Experimental

1. **Dianisylvinyl Bromide and Magnesium.**—Because of the difficulty to induce the grignardization of this bromide we used the entrainment method:

A Grignard solution was prepared from dianisylvinyl bromide (1.6 g.), methyl iodide (0.7 g.) and magnesium (0.27 g.) in ether (40 cc.). After one hour of reflux 3 g. of (II) was added and the mixture was again refluxed for thirty-six hours. A yellow precipitate formed in the mixture. After treatment with dilute sulfuric acid the yellow material was filtered off and washed with ether; m. p. 204°, yield 0.85 g. (25%). Recrystallization from butyl acetate gave yellow needles of m. p. 206–207°, which showed no m. p. depression upon admixture of (III). No attempt was made to isolate the ether-soluble reaction products.

2. **Catalytic Reduction of 1,1,4,4-Tetraanisylbutadiene.**—The diene (1.2 g.), suspended in ethyl acetate (40 cc.), absorbed 155 cc. of hydrogen in the presence of Adams platinum oxide (0.5 g.) within two hours (calcd. for 31°, 755 mm., 164 cc.). The oily reduction product crystallized after treatment with *n*-hexane and was obtained from a benzene–methanol mixture as white rods of m. p. 121°; yield, 1.1 g.

Anal. Calcd. for $C_{32}H_{34}O_4$: C, 79.67; H, 7.05. Found: C, 79.64; H, 7.12.

3. **Condensation of Dianisylethylene and Dianisylvinyl Bromide.**—The bromide (640 mg.) and the ethylene (480 mg.) were thoroughly mixed and heated in an oil-bath with the exclusion of moisture. The mixture melts at 100–110° and gives off fumes of hydrogen bromide. After a few minutes it resolidifies. It was kept at 120° for ten hours and then treated with butyl acetate; yield 0.95 g. (quantitative), m. p. 203–204°. Recrystallization from the same solvent gave yellow rods of m. p. 206–207°, identical with the two previous preparations of (III).

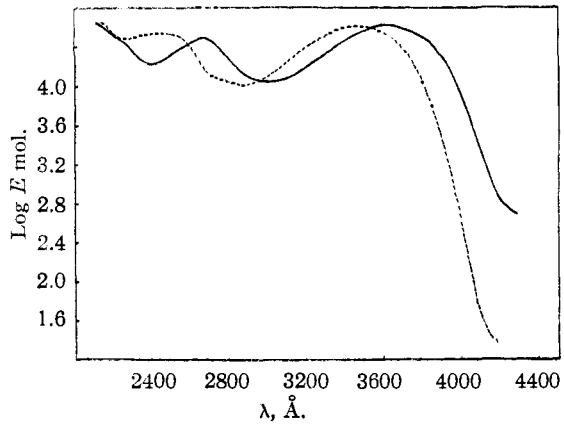

Fig. 1.—Ultraviolet absorption spectrum of — 1,1,4,4-tetraanisylbutadiene, ------ 1,1,4,4-tetraphenylbutadiene.

4. **Absorption Spectra.**—The spectra were measured in 95% ethanol by a Beckman quartz spectrophotometer.

Summary

The so-called "dimer," obtained in the bromination of dianisylethylene, is shown to be 1,1,4,4-tetraanisylbutadiene. The same substance can be prepared by interaction of dianisylethylene and dianisylvinyl bromide. The mechanism of this reaction is discussed.

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[CONTRIBUTION NO. 175 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

3-Pyridols in the Mannich Reaction[1]

BY ARTHUR STEMPEL AND ELAINE C. BUZZI

The Mannich reaction with phenols has recently been extended to 3-pyridols in attempts to prepare pyridoxine,[2] its analogs,[3] and antagonists.[4] A Mannich type of reaction employing sodium hydroxide instead of organic amines for the direct introduction of hydroxymethyl groups in 3-pyridols has also been reported.[5] Since the directive influence of the phenolic group has been studied only in cases where the ortho position is unsubstituted,[5] the following investigation of the scope and direction of the Mannich reaction with 3-pyridols was undertaken.

The substituted 3-pyridol reacted rapidly with formaldehyde and dialkylamines, alkarylamines, and heterocyclic amines such as piperidine and morpholine to give 2-(substituted amino)-methyl-3-pyridols in good yield. In all cases, the products were most readily isolated by distillation *in vacuo*. Where the products were solid, purification by distillation was still preferable to crystallization. The basic pyridols appear to be stable to heat with the exception of 2-di-*n*-butylaminomethyl-3-pyridol which showed signs of decomposition during distillation. Although attempts to prepare an analytically pure crystalline dihydrochloride of this compound were unsuccessful, it has been included since, in work to be reported at a later date, an ester of the correct analysis has been isolated. In general, these compounds have been characterized as the dihydrochlorides. The side chain basic group reacts readily with one mole of methyl bromide in the cold to give nicely crystalline quaternary salts. Quaternization of the pyridine nitrogen requires higher temperatures. Compounds of this type are listed in Table I.

By the catalytic debenzylation of 2-(N-methylbenzylaminomethyl)-3-pyridol, 2-methylaminomethyl-3-pyridol was readily prepared. In this manner, by the selection of the proper N-sub-

(1) Presented at the Meeting-in-Miniature of North Jersey Section, American Chemical Society, January 10, 1949.

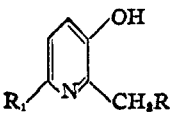
(2) Perez-Medina, Mariella and McElvain, THIS JOURNAL, **69**, 2574 (1947).

(3) Brown and Miller, *J. Org. Chem.*, **11**, 388 (1946).

(4) (a) Martin, Avakian and Moss, *J. Biol. Chem.*, **174**, 495–500 (1948); (b) Martin and Avakian, U. S. Patent 2,455,259, November 30, 1948.

(5) Urbanski, (a) *J. Chem. Soc.*, 1104-1105 (1946); (b) 132-134 (1947).

TABLE I



R	R_1	B. p. °C.	Mm.	Yield, %	M. p., °C.[c]	Hydrochloride analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$N(CH_3)_2$	H	95–96	8[a]	70	178–186	42.68	6.27	12.44	42.80	6.54	12.23
$N(C_2H_5)_2$	H	85–92	1	61	195–197	47.43	7.16	11.07	47.54	7.15	11.06
$N(C_3H_7)_2$	H	103–105	1	44	164–168	51.25	7.89	9.96	51.44	7.62	10.06
$N(C_4H_9)_2$	H	112–114	1.4	51							
NC_5H_{11}	H	153–158	11	74	201–203	49.82	6.84		50.09	6.64	
NC_4H_8O	H	163–167	12[b]	77	206–211	44.95	6.04	10.48	45.07	6.32	10.51
$N(CH_3)CH_2C_6H_5$	H	135–137	0.7	63	210–212	55.82	6.02	9.30	56.13	5.99	9.35
$NH(CH_3)$	H				231–233	39.82	5.73		40.14	5.63	
$N(CH_3)_2$	CH_3	121–125	13		202–206	45.20	6.74	11.71	44.76	6.44	11.75
$N(CH_3)CH_2C_6H_5$	CH_3	157–160	2.7		196–198	56.81[d]	6.85	8.28	56.31	6.65	8.38
$NH(CH_3)$	CH_3				226–230	42.69	6.27	12.44	42.47	6.18	12.28

[a] M. p. 56–59°. [b] M. p. 91–94°. [c] Dihydrochloride, m. p. with dec. [d] Contains 0.5 C_2H_5OH: Cl, calcd., 20.96; found, 20.69.

stituted benzylamine, a series of the secondary amines may be prepared.

The extension of this reaction to the preparation of 2-(N-methylanilinomethyl)-3-pyridol by the reaction of 3-pyridol with formaldehyde and methylaniline was unsuccessful. This compound was, however, prepared with little difficulty by the reaction of 2-bromomethyl-3-pyridol hydrobromide[5a] with methylaniline. The extreme reactivity of the bromine in the side chain made it impossible to isolate free 2-bromomethyl-3-pyridol but the base was prepared in organic solvent by the use of an excess of amine to neutralize the hydrobromic acid. This approach allows the preparation of compounds similar to those obtained by the Mannich reaction in cases where the latter reaction does not occur.

In the preparation of 2-hydroxymethyl-3-pyridol, Urbanski[5a] proved that the hydroxymethyl group is in the 2-position. As proof that the Mannich reaction took the same course, 2-diethylaminomethyl-3-pyridol was synthesized by the reaction of 2-bromomethyl-3-pyridol hydrobromide with diethylamine and on reaction with methyl bromide, (3-hydroxy-2-pyridylmethyl)-diethylmethylammonium bromide was obtained, identical with the substance made by treating the product of a Mannich reaction between 3-pyridol, formaldehyde and diethylamine with methyl bromide.

Brown and Miller[3] have carried out the Mannich reaction with 6-methyl-3-pyridol,[6] formaldehyde and diethylamine, di-*n*-butylamine and piperidine, respectively. In this work we have also used dimethylamine[4a] and methylbenzylamine and prepared the secondary amine by the catalytic debenzylation of the tertiary amine. These compounds are listed in Table I.

It is evident from the work of Urbanski[5b] and Martin and Avakian[4] that the basic group enters the 2-position in 6-methyl-3-pyridol.[7]

A further proof that the basic groups entered the 2-position and not the 4-position was established as follows. In carrying out Urbanski's preparation of 2-hydroxymethyl-3-pyridol, a fraction, isolated as the hydrochloride, was found which analyzed for $C_7H_9O_2N \cdot HCl$ indicating that two hydroxymethyl groups had entered the pyridine ring. The yield was about 20%. Heating with 48% hydrobromic acid gave the corresponding bis-bromomethyl-3-pyridol and this was then reduced to the dimethylpyridol. The product is 2,6-dimethyl-3-pyridol[8] since the same compound was obtained by reduction of 6-methyl-2-bromomethyl-3-pyridol hydrobromide prepared from 6-methyl-3-pyridol.[5b]

The bis-hydroxymethyl compound is probably formed by a secondary reaction between 2-hydroxymethyl-3-pyridol and formaldehyde. This would indicate that the Mannich reaction would probably occur in the 6-position if the 2-position were blocked.

In order to obtain 2-methyl-3-pyridol for further study of the effect of a blocking group in the 2-position, a series of reactions were carried out with the indicated yields

$$\text{3-Pyridol} + CH_2O + (CH_3)_2NH \xrightarrow{70\%} \text{2-Dimethylaminomethyl-3-pyridol} \xrightarrow[87\%]{Ac_2O}$$

(6) McElvain and Goese, THIS JOURNAL, 65, 2233 (1943), and Parker and Shive, *ibid.*, 69, 63 (1947), have shown that the product isolated by sulfonation of α-picoline and subsequent alkali fusion is 6-methyl-3-pyridol and not the 2-methyl-3-pyridol claimed by Brown and Miller[3] and Wolff, U. S. Patent 1,880,645-6 (1932).

(7) The structure of 2-methyl-4-dimethylaminomethyl-3-pyridol proposed by Brown and Miller[3] for the Mannich product was accepted by Martin and Avakian[4] and their end-product was, therefore, erroneously assumed to be 2-methyl-4-hydroxymethyl-3-pyridol.

(8) Plazek, *Ber.*, 72, 577 (1939), prepared 2,6-dimethyl-3-pyridol by nitration of 2,6-lutidine, reduction of the nitro compound to the amine, and diazotization. The product melted at 209°, and the material obtained above melted at 203–204° (uncor.).

2-Acetoxymethyl-3-acetoxypyridine $\xrightarrow[82\%]{48\%\ HBr}$ 2-Bromomethyl-3-pyridol hydrobromide $\xrightarrow[90\%]{H_2 + Pd}$ 2-Methyl-3-pyridol hydrobromide

The over-all yield in a typical run was 45%.

The process has the advantage that the product of the Mannich reaction is readily purified by distillation while the Urbanski method yields an impurity in the preparation of 2-hydroxymethyl-3-pyridol, as shown above, which must be removed by fractional crystallization.

The final proof that the basic group would enter in the 6-position if the 2-position were blocked was hoped to be obtained by the conversion of 2-methyl-3-pyridol to 2,6-dimethylpyridol by the series of reactions shown above for the preparation of 2-methyl-3-pyridol from 3-pyridol. The reactions of 2-methyl-3-pyridol have proved to be unlike those of the isomeric 6-methyl-3-pyridol. We have as yet been unable to isolate any pure product from the reaction of 2-methyl-3-pyridol with formaldehyde and dimethylamine or sodium hydroxide. When the first reaction of the series was carried out using diethylamine, the crude product was acetylated directly without further purification but instead of the expected replacement of the basic group by an acetoxy group, a readily distillable acetate was obtained which on hydrolysis by heating with 48% hydrobromic acid gave the hydrobromide of 2-methyl-6(?)-diethylaminomethyl-3-pyridol. The unusual resistance of the basic group to attack by acetic anhydride is in marked contrast with the behavior of the isomeric 6-methyl-2-diethylaminomethyl-3-pyridol.[4]

Investigation of the position of the basic group in the Mannich reaction with 2-methyl-3-pyridol is still in progress, since the possibility of reaction in the 4-position has not been ruled out. However, Perez-Medina, Mariella and McElvain[2] could not isolate any product after an attempted Mannich reaction with 2-methyl-5-hydroxymethyl-3-pyridol.

There is also the possibility of reaction on the methyl group in the α-position although α-picoline itself gives only small yields of a Mannich base. In the case of 6-methyl-3-pyridol there has been no evidence of reaction on the methyl groups.

Experimental

The preparation of 2-dimethylaminomethyl-3-pyridol is representative of the compounds listed in Table I.

2-Dimethylaminomethyl-3-pyridol.—To a solution of 41 g. of 3-pyridol in 65 cc. of water and 67 cc. of a dimethylamine solution (19.5 g. of dimethylamine), 36 cc. of a 35% formalin solution was added. After heating on a steam-bath for two hours, the solvent was removed by distillation *in vacuo* and the residue distilled. The fraction distilling at 86–96° (3.7 mm.) was collected as a light yellow oil that crystallized rapidly; yield, 46 g. (70%). It could be further purified by sublimation *in vacuo* at 60° and 0.3 mm.; m. p. 56–59°.

Anal. Calcd. for $C_8H_{12}ON_2$: N, 18 41. Found: N, 17.86.

Diacetate of 2-Hydroxymethyl-3-pyridol.—A solution of 10 g. of 2-dimethylaminomethyl-3-pyridol in 35 cc. of acetic anhydride was refluxed for one and one-half hours. The solution turned dark brown soon after heating began. Excess acetic anhydride and acetic acid were removed *in vacuo* and the residue distilled. The product was a light yellow oil distilling at 109–110° (0.8 mm.); literature,[5a] 118–122° (4 mm.); yield, 12 g. (87%).

2-Bromomethyl-3-pyridol Hydrobromide.—A solution of 11 g. of the diacetate of 2-hydroxymethyl-3-pyridol in 60 cc. of 48% hydrobromic acid was refluxed for one-half hour. After distillation of 45 cc. of hydrobromic acid, large crystals of 2-bromomethyl-3-pyridol hydrobromide formed on cooling. The crystals were filtered and washed with a small amount of cold water and acetone: yield, 11.6 g. (82%); m. p. 187–188° (dec.); literature,[5a] 182–184°. A portion of the product was recrystallized from a mixture of methanol and ether; m. p. 186–188° (dec.).

Anal. Calcd. for $C_6H_7ONBr_2$: C, 26.79; H, 2.62; N, 5.21. Found: C, 27.08; H, 2.59; N, 5.35, 5.23.

2-Methyl-3-pyridol.—A solution of 125 g. of 2-bromomethyl-3-pyridol hydrobromide in 1 liter of methanol containing 4–5 g. of 3% palladium on charcoal was shaken at room temperature with hydrogen. The theoretical quantity was taken up rapidly. After removal of the catalyst by filtration, most of the solvent was distilled off and anhydrous ether added to turbidity. Crystals of 2-methyl-3-pyridol hydrobromide formed: yield, 79 g. (90%); m. p. 195–197°. Recrystallization from a mixture of methanol and ether did not change the melting point.

Anal. Calcd. for C_6H_8ONBr: C, 37.92; H, 4.24; N, 7.37. Found: C, 37.72; H, 4.23; N, 7.47, 7.33.

The free base melted at 163–165°; literature, 160–161°,[5b] 167–168°.[9]

2-(N-Methylanilinomethyl)-3-pyridol.—A solution of 23 g. of methylaniline in 10 cc. of chloroform was added slowly to a stirred suspension of 27 g. of 2-bromomethyl-3-pyridol hydrobromide in 250 cc. of chloroform. The temperature rose from 26 to 42° and all the material went into solution. The solution was then heated slowly to reflux. When the temperature reached 50°, a crystalline solid began to separate. The mixture was refluxed for one hour, cooled and the crystalline product filtered off: yield, 26 g. (88%); m. p. 176–180° (dec.). Neutralization with sodium carbonate gave a white crystalline precipitate of 2-(N-methylanilinomethyl)-3-pyridol. After recrystallization from 80% ethanol, the product melted at 136–138°; yield, 16 g.

Anal. Calcd. for $C_{13}H_{14}ON_2$: C, 72.87; H, 6.55; N, 13.06. Found: C, 72.91; H, 6.59; N, 12.67.

(3-Hydroxy-2-pyridylmethyl)-diethylmethylammonium Bromide.—To a suspension of 5 g. of 2-bromomethyl-3-pyridol hydrobromide in 50 cc. of chloroform, 6 cc. of diethylamine was added slowly. The mixture became very warm and all the solid went into solution. After refluxing for one-half hour, the solvent was boiled off and the residue dissolved in water. After neutralization with sodium bicarbonate and evaporation to dryness, an acetone extract of the residue was treated with a 25% solution of methyl bromide in acetone. On standing in the refrigerator, crystals of (3-hydroxy-2-pyridylmethyl)-diethylmethylammonium bromide formed. After recrystallization from a mixture of methanol and ether, the product melted at 132–133° (dec.).

Anal. Calcd. for $C_{11}H_{19}ON_2Br$: C, 48.01; H, 6.96; N, 10.18. Found: C, 48.08; H, 7.13; N, 10.04.

2-Methylaminomethyl-6-methyl-3-pyridol Dihydrochloride.—To a prehydrogenated suspension of 1 g. of 3% palladium on charcoal in 50 cc. of methanol, 2.0 g. of (3-hydroxy-6-methyl-2-pyridylmethyl)-methylbenzylamine dihydrochloride was added. The theoretical amount of hydrogen was taken up after shaking for one-half hour at atmospheric pressure. The catalyst was removed by filtration and the solvent distilled off. The product was recrystallized from ethanol; m. p. 226–230° (dec.).

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

2,6-bis-Hydroxymethyl-3-pyridol Hydrochloride.—Nineteen grams of 3-pyridol was dissolved in 100 cc. of an aqueous solution containing 8 g. of sodium hydroxide. After addition of 42 cc. of a 35% formaldehyde solution, the reaction mixture was kept at room temperature for one hour and then heated on the steam-bath for two hours. The color was a light amber. It was then cooled, acidified with 15 cc. of glacial acetic acid, concentrated to dryness *in vacuo*, and the solid residue extracted with 2 liters of boiling acetone. After removal of the acetone by distillation, the residue was dissolved in about 200 cc. of 9 *N* alcoholic hydrochloric acid. Crystals formed within five minutes. They were kept in the refrigerator overnight, filtered, washed with acetone, and dried; yield, 28 g. About 16 g. of this material was dissolved in 50 cc. of water and acetone added to turbidity. Overnight in the refrigerator, 1.4 g. of 2-hydroxymethyl-3-pyridol hydrochloride crystallized. The melting point was not sharp but the compound darkened slowly above 170° and then decomposed above 200°. On addition of acetone to the filtrate, an additional 2.6 g. of the same material was isolated. At this point, 1175 cc. of acetone had been added. Addition of 900 cc. of acetone to the filtrate gave 10.5 g. of crystalline material, m. p. 135–139°. This fraction was recrystallized from 30 cc. of water and 300 cc. of acetone. This gave 5 g. of 2,6-bis-hydroxymethyl-3-pyridol hydrochloride, m. p. 143–146°. An additional 3.6 g. melting at 136–144° was isolated from the mother liquors. Recrystallization of the product melting at 143–146° from a mixture of methanol and ether raised the m. p. to 145–147°.

Anal. Calcd. for $C_7H_{10}O_2NCl$: C, 43.87; H, 5.26; N, 7.31; Cl, 18.50. Found: C, 44.37; H, 5.37; N, 7.61; Cl, 18.21, 18.52.

2,6-bis-Bromomethyl-3-pyridol Hydrobromide.—A solution of 4.5 g. of 2,6-bis-hydroxymethyl-3-pyridol hydrochloride in 100 cc. of 48% hydrobromic acid was refluxed for one hour. On concentration to a small volume *in vacuo*, crystals of 2,6-bis-bromomethyl-3-pyridol hydrobromide separated. They were filtered, washed with cold water, acetone, and ether, and dried, m. p. 186–188°. Two recrystallizations from a mixture of methanol and ether raised the m. p. to 188–190°.

Anal. Calcd. for $C_7H_8ONBr_3$: C, 23.23; H, 2.23; N, 3.87. Found: C, 23.16; H, 2.04; N, 3.88.

2,6-Dimethyl-3-pyridol.—To a prehydrogenated suspension of 1 g. of 3% palladium on charcoal in 50 cc. of methanol, 2.4 g. of 2,6-bis-bromomethyl-3-pyridol hydrobromide was added. The theoretical amount of hydrogen was taken up rapidly at room temperature and atmospheric pressure. After removal of the catalyst by filtration, most of the solvent was distilled off. Anhydrous ether was then added to turbidity and crystallization of 2,6-dimethyl-3-pyridol hydrobromide occurred rapidly on scratching; m. p. 183–185°. Recrystallization from a mixture of methanol and ether did not change the m. p.

Anal. Calcd. for $C_7H_{10}ONBr$: C, 41.20; H, 4.94; N, 6.86. Found: C, 40.83; H, 5.03; N, 6.90, 6.98.

The free base, m. p. 200–203°, was purified for analysis by sublimation at 0.4 mm. and a bath temperature of 100–110°. The sublimate melted at 202.5–204°.

Anal. Calcd. for C_7H_9ON: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.12; H, 7.40; N, 11.38, 11.47.

Acetate of 2-Methyl-6(?)-diethylaminomethyl-3-pyridol.—To a solution of 10.9 g. of 2-methyl-3-pyridol and 7.3 g. of diethylamine in 25 cc. of water, 9 cc. of a 35% formaldehyde solution was added. The mixture was kept at room temperature for five days, and then warmed for one hour on a steam-bath. An oily layer, that seemed to be soluble in the cold and insoluble when hot, began to separate soon after heating began. On removal of the solvent by distillation *in vacuo*, the residue set to a solid. It was dissolved in 75 cc. of acetic anhydride and refluxed for one hour. The excess of acetic anhydride was distilled off *in vacuo* and the residue then distilled. A rough cut boiling at 78° (5 mm.)–120° (0.5 mm.) was taken and then redistilled. The acetate was collected in the fraction boiling at 111–115° (1.4 mm.); yield, 10.5 g.

2-Methyl-6(?)-diethylaminomethyl-3-pyridol.—A solution of 10.5 g. of acetate of 2-methyl-6(?)-diethylaminomethyl-3-pyridol in 50 cc. of 48% hydrobromic acid was refluxed for one-half hour. After removal of 35 cc. of hydrobromic acid by distillation, addition of acetone to the cooled residue gave crystals of 2-methyl-6(?)-diethylaminomethyl-3-pyridol hydrobromide. The product was filtered and washed with acetone. It melted at 219–220° (dec.); yield, 12 g. Recrystallization from a mixture of methanol and ether did not change the melting point.

Anal. Calcd. for $C_{11}H_{20}ON_2Br_2$: C, 37.10; H, 5.66; N, 7.87. Found: C, 37.29; H, 5.59; N, 7.91.

The free base was liberated with sodium carbonate, the solution evaporated to dryness *in vacuo*, and the base extracted with acetone. After removal of acetone, the free base was recrystallized from benzene; m. p. 139–141°.

Anal. Calcd. for $C_{11}H_{18}ON_2$: C, 68.00; H, 9.34; N, 14.42. Found: C, 68.20; H, 9.03; N, 14.26.

Acknowledgment.—The authors wish to express their appreciation to Dr. J. A. Aeschlimann for many helpful discussions during this investigation. We are also indebted to Mr. L. A. Dolan for the preparation of 3-pyridol and to Dr. A. Steyermark and his staff for the microanalyses reported in this paper.

Summary

Methods of preparation of 2-(substituted amino)-methyl-3-pyridols have been described.

The Mannich reaction with 6-methyl-3-pyridol has been extended.

An improved synthesis of 2-methyl-3-pyridol is described.

2,6-bis-Hydroxymethyl-3-pyridol has been isolated as a by-product in the preparation of 2-hydroxymethyl-3-pyridol.

The behavior of 2-methyl-3-pyridol in the Mannich reaction is discussed.

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