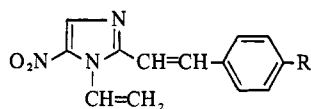


## Antiparasitic Nitroimidazoles. 7. Some 4- and 5-Styrylnitroimidazoles

William J. Ross\* and Alec Todd

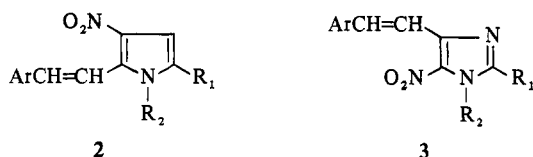
Lilly Research Centre Limited, Erl Wood Manor, Windlesham, Surrey, England. Received October 13, 1972

In part I<sup>1</sup> 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<sup>2</sup> 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.<sup>1,2</sup>



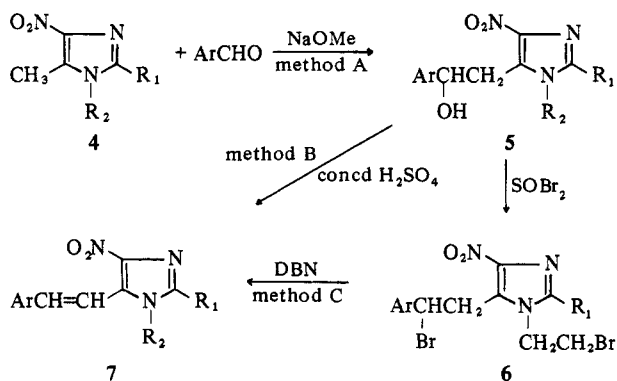
a, Ar = 3,4-dichlorophenyl; R<sub>1</sub> = H; R<sub>2</sub> = Me

b, Ar = Ph; R<sub>1</sub> = Me; R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>O

Ellis and coworkers<sup>3</sup> and later Giraldi, *et al.*,<sup>4</sup> 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



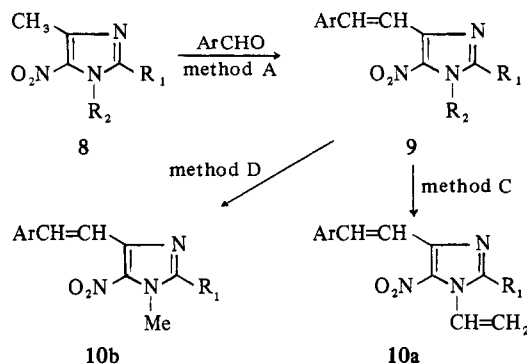
Condensation of the nitroimidazole with arylaldehydes under our conditions invariably led to the isolation of secondary alcohols of type 5. The earlier workers<sup>3,4</sup> obtained the styryl compounds directly but after our studies were complete, Shimada, *et al.*,<sup>5</sup> described the isolation 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<sub>2</sub>SO<sub>4</sub> (method B).

In the reactions of 4 (R<sub>1</sub> = Me) with aldehydes only the 5-Me group reacted as shown by pmr. The chemical shifts in CDCl<sub>3</sub> for the C-methyl groups are as follows; 4 (R<sub>1</sub> = R<sub>2</sub> = Me) δ 2.40, 2.59; 4 (R<sub>1</sub> = Me; R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>OH) δ 2.42, 2.60; 4 (R<sub>1</sub> = H; R<sub>2</sub> = Me) δ 2.60; 4 (R<sub>1</sub> = H; R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>OH) 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<sub>1</sub> = 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<sub>2</sub> = CH=CH<sub>2</sub>) with benzaldehyde gave the corresponding secondary alcohols 5 (R = CH=CH<sub>2</sub>) in low yield. It was thus necessary to devise alternative procedures to obtain compounds of type 7 (R<sub>2</sub> = CH=CH<sub>2</sub>). 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<sub>2</sub> = CH=CH<sub>2</sub>) by conversion of the analogous alcohol 5 (R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>OH) to a dibromide 6 with subsequent dehydrobromination using 1,5-diazabicyclo[4.3.0]non-5-ene.<sup>6</sup> Two methods were used for the preparation of the 5-nitro-4-styrylimidazoles (Scheme II, Table III). Base-

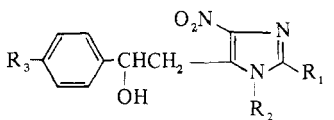
Scheme II



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<sub>1</sub> = H). Where R<sub>1</sub> = Me in 8, only tarry products were obtained and it was necessary to condense the NH compound 8 (R<sub>2</sub> = H) with the aldehydes followed by N-alkylation. Compounds of type 10a (R<sub>2</sub> = CH=CH<sub>2</sub>) were prepared by the bromination-dehydrobromination route (method C) as attempts to form the N-vinyl compounds from 8 (R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>OTs) and 9 (R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>OTs, Ar = 4-MeC<sub>6</sub>H<sub>4</sub>) 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<sup>1</sup> and 3,<sup>2</sup> 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.<sup>1,2</sup> 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.<sup>1</sup> This observation is in keeping with the results obtained by Giraldi, Mariotti, and de Carneri<sup>4</sup> with

Table I

						
Compd	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Yield, <sup>a</sup> %	Mp, °C	Formula <sup>b</sup>
11	H	Me	Me	63	225	C <sub>13</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub>
12	H	Me	CO <sub>2</sub> H	71	283–285	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O <sub>5</sub>
13	Me	Me	H	72	206 <sup>d</sup>	C <sub>13</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub>
14	Me	Me	Me	58	227 <sup>e</sup>	C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub>
15	Me	Me	CO <sub>2</sub> H	69	254–255 dec	C <sub>14</sub> H <sub>15</sub> N <sub>3</sub> O <sub>5</sub>
16	Me	CH <sub>2</sub> CH <sub>2</sub> OH	H	79	200	C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O <sub>4</sub>
17	Me	CH <sub>2</sub> CH <sub>2</sub> OH	Me	65	190 dec	C <sub>15</sub> H <sub>19</sub> N <sub>3</sub> O <sub>4</sub>
18	Me	CH <sub>2</sub> CH <sub>2</sub> OTs	H	47 <sup>c</sup>	195	C <sub>21</sub> H <sub>23</sub> N <sub>3</sub> O <sub>6</sub> S
19	Me	CH=CH <sub>2</sub>	H	21 <sup>c</sup>	178	C <sub>14</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub>

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

Table II

Compd	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Yield, %	Mp, °C	Formula <sup>a</sup>	MIC <sup>d</sup> (μg/ml), <i>T. vaginalis</i>
20	H	Me	Me	91 <sup>b</sup>	141	C <sub>13</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>	0.5
21	H	Me	CO <sub>2</sub> H	69 <sup>b</sup>	302–303	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O <sub>4</sub>	4
22	Me	Me	H	50 <sup>b</sup>	128 <sup>f</sup>	C <sub>13</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>	
23	Me	Me	Me	74 <sup>b</sup>	142 <sup>g</sup>	C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub>	100–1000
24	Me	Me	CO <sub>2</sub> H	71 <sup>b</sup>	310 dec	C <sub>14</sub> H <sub>15</sub> N <sub>3</sub> O <sub>4</sub>	10–100
25	Me	CH <sub>2</sub> CH <sub>2</sub> OH	H	70 <sup>b</sup>	162	C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub>	
26	Me	CH=CH <sub>2</sub>	H	35 <sup>c</sup>	117	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub>	2
27	Me	CH=CH <sub>2</sub>	Me	24 <sup>c,e</sup>	95–97	C <sub>14</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>	

<sup>a</sup>All compounds analyzed for C, H, and N. <sup>b</sup>Prepared by method B. <sup>c</sup>Prepared by method C. <sup>d</sup>Determined by serial dilution *in vitro*. <sup>e</sup>Yield from 4; intermediate 6 was not purified. <sup>f</sup>Mp 124°, ref 5. <sup>g</sup>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  $\pm 0.4\%$  of the theoretical value. Compounds 4 (R<sub>1</sub> = H; R<sub>2</sub> = Me),<sup>7</sup> 4 (R<sub>1</sub> = R<sub>2</sub> = Me),<sup>7</sup> 9 (R<sub>1</sub> = H; R<sub>2</sub> = Me),<sup>8</sup> and 9 (R<sub>1</sub> = R<sub>2</sub> = Me)<sup>9</sup> were prepared by previously described methods.

**5-Methyl-4-nitro-1-imidazoleethanol (4, R<sub>1</sub> = H; R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>OH).** 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<sub>2</sub>O, and extracted with EtOAc. The extract was dried and evaporated and the residual oil was crystallized from CHCl<sub>3</sub>-petroleum ether to give 2.0 g (23%) of product, mp 142°.

**2,5-Dimethyl-4-nitro-1-imidazoleethanol<sup>5</sup> (4, R<sub>1</sub> = Me; R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>OH),** 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<sub>1</sub> = Me; R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>OH) and the 5-nitro isomer 8 (R<sub>1</sub> = Me; R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>OH), mp 120° (purified by crystallization of the HCl salt from EtOH-Et<sub>2</sub>O).

**2,5-Dimethyl-4-nitro-1-vinylimidazole (4, R<sub>1</sub> = Me; R<sub>2</sub> = CH=CH<sub>2</sub>).** 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<sub>1</sub> = Me; R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>OH) (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<sub>1</sub> = Me; R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>OTs), 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<sub>2</sub>O and extracted with Et<sub>2</sub>O. Evaporation and crystallization from Et<sub>2</sub>O-EtOH-hexane gave 0.6 g (36%) of product, mp 105°.

Treatment of a solution of 4 (R<sub>1</sub> = Me; R<sub>2</sub> = CH=CH<sub>2</sub>) (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<sub>2</sub>O 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<sub>2</sub>O to precipitate the solid product which was washed with EtOH-H<sub>2</sub>O and recrystallized from DMF-H<sub>2</sub>O 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<sub>2</sub>O under reflux for 8 hr. The solution was diluted with water and evaporated and the residue was crystallized from EtOH-H<sub>2</sub>O 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<sub>2</sub>O (25 ml) and concentrated H<sub>2</sub>SO<sub>4</sub> (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<sub>2</sub>O precipitated the product which was washed with H<sub>2</sub>O 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 <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Yield, <sup>a</sup> %	Mp, °C	Formula <sup>e</sup>	MIC <sup>f</sup> (μg/ml), <i>T. vaginalis</i>
28	H	Me	Me	50	208	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub>	2
29	H	Me	CO <sub>2</sub> H	49	300–302 dec	C <sub>13</sub> H <sub>11</sub> N <sub>3</sub> O <sub>4</sub>	0.5
30	H	CH <sub>2</sub> CH <sub>2</sub> OH	Me	42	187	C <sub>14</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub>	2
31	H	CH <sub>2</sub> CH <sub>2</sub> OH	CO <sub>2</sub> H	27	208 dec	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> O <sub>5</sub>	100–1000
32	H	CH <sub>2</sub> CH <sub>2</sub> OTs	Me	85 <sup>b</sup>	190	C <sub>21</sub> H <sub>21</sub> N <sub>3</sub> O <sub>5</sub> S	
33	H	CH=CH <sub>2</sub>	H	61 <sup>c</sup>	146	C <sub>13</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub>	1
34	H	CH=CH <sub>2</sub>	Me	58 <sup>c</sup>	136	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub>	2
35	H	CH=CH <sub>2</sub>	CO <sub>2</sub> H	38 <sup>c</sup>	280 dec	C <sub>14</sub> H <sub>11</sub> N <sub>3</sub> O <sub>4</sub>	
36	Me	H	H	40	249 <sup>g</sup>	C <sub>12</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub>	10–100
37	Me	H	Me	21	252 <sup>h</sup>	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub>	
38	Me	Me	H	76 <sup>d</sup>	140 <sup>i</sup>	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub>	2
39	Me	Me	Me	78 <sup>d</sup>	198 <sup>j</sup>	C <sub>14</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>	
40	Me	CH <sub>2</sub> CH <sub>2</sub> OH	H	78 <sup>b</sup>	135	C <sub>14</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub>	
41	Me	CH=CH <sub>2</sub>	H	32 <sup>c</sup>	99	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub>	

<sup>a</sup>Prepared by method A except where noted. <sup>b</sup>Preparation described in the Experimental Section. <sup>c</sup>Prepared by method C. <sup>d</sup>Prepared by method D. <sup>e</sup>All compounds analyzed for C, H, and N. <sup>f</sup>Determined by serial dilution *in vitro*. <sup>g</sup>Mp 245–246°, ref 4. <sup>h</sup>Mp 242°, ref 5. <sup>i</sup>Mp 136–138°, ref 5. <sup>j</sup>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<sub>3</sub>. Evaporation of the extract gave an oil which crystallized from CHCl<sub>3</sub>–petroleum ether to give the product **19**, mp 178°.

**4-Nitro-5-styryl-1-vinylimidazoles (7, R<sub>1</sub> = CH=CH<sub>2</sub>).** Method C. SOBr<sub>2</sub> (3.4 ml, 0.044 mol) was added over 30 min to a stirred solution of the diol **5** (R<sub>1</sub> = CH<sub>2</sub>CH<sub>2</sub>OH) (0.017 mol) in DMF (20 ml). The solution was stirred for 3 hr at 20–25° and poured onto ice. Neutralization with NaHCO<sub>3</sub> 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<sub>2</sub>O, and the precipitate was recrystallized from ethanol.

**4-Methyl-5-nitro-1-imidazoleethanol (8, R<sub>1</sub> = H; R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>OH).** 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)-nitroimidazole (6.35 g, 0.05 mol) in 98% HCO<sub>2</sub>H (150 ml) at 45° and the solution was stirred for a further 1 hr and then evaporated. The residue was diluted with H<sub>2</sub>O (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<sub>3</sub>–petroleum ether to give 3.3 g (39%) of product, mp 100°.

**4-Methyl-5-nitro-1-(2-*p*-toluenesulfonyloxyethyl)imidazole (8, R<sub>1</sub> = H; R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>OTs),** mp 130°, was prepared in 87% yield as described above for **4** (R<sub>1</sub> = Me; R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>OTs). 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<sub>3</sub> = CO<sub>2</sub>H). 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<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>OH) 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<sub>2</sub>O solution of the Na salt.

**Method D.** Compounds **36** and **37** were methylated with a slight excess of Me<sub>2</sub>SO<sub>4</sub> in refluxing dioxane. The solid products were crystallized from EtOH–dilute NH<sub>3</sub>.

**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<sub>2</sub>H (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<sub>3</sub>–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<sub>2</sub>H 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<sub>1</sub> = Me; R<sub>2</sub> = CH<sub>2</sub>CH<sub>2</sub>OTs). An attempted elimination reaction using NaOEt in EtOH at 70° gave a mixture of tarry material and starting tosylate.

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## 4-Vinyl Analog of Pyridoxal, a Potent Antagonist of Vitamin B<sub>6</sub><sup>†</sup>

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As part of our program for the development of new antagonists of vitamin B<sub>6</sub>,<sup>3</sup> 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**)<sup>‡</sup> starts with 3,α<sup>5</sup>-O-di-

<sup>†</sup>Chemistry and Biology of Vitamin B<sub>6</sub>, 32. For the preceding paper in this series, see ref 1. Subseries: Selective Modification of the α<sup>4</sup> Position of Pyridoxol. 2. For the preceding paper in this subseries, see ref 2.

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