SYNTHESIS OF BIS(5-PYRIDOXYL) DISULFIDE (PYRIDITOL)

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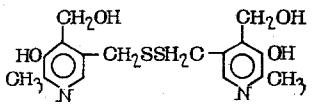
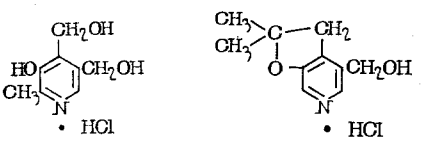
Pyriditol – bis(5-pyridoxyl) disulfide (I) – has become widely used as a well- tolerated psychotropic preparation [1]. It has the properties of an antidepressant with a sedative component, potentiates the antispasmodic effect of phenobarbital, is nontoxic [2], and has an in vivo inhibiting effect on several pyridoxal-dependent enzyme systems [3].



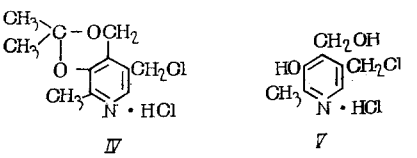
I

Several methods for preparing (I) are known [4-7].

Since we wanted to make a preparation for pharmacological studies, we synthesized (I) from compound (III), which we prepared in 93-95% yield by the method of [4] by passing hydrogen chloride through a suspension of (II) in acetone followed by precipitation with diethyl ether at −30°C. Increase in the temperature of crystallization to −12°C reduced the yield to 87%.



II III

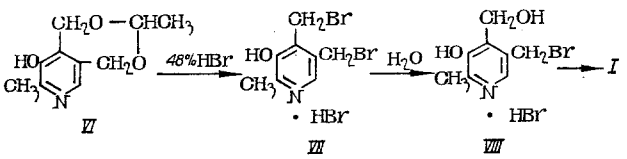


IV V

We carried out the substitution of the 5-hydroxyl group in (III) by chlorine to form (IV) by reaction with thionyl chloride in diethyl ether in the presence of a catalytic amount of dimethylformamide. Dimethylformamide is known [8] to form a complex with thionyl chloride that is more reactive than thionyl chloride itself.

By using dimethylformamide we were able to raise the yield of (IV) from 80 to 97.5% and to reduce the reaction time by a factor of 1.7; replacement of diethyl ether by methylene chloride gave quantitative yields of (IV). Treatment of (IV) with 10% hydrochloric acid at 65-70°C gave 2-methyl-3-hydroxy-4-(hydroxymethyl)-5-(chloromethyl)pyridine (V) [9]. Increased hydrochloric acid concentrations and higher temperature resulted in the formation of a mixture of (V) and (II); reduction in temperature to 40-50°C halved the rate of formation of (V) from (IV). Reaction of (V) with sodium disulfide gave (I) in 70% yield.

To obviate the use of potentially explosive and highly inflammable solvents (diethyl ether, acetone), simplify the synthesis, and reduce the cost we have suggested the following route to (I) [10]:



VI VII VIII

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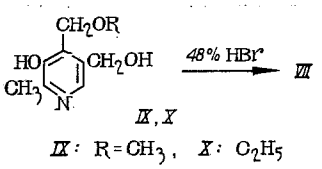
As the starting compound in this synthesis we used the 4,5-ethylidene derivative of pyridoxine (VI), which is an intermediate in the synthesis of vitamin B_6 in one of the published methods [11]. Refluxing (VI) with hydrobromic acid gave (VII) in 83.3% yield. In compound (VII) both bromine atoms are labile and readily react with various nucleophiles. However, treatment of (VII) with water at 50-55°C substituted only the bromine in position 4 by hydroxyl (quantitatively) while leaving the bromomethyl group in position 5 unchanged. The greater lability of bromine in position 4 may be due to the higher positive charge on the C_4 atom of the pyridine ring of compound (VII). We prepared compound (I) in 75.5% yield from the 5-bromo derivative of pyridoxine (VIII) by treatment with sodium disulfide without isolating it from the reaction mixture.

Reflux of the 4-ethyl ether of pyridoxine (X), which is also an intermediate in the synthesis of vitamin B_6, with hydrobromic acid gave (VII) in 66% yield [12].

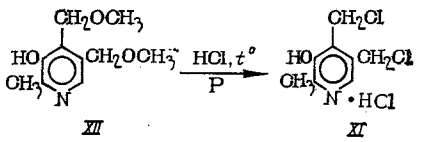


IX, X

IX: R = CH_3, X: C_2H_5

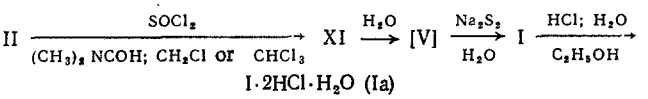
Replacement of (X) by the 4-methyl ether of pyridoxine (IX) gave (VII) in 62% yield.

2-Methyl-3-hydroxy-4,5-bis(chloromethyl)pyridine hydrochloride (XI) can be prepared by heating 2-methyl-3-hydroxy-4,5-bis(methoxymethyl)pyridine (XII) with concentrated hydrochloric acid in a sealed tube in 89.6% yield [13]:



XII XI

Compound (XI) is a convenient intermediate for the synthesis of (I). Starting from this we have developed a new route to (I) [14] that avoids the deficiencies of the other methods. In this synthesis, which is suitable for commercial use, we prepared compound (XI) from pyridoxine hydrochloride (II) by reaction with thionyl chloride in the presence of dimethylformamide in methylene chloride or chloroform. We found the optimum reaction conditions and ratio of (II), methylene chloride (or chloroform), dimethylformamide, and thionyl chloride at which pyridoxine hydrochloride is completely converted to (XI); we isolated this compound in 97.5-98% yield.



I·2HCl·H_2O (Ia)

Compound (V) was prepared by hydrolysis of (XI) at 45-50°C with a (XI): water ratio of 1:15; treatment of (V) with sodium disulfide without isolating it from the reaction mixture gave (I) in 85% yield. Recrystallization of (I) from the alcoholic solution of hydrochloric acid gave the dihydrochloride monohydrate (Ia) in 76% yield. When the reaction was carried out without isolating (I), the yield of (Ia) was 80% based on (XI).

EXPERIMENTAL

3,4'-O-Isopropylidenepyridoxine Hydrochloride (III). This was prepared by the method of [4] and crystallized at −30 to −40°C over a period of 2 h. The yield was 93.5%, mp 204-205°C; R_f 0.597 on Silufol UV_{254} in methyl ethyl ketone−25% aqueous ammonia (85:15). A test for phenolic hydroxyl with ferric chloride was negative.

3,4'-O-Isopropylidene-2-methyl-3-hydroxy-4-(hydroxymethyl)-5-(chloromethyl)pyridine (IV). To (III) (10 g) in ether (110 ml) and dimethylformamide (0.8 ml) was added thionyl chloride (24 ml). The mixture was refluxed with stirring for 3 h. After crystallization at −6 to −8°C over a period of 12 h the precipitate was separated and dried in air. The yield was 10.51 g (97.5%), mp 184-185°C. Found, %: C 50.32, H 5.87, Cl 26.58, N 4.91. $C_{11}H_{14}ClNO_2 \cdot 2HCl$. Calculated, %: C 50.01, H 5.72, Cl 26.85, N 5.30.

2-Methyl-3-hydroxy-4-(hydroxymethyl)-5-(chloromethyl)pyridine Hydrochloride (V). A solution of

(IV) (30 g) in 10% hydrochloric acid (300 ml) was heated at 65-70°C for 1 h and then decolorized with charcoal. The colorless solution was evaporated to dryness under vacuum. The residue was crystallized from 99.8% ethanol (80 ml) at −4 to −6°C. The precipitate was separated, washed with ethanol (15 ml), cooled to −6°C, and dried to give 20.04 g (73.2%), mp 168-170°C; the filtrate gave a further 3.40 g (12.4%), mp 168-170°C. The total yield of (V) was 85.6%. Found %: C 42.86, H 4.98, Cl 31.48, N 6.22, $C_8H_{10}ClNO_2 \cdot HCl$. Calculated, %: C 42.88, H 4.91, Cl 31.65, N 6.25.

2-Methyl-3-hydroxy-4,5-bis(bromomethyl)pyridine Hydrobromide (VII). A. Compound (II) (10 g) was refluxed in 48% hydrobromic acid (120 ml) for 1 h. After crystallization at −4 to −6°C the precipitate was separated, washed with acetone, and dried. The yield was 10.11 g (59%), mp 225-227°C. Literature: mp 224-228°C [15], 223-224°C [12]. Found, %: C 25.64, H 2.75, Br 63.3, N 3.94. $C_8H_9Br_2NO \cdot HBr$. Calculated, %: C 25.55, H 2.68, Br 63.77, N 3.72.

B. Treatment of (IX) with 48% hydrobromic acid and isolation of (VII) was carried out by method A. The yield was 62%, mp 225-227°C.

C. Compound (VII) was prepared from (VI) by method A. The yield was 83.3%, mp 225-227°C.

2-Methyl-3-hydroxy-4,5-bis(chloromethyl)pyridine Hydrochloride (XI). To (II) (10 g) in methylene chloride (10 ml) and dimethylformamide (0.2 ml) was added thionyl chloride (12 ml). The mixture was refluxed for 7 h. After cooling to 20°C the precipitate was separated, washed with methylene chloride, and dried. The yield was 11.50 g (97.5%), mp 200-203°C. Literature: mp 205-208°C [13] and 175-190°C [15]. Found, %: C 39.62, H 4.19, Cl 43.99, N 6.22. $C_8H_9Cl_2NO \cdot HCl$. Calculated, %: C 39.61, H 4.15, Cl 43.83, N 5.77.

Bis(5-pyridoxyl) Disulfide (I). Method A. Compound (V) (15 g) in water (33 ml) was added dropwise at 60°C to a solution of sodium disulfide [from sodium sulfide (15.9 g) and sulfur (2.1 g) in water (33 ml)]. Stirring was continued at this temperature for 2 h. After cooling to 20°C the precipitate was separated and treated with 10% hydrochloric acid (45 ml) while heated to 80°C. Sulfur was filtered off. The filtrate was neutralized with 10% aqueous sodium hydroxide to pH 7.0. The precipitate was separated, washed with water, and dried. The yield was 8.63 g (70%), mp 214-215°C (decomposition). Found, %: C 52.15, H 5.62, N 7.71, S 17.52. $C_{16}H_{20}N_2O_4S_2$. Calculated, %: C 52.17, H 5.43, N 7.61, S 17.32. Method B. To a solution of sodium disulfide [from sodium sulfide (2.26 g) and sulfur (0.29 g) in water (3.2 ml)] was added at 20-18°C (VIII), prepared by heating (VII) (2 g) in water (27 ml) at 60-65°C for 45 min. The reaction mixture was stirred at 50°C for 15 min. The precipitate was separated. Subsequent treatment of the precipitate followed method A. The yield was 0.74 g (75.5%), mp 214-215°C (decomposition). Method C. Compound (XI) (10 g) in water (150 ml) was heated at 45-50°C for 1.5 h. The resulting solution of (V) was added to a solution of sodium disulfide [from sodium sulfide (16.8 g) and sulfur (2.24 g) in water (25 ml)]. The mixture was stirred at 40°C for 2 h and then cooled to 20°C. The precipitate was separated. Subsequent treatment followed method A. The yield was 6.47 g (85%), mp 214-215°C.

Bis(5-pyridoxyl) Disulfide Dihydrochloride Monohydrate (Ia). Method A. Compound (I) (6.47 g) was refluxed for 30 min in a mixture of hydrochloric acid (3.24 ml; d_4^{20} 1.18) and anhydrous alcohol (13 ml). The reaction mixture was then cooled to between −4 and −6°C. The precipitate was separated, dried, and crystallized from 10% hydrochloric acid. The yield was 6.13 g (76%), mp 135-138°C. Found, %: C 41.80, H 5.11, Cl 15.32, N 6.42, S 13.63. $C_{16}H_{20}N_2O_4S_2 \cdot 2HCl \cdot H_2O$. Calculated, %: C 41.82, H 5.26, Cl 15.43, N 6.09, S 13.95. Method B. Compound (XI) (2 g) was heated in water (35 ml) at 60-65°C for 1.5 h. The mixture was cooled to 20°C and poured into a solution of sodium disulfide [from sodium sulfide (3.36 g), sulfur (0.45 g), and water (5 ml)]. The mixture was stirred at 60°C for 2 h and cooled to 20°C. The precipitate was separated and dried. Subsequent treatment followed method A. The yield was 1.51 g (80%), mp 135-138°C.

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SEPARATION OF NUCLEOSIDE 5'-POLYPHOSPHATES ON A MODIFIED GEL CONTAINING DIHYDROXYBORYL GROUPS

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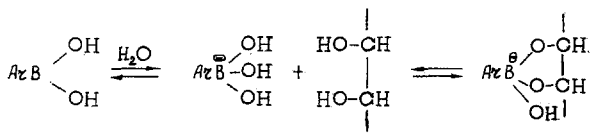
As a result of the increased demand for nucleoside polyphosphates to fulfill the requirements of pharmacology, experimental medicine, and biochemistry, there is a need to investigate new, profitable methods for their preparation, isolation, and purification.

The known methods for the separation of mixtures of nucleosides obtained by fermentation or chemical synthesis in most cases require the use of strongly basic resins such as Dowex 1 or Dowex 2. The solutions obtained in this way are usually of inadequate purity, and require further purification by treatment with decolorizing resins [1], or on columns of activated charcoal [2]. In addition, the mononucleotide fraction cannot always be freed from inorganic phosphate.

In order to develop new methods to supplement the known ones for the isolation of ATP from mixtures obtained by biophosphorylation of adenosine by the enzyme complex of brewer's yeast [3], the behavior of adenosine and the sodium salts of the adenine nucleotides has been examined on columns containing DEAE-Sephadex modified by dihydroxyboryl groups (DEBAE-Sephadex A-25) (I) [4]. The use of polymers containing dihydroxyboryl groups for the separation of mixtures of nucleosides and nucleotides [5] is based on the ability of cis-diols to form complexes in aqueous solution with the anions of arylboric acids.



It might be anticipated that the combination of the complexing and anionic properties of the polymeric gels I would make it possible to utilize them for the separation of mixtures of adenosine and adenosine phosphates, the stability constants of the arylboronate complexes of which are similar [6], whereas the amount of contaminant phosphate groups is different.

Chromatography was carried out on polymer I in its acetate and chloride forms. The solution used contained various molar amounts of adenosine, AMP, ADP, and ATP. Sorption onto the column was carried

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