sourea must be associated with the nitrosated end of the molecule, since considerably less color was obtained with equimolar quantities of 2-fluoroethylamine. Therefore, it remains possible that under physiological conditions 1-alkyl-1-nitrosoureas might yield small quantities of compounds having alkylating activity, but it is still an open question whether this activity is sufficient to cause the observed biological effects.

Experimental Section

A mixture of 2 ml of water, 1 ml of acetate buffer (0.025 *M*, pH 6.0), 1 ml of an acetone solution containing 0.504 μmole/ml (unless otherwise indicated) of the test compound, and 0.4 ml of a 5% (w/w) solution of 4-(*p*-nitrobenzyl)pyridine in acetone was heated in a boiling-water bath for designated periods of time. The mixture was then cooled in an ice bath and to it were added 2 ml of acetone, 5 ml of ethyl acetate, and 1.5 ml of 0.25 *N* NaOH. The tube was shaken 20 times, and the two phases were separated by centrifugation in a clinical centrifuge for 2 min. A portion (2–3 ml) of the upper layer was transferred by pipet to a cuvette, and the optical density at 540 mμ was determined with a Beckman Model DU spectrophotometer. The operation from the introduction of the NaOH through the determination of optical density was performed within a period of 5 min in subdued light.

Diazomethane[15] from N-methyl-N-nitrosourethan was assayed by reaction with benzoic acid and titration of the excess benzoic acid. Measured volumes of this solution were used for the color tests, and equal volumes of ether were added to the control tubes.

(15) W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).

Synthesis of Vitamin B_6. III. 3-Deoxypyridoxine

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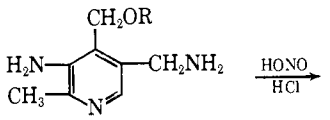
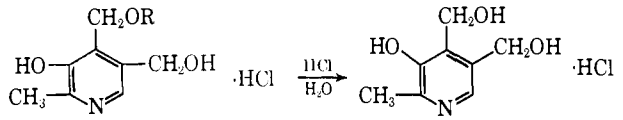
Received November 18, 1966

Preparations of 3-deoxypyridoxine (6-methylpyridine-3,4-dimethanol) have been previously reported.[1,2] We have now isolated it as an unusual by-product in the synthesis of pyridoxine. Harris and Folkers[3] described the following sequence of reactions: 1A → IIA → III. Compounds IV and V have now been

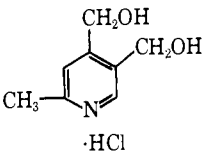


Ia, R = C_2H_5
b, R = CH_3

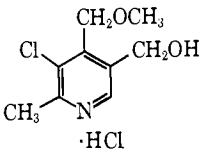


IIa, R = C_2H_5
b, R = CH_3 III

found in the mother liquors from pyridoxine prepared by this route without isolation of IIb, employing the



IV

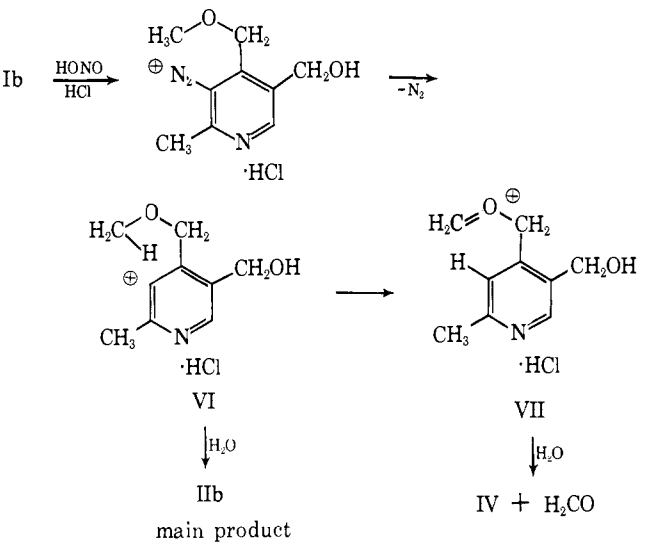


V

methyl ethers instead of the ethyl ether series described in the original publication.

An attempt was made to isolate the 4-methyl ether of IV from the mother liquors of 4-methoxypyridoxine (IIb), but unexpectedly only the demethylated compound IV was found at this stage also. The formation of 3-deoxypyridoxine (IV) during the diazotization can be explained by an intramolecular hydride transfer from the carbon of the neighboring methyl ether to the arylcarbonium ion VI formed from the diazonium salt. The resulting intermediate VII, comparable to that from the hydrolysis of an acetal, would immediately break down under the reaction conditions to form compound IV and formaldehyde (Scheme I).

SCHEME I



Analogous 1,5-hydride transfers have been proposed to explain abnormal products first observed[4] in the syntheses of certain phenanthridones by Pschorr cyclization and later extended to simpler anthranilamides by Cohen[5] and co-workers. For example, these authors reported a 9.9% yield of N-methylbenzamide and of formaldehyde from the diazotization of *o*-amino-N,N-dimethylbenzamide, along with the expected N,N-dimethylsalicylamide as the major product.

The formation of V by reaction of VI with chloride ion is a not-unexpected side path in the diazotization. It is of interest that the methyl ether linkage of V is resistant to the final hydrolytic conditions (II → III), illustrating the labilizing influence of the 3-hydroxyl group on the 4-methylene position.

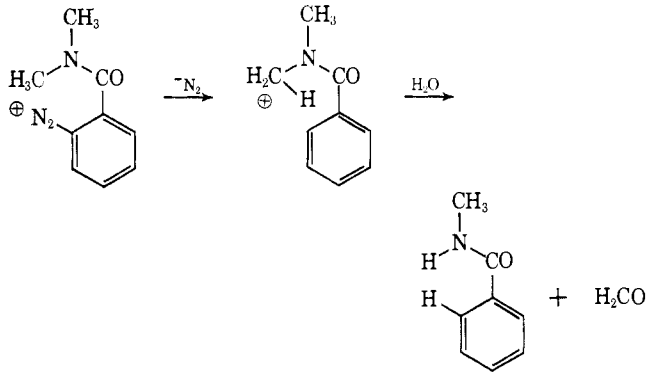
(1) A. Ichiba, K. Michi, and S. Emoto, *Sci. Papers Inst. Phys. Chem. Res.* (Tokyo), **39**, 131 (1941).

(2) R. G. Jones and E. C. Kornfeld, *J. Am. Chem. Soc.*, **73**, 107 (1951).

(3) S. A. Harris and K. Folkers, *ibid.*, **61**, 3307 (1939).

(4) D. H. Hey and D. G. Turpin, *J. Chem. Soc.*, 2471 (1954); T. R. Govindachari and N. Arumugam, *J. Sci. Ind. Res.* (India), **14B**, 250 (1955); L. G. Humber, H. Kondo, K. Kotera, S. Takagi, K. Takeda, W. I. Taylor, B. R. Thomas, Y. Tsuda, K. Tsukamoto, S. Uyeo, H. Yajima, and N. Yanaihara, *J. Chem. Soc.*, 4622 (1954).

(5) T. Cohen, R. M. Moran, Jr., and G. Sorvinski, *J. Org. Chem.*, **26**, 1 (1961); T. Cohen, A. H. Dinwoodie, and L. D. McKeever, *ibid.*, **27**, 3385 (1962).



3-Deoxypyridoxine and its phosphate have been investigated in a number of biological systems as inhibitors of B_6 kinases and amino acid decarboxylases, notably glutamic decarboxylase.[6-10] We have noted antitumor activity; 3-deoxypyridoxine has an effect upon Murphy lymphosarcoma. At 4 mg/rat, the compound caused significant arrest of growth of lymphosarcoma implants in rats maintained on a pyridoxine-deficient diet, while the effect produced by the diet alone was not significant.[11]

Experimental Section

2-Methyl-3-chloro-4-methoxymethyl-5-hydroxymethylpyridine Hydrochloride from Pyridoxine Hydrochloride Mother Liquors.—A crude residue (600 g) from pyridoxine hydrochloride mother liquors was dissolved in water, neutralized (NaOH) to pH 7, and extracted with benzene. After washing well with water the benzene solution was treated with Norit, filtered, and concentrated to dryness. The residue was taken up in ethanol, and treated with dry HCl. The crystalline solid which separated was recrystallized from ethanol to constant mp 180–182°; the yield was 34 g; ultraviolet spectrum, $\lambda_{max}^{0.1\ N\ HCl}$ 292 mμ ($A_{1cm}^{1\%}$ 290), $\lambda_{max}^{pH\ 7\ borate}$ 277 mμ ($A_{1cm}^{1\%}$ 178). $FeCl_3$ and Gibbs tests for 3-hydroxyl were negative.

Anal. Calcd for $C_9H_{12}Cl_2NO_2$: C, 45.39; H, 5.51; Cl, 29.81; N, 5.88. Found: C, 45.11; H, 5.62; Cl, 29.86; N, 5.93.

3-Deoxypyridoxine Hydrochloride from Pyridoxine Hydrochloride Mother Liquors.—A portion of the aqueous layer from the above isolation was made strongly alkaline with 48% NaOH and extracted continuously with ether overnight in a liquid-liquid extractor. The dried ether solution was treated with HCl to yield 28 g of mixed hydrochlorides which gave a positive $FeCl_3$ test for the 3-hydroxy group of pyridoxine. This contaminant was removed by passing an aqueous solution of the hydrochlorides over a column containing an excess of IRA-400 resin on the ^-OH cycle. A second passage over fresh IRA-400 was necessary to remove the last trace of pyridoxine. The eluate, which now gave a negative $FeCl_3$ test, was made acidic with HCl, evaporated to dryness, and recrystallized from boiling ethanol; yield 13.3 g; mp 206–208° (lit.[1,2] mp 202–203°); depressed the melting point of pyridoxine hydrochloride; ultraviolet spectrum, $\lambda_{max}^{0.1\ N\ HCl}$ 264 mμ ($A_{1cm}^{1\%}$ 333); $\lambda_{max}^{pH\ 7\ borate}$ 265 mμ ($A_{1cm}^{1\%}$ 194); Gibbs test negative. The nmr spectrum[12] showed two ring protons at τ 1.48 and 2.55.

Anal. Calcd for $C_8H_{12}ClNO_2$: C, 50.66; H, 6.38; N, 7.38. Found: C, 50.90; H, 6.53; N, 7.36.

3-Deoxypyridoxine Hydrochloride from 4-Methoxypyridoxine Hydrochloride Mother Liquors.—A solution of 4-methoxypyridoxine hydrochloride after the diazotization was concentrated, neutralized to pH 7, and thoroughly extracted with butanol. The dried butanol solution was treated with an excess of dry HCl and the hydrochlorides were allowed to crystallize. A first crop melted at 175–178° and yielded pure 4-methoxypyridoxine hydrochloride upon recrystallization from ethanol. A second crop, amounting to one third of the whole, melted below 170°. This was acetylated with an excess of boiling Ac_2O, which was removed by concentration, and the crude acetylated hydrochloride was filtered off and washed with ethanol; mp 132–135°. Extraction with hot ethyl acetate, in which it was sparingly soluble, raised the melting point to 165–167°. The lower melting point is in agreement with the one which was previously reported.[6] This diacetate proved to be identical by melting point and mixture melting point with the diacetate prepared by acetylating the 3-deoxypyridoxine hydrochloride described above. *Anal.* Calcd for $C_{12}H_{16}ClNO_4$: C, 52.65; H, 6.06; N, 5.17. Found: C, 52.95; H, 6.06; N, 5.17.

(6) T. Sakuragi, C. Argoudelis, and F. A. Kummerow, *Arch. Biochem. Biophys.*, **89**, 160 (1960).
(7) J. Hurwitz, *J. Biol. Chem.*, **217**, 513 (1955).
(8) D. B. McCormick and E. E. Snell, *ibid.*, **236**, 2085 (1961).
(9) E. W. Maynert and H. K. Kaji, *J. Pharmacol. Expl. Therap.*, **137**, 114 (1962).
(10) F. Rosen, R. J. Milholland, and C. A. Nichol, Inhibition of the Nervous System, γ-Aminobutyric Acid, Proceedings of an International Symposium, Duarte, Calif., 1959 (publ. 1960), p 338; *Chem. Abstr.*, **61**, 16660 (1964).
(11) We are obliged to Dr. R. N. Arison for these test results.
(12) W. Korytnyk and R. P. Singh, *J. Am. Chem. Soc.*, **85**, 2813 (1963).

Cyclohexyl Derivatives of Dopacetamide and Dopamine[1]

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Received August 25, 1966

The enzymatic hydroxylations[2-4] of phenylalanine to tyrosine and of tyrosine to dopa have been determined to be important steps in norepinephrine biosynthesis, and several investigators[2,5] have suggested that the inhibition of such aromatic hydroxylation steps may aid in developing useful cardiovascular and psychopharmacological agents.

Efforts toward such an approach have been initiated by Carlsson, Corrodi, and co-workers who reported the synthesis[6-8] of some derivatives of dihydroxyphenylacetamides and their inhibitory activities[8] on the enzymatic hydroxylation of phenylalanine to tyrosine, of tryptophan to 5-hydroxytrytophan, and of tyrosine to dopa, without inhibiting catechol O-methyltransferase.

In order to expand on the structure–activity relationship in this series we undertook the synthesis of α-cyclohexyl-3,4-dihydroxyphenylacetamide (**4a**, α-cyclohexyldopacetamide) and β-cyclohexyl-β-(3,4-dihydroxyphenyl)ethylamine (**5**, β-cyclohexyldopamine) and studied general synthetic pathways to compounds of these types.[9-12]

The synthetic sequence for the preparation of α-cyclohexyl-3,4-dihydroxyphenylacetamide (**4a**) and β-

(1) Presented in part before the Division of Medicinal Chemistry at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March, 1966.
(2) S. Udenfriend, *Pharmacol. Rev.*, **18**, 43 (1966).
(3) S. Udenfriend, P. Zaltzman-Nirenberg, and T. Nagatzu, *Biochem. Pharmacol.*, **14**, 837 (1965).
(4) S. Spector, A. Sjoerdsma, and S. Udenfriend, *J. Pharmacol. Expl. Therap.*, **147**, 86 (1965).
(5) T. Nagatsu, M. Levitt, and S. Udenfriend, *J. Biol. Chem.*, **239**, 2910 (1964).
(6) A. Carlsson, M. Lindqvist, S. Fila-Bromalko, and H. Corrodi, *Helv. Chim. Acta*, **45**, 270 (1962).
(7) A. Carlsson, H. Corrodi, and B. Waldeck, *ibid.*, **46**, 2271 (1963).
(8) A. Carlsson and H. Corrodi, *ibid.*, **47**, 1340 (1964).
(9) K. I. Melville, H. E. Shister, and S. Huq, *Can. Med. Assoc. J.*, **90**, 761 (1964).
(10) S. Casadio, G. Pala, E. Crescenzi, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *J. Med. Chem.*, **8**, 589 (1965).
(11) S. Casadio, G. Pala, T. Bruzzese, E. Crescenzi, E. Marazzi-Uberti, and G. Coppi, *ibid.*, **8**, 594 (1965).
(12) G. Pala, S. Casadio, T. Bruzzese, E. Crescenzi, and E. Marazzi-Uberti, *ibid.*, **8**, 698 (1965).