Studies on Anticoccidial Agents. 1. Synthesis and Anticoccidial Activity of 4-Deoxypyridoxol and Its Esters

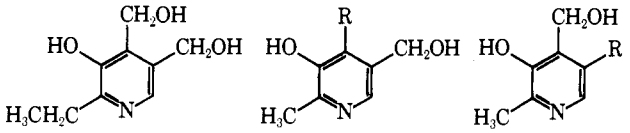
Yasuhiro Morisawa,* Mitsuru Kataoka, Taiichiro Watanabe, Noritoshi Kitano, and Toshiaki Matsuzawa

Central Research Laboratories, Sankyo Company, Ltd., Shinagawa-ku, Tokyo, Japan. *Received March 28, 1974*

Convenient methods for the syntheses of 4-deoxypyridoxol (2, R = CH_3) and ω-methylpyridoxol (1) from pyridoxine were developed. α^5-*O*-Monoacyl-4-deoxypyridoxols were, in general, obtained by selective hydrolysis of 3,α^5-*O*-diacyl-4-deoxypyridoxols. 4-Deoxypyridoxol and its esters were found to exhibit anticoccidial activity against *Eimeria acervulina*.

The coccidia are known to be dependent on a supply of certain vitamins and some vitamin antagonists are used as coccidiostats: 1-(4-amino-2-*n*-propyl-5-pyrimidinylmethyl)-2-picolinium chloride hydrochloride (Amprolium)[1] and 3-(4-amino-2-methyl-5-pyrimidinylmethyl)-5-(2-chloroethyl)-4-methylthiazolium chloride (Beclotiamine)[2] as the thiamine antagonists, 2,4-diaminopyrimidine derivatives[3] as the folic acid antagonists, 6-aminonicotinamide[4] as the nicotinamide antagonist, and 6,7-dimethyl-9-alkylisoalloxazine[5] as the vitamin B_2 antagonists.

As a part of our program for searching the anticoccidial agents, the typical anti-B_6 derivatives,[6] ω-methylpyridoxol (1),[7] 4-deoxypyridoxol[8] (4-DOP, 2, R = CH_3), α^4-*O*-ethylpyridoxol[9] (2, R = $CH_2OC_2H_5$), 5-deoxypyridoxol[10] (3, R = CH_3), α^5-pyridoxylmethanol[11] (3, R = CH_2CH_2OH), and 2-(α^5-pyridoxyl)-1-ethanol[12] (3, R = $CH_2CH_2CH_2OH$), have been synthesized and tested for the anticoccidial activity.



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A new convenient method for the syntheses of 4-DOP (2, R = CH_3)[8] and ω-methylpyridoxol (1),[7] starting from pyridoxine (4), was developed in moderate yield as shown in Scheme I.

Hydrogenolysis of 3,α^4-*O*-diacetylpyridoxol hydrochloride[13] (5) by applying the procedure of Naito, *et al.*,[14] followed by hydrolysis with 10% HCl gave 4-DOP in 76% yield.

The synthesis of ω-methylpyridoxol (1) started also with pyridoxine (4). The tribenzyl ether 7 was prepared in 45% yield from pyridoxine with benzyl chloride and NaH in DMF, and the synthesis of the 2-formylpyridoxol 9 was accomplished in an indirect manner (overall yield, 61.6%): oxidation of the tribenzyl derivative 7 with *m*-chloroperbenzoic acid in $CHCl_3$, rearrangement with acetic anhydride, hydrolysis with HCl, and oxidation with MnO_2. Direct oxidation of the 2-CH_3 function in the tribenzyl compound 7 with SeO_2 was proved to be unsatisfactory because of a mixture of the inseparable products. The Grignard reaction with the 2-CHO (9) gave the secondary alcohol 10 in 74.7% yield, which was readily converted to ω-methylpyridoxol (1) in 48.7% yield *via* 2-(α-chloroethyl)-3-benzyloxy-4,5-dibenzyloxymethylpyridine.

Rabinowitz, *et al.*,[15] indicated that the order of decreasing effectiveness as antagonists of vitamin B_6 for *Saccharomyces carlsbergensis* was ω-methylpyridoxol (1), 4-deoxypyridoxol (2, R = CH_3), and 5-deoxypyridoxol (3, R = CH_3), and Korytnyk, *et al.*,[11] found 5-homopyridoxols (3, R = CH_2CH_2OH and R = $CH_2CH_2CH_2OH$) to be more potent inhibitors for *S. carlsbergensis* than 4-DOP. However, among these several antagonists described above, 4-DOP was the sole desirable substance, showing coccidiostatic effect. The anticoccidial activity of the vitamin B_6 derivatives is not proportional to their antivitamin

Scheme I

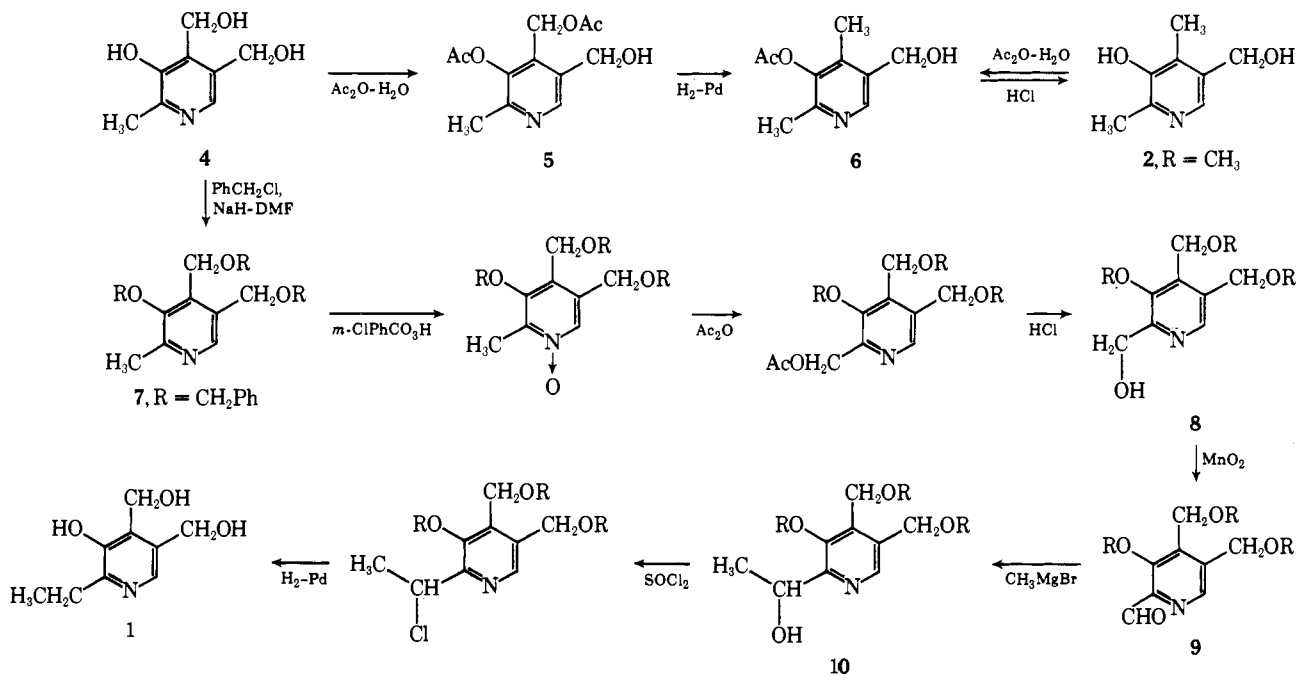
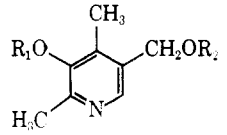


Table I. Anticoccidial Activity[a]



No.	R_1	R_2	Yield from 4-DOP, %	Mp, °C	Formula[c]	ACI[d]
1	H	H		257	$C_8H_{11}NO_2 \cdot HCl$	158
2	COMe	H	75.5	94–96	$C_{10}H_{13}NO_3$	140
3	$COCMe_3$	H	54.0	92–93	$C_{13}H_{19}NO_3$	122
4	COPh	H	30.1	127–129	$C_{15}H_{15}NO_3$	122
5	H	COMe	24.1	153–154	$C_{10}H_{13}NO_3$	134
6	H	COPh	51.6	212–214	$C_{15}H_{15}NO_3 \cdot HCl$	138
7	H	$4\text{-}COPhNO_2$	42.2	185–187	$C_{15}H_{14}N_2O_5 \cdot HCl$	126
8	H	$3,5\text{-}COPh(NO_2)_2$	28.0	203	$C_{15}H_{13}N_3O_7$	132
9	H	4-COPhOMe	52.2	180–183	$C_{16}H_{17}NO_4 \cdot HCl$	120
10	H	4-COPhCl	51.6	207–209	$C_{15}H_{14}NO_3Cl \cdot HCl$	128
11	H	$2,4\text{-}COPhCl_2$	47.6	179–180	$C_{15}H_{13}NO_3Cl_2$	120
12	H	Nicotyl	53.3	160–162	$C_{14}H_{14}N_2O_3$	90
13	H	Furoyl	36.0[b]	147–150	$C_{13}H_{13}NO_4$	110
14	COMe	COMe	54.5	158–159	$C_{12}H_{15}NO_4 \cdot HCl$	158
15	CO-*n*-Pr	CO-*n*-Pr	60.5	135–137	$C_{16}H_{23}NO_4 \cdot HCl$	156
16	CO-*i*-Pr	CO-*i*-Pr	53.0	134–136	$C_{16}H_{23}NO_4 \cdot HCl$	140
17	$CO\text{-}n\text{-}C_5H_{11}$	$CO\text{-}n\text{-}C_5H_{11}$	48.3	131–133	$C_{20}H_{31}NO_4 \cdot HCl$	150
18	COPh	COPh	71.6	110–112	$C_{22}H_{19}NO_4$	128
19	COMe	$4\text{-}COPhNO_2$	58.5	116–118	$C_{17}H_{16}N_2O_6$	126
20	COMe	4-COPhOMe	61.3	90–91	$C_{18}H_{19}NO_5$	122
21	COMe	$2,4\text{-}COPhCl_2$	71.7	108–109	$C_{17}H_{15}NO_4Cl_2$	110
22	1-(4-Amino-2-*n*-propyl-5-pyrimidinylmethyl)-2-picolinium chloride hydrochloride					90, 122[e]
23	ω-Methylpyridoxol (**1**)					110[f]
24	α^4-*O*-Ethylpyridoxol (**2**, R = $CH_2OC_2H_5$)					50[f]
25	5-Deoxypyridoxol (**3**, R = CH_3)					95[f]
26	α^5-Pyridoxylmethanol (**3**, R = CH_2CH_2OH)					90[f]
27	2-(α^5-Pyridoxyl)-1-ethanol (**3**, R = $CH_2CH_2CH_2OH$)					85[f]

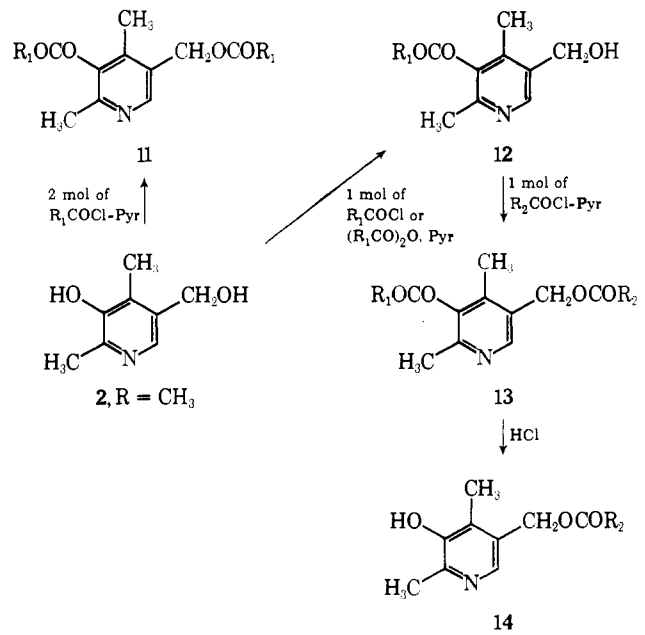
[a]Concentration of the drugs in feed was 0.005%. [b]Selective hydrolysis of **13** (R_1 = Me; R_2 = 2-furyl) with 2 *N* HCl at 80° was completed in 10 min. [c]All compounds were analyzed for C, H, and N and their nmr and ir spectra were in agreement with the assigned structures. [d]ACI = per cent survival + per cent relative weight gain − lesion score − oocyst score. [e]The value at 0.01% drug in feed. [f]The value at 0.02% drug in feed.

B_6 activity. Accordingly, a more extensive program was initiated to study the structural relationship on the anticoccidial activity of this type of compound and, as part of a modification of the 4-DOP molecule on biological activity, some esters of 4-DOP were prepared (Table I).

Sakuragi[16] has prepared the diacetate 11 (R_1 = Me) from 4-DOP with Ac_2O and AcOH under refluxing. In general, disubstituted esters 11 with the same acyl function are readily obtained by treating 4-DOP with 2 mol of an acyl chloride or an acid anhydride in the presence of pyridine and the differently disubstituted derivatives **13** are prepared by the stepwise treatments of 4-DOP with the reagents. 3-*O*-Monoesters 12 are available by the interaction of 4-DOP with 1 mol of an acyl chloride at room temperature or with 1 mol of an acid anhydride at about 100° in the presence of pyridine. This selective esterification can be attributable to the acidity of the phenolic hydroxyl function. Coover, *et al.*,[17] have prepared the 3-*O*-acetate 6 from 3-acetoxy-6-chloro-5-cyano-2,4-dimethylpyridine by hydrogenation and diazotization. 3-*O*-Acetyl-4-deoxypyridoxol (6) was not only obtained from $3,\alpha^4$-diacetylpyridoxol (5) as already described but also from 4-DOP by interaction with Ac_2O and H_2O at 10° under vigorous stirring in 75.5% yield (Scheme II).

Singh, *et al.*,[8c] have reported the synthesis of the α^5-*O*-benzoate 14 (R_2 = Ph) from 5-benzoyloxymethyl-4-chloromethyl-3-hydroxy-2-methylpyridine. We have developed the general method for the preparation of α^5-*O*-monoacyl-4-deoxypyridoxol (14) from $3,\alpha^5$-*O*-diacyl-4-deoxypyridoxol (13) by selective hydrolysis with dilute HCl. α^5-*O*-Acetyl-4-deoxypyridoxol (14, R = CH_3) was obtained by the procedure of Sakuragi, *et al.*[18]

Scheme II



Biological Methods and Results. The compounds were tested against *Eimeria acervulina* as follows. Fourteen-

day-old white Leghorn chickerels, fed with a diet containing no anticoccidial agents and isolated from the risk of extraneous coccidial infections for 13 days, were divided into experimental and control groups composed of ten birds each and placed into battery cages. They were inoculated orally into their crops with approximately 10^5 sporulated oocysts of *E. acervulina*.

For evaluation of coccidiostatic activity, on day 6 after infection, mortality, relative weight gain, coccidial lesion score of small intestine, and oocyst output were determined in control and treated birds, and these were combined into the anticoccidial index (ACI) by the Cuckler method.[19] The ACI above 160 was determined as a marked coccidiostatic effect, 160–140 as a moderate, 140–120 as a slight, and below 120 as an inactive one.

From the biological data in Table I optimal anticoccidial activity is observed when R_1 and R_2 are H or aliphatic esters. The other esters were also active at 0.015–0.025% dose in feed. A new type of anticoccidial drugs has been provided. However, 4-DOP and its esters tested showed a decrease in weight gain of chickerels at an increased dose (0.02–0.05% in feed), indicating toxicity as potent B_6 antagonists. Further studies on structural modifications of 4-DOP are in progress.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.3% of the theoretical values. Melting points are uncorrected. The typical experimental procedures are described for the preparation of the ester derivatives listed in Table I.

3-*O*-Acetyl-4-deoxypyridoxol (6). (A) 3,α^4-*O*-diacetylpyridoxol hydrochloride (5)[11a] (1.45 g, 5 mmol) was dissolved in 35 ml of H_2O and hydrogenolyzed in the presence of 10% Pd-C (1 g). After 15 min, the reaction was complete, and the solution was neutralized with 5% aqueous $NaHCO_3$ solution, extracted with EtOAc, and dried (Na_2SO_4). The extract was concentrated into a small volume and addition of anhydrous HCl in EtOH yielded 0.93 g (80%) of colorless product: mp 184–186°. *Anal.* ($C_{10}H_{13}NO_3$·HCl) C, H, N, Cl.

(B) 4-Deoxypyridoxol hydrochloride (**2**, 3.8 g, 20 mmol) was dissolved in 25 ml of H_2O, neutralized with $NaHCO_3$ (1.7 g), and treated with Ac_2O (2.5 g) under vigorous stirring at room temperature for 20 min. Extraction with EtOAc, drying over Na_2SO_4, concentration into a small volume, and cooling gave 3-*O*-acetyl-4-deoxypyridoxol (**6**, 2.94 g, 75.5%), which was recrystallized from EtOAc–*n*-hexane: mp 94–96°. *Anal.* ($C_{10}H_{13}NO_3$) C, H, N.

4-Deoxypyridoxol Hydrochloride (2, R = CH_3). 3-*O*-Acetyl-4-deoxypyridoxol hydrochloride (**6**, 1.16 g, 5 mmol) was refluxed for 1 hr with 10% HCl (10 ml) and cooled to yield 4-DOP·HCl (0.9 g, 95%), which was recrystallized from EtOH–Et_2O: mp 257° (lit.[8b] mp 255°). *Anal.* ($C_8H_{11}NO_2$·HCl) C, H, N, Cl.

3,α^4,α^5-*O*-Tribenzylpyridoxol (7). Pyridoxine hydrochloride (**4**) (1 g, 4.86 mmol) was added dropwise to a stirred suspension of NaH (0.97 g of a 50% suspension in mineral oil) in DMF (40 ml) under N_2 and the mixture was stirred at room temperature overnight. Under cooling, $PhCH_2Cl$ (1.9 g, 15 mmol) was added dropwise, and the mixture was stirred at room temperature for 20 hr. After careful addition of H_2O, the solution was extracted with EtOAc. The extract was dried, evaporated, and purified by silica gel chromatography to yield an oily product (0.96 g, 45%). *Anal.* ($C_{29}H_{29}NO_3$) C, H, N.

3,α^4,α^5-*O*-Tribenzyl-α^2-hydroxypyridoxol Hydrochloride (8). A solution of *m*-$ClPhCO_3H$ (2.25 g, 13 mmol) in $CHCl_3$ (30 ml) was added to a solution of the tribenzyl derivative **7** (5.1 g, 11.6 mmol) in $CHCl_3$ (30 ml). The mixture was stirred at room temperature for 20 hr, washed with dilute $NaHSO_3$ solution and H_2O, dried, and evaporated to leave an oily product.

The oily *N*-oxide derivative was refluxed in Ac_2O (15 ml) for 2 hr, the solvent was removed under reduced pressure, and the residual oil was extracted with EtOAc. The extract was washed with H_2O and dried, and the oily residue after removal of the solvent was purified by silica gel chromatography to give an oily α^2-*O*-acetyl-3,α^4,α^5-*O*-tribenzylpyridoxol (5.0 g).

The α^2-*O*-acetyl derivative was heated at 80° with 2 *N* HCl for 1 hr, cooled, made alkaline with dilute $NaHCO_3$ solution, and extracted with EtOAc. The extract was worked up as usual to yield an oily product (3.7 g, 70%), which was converted into a hydrochloride: mp 154–156°. *Anal.* ($C_{29}H_{29}NO_4$·HCl) C, H, N, Cl.

3,α^4,α^5-*O*-Tribenzyl-α^2-hydroxy-α^2-methylpyridoxol (10). A solution of the α^2-hydroxypyridoxol derivative **8** (10 g, 22 mmol) in $CHCl_3$ (400 ml) was refluxed with active MnO_2 (60 g) for 48 hr. After removal of the MnO_2, the filtrate was evaporated, affording a syrupy residue, which was placed on a silica gel column (5 × 80 cm) and eluted with *n*-hexane–EtOAc (3:1). The segment containing the product was detected with uv light, and the solvent was evaporated to give 8.8 g (88%) of 3,α^4,α^5-*O*-tribenzyl-2-formyl-2-norpyridoxol as a brown oil.

A solution of the 2-formyl derivative **9** (8.8 g, 19.4 mmol) in THF (100 ml) was added to a stirred solution of CH_3MgBr (Mitsuwa's Pure Chemicals) (6 ml, 23.4 mmol) in Et_2O under N_2. After stirring at room temperature for 1 hr, the solution was poured slowly into ice–H_2O. The mixture was extracted with Et_2O and dried, and the crude material obtained by removing the Et_2O was placed on dry silica gel column (5 × 100 cm) and was eluted with C_6H_6–EtOAc (1:1) to give the secondary alcohol **10** (6.8 g, 74.7%) as an oil. *Anal.* ($C_{30}H_{31}NO_4$) C, H, N.

ω-Methylpyridoxol (1). Compound **10** (6.8 g, 14.5 mmol) was dissolved in Et_2O (150 ml) and treated with $SOCl_2$ (5 ml) under reflux for 3 hr and the mixture was concentrated into dryness, diluted with cold aqueous $NaHCO_3$ solution, and extracted with EtOAc. The material obtained by removal of the EtOAc was placed on a silica gel column (5 × 100 cm) and was eluted with *n*-hexane–EtOAc (1:1). The oily product (6.0 g) thus obtained was dissolved in EtOH (100 ml) containing concentrated HCl (6 ml) and hydrogenated in the presence of 10% Pd-C. After removal of the catalyst, the filtrate was concentrated into dryness to give a crystalline product, which was recrystallized from EtOH–Et_2O to give α^2-methylpyridoxol hydrochloride (1.8 g, 48.7%): mp 176–178° (lit.[7b] mp 186–191°). *Anal.* ($C_9H_{13}NO_3$·HCl) C, H, N, Cl.

3-*O*-Pivaloyl-4-deoxypyridoxol (12). To a solution of 4-DOP·HCl (0.95 g, 5 mmol) in pyridine (10 ml) was added pivaloyl chloride (0.6 g, 5 mmol) under ice–H_2O cooling. After standing at room temperature overnight, H_2O was added and the solution was extracted with EtOAc. The extract was washed with H_2O and dried and the solvent was removed to give a solid. Recrystallization from cyclohexane–benzene afforded 0.6 g (54.0%) of colorless product, mp 92–93°.

3-*O*-Benzoyl-4-deoxypyridoxol (12). A mixture of 4-DOP·HCl (1.9 g, 10 mmol) and benzoic anhydride (2.26 g, 10 mmol) in pyridine (10 ml) was heated at 100–105° for 16 hr. After removal of pyridine, the residue was diluted with H_2O and extracted with EtOAc. The extract was worked up as described above to give an oily product, which was purified on silica gel column and recrystallized from cyclohexane–benzene to yield 0.77 g of product: mp 89–90°.

3,α^5-*O*-Di-*n*-butyryl-4-deoxypyridoxol (11). A mixture of 4-DOP·HCl (1.5 g, 7.9 mmol) and butyric anhydride (3 ml) in pyridine (1 ml) was stirred at 105–110° for 8 hr. After removal of pyridine, the residue was diluted with H_2O, extracted with EtOAc, and worked up as described above to give an oily product (1.39 g, 60.5%), which was converted into a hydrochloride: mp 135–137°.

3-*O*-Acetyl-α^5-*O*-(2,4-dichlorobenzoyl)-4-deoxypyridoxol (13). To a solution of 3-*O*-acetyl-4-deoxypyridoxol (**12**, 1.95 g, 10 mmol) in pyridine (10 ml) was added dropwise 2,4-dichlorobenzoyl chloride (2.1 g, 10 mmol) under ice–H_2O cooling. After 16 hr at room temperature, H_2O was added and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated to give a colorless oil, which was gradually solidified. Recrystallization from EtOAc–*n*-hexane gave a product (3.5 g, 95%): mp 108–109°.

α^5-*O*-(2,4-Dichlorobenzoyl)-4-deoxypyridoxol (14). A solution of 3-*O*-acetyl-α^5-*O*-(2,4-dichlorobenzoyl)-4-deoxypyridoxol (1.0 g) in 2 *N* HCl (10 ml) was stirred at 80° for 1 hr, cooled, neutralized with dilute $NaHCO_3$ solution, and extracted with $CHCl_3$. The extract was dried and evaporated to give a crystalline product. Recrystallization from EtOAc–*n*-hexane gave an analytical product (0.59 g, 66.5%): mp 179–180°.

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Synthesis and Biological Activity of Some Aporphine Derivatives Related to Apomorphine

Walfred S. Saari,* Stella W. King,

Merck Sharp and Dohme Research Laboratories

Victor J. Lotti, and Alexander Scriabine

Merck Institute for Therapeutic Research, Division of Merck & Company, Inc., West Point, Pennsylvania 19486.

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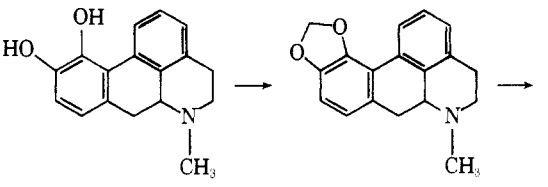
Several aporphine derivatives related to apomorphine were synthesized and evaluated for antihypertensive and central dopaminergic activity. Apocodeine (16) and (6a*R*)-10,11-methylenedioxyaporphine (2) produced apomorphine-like postural asymmetries in caudate lesioned mice but were less potent than apomorphine in this respect. Of the aporphine derivatives tested for antihypertensive activity, 11-hydroxyaporphine (13) proved to be the most potent upon oral administration to spontaneously hypertensive rats.

Apomorphine, (−)-1, has been shown to stimulate the dopaminergic system in the rat and mouse corpus striatum,[1,2] to produce a dopamine-like renal vasodilatation in dogs,[3] and to have a hypotensive effect in cats.[4] On the basis of its dopamine receptor-stimulating properties, apomorphine has been investigated recently for the treatment of Parkinson's disease.[5] We wish to report the synthesis of some aporphine derivatives related to apomorphine and their evaluation as antihypertensive and central dopaminergic agents.



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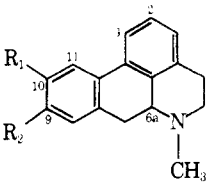

3, R_1 = OH; R_2 = H
4, R_1 = H; R_2 = OH
5, R_1 = R_2 = OH

Chemistry. The disodium salt of apomorphine, (−)-1, was converted directly to methylene ether **2** by reaction with CH_2Br_2 in DMSO-H_2O. In accord with the nmr spectra of other aporphine alkaloids containing methylenedioxy groups,[6,7] the methylene protons of the free base of 2 were observed as a pair of doublets centered at δ 6.17 (J = 1.5 Hz, $CDCl_3$).

Cleavage of the methylenedioxy group of 2 with Na in NH_3(l) gave the expected 10-hydroxyaporphine **3** in 50% yield. The phenolic hydroxyl group in this product was assigned initially to the 10 position by analogy with the behavior of 1,2-methylenedioxyaporphines which have been found to give only 2-hydroxyaporphines under these conditions.[8] This assignment was confirmed later by nmr and tlc nonidentity with an authentic sample of the isomeric 11-hydroxy compound **13**.