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.

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

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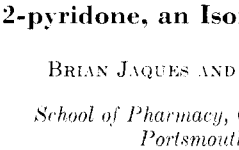
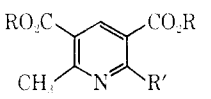
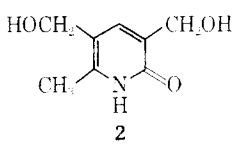
A number of positional isomers of pyridoxine (**1**) have been prepared[1] and a theory concerning the structure–activity relationship for the vitamin B_6 like compounds has been proposed.[2] The preparation and biological testing of 3,5-bishydroxymethyl-6-methyl-2-pyridone (**2**) are now described.



1



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



2

$\rightleftharpoons$ hydroxypyridine tautomer

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.

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

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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.* ($C_{15}H_{13}NO_5$) 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* 1), 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_6H_6); 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.

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

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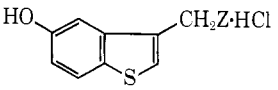
In our continuing study of the synthesis and pharmacological properties of sulfur analogs of biologically

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

active indole derivatives, some 3-aminomethyl-5-hydroxybenzo[*b*]thiophenes (I) were prepared and evaluated pharmacologically. Since 5-hydroxylation of biologically active indole derivatives imparts increased activity,[2] and 5-hydroxygramine produces strong uterine contractions,[3] the pharmacodynamic properties of these derivatives might be of interest.



Ia, Z = NH_2

Ib, Z = N⟨ ⟩

Gramine possesses convulsant, parasympathomimetic,[4] antiepinephrine,[5] oxytocic,[6] serotonin-mimetic, and antiserotonin properties.[2,3,7] The sulfur isosteres of gramine and related derivatives have been prepared and found to exhibit the variety and nonselectivity in pharmacological properties characteristic of the corresponding indole compounds.[8] Iddon has prepared some 5-substituted sulfur analogs of gramine and related tertiary amines and found them to be orally active and to exhibit strong *in vivo* antiserotonin activity, in contrast to gramines which are often extremely active *in vitro* but only weakly active *in vivo*.[9] Some 5-hydroxy- and 5-amino-2-aminomethylbenzo[*b*]thiophenes have been synthesized and the latter have been shown to be weakly antagonistic toward serotonin, histamine, and acetylcholine.[10] A patent has claimed 3-(1,2,3,4-tetrahydroisoquinolinomethyl)- and 3-(isoindolinomethyl)benzo[*b*]thiophene to have useful hypotensive properties.[11]

Compound Ia was prepared *via* a Gabriel reaction involving 3-bromomethyl-5-benzoyloxybenzo[*b*]thiophene[12] (II) and potassium phthalimide in dimethylformamide, followed by hydrolysis of the substituted phthalimide intermediate according to the method of Ing and Manske.[13] Compound Ib was synthesized by treating II with piperidine in benzene solution at room temperature, followed by basic hydrolysis.[14]

Pharmacology.—Compounds Ia and Ib were tested as both substrates and inhibitors of monoamine oxidase and as substrates for bovine plasma amine oxidase.[15]

TABLE I

PHARMACOLOGICAL SCREENING RESULTS

Compd	Substrate act. MAO	Substrate act. PAO	% inhib act. of MAO
Ia	None[a]	None[a]	64 (1×10^{-3} *M*)
Ib	...	...	92 (1×10^{-3} *M*)
			12 (1×10^{-4} *M*)
Pargyline·HCl	...	...	100 (1×10^{-3} *M*)
			100 (1×10^{-4} *M*)

[a] From 1×10^{-3} to 2×10^{-4} *M*.

The results of this evaluation are summarized in Table I. The lack of substrate activity in Ia is surprising in view of Zeller's finding[16] that *meta*-substituted benzylamines are better MAO substrates than either the *ortho*-, *para*-, or unsubstituted benzylamines.

The CNS effect of Ia was studied by amplitude analysis of the cortical electroencephalogram of male albino rabbits.[17] No detectable stimulant or depressant effects were observed within the dose range 0.2–2.0 mg/kg, indicating pharmacological inactivity as compared to 3-β-aminoethyl-5-hydroxybenzo[*b*]thiophene in this test.[12,18]

Experimental Section[19]

3-(N-Phthalimidomethyl)-5-benzoyloxybenzo[*b*]thiophene.—3-Bromomethyl-5-benzoyloxybenzo[*b*]thiophene[12] (2.0 g, 5.76 mmoles) and potassium phthalimide (1.07 g, 5.76 mmoles) were dissolved in 15 ml of DMF. The resulting solution was heated to reflux (153°) for 3 hr, cooled to room temperature, and poured into 200 ml of water. The tan solid which separated was collected and air dried. Recrystallization from EtOAc and decolorization with Norit gave 1.84 g (77%) of white needles, mp 205–206.5°. *Anal.* ($C_{24}H_{15}NO_4S$) N.

3-Aminomethyl-5-hydroxybenzo[*b*]thiophene Hydrochloride (Ia).—3(N-Phthalimidomethyl)-5-benzoyloxybenzo[*b*]thiophene (4.2 g, 0.010 mmole) was dissolved in MeOH and treated with 1.3 ml of N_2H_4 (95+%). The resulting solution was heated to reflux and maintained for 3 hr, whereupon a white precipitate separated. The reaction mixture was cooled to room temperature, H_2O (30 ml) was added, and MeOH was removed under reduced pressure. HCl (12 ml) was added and the mixture was heated to reflux for 1 hr, and cooled to 0° prior to filtration to remove phthalhydrazide. The acidic yellow filtrate was made alkaline with 15% NaOH solution and heated 1 hr to ensure hydrolysis of the benzoyloxy group. The alkaline solution was saturated with CO_2 (pH 8.3) and continuously extracted with ether for 1 week. During the ether extraction the product precipitated from solution. A trace of MeOH was added to the ether extract to complete solution, prior to treatment with dry HCl. The crude product was isolated by evaporation of the ether solution. Recrystallization of the crude product from MeOH–EtOAc and decolorization with Norit gave 1.3 g (59%) of long white needles: mp 231–232°; ν_{max}^{KBr} 2.98 (phenolic OH), 3.23–3.45 (NH_3^+), and strong absorptions at 6.24, 6.70, and 6.94 μ; uv spectrum, $\lambda_{max}^{95\%\ EtOH}$ [mμ (ε)] 235 (15,950), 262 (6500), 270 (5930), 312 (3450), and 317 (3340); uv spectrum with 1 drop of 10% NaOH, $\lambda_{max}^{95\%\ EtOH}$ [mμ (ε)] 250 (22,400) and 334 (5040). *Anal.* ($C_9H_{10}ClNOS$) C, H, N.

3-Piperidonomethyl-5-hydroxybenzo[*b*]thiophene Hydrochloride (Ib).—A solution of 3-bromomethyl-5-benzoyloxybenzo[*b*]-

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(10) S. T. Reid, Ph.D. Thesis, The University of Glasgow, 1960.

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(19) Melting points were taken on a Mel-Temp capillary melting point apparatus and are corrected. The microanalyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind. Where analyses were indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Ir spectra were determined with a Perkin-Elmer Model 137 Infracord and uv spectra with a Bausch and Lomb Spectronic 505.

thiophene (1.0 g, 2.88 mmoles) in 20 ml of dry C_6H_6 was treated with piperidine (0.29 ml, 2.88 mmoles) and allowed to stir at room temperature for 2 weeks. C_6H_6 was removed under reduced pressure, yielding a yellow solid which was dissolved in H_2O (40 ml), treated with excess 10% NaOH, and gently warmed for 1 hr. The reaction mixture was then poured into H_2O (100 ml) and the pH was adjusted to 7 with dilute HCl. The aqueous solution was extracted with four 50-ml portions of ether, and the combined ether extracts were dried (Na_2SO_4) and treated with dry HCl, producing an oil. The oil solidified readily under vacuum, and was recrystallized from EtOH–$CHCl_3$ to yield 0.48 g (58%) of thick white crystals: mp 252–253.5° dec; ν_{max}^{KBr} 3.10 (H-bonded phenolic OH), 3.7–3.9 (HN^{+}), and 6.23 μ (C=C aromatic). *Anal.* ($C_{14}H_{15}ClNOS$) C, H, N.

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Adamantoyl Esters of Pyridoxol[1]

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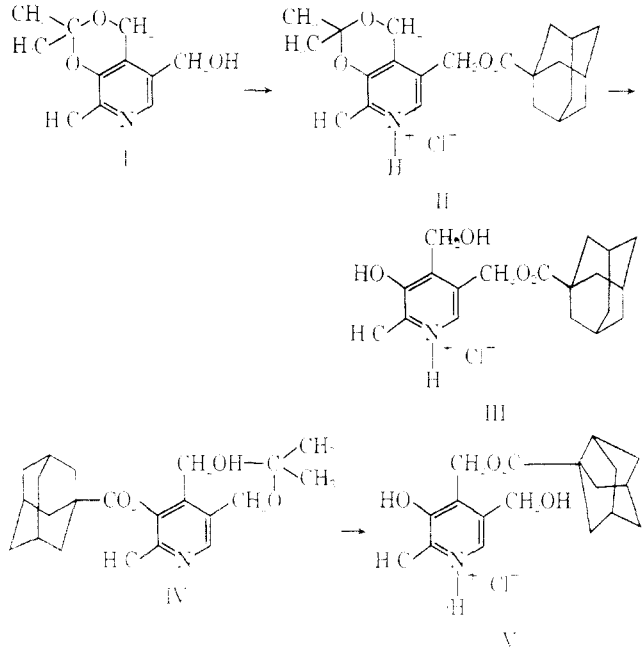
Gerzon and his coworkers[2-5] have shown that introduction of the adamantane group imparts interesting biological properties to representative compounds of various classes. Similarly, Zakrzewski, *et al.*,[6] found that N-adamantyl-*p*-aminobenzamide was an inhibitor of *Escherichia coli*. Hydrophobic binding of the adamantane moiety to the receptor site has been invoked as a probable explanation for the biological activity of the various adamantane derivatives.[3]

In order to investigate the chemical and biological usefulness of the adamantoyl group in vitamin B_6 chemistry and pharmacology, we prepared some adamantoates of pyridoxol (Scheme I). Of particular interest to us is their potential utility in probing for hydrophobic regions within the receptor sites at which pyridoxol analogs bind. The possibility of the existence of such regions suggested itself in the course of our previous studies.[2]

Methods for the selective introduction of the adamantoyl group into the α^5 and α^4 positions of pyridoxol are indicated in Scheme I and utilize the two isomeric isopropylidene derivatives[7,8] of pyridoxol as starting

SCHEME I



materials. Adamantoylation by adamantoyl chloride had to be carried out under more vigorous conditions than the similar reactions with other acyl chlorides,[7,8] indicating steric hindrance. Nevertheless, 3-O-adamantoyl-α^5,α^5-isopropylidenepyridoxol (IV) was found to rearrange to give the α^4-O-ester V; in this respect, adamantoyl does not appear to differ from other acyl groups, although it is conceivable that the bulk of the adamantoyl group could interfere with the formation of the orthoacid intermediate during the rearrangement.[9] The structures of the resulting esters have been confirmed by nmr, ir, and uv spectroscopy. The free phenolic hydroxyl in α^4-O-adamantoylpyridoxol is indicated by a positive Gibbs test and by characteristic shifts in the uv spectra in acidic and basic solutions.[5]

Preliminary evaluation of the α^4- and α^5-adamantoates (III and V) with *Saccharomyces carlsbergensis* (ATCC 9080) indicates that they are comparatively weak growth inhibitors, producing approximately half-maximal growth at 10^{-4} *M*.[10]

Experimental Section

Where analyses are indicated only by symbols of elements, analytical results obtained for those elements were within 0.3% of the theoretical values.

α^4,3-O-Isopropylidene-α^5-O-adamantoylpyridoxol (II).—To a stirred solution of α^4,3-O-isopropylidenepyridoxol[7] (I, 0.50 g) in 5 ml of anhydrous pyridine, adamantoyl chloride (1.0 g) in 3–4 ml of pyridine was added. Stirring was continued for 24 hr and then the mixture was refluxed for 0.5 hr. (The reaction was only partially complete after 4 hr.) Water (few drops) was introduced, the mixture was stirred for 1 hr, poured into ice water (50 ml), let stand overnight, and extracted with ether. The ether extract was washed (Na_2CO_3, H_2O) and dried ($CaSO_4$). Evaporation of the ether solution *in vacuo* left an oil, from which 0.81 g (83%) of the crude hydrochloride (mp 140–160°) was obtained by the addition of anhydrous ethereal HCl. Recrystallization from C_6H_6–ether raised the melting point to 173–174.5°. *Anal.* ($C_{22}H_{30}ClNO_4$) C, H, N.

α^5-O-Adamantoylpyridoxol Hydrochloride (III).—α^4,3-O-Isopropylidene-α^5-O-adamantoylpyridoxol (II, 0.177 g) was re-

(1) Pyridoxine Chemistry. XVII. Previous papers in this series: H. Ahrens and W. Korytnyk, *J. Heterocyc. Chem.*, in press, part XVI of the series; W. Korytnyk and B. Paul, *J. Org. Chem.*, **32**, 3791 (1967), part XV of the series; and ref 2.

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