Synthetic Schistosomicides. XIV. 1,4-Naphthoquinone Mono(O-acyloximes), 4-Amino-1,2-naphthoquinones, 2-Amino-3-chloro-1,4-naphthoquinones, and Other Naphthoquinones[1]

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The over-all promise of 1,4-naphthoquinone monooxime (IX) against *Schistosoma mansoni* and the marked antiglycolytic effects of various naphthoquinones against these worms prompted a more comprehensive investigation of the antischistosome properties of 1,2- and 1,4-naphthoquinone derivatives. Various 1,4-naphthoquinone mono(O-acyloximes) (XV) were synthesized by acylation of 4-nitroso-1-naphthol, while 2-[(dialkylamino)methyl]-1,4-naphthoquinone 4-oximes (XVIIa and b) were prepared by nitrosation of the corresponding 2-[(dialkylamino)methyl]-1-naphthols. The condensation of 1,2-naphthoquinone-4-sulfonic acid sodium salt with amines afforded a series of 4-amino-1,2-naphthoquinones (XVIII), and treatment of 2,3-dichloro-1,4-naphthoquinone with amines gave the corresponding 2-amino-3-chloro-1,4-naphthaquinones (XIX). Many other 1,4-naphthoquinone derivatives were also prepared. 1,4-Naphthoquinone mono[O-(chloroacetyl)oxime] (1), 1,4-naphthoquinone mono(O-methyloxime) (XIV), and 2-(piperidinomethyl)-1,4-naphthoquinone 4-oxime (XVIIb) effected a 50–71% reduction of live *S. mansoni* in mice at daily oral doses ranging from 301 to 632 mg/kg for 14 days, but none was as active as IX. Structure–activity relationships are presented.

1,2-Naphthoquinone, 1,4-naphthoquinone, and numerous substituted naphthoquinones have been reported to be potent inhibitors of the glycolysis of adult *Schistosoma mansoni in vitro*, but none of these has appreciable chemotherapeutic activity against *S. mansoni* infections in mice.[2,3] This lack of *in vivo* activity can be explained in part by the known interaction of naphthoquinones with, and their inactivation by, serum proteins, and in part by lack of absorption.[3] A similar effect may also be responsible for the schistosomicidal activity of the N,N-diaklyl-N′-(4-nitroso-1-naphthyl)alkylenediamines (Ib)[4] and the 4-azo-1-naphthylamines (IVa and b),[1,5–13] which can exist in quinoid forms (Vb, VIIIa and b), and for various potential metabolites thereof (Chart I).[13,14]

The initial step of one likely metabolic pathway of the 4-azo-1-naphthylamines (IVa and b) involves reductive scission to the corresponding 1,4-naphthalenediamines (IIIa and b).[13] Indeed, certain N-[(dialkylamino)alkyl]-1,4-naphthalenediamines (IIIb) are more active against schistosomes and less toxic for mice than the N,N-dialkyl-N′-(4-azo-1-naphthyl)alkylenediamines from which they are derived.[13] However, the 1,4-naphthalenediamines are very susceptible to oxidation and are unstable both in acidic and basic media. Although the decomposition products of the naphthalenediamines have not been isolated and characterized, it is likely that oxidation products such as the N,N-dialkyldihydro-4-imino-1-naphthylidenealkylenediamines (IIb) are formed initially. Subsequent hydrolysis would lead to N-[(dialkylamino)alkyl]-1,4-naphthoquinone imines (VIb) or 1,4-naphthoquinone imine (VIa), and ultimately to 1,4-naphthoquinone (X). Similarly, oxidation of 1,4-naphthalenediamine (IIIa) would afford 1,4-naphthoquinone diimine (IIa), which upon hydrolysis would give 1,4-naphthoquinone imine (VIa) and 1,4-naphthoquinone (X). It is noteworthy that N,N,N′-trialkyl-N′-(4-azo-1-naphthyl)alkylenediamines,[6,7,9] which cannot exist in quinoid form, and N-alkyl-N-[(dialkylamino)alkyl]-1,4-naphthalenediamines,[13] which presumably cannot be oxidized to quinone imines, are devoid of antischistosome activity.[6,7,9]

The 4-azo-1-naphthylamine compounds (IVa and b) may also undergo metabolic alteration *via* hydrolysis of their tautomeric hydrazone forms (VIIIa and b) to give 4-azo-1-naphthols (XII), which can exist in quinoid form (VII). Alternatively, reductive scission of the 4-azo-1-naphthols may occur with the formation of 4-amino-1-naphthol (XI), which following oxidation and hydrolysis could lead to 1,4-naphthoquinone (X) *via* 1,4-naphthoquinone imine (VIa). Indeed, certain 4-azo-1-naphthols (XII) and 4-amino-1-naphthol (XI) possess significant activity against *S. mansoni*.[14]

The N,N-dialkyl-N′-(4-nitroso-1-naphthyl)alkylenediamines (Ib) undergo facile hydrolytic cleavage in aqueous media to 4-nitroso-1-naphthol, a tautomer of 1,4-naphthoquinone monooxime (IX).[4] Moreover, IX kills adult *S. mansoni in vitro* within 20 hr at a concentration of 50 μg/ml and within 51–96 hr at 12.5 μg/ml and has been postulated to be one likely metabolite of the N,N-dialkyl-N′-(4-nitroso-1-naphthyl)alkylenediamines (Ib).[4] Other studies in these laboratories revealed that 1,4-naphthoquinone monooxime (IX) is also active against *S. mansoni* in mice and in rhesus monkeys. The drug effected a 70–100% reduction of live schistosomes in mice at daily oral drug-diet doses

(1) For paper XIII, see E. F. Elslager, F. H. Tendick, L. M. Werbel, and D. F. Worth, *J. Med. Chem.*, **12**, 970 (1969).

(2) E. Bueding, L. Peters, and J. F. Waite, *Proc. Soc. Exptl. Biol. Med.*, **64**, 111 (1947).

(3) E. Bueding and L. Peters, *J. Pharmacol. Exptl. Therap.*, **101**, 210 (1951).

(4) L. M. Werbel, E. F. Elslager, and D. F. Worth, *J. Med. Chem.*, **11**, 959 (1968).

(5) E. F. Elslager and D. F. Worth, *ibid.*, **6**, 444 (1963).

(6) E. F. Elslager, D. B. Capps, L. M. Werbel, D. F. Worth, J. E. Meisenhelder, H. Najarian, and P. E. Thompson, *ibid.*, **6**, 217 (1963).

(7) E. F. Elslager, D. B. Capps, D. H. Kurtz, L. M. Werbel, and D. F. Worth, *ibid.*, **6**, 646 (1963).

(8) S. T. Ch'en, I. F. Ch'en, P. C. Kun, Y. C. Hu, J. H. Yao, and T. H. Chou, *Yao Hsueh Hsueh Pao*, **13**, 30 (1966).

(9) E. F. Elslager, D. B. Capps, D. H. Kurtz, F. W. Short, L. M. Werbel, and D. F. Worth, *J. Med. Chem.*, **9**, 378 (1966).

(10) A. Korolkovas, *Rev. Fac. Farm. Bioquim. Sao Paulo*, **5**, 5 (1967).

(11) E. F. Elslager, D. B. Capps, D. H. Kurtz, and D. F. Worth, *J. Med. Chem.*, **11**, 1201 (1968).

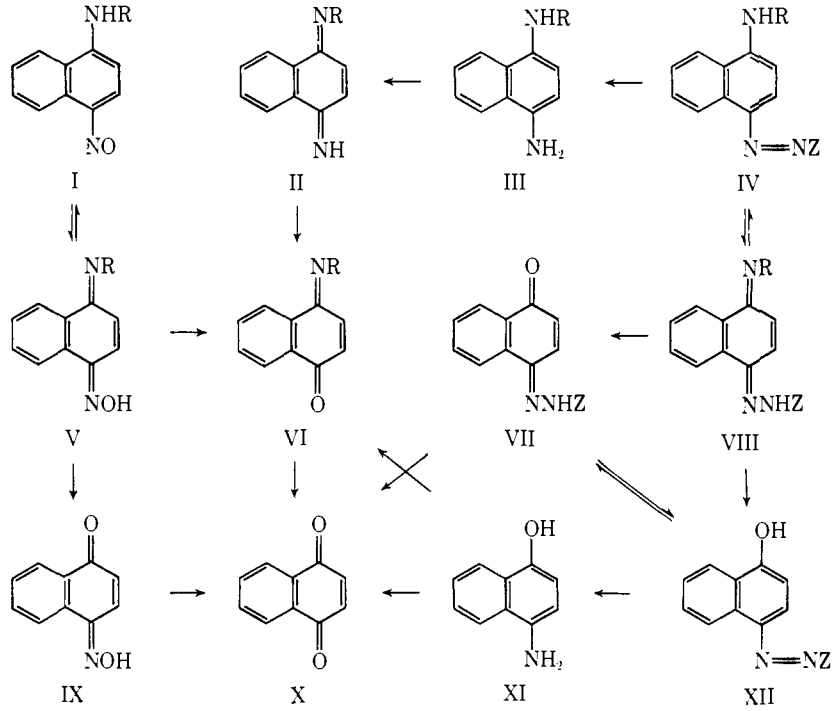
(12) A. Korolkovas, *Rev. Fac. Farm. Bioquim. Sao Paulo*, **6**, 115 (1968).

(13) E. F. Elslager, D. B. Capps, L. M. Werbel, D. F. Worth, J. E. Meisenhelder, and P. E. Thompson, *J. Med. Chem.*, **7**, 487 (1964).

(14) E. F. Elslager, D. B. Capps, and L. M. Werbel, *ibid.*, **7**, 658 (1964).

CHART I

POSSIBLE INTERRELATIONSHIPS AMONG SCHISTOSOMICIDES IN THE NAPHTHALENE SERIES

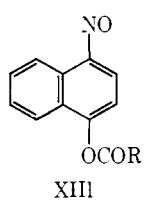


Z = aryl or heterocyclic; a, R = H; b, R = YNR_1R_2

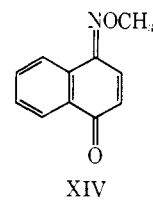
ranging from 273 to 777 mg/kg for 14 days. In rhesus monkeys, IX caused moderate permanent egg suppression at doses of 50 mg/kg/day for 10 days, but failed to cure the animals.

The over-all promise of 1,4-naphthoquinone monooxime (IX) against *S. mansoni*, the antiglycolytic properties of various naphthoquinones,[2,3] and the likelihood that quinoid metabolites may be involved in the mode of action of other classes of schistosomicides (Chart I) stimulated a more comprehensive investigation of the antischistosome properties of 1,2- and 1,4-naphthoquinone derivatives. The present communication describes the synthesis of various 1,4-naphthoquinone O-acyloximes, 4-(mono- and dialkylamino)-1,2-naphthoquinones, 2-amino-3-chloro-1,4-naphthoquinones, and related nitrogenous naphthoquinone derivatives.

Acylation of 4-nitroso-1-naphthol with Ac_2O in HOAc (procedure II) afforded a crystalline yellow product, mp 132.5–134°, which was apparently identical with the compound (mp 132.5°) obtained earlier by Beckmann and Liesche[15] utilizing a similar procedure. These authors designated the product as 4-nitroso-1-naphthol acetate ester (XIII, R = CH_3).[15] However, 4-nitroso-

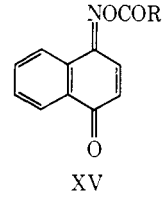


XIII

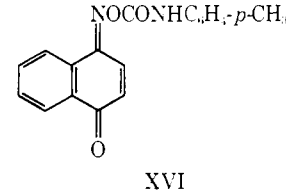


XIV

1-naphthol has been shown to exist in solution in the 1,4-naphthoquinone monooxime form (IX), exhibiting an α,β-unsaturated ketone absorption in the ir at 1650 cm^{-1}.[16,17] Moreover, 1,4-naphthoquinone mono(O-methyloxime) (XIV), which is fixed in the quinoid form, also exhibits carbonyl absorption at 1650 cm^{-1}.[16] The highest carbonyl absorption in 1,4-naphthoquinone appears at 1667 cm^{-1}. The product (**2**, Table I), mp 132.5–134°, obtained from the acylation of 4-nitroso-1-naphthol with Ac_2O, as well as the compounds (**1**, **3**, **4**, Table I) produced by treatment of 4-nitroso-1-naphthol with chloroacetyl chloride, heptanoyl chloride, and palmitoyl chloride in the presence of Et_3N (procedure I), all exhibited α,β-unsaturated ketone absorption at 1660–1675 cm^{-1} and also possessed strong ester carbonyl absorption at 1780–1795 cm^{-1} in the ir (KBr). The ester carbonyl appeared as expected at a higher wave number than does a normal ester as a result of the influence of the C=N group attached to the alcohol oxygen. These data cannot be accommodated by the 4-nitroso-1-naphthol ester structure XIII, and the compounds were therefore assigned the 1,4-naphthoquinone mono(O-acyloxime) structure XV. The prod-



XV



XVI

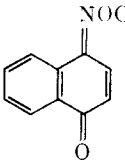
uct of the reaction of 4-nitroso-1-naphthol with *p*-tolyl isocyanate also displayed carbonyl absorption in the ir at 1650 and 1775 cm^{-1} and was designated as 1,4-naphthoquinone mono[O-(*p*-tolylcarbamoyl)oxime] (XVI).

(15) E. Beckmann and O. Liesche, *Ber.*, **56**, 1 (1923).

(16) A. Fischer, R. M. Golding, and W. C. Tennant, *J. Chem. Soc.*, 6032 (1965).

(17) D. Hadzi, *ibid.*, 2725 (1956).

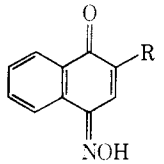
TABLE I
1,4-NAPHTHOQUINONE MONO(O-ACYLOXIMES)[a]

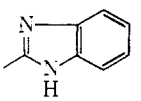


No.	R	Mp, °C	Yield purified, %	Purifen solvent	Procedure	Formula[c]
1	CH_2Cl	128–132	64	Et_2O–petr ether	I	$C_{12}H_8ClNO_3$
2	CH_3	132.5–134[b]	35	95% EtOH	II	$C_{13}H_9NO_3$[d]
3	$(CH_2)_5CH_3$	46–47	33	Petr ether	I	$C_{17}H_{19}NO_3$
4	$(CH_2)_{14}CH_3$	78–79	30	MeCN	I	$C_{30}H_{47}NO_3$

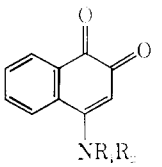
[a] Compounds are yellow. [b] Lit.[15] mp 132.5°; compound erroneously was reported as 4-nitroso-1-naphthol acetate ester. [c] All compounds were analyzed for C, H, N[34] unless otherwise noted. [d] N: calcd, 6.51; found, 6.02.

Nitrosation of 2-[(diethylamino)methyl]-1-naphthol,[18a] 2-(piperidinomethyl)-1-naphthol, and 2-(2-benzimidazolyl)-1-naphthol[18b] afforded 2-[(diethylamino)methyl]-1,4-naphthoquinone 4-oxime (XVIIa) (31%), 2-(piperidinomethyl)-1,4-naphthoquinone 4-oxime (XVIIb) (72%), and 2-(2-benzimidazolyl)-1,4-naphthoquinone 4-oxime (XVIIc) (61%), respectively. Ir curves (KBr) from XVIIa-c show strong carbonyl absorption comparable to that displayed by IX and XV indicating that, at least in the solid state, the depicted quinoid tautomer predominates.



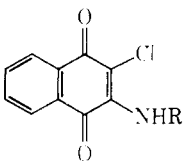
XVIIa, R = $CH_2N(C_2H_5)_2$
b, R = CH_2N (piperidino)
c, R = 

Since 1,2-naphthoquinones also possess marked antiglycolytic activity against *S. mansoni*,[3] a group of 4-amino-1,2-naphthoquinones (XVIII) (**5**-**14**, Table II)



XVIII

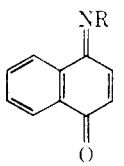
was prepared. These compounds were obtained in 9–53% yield by condensing 1,2-naphthoquinone-4-sulfonic acid sodium salt with the appropriate amine in H_2O or aqueous EtOH (procedures III and IV). Treatment of 2,3-dichloro-1,4-naphthoquinone with an excess of N,N-diethyl-1,3-propanediamine, 2,2′-[(3-aminopropyl)imino]diethanol, or octylamine afforded 2-chloro-3-{[3-(diethylamino)propyl]amino}-1,4-naphthoquinone (XIXa) (53%), 2-({3-[bis(2-hydroxyethyl)-amino]propyl}amino)-3-chloro-1,4-naphthoquinone



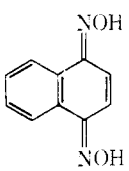
XIXa, R = $(CH_2)_3N(C_2H_5)_2$
b, R = $(CH_2)_3N[(CH_2)_2OH]_2$
c, R = $(CH_2)_7CH_3$

(XIXb) (72%), and 2-chloro-3-(octylamino)-1,4-naphthoquinone (XIXc) (57%), respectively (Table III).

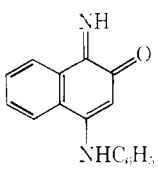
To enable a broader delineation of structure-schistosomicidal relationships among the naphthoquinone derivatives, a variety of known substances were resynthesized or procured from commercial sources. The quinone imine derivatives N-chloro-1,4-naphthoquinone imine (XXa),[19] 1,4-naphthoquinone mono(O-methyloxime) (XIV),[16,20] 1,4-naphthoquinone monosemicarbazone (XXb),[21] [(4-oxo-1(4H)-naphthylidene)-amino]guanidine (XXc),[21] 1,4-naphthoquinone dioxime (XXI),[22] 1,4-dihydro-1-imino-4-(phenylimino)-2-naphthol (XXII),[23] and 4-anilino-1,2-naphthoquinone 1-oxime (XXIII)[24] were prepared according to literature



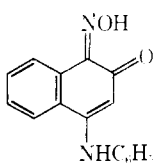
XXa, R = Cl
b, R = NHCONH$_2$
c, R = NHC(=NH)NH$_2$



XXI



XXII

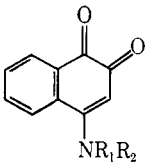


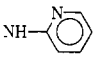
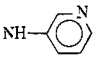
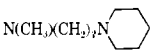
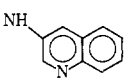
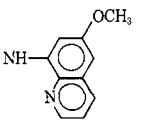
XXIII

(18) (a) P. E. Thompson, J. W. Reinertson, A. Bayles, D. A. McCarthy, and E. F. Elslager, *Am. J. Trop. Med. Hyg.*, **4**, 224 (1955); (b) W. B. Hardy, W. S. Foster, and J. F. Hosler, U. S. Patent 3,049,507 (1962).

(19) P. Friedländer and O. Reinkardt, *Ber.*, **27**, 238 (1894).
(20) J. Meisenheimer, *Ann.*, **355**, 305 (1907).
(21) J. Thiele and W. Barlow, *ibid.*, **302**, 320 (1898).
(22) R. Nietzki and A. L. Guiterman, *Ber.*, **21**, 433 (1888).
(23) R. Lantz and A. Wahl, *Compt. Rend.*, **185**, 1489 (1927).
(24) H. Goldstein and H. Radovanovitch, *Helv. Chim. Acta*, **9**, 783 (1926).

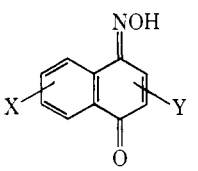
TABLE II
4-AMINO-1,2-NAPHTHOQUINONES[a]



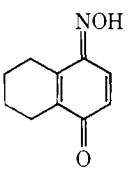
No.	NR_1R_2	Mp, °C	Yield purified, %	Purifcn solvent	Procedure	Formula[c]
5		159–164[b]	37	MeOH–Me_2CO	III	$C_{12}H_9NO_2$
6		155–156 dec	19	EtOH	IV	$C_{14}H_{13}NO_2$
7		228 dec	19	DMA–H_2O	III	$C_{15}H_{10}N_2O_2$
8		235–236 dec	22	DMA–H_2O	III	$C_{15}H_{10}N_2O_2$
9		130–131	53	*i*-PrOH	III	$C_{15}H_{13}NO_2$
10		170–172	32	*i*-PrOH	III	$C_{16}H_{16}N_2O_3$
11		121–125	10	*i*-PrOH	IV	$C_{16}H_{17}NO_2$
12		97–99	9	C_6H_6–petr ether	IV	$C_{18}H_{22}N_2O_2$
13		>300	32	DMA–H_2O	III	$C_{19}H_{12}N_2O_2$
14		210–212	50	EtOH	III	$C_{20}H_{14}N_2O_3$

[a] Compounds ranged from orange to reddish brown. [b] Lit., Farbenfabriken Bayer Aktiengesellschaft, British Patent 806,079 (1958), reports mp 173–175°. [c] All compounds were analyzed for C, H_1 N.[34]

methods,[19–24] and their physical constants were in accord with those described previously. 3-Hydroxy-1,4-naphthoquinone 4-oxime (XXIVa),[25] 6-hydroxy-1,4-naphthoquinone 4-oxime (XXIVb),[26] 3-amino-1,4-naphthoquinone 4-oxime (XXIVc),[27] 2-methyl-1,4-naphtho-

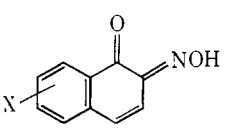


XXIVa, X = H; Y = 3-OH
b, X = 6-OH; Y = H
c, X = H; Y = 3-NH_2
d, X = H; Y = 2-CH_3

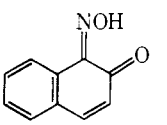


XXV

quinone 4-oxime (XXIVd),[28] 5,6,7,8-tetrahydro-1,4-naphthoquinone monooxime (XXV),[16,17,29] 1,2-naphthoquinone 2-oxime (XXVIa),[28] 4-chloro-1,2-naphthoquinone 2-oxime (XXVIb),[30] 6-hydroxy-1,2-naphthoquinone 2-oxime (XXVIc),[26] 1,2-naphthoquinone 1-oxime

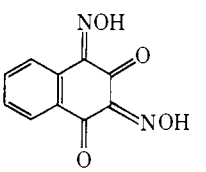


XXVIa, X = H
b, X = 4-Cl
c, X = 6-OH

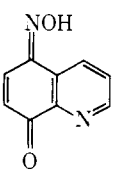


XXVII

(XXVII),[28] and 1,2,3,4-naphthalenetetrone 1,3-dioxime (XXVIII)[28] were obtained in a similar manner by resynthesis or by acquisition.[25–30] Three hetero-



XXVIII



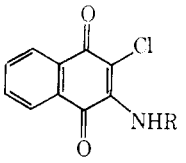
XXIX

cyclic quinone monooximes were also studied, namely, 5,8-quinolinedione 5-oxime (XXIX),[28] 5,6-quinolinedione 5-oxime (XXX),[31] and 5,8-isoquinolinedione 8-oxime (XXXI).

The quinone derivatives described in the present communication were supplied to Dr. Paul E. Thompson

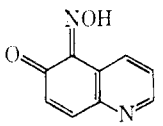
(25) H. Goldstein and P. Grandjean, *Helv. Chim. Acta.*, **264**, 468 (1943).
(26) O. Fischer and C. Bauer, *J. Prakt. Chem.*, **94**, 1 (1916).
(27) F. Kehrmann and M. Hertz, *Ber.*, **29**, 1418 (1896).
(28) These analogs were purchased from Distillation Products Industries Division of Eastman Kodak Company.
(29) G. Schroeter, *Ann.*, **426**, 152 (1922).
(30) A. Reissert, *Ber.*, **44**, 868 (1911).
(31) G. W. Hargreaves, *J. Am. Pharm. Assoc.*, **15**, 750 (1926).

TABLE III
2-AMINO-3-CHLORO-1,4-NAPHTHOQUINONES[a,b]

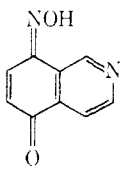


No.	R	Mp, °C	Yield purified, %	Formula[c]
XIXa	$(CH_2)_3N(C_2H_5)_2$	205–206	53	$C_{13}H_{11}ClN_2O_2 \cdot HCl$
XIXb	$(CH_2)_3N(CH_2CH_2OH)_2$	149–151	72	$C_{17}H_{21}ClN_2O_4 \cdot HCl$
XIXc	$(CH_2)_7CH_3$	91–92	57	$C_{18}H_{21}ClNO_2$

[a] Compounds were orange or orange-red. [b] Compounds were crystallized from EtOH. [c] See Table II, footnote *c*.



XXX



XXXI

and coworkers of these laboratories for evaluation against a Puerto Rican strain of *S. mansoni* in mice.[32] Drugs were administered in a powdered diet for 14 days and drug amounts are expressed as free base. 1,4-Naphthoquinone mono[O-(chloroacetyl)oxime] (**1**), 1,4-naphthoquinone mono(O-methyloxime) (XIV), and 2-(piperidinomethyl)-1,4-naphthoquinone 4-oxime (XVIIb) possessed significant schistosomicidal activity and effected a 50–71% reduction of live schistosomes in infected mice at daily doses ranging from 301 to 632 mg/kg when given orally in the diet for 14 days. However, none was as promising as 1,4-naphthoquinone monooxime (IX). All other compounds lacked appreciable antischistosome effects when administered to mice at near-toxic dose levels ranging from 173 to 742 mg/kg per day for 14 days.

Experimental Section[33,34]

1,4-Naphthoquinone Mono(O-acyloximes) (XV) (1–4, Table I). Procedure I.—Heptanoyl chloride (9.0 g, 0.06 mole) was added with stirring to a solution of 10.2 g (0.06 mole) of 4-nitroso-1-naphthol (Eastman) in Et_2O. Et_3N (15 ml) was then added dropwise and the mixture was stirred at room temperature for 3 hr. The $Et_3N \cdot HCl$ that precipitated was collected and discarded. The Et_2O solution was concentrated on a steam bath and petroleum ether (bp 40–60°) was added to induce crystallization. The product was collected by filtration and recrystallized four times from petroleum ether to give 5.6 g (33%) of 1,4-naphthoquinone mono(O-heptanoyloxime) (**3**) as yellow crystals, mp 46–47°.

Procedure II.—4-Nitroso-1-naphthol (Eastman) (5.0 g, 0.029 mole) was heated on a steam bath with 10.0 g of Ac_2O and 60.0 g of HOAc for 0.5 hr. The mixture was poured into H_2O with vigorous stirring and the precipitate that separated was collected by filtration and dried *in vacuo*. The crude product (5.3 g) was crystallized twice from 95% EtOH to give 1,4-naphthoquinone mono(O-acetyloxime) (**2**) as yellow needles (2.2 g, 35%), mp 132.5–134° (lit.[15] mp 132.5°).

1,4-Naphthoquinone Mono[O-(*p*-tolylcarbamoyl)oxime] (XVI).—A mixture of 6.2 g (0.035 mole) of 4-nitroso-1-naphthol and 4.8 g (0.036 mole) of *p*-tolyl isocyanate in 250 ml of Me_2CO was heated under reflux for 4 hr. A yellow solid formed. The product was collected by filtration and crystallized from MeCN to give 3.7 g (34%) of bright yellow crystals, mp 186.5–192°. *Anal.* ($C_{18}H_{14}N_2O_3$) C, H, N.

2-[(Diethylamino)methyl]-1,4-naphthoquinone 4-Oxime (XVIIa).—2-[(Diethylamino)methyl]-1-naphthol hydrochloride[18b] (2.73 g, 0.0103 mole) was dissolved in 100 ml of H_2O and 10 ml of 1 *N* HCl, the solution was cooled to 5°, and an aqueous solution of 0.71 g (0.0103 mole) of $NaNO_2$ was added portionwise at 4–6° with external cooling. The mixture was stirred at 0–5° for 0.5 hr and neutralized with 10 ml of 1 *N* NaOH. The crude product that separated (1.90 g) was crystallized from EtOH–H_2O to give 0.84 g (31%) of shiny brown needles, mp 136–138° dec. *Anal.* ($C_{15}H_{18}N_2O_2$) C, H, N.

2-(Piperidinomethyl)-1,4-naphthoquinone 4-Oxime (XVIIb).—2-(Piperidinomethyl)-1-naphthol (20.0 g, 0.083 mole) was nitrosated with 5.7 g (0.083 mole) of $NaNO_2$ utilizing the procedure described for the preparation of 2-[(diethylamino)methyl]-1,4-naphthoquinone 4-oxime (XVIIa). The product (16.2 g, 72%) was obtained as brown needles from *i*-PrOH, mp 160° dec. *Anal.* ($C_{16}H_{18}N_2O_2$) C, H, N.

2-(2-Benzimidazolyl)-1,4-naphthoquinone 4-Oxime (XVIIc).—A solution of 0.92 g (0.00354 mole) of 2-(2-benzimidazolyl)-1-naphthol[18b] in 50 ml of hot HOAc was cooled rapidly to 15° and a cold solution of 0.24 g (0.00354 mole) of $NaNO_2$ in 5 ml of H_2O was added. The dark green mixture was diluted with 150 ml of H_2O and stirred at 15° for 1 hr. The green solid that precipitated was collected by filtration, washed with H_2O, and dried. The crude product (0.92 g) was crystallized from DMA–H_2O to give 0.62 g (61%), mp 273° dec. *Anal.* ($C_{17}H_{11}N_3O_2$) C, H, N.

4-Amino-1,2-naphthoquinones (XVIII) (5–14, Table II). Procedure III.—A solution of 13.0 g (0.05 mole) of 1,2-naphthoquinone-4-sulfonic acid sodium salt (Eastman)[35] in 250 ml of H_2O was cooled to 15° and 7.4 ml (0.075 mole) of piperidine was added with stirring. An exothermic reaction occurred and the temperature rose to 20°. The mixture was stirred at 10–20° for 0.5 hr and the red crystalline precipitate that separated was collected by filtration and dried. Crystallization from *i*-PrOH gave 6.4 g (53%) of 4-piperidino-1,2-naphthoquinone (**9**) as dark red crystals, mp 130–131°.

Procedure IV.—A solution of 13.0 g (0.5 mole) of 1,2-naphthoquinone-4-sulfonic acid sodium salt (Eastman)[35] in 3 l. of H_2O was cooled to 15° and treated with 63 ml (0.75 mole) of pyrrolidine. The temperature rose to 19° and the solution turned brown-red. The mixture was stirred for 2 hr at 5–20°. When no precipitate appeared, the reaction mixture was extracted with $CHCl_3$ and the combined $CHCl_3$ extracts were washed once with H_2O and dried (K_2CO_3). The $CHCl_3$ was removed *in vacuo* and the residue was crystallized from *i*-PrOH to give 46 g (41%) of crude product, mp 149–152°. Recrystallization from EtOH afforded 21.0 g (19%) of pure 4-(1-pyrrolidinyl)-1,2-naphthoquinone (**6**) as reddish brown crystals, mp 155–156° dec.

2-Amino-3-chloro-1,4-naphthoquinones (XIXa–c) (Table III).—2,2′-[(3-Aminopropyl)imino]diethanol (40.0 g, 0.25 mole) was added to 20.0 g (0.087 mole) of 2,3-dichloro-1,4-naphthoquinone. An exothermic reaction occurred immediately and the temperature rose to 135°. The viscous dark red oil was allowed to cool, and diluted with hot H_2O, and the mixture was filtered. The residue was washed with H_2O and dissolved in C_6H_6, and the C_6H_6 solution was treated with decolorizing charcoal and filtered. The filtrate

(32) For a description of test methods, see P. E. Thompson, J. E. Meisenhelder, and H. Najarian, *Am. J. Trop. Med. Hyg.*, **11**, 31 (1962).

(33) Melting points (corrected) were taken on a Thomas–Hoover capillary melting point apparatus.

(34) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

(35) E. L. Martin and L. F. Fieser in "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley & Sons, Inc., New York, N. Y., 1955, p 633.

was treated with excess HCl and the precipitate was collected by filtration and crystallized from EtOH. 2-({3-[Bis(2-hydroxyethyl)amino]propyl}amino)-3-chloro-1,4-naphthoquinone hydrochloride (XIXb) was obtained (24.5 g, 72%) as orange crystals, mp 149–151°.

5,8-Isoquinolinedione 8-Oxime (XXXI).—5-Isoquinolinol (7.3 g, 0.05 mole) was dissolved in 50 ml of H_2O and 6.5 ml of concentrated HCl and was treated at 5–10° with a solution of 3.5 g (0.05 mole) of $NaNO_2$ in H_2O. The mixture was stirred at 5–10° for 3 hr and the product was collected by filtration and crystallized from DMF. The product (1.4 g, 16%) was obtained as olive crystals, mp 235° dec. *Anal.* ($C_9H_6N_2O_2$) C, H, N.

2-(Piperidinomethyl)-1-naphthol.—A solution of 72.0 g (0.5 mole) of 1-naphthol, 43.0 g (0.5 mole) of piperidine, and 38 ml (0.5 mole) of 40% formalin in 500 ml of EtOH was heated under reflux on a steam bath for 2.5 hr and chilled. The crystalline precipitate that separated was collected by filtration and dried at 45° *in vacuo* (70.1 g, mp 120–132°). The crude product was crystallized twice from EtOH, slurried into 500 ml of H_2O, and treated with 50 ml of concentrated HCl. The precipitate was collected and heated to 90° in 2 l. of H_2O, and the mixture was filtered. The insoluble material was discarded. The filtrate was treated with decolorizing charcoal, chilled, and made strongly alkaline with 50% NaOH. The precipitate was collected, washed with H_2O, and dried at 65° *in vacuo*. Crystallization from EtOH afforded 33.0 g (27%) of pure product, mp 134–135°. *Anal.* ($C_{16}H_{19}NO$) C, H, N.

Acknowledgments.—The authors express their appreciation to Dr. Paul E. Thompson and coworkers for the antischistosome testing, Mrs. Maria L. Zamora for chemical assistance, Mr. C. E. Childs and associates for the microanalyses, and Dr. J. M. Vandenbelt and coworkers for the spectral data.

Novel Anthelmintic Agents. IV. Noncyclic Amidines Related to Pyrantel

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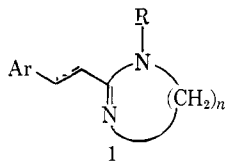
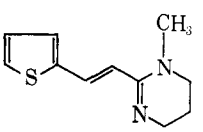
Received July 14, 1969

Anthelmintic activity has been discovered among some N,N-disubstituted thiophenepropionamidines and thiopheneacrylamidines. Activity is associated with compounds in which one N substituent is Me and the other is Me, Et, allyl, MeO, or MeNH. Substitution at the N′ position abolishes activity. Synthetic methods and structure–activity relationships are discussed.

The discovery of a new class of anthelmintic agents was reported in the first papers of this series.[1,2] It was observed that certain compounds of the type represented by **1** are highly effective against the intestinal nematode *Nematospiroides dubius* when tested in mice; indeed one member of the series, pyrantel (**2**), has undergone extensive evaluation in domestic animals and in man.



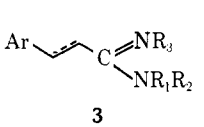
1



2

Ar = C_4H_3S, C_4H_3O, C_6H_5
R = H, CH_3
n = 2,3
··· = optional bond

In pursuing the structure–activity relationships in this series, we became concerned over the question of whether a cyclic amidine system was essential to good anthelmintic activity. Therefore, a number of noncyclic compounds (**3**) were prepared and tested. Very early in this work N,N-dimethyl-2-thiophenepropionamidine (**10**) emerged as an analog active not only against *N. dubius* but also against the tapeworm *Hymenolepis nana;* other active compounds were subsequently discovered. The present work will describe the structure–activity relationships within the noncyclic series of compounds, and will attempt to correlate these findings with those of the cyclic series.



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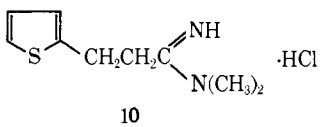
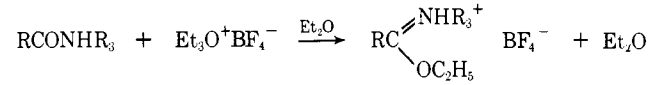


10

Chemistry.—Most of the compounds under discussion were prepared by the action of imidate salts on amines or aminelike substances. However, when an amine was more conveniently available as its HCl salt, an alternate combination was employed: the imidate salt was converted to its free base, and the base was then allowed to react with the amine salt.

Three general procedures were used to prepare the requisite imidate salts. Method A followed the technique of Pinner, *i.e.*, the reaction of a nitrile with dry HCl and an alcohol in dry Et_2O. This method is useful for preparing N-substituted and N,N-disubstituted amidines, but is not suitable for the preparation of N′-substituted compounds. Intermediates for the latter substances are readily prepared by method B, the formation of ethyl N-alkylimidates by the action of $Et_3O^+BF_4^-$ on an N-alkylamide. Some α,β-unsaturated nitriles tended to react very slowly or not at all in the Pinner reaction; in such instances the reaction of the corresponding amides with 1,3-propane sultone (method C) served to prepare the desired imidate salt.[3]



(1) W. C. Austin, W. Courtney, J. C. Danilewicz, D. H. Morgan, R. L. Cornwell, L. H. Conover, H. L. Howes, Jr., J. E. Lynch, J. W. McFarland, and V. J. Theodorides, *Nature*, **212**, 1273 (1966).

(2) J. W. McFarland, L. H. Conover, H. L. Howes, Jr., J. E. Lynch, D. R. Chisholm, W. C. Austin, R. L. Cornwell, J. C. Danilewicz, W. Courtney, and D. H. Morgan, *J. Med. Chem.*, **12**, 1066 (1969).

(3) W. Ried and E. Schmidt, *Ann.*, **676**, 114 (1964).