analysis by preparative glpc. Nmr analysis gave peaks at τ 1.84 (s, ring protons, 2 H), 7.24 (q, CH_2, 4 H), 8.75 (t, chain CH_3, 6 H).

Anal. Calcd for $C_8H_{12}N_2$: C, 70.55; H, 8.88; N, 20.57. Found: C, 70.7; H, 8.9; N, 20.7.

2,3-Dimethyl-5-ethylpyrazine (18).—A 50-ml portion of 2.22 *M* ethyllithium in benzene (0.111 mol, Alpha Inorganics, Inc.) was stirred and cooled to 10° while a solution of **14** (2.17 g, 0.020 mol) in benzene (10 ml) was added dropwise. The dark red slurry which formed was stirred 0.5 hr at 0° and 21.5 hr at 25°. After recooling to 0°, water was admitted and organic products were extracted with ether. Short-path distillation yielded 0.548 g of pale yellow oil, bp 60–102° (15 mm). Analysis of this oil by glpc indicated two major products, recovered **14** and 2,3-dimethyl-5-ethylpyrazine. The glpc yields of **14** and **18** were 18 and 6%, respectively. An analytical specimen of **18** was isolated by preparative glpc and further purified by evaporative distillation. Nmr analysis gave peaks at τ 2.03 (s, ring proton, 1 H), 7.61 (s, ring methyls, 6 H), 7.36 (q, CH_2, 2 H), 8.76 (t, ethyl CH_3, 3 H).

Anal. Calcd for $C_8H_{12}N_2$: C, 70.55; H, 8.88; N, 20.57. Found: C, 70.6; H, 8.9; N, 20.6.

2-*n*-Butyl-5,6-dimethylpyrazine (19).—A mixture containing 10 ml of dry hexane and 20.0 ml (0.032 mol) of 1.6 *M* *n*-butyllithium in hexane (Foote Mineral Co.) was stirred at 0° and treated dropwise (over 10 min) with a solution of **14** (1.74 g, 0.016 mol) in 5 ml of hexane. After stirring 1 hr at 0° and 1 hr at 25°, the reaction mixture was cooled and decomposed with water (10 ml). Ether extraction afforded 1.8 g of crude product which, after short-path distillation, yielded 1.01 g of a yellow oil, bp 59–114° (16 mm). Glpc analysis indicated two oily components which were trapped and identified as **14** and 2-*n*-butyl-5,6-dimethylpyrazine (**19**). Glpc yields of **14** and **19** were 42 and 8%, respectively. A sample of **19** was evaporatively distilled prior to analysis. Nmr analysis gave peaks at τ 2.07 (s, ring proton, 1 H), 7.64 (s, ring methyl, 6 H), 7.42 (t, ring CH_2, 2 H), 9.11 (t, *n*-butyl CH_3, 3 H).

Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.12; H, 9.82; N, 17.06. Found: C, 72.9; H, 9.8; N, 17.2.

Registry No.—**1,** 123-32-0; **10,** 15707-19-4; **10** 2,4-dinitrophenylhydrazone, 15707-20-7; **11,** 14667-55-1; **13,** 108-50-9; **14,** 5910-89-4; **15,** 15707-23-0; **16,** 15707-24-1; **17,** 15707-25-2; **18,** 15707-34-3; **19,** 15834-78-3.

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Synthesis of a Pyridoxal Analog, 4,5-Diformyl-3-hydroxy-2-methylpyridine[1a]

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A route for the synthesis of the compound 4,5-diformyl-3-hydroxy-2-methylpyridine (X) (an analog of pyridoxal) is described. The key intermediate in this synthesis was the previously undescribed dimethyl acetal of isopyridoxal (VI) which was synthesized from the corresponding acetylated diethyl mercaptal (V) by demercaptalation in methanol using mercuric chloride and mercuric oxide. For the removal of the mercuric chloride, ammonium hydroxide has been found to be the most suitable reagent. Oxidation of the 4-hydroxymethyl group of this intermediate (VI) with manganese dioxide "B" and acid hydrolysis of the product of oxidation gave the desired dialdehyde X which has been shown to exist in a hydrated form as a dihemiacetal. Derivatives like the bismethoxyoxime (XI) and bisthiosemicarbazone (XII) were prepared. Reduction of the *o*-dialdehyde X with sodium borohydride gave pyridoxol.

In the course of investigations concerning the biosynthetic pathway of vitamin B_6 in yeast[2] and its catabolism in rats,[3,4] we have isolated compounds, related to this vitamin, that showed growth-promoting activity for *Lactobacillus casei* and/or *Saccharomyces carlsbergensis*. Pyridoxal and isopyridoxal,[5] which have a formyl group in place of the hydroxymethyl group at the 4 or 5 position of the pyridoxol molecule, respectively, are both growth-promoting factors for *Saccharomyces carlsbergensis*.[6,7] Therefore, the compound 4,5-diformyl-3-hydroxy-2-methylpyridine (*o*-pyridoxidial[8]) (X, Scheme I), which has both the 4- and 5-hydroxymethyl groups of the pyridoxol molecule replaced by formyl groups, was needed to be tested as a possible precursor or catabolite of the vitamin. A synthesis of this pyridoxal analog is herein described; its biological properties are under investigation.

Gardner, *et al.*,[9] have described a synthesis of the bisthiosemicarbazone derivative of compound X using a double Sommelet reaction; however, the identity of this product was not conclusively established.[10] A detailed study[10–15] of the Sommelet reaction seems to show no promise for the synthesis of *o*-dialdehydes through a double Sommelet reaction. Ried and Bodem[16] have made many aromatic and heteroaromatic *o*-dialdehydes using vicinal dibromides and N-bromosuccinimide in the presence of peroxides, but this method did not seem to be applicable in the

(1) (a) This investigation was supported by a U. S. Public Health Service Research Grant (AM 00257). (b) To whom inquiries should be addressed.

(2) R. S. Pardini and C. J. Argoudelis, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, p C309.

(3) C. J. Argoudelis and F. A. Kummerow, *Biochemistry*, **5**, 1 (1966).

(4) C. J. Argoudelis, unpublished data.

(5) The growth-promoting activity of isopyridoxal is, unquestionably, a result of its conversion into pyridoxol and thence to pyridoxal phosphate: E. E. Snell, *Vitamins Hormones*, **16**, 77 (1958)).

(6) E. E. Snell, *J. Biol. Chem.*, **154**, 313 (1944).

(7) E. E. Snell and A. N. Rannefeld, *ibid.*, **157**, 475 (1945).

(8) Three new pyridine dialdehydes related to vitamin B_6 have been named trivially as *o*-, *m*-, and *p*-pyridoxidial. These dialdehydes have the two formyl groups in the *ortho* (4,5), *meta* (2,4), and *para* (2,5) positions of the pyridoxol molecule, respectively. Syntheses of the *m*- and *p*-pyridoxidials are in progess.

(9) T. S. Gardner, F. A. Smith, E. Wenis, and J. Lee, *J. Org. Chem.*, **16**, 1121 (1951).

(10) S. J. Angyal, *Org. Reactions*, **8**, 197 (1954).

(11) S. A. Harris, D. Heyl, and K. Folkers, *J. Amer. Chem. Soc.*, **66**, 2088 (1944).

(12) S. J. Angyal, P. J. Morris, R. C. Rassac, and J. A. Waterer, *J. Chem. Soc.*, 2704 (1949).

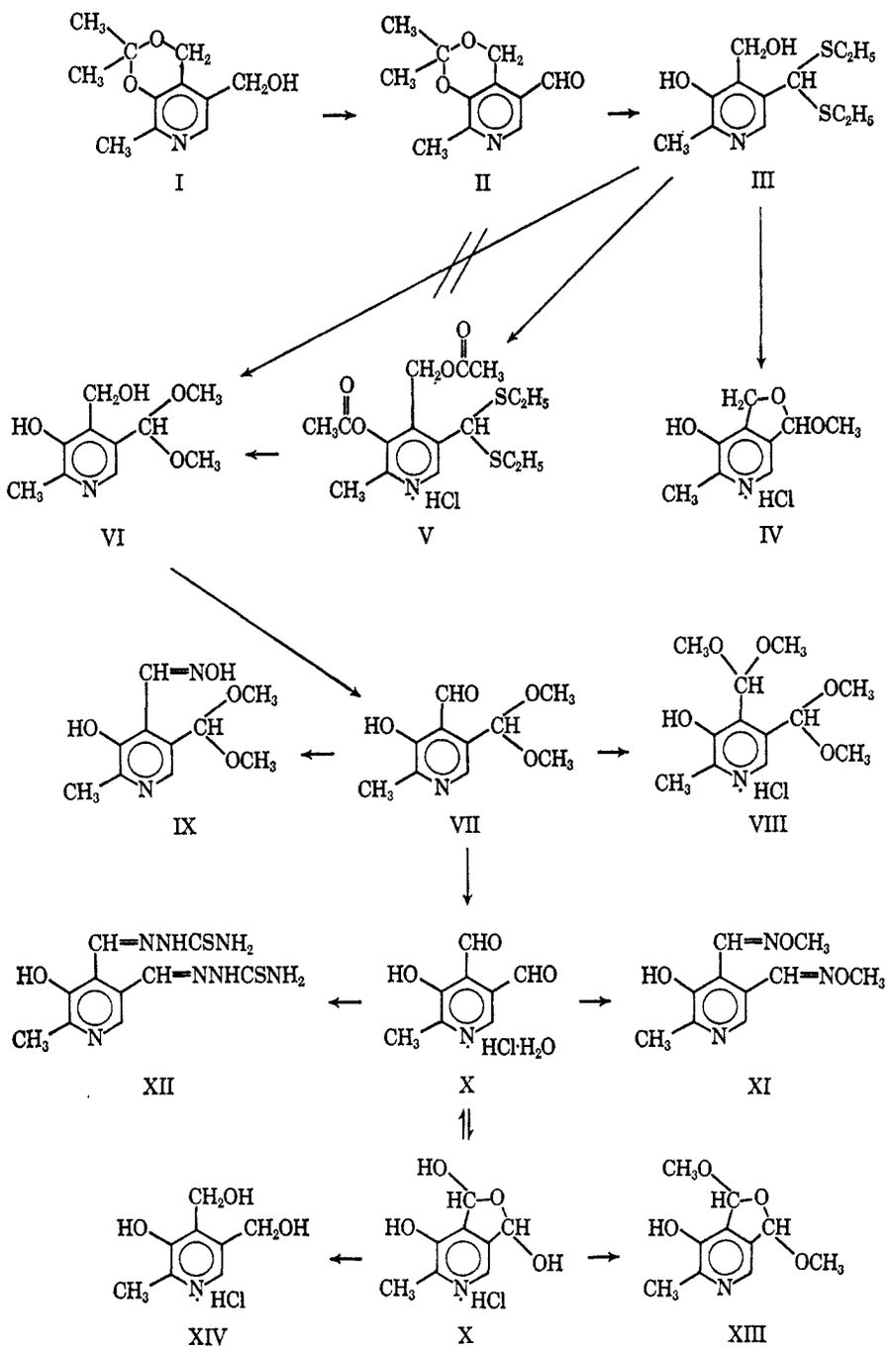
(13) R. C. Fuson and J. J. Denton, *J. Amer. Chem. Soc.*, **63**, 654 (1941).

(14) S. J. Angyal, G. B. Barlin, and P. C. Wailes, *J. Chem. Soc.*, 1740 (1953).

(15) J. H. Wood, C. C. Tung, M. A. Perry, and R. E. Gibson, *J. Amer. Chem. Soc.*, **72**, 2992 (1950).

(16) W. Ried and H. Bodem, *Chem. Ber.*, **89**, 708 (1956); **89**, 2328 (1956).

SCHEME I



present case. Ried[17] has reported that Weygand synthesized pyridine 2,3- and 3,4-dialdehydes by reducing the bis-N-methyl anilides of the corresponding dicarboxylic acids with lithium aluminium hydride; however, no experimental data are available. Paul and Korytnyk[18] reported the synthesis of *o*-pyridoxidial (X) along similar lines, but they also did not furnish any experimental details or physical data.

In the pyridoxol molecule, the 4-hydroxymethyl group is known to be more reactive than the 5-hydroxymethyl group toward oxidizing agents.[11,19] An attempt was therefore made to oxidize with manganese dioxide "B" the 4-hydroxymethyl group of isopyridoxal to obtain the *o*-pyridoxidial (X). Oxidation of benzylic alcohols with manganese dioxide "B" is known to stop at the aldehyde stage;[20] however, in this case 5-pyridoxic acid lactone was isolated. Apparently, the predominating hemiacetal form of isopyridoxal[21] is oxidized preferentially to the open form. Similarly when pyridoxal was oxidized, 4-pyridoxic acid lactone was obtained.

Direct attempts to make the dimethyl or diethyl acetals of isopyridoxal failed, as it exists mainly in the hemiacetal form.[21] Preparation of dimethyl acetals from the corresponding diethyl mercaptals using mer-

(17) W. Ried, *Angew. Chem.*, **67**, 357 (1955).

(18) B. Paul and W. Korytnyk Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, P063.

(19) I. Tomita, H. G. Brooks, and D. E. Metzler, *J. Heterocycl. Chem.*, **3**, 178 (1966).

(20) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

(21) W. Korytnyk, E. J. Kris, and R. P. Singh, *ibid.*, **29**, 574 (1964).

curic chloride and mercuric oxide is a very common reaction in carbohydrate chemistry. This method has not been used in pyridine chemistry since pyridine and some of its derivatives form insoluble salts with mercuric chloride. The diethyl mercaptal of isopyridoxal (III) was obtained in a one-step reaction from isopropylidine isopyridoxal (II) and ethyl mercaptan. The conversion of diethyl mercaptal into dimethyl acetal followed a pattern similar to that observed in the case of carbohydrates.[22,23] In an attempt to convert the diethyl mercaptal III, which has the neighboring hydroxymethyl group free, into the dimethyl acetal VI, the monomethyl acetal IV was formed, but when the neighboring hydroxymethyl group of this mercaptal (III) was esterified (V) it was possible to convert it into the desired dimethyl acetal (VI). The isolation of the acetal VI presented difficulties due to the mercuric chloride which could not be completely removed from the reaction mixture by the usual methods.[24] Concentrated aqueous ammonium hydroxide solution was found to be the most suitable reagent for this purpose; it removed mercuric chloride almost completely from the reaction mixture as an insoluble precipitate of mercuric aminochloride $Hg(NH_2)Cl$. In addition to removing mercuric chloride, it also hydrolyzed the ester groups simultaneously which was quite advantageous in the present case.[25]

With the key intermediate (VI) in hand, the synthesis of the *o*-pyridoxidial (X) was a straightforward process. Oxidation of the 4-hydroxymethyl group with manganese dioxide "B" yielded the aldehyde VII. The aldehyde VII formed an oxime (IX) with hydroxylamine and a bisdimethyl acetal (VIII) with methanol. Acid hydrolysis of the aldehyde VII yielded the desired dialdehyde X. Despite the presence of two formyl groups in the molecule, compound X did not have any carbonyl absorption in its infrared spectrum. It has been reported[26] that pyridine aldehydes have a pronounced tendency (in aqueous media) to form hydrates of the general structure $RCH(OH)_2$. In general, the stronger the electron-attracting power of the neighboring group, the easier is the hydration of the aldehyde.[26,27] As a result of the two formyl groups being *ortho* to each other in *o*-pyridoxidial hydrochloride (X), when one of them is hydrated, it interacts with the other forming a dihemiacetal type of structure which is stable even in the solid state, thereby explaining the lack of a carbonyl band in the infrared spectrum. Absence of carbonyl peaks in the infrared spectrum of pyridoxal[28] and isopyridoxal[21] have similarly been explained on the basis of their existence in the hemiacetal form. Existence of the dialdehyde X as a monohydrate is in agreement with its analytical data. *o*-Pyridoxidial (X) formed a cyclic dimethyl acetal (XIII) with methanol which was very different from the dimethyl acetal VII. Although no crystalline derivative could be isolated by treating the dialdehyde X with hydroxylamine hydrochloride, a bismethoxy oxime (XI) and a bisthiosemicarbazone[29] (XII) were obtained when the dialdehyde X was treated with methoxyamine hydrochloride or thiosemicarbazide, respectively. Formation of the above derivatives indicates that in solution there is an equilibrium between the free dialdehyde and its cyclic dihemiacetal form.

When pyridoxal, isopyridoxal, and the dialdehyde X were reduced with sodium borohydride under similar conditions, pyridoxol was obtained, indicating thereby, that in *o*-pyridoxidial (X) the two formyl groups are present in the 4 and 5 positions of the pyridine ring.

Experimental Section[30]

5-(Hydroxymethyl)-2,2,8-trimethyl-4H-*m*-dioxino[4,5-*c*]pyridine (isopropylidene pyridoxol) (I) was synthesized by the method of Korytnyk and Wiedeman.[31]

5-Formyl-2,2,8-trimethyl-4H-*m*-dioxino[4,5-*c*]pyridine (isopropylidene isopyridoxal) (II) was prepared by a modification of the method reported by Brooks, *et al.*[32] A mixture of 80 g of manganese dioxide "B" and 20 g of isopropylidene pyridoxol free base in 200 ml of chloroform was stirred at room temperature for 24 hr. The reaction mixture was diluted with 400 ml of chloroform and filtered with suction through a layer of "Celite." The contents of the funnel were washed with five 200-ml portions of boiling chloroform. The combined filtrate and washings were evaporated under reduced pressure to an oily residue to which was added 400 ml of petroleum ether (bp 40–50); it was then warmed and filtered. The filtrate was treated with a small amount of activated charcoal, filtered again, and kept in a refrigerator overnight when crystalline isopropylidene isopyridoxal was obtained. The total yield of the product, mp 62–63° (lit.[32] mp 62–63°), was 17.2 g (86.7%).

5'-(Diethyl mercaptal)-3-hydroxy-4-hydroxymethyl-2-methylpyridine (Isopyridoxal Diethyl Mercaptal) (III).—Isopropylidene isopyridoxal (II) (31.8 g) was dissolved in 150 ml of cold (−5 to −10°) ethyl mercaptan; dry hydrogen chloride gas was passed through the solution for 10 min, taking care to keep the temperature of the reaction mixture below −5°; and the solution was kept in a deep freeze for 24 hr. Excess of mercaptan was removed under reduced pressure; 400 ml of water was added to the residue; and the mixture was left overnight to hydrolyze the isopropylidene ring. This was neutralized with sodium bicarbonate solution and extracted with four 500-ml portions of ether. The ether extract was washed free of alkali, dried over anhydrous sodium sulfate, and concentrated to about 200 ml. Petroleum ether was added until turbidity occurred, and the solution was kept in a refrigerator; 31.8 g of white shining crystals of the mercaptal III, mp 99–100°, was obtained. An additional 6 g of compound III was obtained by concentrating the mother liquor and adding more petroleum ether, making the total yield 37.8 g (90.2%) (recrystallization from diethyl ether–petroleum ether mixture did not change the melting point): $\lambda_{max}^{0.1\ N\ HCl}$ 298 mμ (ε 8.7 × 10³) and 230 (sh) (4.5 × 10³); $\lambda_{max}^{0.1\ N\ NaOH}$ 315 mμ (ε 8.4 × 10³) and 245 (6.2 × 10³).

(22) J. W. Green and E. Pacsu, *J. Amer. Chem. Soc.*, **60**, 2056 (1938).

(23) D. L. MacDonald and H. G. Fletcher, Jr., *ibid.*, **81**, 3719 (1959).

(24) Extraction with solvents such as chloroform [H. R. Bolliger and M. D. Schmid, *Helv. Chim. Acta*, **34**, 1597 (1951)], ether, or methylene chloride,[23] and washing the extract with saturated potassium iodide solution to remove mercuric chloride was a very inefficient process, and mercuric chloride could not be completely removed in this way without losing much of the product. Isolation procedures involving prolonged contact of mercuric chloride with the reaction mixture were unsuitable because mercuric chloride seemed to catalyze the hydrolysis of the dimethyl acetal, resulting in a mixture of products.

(25) When mercuric aminochloride was precipitated by passing anhydrous ammonia gas into the reaction mixture, acetamide was formed which was difficult to separate from the product VI.

(26) K. Nakamoto and A. E. Martell, *J. Amer. Chem. Soc.*, **81**, 5857 (1959); **81**, 5863 (1959).

(27) S. F. Mason, *J. Chem. Soc.*, 5010 (1957).

(28) D. Heinert and A. R. Martell, *J. Amer. Chem. Soc.*, **81**, 3933 (1959).

(29) The bisthiosemicarbazone was extremely hygroscopic, and consequently the analytical data were not in good agreement with the theoretical values. The crude precipitate had a weak carbonyl absorption at 1692 cm^{-1} which disappeared on recrystallization indicating that initially a mixture of mono- and bisthiosemicarbazone was formed.

(30) All melting points are corrected. Microanalyses were carried out by Clark Microanalytical Laboratories, Urbana, Ill. Ultraviolet absorption spectra were determined on a Model 11 M Cary recording spectrophotometer. Infrared spectra were determined in potassium bromide pellets with the aid of a Beckman Model IR-7 recording spectrophotometer.

(31) W. Korytnyk and W. Wiedeman, *J. Chem. Soc.*, 2531 (1962).

(32) H. G. Brooks, Jr., J. W. Laakso, and D. E. Metzler, *J. Heterocycl. Chem.*, **3**, 126 (1966).

Anal. Calcd for $C_{12}H_{19}NO_2S_2$: C, 52.72; H, 7.00; N, 5.12; S, 23.45. Found: C, 52.46; H, 6.68; N, 5.15; S, 23.62.

3-Acetoxy-4-acetoxymethyl-5′-(diethyl mercaptal)-2-methylpyridine Hydrochloride (Isopyridoxal Diethyl Mercaptal 3,4-Diacetate Hydrochloride) (V).—Isopyridoxal mercaptal (III) (30 g), 120 ml of pyridine (freshly distilled over potassium hydroxide), and 50 ml of acetic anhydride were mixed in a round-bottom flask. After standing overnight at room temperature, the reaction mixture was evaporated under vacuum at 80–90° bath temperature. The last traces of pyridine were removed by repeated evaporations with anhydrous ether. The residue was extracted with 300 ml of anhydrous ether and filtered, and dry hydrogen chloride gas passed into the filtrate; crude isopyridoxal mercaptal-3,4-diacetate hydrochloride precipitated. Recrystallization was carried out by dissolving the hydrochloride in ethanol at room temperature, adding ether until turbidity occurred, and refrigerating. The yield obtained was 40.7 g (94%): mp 132–133°; $\lambda_{max}^{0.1\ N\ HCl}$ 274 mμ (ε 6.1 × 10³) and 218 (sh) (6.4 × 10³); $\lambda_{max}^{0.1\ N\ NaOH}$ 315 mμ (ε 8.3 × 10³) and 245 (6.4 × 10³).

Anal. Calcd for $C_{16}H_{23}NO_4S_2 \cdot HCl$: C, 48.78; H, 6.14; N, 3.55; S, 16.27. Found: C, 48.35; H, 6.09; N, 3.58; S, 16.56.

5′-(Dimethyl acetal)-3-hydroxy-4-hydroxymethyl-2-methylpyridine (Isopyridoxal Dimethyl Acetal) (VI).—To a solution of 12 g of the diacetate V in 1200 ml of boiling methanol (dried over magnesium methoxide and iodine)[33] was added 37 g of mercuric oxide and vigorous stirring started. A solution of 35 g of mercuric chloride in 140 ml of methanol was added to the above suspension; the mixture was refluxed with stirring for 30 min and then filtered hot under suction. The residue on the funnel was washed with five 200-ml portions of boiling methanol. The combined filtrate and washings were concentrated to about 750 ml under reduced pressure at 70° bath temperature and cooled and 250 ml of concentrated ammonium hydroxide solution was added to it. The copious white precipitate of mercuric aminochloride was filtered under suction and washed with methanol. The filtrate was filtered once more under gravity in order to remove suspended inorganic salts. The clear filtrate was evaporated under reduced pressure at a bath temperature of 35–45° until a white residue precipitated. The contents of the flask were extracted with ether several times, to the combined ether extracts excess of petroleum ether was added, and this was refrigerated overnight, yielding 5.89 g (89.6%) of dimethyl acetal VI in the form of white needles: mp 167–168° (recrystallization from moist diethyl ether–petroleum ether mixture did not change the melting point); $\lambda_{max}^{0.1\ N\ HCl}$ 291 mμ (ε 10.5 × 10³) and 228 (sh) (3.4 × 10³); $\lambda_{max}^{0.1\ N\ NaOH}$ 309 mμ (ε 8.3 × 10³) and 246 (7.9 × 10³).

Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.52; H, 6.87; N, 6.62.

The structure of the dimethyl acetal VI was supported by a negative Gibb's test in the presence of borate buffer,[34] by its ultraviolet spectrum in alkaline solution, which was similar to pyridoxol, and, finally, by its hydrolysis to isopyridoxal with hydrochloric acid.

Starting from isopyridoxal diethyl mercaptal (III) and following a procedure as described in detail for preparing compound VI only a monomethyl acetal (IV) was obtained, which gave a positive 2,6-dichloroquinone chloroimide test in the presence of borate buffer, indicating thereby that the 4-hydroxymethyl group was not free in this compound. The hydrochloride of compound IV was found to be identical with the hydrochloride of the monomethyl acetal of isopyridoxal prepared by the method of Korytnyk, *et al.*,[20] in its melting point and infrared and ultraviolet spectra.

5′-(Dimethyl acetal)-4-formyl-3-hydroxy-2-methylpyridine (VII).—A mixture of 2 g of the dimethyl acetal VI and 8 g of manganese dioxide "B" in 1500 ml of chloroform was stirred with a mechanical stirrer for 5 hr. The suspension was filtered and the solvent removed from the filtrate under reduced pressure at 30–35°. The residue was extracted with petroleum ether, decolorized with activated carbon at room temperature, concentrated to about 10 ml, and kept in a refrigerator. The precipitated compound was recrystallized twice from petroleum ether to yield 1.35 g (68.2%) of aldehyde dimethyl acetal (VII): mp 58–59°; $\lambda_{max}^{0.1\ N\ HCl}$ 337 mμ (ε 1.7 × 10³) and 294 (7.2 × 10³); $\lambda_{max}^{0.1\ N\ NaOH}$ 387 mμ (ε 7.1 × 10³) and 230 (15.1 × 10³).

(33) A. I. Vogel in "Practical Organic Chemistry," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1962, p 169.

(34) J. V. Scudi, W. A. Bastedo, and T. J. Webb, *J. Biol. Chem.*, **136**, 399 (1940).

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.70; H, 6.26; N, 6.78.

The structure of compound VII was verified from the fact that its infrared spectrum had a strong sharp carbonyl peak at 1673 cm^{-1} and its ultraviolet spectrum in alkaline medium had an absorption at λ_{max} 387 mμ and no absorption near 300 mμ. These data are in agreement with those reported for aldehydes that cannot form a cyclic hemiacetal (*e.g.*, isopropylidene isopyridoxal,[21] 5-deoxypyridoxal,[35] and pyridoxal-5-phosphate[36]).

4′,5′-Bis(dimethyl acetal)-3-hydroxy-2-methylpyridine Hydrochloride (VIII).—A slow stream of dry hydrogen chloride gas was passed in approximately 20 ml of sodium-dried ether for about 1 min with protection from moisture. This hydrogen chloride–ether solution was added drop by drop to a solution of 210 mg of compound VII in 40 ml of anhydrous ether with constant stirring until precipitation was complete. The precipitated hydrochloride was immediately filtered under suction, washed a few times with anhydrous ether, and dried in a vacuum desiccator over phosphorous pentoxide; 230 mg of a creamy white powder melting at 123–124° dec was obtained. A 200-mg portion of this hydrochloride was dissolved in 50 ml of absolute methanol[37] and refluxed in an oil bath at 70° for 14 hr. Part of the methanol was evaporated, ether was added to the point of turbidity, and the mixture was kept in a refrigerator whereupon impure crystals of compound VIII were obtained. The crystals were suspended in anhydrous ether and dry ammonia gas was passed into it. The precipitated ammonium chloride was filtered off. The filtrate was evaporated to dryness *in vacuo* at 40°; the residue was dissolved in 15 ml of petroleum ether and kept in a refrigerator for about 2 hr. A small amount of white crystalline material precipitated which was filtered off and identified by its melting point and ultraviolet and infrared spectra as the cyclic dimethyl acetal XIII. The filtrate was evaporated under vacuum leaving an oily residue which was carefully converted into the solid hydrochloride VIII as described earlier. The yield was 180 mg (75.8%): mp 149–150° dec; $\lambda_{max}^{0.1\ N\ NaOH}$ 316 mμ (ε 7.9 × 10³) and 247 (7.8 × 10³).[37]

Anal. Calcd for $C_{12}H_{19}NO_5 \cdot HCl$: C, 49.06; H, 6.86; N, 4.77. Found: C, 49.06; H, 6.88; N, 4.69.

5′-(Dimethyl acetal)-4′-oxime-3-hydroxy-2-methylpyridine (IX).—The dimethyl acetal VI (1 g) was oxidized to the aldehyde VII with manganese dioxide "B" in chloroform as described earlier. The petroleum ether extract obtained at the end of the reaction was evaporated to dryness, and 50 ml of 0.1 *N* hydrochloric acid added to it. The reaction mixture was diluted to 200 ml with distilled water and stirred to dissolve all the compound. A solution of 0.53 g of hydroxylamine hydrochloride in 2 ml of water was added; the oxime precipitated immediately. Solid sodium acetate was added to bring the pH to 5–6. After adding some ice crystals to cool the mixture to about 5°, the oxime was filtered under suction to yield 0.821 g (77.4%), mp 195–197° dec. An analytical sample was recrystallized from ethanol–water mixture: no change in the melting point was observed; $\lambda_{max}^{0.1\ N\ HCl}$ 324 mμ (ε 9.4 × 10³) and 272 (10.2 × 10³); $\lambda_{max}^{0.1\ N\ NaOH}$ 332 mμ (ε 8.4 × 10³) and 242 (14.9 × 10³).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.98; H, 6.07; N, 11.90.

4,5-Diformyl-3-hydroxy-2-methylpyridine Hydrochloride (*o*-Pyridoxidial Hydrochloride) (X).—The aldehyde dimethyl acetal (VII) (2 g) was heated with 100 ml of 1 *N* hydrochloric acid at 60° (water bath) for 30 min. A small amount of activated carbon was added and the reaction mixture filtered after about 10 min of heating. The filtrate was concentrated to about 1 ml, excess of acetone was added, and the solution was kept in a refrigerator overnight to yield 1.8 g (90%) of crystalline *o*-pyridoxidial hydrochloride (X), which decomposed without melting at 158–161°: $\lambda_{max}^{0.1\ N\ HCl}$ 288 mμ (ε 8.9 × 10³) and 227 (3.5 × 10³); $\lambda_{max}^{0.1\ N\ NaOH}$ 303 mμ (ε 6.2 × 10³) and 243 (6.8 × 10³); $\lambda_{max}^{pH\ 10}$ 394 mμ (ε 1.9 × 10³), 303 (4.8 × 10³), and 243 (8.7 × 10³).[38]

(35) D. Heyl, S. A. Harris, and K. Folkers, *J. Amer. Chem. Soc.*, **75**, 653 (1953).

(36) N. Viscontini, C. Ebnöther, and P. Karrer, *Helv. Chim. Acta*, **34**, 1834 (1951).

(37) The bisdimethyl acetal hydrochloride (VIII) was hydrolyzed almost immediately in 0.1 *N* HCl solution.

(38) When the spectrum at pH 10 (sodium carbonate–sodium bicarbonate buffer) was recorded immediately the absorption was at λ_{max} 400 mμ which shifted toward lower wave lengths with time. The extinction coefficient reported here was taken after 5–10 min from the time the compound was added to the buffer solution. The absorptions at λ_{max} 303 and 243 mμ did not change during this interval.

Anal. Calcd for $C_8H_9NO_4 \cdot HCl$: C, 43.75; H, 4.59; N, 6.38. Found: C, 43.84; H, 4.73; N, 6.42.

4′,5′-(Dimethoxyoxime)-3-hydroxy-2-methylpyridine (*o*-Pyridoxidial Dimethoxyoxime) (XI).—To a solution of 204 mg (2.4 mmol) of methoxyamine hydrochloride in 20 ml of distilled water 220 mg (1 mmol) of *o*-pyridoxidial hydrochloride (X), dissolved in 10 ml of distilled water, was added drop by drop with stirring. After the addition was complete, 500 mg of sodium acetate dissolved in 10 ml of distilled water was added to bring the reaction mixture to pH 5–6. The mixture was cooled in a refrigerator and the precipitated oxime was filtered and recrystallized from an ethanol–water mixture to yield 198 mg (88.5%) of white, needle-shaped crystals of dimethoxyoxime (XI): mp 106–107°; $\lambda_{max}^{0.1\ N\ HCl}$ 331 mμ (sh) (ε 8.5 × 10³), 311 (11.3 × 10³), 305 (sh) (11.0 × 10³), and 243 (16.8 × 10³); $\lambda_{max}^{0.1\ N\ NaOH}$ 362 mμ (ε 7.8 × 10³) and 236 (20.2 × 10³).

Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.82. Found: C, 54.04; H, 5.37; N, 19.16.

4′,5′-Bisthiosemicarbazone-3-hydroxy-2-methylpyridine (*o*-Pyridoxidial Bisthiosemicarbazone) (XII).—A solution of 220 mg of *o*-pyridoxidial hydrochloride (X) in 5 ml of distilled water was added drop by drop with stirring to the warm solution of 250 mg of thiosemicarbazide in 10 ml of distilled water. After adding 170 mg of sodium acetate, the reaction mixture was allowed to cool, whereupon 200 mg (64.3%) of crude bisthiosemicarbazone precipitated out. A portion was recrystallized from 95% ethanol and dried over phosphorous pentoxide at 80° under high vacuum when an orange red compound, mp 172–174° dec, was obtained.

Anal. Calcd for $C_{10}H_{13}N_7OS_2 \cdot H_2O$: C, 36.46; H, 4.59; N, 29.76; S, 19.46. Found: C, 37.26; H, 4.33; N, 30.16; S, 19.89.

1,3-Dihydro-1,3-dimethoxy-6-methyl furo[3,4-*c*]pyridin-7-ol[39] (*o*-Pyridoxidial Dimethyl Acetal) (XIII).—*o*-Pyridoxidial hydrochloride (X) (0.5 g) dissolved in 50 ml of anhydrous methanol[33] was heated with protection from moisture in an oil bath and kept at 50–60° for 5 days. The reaction mixture was cooled, ammonia gas was bubbled into it, and then it was concentrated to a very small volume. Excess of ether was added and the mixture was filtered. The filtrate was evaporated to dryness, the residue was extracted with chloroform, the extract was concentrated to about 50 ml, and excess of petroleum ether was added to it. The mixture was kept in a refrigerator overnight, yielding the dimethyl acetal XIII. It was recrystallized four times with chloroform–petroleum ether mixture to yield 0.215 g (44.8%): mp 164–165°; $\lambda_{max}^{0.1\ N\ HCl}$ 288 mμ (ε 9.3 × 10³) and 227 (3.8 × 10³); $\lambda_{max}^{0.1\ N\ NaOH}$ 304 mμ (ε 8.1 × 10³) and 241 (9.7 × 10³).

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 57.13; H, 6.25; N, 6.61.

Sodium Borohydride Reduction of 4,5-Diformyl-3-hydroxy-2-methylpyridine Hydrochloride (*o*-Pyridoxidial Hydrochloride) (X).—Over a period of 15 min, a solution of 100 mg of *o*-pyridoxidial hydrochloride (X) in 5 ml of 90% methanol was added drop by drop with stirring to a solution of 50 mg of sodium borohydride in 5 ml of 0.1 *N* methanolic sodium hydroxide. In another 15 min of stirring the reaction was complete. The excess of sodium borohydride was decomposed with a few drops of concentrated hydrochloric acid. The solution was evaporated to dryness under reduced pressure; the solid residue extracted twice with 5-ml portions of absolute ethanol and filtered. To the filtrate excess of anhydrous acetone was added and the mixture was kept overnight in a refrigerator yielding 80 mg (85%) of needle-shaped crystals. This compound was identified as pyridoxol hydrochloride (XIV), based upon its melting point and mixture melting point of 208–209° with an authentic sample and its ultraviolet and infrared spectra which were found to be identical with those of the authentic sample. Pyridoxol was also obtained when pyridoxal and isopyridoxal were treated with sodium borohydride under the conditions described above.

Registry No.—III, 15833-01-9; V, 15833-02-0; VI, 15833-03-1; VII, 15833-04-2; VIII, 15833-05-3; IX, 15832-16-3; X, 15832-17-4; XI, 15832-18-5; XII, 15832-19-6; XIII, 15832-20-9.

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N-Vinyl Derivatives of Substituted Pyrimidines and Purines[1]

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The preparation of potentially polymerizable compounds containing heterocyclic moieties of nucleic acids is described. 1-Vinyluracil was prepared by dehydrochlorination of 1-(2-chloroethyl)uracil (**3**). 1-Vinyl-3-methyluracil, 1-vinyl-4-ethoxy-2-pyrimidinone (**7**), 6-chloro-9-vinylpurine (**8**), and 2,6-dichloro-9-vinylpurine (**9**) were prepared from the unsubstituted heterocycles by a vinyl interchange reaction with vinyl acetate, catalyzed by mercuric acetate and sulfuric acid.

The importance of nucleic acids has resulted in many studies on their intramolecular forces using model systems.[2,3] Among possible model systems are polymers containing the heterocyclic moieties of nucleic acids but differing from them in the connecting backbone. To date only a few papers have been published on such models. The necessary macromolecules were usually prepared by attaching heterocycles to cellulose derivatives.[4–9] Only recently Cassidy and Jones[10] described the preparation and properties of polymers based on 5′-O-acrylthymidine. In our laboratory, a program has been started in this direction. The present paper describes the preparation of the N-vinyl derivatives of substituted pyrimidine and purine heterocycles with substituents suitable for subsequent conversion into heterocycles of nucleic acids (uracil, cytosine, adenine and guanine). This approach avoids possible difficulties with functional groups (*e.g.*, the amino group) during the polymerization reaction. N-Vinyl polymers were chosen since they have been well studied and because related poly-

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