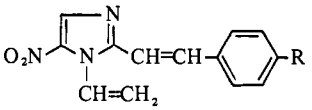
# Antiparasitic Nitroimidazoles. 7. Some 4- and 5-Styrylnitroimidazoles

William J. Ross* and Alec Todd

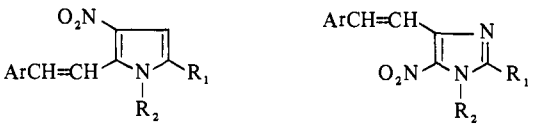
*Lilly Research Centre Limited, Erl Wood Manor, Windlesham, Surrey, England.* *Received October 13, 1972*

In part I[1] of this series of papers, we described the antiparasitic activity of a series of 2-styryl-5-nitroimidazoles with particular emphasis on their antitrypanosomal properties. Our investigations led us to the conclusion that for maximum antiprotozoal activity *in vivo* the compounds should have general structure **1**.



**1a**, R = small primary or secondary alkyl group
**b**, R = COOH
**c**, R = Me

In a subsequent paper[2] we discussed the synthesis and biological activity of **1b** (R = COOH), a urinary metabolite of **1c** (R = Me). In order to complete our structure-activity relationships in the styrylnitroimidazole area, it was necessary to prepare compounds of types **2** and **3** corresponding to the active compounds discussed in our earlier papers.[1,2]



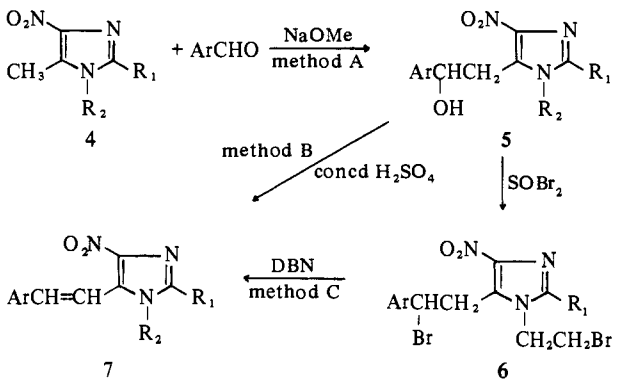
**2** **3**

a, Ar = 3,4-diClPh; $R_1$ = H; $R_2$ = Me
b, Ar = Ph; $R_1$ = Me; $R_2$ = $CH_2CH_2N$⟨O⟩

Ellis and coworkers[3] and later Giraldi, *et al.*,[4] have described the synthesis and the antitrichomonal properties of a number of 4- and 5-styrylnitroimidazoles but these compounds were not tested against the various trypanosoma species.

**Chemistry.** The 4-nitro-5-styrylimidazoles (Table II) were prepared by the general routes shown in Scheme I.

Scheme I



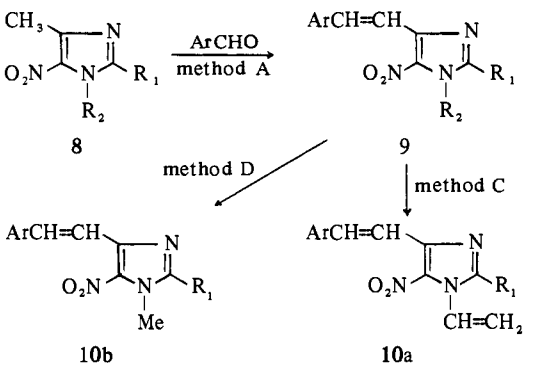
**4** **5** **7** **6**

Condensation of the nitroimidazole with arylaldehydes under our conditions invariably led to the isolation of secondary alcohols of type **5**. The earlier workers[3,4] obtained the styryl compounds directly but after our studies were complete, Shimada, *et al.*,[5] described the isolation and dehydration of this type of compound. The secondary alcohols (Table I) proved resistant to dehydration with refluxing acetic anhydride but were readily dehydrated using concentrated $H_2SO_4$ (method B).

In the reactions of **4** ($R_1$ = Me) with aldehydes only the 5-Me group reacted as shown by pmr. The chemical shifts in $CDCl_3$ for the *C*-methyl groups are as follows; **4** ($R_1$ = $R_2$ = Me) δ 2.40, 2.59; **4** ($R_1$ = Me; $R_2$ = $CH_2CH_2OH$) δ 2.42, 2.60; **4** ($R_1$ = H; $R_2$ = Me) 2.60; **4** ($R_1$ = H; $R_2$ = $CH_2CH_2OH$) δ 2.63. Thus, we can assign the singlet at *ca.* δ 2.60 to the 5-methyl substituent of compounds of type **4** ($R_1$ = Me) and since the pmr spectra of the products **7** show a singlet in the range δ 2.44-2.47, we can assume the 5-methyl group has reacted with the aldehyde.

Reaction of compounds having general structure **4** ($R_2$ = $CH_2$=$CH_2$) with benzaldehyde gave the corresponding secondary alcohols **5** (R = CH=$CH_2$) in low yield. It was thus necessary to devise alternative procedures to obtain compounds of type **7** ($R_2$ = CH=$CH_2$). Compound **16** (Table I) was readily converted to the monotosylate **18** (Table I) and treatment of this compound with sodium ethoxide gave compound **19** (Table I) which was dehydrated by method B to yield the styrylimidazole **26** (Table II). However, it was found more convenient to prepare compounds of type **7** ($R_2$ = CH=$CH_2$) by conversion of the analogous alcohol **5** ($R_2$ = $CH_2CH_2OH$) to a dibromide **6** with subsequent dehydrobromination using 1,5-diazabicyclo[4.3.0]-non-5-ene.[6] Two methods were used for the preparation of the 5-nitro-4-styrylimidazoles (Scheme II, Table III). Base-

Scheme II

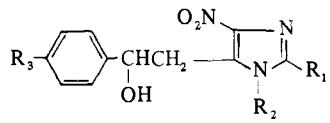


**8** **9** **10b** **10a**

catalyzed condensation (method A, Scheme II) of 4-methyl-5-nitroimidazole (**8**) with aromatic aldehydes gave the 4-styryl compounds **9** directly when the 2 position of the nitroimidazole was unsubstituted (*i.e.*, $R_1$ = H). Where $R_1$ = Me in **8**, only tarry products were obtained and it was necessary to condense the NH compound **8** ($R_2$ = H) with the aldehydes followed by N-alkylation. Compounds of type **10a** ($R_2$ = CH=$CH_2$) were prepared by the bromination-dehydrobromination route (method C) as attempts to form the *N*-vinyl compounds from **8** ($R_2$ = $CH_2CH_2OTs$) and **9** ($R_2$ = $CH_2CH_2OTs$, Ar = 4-$MeC_6H_4$) gave tarry products.

**Biological Results.** All the compounds in Tables II and III were tested both po and ip against infections of *Trypanosoma rhodesiense* and *Trypanosoma cruzi* in mice using the methods referred to in parts 1[1] and 3,[2] but none showed activity. Compound **27** (Table II) and compounds **34**, **35**, and **41** (Table III) are analogs of some of the more active 2-styryl-5-nitroimidazoles described in our earlier papers.[1,2] Although some of the compounds have *in vitro* activity against *Trichomonas vaginalis* similar to that of metronidazole (MIC 0.5 μg/ml), none showed *in vivo* activity when tested in mice.[1] This observation is in keeping with the results obtained by Giraldi, Mariotti, and de Carneri[4] with

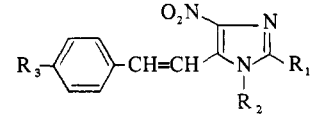
Table I



| Compd | $R_1$ | $R_2$ | $R_3$ | Yield,[a] % | Mp, °C | Formula[b] |
|---|---|---|---|---|---|---|
| 11 | H | Me | Me | 63 | 225 | $C_{13}H_{15}N_3O_3$ |
| 12 | H | Me | $CO_2H$ | 71 | 283–285 | $C_{13}H_{13}N_3O_5$ |
| 13 | Me | Me | H | 72 | 206[d] | $C_{13}H_{15}N_3O_3$ |
| 14 | Me | Me | Me | 58 | 227[e] | $C_{14}H_{17}N_3O_3$ |
| 15 | Me | Me | $CO_2H$ | 69 | 254–255 dec | $C_{14}H_{15}N_3O_5$ |
| 16 | Me | $CH_2CH_2OH$ | H | 79 | 200 | $C_{14}H_{17}N_3O_4$ |
| 17 | Me | $CH_2CH_2OH$ | Me | 65 | 190 dec | $C_{15}H_{19}N_3O_4$ |
| 18 | Me | $CH_2CH_2OTs$ | H | 47[c] | 195 | $C_{21}H_{23}N_3O_6S$ |
| 19 | Me | $CH{=}CH_2$ | H | 21[c] | 178 | $C_{14}H_{15}N_3O_3$ |

[a] Prepared by method A except where noted. [b] All compounds analyzed for C, H, and N. [c] Preparation described in the Experimental Section. [d] Mp 196° dec, ref 5. [e] Mp 196–197° dec, ref 5

Table II



| Compd | $R_1$ | $R_2$ | $R_3$ | Yield, % | Mp, °C | Formula[a] | MIC[d] (μg/ml), *T. vaginalis* |
|---|---|---|---|---|---|---|---|
| **20** | H | Me | Me | 91[b] | 141 | $C_{13}H_{13}N_3O_2$ | 0.5 |
| **21** | H | Me | $CO_2H$ | 69[b] | 302–303 | $C_{13}H_{11}N_3O_4$ | 4 |
| **22** | Me | Me | H | 50[b] | 128[f] | $C_{13}H_{13}N_3O_2$ | |
| **23** | Me | Me | Me | 74[b] | 142[g] | $C_{14}H_{15}N_3O_2$ | 100–1000 |
| **24** | Me | Me | $CO_2H$ | 71[b] | 310 dec | $C_{14}H_{13}N_3O_4$ | 10–100 |
| **25** | Me | $CH_2CH_2OH$ | H | 70[b] | 162 | $C_{14}H_{15}N_3O_3$ | |
| **26** | Me | $CH{=}CH_2$ | H | 35[c] | 117 | $C_{14}H_{13}N_3O_2$ | 2 |
| **27** | Me | $CH{=}CH_2$ | Me | 24[c,e] | 95–97 | $C_{14}H_{15}N_3O_2$ | |

[a] All compounds analyzed for C, H, and N. [b] Prepared by method B. [c] Prepared by method C. [d] Determined by serial dilution *in vitro*. [e] Yield from 4; intermediate **6** was not purified. [f] Mp 124°, ref 5. [g] Mp 193°, ref 5.

their series of 4- and 5-styrylnitroimidazoles. From our results, we would conclude that for antitrypanosomal activity in the styrylnitroimidazole group of compounds it is essential for the styryl function to be placed in the 2 position of the imidazole nucleus.

## Experimental Section

All compounds were characterized by ir, uv, and nmr spectra and by elemental analyses (C, H, N) which were within ±0.4% of the theoretical value. Compounds 4 ($R_1$ = H; $R_2$ = Me),[7] 4 ($R_1$ = $R_2$ = Me),[7] 9 ($R_1$ = H; $R_2$ = Me),[8] and 9 ($R_1$ = $R_2$ = Me)[9] were prepared by previously described methods.

**5-Methyl-4-nitro-1-imidazoleethanol (4, $R_1$ = H; $R_2$ = $CH_2CH_2OH$).** 4(5)-Methyl-5(4)-nitroimidazole (6.35 g, 0.05 mol) and ethylene carbonate (13.2 g, 0.15 mol) were fused together at 160° for 1 hr. The dark liquid was cooled, diluted with $H_2O$, and extracted with EtOAc. The extract was dried and evaporated and the residual oil was crystallized from $CHCl_3$–petroleum ether to give 2.0 g (23%) of product, mp 142°

**2,5-Dimethyl-4-nitro-1-imidazoleethanol[5] (4, $R_1$ = Me; $R_2$ = $CH_2CH_2OH$),** mp 170°, was similarly prepared in 60% yield. Reaction of 2,4(5)-dimethyl-5(4)-nitroimidazole with ethylene oxide in EtOH–NaOH gave a mixture of 4 ($R_1$ = Me; $R_2$ = $CH_2CH_2OH$) and the 5-nitro isomer **8** ($R_1$ = Me; $R_2$ = $CH_2CH_2OH$), mp 120° (purified by crystallization of the HCl salt from EtOH–$Et_2O$).

**2,5-Dimethyl-4-nitro-1-vinylimidazole (4, $R_1$ = Me; $R_2$ = $CH{=}CH_2$).** A solution of TsCl (6.0 g, 0.031 mol) in dry pyridine (10 ml) was added over 1 hr to a stirred suspension of 1 ($R_1$ = Me; $R_2$ = $CH_2CH_2OH$) (5.55 g, 0.03 mol) in dry pyridine (10 ml) at 0–5°. The mixture was stirred for 4 hr at 0–5°; the solid was filtered off, washed with EtOH, and recrystallized from DMF–EtOH to give 7.0 g (70%) of tosylate 4 ($R_1$ = Me; $R_2$ = $CH_2CH_2OTs$), mp 196°. A solution of Na (0.25 g) in EtOH (5 ml) was added over 15 min to a stirred suspension of the tosylate (3.4 g, 0.01 mol) in EtOH (5 ml) at 70°. The dark brown mixture was heated at 70° for 30 min and then evaporated and the residue was dissolved in $H_2O$ and extracted with $Et_2O$. Evaporation and crystallization from $Et_2O$–EtOH–hexane gave 0.6 g (36%) of product, mp 105°.

Treatment of a solution of 4 ($R_1$ = Me; $R_2$ = $CH{=}CH_2$) (0.5 g) and PhCHO (0.3 ml) in DMSO (3 ml) with a solution of Na (0.1 g) in MeOH (3 ml) for 4.5 hr at 0–5° gave, on dilution with water, a tarry brown solid. Recrystallization from EtOH–$H_2O$ gave 0.1 g of product, mp 175°, with identical ir spectrum to that of compound 19 described below.

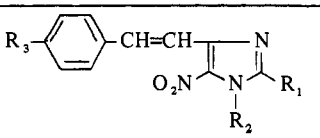
**5-(2-Aryl-2-hydroxyethyl)-4-nitroimidazoles (5, Table I). Method A.** A cold solution of Na (1.0 g, 0.045 g-atom) in MeOH (30 ml) was added rapidly to a stirred suspension of the 5-methyl-4-nitroimidazole (0.03 mol) and the aldehyde (0.03 mol) in DMSO (30 ml) with cooling in ice. The resulting solution was stirred at 0–5° for 4–20 hr and, if necessary, diluted with $H_2O$ to precipitate the solid product which was washed with EtOH–$H_2O$ and recrystallized from DMF–$H_2O$ or DMF–EtOH. In reactions using 4-carboxybenzaldehyde, an additional 1 equiv of Na was used and the final solution was acidified to precipitate the product. Compound 13 (0.2 g) was heated in $Ac_2O$ under reflux for 8 hr. The solution was diluted with water and evaporated and the residue was crystallized from EtOH–$H_2O$ to give 0.15 g of **5-(2-acetoxy-2-phenylethyl)-1,2-dimethyl-4-nitroimidazole**, mp 126°.

**4-Nitro-5-styrylimidazoles (7) (Table II). Method B.** The solid intermediate **5** (5 g) was added to a mixture of $H_2O$ (25 ml) and concentrated $H_2SO_4$ (50 ml) at 20–25° and the solution was either stored at 20–25° for 16 hr or heated on steam for 1–2 hr. Dilution with $H_2O$ precipitated the product which was washed with $H_2O$ and crystallized from EtOH (or DMF for compounds **21** and **24**).

**5-(2-Hydroxy-2-phenylethyl)-2-methyl-4-nitro-1-(2-*p*-toluenesulfonyloxyethyl)imidazole (18).** A mixture of the diol **16** (1.5 g, 0.005 mol) and TsCl (1.9 g, 0.01 mol) in dry pyridine (10 ml) was stirred for 4 hr at 0–5° and then 2 hr at 20–25°. The clear solution was poured onto water and the resulting solid was crystallized from EtOH to give the product **18**.

**5-(2-Hydroxy-2-phenylethyl)-2-methyl-4-nitro-1-vinylimidazole (19).** A solution of Na (0.11 g) in EtOH (5 ml) was added to a

Table III



| Compd | $R_1$ | $R_2$ | $R_3$ | Yield,[a] % | Mp, °C | Formula[e] | MIC[f] (μg/ml), *T. vaginalis* |
|---|---|---|---|---|---|---|---|
| **28** | H | Me | Me | 50 | 208 | $C_{13}H_{13}N_3O_2$ | 2 |
| **29** | H | Me | $CO_2H$ | 49 | 300–302 dec | $C_{13}H_{11}N_3O_4$ | 0.5 |
| **30** | H | $CH_2CH_2OH$ | Me | 42 | 187 | $C_{14}H_{15}N_3O_3$ | 2 |
| **31** | H | $CH_2CH_2OH$ | $CO_2H$ | 27 | 208 dec | $C_{14}H_{13}N_3O_5$ | 100–1000 |
| **32** | H | $CH_2CH_2OTs$ | Me | 85[b] | 190 | $C_{21}H_{21}N_3O_5S$ | |
| **33** | H | $CH{=}CH_2$ | H | 61[c] | 146 | $C_{13}H_{11}N_3O_2$ | 1 |
| **34** | H | $CH{=}CH_2$ | Me | 58[c] | 136 | $C_{14}H_{13}N_3O_2$ | 2 |
| **35** | H | $CH{=}CH_2$ | $CO_2H$ | 38[c] | 280 dec | $C_{14}H_{11}N_3O_4$ | |
| **36** | Me | H | H | 40 | 249[g] | $C_{12}H_{11}N_3O_2$ | 10–100 |
| **37** | Me | H | Me | 21 | 252[h] | $C_{13}H_{13}N_3O_2$ | |
| **38** | Me | Me | H | 76[d] | 140[i] | $C_{13}H_{13}N_3O_2$ | 2 |
| **39** | Me | Me | Me | 78[d] | 198[j] | $C_{14}H_{15}N_3O_2$ | |
| **40** | Me | $CH_2CH_2OH$ | H | 78[b] | 135 | $C_{14}H_{15}N_3O_3$ | |
| **41** | Me | $CH{=}CH_2$ | H | 32[c] | 99 | $C_{14}H_{13}N_3O_2$ | |

[a]Prepared by method A except where noted. [b]Preparation described in the Experimental Section. [c]Prepared by method C. [d]Prepared by method D. [e]All compounds analyzed for C, H, and N. [f]Determined by serial dilution *in vitro*. [g]Mp 245–246°, ref 4. [h]Mp 242°, ref 5. [i]Mp 136–138°, ref 5. [j]Mp 197–198°, ref 5.

stirred suspension of **18** (2.0 g, 0.0045 mol) in EtOH (5 ml) at 70°. The mixture was heated at 70° for 30 min and then evaporated and the residue was dissolved in water and extracted with $CHCl_3$. Evaporation of the extract gave an oil which crystallized from $CHCl_3$–petroleum ether to give the product **19**, mp 178°.

**4-Nitro-5-styryl-1-vinylimidazoles (7, $R_2$ = $CH{=}CH_2$).** Method C. $SOBr_2$ (3.4 ml, 0.044 mol) was added over 30 min to a stirred solution of the diol **5** ($R_2$ = $CH_2CH_2OH$) (0.017 mol) in DMF (20 ml). The solution was stirred for 3 hr at 20–25° and poured onto ice. Neutralization with $NaHCO_3$ and extraction with EtOAc gave the crude dibromo compound **6** as an oil. This oil was dissolved in DMSO (50 ml) and 1,5-diazabicyclo[4.3.0]non-5-ene (13.5 ml) and the dark solution was heated at *ca.* 45° for 1 hr and then poured onto ice–$H_2O$, and the precipitate was recrystallized from ethanol.

**4-Methyl-5-nitro-1-imidazoleethanol (8, $R_1$ = H; $R_2$ = $CH_2CH_2OH$).** Ethylene oxide (25 ml, 0.5 mol) was added in small portions over 1 hr to a stirred solution of 4(5)-methyl-5(4)-nitroimidaozle (6.35 g, 0.05 mol) in 98% $HCO_2H$ (150 ml) at 45° and the solution was stirred for a further 1 hr and then evaporated. The residue was diluted with $H_2O$ (10 ml) and filtered to remove unreacted starting material. The filtrate was made alkaline with 5 *M* NaOH and extracted with EtOAc. Evaporation of the extract yielded an oil which crystallized from $CHCl_3$–petroleum ether to give 3.3 g (39%) of product, mp 100°.

**4-Methyl-5-nitro-1-(2-*p*-toluenesulfonyloxyethyl)imidazole (8, $R_1$ = H; $R_2$ = $CH_2CH_2OTs$),** mp 130°, was prepared in 87% yield as described above for **4** ($R_1$ = Me; $R_2$ = $CH_2CH_2OTs$). Treatment of this tosylate with NaOEt in EtOH at 70° gave a dark brown solution from which only unreacted tosylate could be isolated.

**5-Nitro-4-styrylimidazoles (Table III). Method A.** 4-Methyl-5-nitroimidazoles were condensed with aromatic aldehydes using the procedure described above in method A for the preparation of **5.** The products were recrystallized from EtOH (+DMF where $R_3$ = $CO_2H$). In the preparation of compounds **36** and **37**, the reaction mixtures were heated under reflux for 1–2 hr and the products were isolated by extraction of the diluted and neutralized reaction mixture with EtOAc.

Method C. Compounds **9** ($R_2$ = $CH_2CH_2OH$) were converted to the corresponding *N*-vinyl compounds **33–35** and **41** by the procedure described above in method C for the preparation of compounds **7.** The intermediate bromo compounds were solids but were not purified. Compound **35** was purified by acidification of an EtOH–$H_2O$ solution of the Na salt.

Method D. Compounds **36** and **37** were methylated with a slight excess of $Me_2SO_4$ in refluxing dioxane. The solid products were crystallized from EtOH–dilute $NH_3$.

**2-Methyl-5-nitro-4-styryl-1-imidazoleethanol (40).** Ethylene oxide (50 ml) was added in small portions over 1 hr to a stirred solution of **36** (9.0 g, 0.039 mol) in 98% $HCO_2H$ (150 ml) at 50–60°. The mixture was stirred for a further 1 hr and then evaporated, and the residue was heated to 70° with EtOH (100 ml) and 5 *M* NaOH (130 ml) to hydrolyze some esterified product. On cooling the solution yellow solid formed and was crystallized from $CHCl_3$–hexane and then from EtOH to give pure **40.** Further material obtained from the crystallizations was a mixture of **40** with **36** and was again allowed to react with ethylene oxide in $HCO_2H$ to give more product.

**4-(4-Methylstyryl)-5-nitro-1-(2-*p*-toluenesulfonyloxyethyl)-imidazole (32).** Compound **30** was tosylated as described above for compound **4** ($R_1$ = Me; $R_2$ = $CH_2CH_2OTs$). An attempted elimination reaction using NaOEt in EtOH at 70° gave a mixture of tarry material and starting tosylate.

## References


(1) W. J. Ross, W. B. Jamieson, and M. C. McCowen, *J. Med. Chem.*, **15**, 1035 (1972).
(2) W. J. Ross, W. B. Jamieson, and M. C. McCowen, *ibid.*, **16**, 347 (1973).
(3) G. P. Ellis, C. Epstein, C. Fitzmaurice, L. Goldberg, and G. H. Lord, *J. Pharm. Pharmacol.*, **16**, 801 (1964).
(4) P. N. Giraldi, V. Mariotti, and I. de Carneri, *J. Med. Chem.*, 11, 66 (1968).
(5) K. Shimada, S. Kuriyama, and M. Satoh, *J. Pharm. Soc. Jap.*, 91, 231 (1971).
(6) K. Eiter and H. Oediger, *Justus Liebigs Ann. Chem.*, **682**, 62 (1965).
(7) F. L. Pyman, *J. Chem. Soc.*, **121**, 2621 (1921).
(8) W. E. Allsebrooke, J. M. Gulland, and L. F. Story, *ibid.*, 232 (1942).
(9) J. S. G. Cox, C. Fitzmaurice, and G. J. T. Tiddy, *J. Chem. Soc. B*, 1251 (1967).


# 4-Vinyl Analog of Pyridoxal, a Potent Antagonist of Vitamin $B_6$†


W. Korytnyk,* G. B. Grindey, and B. Lachmann

*Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York 14203.*

*Received November 20, 1972*

As part of our program for the development of new antagonists of vitamin $B_6$,[3] we have synthesized a close analog **3** of pyridoxal, in which the O atom of the aldehyde has been replaced with methylene. The synthesis of 4-deformyl-4-vinylpyridoxal ("4-VPAL," **3**)‡ starts with 3,$\alpha^5$-*O*-di-

†Chemistry and Biology of Vitamin $B_6$. 32. For the preceding paper in this series, see ref 1. Subseries: Selective Modification of the $\alpha^4$ Position of Pyridoxol. 2. For the preceding paper in this subseries, see ref 2.

‡Nomenclature and the abbreviations used were those recommended by the IUPAC-IUB Commission on Biochemical Nomenclature; see, *e.g.*, ref 4.