pooled and lyophilized to give 45.75 mg of [2,4-diisoleucine]-oxytocin as a white powder, $[\alpha]^{25}D$ $-35.7°$ (c 0.47, 1 N AcOH). *Anal.* ($C_{41}H_{72}N_{11}O_{10}S_2$) C, H, N.

The sample was hydrolyzed for 90 hr in 6 N HCl at 110° and analyzed on a Beckman/Spinco amino acid analyzer according to the method of Spackman, Stein, and Moore.[24] The molar ratios obtained with glycine taken as 1.0 were: aspartic acid, 1.0; proline, 1.1; glycine, 1.0; cystine, 0.95; isoleucine, 3.0; leucine, 1.0; and NH_3, 2.0. Prolonged hydrolysis was necessitated by the difficulty in the hydrolysis of an isoleucyl-isoleucine peptide bond.[2,6,25]

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Selective Modifications of the α^4-Position of Pyridoxol. I. Extension and Branching of the 4-Side Chain[1]

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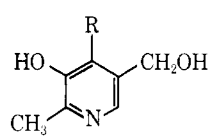
To develop general methods for modifying the 4-position, various blocking groups have been introduced into the α^5- and 3-O-positions of pyridoxol. Starting with 3,α^5-O-dibenzylpyridoxol, we have synthesized a homolog of pyridoxol with a 3-C side chain in the 4-position. α^4-Methylpyridoxol has also been synthesized. The method appears to be of considerable promise for introducing various modifications into the 4-position. In some cases, however, certain deblocking procedures give anomalous results. Thus deblocking of 3,α^5-dibenzyl-α^4-phenylpyridoxol with HCl gives a cyclic derivative, whereas hydrogenolysis gives α^4-phenyl-4-deoxypyridoxol.

Pyridoxol analogs obtained by modification of the 4-position (I, R = CH_2OH) have been of considerable



I

interest in enzymatic and pharmacological studies. 4-Deoxypyridoxol (4-DOP; I, R = CH_3) is a potent antagonist of vitamin B_6 in a number of systems, and its antitumor effects have been studied extensively.[2b] α^4-O-Methylpyridoxol ("4-methoxypyridoxol"; I, R = CH_2OCH_3) was also found to be a potent antagonist of vitamin B_6 in some mammalian systems,[3] but in some tissues was subject to demethylation.[4] Replacement of the 4-methyl H's in 4-DOP with F (I, R = CF_3) renders the compound less active in various systems,[5] and replacement of the entire 4-side chain with H (I, R = H)[6] or with OH[7] considerably reduces inhibitory potency (test organism: *Saccharomyces carlsbergensis*). On the other hand, replacement of the aldehydic oxygen of pyridoxal with bulky nitrogenous groups, such as hydroximino, azino, and various hydrazone groups (I, R = CH=NHNHR), makes them powerful inhibitors of pyridoxal phosphokinase *in vitro*.[8a] Compounds of this type have also been found to be of some biological interest as inhibitors of human neoplastic cells *in vitro*[9a] and retarders of S-180 tumor growth.[9b]

Some pyridoxol analogs that have the 5-CH_2OH unchanged, such as in I, have been found to be susceptible to phosphorylation catalyzed by pyridoxal phosphokinase,[8] and the phosphorylated analogs are capable of effective competition with the cofactor pyridoxal phosphate for the same site on the apoenzyme.[2a]

In this study we have developed methods for the selective modification of the 4-position. A suitable intermediate was required which would parallel the general utility of α^4,3-O-isopropylidenepyridoxol (II) for modifying the 5-CH_2OH group.[10] Pyridoxal (I, R = CHO) or pyridoxic acid (I, R = CO_2H) could not be used because of the tendency of these compounds to form a hemiacetal or a lactone, respectively.[11] Thus at least the α^4-OH of pyridoxol had to be blocked.[12] A suitable blocking group was benzyl, which was introduced by either one of the methods outlined in Scheme I to give α^5-O-benzylpyridoxol (V).

It was also desirable to block the phenolic OH in V with a suitable blocking group in order to prevent it from interfering with the substitution reactions and to make the intermediate soluble in organic solvents. Benzylation of the phenolic OH of 5-O-benzylpyridoxol was readily accomplished with dimethylphenylbenzylammonium hydroxide ("leucotrope"),[13] which re-

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(12) R. P. Singh and W. Korytnyk [*J. Med. Chem.*, **8**, 116 (1965)] have been using benzoyl groups for selective blockage of the α^5-hydroxyl group. This approach had serious limitations because of the instability of the group and other factors.

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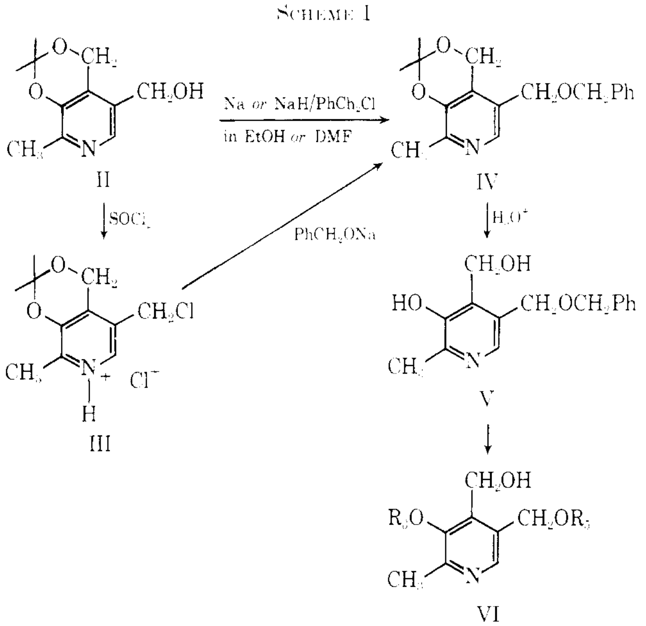
acts selectively with the phenolic OH, and does not attack the pyridine N. The resulting 3,α^5-*O*-dibenzylpyridoxol (VI, R_3 = R_5 = CH_2Ph) served as the key intermediate in further syntheses.

In addition to these intermediates other 3,5-blocked pyridoxol derivatives have also been prepared by us. Thus methylation of V with CH_2N_2 gave the more stable 3-*O*-methyl-α^5-*O*-benzylpyridoxol (VI, R_3 = CH_3, R_5 = CH_2Ph). Two additional 3,α^5-*O*-blocked derivatives, the 3-*O*-SO_2Me and 3-*O*-Me derivatives of α^5-*O*-benzoylpyridoxol (VI, R_3 = CH_3SO_2 and CH_3, R_5 = COPh), have also been prepared as the result of our earlier studies.[14] The 4-CH_2OH groups in these compounds have been converted into CH_2Cl and CHO, but we have not as yet utilized the resulting intermediates for further syntheses.

Next, various methods and conditions for removing the blocking groups in 3,α^5-*O*-dibenzylpyridoxol (VI, R_3 = R_5 = CH_2Ph) were investigated. Benzyl can be removed in two steps. Heating a 1 *N* HCl solution

SCHEME I

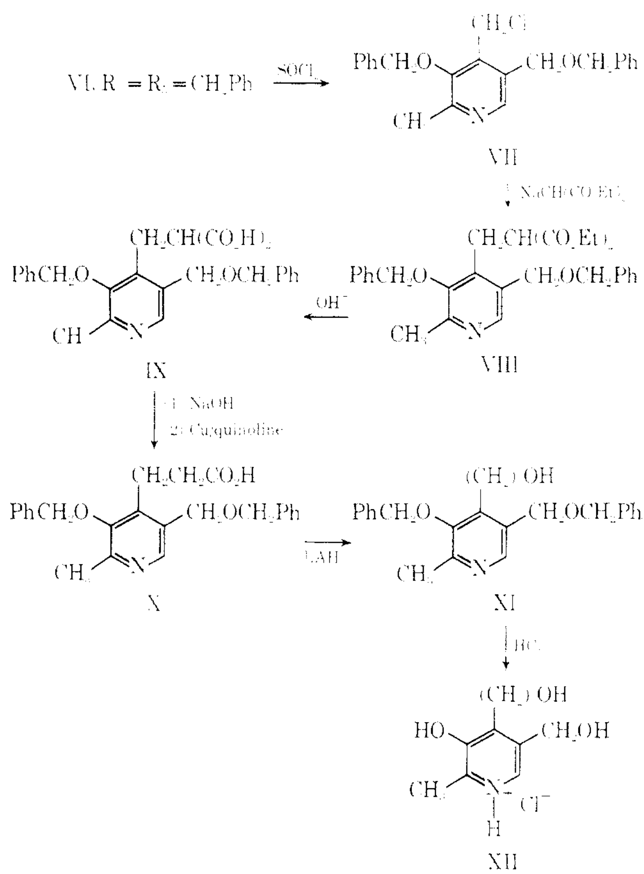


for 1 hr on a steam bath removes the phenolic benzyl giving α^5-*O*-benzylpyridoxol, and heating for an additional 20 hr removes the alcoholic benzyl, giving pyridoxol. Hydrogenolysis with Pd–C catalyst removes the benzyl groups in the same order. Acetolysis with Ac_2O and H_2SO_4[15] gave pyridoxol triacetate, which can readily be deacetylated to pyridoxol. Na in liquid NH_3[16] proved to be too powerful, giving 5-deoxypyridoxol as the main product.

Having established the deblocking procedures, we turned to the synthesis of a homolog of pyridoxol having the 4-side chain extended by two C as indicated in Scheme II. It will be recalled that an analogous extension of the 5-side chain gave a potent antagonist of vitamin B_6 (test organism: *S. carlsbergensis*).[10]

The reactions outlined in Scheme II proceeded smoothly until the intermediate VIII. An attempt

SCHEME II



to deblock this intermediate with concentrated HCl gave a mixture of products. Accordingly, this ester was hydrolyzed and decarboxylated stepwise. After saponification to the dicarboxylic acid IX, it was converted into the monosodium salt, which was then decarboxylated, giving X. LAH reduction gave the alcohol XI, which was deblocked with HCl, giving the pyridoxol homolog XII. Previously the side chains in the 2-position[2a] and 5-position[10,17] were extended, and provided compounds with interesting biological activities.

Syntheses of some branched chain compounds are indicated in Scheme III. The 4-CH_2OH in VI (R_3 = R_5 = CH_2Ph) was oxidized with MnO_2, providing the aldehyde XIII in excellent yield. Reactions of Grignard reagents with the aldehyde gave the α^4-methyl- and α^4-phenylpyridoxol derivatives (XIV and XVI, respectively). Deblocking of the benzyl group in XIV could be achieved both with HCl and by hydrogenolysis, but the latter procedure gave the secondary alcohol XV in much purer form.

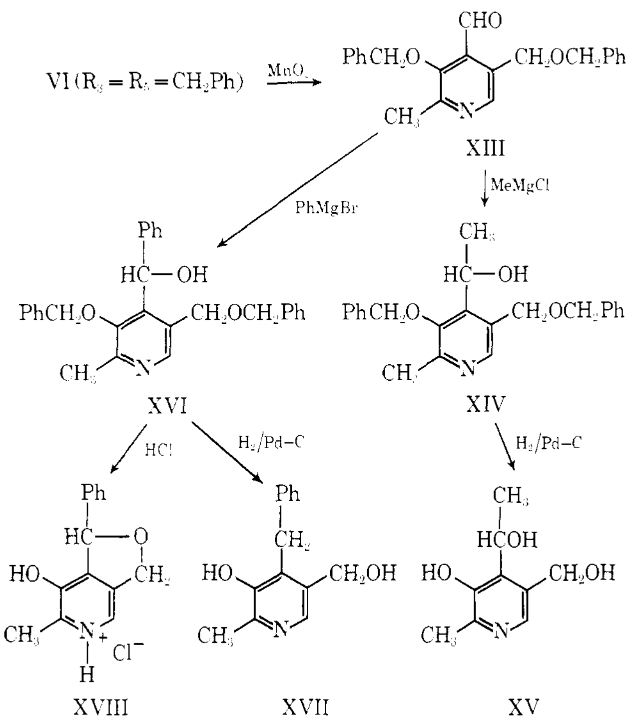
Although giving the expected analogs in the preceding instances, deblocking gave anomalous products with the phenyl derivative XVI. On treatment with HCl, XVI gave the cyclic derivative XVIII; in its nmr spectrum, the 5-CH_2 protons appear as an AB quadruplet, a result that could be expected for XVIII from analogy with the cyclic hemiacetal structure of pyridoxal.[18] The α^4 proton, on the other hand, is a

(14) W. Korytnyk and B. Paul, *J. Org. Chem.*, **32**, 3791 (1967).
(15) R. Allerton and H. G. Fletcher, *J. Amer. Chem. Soc.*, **76**, 1757 (1954).
(16) E. J. Reist, V. J. Bartuska, and L. Goodman, *J. Org. Chem.*, **29**, 3725 (1964).
(17) W. Korytnyk, B. Paul, A. Bloch, and C. A. Nichol, *J. Med. Chem.*, **10**, 345 (1967).
(18) W. Korytnyk and B. Paul, *Tetrahedron Lett.*, 777 (1966); *Tetrahedron*, **25**, 1071 (1969).

singlet, and is not coupled with one of the α^5-CH_2 protons as in the hemiacetal structure.

Hydrogenolysis of the intermediate XVI resulted not only in removal of the benzyl groups, but also in replacement of the α^4-OH with H. Hydrogenolysis of the α^4-OH is probably related to the activation of the α^4 position by the two aromatic rings, and provides a general route for the synthesis of 4-aryl-4-deoxypyridoxol analogs.

SCHEME III



A preliminary evaluation of the 4-homolog XII and of α^4-methylpyridoxol (XV) indicates that they inhibit S-180 cells[19] at 8×10^{-5} *M* (50% growth inhibition in vitamin B_6-free medium), and *S. carlsbergensis*[20] at 5×10^{-4} *M*. This is opposite to the effect observed with the corresponding 5-analogs, which inhibit *S. carlsbergensis*[10,17] at 10^{-7} *M* to 10^{-8}*M*, but do not inhibit S-180 cells[19] at 10^{-4} *M*.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. Tlc was used routinely as described earlier.[1a,14] Ir spectra were determined with a Perkin-Elmer 137B or 457 spectrophotometer, nmr spectra with a Varian A60A instrument as 8–15% solutions in the $CDCl_3$ or D_2O; positions of peaks are expressed in cycles/sec from TMS or from sodium 3-(trimethylsilyl)-1-propanesulfonic acid as internal standards. Peaks were assigned on the basis of previous work.[21]

α^4,3-*O*-Isopropylidenepyridoxol (II).—This compound was synthesized by the method of Korytnyk and Wiedeman.[22]

α^5-*O*-Benzyl-α^4,3-*O*-isopropylidenepyridoxol (IV). A. From II.—(a) Na (0.9 g) was dissolved in 200 ml of absolute EtOH, the solution was cooled in ice, and II (7.5 g) was added. After refluxing for 1 hr, EtOH was removed *in vacuo*. Dry PhMe was then added and evaporated. To the residual solid cake, dry PhMe (200 ml) and $PhCH_2Cl$ (15 ml) were added, and the mixture was refluxed until all of the solid cake had gone into solution (approximately 9 hr). After evaporation to dryness *in vacuo*, H_2O (50 ml) was added, and the solution was extracted several times with petroleum ether (bp 37–54°). The combined extracts were dried ($CaSO_4$), filtered, and evaporated to an oily residue (5.5 g, 51%), which was converted into a hydrochloride, mp 193–194°. *Anal.* ($C_{18}H_{22}ClNO_3 \cdot 0.5H_2O$) H, N; C: calcd, 62.70; found, 63.14.

(b) Isopropylidenepyridoxol (II, 10 g) was added to a stirred suspension of NaH [13.7 g of a 53% suspension in mineral oil, washed free of mineral oil with petroleum ether (bp 37–54°) in DMF (80 ml, purified by distillation over CaH_2)], while the reaction mixture was being stirred and heated to 65° and then gradually (for 90 min) cooled to 45°. The flask was cooled in ice, 7.15 ml of $PhCH_2Cl$ was added dropwise, and the mixture was stirred overnight at 0° After careful addition of H_2O, the solution was extracted five times with petroleum ether. The extracts were dried and evaporated, yielding an oily α^5-*O*-benzyl-α^4,3-*O*-isopropylidenepyridoxol. Hydrolysis (see "α^5-*O*-Benzylpyridoxol") provided 9.68 g (78%) of α^5-*O*-benzylpyridoxol, mp 110–111°.[23]

B. From III.—Na (1.25 g) was dissolved in $PhCH_2OH$ (20 ml), and the solution was cooled. α^4,3-*O*-Isopropylidene-5-pyridoxyl chloride·HCl (III) was dissolved in $PhCH_2OH$ (20 ml) by warming, cooled, and added to the $NaOCH_2Ph$ solution, and the mixture was refluxed for 2 hr. After evaporation of $PhCH_2OH$ *in vacuo*, H_2O was added, and the solution was then extracted with Et_2O. The combined Et_2O extracts were dried, filtered, and evaporated. The oily residue consisted mainly of IV, as shown by tlc.

α^5-*O*-Benzylpyridoxol (V).—The oily material from the preceding experiment was dissolved in 100 ml of 1 *N* HCl, and was heated on a steam bath for 1 hr. The aqueous layer was separated from the oily residue, and was evaporated under reduced pressure. The oily residue was dissolved in EtOH, and crystallized on the addition of Et_2O; mp 152–153°. *Anal.* ($C_{15}H_{18}ClNO_3$) N.

The free base of VI was isolated by dissolving the hydrochloride in H_2O, adding $NaHCO_3$ till the solution was basic, and extracting the aqueous solution with EtOAc. Evaporation and crystallization from Et_2O yielded VI (free base), mp 117–118°; yield 4.7 g (67%). *Anal.* ($C_{15}H_{17}NO_3$) C, H, N.

A. 3,α^5-*O*-Dibenzylpyridoxol (VI, R_3 = R_4 = CH_2Ph).—Benzyldimethylphenylammonium chloride (6.5 g) was dissolved in absolute EtOH (50 ml), and was cooled in a mixture of Dry Ice and Me_2CO. A cold solution of Na (0.46 g) in 25 ml of absolute EtOH was added drop by drop over a period of 15 min, with stirring and cooling. The reaction mixture was stirred for another 15 min, and was then added to a stirred and cooled (Dry Ice and Me_2CO) solution of 5-*O*-benzylpyridoxol (VI) in absolute EtOH (50 ml). The reaction mixture was stirred for 30 min, while the temperature was allowed to rise gradually to room temperature. EtOH was removed *in vacuo*, and dry toluene (25 ml) was added and then evaporated again to remove traces of EtOH. Dry xylene (50 ml) was added, and the solution was refluxed for 4 hr. By the end of that time, it had turned red. The xylene solution was evaporated completely under reduced pressure, and H_2O was added to the residue which was extracted with Et_2O. The combined Et_2O extracts were concentrated, and the residue was steam-distilled to remove traces of $PhNMe_2$, and was then extracted with Et_2O. The extract was concentrated, and petroleum ether (bp 37–54°) was added, which resulted in crystallization (mp 59–60°). After recrystallization from petroleum ether (bp 37–54°), 4.75 g (70%) of the dibenzyl derivative was obtained, mp 68–69°. *Anal.* ($C_{22}H_{23}NO_3$) C, H, N.

B. Benzyldimethylphenylammonium chloride (14.25 g) in 30 ml of MeOH was added to a solution of 1.65 g of Na in 30 ml of MeOH. To this solution, 9.6 g of α^5-*O*-benzylpyridoxol in 100 ml of MeOH was added. The mixture was left standing for 20 min, and was then added over a period of 30 min to approximately 750 ml of hot (approximately 100°) PhMe while the volatile material was being distilled off slowly (65–100°) until approximately 400 ml of residual PhMe was left. After cooling, PhMe was decanted off, and the residue was washed with fresh PhMe. The conbined solutions were evaporated *in vacuo* to an oil, which was taken up in a minimum volume of Et_2O, from which 8.5 g of α^5,3-*O*-dibenzylpyridoxol (mp 69.5–72°) crystallized. The

(19) Dr. M. Hakala, personal communication.

(20) Dr. A. Bloch, personal communication.

(21) W. Korytnyk and R. P. Singh, *J. Amer. Chem. Soc.*, **85**, 2813 (1963); W. Korytnyk and B. Paul, *J. Heterocycl. Chem.*, **2**, 481 (1965).

(22) W. Korytnyk and W. Wiedeman, *J. Chem. Soc.*, 2853 (1962).

(23) We are indebted to Dr. H. Dunathan for this procedure.

mother liquor was evaporated to an oil and subjected to steam distillation, the residue was extracted with Et_2O, and the extract was washed with H_2O. After drying ($CaSO_4$), petroleum ether (bp 37–54°) was added, which precipitated additional material (2.0 g, mp 64–69°). The combined yield was 11.5 g (81%).

3-*O*-Methyl-α^5-*O*-benzylpyridoxol (VI, R_3 = CH_3; R_5 = CH_2Ph).—α^5-*O*-Benzylpyridoxol (1.00 g, 3.50 mmol) was dissolved in *t*-BuOH, and the solution was cooled to −15° with Dry Ice. CH_2N_2 in Et_2O was added dropwise for 3 hr, and stirring was continued for a total of 21 hr. The solvent was removed *in vacuo*, leaving a bright yellow oil. Tlc (10% MeOH, 90% $CHCl_3$) indicated the presence of pyridoxol as an impurity. The oil was taken up in Et_2O, washed twice with 1 *N* NaOH and five times with H_2O, dried, and evaporated. The oily material could not be crystallized. It was redissolved in Et_2O, precipitated as a hydrochloride from solution, and recrystallized from EtOH–Et_2O; mp 140–141°. *Anal.* ($C_{16}H_{20}NClO_3$) C, H, N.

3,α^5-*O*-Dibenzyl-α^4-pyridoxyl Chloride (VII)·HCl. To a stirred solution of 3,α^5-*O*-dibenzylpyridoxol (VI, 0.93 g) in dry C_6H_6 (25 ml), $SOCl_2$ (0.35 ml) in dry C_6H_6 (15 ml) was added drop by drop for 30 min, while the reaction mixture was cooled in ice. Stirring was continued for 15 min, and the reaction mixture was heated to reflux for 1 min and was cooled immediately. After filtration, Et_2O was added until turbidity. The precipitated chloride was washed with dry Et_2O, yielding 1.05 g (97%) of product, mp 145–148°. *Anal.* ($C_{22}H_{23}Cl_2NO_2$) C, H, N.

The base of the preceding compound was obtained by dissolving 300 mg of the hydrochloride in 10 ml of H_2O, cooling in ice, adding Et_2O (25 ml), and making the aqueous layer alkaline with Na_2CO_3. The Et_2O layer was separated, and the aqueous phase was extracted again with Et_2O, dried ($CaSO_4$), and evaporated completely *in vacuo*, yielding 250 mg (91.5%) of an oil, which was characterized as the picrate, mp 154–155°. *Anal.* ($C_{22}H_{22}ClNO_2 \cdot C_6H_2(NO_2)_3OH$) N, Cl.

3,α^5-*O*-Dibenzyl-α^4-pyridoxylmalonic Acid Diethyl Ester (VIII)·HCl. To a stirred solution of Na (0.092 g) in absolute EtOH (5 ml), diethyl malonate (0.64 ml, freshly distilled) was added drop by drop, and was allowed to react for a total of 15 min. 3,α^5-Dibenzyl-α^4-pyridoxyl chloride hydrochloride (VII, 0.72 g), finely powdered, was added at once, followed by KI (0.1 g, dried), and the reaction mixture was stirred at room temperature for 48 hr and then was evaporated completely under reduced pressure. The residue was diluted with H_2O (5 ml), and the mixture was extracted with Et_2O. The combined Et_2O extract was dried ($MgSO_4$), and was evaporated *in vacuo*. The gummy residue was dissolved in Et_2O (dried), and was then treated with ethereal HCl, when an oily mass separated out. After the ethereal layer was decanted, the oily gum was washed twice with anhydrous Et_2O. Fresh Et_2O was added, the mixture was allowed to stand in the cold, and the oily gum crystallized in needles, mp 106–107°, yield 0.82 g (86%). Recrystallization from MeOH–Et_2O raised the melting point to 109–110°. *Anal.* ($C_{29}H_{34}ClNO_6$) C, H, N.

3,α^5-*O*-Dibenzyl-α^4-pyridoxylmalonic Acid (IX).—3,α^5-*O*-Dibenzyl-α^4-pyridoxylmalonic acid diethyl ester (VIII)·HCl (200 mg) was added to alcoholic KOH (2.8 g of KOH in 5 ml of EtOH) and refluxed for 2 hr. After evaporation *in vacuo*, the residue was taken up in H_2O (5 ml), cooled in ice, and acidified with HCl to pH 3–4. The precipitated acid was filtered, washed with cold H_2O, and dried, yield 125 mg (76%). The product was crystallized from MeOH–EtAc, and had mp 173–174°. *Anal.* ($C_{25}H_{25}NO_6$) C, H.

3,α^5-*O*-Dibenzyl-α^4-pyridoxylacetic Acid (X).—The monosodium salt of IX was obtained by adding IX (120 mg) to alcoholic NaOH (4.5 ml of 0.1 *N* NaOH in 10 ml of EtOH) and heating on a steam bath until a clear solution was obtained. The solution was evaporated to dryness *in vacuo*, quinoline (2.5 ml) and a speck of fine Cu powder were added, and the reaction mixture was heated at 160–175° for 4 hr. The reaction mixture was cooled, two drops of 1 *N* NaOH were added to keep the solution alkaline during evaporation of the quinoline, and the quinoline was completely removed under reduced pressure. The residue was dissolved in H_2O (5 ml), cooled in ice, and acidified to pH 6 with 1 *N* HCl, when a white solid separated out. Filtration and washing with H_2O yielded 60 mg (81%) of material, which on crystallization from EtOH–Et_2O (decolorized with charcoal) had mp 175–176°. *Anal.* ($C_{24}H_{25}NO_4 \cdot 0.5H_2O$) C, H, N.

3,α^5-*O*-Dibenzyl-α^4-pyridoxyl-β-ethanol (XI).—Compound X (100 mg) was dissolved in warm THF (25 ml, distilled over LAH) and was added slowly to a stirred suspension of LAH (200 mg) in THF under N_2. The reaction mixture was stirred at room temperature for 1–5 hr, gently refluxed for 0.5 hr, and cooled, and excess LAH was decomposed by slow addition of EtAc (20 ml) followed by H_2O (20 ml). $CHCl_3$ extraction, drying, and evaporation *in vacuo* gave an oil which was taken up in Et_2O, and a small volume of petroleum ether was added till turbidity, when 60 mg (63%) of the alcohol, mp 64–65°, was obtained. *Anal.* ($C_{24}H_{27}NO_3$) C, H, N.

α^4-Pyridoxyl-β-ethanol·HCl (XII). Compound XI (45 mg), dissolved in 1 *N* HCl (15 ml), was heated on a steam bath for 24 hr, and the solution was evaporated *in vacuo*. The residue was redissolved in H_2O, and the solution was evaporated again. After recrystallization from MeOH–Et_2O, 22 mg (79%) of the hydrochloride, mp 161–162°, was obtained: ir (Nujol) 3390 cm^{-1} (OH stretching); nmr (DMSO-d_6) 2-CH_3 −158, C_6-H −484, 5-CH_2 −279, α^4-CH_2 −201, −207, −213 (tr), β^4-CH_2 −85, −92, −99, −106, −113 (quint), γ^4-CH_2 −161, −169, −177. *Anal.* ($C_{10}H_{16}ClNO_3$) C, H.

3,α^5-*O*-Dibenzylpyridoxal (XIII).—To a stirred and cooled (ice bath), dry $CHCl_3$ solution (500 ml) of 3,α^5-*O*-dibenzylpyridoxol (VI, R_3 = R_5 = CH_2Ph; 10.06 g), freshly prepared active MnO_2 (60 g, prepared by heating $MnCO_3$ at 280–300° for 36–48 hr), suspended in dry $CHCl_3$ (200 ml), was added. The mixture was stirred at room temperature for 17 hr, at the end of which time tlc (with EtAc as solvent, the aldehyde has R_f 0.9, and the alcohol R_f 0.7) indicated the absence of the starting alcohol. The mixture was filtered with Celite filter aid, the residue was washed with $CHCl_3$, and the $CHCl_3$ filtrates were evaporated *in vacuo* to a viscous oil. Addition of a few ml of Et_2O resulted in crystallization, yielding 9.80 g (98.5%) of the hydrated aldehyde, mp 60–70°. The anhydrous form was readily obtained on drying at 35° over P_2O_5 *in vacuo*: mp 72°; nmr ($CDCl_3$), 2-CH_3 −155, C_6H −514, 3 × CH_2 −276, −287, −296, 4-CHO −617, phenyls −438, −440. *Anal.* ($C_{22}H_{21}NO_3 \cdot 0.5H_2O$) C, H, N.

α^4-Methyl-3,α^5-*O*-dibenzylpyridoxol (XIV). To a stirred suspension of XIII (4.01 g) in anhydrous Et_2O (50 ml), MeMgCl (12 ml of a 1.7 *M* solution in Et_2O) was added dropwise, and the mixture was stirred overnight (*ca.* 12 hr) at room temperature. The reaction mixture was poured into 100–175 ml of an ice–H_2O solution of NH_4Cl (24 g), was allowed to stand for a few minutes, and was extracted several times with Et_2O. The combined extracts were washed with H_2O, dried ($MgSO_4$), and evaporated to a small volume, and the product crystallized, yielding 3.82 g (90%), mp 72–74°. Recrystallization from MeCN raised the melting point to 83–84°; nmr ($CDCl_3$) 2-CH_3 −152, α^4-CH_3 −88, −94 (d), 3 × CH_2 −273, −281, −292, α^4-CH −316 (q), phenyls −438, −442. *Anal.* ($C_{23}H_{25}O_2$) C, H, N.

α^4-Methylpyridoxol (XV).—α^4-Methyl-3,α^5-*O*-dibenzylpyridoxol (0.80 g) was dissolved in 67 ml of EtOH and was hydrogenolyzed in the presence of 0.33 g of Pd–C. After 4 days, the reaction was complete, and the solvent was evaporated *in vacuo*. The oily residue was taken up in a small amount of EtOH. The product precipitated as the hydrochloride on the addition of Et_2O containing HCl. The yield was 0.29 g (60%): mp 177–178°; nmr (DMSO-d_6), 2-CH_3 −155, α^4-CH_3 −82, −89, 5-CH_2OH −280, α^4-CH −322 (q), C_6H −485. *Anal.* ($C_9H_{14}ClO_2$) C, H, N.

α^4-Phenyl-3,α^5-dibenzylpyridoxol (XVI).—To a stirred suspension of 3,α^5-dibenzylpyridoxal hydrate (2.80 g, 8.06 mmol) in anhyd Et_2O (40 ml), PhMgBr (7.34 ml, 2.2 *M* in Et_2O) was added slowly, and the mixture was stirred for 75 min under N_2. The reaction mixture was poured into 170 ml of an ice–water solution of NH_4Cl (17 g), and was extracted five times with Et_2O. The combined Et_2O layers were washed with H_2O, dried, and evaporated. Crystallization from Et_2O yielded 2.64 g (81%) of material, mp 100–103°; analytical sample: mp 102–104°; nmr ($CDCl_3$), 2-CH_3 −105, 3 × CH_2 −250, −262, −287, α^4-H −381, 3 × phenyl −433, −435, −438, C_6-H −489. *Anal.* ($C_{28}H_{27}NO_3$) C, H, N.

α^4-Phenyl-4-deoxypyridoxol (XVII).—To a solution of XVI (250 mg) in EtOH (21 ml), 10% Pd–C (417 mg) was added; hydrogenation was performed under a slight positive pressure of H_2 until no starting material could be detected by tlc. After filtration (Celite filter aid), washing with EtOH, and evaporation *in vacuo* to an oil, the product was taken up in EtAc to crystallize. The yield was 99 mg (74%): mp 190–191° (after recrystallization from EtAc); nmr (DMSO-d_6), 2-CH_3 −144, 2 × CH_2 −244, −265, phenyl −450, C_6-H, −477. *Anal.* ($C_{14}H_{15}NO_2$) C, H, N.

Hydrolysis of XVI. 7-Hydroxy-6-methyl-1-phenylfuro[3,4-*c*]pyridine (XVIII).—To a solution of XVI (250 mg) in 95% EtOH

(5 ml), concentrated HCl (5 ml) was added. After refluxing for 12 hr, the solution was evaporated *in vacuo*, taken up in H_2O, neutralized ($NaHCO_3$), and extracted three times with $CHCl_3$. The $CHCl_3$ solution was evaporated, and the oil obtained was taken up in a minimum amount of EtOH. The yield of XVIII was 37 mg (28%): mp 238–242°; nmr of the hydrochloride (DMSO-d_6), 2-CH_3 −162, 5-CH_2 −257, −272, −275, −290 (AB quadruplet), α^4-H −388, phenyl −441, C_6-H −490. *Anal.* ($C_{14}H_{13}NO_2$) C, H, N.

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Antidepressants. II.[1] Bridged Ring Ether Derivatives in the Dibenzocycloheptene Series[2]

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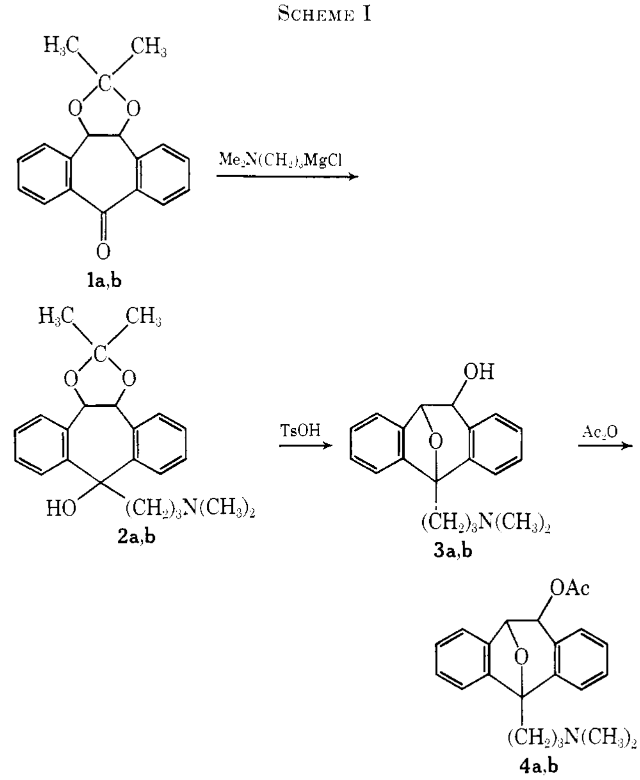
The synthesis and proof of structure of novel 11-substituted 5,10-epoxy-5H-dibenzo[*a,d*]cycloheptene-5-propylamine derivatives is reported. These compounds exhibit potent tetrabenzazine-antagonizing activity.

5H-Dibenzo[*a,d*]cycloheptene-5-propylamine derivatives related to amitriptyline and protriptyline have been the subject of a synthetic program in our laboratories.[1] In an extension of this investigation to 10- and 11-substituted dibenzocycloheptenes, novel bridged ring ether derivatives that have shown significant antidepressant activity were synthesized and are described in this paper.

The carbinol **2a** was obtained by the Grignard reaction of the known acetonide of *cis*-10,11-dihydro-10,-11-dihydroxy-5H-dibenzo[*a,d*]cyclohepten-5-one[3] (**1a**) with 3-dimethylaminopropylmagnesium chloride. When **2a** was subjected to *p*-toluenesulfonic acid catalyzed hydrolysis in refluxing MeOH, the product was a crystalline base that was not the expected 5,10,11-triol **10**. The empirical formula, $C_{20}H_{23}NO_2$, corresponded with the loss of one molecule of H_2O from this structure. The uv spectrum of the product showed no strong maximum in the 230–240-mμ region characteristic of unsaturation at the 5,α-positions[4] and the ir spectrum, showing strong C–O stretching bands at 1020 and 1080 cm^{-1}, was consistent with an ether linkage in addition to OH. The product afforded a monoacetyl derivative upon treatment with Ac_2O, but failed to react with LAH, $NaOCH_3$ in refluxing MeOH, or KOH in ethylene glycol. This behavior eliminated 10,11-dihydroxy-5,α-unsaturated and 10,11-epoxide structures from consideration and seemed consistent only with the 5,10-bridged ether **3a**. A similar sequence starting from the *trans* acetonide **1b** afforded the isomeric *trans* ether **3b** (Scheme I).

SCHEME I



a = *cis* isomer
b = *trans* isomer

The significant nmr characteristics of the carbinols **3a** and **3b** and the corresponding acetates **4a** and **4b** are summarized in Table I and are in accord with the chemical nonequivalence of the 10 and 11 protons, the position of the secondary alcohol substituent, and the 5,10-epoxy linkage in the bridged ring ether structure. The lack of spin coupling between the 10 and 11 protons in the *cis* isomers **3a** and **4a** as compared to their *trans* counterparts is also shown by the precursor acetonide **2a** and apparently is attributable to the H–C_{10}–C_{11}–H bond angles.[5] The downfield position of the OH signal

(1) Previous paper: E. L. Engelhardt, M. E. Christy, C. D. Colton, M. B. Freedman, C. C. Boland, L. M. Halpern, V. G. Vernier, and C. A. Stone, *J. Med. Chem.*, **11**, 325 (1968).

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(3) G. L. Buchanan and D. B. Jhaveri, *J. Org. Chem.*, **26**, 4295 (1961).

(4) S. O. Winthrop, M. A. Davis, G. S. Myers, J. G. Gavin, R. Thomas, and R. Barber, *ibid.*, **27**, 230 (1962).

(5) Examination of Dreiding models reveals that the dihedral angle at the intersection of the planes formed by $HC_{10}C_{11}$ and $C_{10}C_{11}H$ is approximately 75° in the *cis* isomer **3a** and 25° in the *trans* isomer **3b**. From the Karplus equation, *J* would be expected to approach zero as the dihedral angle approaches 90° and to have its largest value as the dihedral angle approaches 0°.