(9) M. Monahan, W. Vale, J. Rivier, G. Grant, and R. Guillemin, *Proc. Meet. Endocrine Soc., 55th*, 194 (1973).
(10) R. Guillemin, M. Amoss, R. Blackwell, R. Burgus, G. Grant, N. Ling, M. Monahan, J. Rivier, and W. Vale, *J. Reprod. Fert., Suppl.*, 18, 23 (1973).
(11) D. H. Coy, E. J. Coy, Y. Hirotsu, and A. V. Schally, *J. Med. Chem.*, 17, 140 (1974).
(12) R. B. Merrifield, *J. Amer. Chem. Soc.*, 85, 2149 (1963).
(13) P. G. Pietta and G. R. Marshall, *Chem. Commun.*, 650 (1970).
(14) M. W. Monahan and J. Rivier, *Biochem. Biophys. Res. Commun.*, 48, 1100 (1972).
(15) W. Vale, G. Grant, M. Amoss, R. Blackwell, and R. Guillemin, *Endocrinology*, 91, 562 (1972).
(16) N. H. Grant, D. E. Clark, and E. I. Rosanoff, *Biochem. Biophys. Res. Commun.*, 51, 100 (1973).
(17) D. H. Coy, J. A. Vilchez-Martinez, E. J. Coy, Y. Hirotsu, N. Nishi, and A. V. Schally, *Proc. Meet. Endocrine Soc., 56th*, 48 (1974).

Synthesis and Antiprotozoal Activity of 1-(3-Chloro-2-hydroxypropyl)-Substituted Nitroimidazoles

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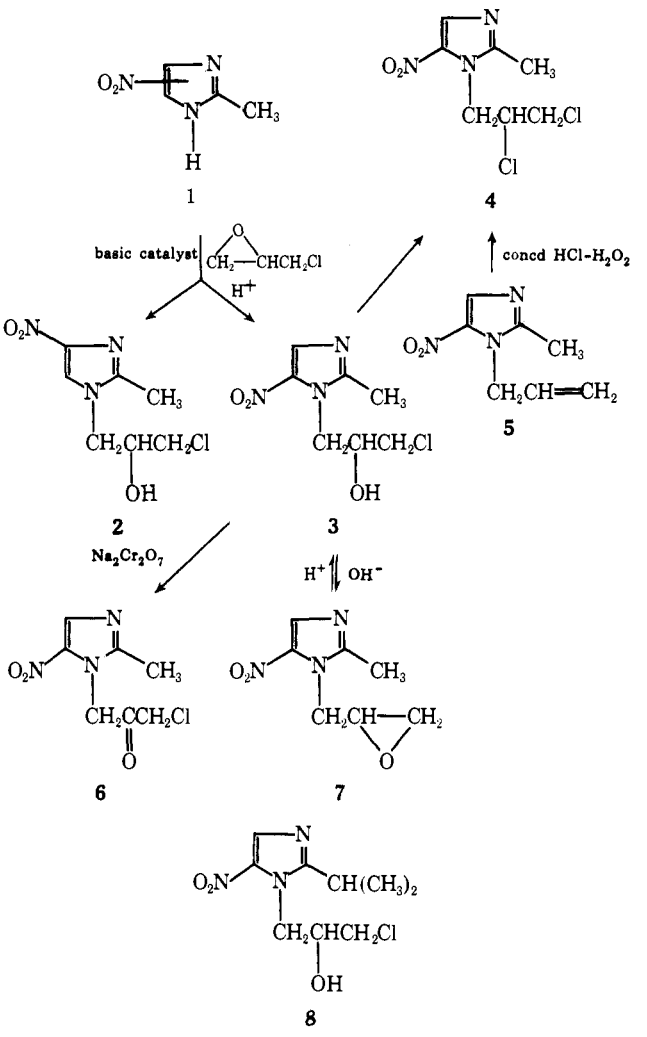
Nitroimidazoles are chemotherapeutically important as antiprotozoal and antibacterial agents.[1] For example, metronidazole† [1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole] is both an amebicide[2] and trichomonacide[3] while azomycin (2-nitroimidazole) exhibits antibiotic properties.[4] Other compounds of this type are effective against a variety of protozoan infections.[1,5] A partial list includes dimetridazole (1,2-dimethyl-5-nitroimidazole) which is used against trichomonas in cows and *H. meleagridis* infections in fowl, ronidazole (1-methyl-2-carbamylmethyl-5-nitroimidazole) and ipronidazole (1-methyl-2-isopropyl-5-nitroimidazole) which are potent histomonastats, some 2-styryl-5-nitroimidazoleswhich are effective against trichomonas, and flunidazole [1-(2-hydroxyethyl)-2-(*p*-fluorophenyl)-5-nitroimidazole], a trichomonacide which is also an active local and oral amebicide in test animals. In view of this wide continued interest in this class of compounds,[5] we now wish to report the synthesis and antiprotozoal activity of a number of 1-(3-chloro-2-hydroxypropyl)-substituted nitroimidazoles and related compounds.

Chemistry. Treatment of 2-methyl-4- (or 5-) nitroimizole (**1**) with epichlorohydrin in the presence of a base furnished 1-(3-chloro-2-hydroxypropyl)-2-methyl-4-nitroimidazole (**2**) while the reactants under acidic conditions formed the 5-nitro-substituted isomer **3**. The structure of **3**, readily assigned by uv spectroscopy and pK measurements,[6] was confirmed by conversion with $POCl_3$ and PCl_5 into the dichloro derivative **4** which was also obtained by chlorination of the known[7] 1-allyl-2-methyl-5-nitroimidazole (**5**). The 5-nitro isomer **3** was also transformed by oxidation into the chloro ketone **6** and by aqueous alkali into the epoxide **7** which regenerated **3** upon treatment with HCl. Using a procedure similar to that for **3**, the 2-isopropyl homolog **8** was also prepared (Scheme I).

Alternatively, treatment of 2-methyl-4- (or 5-) iodo-5- (or 4-) nitroimidazole[6] with epichlorohydrin in refluxing ethanol afforded a separable mixture of the iodinated isomers **9** and **10** while azomycin[8] was converted under these conditions to the chlorohydroxy derivative **11**.

†Flagyl.

Scheme I



Biological Results. Compounds **2–4** and **7–11** were tested *in vivo* and compared with metronidazole for their activity against the *Trichomonas vaginalis* and *T. foetus* infections in mice and the intracecal *Endamoeba histolytica* infection in rats according to previously cited test methodologies.[9] The desired concentrations of the compound were administered in 1.0-ml volumes in water or 1% methylcellulose as follows: *T. vaginalis*, sc by infiltration at the site of infection 2 and 24 hr after infection or po 1, 24, 48, and 72 hr after infection; *T. foetus*, po 1, 24, and 72 hr after infection; *E. histolytica*, po once daily for 3 days. The results of treatment were evaluated as follows: *T. vaginalis*, the presence or absence of subcutaneous lesions 24 hr after the last treatment; *T. foetus*, survival of the mice for 14 days after infection; *E. histolytica*, the presence or absence of organisms in the cecum 6 days after infection. The CD_{50} and LD_{50} values were calculated by the method of Reed and Muench.[10]

From the results shown in Table I, it can be seen that the compounds exhibited varying degrees of activity against

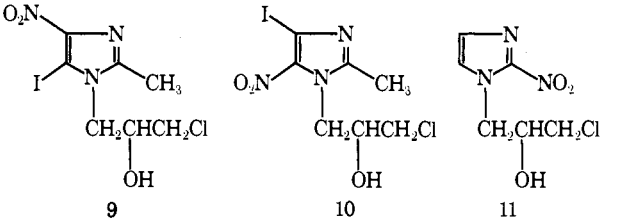


Table I. Antiprotozoal Activity of 1-(3-Chloro-2-hydroxypropyl)nitroimidazoles and Derivatives

Compd no.	*T. vaginalis* μg/ml sc	*T. vaginalis* mg/kg po	*T. foetus*, mg/kg po	*E. histolytica*, mg/kg po	LD_{50} (mouse) mg/kg ip	LD_{50} (mouse) mg/kg po
2	>1000	>250	85	>300	>500	>500
3	86	37	3	10	>2000	>2000
4	211	75	13	433	707	>2000
7	21	76	46	29	1000	1414
8	37	21	9	137	354	595
9	>1000	>250	>250	>300	354	901
10	>1000	>250	>250	>300	420	707
11	0.4	17	6	25	158	330
Metronidazole	100	16	17	49	>2000	>2000

the various protozoal infections. Compound **3**, previously reported,[11] showed the same spectrum of activity as metronidazole and was as well tolerated. Compounds **4**, **7**, **8**, and **11**, while showing the same spectrum of activity as compound **3** and metronidazole, were overall more toxic. Compounds **2**, **9**, and **10** were without antiprotozoal activity except that **2** exerted an effect against *T. foetus*.

Experimental Section‡

1-(3-Chloro-2-hydroxypropyl)-2-methyl-4-nitroimidazole (2). A mixture of 15 g (0.12 mol) of 2-methyl-4- (or 5-) nitroimidazole (**1**) and 0.5 g of anhydrous K_2CO_3 in 100 ml of epichlorohydrin was stirred and refluxed for 10–15 min and cooled. The crystals were collected and recrystallized from EtOH to give 12.5–15 g (50–60%) of **2**: mp 151°; uv λ_{max} 300 nm (ε 7120); $pK_a = 0.3 \pm 0.1$. *Anal.* ($C_7H_{10}ClN_3O_3$) C, H, Cl, N.

1-(3-Chloro-2-hydroxypropyl)-2-methyl-5-nitroimidazole (3). To a solution of 127 g (1.0 mol) of **1** in 1.17 l. of 85% HCO_2H at 5–10° was added 460 ml of epichlorohydrin over 5 hr. The mixture was stored at 5–10° for 48 hr and 20–25° for 24 hr, and the volatiles were evaporated under reduced pressure. To the residual oil 200 g of ice–water was added and the solution adjusted to pH 7–7.5 with concentrated NH_4OH. After addition of 100 g of $(NH_4)_2SO_4$, the mixture was repeatedly extracted with C_6H_6. The crystals that formed in the aqueous layer were filtered to give 25 g of **1**. The benzene layers were extracted with 10 *N* H_2SO_4 and saturated with $(NH_4)_2SO_4$ and the resulting aqueous layer was then neutralized with NH_4OH to give an oil which slowly crystallized upon seeding. Recrystallization from toluene gave 92 g (42%) of **3**: mp 78°; uv λ_{max} 228 nm (ε 3720), 312 (9150); $pK_a = 2.4 \pm 0.1$. *Anal.* ($C_7H_{10}ClN_3O_3$) C, H, Cl, N.

1-(2,3-Dichloropropyl)-2-methyl-5-nitroimidazole (4). Addition of 5 g (0.022 mol) of **3** to 2 g (0.013 mol) of $POCl_3$ and 6 g (0.024 mol) of PCl_5 generated heat and HCl and the mixture liquified. The reaction was cooled; ice–water was slowly added and neutralized with aqueous NaOH. The resulting precipitate was filtered, dried, and crystallized from EtOH to give 4.1 g (75%) of **4**: mp 123–124°. *Anal.* ($C_7H_9Cl_2N_3O_2$) C, H, Cl, N.

Alternatively, to a solution of 20 g (0.12 mol) of 1-allyl-2-methyl-5-nitroimidazole[7] (**5**) in concentrated HCl at 50–70° was slowly added 30% H_2O_2. The reaction mixture was diluted with H_2O, charcoaled, and neutralized to give 15 g of **4**, identical in mixture melting point with **4** obtained from **3**.

1-(3-Chloroacetonyl)-2-methyl-5-nitroimidazole (6). To a stirred solution of 12 g (0.055 mol) of **3** in 60 ml of 10 *N* H_2SO_4 was added dropwise a warm solution of 15 g (0.057 mol) of $Na_2Cr_2O_7$ in 50 ml of H_2O. The reaction mixture was extracted with EtOAc, the extracts were evaporated, and the residue was crystallized from EtOH to give 5 g (42%) of **6**: mp 111°; uv λ_{max} 228 nm (ε 3350), 311 (9000); $pK_a = 1.9 \pm 0.1$. *Anal.* ($C_7H_8ClN_3O_3$) C, H, Cl.

1-(2,3-Epoxypropyl)-2-methyl-5-nitroimidazole (7). A solution of 5 g (0.22 mol) of **3** in 3 *N* NaOH was heated at 60–70° for 10–15 min and cooled, and the crystals were collected and recrystallized from EtOAc to give 3.4–3.6 g (80–85%) of **7**: mp 111°. *Anal.* ($C_7H_9N_3O_3$) C, H, N.

1-(3-Chloro-2-hydroxypropyl)-2-isopropyl-5-nitroimidazole (8). In a manner similar to the procedure given for **3**, 15.5 g (0.1 mol) of 2-isopropyl-4- (or **5**-) nitroimidazole[12] and 50 g of epichlorohydrin in 140 ml of 85% HCO_2H afforded 12.4 g (50%) of **8**: mp 103° (from H_2O); uv λ_{max} 230 nm (ε 3400), 314 (9180); $pK_a = 2.1 \pm 0.1$. *Anal.* ($C_9H_{14}ClN_3O_3$) C, H, Cl, N.

1-(3-Chloro-2-hydroxypropyl)-5-iodo-2-methyl-4-nitroimidazole (9) and 1-(3-Chloro-2-hydroxypropyl)-4-iodo-2-methyl-5-nitroimidazole (10). A mixture of 4- (or 5-) iodo-2-methyl-5- (or 4-) nitroimidazole[6] (101 g, 0.4 mol) and 80 ml of epichlorohydrin in 100 ml of EtOH was refluxed for 12 hr, cooled, and diluted with 1.5 l. of H_2O. The semicrystalline precipitate was collected, slurried with a mixture of EtOAc and Et_2O, filtered, and dried to give 44 g (32%) of **9**: mp 142°; uv λ_{max} (H_2O) 307 nm (ε 7400); $pK_a = 0.7 \pm 0.1$. *Anal.* ($C_7H_9ClIN_3O_3$) C, H, N.

The above aqueous mother liquor was extracted with EtOAc and the combined organic layers were evaporated. The residual syrup was dissolved in 100 ml of MeOH and addition of 100 ml of concentrated HCl precipitated 12 g of **9** as the hydrochloride. The filtrate was neutralized with NH_4OH, and the crystals were filtered and recrystallized from EtOH to give 22 g (16%) of **10**: mp 136–137°; uv λ_{max} (H_2O) 272 nm (ε 4320), 340 (7800); $pK_a = 0.8 \pm 0.1$. *Anal.* ($C_7H_9ClIN_3O_3$) C, H, N.

1-(3-Chloro-2-hydroxypropyl)-2-nitroimidazole (11). By the procedure given for the preparation of **10** and **11**, 11.3 g (0.1 mol) of azomycin[8] and epichlorohydrin in ethanol gave 13.3 g (65%) of **11**: mp 158° (EtOH).§ *Anal.* ($C_6H_8ClN_3O_3$) C, H, Cl, N.

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References

(1) M. Hoffer and A. I. Rachlin, *Annu. Rep. Med. Chem.*, **7**, 147 (1972).
(2) S. J. Powell, J. MacLeod, A. J. Wilmot, and R. Elsdon-Dew, *Lancet*, 1329 (1966).
(3) C. Cosar, J. Julou, and M. Bénazet, *Ann. Inst. Pasteur, Paris*, **96**, 238 (1959).
(4) K. Maeda, T. Osato, and H. Umezawa, *J. Antibiot., Ser. A*, **6**, 182 (1953).
(5) M. Hoffer and C. W. Perry, *Annu. Rep. Med. Chem.*, **8**, 141 (1973).
(6) M. Hoffer, V. Toome, and A. Brossi, *J. Heterocycl. Chem.*, **3**, 454 (1966).
(7) C. Cosar, C. Crisan, R. Horclois, R. M. Jacob, J. Robert, S. Tchelitcheff, and R. Vaupré, *Arzneim.-Forsch.*, **16**, 23 (1966).
(8) A. G. Beaman, W. Tautz, T. Gabriel, and R. Duschinsky, *J. Amer. Chem. Soc.*, **87**, 389 (1965).
(9) E. Grunberg, H. N. Prince, E. Titsworth, G. Beskid, and M. D. Tendler, *Chemotherapia*, **11**, 249 (1966).
(10) L. J. Reed and H. A. Muench, *Amer. J. Hyg.*, **27**, 493 (1938).
(11) E. Grunberg, R. Cleeland, H. N. Prince, and E. Titsworth, *Proc. Soc. Exp. Biol. Med.*, 133, 490 (1970).
(12) K. Butler, H. L. Howes, J. E. Lynch, and D. K. Pirie, *J. Med. Chem.*, **10**, 891 (1967).

‡All new compounds gave acceptable analytical data. The ultraviolet spectra were measured in 2-propanol unless otherwise noted.

§First prepared in these laboratories by Drs. A. G. Beaman and R. Duschinsky.

Conformationally Restricted Analogs of Histamine H_1 Receptor Antagonists. 2-Phenyl- and 2-Benzyl-1,2,3,4-tetrahydro-4-dimethylaminoisoquinoline

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Previous reports from this laboratory have described the use of conformationally restricted analogs of ethylenediamine histamine antagonists as model compounds for as-