Synthesis and Biological Activity of Some Vinyl-Substituted 2-Nitroimidazoles

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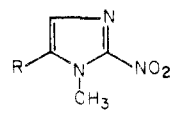
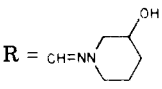
In previous studies, 1-methyl-2-nitro-1*H*-imidazole-5-carboxaldehyde and 1-methyl-2-nitro-5-vinyl-1*H*-imidazole were found to possess interesting antimicrobial activities. We have now prepared some 2-nitro-1*H*-imidazoles in which the 5-vinyl chain bears selected functional groups (CHO, $COCH_3$, NO_2) as well as nitrogen-condensation derivatives of the carbonyl functions. Furthermore, 5-methyl-2-nitro-1-vinyl-1*H*-imidazole has been synthesized. All the compounds, and some intermediates, have been assayed for antimicrobial activity. Several of them exhibited significant antibacterial and antitrichomonal activity in mice.

In a previous paper[1] we described the synthesis and the biological characteristics of some 1-methyl-2-nitro-1*H*-imidazoles functionally substituted in position 5. Among them, compounds **1a,c** and **2** showed good antibacterial and antifungal activity in vitro. In experimental infections in mice, the 5-carboxaldehyde **1a** was found to be inactive against *Escherichia coli* but protected the animals against *Trichomonas vaginalis* infection.

Several derivatives have been prepared[2-5] from **1a** in order to improve its antimicrobial activity. Some hydrazones and a series of N-substituted nitrones were found to possess good in vivo activity. Compounds **1d** and **1e** appeared to be the most promising ones. For these



1a, R = CHO
b, R = $COOCH_3$
c, R = $COCH_3$
d, R = $CH{=}N(\rightarrow O)CH_3$



e, R =

2, R = $CH{=}CH_2$

reasons, we were prompted to synthesize the vinylogues of compounds **1a–c** and of some other active derivatives previously described. Moreover, we have prepared some 5-(2-nitrovinyl) derivatives and the 1-vinyl isomer of compound **2**. The chemicophysical data for these compounds and of a few intermediates are listed in Table I.

Chemistry. Attempts to synthesize (1-methyl-2-nitro-1*H*-imidazol-5-yl)acrolein (**3**) by treating the nitroimidazolecarboxaldehyde (**1a**)[6] with formylmethylenetriphenylphosphorane failed. However, compound **3** was obtained in poor yields by condensation of **1a** with acetaldehyde in the presence of potassium hydroxide.

On the other hand, we were successful in making compounds **6**, **7**, and **8** in fairly good yields by the Wittig reaction. Reaction of **3** and **8** with *N*-methylhydroxylamine and with the appropriate substituted hydrazines gave the derivatives listed in Table I. The Schiff base **5** with 1,5-dimethyl-1*H*-imidazole-2-amine and the thiosemicarbazone **10** were also prepared. The reaction of **8** with 2-hydroxyethylhydrazine yielded instead of the expected hydrazone the substituted (2-nitroimidazol-5-yl)-1*H*-pyrazole **25**, whose structure was confirmed by ^1H NMR and MS data.

Condensation of **1a** with nitromethane and with 1-nitropentane in ethanol in the presence of *n*-propylamine at room temperature was found to be the best way to prepare the nitro alcohols **16** and **18**. Small quantities of the corresponding nitrovinyl compounds were detected in the reaction mixtures. The latter (**19** and **21**) could be obtained by dehydration of **16** and **18** with acetic anhydride. When the condensation was made with nitroethane, both the nitro alcohol **17** and the nitrovinyl compound **20** were present in sizable amounts in the reaction mixture and were separated by crystallization.

Finally, the previously described[7] 5-methyl-2-nitro-1*H*-imidazole-1-ethanol was readily converted into the methanesulfonate **22** and into the tosylate **23** which yielded the *N*-vinyl compound **24** in 60 and 67% yield, respectively.

The IR spectra were consistent with the structures assigned. The trans nature of the vinyl bond was confirmed by ^1H NMR spectra, which showed the characteristic coupling constant of 16 Hz (13 Hz for compound **19**).

Biological Results. The in vitro and in vivo biological activity data were obtained using methods previously described.[7-9]

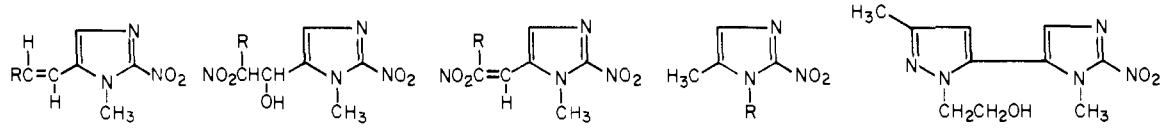
Comparing the data presented in Table II for compounds **3**, **6**, and **8** with those found for **1a–c**, it can be observed that the insertion of a vinyl function between the substituent groups and the imidazole nucleus does not substantially increase the in vitro antimicrobial activity. The activity of **3** is slightly greater than that of **1a** toward gram-positive bacteria. *N*-Methylnitrones **4** and **9** are less active than **1d**, which was found to be the most active compound in the series.[3] A decrease in the activity, except toward some particular strains, is shown by compounds **5** and **10–15**, when compared with the previously described[2,4,5] analogues.

When tested in experimental infections in mice, compounds **3** and **8** were ineffective against *E. coli* at 300 and 200 mg/kg, respectively (os and sc). Compound **4**, at 200 mg/kg (os and sc), saved 5/5 infected animals (*Staphylococcus aureus*). Against an *E. coli* infection, oral or subcutaneous administration of 250 mg/kg of compound **9** resulted in 1/5 and 2/5 survivals, respectively. The approximate LD_{50} of the two compounds is 700 mg/kg. Both could be microbiologically detected in the urines.

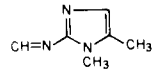
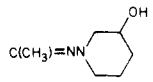
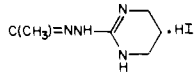
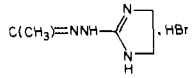
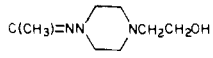
Broad-spectrum antibacterial and antifungal activity in vitro is shown by the nitro alcohols **16–18** and by the nitrovinyl derivatives **19–21**. The introduction of a nitro group onto the vinyl chain of compound **2** strongly enhances the activity in general and, in particular, toward gram-positive bacteria. The position of the vinyl group is critical since the good in vitro antibacterial activity shown by the 5-substituted compound **2** disappears in the N-substituted analogue **24**. Compounds **16**, **19**, and **21** were ineffective in experimental infections (mice) against selected strains.

Compound **3** and compounds **5–15** also possess a certain degree of antitrichomonas activity. The previously described[1-5] analogues had very little of this activity or none at all. On the contrary, the nitrovinyl compounds **19–21** and the *N*-vinyl compound **24** are considerably less active against *T. vaginalis* in vitro than is compound **2**

Table I



3-15 16-18 19-21 22-24 25

Compd	R	Mp, °C[a]	Recrystn solvent	Yield, %[b]	UV λ_{max}, nm (log ε)	Formula[c]
3	CHO	165-168	EtOAc	11	348 (4.24)[e]	$C_7H_7N_3O_3$[d]
4	$CH{=}N(\rightarrow O)CH_3$	183-187	EtOAc	36		$C_8H_{10}N_4O_3$
5		262	f	18		$C_{12}H_{14}N_6O_2$
6	$COOCH_3$	140-142	EtOH	83	391 (4.22)[g]	$C_8H_9N_3O_4$
7	$COOC_2H_5$	117-118	EtOH	61	392 (4.22)[g]	$C_9H_{11}N_3O_4$
8	$COCH_3$	105-107	EtOH	83		$C_8H_9N_3O_3$[d]
9	$C(CH_3){=}N(\rightarrow O)CH_3$	193-194	EtOH	47		$C_9H_{12}N_4O_3$
10	$C(CH_3){=}NNHCSNH_2$	248	MeOH	37		$C_9H_{12}N_6O_2S$
11	$C(CH_3){=}NN(CH_3)_2$	101-103	PhH-petr ether	19		$C_{10}H_{15}N_5O_2$
12		112-115	PhH	25		$C_{13}H_{19}N_5O_3$
13		213-215	EtOAc	11		$C_{12}H_{18}IN_7O_2$
14		287-288	MeOH	14		$C_{11}H_{16}BrN_7O_2$
15		122-125	PhH-Et_2O	21		$C_{14}H_{22}N_6O_3$
16	H	163-165	EtOH	25	322 (3.98)[g]	$C_6H_8N_4O_5$[d]
17	CH_3	138-140	EtOAc	49	322 (3.96)[g]	$C_7H_{10}N_4O_5$[d]
18	n-C_4H_9	102-106	Et_2O	33		$C_{10}H_{16}N_4O_5$
19	H	116-118	PhH	33	353 (4.28)[e]	$C_6H_6N_4O_4$
20	CH_3	143-145	h	10	365 (4.24)[g]	$C_7H_8N_4O_4$
21	n-C_4H_9	83-85	Et_2O-petr ether	9		$C_{10}H_{14}N_4O_4$
22	$CH_2CH_2OSO_2CH_3$	112-115	EtOH	87		$C_7H_{11}N_3O_5S$
23	$CH_2CH_2OSO_2C_6H_4$-p-CH_3	127-129	EtOH	61		$C_{13}H_{15}N_3O_5S$
24	$CH{=}CH_2$	54-56	Et_2O-petr ether	67	331 (3.97)[e]	$C_6H_7N_3O_2$[d]
25		175-177	EtOH	18		$C_{10}H_{13}N_5O_3$[d]

[a] Uncorrected. Determined in open capillary tubes. [b] No attempts were made to improve the yields. [c] Analytical results were within ±0.4% of the theoretical values (C, H, N, and, where applicable, Br, I, and S). [d] Molecular weight confirmed by the M^+ peak in the mass spectrum. [e] Methanol. [f] Washed with H_2O and then with EtOH. [g] Phosphate buffer pH 7.38. [h] Washed with Et_2O.

(MIC, 1 μg/mL).[1]

A selected number of compounds have been evaluated for activity in vivo against *T. vaginalis*. In Table III the ratios between the ED_{50} values of the compounds and that of metronidazole (2-methyl-5-nitro-1*H*-imidazole-1-ethanol) are reported. It appears that against *Trichomonas* there is no clear correlation between the in vitro and the in vivo activity, both with these compounds and others we have tested over the years. The introduction on the vinyl moiety of **2** of an acetyl group led to **8**, which is three times more active and also less toxic. The nitrone **9**, which also showed antibacterial activity in vivo, is slightly more active than **2**. When the vinyl group is in position 1 of the imidazole nucleus (compound **24**), the antibacterial activity shown by **2** disappears, and the in vivo activity against *T. vaginalis* is enhanced to an ED_{50} value of 14 mg/kg. However, the therapeutic index is rather disappointing due to a great increase in toxicity. The most active compound is **22**, which has an ED_{50} of 8.12 mg/kg (metronidazole, 12.3 mg/kg).

Experimental Section

IR spectra were determined with a Perkin-Elmer Model 137 spectrophotometer as Nujol mulls. ^1H NMR spectra were recorded at 60 MHz on Varian A-60 spectrometer in Me_2SO-d_6 solution (δ relative to Me_4Si, 0.00 ppm). UV spectra were recorded with a Unicam S.P. 800 spectrophotometer. TLC were run on silica gel HF-UV_{254} plates to a distance of 10.0 cm (developed with a 1:9 mixture of MeOH and $CHCl_3$ except when otherwise indicated). The spots were detected by visual examination under UV light. Evaporation of solvents was done under reduced pressure using a rotary evaporator.

trans-**3-(1-Methyl-2-nitro-1*H*-imidazol-5-yl)-2-propenal (3).** With cooling (ice–salt bath), 4.5 mL of freshly distilled Ac_2O was added dropwise with stirring to 1.55 g (0.01 mol) of **1a**.[6] The temperature was allowed to rise to 5 °C and 0.2 mL of a 25% MeOH solution of KOH was added. A sudden rise of temperature to 30 °C was observed and the product dissolved completely. After rapid cooling, 3 mL of Ac_2O was added and the solution was boiled for 20 min and then cooled to 10 °C. After addition of 9 mL of H_2O and 1.05 mL of concentrated HCl, the mixture was refluxed for 30 min, cooled, and then evaporated to dryness. The residue was extracted with boiling AcOEt, filtered, and concentrated to a small volume. Crystals were collected: TLC (C_6H_6–AcOEt 1:1) R_f 0.74 (relative to **1a**); IR 1675 (ν C=O), 1530 (ν_{asym} NO_2), 1360 (ν_{sym} NO_2), 965 (γ CH trans), 840 cm^{-1} (skeletal imidazole); ^1H NMR δ 4.14 (s, 3 H, CH_3), 7.09 [dd, 1 H, J = 7.5 Hz and $J_{CH=CH}$ = 16 Hz, =CH(CHO)], 8.01 (d, 1 H, =CHCN), 8.10 (s, 1 H, =CH ring), 9.94 (d, 1 H, J = 7.5 Hz, CHO).

Table II. In Vitro Activity against Selected Organisms,[f] MIC, μg/mL[a]

Compd	*S.a.* Tour[b]	*S.h.* C 203	*D.p.* UC 41	*C.p.* ISS 30543	*P.v.* X19 H ATCC 881	*E.c.* SKF 12140	*S.s.* ATCC 9290	*S.t.* Kh	*K.p.* I.S.M.	*P.a.* ATCC 10145	*C.a.* SKF 2270	*T.m.* SKF 17410	*M.t.* H37Rv ATCC 9360	*M.g.* H21 C.Z.B.	*T.v.*[c] Static	*T.v.*[c] "Cidal"
1a	50	50	20	10	50	10	20	2	10	10	50	10	10		100	>100
1b	50	>100	50	5	>100	20	100	100	>100	>100	>100	>100	>100	>100	>50	
1c	50	100	20	20	100	10	50	100	100	>100	>100	50	50	100	50	>100
1d	50	50	50	10	20	10	20	20	50	100	>100	>100	50	20	100	>100
2	50	>100	>100	0.5	100	10	20	5	10	20	100	50	20		1	1
3	20	10	5	20	20	5	20	5	10	100	>100	10	50	50	20	50
4	10	20	100	5	>100	50	20	20	20	>100	>100	>100	100	10	>100	
5[d]	>20	>20	>20	10	>20	>20	>20	>20	>20	>20	>20	>20	>20	>20	50	100
6	>100	>100	>100	>100	>100	50	100	100	>100	>100	>100	100	50	>100	10	50
7	>100	100	100	50	>100	50	>100	>100	>100	>100	>100	100	50	100	20	100
8	50	100	100	5	100	20	50	50	100	>100	>100	100	20	50	10	50
9	50	100	50	10	100	50	100	100	100	>100	>100	>100	>100	50	50	100
10[d]	10	20	>50	5	>50	>50	>50	>50	>50	>50	>50	>50	10	>50	50	100
11	100	>100	>100	10	>100	50	>100	>100	>100	>100	>100	>100	20	>100	20	50
12	20	>100	100	20	>100	100	>100	>100	>100	>100	>100	100	50	>100	20	50
14	50	20	20	100	>100	100	>100	>100	>100	>100	>100	>100	>100	100	20	100
15	50	100	100	5	>100	100	>100	>100	>100	>100	>100	>100	50	>100	20	50
16	20	>100	50	20	50	10	50	50	100	50	50	50	20	100	50	100
17	50	>100	100	10	50	5	50	50	50	50	>100	20	50	100	>100	
18	50	>100	100	20	100	50	50	50	100	20	50	50	50	50	>100	
19	5	5	5	20	5	5	5	5	5	10	20	1	10	5	10	20
20	5	10	5	5	5	1	5	2	10	50	5	5	10	5	20	>100
21	2	5	2	5	50	10	50	50	100	100	20	1	2	5	10	50
22	100	100	>100	20	>100	100	100	100	>100	>100	>100	>100	>100	>100	50	100
23	>100	>100	>100	50	>100	>100	>100	>100	>100	>100	>100	>100	100	>100	50	100
24	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	20	50
25	20	50	50	100	>100	50	>100	>100	>100	>100	>100	>100	>100	>100	10	50
Nitrofurantoin[e]	10		1		100	5	10	20	50	>100			50			

[a] Tube dilution test. Methods as in ref 9. [b] All the compounds were not inactivated by 30% bovine serum albumin when tested on *S. aureus* Tour. [c] Metronidazole: minimal trichomonastatic concentration 0.5–1 μg/mL; minimal trichomonacidal concentration 2–10 μg/mL. [d] Higher concentrations not tested due to the poor solubility of the compounds. [e] 1-[[(5-Nitro-2-furanyl)methylene]amino]-2,4-imidazolidinedione. [f] *S.a.* = *Staphylococcus aureus*; *St.h.* = *Streptococcus haemolyticus*; *D.p.* = *Diplococcus pneumoniae*; *C.p.* = *Clostridium perfringens*; *P.v.* = *Proteus vulgaris*; *E.c.* = *Escherichia coli*; *S.s.* = *Shigella sonnei*; *S.t.* = *Salmonella typhimurium*; *K.p.* = *Klebsiella pneumoniae*; *P.a.* = *Pseudomonas aeruginosa*; *C.a.* = *Candida albicans*; *T.m.* = *Trichophyton mentagrophytes*; *M.t.* = *Mycobacterium tuberculosis*; *M.g.* = *Mycoplasma gallisepticum*; *T.v.* = *Trichomonas vaginalis*.

Table III. In Vivo Activity against *Trichomonas vaginalis*[a]

Compd	Rel ED_{50}[b] (metronidazole)	LD_{50}, mg/kg os[c]
2	3	480.0
6	>2.8	>1000
8	1.1	800
9	2.6	700
21	>2.9	500
22	0.6	800
23	>7	>1000
24	0.6	75

[a] Subcutaneous infection (mice); oral treatment. Details are given in ref 7. [b] The figures express the ratio between the ED_{50} (compound) and ED_{50} (metronidazole) run in parallel. [c] Approximate (except for 2) values determined employing from 15 to 50 animals (mice).

The Schiff base (compound **5**) was prepared by adding an equivalent amount of NaOEt in EtOH to a cooled (0 °C) solution of equimolecular amounts of **3** and 1,5-dimethyl-1*H*-imidazole-2-amine hydrochloride in EtOH. After standing at room temperature for a week, the precipitate was filtered, washed with water until chlorides were absent and then with EtOH, and dried in vacuo.

4-(1-Methyl-2-nitro-1*H*-imidazol-5-yl)-3-buten-2-one (8). A suspension of 6.2 g (0.04 mol) of **1a** and of 37.3 g (0.11 mol) of acetylmethylenetriphenylphosphorane in 480 mL of THF was refluxed for 2 h. The solid dissolved. The reaction mixture was evaporated to dryness and the residue was treated with 10% HCl. The acid solution was extracted with AcOEt. The extracts were dried over Na_2SO_4 and evaporated, and the product so obtained was recrystallized: TLC R_f 1.1 (relative to **1a**); IR 1700 (ν C=O), 1520 (ν_{asym} NO_2), 1360 (ν_{sym} NO_2), 970 (γ CH trans), 840 cm^{-1} (skeletal imidazole); ^1H NMR δ 2.39 (s, 3 H, CH_3CO), 4.05 (s, 3 H, CH_3N), 6.94 (s, 1 H, =CHCO), 7.55 (d, 1 H, =CHCN), 7.85 (s, 1 H, =CH ring).

The **2,4-dinitrophenylhydrazone** melted at 260–264 °C (crystallized from TMF). Compounds **6** and **7** were synthesized from **1a** and the proper carbalkoxymethylenetriphenylphosphoranes by the method reported above.

***N*-Methyl- and *N*,α-Dimethyl-α-[(1-methyl-2-nitro-1*H*-imidazol-5-yl)vinyl]nitrone (4 and 9).** Equimolecular amounts of **3** or **8** (1.6 mmol) and of *N*-methylhydroxylamine hydrochloride in 30 mL of EtOH were refluxed for 2 h in the presence of 0.14 g (1.7 mmol) of $NaHCO_3$. After cooling, the reaction mixture was filtered and evaporated to dryness (for compound **4**) to obtain a solid which was recrystallized; compound **9** crystallized upon concentration to a small volume.

Derivatives of 4-(1-Methyl-2-nitro-1*H*-imidazol-5-yl)-3-buten-2-one (8). A 10% excess over the equimolecular amount of the proper substituted hydrazines (free bases or salts) or *N*-amino heterocyclic amines and of **8** in a suitable solvent (EtOH for **11**, **14**, **15**, MeOH for **12** and **13**) was left to stand at room temperature for 1–6 days. The progress of the reaction was monitored by TLC. For each compound complex mixtures of products were formed which led to difficulties in the separation of the desired compounds. Compounds **11**, **12**, and **15** were purified by column chromatography on silica gel (0.06–0.2 mm) in $CHCl_3$. Compounds **13** and **14**, which were obtained as salts, were repeatedly crystallized from the solvents indicated in Table I.

Compound **10** (thiosemicarbazone) was prepared by the standard procedure in MeOH–H_2O solution.

1-(2-Hydroxyethyl)-3-methyl-5-(1-methyl-2-nitro-1*H*-imidazol-5-yl)-1*H*-pyrazole (25). A solution of 0.7 g (3.6 mmol) of **8** and 0.28 mL (4 mmol) of 2-hydroxyethylhydrazine in 30 mL of MeOH was left at room temperature overnight. An additional amount (0.05 mL) of the reagent was added and the reaction mixture was allowed to stand for a week. The precipitate was collected and recrystallized: TLC R_f 0.64 (relative to **8**); IR 3320 (ν OH), 3100 (ν CH ring), 1520 (ν_{asym} NO_2), 1350 (ν_{sym} NO_2), 1065 (ν CO), 840 cm^{-1} (skeletal imidazole); ^1H NMR δ 2.32 (s, 3 H, CH_3C), 3.79 (t, 2 H, J = 5 Hz, CH_2N), 4.15 [dt, 2 H, J = 5 Hz, $CH_2(OH)$], 4.18 (s, 3 H, CH_3N), 4.86 (t, 1 H, J = 5 Hz, OH), 6.50 (s, 1 H, =CH imidazole), 7.41 (s, 1 H, =CH pyrazole).

5-(1-Hydroxy-2-nitroethyl)-1-methyl-2-nitro-1*H*-imidazole (16). A solution of 0.62 g (4 mmol) of **1a** and of 0.22 mL (4 mmol) of nitromethane in 30 mL of EtOH at room temperature was treated with 0.02 mL of *n*-propylamine. After 3 h at room temperature, the reaction mixture was analyzed by TLC. Additional amounts of CH_3NO_2 (0.22 mL) and of *n*-propylamine (0.02 mL) were added and the reaction was allowed to stand at room temperature overnight. The solvent was evaporated to dryness and the residue was filtered and washed with Et_2O: TLC R_f 0.65 (relative to **1a**); IR 3200 (ν OH), 1550 (ν C=C and ν C=N ring), 1570 and 1520 (ν_{asym} NO_2), 1370 (ν_{sym} NO_2), 1120 (ν CO), 845 cm^{-1} (skeletal imidazole); ^1H NMR δ 4.00 (s, 3 H, CH_3N), 4.75–5.7 [m, 3 H, CH_2 and CH(OH)], 6.49 (d, 1 H, J = 7 Hz, OH), 7.26 (s, 1 H, =CH ring).

Compound **18** was obtained by the same procedure.

1-Methyl-2-nitro-5-(2-nitroethenyl)-1*H*-imidazole (19). A mixture of 0.2 g (0.9 mmol) of **16**, 0.33 g of anhydrous AcONa, and 1.5 mL of Ac_2O was heated at 110 °C (bath temperature) with stirring for 30 min, cooled, and poured into 40 mL of water. The pH was brought to 7.3 with 10% NaOH and the solution was extracted with AcOEt. The extracts were dried over Na_2SO_4 and evaporated. The oily residue was triturated with Et_2O until a solid was obtained: TLC R_f 1.2 (relative to **1a**); IR 1640 (ν C=C), 1540 (ν C=C and ν C=N ring), 1525 (ν_{asym} NO_2), 1340 and 1320 (ν_{sym} NO_2), 965 (γ CH trans), 840 cm^{-1} (skeletal imidazole); ^1H NMR δ 4.07 (s, 3 H, CH_3N), 8.00 (s, 1 H, =CH ring), 8.07 (d, 1 H, J = 13 Hz, =CH), 8.35 (d, 1 H, =$CHNO_2$).

Compound **21** was prepared as above.

5-(1-Hydroxy-2-nitropropyl)-1-methyl-2-nitro-1*H*-imidazole (17) and 1-Methyl-2-nitro-5-(2-nitro-1-propenyl)-1*H*-imidazole (20). Nitroethane (0.23 mL, 3 mmol) and **1a** (0.46 g, 2.9 mmol) were condensed under the same conditions described for **16**. The ethanol solutions obtained from five preparations were pooled and concentrated to a small volume. A crystalline precipitate was formed which was filtered and washed with a small amount of EtOH and then with Et_2O (compound **17**): TLC R_f 0.9 (relative to **1a**).

The mother liquor was evaporated to dryness and the residue was recrystallized from AcOEt (compound **20**): TLC R_f 1.8 (relative to **1a**).

5-Methyl-2-nitro-1-(2-*p*-toluenesulfonyloxyethyl)-1*H*-imidazole (23). To a solution of 6.8 g (0.04 mol) of 5-methyl-2-nitro-1*H*-imidazole-1-ethanol[7] in 30 mL of dry pyridine, 8.4 g (0.044 mol) of TsCl was added at 5–10 °C. The reaction mixture was stirred for 3 h at room temperature and left to stand overnight. After filtering, Et_2O was added to the solution. A precipitate was formed which was collected and recrystallized: TLC (C_6H_6–acetone 4:1) R_f 2.6 (relative to the starting compound); IR 3000 (ν CH phenyl), 1550 (ν C=C and ν C=N imidazole), 1600 (ν C=C phenyl), 1525 (ν_{asym} NO_2), 1355 (ν_{sym} NO_2), 1350 (ν_{asym} SO_2), 1180 (ν_{sym} SO_2), 840 (skeletal imidazole), 820 cm^{-1} (γ CH phenyl).

Compound **22** was prepared from methanesulfonyl chloride by the same procedure.

5-Methyl-2-nitro-1-ethenyl-1*H*-imidazole (24). On heating a suspension of 2.04 g (6.2 mmol) of **23** in 40 mL of EtOH at 60 °C the solid dissolved. A solution of 0.15 g (6.5 mmol) of Na in 5.4 mL of EtOH was added and the reaction mixture was refluxed for 45 min. After filtering, the solvent was evaporated and the residue (1.2 g) was dissolved in a few milliliters of $CHCl_3$ and chromatographed on 50 g of silica gel (0.06–0.2 mm) in $CHCl_3$. Fractions of 200 mL were collected, eluting with $CHCl_3$, and checked by TLC (C_6H_6–acetone 1:1): R_f 0.79 (relative to **23**); IR 1640 (ν C=C), 1530 (ν C=C and C=N imidazole), 1510 (ν_{asym} NO_2), 1340 (ν_{sym} NO_2), 970 and 940 (γ CH trans), 840 cm^{-1} (skeletal imidazole); ^1H NMR δ 2.30 (s, 3 H, CH_3), 5.51 and 5.58 (two dd, 2 H, J_{gem} = 1 Hz, =CH_2), 7.14 (s, 1 H, =CH ring), 7.15 [dd, 1 H, J_{cis} = 8.5 Hz, J_{trans} = 16 Hz, NCH=(CH_2)].

Alternatively, compound **24** was obtained in a 60% yield by treating 5-methyl-1-(2-methylsulfonyloxyethyl)-2-nitro-1*H*-imidazole (**22**) as described above.

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Synthesis and Anti-Herpes Simplex Activity of Analogues of Phosphonoacetic Acid

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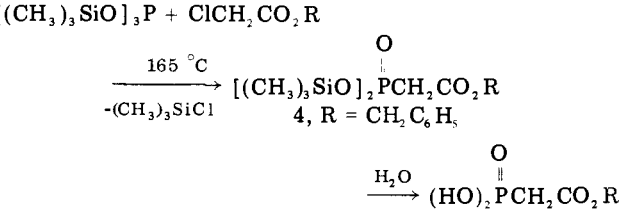
The synthesis of monoesters (P and C) of phosphonoacetic acid (PA) is given. The carboxyl esters were prepared by two methods: the reaction of chloroacetates with tris(trimethylsilyl) phosphite, followed by hydrolysis; and by the acid-catalyzed esterification of PA with the appropriate alcohol. P-Monoesters of PA were prepared either by the reaction of alkyl[bis(trimethylsilyl)] phosphite with benzyl chloroacetate followed by deprotection or by the reaction of dimethylphenyl phosphite with benzyl bromoacetate followed by hydrogenolysis. Three aryl- (alkyl-) phosphinic acid derivatives are reported. The above compounds were evaluated for anti-herpes activity against HSV-induced DNA polymerase and in animals infected with herpes dermatitis.

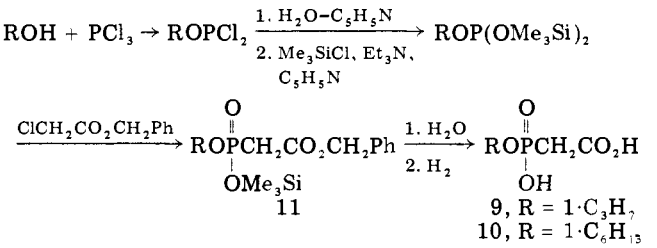
Since the original report of the suppression of herpes simplex virus (HSV) in rabbits by phosphonoacetic acid (1),[1] Gerstein et al.[2] have reported 1 to be equivalent to idoxuridine against an established herpes infection in rabbits. Phosphonoacetic acid has been shown to specifically inhibit HSV-induced DNA polymerase.[3] These promising early results with 1 encouraged a synthetic program to find an analogue of 1 with an improved therapeutic ratio. Prior to the start of the synthetic program, J. Mao (unpublished results) had found simple P-diesters of 1 [$(RO)_2P(O)CH_2CO_2H$] to be inactive against HSV-induced DNA polymerase. Therefore, the major effort was directed toward the synthesis of monoesters of 1. We wish to report some of the results from this study.

Chemistry. Simple alkylcarboxyl esters of 1 may be prepared by direct esterification of 1 with the appropriate alcohol and HCl.[4] Compounds **2** and **3** were prepared by this method. A more versatile method of preparation of carboxyl esters of 1 was suggested by a paper by Hata and Sekine.[5] These workers reported the reaction of tris(trimethylsilyl) phosphite [$(Me_3SiO)_3P$] and 5′-bis(trimethylsilyl) phosphite esters of nucleosides with diphenyl disulfide to give *S*-phenylphosphorothioates. A successful Arbuzov reaction with $(Me_3SiO)_3P$ and the appropriate chloroacetate would provide ready access to carboxyl esters of 1. When a solution of $(Me_3SiO)_3P$ and benzyl chloroacetate was heated to 165 °C, a vigorous reaction occurred as evidenced by the formation of chlorotrimethylsilane. Distillation of the pot residue yielded benzyl *P,P*-bis(trimethylsilyl)phosphonoacetate (**4**) in 83% yield (Scheme I). Treatment of the silyl ester **4** with H_2O yielded benzyl phosphonoacetate. The chloroacetates of two other alcohols were converted to the corresponding carboxyl esters of 1 (**6** and **7**) in a similar manner and these esters are listed in Table I. As this part of the work was being completed, Rosenthal et al.[6] and Hata et al.[7] reported the utility of $(Me_3SiO)_3P$ in Arbuzov reactions to yield readily hydrolyzable bis(trimethylsilyl)phosphonate esters.

Scheme I



Scheme II



Monoesters of phosphonic acids have been prepared by coupling phosphonic acids and alcohol with dicyclohexylcarbodiimide in refluxing THF.[8] Application of this method to the preparation of P-monoesters of 1 using benzyl phosphonoacetate and 1-propanol gave a mixture of benzyl *P*-propylphosphonoacetate and unreacted benzyl phosphonoacetate (10–20%). Debenzylation of the ester mixture gave a mixture of *P*-propylphosphonoacetic acid and 1 which was difficult to purify by crystallization. The coupling of benzyl phosphonoacetate and 1-hexanol gave a mixture of di- and monohexyl esters of *C*-benzyl phosphonoacetate. A cleaner method of preparation of *P*-propyl- and *P*-hexylphosphonoacetic acid (**9** and **10**, respectively) is outlined in Scheme II. Propyl phosphorodichloridite[4b] was hydrolyzed with 2 equiv of H_2O to give propyl phosphite, which was converted to propylbis(trimethylsilyl) phosphite with chlorotri-