Synthesis of 4-Hydroxy-3-isopentylbenzoic Acid.—A solution of 3 g. of ethyl 4-hydroxy-3-(3-methyl-2-butenyl)-benzoate in 50 ml. of ethanol was hydrogenated over 0.5 g. of platinum oxide catalyst. The theoretical amount of hydrogen was absorbed within one hour. After removal of the catalyst by filtration, the alcohol was distilled under reduced pressure. The residue was dissolved in 20 ml. of 4 *N* sodium hydroxide and the solution was heated on the steam-cone for four hours. After acidification with hydrochloric acid, the mixture was extracted with ether. The ether extract was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was dissolved in hot benzene and cyclohexane was added. After cooling, the product was collected on a filter. The product was recrystallized from a mixture of chloroform and cyclohexane; m.p. 108–109°.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.20; H, 7.75. Found: C, 68.98; H, 7.29.

2,2-Dimethyl-6-carboxychroman from Hydrolysis of Cyclonovobiocic Acid.—A solution of 500 mg. of cyclonovobiocic acid in 20 ml. of 2.5 *N* sodium hydroxide was heated on the steam-cone for 18 hours. The dark brown solution was then acidified with dilute sulfuric acid to *ca.* *p*H 2. A dark colored crystalline precipitate formed and was separated, washed with water and dried. The crude product melted at 170–176°, with sublimation on the micro-block at *ca.* 125°. Purification was accomplished by sublimation *in vacuo* and recrystallization of the sublimate from ether by dilution with petroleum ether. The colorless 2,2-dimethyl-6-carboxychroman melted at 178–180°.

The ultraviolet absorption spectrum of the substance in solution (*ca.* *p*H 11) showed a single maximum at 252 mμ and in solution at *ca.* *p*H 2 a maximum at 262 mμ.

This compound proved to be identical with synthetic 2,2-dimethyl-6-carboxychroman and with the sample obtained from Dr. Lauer.[8]

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.90; H, 6.86; mol. wt., 206. Found: C, 69.96; H, 6.52; equiv. wt., 210.

Synthesis of 2,2-Dimethyl-6-carboxychroman.—A solution of 2 g. of ethyl 4-hydroxy-3-(3-methyl-2-butenyl)-benzoate in 15 ml. of methanol and 5 ml. of hydrochloric acid was heated under reflux for one-half hour. After concentration to dryness under reduced pressure, the residue was dissolved in a 15% aqueous solution of sodium hydroxide and the solution was heated for six hours on the steam-cone. After cooling in an ice-bath, the alkaline mixture was neutralized with 2.5 *N* hydrochloric acid. The product was collected. Recrystallization from ethanol gave colorless 2,2-dimethyl-6-carboxychroman melting at 176–178°. The melting point reported in the literature[7] is 176–177°.

The methyl ester was prepared with diazomethane in ether solution. The ester, after recrystallization from ether melted at 79–80°.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 71.03; H, 7.60.

The *p*-bromophenacyl ester was prepared in ethanol solution from the sodium salt of the acid and *p*-bromophenacyl bromide. The ester, after recrystallization from hot ethanol, melted at 149°.

Anal. Calcd. for $C_{20}H_{19}O_4Br$: C, 59.56; H, 4.75. Found: C, 59.36; H, 4.94.

Acknowledgment.—We are grateful to Mr. R. W. Walker and Dr. N. R. Trenner for infrared analyses; Mrs. H. Gager and Mr. F. A. Bacher for potentiometric titrations and ultraviolet absorption analyses; Mr. R. N. Boos and his associates for the microanalyses; and to Dr. D. E. Williams for X-ray determinations.

RAHWAY, NEW JERSEY

[CONTRIBUTION NO. 971 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Pyridylethylation of Active Hydrogen Compounds. V. The Reaction of Ammonia, Certain Amines, Amides and Nitriles with 2- and 4-Vinylpyridine and 2-Methyl-5-vinylpyridine[1]

BY GEORGE MAGNUS AND ROBERT LEVINE

RECEIVED JANUARY 25, 1956

The reactions of (1) a series of amines with 4-vinylpyridine, (2) three nitriles with 2- and 4-vinylpyridine, (3) three amines with 2-methyl-5-vinylpyridine and (4) two amides with 2- and 4-vinylpyridine are reported. The N-pyridylethylated amides, 2- and 4-$C_5H_4NCH_2CH_2NHCOR$ (R = CH_3 and C_2H_5), may be hydrolyzed to the corresponding amines, 2- and 4-$C_5H_4NCH_2CH_2NH_2$, which may also be obtained in good yields by the reactions of 2- and 4-vinylpyridine with ammonium chloride.

In previous papers from this Laboratory, the reactions of ketones[2,3] and primary[4] and secondary[5] amines with 2-vinylpyridine were discussed.

In the present paper we report the results of the reaction of (1) nine amines (two primary and seven secondary) with 4-vinylpyridine, (2) ammonia with 2- and 4-vinylpyridine, (3) three amines with 2-methyl-5-vinylpyridine, (4) two amides with 2- and 4-vinylpyridine and (5) three nitriles with 2- and 4-vinylpyridine.

The results of the additions of the amines to 4-vinylpyridine are found in Table I. It may be seen that cyclohexylamine was pyridylethylated in fair yield using a catalytic amount of acetic acid as the condensing agent. Although under these conditions or when a catalytic amount of sodium metal was used to effect the addition of aniline to 4-vinylpyridine no reaction occurred, the interaction of equivalents of aniline, 4-vinylpyridine and glacial acetic acid in methanol gave a 73.5% yield of 4-(2-anilinoethyl)-pyridine. It may be seen that the secondary amines, with the exception of pyrrole, may be condensed effectively with 4-vinylpyridine using acetic acid or hydrogen chloride as the condensing agent. Furthermore, the pseudo-acid, pyrrole, may be condensed with 4-vinylpyridine in 93% yield if sodium metal instead of an acid is used as the catalyst.

Based on previous work[4,5] there is little doubt that the products obtained from the reactions of 4-vinylpyridine with amines are derivatives of 4-(2-aminoethyl)-pyridine, *i.e.*, 4-$C_5H_4NCH_2CH_2NH_2$. However, to settle this point definitely the structures of two of the products, *i.e.*, the adducts

(1) This work was performed under Contract No. AT(30-1)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.

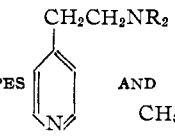
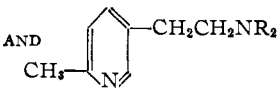
(2) R. Levine and M. H. Wilt, THIS JOURNAL, **74**, 342 (1952).

(3) M. H. Wilt and R. Levine, *ibid.*, **75**, 1368 (1953).

(4) H. E. Reich and R. Levine, *ibid.*, **77**, 5434 (1955).

(5) H. E. Reich and R. Levine, *ibid.*, **77**, 4913 (1955).

TABLE I

AMINES OF THE TYPES  AND 

(A) (B)

NR_2	Catalyst (mole)	Reflux time (hours)	Yield (%)	B.p. °C.	Mm.	Formula	% Nitrogen Calcd.	% Nitrogen Found	M.p., °C.	Picrate Formula	% Nitrogen Calcd.	% Nitrogen Found
(A) 4-Vinylpyridine–Amine Adducts												
NHC_6H_5	HOAc(0.1)[a]	8	0									
	HOAc(0.5)[b]	8	73.5	165–166	3	$C_{13}H_{14}N_2$	14.15	14.26	143.5–144	$C_{25}H_{20}N_8O_{14}$[c]	17.07	16.93
	Na(0.03)[c]	2	0	67–68[d]								
NHC_6H_{11}[f]	HOAc(0.1)[a]	8	33.5	145–147	3	$C_{13}H_{19}N_2$	13.81	13.41	182.5–183.5	$C_{19}H_{23}N_5O_7$[g]	16.17	15.88
	HOAc(0.5)[b]	8	36									
$N(CH_3)_2$	HCl[h]	8	74.2	131–132	37	$C_9H_{14}N_2$	18.66	18.51	159.5–160.5	$C_{21}H_{20}N_8O_{14}$[e,i]		
$N(C_2H_5)_2$	HOAc(0.1)[j]	8	42.7									
		24	79.2	105–107	5	$C_{11}H_{18}N_2$	15.72	16.01	142.5–143	$C_{23}H_{24}O_8O_{14}$[e,k]		
C_4H_4N[l]	Na(0.03)[c]	2	93	146–148	5				136.5–137.5	$C_{17}H_{15}N_5O_7$[g,n]		
				90–91[d]		$C_{11}H_{12}N_2$[m]						
C_4H_8N[o]	HOAc(0.1)[a]	8	80.6	105–107	2	$C_{11}H_{16}N_2$	15.90	16.04	169–170	$C_{23}H_{22}N_8O_{14}$[e]	17.70	17.75
C_4H_8ON[p]	None[q]	20	64.6									
	HOAc(0.1)[a]	8	63	142–144	4	$C_{11}H_{16}N_2O$	14.58	14.44	193–194	$C_{17}H_{19}N_8O_8$[g]	16.62	16.63
$C_5H_{10}N$[r]	HOAc(0.1)[a]	8	88.5	121–122	3	$C_{12}H_{18}N_2$	14.75	15.25	152.5–153.5	$C_{18}H_{21}N_5O_7$[g]	16.70	16.49
$N(C_2H_5)C_6H_5$	HOAc(0.1)[a]	8	12.5	175–176	3.5	$C_{15}H_{18}N_2$	12.80	12.77	136–137	$C_{21}H_{21}N_5O_7$[g]	15.40	15.48
(B) 2-Methyl-5-vinylpyridine–Amine Adducts												
NHC_6H_5	Na(0.06)		75.5[s]	192–194	6	$C_{14}H_{16}N_2$	13.21	13.26	134–135	$C_{21}H_{11}N_3S$[t]	12.10	11.97
			33.6[u]									
C_4H_8ON[p]	Na(0.06)		50.2[u]	122–124	0.5	$C_{13}H_{18}N_2O$	13.59	13.47	213–214	$C_{24}H_{24}N_8O_{15}$[e,v]		
			5.7[s]									
$N(CH_3)C_6H_5$	Na(0.06)		65.0[s]	160–162	1.5	$C_{15}H_{18}N_2$[w]	12.39	13.15	157–158	$C_{27}H_{24}N_8O_{14}$[e]	16.37	16.08
			16.3[u]									

[a] 0.5 mole of amine, 0.5 mole of 4-VP (*i.e.*, 4-vinylpyridine) and 150 ml. of methanol were used. [b] Same as footnote *a* except that 250 ml. of methanol was used. [c] 0.6 mole of amine and 0.3 mole of 4-VP were used. [d] Melting point, recrystallized from 60–70° petroleum ether. [e] Dipicrate. [f] NHC_6H_{11} = the cyclohexylamino radical. [g] Monopicrate. [h] 0.8 mole of the amine as its hydrochloride, 0.4 mole of 4-VP and 250 ml. of methanol were used. [i] *Anal.* Calcd.: C, 41.44; H, 3.28. Found: C, 41.02; H, 3.28. [j] 1.0 mole of amine, 0.5 mole of 4-VP and 150 ml. of methanol were used. [k] *Anal.* Calcd.: C, 43.40; H, 3.77. Found: C, 43.80; H, 4.04. [l] C_4H_4N = the 1-pyrryl radical. [m] *Anal.* Calcd.: C, 76.70; H, 7.02. Found: C, 76.56; H, 6.73. [n] *Anal.* Calcd.: C, 50.87; H, 3.76. Found: C, 50 56; H, 3.75. [o] C_4H_8N = the 1-pyrrolidino radical. [p] C_4H_8ON = the 1-morpholino radical. [q] 0 5 mole of amine was treated with 0.5 mole of 4-VP in the absence of a solvent. [r] $C_5H_{10}N$ = the 1-piperidino radical. [s] The amine (0.6 mole), the vinylpyridine (0.3 mole) and the sodium were mixed and the mixture was maintained at 95–100° for 3 hours. [t] This derivative is a phenylthiourea. [u] The mixture of the amine (0.6 mole) and sodium was warmed to 96°. Then the vinylpyridine (0.3 mole) was added over a one-hour period at 95–100° and the mixture was maintained at this temperature for 3 hours. [v] *Anal.* Calcd.: C, 43.37; H, 3.61. Found: C, 43.15; H, 3.40. [w] Behaved erratically on analysis.

between 4-vinylpyridine and diethylamine and morpholine, were established by showing that they are identical with the materials obtained in low yields by Mannich reactions.[6]

$$\left.\begin{array}{l} 4\text{-}C_5H_4NCH{=}CH_2 + R_2NH \\ R_2NH\cdot HCl + CH_2O + 4\text{-}C_5H_4NCH_3 \end{array}\right]\rightarrow 4\text{-}C_5H_4NCH_2CH_2NR_2$$

R_2NH = diethylamine or morpholine

It was also of interest to determine whether ammonia could be directly pyridylethylated to give 2-(aminoethyl)-pyridine (A), and 4-(2-aminoethyl)-pyridine (B). The former amine has been prepared previously[7] by condensation of phthalimide with 2-vinylpyridine to give N-[2-(2-pyridyl)-ethyl]-phthalimide, which was then cleaved to the desired amine by reaction with hydrazine hydrate. Amine B, as its dihydrochloride, also has been synthesized previously by a seven-step process starting with 2-picoline.[8]

It has now been found that A may be obtained in 84.5% yield and B may be obtained in 65.5% yield by the reaction of 2- and 4-vinylpyridine, respectively, with an aqueous methanolic solution of ammonium chloride. Amine B also has been prepared in 77% yield by replacing the ammonium chloride by ammonium acetate.

As another route to compounds A and B, it has been possible to pyridylethylate acetamide and propionamide with both 2- and 4-vinylpyridine to give the corresponding N-pyridylethylated amides, which were then hydrolyzed to the corresponding amines by refluxing with 10% aqueous sodium hydroxide solution.

As a by-product in the reaction of acetamide with 4-vinylpyridine, there was obtained a low yield (9.4%) of the bimolecular reduction product of 4-vinylpyridine, *i.e.*, 1,4-di-(4-pyridyl)-butane. It is interesting to note that acrylonitrile, which may be regarded as a vinylogous, open-chain analog of 4-vinylpyridine, has been reductively coupled by

(6) While our work was in progress, a paper appeared [A. J. Matuszko and A. Taurins, *Can. J. Chem.*, **32**, 538 (1954)] in which the syntheses of five of the adducts listed in Table I were reported. However, in most cases the yields of products obtained were lower than and the experimental procedures employed were different from those in the present study.

(7) F. K. Kirchner, J. R. McCormick, C. J. Cavallito and L. C. Miller, *J. Org. Chem.*, **14**, 388 (1949).

(8) L. A. Walter, W. H. Hunt and R. J. Fosbinder, THIS JOURNAL, **63**, 2771 (1941).

reaction with magnesium in anhydrous methanol or with sodium amalgam in aqueous solution.[9]

It has also been possible to add aniline, N-methylaniline and morpholine to 2-methyl-5-vinylpyridine (Table I) using sodium as the condensing agent. However, cyclohexylamine, di-*n*-butylamine, pyrrole and piperidine failed to undergo reaction. These successful additions of amines to a 3-vinylpyridine, although surprising in relation to the findings of Doering and Weil,[10] seem entirely reasonable when related to the similar reactions of amines with styrene as effected by Wegler and Pieper.[11] Although the structures of these adducts have not been established definitely by the synthesis of authentic samples, they are probably analogous to the corresponding compounds obtained from amines and 2-vinyl- and 4-vinylpyridine.[4,5] Thus, the compound derived from aniline is probably 2-methyl-5-(2-anilinoethyl)-pyridine.

Finally, we studied the reactions of 2- and 4-vinylpyridine with three nitriles. The reactions involved are illustrated by the equation

$$2 = C_5H_4NCH{=}CH_2 + C_6H_5CH_2CN \xrightarrow{Na} 2\text{-}C_5H_4NCH_2CH_2CHC_6H_5CN$$

Thus, phenylacetonitrile has been pyridylethylated in 39.6% yield by 2-vinylpyridine and in 58.6% yield by 4-vinylpyridine, acetonitrile is pyridylethylated in 8.0% yield by either 2- or 4-vinylpyridine, and isobutyronitrile is pyridylethylated by 2-vinylpyridine in 27.4% yield but fails to react with 4-vinylpyridine.

Experimental[12]

Reactions of 4-Vinylpyridine with Amines.—These reactions were effected using the methods described earlier for the analogous reactions of 2-vinylpyridine with amines.[4,5]

Mannich Reactions between 4-Picoline, Formaldehyde and Amines.—The procedure described earlier[5] for similar reactions involving 2-vinylpyridine was used. Thus, N-(2-(4-pyridyl)-ethyl)-morpholine and 4-(β-diethylaminoethyl)-pyridine were obtained in 22 and 14% yields, respectively.

Reaction of 2-Vinylpyridine with Ammonium Chloride.—A solution of ammonium chloride (53.5 g., 1.0 mole) and 2-vinylpyridine (52.5 g., 0.5 mole) in 150 ml. of water and 25 ml. of methanol was refluxed for eight hours and allowed to come to room temperature. The mixture was then poured onto ice and made strongly basic with a 30% aqueous solution of sodium hydroxide. The basic solution was extracted with several portions of chloroform, the combined extracts were dried over sodium sulfate, the solvent was removed and the residue was distilled in vacuum to give 51.5 g. (84.5%) of 2-(2-aminoethyl)-pyridine, b.p. 90–93° at 9 mm., 97–100° at 12 mm.[7]; dipicrate, m.p. 223–224° from 95% ethanol (lit. value[13] 215–216°). *Anal.* Calcd. for $C_{19}H_{16}N_8O_{14}$: C, 39.25; H, 2.76. Found: C, 39.55; H, 2.55.

A similar experiment using 4-vinylpyridine gave 40.0 g. (65.5%) of 4-(2-aminoethyl)-pyridine, b.p. 117–120° at 17 mm. This compound gave a dipicrate, m.p. 186–187° (from 95% ethanol). *Anal.* Calcd. for $C_{19}H_{16}N_8O_{14}$: C, 39.25; H, 2.76. Found: C, 39.40; H, 2.65.

Reaction of Aniline with 2-Methyl-5-vinylpyridine.—To a rapidly stirred solution of aniline (55.8 g., 0.6 mole), 2-methyl-5-vinylpyridine (35.7 g., 0.3 mole), 1.38 g. (0.06 mole) of small pieces of sodium was added. Since no apparent reaction occurred, the mixture was cautiously heated to 96° and kept at 95–100° for three hours. To the cooled mixture 5 ml. of absolute ethanol was added and then the reaction was processed as described previously.[4,5] In this way there was obtained 48.0 g. (75.5%) of 2-methyl-5-(2-anilinoethyl)-pyridine, b.p. 192–194° at 6 mm.

Reaction of Acetamide with 4-Vinylpyridine.—To a rapidly stirred solution of acetamide (28.6 g., 0.4 mole) and 4-vinylpyridine (84.8 g., 0.8 mole), 1.84 g. (0.08 mole) of small pieces of sodium metal was added. The mixture was heated to 96° at which point a highly exothermic reaction occurred. The reaction was moderated by cooling in an ice–water-bath. After the exothermic reaction had subsided, the mixture was heated to and kept at the reflux temperature for 15 minutes. The mixture was allowed to cool to room temperature, poured onto a mixture of ice and water, extracted with chloroform and processed in the regular manner to give 24.5 g. (37.4%) of N-(2-(4-pyridyl)-ethyl-acetamide (I), b.p. 185–187° at 5 mm., and 8.0 g. (9.4%) of 1,4-di-(4-pyridyl)-butane (II), m.p. 117.5–118.5° (from 60–70° petroleum ether) (lit. value[14] 111–115°). *Anal.* Calcd. for $C_9H_{12}N_2O$ (I): N, 17.07. Found: N, 16.97. This compound gave a picrate, m.p. 186.5–187.5°. *Anal.* Calcd. for $C_{15}H_{15}N_5O_8$: N, 17.81. Found: N, 17.75. *Anal.* Calcd. for $C_{14}H_{16}N_2$ (II): N, 13.19. Found: N, 12.92. This compound gave a dipicrate, m.p. 219.5–220.5° (from 95% ethanol). *Anal.* Calcd. for $C_{26}H_{22}N_8O_{14}$: N, 16.72. Found: N, 16.22.

When acetamide was condensed with 2-vinylpyridine, there was obtained a 62.0% yield of N-(2-(2-pyridyl)-ethyl)-acetamide, b.p. 138–140° at 1 mm. *Anal.* Calcd.: N, 17.07. Found: N, 17.00. This compound gave a picrate, m.p. 164.8–165.8°. *Anal.* Calcd.: C, 45.80; H, 3.81. Found: C, 46.15; H, 3.38. From the reactions of propionamide with 2-vinylpyridine and propionamide with 4-vinylpyridine there were obtained 46 and 51%, respectively, of N-(2-(2-pyridyl)-ethyl)-propionamide (III), b.p. 165–170° at 5 mm. and N-(2-(4-pyridyl)-ethyl)-propionamide (IV), b.p. 162–164° at 1.5 mm. *Anal.* Calcd. for $C_{10}H_{14}N_2O$: N, 15.73. Found for III: N, 15.39. Found for IV: N, 15.37. Compound III gave a picrate, m.p. 133–134°. *Anal.* Calcd. for $C_{16}H_{17}N_5O_8$: N, 17.19. Found: N, 17.33. Compound IV did not give an analytically pure picrate.

Hydrolysis of N-[2-(4-Pyridyl)-ethyl]-acetamide.—A mixture of N-[2-(4-pyridyl)-ethyl]-acetamide (19.0 g., 0.116 mole) and 200 ml. of 10% aqueous sodium hydroxide solution was refluxed for six hours and allowed to come to room temperature. The mixture was poured onto ice and extracted with several portions of chloroform. The combined extracts were dried over sodium sulfate, the solvent was removed and the residue was distilled in vacuum to give 7.5 g. (53%) of 4-(2-aminoethyl)-pyridine, b.p. 112–113° at 12 mm., b.p. 117–120° at 17 mm. This compound gave a dipicrate, m.p. 186–187° alone and when mixed with a sample obtained from the reaction of 4-vinylpyridine and ammonium chloride.

Similarly the adducts from 2-vinylpyridine with acetamide and from 2-vinyl- and 4-vinylpyridine with propionamide gave the corresponding amines in 45.6, 58.4 and 66.5% yields, respectively.

Reaction of Phenylacetonitrile with 4-Vinylpyridine.—To a rapidly stirred solution of phenylacetonitrile (58.5 g., 0.5 mole) and 4-vinylpyridine (26.3 g., 0.25 mole), 1.15 g. (0.05 mole) of small pieces of sodium metal was added. After a few minutes a highly exothermic reaction occurred. The reaction was moderated by cooling in an ice–water-bath. After the exothermic reaction subsided, the mixture was heated to and kept at its reflux temperature for 45 minutes. The mixture was then allowed to cool to room temperature, poured onto ice and made strongly acid with

(9) American Cyanamid Booklet, "The Chemistry of Acrylonitrile," page 24.

(10) W. E. Doering and R. A. N. Weil, THIS JOURNAL, **69**, 2461 (1947). These workers have found that although both 2- and 4-vinylpyridine react exothermically with sodium bisulfite solution to give 2- and 4-(2-pyridyl)-ethylsulfonic acids, respectively, a similar reaction with 3-vinylpyridine fails. This reaction also fails with 2-methyl-5-vinylpyridine.

(11) R. Wegler and G. Pieper, *Ber.*, **83**, 1 (1950).

(12) The 2- and 4-vinylpyridine were supplied through the courtesy of Dr. F. E. Cislak, Reilly Tar and Chemical Corp., and the 2-methyl-5-vinylpyridine was generously supplied by Mr. J. Roach, Phillips Chemical Co.

(13) K. Löffler, *Ber.*, **37**, 161 (1904).

(14) L. M. Jampolsky, M. Baum, S. Kaiser, L. H. Sternbach and M. W. Goldberg, THIS JOURNAL, **74**, 5222 (1952).

concentrated hydrochloric acid. This acidic mixture was extracted several times with chloroform and the extracts discarded. The residue was made basic with sodium carbonate solution and extracted several times with chloroform. The combined chloroform extracts of the basic solution were dried over sodium sulfate and the solvent distilled. The residue was distilled in vacuum to give 32.5 g. (58.6%) of α-phenyl-γ-(4-pyridyl)-butyronitrile, b.p. 185–187° at 2 mm. *Anal.* Calcd. for $C_{15}H_{14}N_2$: N, 12.61. Found: N, 12.45. Picrate, m.p. 136–137°. *Anal.* Calcd. for $C_{21}H_{17}N_5O_7$: N, 15.52. Found: N, 15.40. From the reaction of phenylacetonitrile and 2-vinylpyridine there was obtained a 39.6% yield of α-phenyl-γ-(2-pyridyl)-butyronitrile, b.p. 158–160° at 1.5 mm. *Anal.* Calcd.: N, 12.61. Found: N, 15.69. Picrate, m.p. 135–136°. *Anal.* Calcd.: N, 15.52. Found: N, 15.69.

From similar experiments between acetonitrile with 2-vinylpyridine and 4-vinylpyridine and isobutyronitrile with 2-vinylpyridine, there were obtained γ-(2-pyridyl)-butyronitrile (8.0%, V), b.p. 95–97° at 1 mm.; γ-(4-pyridyl)-butyronitrile (8.0%, VI), b.p. 122–125° at 1 mm., and α,α-dimethyl-γ-(2-pyridyl)-butyronitrile (27.0%, VII), b.p. 95–97° at 1.5 mm. Isobutyronitrile failed to react with 4-vinylpyridine. *Anal.* Calcd. for $C_9H_{10}N_2$ (V): N, 19.17. Found: N, 19.26. Picrate, m.p. 114–115°. *Anal.* Calcd. for $C_{15}H_{13}N_5O_7$: N, 18.66. Found: N, 18.41. Compound VI behaved erratically on analysis. However it gave an analytically pure picrate, m.p. 132.5–133.5°. *Anal.*: N, 18.66. Found: N, 18.23. *Anal.* Calcd. for $C_{11}H_{15}N_2$ (VII): N, 16.00. Found: N, 15.70. Picrate, m.p. 132–133°. *Anal.* Calcd. for $C_{17}H_{17}N_5O_7$: N, 17.36. Found: N, 17.66.

PITTSBURGH 13, PENNSYLVANIA

[CONTRIBUTION FROM THE BIOLOGICAL LABORATORY OF AMHERST COLLEGE]

The Synthesis of 5-Amino-7-hydroxy-1,3,4-imidazopyridine (1-Deazaguanine) and Related Compounds

BY D. G. MARKEES AND G. W. KIDDER

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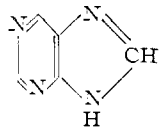
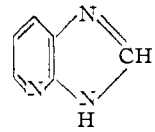
The preparation and Curtius reaction of 4-chloro- and 4-alkoxypyridine-2,6-dicarboxylates is reported. Two of the resulting diamines were aminated in position 3 and the triamines were converted to derivatives of 1,3,4-imidazopyridine.

A number of analogs of naturally occurring purine bases, which differ from the latter by replacement of a CH–group of the ring system by the isosteric N-atom have been shown to inhibit the growth of certain microörganisms. Among the compounds studied are derivatives of imidazo-1,2,3-triazine[1] and 5-amino-7-hydroxy-1-v-triazolo(d)-pyrimidine.[2,3]

We wished to study analogs of purine bases in which one nitrogen atom of the pyrimidine ring is replaced by the isosteric CH– group, and this paper deals with the synthesis of derivatives of 1,3,4-imidazopyridine.



Purine



1,3,4-Imidazopyridine (1-Deazapurine)

The parent compound 1,3,4-imidazopyridine[4] as well as a number of its derivatives are described in the literature.[4–6] However there is little information on their biological activity. Vaughan, *et al.*,[5] reported that their products failed to show any inhibition of the growth of a number of bacterial organisms. This is not too surprising as the positions of the substituents in their compounds were not the same as in the natural products. A publication by Dimmling and Hein[7] gives some information on the *in vitro* antibacterial activity of 7-amino-1,3,4-imidazopyridine (1-deazaadenine).

We were particularly interested in 5-amino-7-hydroxy-1,3,4-imidazopyridine (1-deazaguanine) (XII) and it was hoped that *Tetrahymena pyriformis*, because of its absolute guanine requirement,[8] could be used for the detection of any possible antimetabolite activity. Furthermore it has been established that the guanine antimetabolite 8-azaguanine[2] is incorporated into the nucleic acids of this organism,[9] and a similar metabolic fate of 1-deazaguanine was considered possible. Additional interest was lent to this project by the fact that 8-azaguanine is also an inhibitor of certain tumors in higher animals.[10]

For the synthesis of 1-deazaguanine we started with the pyridine moiety of the molecule and attached to it the imidazole ring. Since derivatives of 4-hydroxypyridine could cause difficulties, due to their tautomerism with isomeric 4-pyridones, we avoided their use and introduced the hydroxyl with the last operation. Esters of 4-chloropyridine-2,6-dicarboxylic acid (Ia, Ib) and 4-alkoxypyridine-2,6-dicarboxylic acids (IIIa, IIIb) were subjected to the Curtius degradation and gave 4-chloro-2,6-diaminopyridine (IVa) and 4-alkoxy-2,6-diaminopyridines (IVb, IVc). In two cases an additional amino group was introduced and gave 4-chloro-2,3,6-triaminopyridine (Xa) and 4-ethoxy-2,3,6-triaminopyridine (Xb), respectively. By ring closure involving the amino groups in position 2 and 3 we prepared 5-amino-7-chloro-1,3,4-imidazopyridine (XIa) and 5-amino-7-ethoxy-1,3,4-imidazo-

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