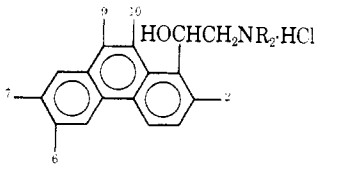
TABLE IX
PROPERTIES AND ANTIMALARIAL ACTIVITY OF PHENANTHRENE-1-AMINO ALCOHOLS



2	6	7	9	10	R[a]	Mp, °C	% yield[b]	Formula[c]	Antimalarial activity[d] 1MST[e] at indicated dosage (mg/kg) 40	80	160	320	640	Cures 320	640
Br	H	H	H	H	C_7	155–157	86	$C_{30}H_{43}BrClNO$	1.4	4.0	5.8	12.2	14.2	Active	Active
H	H	H	H	Br	C_7	126–129	66	$C_{30}H_{43}BrClNO$	0.3	3.7	4.3	7.9	9.5	Active	Active
H	Cl	H	H	H	C_7	109–112	28	$C_{30}H_{43}Cl_2NO$	0.6	2.4	4.2	5.2			
H	Cl	Cl	H	H	C_4	74–75[f]	52	$C_{24}H_{29}Cl_2NO$	3.0	6.6	10.4	15.1	14.8	1	3
H	Cl	Cl	H	H	C_7	150–155	22	$C_{30}H_{42}Cl_3NO$	0.2	0.4	4.2	4.8			
H	Cl	H	Cl	H	C_7	197–198.5	22	$C_{30}H_{42}Cl_3NO$	1.0	6.6	7.8	15.3		3	5
H	Cl	Cl	Cl	H	C_7	193–196	38	$C_{30}H_{41}Cl_4NO$	0.3	3.3	5.9	7.1	10.4	Active	1

[a] All *n*-alkyl groups. [b] From the epoxide. [c] Correct analyses for C, H, and N were obtained for all compds. [d] For details of test procedure, see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967). Test data supplied by Walter Reed Army Institute of Research. [e] Increase in mean survival time. Mean survival time for mice infected with *P. berghei*, 6.5 ± 0.5 days. [f] Isolated and submitted as the free base.

Diglyme was used as solvent, the reduction and treatment with NaOH were carried out at a slightly above room temp, and the reaction mixture was worked up by addn to ice–water. The pptd product was collected by filtration.

Phenanthrene-1-amino Alcohols (Table IX).—All of the phenanthrene amino alcohols were prepd by reaction of the corresponding epoxide with an excess of the appropriate amine.[23] In accordance with earlier recommendations,[4] the reaction was carried out at 125° for 16 hr. Under these conditions, ir, nmr, and mass spectra of the products were as expected for the structure indicated, with no evidence for the presence of the isomer resulting from attack by the secondary amine at the secondary epoxide carbon, *i.e.*, the undesired $ArCH(CH_2OH)NR_2$. The reaction products were purified by removal of excess amine by vacuum and/or steam distillation and usually were isolated as the hydrochlorides from Et_2O, followed by recrystn from C_6H_6 and/or cyclohexane.

The antimalarial activity of the halogen-substituted phenanthrene-1-amino alcohols was comparable with the activity of related compds that we described earlier.[4] Some showed moderate curative activity against *P. berghei* in mice. None of the intermediates had any antimalarial activity, and no toxic deaths resulted from treatment with either target or intermediate compds.

Acknowledgment.—We express our appreciation to Drs. E. Sweeney, R. Strube, D. P. Jacobus of WRAIR, and Professor R. Mariella of Loyola University for helpful advice.

(23) (a) W. H. Horne and R. L. Shriner, *J. Amer. Chem. Soc.*, **54**, 2925 (1932); (b) A. J. W. Headlee, A. R. Collett, and C. L. Lazzell, *ibid.*, **55**, 1066 (1933); (c) K. Rice, U. S. Army, WRAIR Symposium, Nov 27, 1967.

Chemotherapeutic Nitroheterocycles. 6.[1] Substituted 5-Aminomethyl-3-(5-nitro-2-imidazolylmethyleneamino)-2-oxazolidinones[2]

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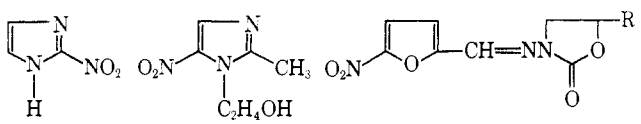
Received June 9, 1970

A series of nitroimidazole derivatives was synthesized by condensation of 1-substituted 5-nitroimidazole-2-carboxaldehydes with 3-amino-5-methyl-2-oxazolidinones substituted at the 5-methyl group by secondary amines. The compounds displayed high activity against *Trichomonas vaginalis in vitro* and most of them *in vivo*.

The antibiotic azomycin[3] (**1**) was the first nitroimidazole which was reported to be active against *Trichomonas vaginalis*. Later 5-nitroimidazoles were shown to have better therapeutic qualities and of this series metronidazole[4] (**2**) became the drug of choice against trichomoniasis. In contrast to the 5-nitromidazoles biologically active nitrofurans such as furazolidone[5] (**3**, R = H) and furaltadone[6] (**3**, R = morpholinomethyl) are in general derived from a carboxaldehyde or carboxyl group in position 2 of this heterocycle.



1 2 3

In some patents[7,8] corresponding 5-nitroimidazoles

(*) To whom inquiries should be addressed.

(1) Part V: R. Albrecht, H.-J. Kessler, and E. Schröder, *Chim. Ther.*, in press.

(2) A preliminary report of part of this work has been presented at the VIth International Congress of Chemotherapy, Tokyo, August 1969.

(3) S. Nakamura and H. Umezawa, *J. Antibiot., Ser. A*, **9**, 66 (1955).

(4) C. Cosar, *Arzneim-Forsch.*, **16**, 23 (1966).

(5) G. S. Rogers, G. B. Belloff, M. F. Paul, J. A. Yurchenko, and G. Gever, *Antibiot. Chemother.*, **6**, 231 (1956).

(6) D. F. Kefauver, I. Paberzs, and T. F. McNamara, *Antibiot. Annu.*, **1958–1959**, 81 (1959).

(7) Merck and Co., Inc., Netherlands Application 6,413,814 (1965); *Chem. Abstr.*, **63**, 18097 (1965).

(8) Merck and Co., Inc., Belgium Application 661,262 (1965); *Chem. Abstr.*, **64**, 2093 (1966).

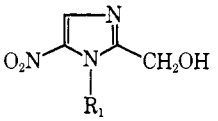
with functional group in position 2 have been described, but only limited information on the biological activity of these derivatives is available. An exception is the well-known broad antimicrobial activity of 2-amino-5-(5-nitro-1-methyl-2-imidazolyl)-1,3,4-thiadiazole.[9]

In this paper the synthesis and antitrichomonal properties of a new class of nitroimidazoles (**12**) related to compounds of the furaltadone type are presented.

Chemistry.—The synthesis of substituted 5-aminomethyl-3-(5-nitro-2-imidazolylmethyleneamino)-2-oxazolidinones (**12,** see Table II) was accomplished by condensation of 1-substituted 5-nitroimidazole-2-carboxaldehydes (**6**) with 3-amino-5-methyl-2-oxazolidinones substituted at the 5-Me group by secondary amines (**11**). The starting compounds, **6** and **11**, respectively, were obtained following known procedures as shown in the reaction scheme: reaction of 1-substituted 5-nitroimidazoles (**4**) with paraformaldehyde and subsequent oxidation of 1-substituted 5-nitroimidazole-2-methanols (**5**, Table I) led to aldehydes **6**;[7,8] compounds **11** were

TABLE I

1-SUBSTITUTED 5-NITROIMIDAZOLE-2-METHANOLS (**5**)



R_1	Method	Crystn solvent	Mp, °C	Yield, %	Formula	*Anal.*
CH_3[a]	A	C_6H_6	111	66	$C_5H_7N_3O_3$	C, H
C_2H_5	A	C_6H_6	102	73	$C_6H_9N_3O_3$	C, H
C_4H_9	A	CH_2Cl_2–petr ether	71	62	$C_8H_{13}N_3O_3$	N
$C_2H_4OCOCH_3$[b]	B	Me_2CO–petr ether	88	77	$C_8H_{11}N_3O_5$	N

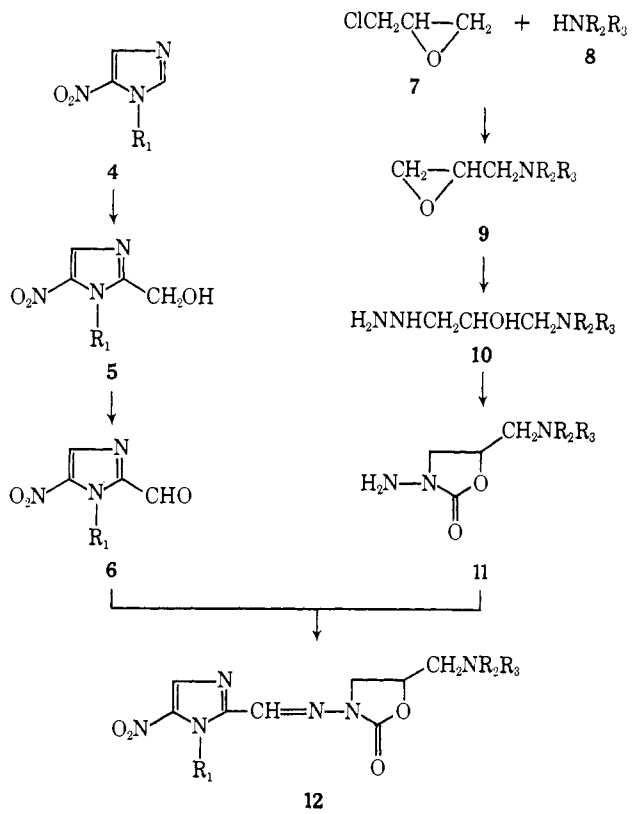
[a] See ref 7. [b] See ref 8.

prepared from epichlorohydrin (**7**) and secondary amines **8** *via* reaction to substituted 1-amino-2,3-epoxypropanes (**9**), ring opening with hydrazine to **10** and subsequent ring closure with diethyl carbonate.[10,11] 5-Diethylaminomethyl-3-[5-nitro-1-(2-hydroxyethyl)-2-imidazolylmethyleneamino]-2-oxazolidinone (**12p**, Table II) was obtained as the hydrochloride by saponification of the corresponding O-Ac derivative (**12q**, Table II).

In addition to the analytical data measurements of the ir, uv, or nmr spectra which are in accordance with the structures shown have been carried out for all compounds.

Biological Results.—No compound showed an interesting *in vitro* activity (disc assay and tube dilution assay, respectively) against bacteria and fungi, but all were active *in vitro* against *T. vaginalis* (tube dilution assay). The minimal inhibitory concentrations (MIC's) are listed in Table II; metronidazole (**2**) was taken as a reference substance.

Within the series with a N^1-Me group at the imidazole moiety and a dialkylamino side chain (**12a–f**) the optimal number of C atoms in a *N*-alkyl residue seems to be 3 (**12c–e**). When the substituted amino group NR_2R_3 is represented by the pyrrolidine, piperidine, or hexamethyleneimine ring system (**12g–j**) the MIC values



are also very low, but introduction of another heteroatom into the six-membered ring (**12k,l**) leads to decreased activity. The compound with the *N*-methylanilino side chain (**12m**) is again very active.

The length of the alkyl substituent R_1 of the imidazole does not influence the *in vitro* activity against *T. vaginalis* (but see *in vivo* results below) as is shown by substances **12b,n,o**. Introduction of the $(CH_2)_2OH$ or $(CH_2)_2OAc$ group at this site of the molecule, however, leads to compounds of lower activity (**12p,q**). This was surprising since metronidazole (**2**) has a $(CH_2)_2OH$ side chain. Nearly all compounds investigated further were active *in vivo* at 50 mg/kg sc in infected mice by the oral route. The results are shown in Table II. It seems that the alkyl group R_1 at N^1 of the imidazole moiety may not be too large for systemic activity in this class of 5-nitroimidazole derivatives.

One of the best compounds, 5-diethylaminomethyl-3-(5-nitro-1-methyl-2-imidazolylmethyleneamino)-2-oxazolidinone hydrochloride (**12b**) showed an oral ED_{50} of 5.5 mg/kg against a *T. vaginalis* sc infection in mice (metronidazole **2**, ED_{50} = 4.6 mg/kg). The toxicity was very low (acute LD_{50}, mice ip 0.97 g/kg, po 3.4 g/kg) and the substance is under further investigation.

Experimental Section[12]

1-Substituted 5-Nitroimidazole-2-methanols (5) (See Table I). Method A.—1-Substituted 5-nitroimidazole (**4**) (0.1 mole) was heated in a sealed tube for 48 hr with 15 g (0.5 mole) of paraformaldehyde and 75 ml of DMSO. After removal of solvent *in vacuo* paraformaldehyde was steam distd (*ca.* 600 ml of distillate). The distn residue was cooled, and the ppt filtered off. This material was used for further reaction.

(9) G. Berkelhammer and G. Asato, *Science*, **162**, 1146 (1968).

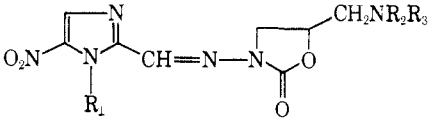
(10) The Norwich Pharmacal. Co., German Patent 1,126,877 (1962); *Chem. Abstr.*, **58**, 4578 (1963).

(11) La Failla, R. Scuri, and G. Signorelli, *Farmaco Sci.*, **19**, 269 (1964).

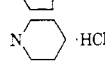
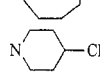
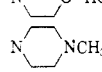
(12) Melting points are uncorrected and taken on a Tottoli melting point apparatus (Fa. W. Büchi, Switzerland). Where analytical results are indicated only by symbols of the elements values found for those elements were within ±0.4% of the calcd values.

TABLE II

SUBSTITUTED 5-AMINOMETHYL-3-(5-NITRO-2-IMIDAZOLYLMETHYLENEAMINO)-2-OXAZOLIDINONES (**12**)



12

Compd	R_1	NR_2R_3	Method	Yield, %	Crystn solvent	Mp, °C	Formula[l]	Activity against *T. vaginalis* MIC (μg/ml)	*in vivo*[a]
a	CH_3	$N(CH_3)_2$	A	38	MeOH	174[b]	$C_{11}H_{16}N_6O_4$	0.4	+
b	CH_3	$N(C_2H_5)_2 \cdot HCl$	C	68	MeOH–*i*-PrOH	238[c]	$C_{13}H_{21}ClN_6O_4$	0.4	+
c	CH_3	$N(n\text{-}C_3H_7)_2$	A	58	MeOH–*i*-PrOH	170	$C_{15}H_{24}N_6O_4$	0.05	+
d	CH_3	$N(i\text{-}C_3H_7)_2$	A	34	MeOH	206	$C_{15}H_{24}N_6O_4$	0.1	+
e	CH_3	$N(CH_2CH{=}CH_2)_2$	A	78	*i*-PrOH	162	$C_{15}H_{20}N_6O_4$	0.1	+
f	CH_3	$N(n\text{-}C_4H_9)_2$	C[d]	28	EtOH	136	$C_{17}H_{28}N_6O_4$	0.2	+
g	CH_3		C	12	*i*-PrOH	222	$C_{13}H_{19}ClN_6O_4$[e]	0.8	Nt
h	CH_3		C	69	H_2O–Me_2CO	233[f]	$C_{14}H_{21}ClN_6O_4$	0.2[f]	+
i	CH_3		C[d]	15	MeOH	165[g]	$C_{15}H_{22}N_6O_4$	0.2	Nt
j	CH_3		C	63	MeOH	230	$C_{15}H_{23}ClN_6O_4$	0.2	+
k	CH_3		C	76	MeOH	240	$C_{13}H_{19}ClN_6O_5$[k]	1.6	+
l	CH_3		B	46	MeOH	250	$C_{14}H_{22}ClN_7O_4$	6.3	−
m	CH_3		B	37	DMF	235	$C_{16}H_{18}N_6O_4$	0.4	+
n	C_2H_5	$N(C_2H_5)_2 \cdot HCl$[i]	C	46	MeOH–*i*-PrOH	176	$C_{14}H_{23}ClN_6O_4$	0.4	+
o	C_4H_9	$N(C_2H_5)_2$	D	28	MeOH–*i*-Pr_2O	83[j]	$C_{16}H_{26}N_6O_4$	0.4	−
p	C_2H_4OH	$N(C_2H_5)_2 \cdot HCl$	E	85	EtOH	175	$C_{14}H_{23}ClN_6O_5$	12.5	Nt
q	$C_2H_4OCOCH_3$	$N(C_2H_5)_2 \cdot HCl$	C	61	*i*-PrOH	203	$C_{16}H_{25}ClN_6O_6$	6.3	Nt
Metronidazole								1.6	+

[a] Mice, infected sc with approx 10^6 living parasites, one daily oral treatment with 50 mg/kg for 5 subsequent days; first treatment immediately after infection. Therapeutic activity was detd on the 10th day on the presence or absence of living parasites at the site of infection. + = active ($p \leq 0.05$); − = nonactive ($p > 0.05$); Nt = not tested. [b] Hydrochloride, mp 252°. [c] Base, mp 170°. [d] Free base was precipitated although being in acidic medium. [e] Structure was proved only by ir and mass spectrum. [f] Free base showed mp 173° and MIC 0.2/μg/ml. [g] Hydrochloride, mp 238°. [h] Substance contained 9.8% H_2O. [i] Substance contained 2.5% *i*-PrOH. [j] Hydrochloride, mp 125°. [k] C, calcd 41.70; found 40.82; H, calcd 5.10; found 5.91. [l] All compounds were analyzed or N except for compds g and k.

Method B.—As in method A but the mixture was only heated for 24 hr and the product was recrystd from C_6H_6 after removal of the solvent.

1-Substituted 5-Nitroimidazole-2-carboxaldehydes (6).—Compd **5** (0.1 mole) in 500 ml of $CHCl_3$ was stirred with 85 g of MnO_2 for 48 hr. The mixture was filtered and the solvent removed under reduced pressure, yield 85–95%. Crude material was used in the next step.

3-Amino-5-methyl-2-oxazolidinones Substituted at the 5-Me Group by Secondary Amines (11).—Compds **11** not yet described in the literature[10,11] [NR_2R_3 = $N(CH_3)_2$, $N(n\text{-}C_3H_7)_2$, $N(i\text{-}C_3H_7)_2$, hexamethyleneimino, and 4-methylpiperidino] were synthesized as follows: 0.1 mole of N-substituted 1-amino-2,3-epoxypropane (**9**)[13] was added drop by drop to $N_2H_4 \cdot H_2O$ preheated at 55°. The mixture was then heated to 100°; in some cases [NR_2R_3 = $N(n\text{-}C_3H_7)_2$, $N(i\text{-}C_3H_7)_2$] the temp was reached by exothermic reaction. After 30 min at 100° $N_2H_4 \cdot H_2O$ was thoroughly removed *in vacuo;* yields of 80–92% crude **10** were sufficient for further reaction. Only **10** [NR_2R_3 = $N(CH_3)_2$] was distd; bp 85–95° (0.05 mm); yield 72%.

(13) Compounds **9** [NR_2R_3 = $N(i\text{-}C_3H_7)_2$ and 4-methylpiperidino] were unknown and synthesized from epichlorhydrin (**7**) and the corresponding amines (**8**) according to D. L. Heiywood and B. Phillips, *J. Amer. Chem. Soc.*, **80**, 1257 (1958); *i*-Pr_2NH and epichlorhydrin showed no exothermic reaction and the mixture was heated to 50° for 8 hr.

Compd **10** (0.1 mole) was mixed with 13.2 g (0.11 mole) of diethyl carbonate and added drop by drop to a soln of 0.37 g (0.016 mole) of Na in 16 ml of MeOH. The bath was heated to 130° within 1 hr and within an additional 2 hr at this temp 23 ml of solvents (theory: 16 ml of MeOH + 9 ml of EtOH) was distd off; yields of 90–100% of crude **11** were sufficient for condensation with aldehydes (**6**). Only **11** [NR_2R_3 = 4-methylpiperidino] was recrystd twice from *i*-PrOH, yield 23% (no melting point could be taken).

Substituted 5-Aminomethyl-3-(5-nitro-2-imidazolylmethyleneamino)-2-oxazolidinones (12) (See Table II). Method A.—Compds **6** (0.01 mole) and **11** (0.01 mole) in 25 ml of 0.5 *N* HCl were stirred for 3 hr. Subsequently the soln was made alkaline with 1 *N* KOH and the ppt was filtered off.

Method B.—As in method A, but crystals pptd in acidic medium and were filtered off.

Method C.—Compds **6** (0.01 mole) and **11** (0.01 mole) in 28 ml of EtOH (for **12h**: 200 ml) were refluxed for 2 hr with 0.9 ml of satd methanolic HCl (about 12.5 *N*). The mixture was cooled, in some cases *i*-PrOH was added, and the ppt was filtered off.

Method D.—As in method B, but the pptd hydrochloride was dissolved in H_2O, the soln was made alkaline with 1 *N* KOH, and the ppt was filtered off.

Method E. Compd **12g** (0.01 mole) in 120 ml of EtOH was refluxed for 3 hr with 0.2 ml of 12.5 *N* methanolic HCl. The mixture was cooled and the ppt filtered off.