(IX) were obtained in quantities approximating those shown in Table I for the bromo compound, VIIa.

(c) **From Heating 1-(β-Chloroethyl)-2,2,5,5-tetramethylpiperazine Dihydrochloride (VII).**—This salt was heated alone and suspended in Stanolind mineral oil. The results of four such experiments are given in Table II.

TABLE II

PYROLYSIS OF VII

Run	Condition	Temp., °C.	Time, min.	Mole HCl/mole VII evolved	I, %, recovered
1	Alone	230–245	30	0.82	69
2	Alone	210–240	35	.82	76.3
3	In oil	180–220	80	.77	56.3
4	In oil	213–220	80	.88	29.4

A typical experiment (run 3) follows: In a 200-ml. three-neck, round-bottom flask fitted with a stirrer, a thermometer, an air inlet and an outlet leading to 50 ml. of water in an erlenmeyer flask were placed 5 g. of VII and 50 ml. of Stanolind mineral oil. The flask was heated in a metal-bath and the hydrogen chloride evolved collected in water and titrated periodically with standard alkali. Above 180° the evolution of hydrogen chloride was steady. After the evolution of hydrogen chloride slowed, the oil suspension was diluted with petroleum ether (b. p. 60–68°), filtered, and the insoluble solid washed with petroleum ether; it weighed 3.48 g. after drying. The solid was dissolved in water, and the solution filtered; 0.06 g. of insoluble material remained. To the aqueous solution was added 5% sodium hydroxide solution; no precipitate formed. The solution was distilled until the distillate was no longer alkaline. Titration of the distillate with standard 1 *N* hydrochloric acid against methyl orange showed the presence of sufficient base to amount to 56.3% of I. Conversion of the salt, remaining from evaporation of the titrated solution, to the dibenzoyl derivative of I, m. p. 273–276°, identified this base as the reaction product. The filtrate from the preparation of the benzoyl derivative was distilled and a non-alkaline distillate obtained, indicating the absence of any of the tertiary, bicyclic amine II.

Summary

The preparation of 2,2,5,5-tetramethyl-3,6-diketopiperazine (IV) from α-aminoisobutyric acid is described. This diketopiperazine has been converted to 2,2,5,5-tetramethylpiperazine (I) and 2,2,5,5-tetramethyl-3-ketopiperazine (V) by catalytic hydrogenation over copper–chromium oxide as well as by reduction with sodium in butanol.

Attempts to convert the 1-(β-hydroxyethyl)- and the 1-(β-haloethyl)-2,2,5,5-tetramethylpiperazines to the tetramethyl-1,4-diazabicyclo-(2,2,2)-octane (II) were unsuccessful. The hydroxy compound lost the 1-substituent and reverted to I; the 1-haloethyl derivatives in aqueous alkaline solution yielded the 1-hydroxyethyl derivative and polymers (IX) *via* an intermediate ethylene immonium ion, or when heated as salts, lost the 1-substituent to form the piperazine I.

MADISON, WISCONSIN RECEIVED SEPTEMBER 25, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Synthesis of Some Isomeric Dimethyl-hydroxymethylpyridines. 3,4-Didesoxypyridoxin

BY RAYMOND P. MARIELLA AND JOHN L. LEECH[1]

Recent interest in antibiotics has led us to investigate the effect of the variation of the substituents in pyridoxin on possible anti-pyridoxin activity.

It has been shown by Ott[2] that 4-desoxypyridoxin was a powerful competitor to pyridoxin in the chick, and that methoxypyridoxin[3] exhibited similar activity, but to a lesser extent. Recently,[4] 5-deshydroxymethylpyridoxin was shown to be a weak inhibitor of pyridoxin in *Saccharomyces Cerevisiae*, while more recent work with 4-deshydroxymethylpyridoxin[5] has shown that this compound also exhibited very weak anti-pyridoxin properties.[6]

In the present work 2,3-dimethyl-5-hydroxymethylpyridine (VII), and 2,4-dimethyl-5-hydroxymethylpyridine (III) (3,4-didesoxypyridoxin) were synthesized as shown in Fig. 1.

As might be expected, VII exhibited neither pyridoxin nor anti-pyridoxin activity, but III did show weak anti-pyridoxin activity when tested against *Neurospora Sitophila*.[7]

From our work and previously cited work, it would appear that those structures similar to pyridoxin (with one or two groups removed) can exhibit this effect of anti-vitamin activity, and this could be explained on the basis of failure of the organism to differentiate between the vitamin and the similar molecule. With this reasoning, however, it would be difficult to explain why 3-amino-5-aminomethyl-4-ethoxymethyl-2-ethylpyridine has turned out to be the most potent anti-pyridoxin compound yet reported.[4] Work on the synthesis of other compounds related to pyridoxin is continuing in this Laboratory and will be reported soon.

Acknowledgement.—The authors wish to thank the Graduate School for a grant which made some of this work possible.

(1) Taken in part from a Master of Science thesis of John L. Leech.

(2) Ott, *Proc. Soc. Exp. Biol. Med.*, **61**, 125 (1946).

(3) Ott, *ibid.*, **66**, 215 (1947).

(4) Reported by Martin, Avakian and Moss at the April, 1948, meeting of the American Chemical Society.

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

(6) Private communication from Professor S. M. McElvain.

(7) These experiments were conducted by the Biochemical Group of the Lilly Research Laboratories, Indianapolis, Indiana.

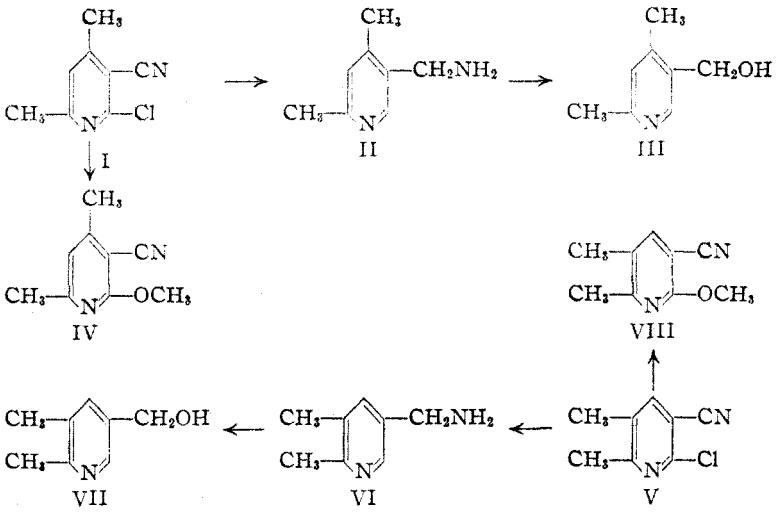


Fig. 1.

Experimental[8]

3-Cyano-4,6-dimethyl-2(1)-pyridone.—This was prepared from acetylacetone and cyanoacetamide.[9] The product was obtained as colorless needles, m. p. 286° (uncor.).

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

2-Chloro-3-cyano-4,6-dimethylpyridine (I).—An intimate mixture of the two solids, 43 g. of the above pyridone and 66 g. of phosphorus pentachloride, was heated until gentle refluxing began, and the refluxing was continued for two hours. The generated phosphorus oxychloride was removed under reduced pressure, and the remaining brown solid broken up, mixed with ice, and made basic with concentrated sodium hydroxide. The black mixture was then steam distilled, and a yellow solid came over with the water, 37 g. (77%), m. p. 91–94°. After several recrystallizations from alcohol–water, white plates were obtained, m. p. 94.5–95.0°.

Anal. Calcd. for $C_8H_7ClN_2$: N, 16.8. Found: N, 16.6.

3-Cyano-4,6-dimethyl-2-methoxypyridine (IV).—Sodium methoxide was prepared by adding 0.35 g. of sodium to 25 cc. of methyl alcohol. To this solution, 1.0 g. of chloropyridine (I) was added, and the resulting solution was refluxed for twenty-four hours. The methyl alcohol was removed on a steam cone, and the yellow solid which remained was extracted with anhydrous ether, and the insoluble sodium chloride filtered off. Evaporation of the ether left 0.45 g. (46%) of product, m. p. 93–94°. The material was further purified by sublimation, m. p. 93.5–94.0°. A mixed m. p. with the chloro compound (I) was depressed 30°.

Anal. Calcd. for $C_9H_{10}N_2O$: N, 17.3. Found: N, 17.0.

5-Aminomethyl-2,4-dimethylpyridine Dihydrochloride (II).—To a solution of 5.54 g. of 2-chloro-3-cyano-4,6-dimethylpyridine (I) in 125 cc. of absolute ethyl alcohol were added in order, a solution of 1.18 g. of palladium chloride in 2 cc. of concentrated hydrochloric acid, 15 cc. of 15% hydrogen chloride in absolute alcohol, and 3 g. of Norit. The suspension was shaken with hydrogen at twenty pounds pressure for two hours, after which time the uptake of hydrogen had ceased. Another solution of 1.10 g. of palladium chloride in 2 cc. of concentrated hydrochloric acid was added and the reduction resumed. After an additonal six hours, the hydrogen absorption had stopped. The catalyst and support were filtered, washed well with absolute alcohol and then water. The water solution was taken to dryness and contained no solid. The alcohol solution was evaporated to 10 cc., cooled in ice, and 1.45 g. of starting compound, m. p. 91°, was obtained. The filtrate was concentrated then to 2 cc. and 50 cc. of absolute alcohol added. This caused the precipitation of 2.09 g. (41% based on recovered starting material) of a voluminous white solid. Recrystallization from a concentrated hydrochloric acid and absolute alcohol mixture, gave small prisms, m. p. 204–206°.

Anal. Calcd. for $C_8H_{14}Cl_2N_2$: N, 13.4. Found: N, 13.8.

2,4-Dimethyl-5-hydroxymethylpyridine Hydrochloride (III).—To a solution of 2.2 g. of 5-aminomethyl-2,4-dimethylpyridine dihydrochloride (II) in 10 cc. of water was added a solution of 40 cc. of concentrated hydrochloric acid in 80 cc. of water, and the resulting solution was heated to 95°. A solution of 4.5 g. of sodium nitrite in 10 cc. of water was then added, all at once, with vigorous shaking, and the temperature was maintained at 90–95° until all the gas had evolved. The solution was then evaporated to dryness and the remaining white crystalline residue extracted with three 20-cc. portions of boiling absolute alcohol. After filtering off the insoluble sodium chloride, the combined extracts were evaporated to dryness, leaving a yellow solid, 1.6 g. (87%). Subsequent recrystallizations from alcohol–dioxane gave a white product, m. p. 215–220°, which did not give the correct analytical figures. Treatment with acetyl chloride (20 cc.), refluxing one hour, boiling the resulting solution to dryness, and recrystallization of the residue from alcohol–dioxane gave beautiful white plates, m. p. 225–227°.

Anal. Calcd. for $C_8H_{12}ClNO$: N, 8.1. Found: N, 8.2.

2-Chloro-3-cyano-5,6-dimethylpyridine (V).—An intimate mixture of 20 g. of 3-cyano-5,6-dimethyl-2(1)-pyridone,[10] and 37 g. of phosphorus pentachloride was heated until gentle refluxing began, and the mixture treated in the manner described above for the isomer. The product from the steam distillation was a water-insoluble oil. This oil was extracted with ether, the ether layer dried with anhydrous sodium sulfate, and the ether then removed on a steam cone. The resulting liquid was distilled *in vacuo*, and 16 g. (71%) b. p. 141.5–142.5° at 12 mm., of colorless liquid was collected, $n^{20}D$ 1.5496.

Anal. Calcd. for $C_8H_7ClN_2$: N, 16.8. Found: N, 16.3.

3-Cyano-5,6-dimethyl-2-methoxypyridine (VIII).—To a sodium methoxide solution, prepared by adding 0.35 g. of sodium to 25 cc. of methyl alcohol, was added 1.0 g. of 2-chloro-3-cyano-5,6-dimethylpyridine (V), and the resulting solution treated in the manner described above for its isomer. Evaporation of the ether from the ether extraction left a wine-colored liquid. This was distilled *in vacuo* and a colorless liquid collected, 0.71 g. (73%), b. p. 145° at 17 mm., $n^{20}D$ 1.5278.

Anal. Calcd. for $C_9H_{10}N_2O$: N, 17.3. Found: N, 17.5.

5-Aminomethyl-2,3-dimethylpyridine Dihydrochloride (VI).—To a solution of 5.12 g. of 3-cyano-2-chloro-5,6-dimethylpyridine (V) in 75 cc. of absolute alcohol was added in order a solution of 1.55 g. of palladium chloride in 3 cc. of concentrated hydrochloric acid, 15 cc. of a 15% solution of hydrogen chloride in absolute alcohol and 3 g. of Norit. The resulting solution was shaken with hydrogen at fifty pounds pressure for three hours, at which time

(8) Microanalyses by Misses Guy, Hobbs and Hines.

(9) Wagtendonk and Wibaut, *Rec. trav. chim.*, **61**, 728 (1942).

(10) Mariella, THIS JOURNAL, **69**, 2670 (1947).

the hydrogen absorption had ceased. Another solution of 1.00 g. of palladium chloride in 2 cc. of concentrated hydrochloric acid was added and the reduction resumed. After six additional hours, the hydrogen uptake had again ceased. The catalyst and support were filtered, washed well with absolute alcohol and then water. The aqueous solution was taken to dryness on a steam cone and contained no organic material. The alcohol layer was evaporated to 2 cc. and 50 cc. of absolute alcohol added, causing the precipitation of 3.7 g. (58%) of product as voluminous white crystals, m. p. 204–207°. This material was very hygroscopic. Recrystallization from alcohol–ether gave small white needles. After drying at 100° and 1 mm. for six hours the m. p. was 216–218°.

Anal. Calcd. for $C_8H_{14}Cl_2N_2$: N, 13.4. Found: N, 13.3.

2,3-Dimethyl-5-hydroxymethylpyridine and Hydrochloride (VII).—To a solution of 2.3 g. of 5-aminoethyl-2,3-dimethylpyridine dihydrochloride (VI) in 10 cc. of water was added a solution of 40 cc. of concentrated hydrochloric acid in 80 cc. of water, and the resulting solution heated to 95°. A solution of 4.5 g. of sodium nitrite in 10 cc. of water was then added all at once, with vigorous shaking. The temperature was maintained at 85–90° until the gas evolution had ceased. The solution was then evaporated until a semi-crystalline mass remained. Attempts to obtain the crystalline hydrochloride by the method described for its isomer failed, as a liquid was always obtained. This liquid hydrochloride was then added to 10 cc. of water containing 1 g. of sodium bicarbonate. The water was removed *in vacuo*, and the residue extracted with three 15-cc. portions of boiling absolute alcohol. After filtering off the inorganic salts, the combined alcoholic extracts were concentrated until an oil remained. This was distilled and a colorless liquid, 0.45 g. (30%), b. p. 108° at 0.5 mm., was obtained.

Anal. Calcd. for $C_8H_{11}NO$: N, 10.2. Found: N, 9.9.

The hydrochloride was finally prepared by dissolving this free base in 100 cc. of dry ether and passing in dry hydrogen chloride gas as a voluminous white solid separated out. This was very hygroscopic. A sample dried at 40° and 1 mm. for seventy-two hours had a m. p. 103–106°.

Summary

2,3-Dimethyl-5-hydroxymethylpyridine and 2,-4-dimethyl-5-hydroxymethylpyridine (3,4-didesoxypyridoxin) have been synthesized. The former compound exhibited neither vitamin nor anti-vitamin activity, while the latter compound proved to be a weak antagonist for pyridoxin.

EVANSTON, ILL. RECEIVED JULY 30, 1948

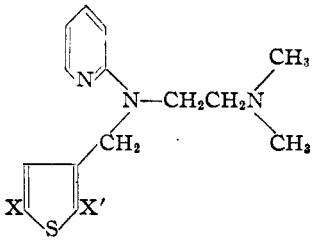
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

3-Substituted Thiophenes. III. Antihistaminics of the N-(3-Thenyl)-ethylenediamine Series[1]

BY E. CAMPAIGNE AND WILLIAM M. LESUER[2]

Recently it has been discovered that incorporation of the thiophene nucleus in antihistaminic compounds leads to desirable properties.[3–6] The work of Clapp, *et al.*,[5] indicates that the inclusion of a halogen atom on the thiophene ring improves the therapeutic ratio. Continuing a study of the properties of 3-thienyl analogs of physiologically active compounds,[7–9] attention was turned to the antihistaminic series. The preparation of four N-substituted dimethylaminoethylaminopyridines, containing the 3-thenyl and halogen-substituted 3-thenyl nucleus are described in this paper. The compounds prepared were: I, N,N-dimethyl-N′-(2-pyridyl)-N′-(3-thenyl)-ethylenediamine; II, N,N-dimethyl-N′-(2-pyridyl)-N′-(2-chloro-3-thenyl)-ethylenediamine; III, N,N-dimethyl-N′-(2-pyridyl)-N′-(2-bromo-3-thenyl)-ethylenediamine; and IV, N,N-dimethyl-N′-(2-pyridyl)-N′-(2,5-dichloro-3-thenyl)-ethylenediamine.

These compounds were readily synthesized by the reaction of the sodio-derivative of 2-dimethylaminoethylaminopyridine with the appropriate 3-thenyl bromide, obtained when the proper 3-methylthiophene reacted with N-bromosuccinimide.[7] In order to produce the corresponding halogenated compounds, it was necessary to extend the N-bromosuccinimide reaction to the halogenated 3-methylthiophenes, and characterize the halogenated thenyl bromides. As was expected, it was found that blocking the active 2-position with a halogen greatly improved the yield of side-chain bromination with N-bromosuccinimide. The reactions carried out in the preparation of the four antihistaminics and intermediates are outlined in the accompanying diagram. In each case the thenyl bromide was converted to the hexamethylenetetramine salt, the salt steam distilled to obtain the aldehyde, which was then oxidized to the acid with silver oxide.



I, X = H, X′ = H
II, X = H, X′ = Cl
III, X = H, X′ = Br
IV, X = Cl, X′ = Cl

The chlorination of 3-methylthiophene with sulfuryl chloride[10] was extended to the preparation

(1) Taken from part of the thesis submitted by William M. LeSuer in partial fulfilment of the requirements for the degree Doctor of Philosophy at Indiana University, June, 1948.

(2) Sterling-Winthrop Fellow in Chemistry, 1947. Present address: Lubrizol Corporation, Cleveland, Ohio.

(3) Weston, THIS JOURNAL, **69**, 980 (1947).

(4) Lee, Dinwiddie and Chen, *J. Pharm.*, **90**, 83 (1947).

(5) Clapp, *et al.*, THIS JOURNAL, **69**, 1549 (1947).

(6) Kyrides, Meyer and Zienty, *ibid.*, **69**, 2239 (1947).

(7) Campaigne and LeSuer, *ibid.*, **70**, 1555 (1948).

(8) Campaigne, *et al.*, *ibid.*, **70**, 2611 (1948).

(9) Campaigne and LeSuer, *ibid.*, **70**, 3498 (1948).

(10) Campaigne and LeSuer, *ibid.*, **70**, 415 (1948).