terial boiled at 165–166° (4 mm.); $n^{20}D$ 1.5899. Analysis showed it to be impure. In an effort to convert it to the nitrile the procedure of Newman[24] for 1-naphthonitrile was applied. Among the products was a solid which had the composition of benzylisodurene. It distilled at 154–160° (5 mm.) and crystallized from ethanol from which it separated in glistening white plates; m. p. 57.5–58.5°.

Anal. Calcd. for $C_{17}H_{20}$: C, 91.01; H, 8.99. Found: C, 91.08; H, 9.14.

Mesitylphenylmethyl Ether.—Reduction of 129 g. of benzoylmesitylene according to the procedure of Wiselogle and Sonneborn[23] for benzohydrol gave 80 g. of a liquid which set to a glassy solid in the receiver. By means of fractional crystallization of this material from acetone two compounds were obtained. They are thought to be the meso and racemic modifications of mesitylphenylmethyl ether. The less soluble isomer formed prisms melting at 168.5–169°.

Anal. Calcd. for $C_{32}H_{34}O$: C, 88.43; H, 7.89. Found: C, 88.59; H, 7.83.

The more soluble isomer was recrystallized repeatedly from methanol; m. p. 135–136.5° (cor.). It formed fine, white needles.

Anal. Calcd. for $C_{32}H_{34}O$: C, 88.43; H, 7.89. Found: C, 88.59; H, 7.69.

This substance appears to be the same as that reported by Louise,[25] as melting at 137°.

1,1-Dimesityl-1-propen-2-ol.—A solution of 8.4 g. of dimesitylketene in 75 ml. of dry benzene was added over a period of one hour to a Grignard reagent prepared from 3.0 ml. of methyl idodide, 1.2 g. of magnesium and 75 ml. of dry ethyl ether. The mixture was stirred under reflux during the addition and at 50° for thirty hours thereafter. The crude enol, isolated in the usual way, melted at 94–97° and weighed 7 g. It was recrystallized from ethanol; m. p. 97–98°.

Anal. Calcd. for $C_{21}H_{26}O$: C, 85.66; H, 8.90. Found: C, 86.16; H, 9.20.

(24) Newman, "Organic Syntheses," **21**, 84 (1941).

(25) Louise, *Ann. chim. phys.*, [6] **6**, 213 (1885).

The infrared absorption spectrum showed the presence of a hydroxyl group.

The **acetate**, prepared by the use of acetic anhydride and pyridine, was recrystallized from ethanol; m. p. 114–115°.

Anal. Calcd. for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 82.31; H, 8.61.

Dry hydrogen chloride was passed for thirty hours through a solution of 5 g. of 1,1-dimesityl-1-propen-2-ol in 75 ml. of dry methanol. The product, **α,α-dimesitylacetone**, was recrystallized from ethanol; m. p. 145.5–146.5°; yield 2.4 g.

Anal. Calcd. for $C_{21}H_{26}O$: C, 85.66; H, 8.90. Found: C, 85.68; H, 9.23.

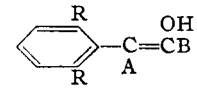
Efforts to prepare this ketone by treating dimesitylacetyl chloride with methylmagnesium iodide or lithium methyl were unsuccessful.

Summary

Eight new vinyl alcohols have been studied, two of which proved to be stable. From a consideration of the behavior of these and other enols examined previously the following generalization emerges.

The necessary and sufficient condition for stability in a trisubstituted vinyl alcohol is the presence of two radicals of the mesityl type. The position of these two and the size of the third radical are immaterial.

Stable vinyl alcohols of all types and the related enediols have the following structure in which A or B is an aryl radical.



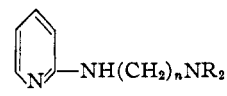
URBANA, ILLINOIS RECEIVED NOVEMBER 9, 1944

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Heterocyclic Basic Compounds. I. 2-Aminoalkylamino-pyridines[1]

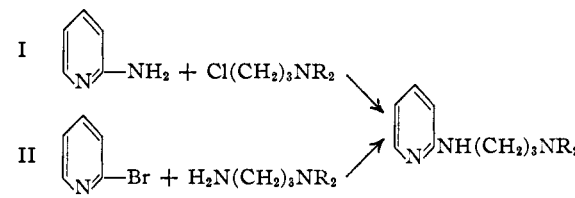
BY FRANK C. WHITMORE, HARRY S. MOSHER,[2,3] DALE P. J. GOLDSMITH,[2,3,4] AND ANTON W. RYTINA

In this paper compounds of the following general type are reported



in which the side chain is varied to include radicals of aminoalkylamines, dialkylaminoalkylamines, heterocyclic aminoalkylamines, and side chains which are interrupted with nitrogen and oxygen.

Two methods were available for the preparation of these compounds, either the action of an aminoalkyl halide on 2-aminopyridine as in I, below, or the action of an aminoalkylamine on a halopyridine as in II.



It is a well established fact that sodamide should be used in the first type reaction if substitution on the ring nitrogen via the imino form of α-amino-pyridine is to be prevented.[5] The synthesis of 2-(γ-morpholinopropylamino)-pyridine by both methods has been accomplished and the structure of this product is thus proved. The

(1) Presented before the Organic Division of The American Chemical Society at Detroit, April 12, 1943.

(2) The material herein presented is taken in part from theses presented by Dale P. J. Goldsmith and Harry S. Mosher to The Pennsylvania State College in partial fulfillment of the requirements for the Ph.D. degree.

(3) Parke, Davis and Company Research Fellow, 1942.

(4) Present Address: Research and Development Department, Merck and Company, Rahway, New Jersey.

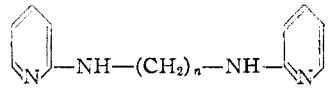
(5) Tschitschibabin, Konovalova and Konovalova, *Ber.*, **54**, 814 (1921).

sodamide reaction proceeded in 51–78% yields, and although the method is simple, most of the derivatives were prepared from 2-bromopyridine because the aminoalkylamines were more readily available than the aminoalkyl halides.[6]

In the preparation of 2-bromopyridine by the method of Craig[7] there was also obtained a high boiling solid which was identified as 2,5-dibromopyridine.[8]

2-Bromopyridine was treated with γ-diethylaminopropylamine in several ways with only slight success: first, without solvent at 180°; second, in the presence of sodium acetate at 160°; and third, in boiling toluene with copper catalyst. It was finally discovered that the reaction proceeded smoothly in pyridine at 140–160° in a sealed tube. When the reactants are mixed in a 1:1 mole ratio, the product was obtained in approximately 50% yield but, upon the addition of a 1 mole excess of the aliphatic diamine, the yield rose to 74% and up to 82.5% when a two molar excess was employed. From this it seems likely that there is a competition for the hydrogen bromide split out in the reaction and that the aliphatic amine is a stronger base than either pyridine, 2-bromopyridine, or the product.

The compounds of this series are reported in Table I along with two bis-di-pyridyldiamines of the following nature



where n is 3 and 6. These were obtained as by-products in the reaction of 2-bromopyridine with trimethylenediamine and hexamethylenediamine,[9] respectively. This series of compounds where n is 2, 5, 6, 7, 8, 9 and 10 has been prepared by Sharp[10] for testing in trypanasomial infections. He prepared these by the action of alkylene dibromides on 2-aminopyridine with the use of sodamide. Of the two compounds in this series reported here, one is new (n = 3) and the other (n = 6) corresponds in its melting point and the melting point of its derivatives to the same compound reported by Sharp. This is additional proof of the structure of these products.

Experimental

Method I. 2-(β-Diethylaminoethylamino)-pyridine.—To a mixture of 114 g. (2.92 moles) of sodamide and 610 cc. of dry toluene at 100° was added a solution of 275 g. (2.92 moles) of 2-aminopyridine[11] in 225 cc. of dry toluene. The mixture was heated for three hours on the steam-bath and then treated with 198 g. (1.46 moles) of freshly distilled β-diethylaminoethyl chloride (b. p. 42–44° at 18 mm. press.). The reaction mixture was heated and stirred for thirteen hours, cooled and washed with water. The toluene layer was separated and the water layer saturated with potassium carbonate and extracted three times with ether. The combined extracts and the toluene layer were distilled through a Claisen flask until the excess 2-aminopyridine (131 g.) had been recovered and the residue then fractionated through a small fractionating column.[12] A total of 222 g. (78.5% yield), b. p. 112–115° (4 mm.), n^{20}D 1.5320, was obtained. An additional 24 g. boiling slightly higher with n^{20}D 1.5320–1.5314 brought the crude yield up to 87%. The product was a clear, viscous, stable liquid.[13] This base was converted to the hydrochloride by bubbling dry hydrogen chloride through its dry ether solution and recrystallizing the precipitated salt first from absolute alcohol and ether, and finally from absolute alcohol alone; yield 64%, m. p. 170–171°. *Anal.* Calcd. for $C_{11}H_{19}N_3 \cdot 2HCl$: Cl, 26.65. Found: Cl, 26.62, 26.66.

2-(β-Diethylaminoethylamino)-piperidine Dihydrochloride.—A solution of 15 g. (0.056 mole) of 2-(β-diethylaminoethylamino)-pyridine dihydrochloride in 150 cc. of absolute alcohol was hydrogenated in the presence of 0.2 g. of platinum oxide catalyst at 55–65° and 3 atm. pressure. Evaporation of the alcohol gave a viscous oil which was recrystallized from alcohol and ether to give 5.8 g. (38%) of the hexahydro product melting at 171–173°. A mixed m. p. with the starting material was 158–164°. *Anal.* Calcd. for $C_{11}H_{25}N_3 \cdot 2HCl$: Cl, 26.06. Found: Cl, 26.10, 26.05. An unstable, non-crystallizable material (9 g.) was obtained by evaporation of the mother liquors.

2-Bromopyridine was prepared according to the method of Craig[3] to give 846 g. (81%) of 2-bromopyridine; b. p. 85° (20 mm.), n^{20}D 1.5742, m. p. of picrate 105.5–106°. A similar run in which the temperature of diazotization was allowed to rise to 10° gave a 63.5% yield of 2-bromopyridine and a 10% yield of a high boiling substance that melted at 91.5–93° when crystallized from methanol. This melting point corresponds to that in the literature reported for 2,5-dibromopyridine[8]; the hydrochloride (m. p. 186–188°) was analyzed. *Anal.* Calcd. for $C_5H_3NBr_2 \cdot HCl$: Cl, 13.70. Found: Cl, 13.62. Since all of the other dibromopyridines have greatly different melting points, this is probably the expected 2,5-isomer. This compound was not basic enough to give a picrate and boiling ether converted its hydrochloride into the free base.

Method II. 2-(γ-Morpholinopropylamino)-pyridine.—2-Bromopyridine, 15.8 g. (0.1 mole), γ-morpholinopropylamine, 29 g. (0.2 mole) and 10 g. of pyridine were heated in a bomb tube at 155° for six hours. The product was removed with the aid of a little pyridine, warmed over 20 g. of solid sodium hydroxide on the steam-bath for thirty minutes, filtered and distilled. After the pyridine solvent and excess γ-morpholinopropylamine had distilled, 16.3 g. (74%) of a colorless, viscous liquid was collected at 164–70° under 4 mm. pressure. On cooling this solidified to a white solid; m. p. 55–58°. The product dissolves in water to give a basic solution, and forms a picrate which is readily recrystallized from dilute alcohol and melts at 220°. When the above procedure was duplicated using only equal molar quantities of 2-bromopyridine and γ-morpholinopropylamine, a 48% yield of the product was obtained. An identical product as shown by its melting point, 56–58°, boiling point, 165–6° (3.5 mm.), and melting point and mixed melting point of the picrate derivative, 220°, was obtained by Method I.

2-(ζ-Aminohexylamino)-pyridine and 1,6-Di-(2-pyridylamino)-hexane.—In a 500-ml. flask were mixed 46.4 g. (0.3 mole) of 2-bromopyridine and 104.4 g. (0.9 mole) of hexamethylenediamine[10] and the solution was heated under a reflux condenser at 150–160° for six hours. The reaction

(6) Whitmore, Mosher, Adams, Taylor, Chapin, Weisel and Yanko, THIS JOURNAL, **66**, 725 (1944).

(7) Craig, *ibid.*, **56**, 231 (1934).

(8) Tschitschibabin and Tyozhelova, *Chem. Abst.*, **18**, 495 (1924).

(9) Furnished through the courtesy of E. I. du Pont de Nemours and Co., Inc.

(10) Sharp, *J. Chem. Soc.*, 1191 (1938).

(11) Furnished through the courtesy of Reilly Tar and Chemical Company.

(12) This column was 60 cm. long, had a diameter of 12 mm., was packed with 3/32 Pyrex helices and was of the conventional Whitmore–Lux design.

(13) German Patent 602,049, Aug. 30, 1934.

TABLE I

PYRIDINE DERIVATIVES

2-Substituent	B. p., °C.	Mm.	M. p., °C., or $n^{20}D$	Yield, %	Derivative M. p., °C.	Formula	Analyses, % Calcd.	Found
β-Dimethylaminoethylamino-	105	4	1.5320	78.5[a]	223–224[e]	$C_9H_{15}N_3 \cdot 2HCl$	Cl, 29.79	29.78
β-Diethylaminoethylamino-	112–134	4		51[a]	170–171[g]	$C_{11}H_{19}N_3 \cdot 2HCl$	Cl, 26.65	26.62
γ-Aminopropylamino-	128	2	1.5750	20.7[b] 68.2[d]	204.5–205.0[f]	$C_8H_{12}N_2 \cdot 3$ p. a.[i]	N, 20.03	20.28
γ-(2-Pyridylamino)-propylamino-	220–225	1	113.5–114.0	33.8[c] 9.7[d]	218[f]	$C_{13}H_{13}N_4$	N, 24.50	24.35
ζ-Aminohexylamino-	147–148	1		28[b]	165–166[f]	$C_{11}H_{18}N_2 \cdot 3$ p. a.[i]	N, 19.17	19.37
	162	3		66.5[c]				
ζ-(2-Pyridylamino)-hexylamino-	205–220	3	149–149.7	31[b]	222[f]	$C_{16}H_{22}N_4$	N, 20.71	20.66
	185–198	1		16[c]				
γ-Diethylaminopropylamino-	105–107	0.8	1.5309	40[b]	163.5–164[f]	$C_{10}H_{21}N_3$	N, 20.26	20.03
γ-Di-*n*-butylaminopropylamino-	144–150	2	1.5087	26[b]	149–150[f]	$C_{16}H_{29}N_3 \cdot 3$ p. a.[i]	N, 17.28	17.11
γ-Piperidinopropylamino-	135	0.5	1.5505	48[b]	168.5–169[f]	$C_{13}H_{21}N_3 \cdot 2HCl$	N, 14.37	14.28
							Cl, 24.26	24.19
γ-Morpholinopropylamino-	154–156	2	55–58	48[b] 74[c] 35[a]	220[f]	$C_{12}H_{19}N_3O$	N, 18.98	18.82
γ-Morpholinopropylamino-5-bromo-	182–185	1	76–77	51.6[b]	170–171[f]	$C_{12}H_{18}N_3OBr$	N, 13.99	14.10
δ-Morpholinobutylamino-	139–144	1	1.5455	28[b] 92.5[g]	191–192[f]	$C_{13}H_{21}N_3O \cdot 3$ p. a.[i]	N, 18.21	18.33
Di-(γ-piperidinopropyl)amino-	186–192	1	1.5337	48[b]	167.5–168[f]	$C_{21}H_{36}N_4 \cdot 3$ p. a.[i]	N, 17.91	18.11
p-Diethylaminophenylamino-	185–200	2	.....	40[b]	231[e] dec.	$C_{14}H_{19}N_3 \cdot 2HCl$	N, 13.36	13.21
p-Methoxyphenylamino-	.....	..	84	42[a]	165–166[f]	$C_{12}H_{12}N_2O$	N, 13.97	13.76
α-Methyl-γ-morpholinopropylamino-	165–168	2.5	45–47	40[b]	165–166[f]	$C_{13}H_{21}N_3O$	N, 17.85	17.84
α-Methyl-γ-piperidinopropylamino-	138–142	3	.....	48[b]	145–146.5[e]	$C_{14}H_{23}N_3 \cdot 2HCl$	N, 13.71	13.55
δ-Piperidinobutylamino-	148–152	2	1.5351	63.5[d]	148–149[e]	$C_{14}H_{23}N_3 \cdot 2HCl$	N, 13.71	13.78
γ-(β-Morpholinoethylamino)-propylamino-	170–171	2	1.5525[h]	30[c]	178[f]	$C_{14}H_{24}N_4O \cdot 3HCl$	N, 14.98	14.90
γ-(β-Diethylaminoethoxy)-propylamino-	140–142	1	1.5185	68.5[c]	111–112[f]	$C_{14}H_{25}N_3O$	N, 16.71	16.68

[a] Method I. [b] Method II. Equal molar amounts of reactants were used. [c] Method II. One molar excess of aliphatic diamine used. [d] Synthesized according to Method II. Two molar excess of aliphatic diamine used. [e] Hydrochloride. [f] Picrate derivative. [g] Yield based on the amount of aliphatic diamine used. [h] This material solidified on standing to a white, low melting solid. [i] The abbreviation p. a. is used for picric acid, $C_6H_3N_3O_7$.

mixture was then warmed with 20 g. of powdered sodium hydroxide in pyridine, the mixture filtered, and the filtrate distilled through a Claisen flask. After the pyridine and hexamethylenediamine had distilled over, 38.4 g. (66.5%) of 2-(ζ-aminohexylamino)-pyridine (b. p. 162–165 at 3 mm.) and 6.8 g. (16%) of 1,6-di-(2-pyridylamino)-hexane (b. p. 195–200 at 3 mm.) were collected. Both products solidified on cooling, the first to a low melting solid and the second, on crystallization from methanol, gave clusters of needles melting at 149–149.7°. Both gave crystalline picrates, the first melting at 165–166° and the second at 222°. The latter compound gave a hydrochloride which melted at 216°; Sharp[5] reported 216–218°.

Summary

Twenty basically-substituted 2-aminopyridine derivatives have been synthesized from 2-bromopyridine and an aminoalkylamine or from 2-aminopyridine and an aminoalkyl halide.

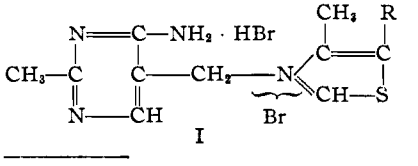
STATE COLLEGE, PA. RECEIVED NOVEMBER 4, 1944

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 994]

Thiamin Analogs. II. 4-Methylthiazole Analogs[1,2]

BY EDWIN R. BUCHMAN AND EDWIN M. RICHARDSON

The thiamin (vitamin B_1) molecule may be represented by formula (I)



I

(a) R = —H
(b) = —C_2H_5
(c) = —CH=CH_2
(d) = —CHOHCH_3
(e) = —$CH_2CH_2CH_2OH$
(f) = —$CH_2CHOHCH_3$
(g) = —CH_2OH

in which R = —CH_2CH_2OH. The present paper reports the synthesis and antineuritic properties of the seven vitamin analogs (Ia) to (Ig). These analogs were prepared by condensing the appropriate thiazole with a bromopyrimidine derivative, following the procedure used by Williams and Cline[3] in their synthesis of the vitamin. Compound (Ia) has previously been reported on by Bergel and Todd,[4] who obtained it by another method, the

(1) Paper XXII in the R. R. Williams series.

(2) The data relating to analogs (Ia)–(If) were presented before the Organic Division of the American Chemical Society at the Dallas meeting, April 1938. Analog (Ig) prepared by Dr. Herbert Sargent is included in the present paper.

(3) Williams and Cline, THIS JOURNAL, **58**, 1504 (1936); Cline, Williams and Finkelstein, *ibid.*, **59**, 1052 (1937).

(4) Bergel and Todd, *J. Chem. Soc.*, 1504 (1937).