elemental compositions and were confirmed by nmr spectra.[3]

In the nmr spectra of the 4-(4-pyridyl)pyrimidine bases **3a–d**, the pyridyl protons appear as two doublets at τ 1.98–2.05 and 1.22–1.40. Upon quaternization of **3a–c**, these signals shift to new values of τ 1.23–1.43 and 0.84–1.04. These changes, a downfield displacement of both doublets, as well as a smaller separation between chemical shifts, were found to be diagnostic of pyridine quaternization in our earlier study of pyrazolylpyridinium salts.[1] The newly introduced quaternary methyl groups of **2a–c** appear at τ 5.29–5.50. The salt **3e** fails to display this methyl signal, and instead exhibits a singlet at τ 7.48, consistent with the SCH_3 formulation.[4]

The compounds **2a–c** were tested[5] for hypoglycemic activity in normal mice or chicks. Test compounds were administered orally as saline solutions or carboxymethylcellulose suspensions; controls received an equal volume of vehicle. Blood glucose levels, determined by the method of Hoffman[6] as adapted for the Technicon Auto-Analyzer 2–5 hr after dosing, were not significantly different from controls.

Experimental Section[7]

4-Methyl-6-(4-pyridyl)pyrimidine (3a).—A solution of 23 g (0.14 mole) of acetoacetylpyridine[2] and 100 ml of formamide was heated under reflux for 3 hr, diluted with 500 ml of H_2O, and extrated ($CHCl_3$). The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated to a brown oil, which was chromatographed on 300 g of silica gel. Eluted with $CHCl_3$–MeOH (99:1) was a pale yellow solid. Recrystallization (cyclohexane) gave 1.7 g (7%) of crystals, mp 82–83°, which was sublimed at 150° (0.01 mm) to provide pale yellow crystals, mp 82–83°. *Anal.* ($C_{10}H_9N_3$), C, H, N.

2-Hydroxy-4-methyl-6-(4-pyridyl)pyrimidine (3b).—A mixture of 4.9 g (0.03 mole) of 4-acetoacetylpyridine,[2] 3.0 g (0.05 mole) of urea, 10 ml of HCl, and 50 ml of EtOH was heated under reflux for 16 hr. The solution was concentrated to a small volume under reduced pressure, and the residue was neutralized with NH_4OH. The solid which separated was recrystallized (MeOH) to provide 1.5 g (27%) of colorless crystals, mp 284–286° dec. *Anal.* ($C_{10}H_9N_3O$) C, N; H: calcd, 4.81; found, 5.58.

2-Amino-4-methyl-6-(4-pyridyl)pyrimidine (3c) was prepared by the method of Budesinsky and Musil;[8] tan solid, mp 182–184° (lit.[8] mp 181–182°).

2-Mercapto-4-methyl-6-(4-pyridyl)pyrimidine (3d) was prepared by the method of Longo and Mugnaioni;[9] tan crystals (from DMF), mp 293–295° dec. *Anal.* ($C_{10}H_9N_3S$) C, H, N.

1-Methyl-4-(4-methyl-6-pyrimidinyl)pyridinium Chloride (2a).—A mixture of 1.7 g (0.01 mole) of **3a** and 5 ml of MeCl was heated at 130° in a bomb for 18 hr. The excess MeCl was allowed to evaporate, and the black residue was dissolved in MeOH and treated with charcoal. Addition of ether to the solution gave 2.0 g (90%) of tan solid, mp 252° dec. Recrystallization (*i*-PrOH) provided colorless needles, mp 265° dec. *Anal.* ($C_{11}H_{12}ClN_3$) HCl, N; C: calcd, 59.6; found, 59.0.

1-Methyl-4-(2-hydroxy-4-methyl-6-pyrimidinyl)pyridinium chloride (2b) was prepared in 28% yield from **3b** and MeCl by the method described for the synthesis of **2a**. Recrystallization (MeOH) provided tan crystals, mp 247–248° dec. *Anal.* ($C_{11}H_{12}ClN_3O \cdot 0.5H_2O$) C, H, Cl, N.

1-Methyl-4-(2-amino-4-methyl-6-pyrimidinyl)pyridinium Iodide (2c).—A solution of 1.86 g (0.01 mole) of **3c**, 7.1 g (0.05 mole) of MeI, and 25 ml of MeOH was heated under reflux for 3 hr and cooled. An orange solid, 3 g (91%), mp 279–280° dec, separated and was recrystallized (EtOH) to provide orange crystals, mp 276–277° dec. *Anal.* ($C_{11}H_{13}IN_4$) C, H, I, N.

4-Methyl-2-methylthio-6-(4-pyridyl)pyrimidine hydrochloride (3e) was prepared in 88% yield from **3d** and MeCl by the method described for the synthesis of **2a**. Recrystallization (EtOH) provided colorless crystals, mp 261–262° dec. *Anal.* ($C_{11}H_{12}ClN_3S \cdot 0.5H_2O$) C, H, Cl, N, S.

(3) Extensive studies [A. R. Katritzky and J. M. Lagowski, *Advan. Heterocyclic Chem.*, **1**, 339 (1963)] have shown that 2-hydroxy-, 2-amino-, and 2-mercaptopyrimidines exist preferentially as the keto, amino, and thione tautomers. The spectral data on compounds **2b,c** and **3b–d** do not permit unequivocal assignment of tautomeric structures.

(4) Thioanisole exhibits τ 7.53 (S, SCH_3) (N. S. Bhacca, *et al.*, "Nmr Spectra Catalog," Varian Associates, Palo Alto, Calif., 1963, Spectrum No. 490).

(5) Testing data were supplied by Drs. D. A. Blickens, S. J. Riggi, and E. C. Tocus of the Metabolic Chemotherapy Department of these laboratories.

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(7) Melting points were determined in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Nmr spectra were obtained on a Varian A-60 spectrometer with TMS or 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as an internal standard by Mr. W. Fulmor and staff and were as expected.

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1-Imidazolyl Derivatives of 2-Hydroxy-3-phenoxypropane

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The high antitrichomonal activity of derivatives of 1-substituted 2-methyl-5-nitroimidazole[2,3] on the one hand, and the local anesthetic[4] and β-adrenergic receptor blocking action[5,6] of derivatives of 1-amino-2-hydroxy-3-phenoxypropane on the other hand, suggested the preparation of the title compounds. The low toxicity of 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole[2] and the high antitrichomonal activity of the compounds containing an ether linkage[7] in position 1 of the imidazole moiety suggested[7] that the compounds of group I might have both of the desired properties. In view of the observed[8] and clinically confirmed[9] effectiveness of 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole in the treatment of alcoholism, compounds of group I are of further interest.

In addition to the screening data for analgetic and *in vitro* antitrichomonal activity listed in Table I, preliminary evaluation of the compounds of types II and III has revealed that they have some spasmolytic and muscle relaxant activity; some synergistic effects in these compounds were noted.

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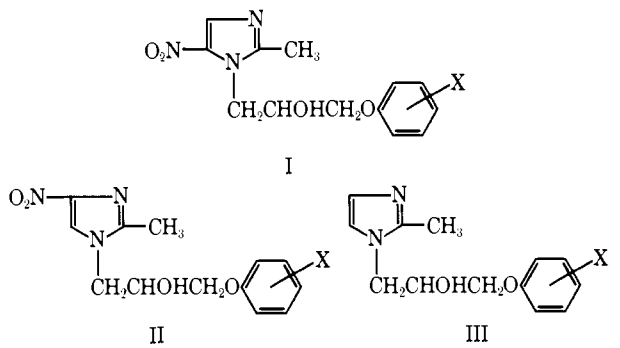
TABLE I

No.	Group	X	Mp, °C	Yield,[a] %	Recrystn solvent[b]	Formula[c]	Analgetic act.[f]	Antitrichomonal *in vitro* act.: g/ml × 10^{-3} [g]
1	I	H	132–133	44.5	A	$C_{13}H_{15}N_3O_4$		1:250
2		*o*-CH_3	141–142	36.2	B	$C_{14}H_{17}N_3O_4$		1:300
3		*m*-CH_3	105–106	38.0	A	$C_{14}H_{17}N_3O_4$		
4		*p*-CH_3	104–105	31.0	A	$C_{11}H_{17}N_3O_4$		
5		*o*-Cl	137–138	29.0	B	$C_{13}H_{14}ClN_3O_4$		1:300
6		*p*-Cl	157–158	23.0	B	$C_{13}H_{14}ClN_3O_4$		
7		*o*-OCH_3	114–115	41.0	A	$C_{14}H_{17}N_3O_5$		1:80
8		*p*-OCH_3	107.5–108.5	43.0	A	$C_{14}H_{17}N_3O_5$		
9	II	H	161–162	56.8	A	$C_{13}H_{15}N_3O_4$	+	
10		*o*-CH_3	167–168.5	58.0	A	$C_{14}H_{17}N_3O_4$[d]	+	
11		*m*-CH_3	159–160	46.0	A	$C_{14}H_{17}N_3O_4$[e]		
12		*p*-CH_3	158–159	44.2	A	$C_{14}H_{17}N_3O_4$		
13		*o*-Cl	205–206	40.7	C	$C_{13}H_{14}ClN_3O_4$	±	
14		*p*-Cl	173–174	38.0	C	$C_{13}H_{14}ClN_3O_4$		
15		*o*-OCH_3	155–156	47.0	A	$C_{14}H_{17}N_3O_5$	+	
16		*p*-OCH_3	129–131	51.0	A	$C_{14}H_{17}N_3O_5$		
17	III	H	99–100	78.0	A	$C_{14}H_{18}N_2O_2$	+	
18		*p*-CH_3	113–114	68.0	D	$C_{14}H_{18}N_2O_2$		
19		*p*-Cl	138–140	66.5	D	$C_{13}H_{15}ClN_2O_2$		
20		*o*-OCH_3	108–109	82.0	D	$C_{14}H_{18}N_2O_3$		

[a] Yields are given for the recrystallized products. [b] A = EtOH–H_2O (1:1), B = EtOH, C = *n*-BuOH, D = cyclohexane–EtOH (2:1). [c] Analytical results obtained for C, H, and N were within ±0.4% of the theoretical values unless listed otherwise. [d] *Anal.* C, N; H: calcd, 5.89; found, 5.44. [e] *Anal.* H, N; C: calcd, 57.72; found, 57.29. [f] Measured by the hot plate method of P. A. J. Janssen and A. Jageneau, *J. Pharm. Pharmacol.*, **9**, 381 (1957), at doses of 30 mg/kg. Data in reference to codeine phosphate as a standard; + means effect prolonging response time of animal 50% above that of standard; ±, 10% above that of standard. [g] Compared with metronidazole, 1:100 g/ml × 10^{-3}; *cf.* F. Kajfež, V. Šunjić, D. Kolbah, T. Fajdiga, and M. Oklobdžija, *J. Med. Chem.*, 11, 167 (1968).



I

II III

All compounds were prepared by the interaction of the appropriate imidazole with different derivatives, substituted in the ring, of 1,2-epoxy-3-phenoxypropane. In order to obtain derivatives of 5-nitroimidazole (I), formic acid was used in accord with earlier investigations.[10]

Experimental Section[11]

Group I.—2-Methyl-4(5)-nitroimidazole (3.15 g, 0.025 mole) and 0.03 mole of the particular 1,2-epoxy-3-substituted phenoxypropane in 4.9 g (4.0 ml) of formic acid were heated at 90–95° with stirring for 24 hr; 30 ml of 10% HCl was added and heated until all dissolved. On cooling, an oily layer was formed which was separated and extracted with 15 ml of 10% HCl. The acid fractions were combined, extracted ($CHCl_3$), and made basic. Crude products were collected on the filter, washed (H_2O), and recrystallized from solvents listed in Table I. Acidification of the basic filtrate yielded 1.5–1.8 g of unreacted 2-methyl-4(5)-nitroimidazole. Alcohols of the type $CH_2OHCHOHCH_2OC_6H_4X$ have been obtained from the oily residue after extraction with dilute HCl in yields of 20–30% based on the epoxide used.

Group II.—2-Methyl-4(5)-nitroimidazole (3.15 g, 0.025 mole), 0.03 mole of the particular 1,2-epoxy-3-substituted phenoxypropane, and 0.5 ml (0.49 g) of pyridine in 20.0 ml (24 g) of $C_6H_5NO_2$ were stirred and heated to 140°. When a slight evolution of brown gas was observed heating was discontinued for 1 hr. After additional heating at 140–150° for 12 hr $C_6H_5NO_2$ was removed at 0.2 mm. The residue was washed (MeOH), filtered off, and recrystallized.

Group III.—2-Methylimidazole (4.1 g, 0.05 mole) and 0.05 mole of the particular 1,2-epoxy-3-substituted phenoxypropane were refluxed in 8 ml (6.5 g) of *n*-BuOH for 1 hr. The reaction mixture was cooled, 5 ml of cyclohexane was added, and then the mixture was chilled on ice for 48 hr. Crude product was collected on a filter, washed with cyclohexane, and recrystallized.

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Topical Mosquito Repellents. II.[1] Repellent Potency and Duration in Ring-Substituted N,N-Dialkyl- and -Aminoalkylbenzamides[2]

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