-R-ω-phenylalkyl)-piperidines. The only piperidylphenylacetonitriles found were α-phenyl-α-(N-methyl-3-piperidyl)-acetonitrile[4] and α,α-diphenyl-(N-methyl-3-piperidyl)-acetonitrile[5] prepared by alkylating the nitriles with N-methyl-3-chloropiperidine.

From the 2- and 4-pyridylalkanols were prepared the corresponding N-methylpiperidylalkanols which were then chlorinated with thionyl chloride to give the N-methyl-2- and 4-piperidylethyl chloride and propyl chloride hydrochlorides. These basic side chains were used to alkylate diphenylacetonitrile,



(1) Chilcott Laboratories, Morris Plains, N. J.

(2) A. W. Ruddy, THIS JOURNAL, **73**, 4096 (1951).

(3) M. Bockmühl, E. Ehrhart and L. Stein, U. S. Patent 2,446,522, Aug. 10, 1948.

(4) Society of Chemical Industry of Basle, British Patent 589,625.

(5) I. G. Farbenindustrie A. G., German patent 731,560, Jan. 14, 1943.