50 ml of EtOH. The benzil employed (2 g) was added in small portions and the mixture was refluxed for 50 min. Most of the EtOH was removed by distillation and H_2O (100 ml) was added. The mixture stood overnight and was filtered, the filtrate was acidified with 10% HCl, and the solid was filtered off, washed, and recrystallized (EtOH); yield 70-75% (Table II).

The methoxybenzil derivatives were prepared by condensing the respective aldehydes,[8] and the product was then oxidized with $CuSO_4$ solution in pyridine on a boiling-water bath.[9]

Acknowledgment.—This work was carried out with a grant from the C.N.I.C.y T.

(8) N. J. Leonard, R. T. Rapala, H. L. Herzog, and E. R. Blout, *J. Am. Chem. Soc.*, **71**, 2997 (1949).

(9) H. T. Clarke and E. E. Dreger, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1958, p 87.

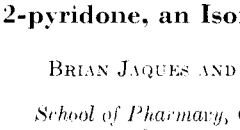
Synthesis of 3,5-Bishydroxymethyl-6-methyl-2-pyridone, an Isomer of Pyridoxine

BRIAN JAQUES AND JOHN W. HUBBARD

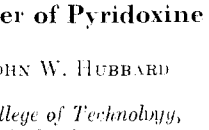
School of Pharmacy, College of Technology, Portsmouth, England

Received September 8, 1967

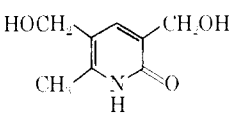
A number of positional isomers of pyridoxine (**1**) have been prepared[1] and a theory concerning the structure–activity relationship for the vitamin B_6 like compounds has been proposed.[2] The preparation and biological testing of 3,5-bishydroxymethyl-6-methyl-2-pyridone (**2**) are now described.



1



3, R′ = OH; R = H
4, R′ = OH; R = Et
5, R′ = OCH_2Ph; R = H



2

The known dibasic acid[3] **3** was converted to the diethyl ester **4** on treatment with ethanol and sulfuric acid in refluxing benzene. Reaction with $POCl_3$ followed by sodium in benzyl alcohol yielded the corresponding benzyl ether dibenzyl ester. Reduction of the benzyl ether diacid **5**, which was easier to handle than the diester, with lithium aluminum hydride afforded the ether diol which was hydrogenolyzed to give the required pyridoxine isomer.

Compound **2** exhibited no vitamin B_6 like activity against *Saccharomyces carlsbergensis* in the range 5–500 ng/ml which is consistent with the proposed structure–activity theory.[2] It showed a slight anti-B_6 activity which did not merit further investigation on higher organisms.

(1) (a) R. G. Jones, *J. Am. Chem. Soc.*, **74**, 1489 (1952); (b) F. Hoffman Swiss Patent 224,314; *Chem. Abstr.*, **43**, 1811g (1949); (c) D. Heyl, E. Luz, and S. A. Harris, *J. Am. Chem. Soc.*, **76**, 4474 (1956); (d) D. B. McCormick, M. E. Gregory, and E. E. Snell, *J. Biol. Chem.*, **236**, 2085 (1961); (e) B. van der Wal, Th. J. de Boer, and H. O. Huisman, *Rec. Trav. Chim.*, **80**, 221 (1961).

(2) E. E. Snell, *Vitamins Hormones*, **16**, 77 (1958).

(3) J. L. Simonsen, *J. Chem. Soc.*, 1022 (1908); G. Errera, *Ber.*, **33**, 2959 (1900).

Experimental Section[4]

3,5-Dicarboethoxy-6-methyl-2-pyridone (4). 6-Methyl-2-pyridone-3,5-dicarboxylic acid (19.7 g, 0.1 mole) was refluxed with absolute EtOH (300 ml), PhH (300 ml), and concentrated H_2SO_4 (5.5 ml) below a Soxhlet containing 40 g of Molecular Sieves, Union Carbide 4A, for 7 days.[5] Reduction to half-volume by evaporation under reduced pressure and cooling gave the diester as white needles: recrystallized from EtOH, mp 196–198°; 17 g (68%); ir (KCl) (cm^{-1}) 1670, 1703, 1725; nmr ($CDCl_3$) (ppm) 1.24 (*s* 1), 5.62 (*q* 4), 7.2 (*s* 3), 8.65 (*tr* 6). *Anal.* ($C_{12}H_{15}NO_5$) C, H, N.

2-Chloro-3,5-dicarboethoxy-6-methylpyridine.—3,5-Dicarboethoxy-6-methyl-2-pyridone (15 g, 0.059 mole) and $POCl_3$ (75 ml) were refluxed together for 3.5 hr under anhydrous conditions. The cooled solution, in 5-ml portions, was cautiously added to ice water with shaking. The buff precipitate (15.3 g) was filtered and dried in a vacuum desiccator. Ether extraction of the filtrate afforded further material (1.14 g). Crystallization from EtOH–H_2O gave white needles: mp 53.5–54.5°; 14 g (85%); ir (KCl) (cm^{-1}) 1730; nmr ($CDCl_3$) (ppm) 1.5 (*s* 1), 5.65 (*q* 4), 7.2 (*s* 3), 8.6 (*tr* 6). *Anal.* ($C_{12}H_{14}ClNO_4$) C, H, Cl, N.

2-Benzoxy-6-methylpyridine-3,5-dicarboxylic Acid (5).—To Na (1.6 g, 0.0695 g-atom) dissolved in benzyl alcohol (200 ml) was added 2-chloro-3,5-dicarboethoxy-6-methylpyridine (11.5 g, 0.0425 mole) and the mixture stirred at about 18° for 17 hr. AcOH (4.2 ml, 0.07 mole) was added dropwise to the stirred solution and the bulk of the solvent was removed under reduced pressure. The residue was dissolved in absolute EtOH (75 ml), 10% aqueous NaOH (75 ml) was added, and the whole was refluxed for 3 hr. Evaporation to half-volume under reduced pressure and cautious acidification of the residual liquor with dilute HCl gave a white precipitate, 9.08 g (74%). Crystallization from EtOH–H_2O gave the analytical sample: softens 186–188°, decomposes 260°; ir (KCl) (cm^{-1}) 1695, 1720. *Anal.* ($C_{14}H_{13}NO_5$) C, H, N.

2-Benzoxy-3,5-bis(hydroxymethyl)-6-methylpyridine.—A solution of crude benzyl ether diacid (9 g, 0.0314 mole) in dry THF (500 ml) was refluxed for 3 hr below a Soxhlet containing $LiAlH_4$ (2.5 g, 0.066 mole). The mixture was cooled and stirred, and 7% aqueous NaOH (7.5 ml) was added dropwise. Filtration of the gray precipitate and evaporation of the filtrate under reduced pressure gave crude benzyl ether diol. Crystallization from petroleum ether (bp 40–60°) gave white needles: mp 86.5–87°; 3.14 g (38%) first crop; ir (KCl) (cm^{-1}) 1200, 1000; nmr ($CDCl_3$) (ppm) 4.6 (*s* 2), 5.48 (*s* 2) 5.51 (*s* 2) 7.15 (broad 2). *Anal.* ($C_{15}H_{17}NO_3$) C, H, N.

3,5-Bishydroxymethyl-6-methyl-2-pyridone (2).—The benzyl ether diol (5.4 g, 0.021 mole) in absolute EtOH (100 ml) was shaken with 5% Pd–C (250 mg) under H_2 at the ambient temperature and pressure, resulting in an uptake of 505 ml of H_2 (equivalent to 2H/mole). Removal of the catalyst and evaporation of the liquor gave the pyridone in quantitative yield. Crystallization from EtOH gave fine white needles: mp 181–181.5°; ir (KCl) (cm^{-1}) 1650; nmr (D_2O) (ppm) 2.2 (*s* 3), 5.4 (*s* 4), 7.5 (*s* 3). *Anal.* ($C_8H_{11}NO_3$) C, H, N.

The **diacetate** was prepared in AcOH: mp 146–148° (C_8H_{15}); ir (KCl) (cm^{-1}) 1240, 1650, 1725. *Anal.* ($C_{12}H_{15}NO_5$) C, H, N.

Acknowledgment.—We thank Nederlands Instituut voor Volksvoeding for testing compound **2**.

(4) Melting points are uncorrected. The notation in parentheses used in describing nmr spectra refers to the type and proton integral of the signal.

(5) Y. Ito, *Nippon Zaseka Zasshi*, **83**, 195 (1962).

3-Aminomethyl-5-hydroxybenzo[*b*]thiophenes[1]

E. CAMPAIGNE AND T. R. BOSIN

Chemistry Laboratories of Indiana University Bloomington, Indiana 47401

Received September 22, 1967

In our continuing study of the synthesis and pharmacological properties of sulfur analogs of biologically

(1) Contribution No. 1516. Benzo[*b*]thiophene Derivatives. XI. Part X: E. Campaigne and T. Bosin, *J. Med. Chem.*, **10**, 945 (1967).