Synthetic Schistosomicides. IX. N-(Dialkylaminoalkyl)-4-nitroso-1-naphthylamines[1]

LESLIE M. WERBEL, EDWARD F. ELSLAGER, AND DONALD F. WORTH

Research Laboratories, Parke, Davis & Company, Ann Arbor, Michigan 48106

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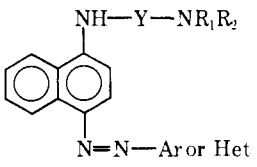
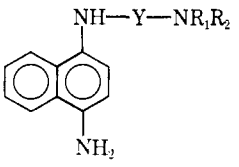
Various N-(dialkylaminoalkyl)-4-nitroso-1-naphthylamines (III) were prepared by nitrosation of the corresponding naphthylamines in anhydrous ethanol. These materials undergo facile hydrolytic cleavage to 4-nitroso-1-naphthol in aqueous media. Several of the nitrosonaphthylamines (III) were highly active against *Schistosoma mansoni* in mice. The most promising compound, 1-{3-[(4-nitroso-1-naphthyl)amino]propyl}-piperidine, also exhibited strong therapeutic effects in rhesus monkeys.

The potent chemotherapeutic activity of various 1-(dialkylaminoalkylamino)-4-naphthylazo compounds I[1-4] and the corresponding 1,4-naphthalenediamines II[5] against infections of *Schistosoma mansoni* and *Schistosoma japonicum* in experimental animals led us to consider the preparation of the nitroso analogs III. These materials are intermediate in the oxidation pathway



I



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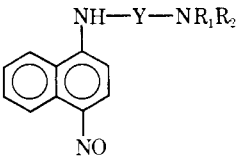
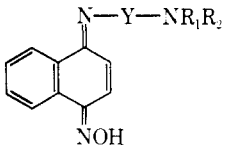


III

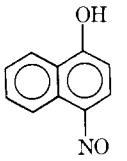


IV

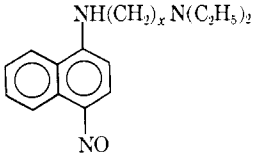
between the arylazo compounds I and the arylamines II, and also have the potential to exist in the tautomeric quinoid structure IV, a form possibly necessary for biological activity within these series.[5,6]

In previous studies[1-5] the diethylaminoethyl derivatives among types I and II exhibited optimum activity; therefore, we undertook initially the nitrosation of N,N-diethyl-N′-1-naphthylethylenediamine (Table I).[7] Nitrosation under standard conditions, *i.e.*, in aqueous acid, glacial acetic acid, or dilute aqueous acid–ethanol mixtures with sodium nitrite, gave only 4-nitroso-1-naphthol (V), presumably resulting from rapid hydrolytic cleavage of the desired N,N-diethyl-N′-4-nitroso-1-naphthylethylenediamine (VIa). With the hope of obtaining a more stable product, the nitrosation of N,N-diethyl-N′-1-naphthyl-1,3-propanediamine[7] was then investigated. Addition of a saturated aqueous solution of sodium nitrite to an ethanol solution of the diamine containing 3 equiv of concentrated HCl at 5° led to rapid separation of green crystals of the hydrochloride salt of N,N-diethyl-N′-(4-nitroso-1-naphthyl)-1,3-propanediamine (VIb). Isolation was effected by filtration or, more satisfactorily, by pouring the reaction mixture into ether, decanting, and rapidly recrystallizing the precipitate from 2-propanol. Using a similar procedure, a series of analogs (Tables II–IV) of general structure III was prepared. Occasionally the products were isolated by pouring the reaction mixture into cold aqueous base, rapidly extracting the mixture with ether, and bubbling HCl into the dried ether extracts.

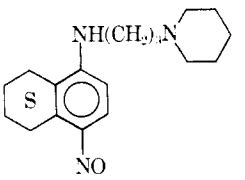
Utilizing similar procedures, representative N-(alkyl-, -hydroxyalkyl-, and -alkoxyalkyl)-4-nitroso-1-naphthylamines (Table V) were synthesized, as well as 1-{3-[(5,6,7,8-tetrahydro-4-nitroso-1-naphthyl)amino]propyl}piperidine (VII) and 8-[(2-diethylaminoethyl)-amino]-6-methoxy-5-nitrosoquinoline (VIII). N-Methyl-1-nitroso-2-naphthylamine (IX) was prepared by the reaction of 1-nitroso-2-naphthol with methylamine.[8]



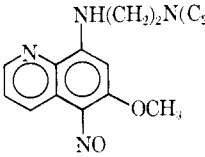
V



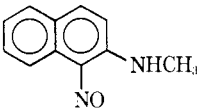
VIa, $x = 2$
b, $x = 3$



VII



VIII



IX

The assignment of structure III for the compounds summarized in Tables II–IV is predicated on their conversion to the known V and their uv and nmr spectra. Their hydrolytic conversion to V confirms the 1,4

(1) Previous paper: 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).

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

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

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

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

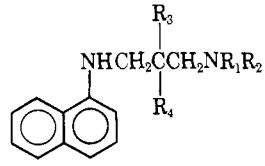
(6) E. F. Elslager, D. B. Capps, and L. M. Werbel, *ibid.*, **7**, 658 (1964).

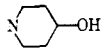
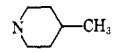
(7) L. M. Werbel, D. B. Capps, E. F. Elslager, W. Pearlman, F. W. Short, E. A. Weinstein, and D. F. Worth, *ibid.*, **6**, 637 (1963).

(8) O. Fischer, C. Dietrich, and F. Weiss, *J. Prakt. Chem.*, **100**, 168 (1920).

TABLE I

N,N-DIALKYL-N′-1-NAPHTHYLALKYLENEDIAMINES[a]

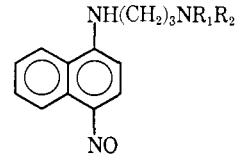


NR_1R_2	R_3	R_4	Mp, °C	Yield purified, %	Purifn solvent	Formula	Analyses[b]
	H	H	221–224 dec	41	MeOH	$C_{17}H_{20}N_2 \cdot 2HCl$[b]	H, N; C[c]
	H	H	127–129	68	*i*-PrOH	$C_{18}H_{24}N_2O$	C, H, N
	H	H	228 dec	63	MeOH–Et_2O	$C_{18}H_{25}N_3 \cdot 3HCl$	C, H, N
	H	H	206 dec	66	EtOH	$C_{19}H_{26}N_2 \cdot 2HCl$	C, H, N
	H	H	57–59	26	*i*-Octane	$C_{19}H_{26}N_2$	C, H, N
	H	OH	243–246	75	MeOH–petr ether	$C_{18}H_{24}N_2O \cdot 2HCl$[d]	C, H, N, Cl

[a] These compounds were prepared *via* method VIIIA described in ref 7. [b] 3-Bromopropylnaphthylamine hydrobromide was purchased from Kaplop Laboratories, Detroit, Mich. [c] Carbon: calcd, 62.76; found, 62.30. [d] 3-Chloro-2-hydroxypropyl-1-naphthylamine hydrochloride was prepared according to E. Fourneau, J. Tréfouel, and G. Benoit, *Ann. Inst. Pasteur*, **44**, 719 (1930).

TABLE II

N,N-DIALKYL-N′-(4-NITROSO-1-NAPHTHYL)-1,3-PROPANEDIAMINES



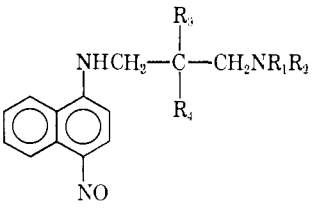
No.	NR_1R_2	Mp, °C	Yield purified, %	Purifn solvent	Formula	Analyses[b]
1	$N(CH_3)_2$	156–157.5 dec	73	MeOH	$C_{15}H_{19}N_3O \cdot 2HCl \cdot H_2O$	H, N, H_2O; C[a]
2		150 dec	30	MeOH	$C_{17}H_{19}N_3O \cdot 2HCl \cdot H_2O$	C, H, N, Cl; H_2O[b]
3		160–165 dec	19		$C_{15}H_{21}N_3O \cdot 2HCl \cdot H_2O$	C, H, N, H_2O
4		157–159	68		$C_{17}H_{21}N_3O_2 \cdot 2HCl \cdot 2.25H_2O$[c]	C, H, N, H_2O
5	$N(_2CH_5)_2$	135–136	46	*i*-PrOH	$C_{15}H_{23}N_3O \cdot 2HCl \cdot H_2O$	C, H, N, H_2O
6		159–160	20	*i*-PrOH	$C_{18}H_{23}N_3O$	C, H, N
7		176 dec	7	MeOH–Et_2O	$C_{18}H_{23}N_3O_2 \cdot 2HCl \cdot H_2O$	H, N; C[d]
8		165 dec	22	EtOH–Et_2O	$C_{18}H_{24}N_4O \cdot 3HCl \cdot 1.33H_2O$	C, H, N, Cl
9		133–135	16	MeCN	$C_{19}H_{25}N_3O$	C, H, N
10		133 dec	38	*i*-PrOH	$C_{19}H_{25}N_3O \cdot 0.33H_2O$	H, N, H_2O; C[e]

[a] C: calcd, 51.73; found, 51.29. [b] H_2O: calcd, 4.84; found, 3.86. [c] Base, mp 149–153° dec, from C_6H_6. *Anal.* ($C_{17}H_{21}N_3O_2$) C, H, N. [d] C: calcd, 53.47; found, 52.87. [e] C: calcd, 71.74; found, 72.18.

orientation in III, as does the nmr spectra (in deuterioacetone) which indicate the presence of the ring proton *ortho* to the secondary aromatic amine as a doublet at 6.6, 6.75 ppm shifted upfield from the other aromatic protons. Such a shift is also observed for the *ortho* proton of the naphthylamines used as starting materials (Table I). The uv spectra of III present a consistent, pH-dependent picture (Figure 1). These curves are in excellent agreement with those of N-ethyl-4-nitroso-1-naphthylamine, but in contradistinction to the spectrum of N-nitroso-N-ethylaniline, which has a single peak at 270 mμ in methanol and does not shift in either acid or base, and of N-nitroso-N-ethyl-1-naphthylamine, which has a peak in methanol

TABLE III

N,N-DIALKYL-2-SUBSTITUTED N'-(4-NITROSO-1-NAPHTHYL)-1,3-PROPANEDIAMINES

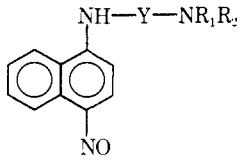


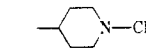
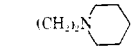
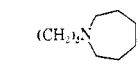
No.	R_3	R_4	NR_1R_2	Mp dec, °C	Yield purified, %	Purifn solvent	Formula	Analyses[a]
11	H	CH_3	$N(CH_3)_2$	138.5–139.5	9	*n*-PrOH	$C_{16}H_{21}N_3O \cdot 2HCl \cdot H_2O$	C, H, N, H_2O
12	H	OH		173–176	41	EtOH–Et_2O	$C_{18}H_{23}N_3O_2 \cdot 2HBr$	H, N; C[b]
13	CH_3	CH_3	$N(C_2H_5)_2$	109–111	20	*i*-PrOH	$C_{19}H_{27}N_3O \cdot 2HCl \cdot 2H_2O$	H, N, H_2O; C[b]
14	CH_3	CH_3		124–127	39	*n*-BuOH	$C_{20}H_{27}N_3O \cdot 2HCl \cdot 1.67H_2O$	C, H, N, H_2O

[a] C: calcd, 45.49; found, 45.01. [b] C: calcd, 54.03; found, 53.32.

TABLE IV

OTHER N,N-DIALKYL-N'-(4-NITROSO-1-NAPHTHYL)ALKYLENEDIAMINES

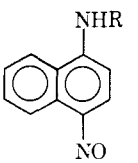


No.	Y-NR_1R_2	Mp dec, °C	Yield purified, %	Purifn solvent	Formula	Analyses[a]
15		210	38	MeOH	$C_{16}H_{19}N_3O \cdot 2HCl \cdot 0.67H_2O$	H, N, H_2O; C[c]
16	$(CH_2)_2N(C_2H_5)_2$	133–135		*n*-BuOH	$C_{16}H_{24}N_3O \cdot 2HCl$	N, Cl
17		230–240	41		$C_{17}H_{21}N_3O \cdot 2HCl$[d]	C, H, N
18		122–124	10	C_6H_6	$C_{18}H_{23}N_3O$	C, H, N
19	$(CH_2)_3N(C_2H_5)_2$	139–140	8	*i*-PrOH	$C_{19}H_{27}N_3O \cdot 2HCl \cdot H_2O$	C, H, H_2O; N[c]
20	$CHCH_3(CH_2)_3N(C_2H_5)_2$	145–147	26	*i*-PrOH	$C_{19}H_{27}N_3O \cdot 2HCl$[d]	C, H, N

[a] C: calcd, 54.24; found, 53.71. [b] Base, mp 154–161° dec (EtOH). *Anal.* ($C_{17}H_{21}N_3O$) C, H, N. [c] N: calcd, 10.39; found, 9.89. [d] Found values are corrected for 5.76% H_2O. The reaction mixture was filtered, triturated with ether, and decanted, the residual gum was triturated with *i*-PrOH saturated with gaseous HCl, and the solid was recrystallized from *i*-PrOH.

TABLE V

MISCELLANEOUS N-ALKYL-4-NITROSO-1-NAPHTHYLAMINES



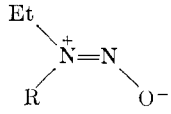
No.	R	Mp, °C	Yield purified, %	Purifn solvent	Formula	Analyses[a]
21	C_2H_5	>310	70		$C_{12}H_{12}N_2O \cdot HCl$	C, H, N
22	$(CH_2)_2OH$	>300	8	MeOH	$C_{12}H_{12}N_2O_2 \cdot HCl$	C, H; N[b]
23	$(CH_2)_3OCH_3$	135–136 dec	22	*i*-PrOH	$C_{14}H_{16}N_2O_2 \cdot HCl$	C, H, N
24	$CH_2CH(C_2H_5)_2$	153 dec	14	EtOH	$C_{16}H_{20}N_2O \cdot HCl$	C, H, N

[a] N: calcd, 11.09; found, 10.55.

at 281 mμ with shoulders at 270 and 290 mμ and is also independent of change in pH.

The reference compound, N-nitroso-N-ethyl-1-naphthylamine, was prepared by nitrosation of N-ethyl-1-naphthylamine with sodium nitrite in aqueous HCl at 5°. The reaction mixture was extracted with ether, the solvent was removed at room temperature, and the residue was subjected to spectral analysis immediately. In addition to the uv data, the absence of NH or OH absorption in the ir spectrum confirms the N-nitroso structure. The other isomer, N-ethyl-4-nitroso-1-naphthylamine, was prepared by nitrosation in ethanol

(*cf.* Experimental Section), and its spectral properties clearly confirm the structure assignment. While it is possible that the N-(dialkylaminoalkyl)-N-nitroso-1-naphthylamines are formed initially and rearrange to the C-nitroso isomer during work-up, the rapid separation of the hydrochloride salts of the 4-nitroso-1-naphthylamines III directly from the reaction mixtures suggests direct C-nitrosation. Blangey[9] has postulated nitrosation on carbon when simple 1-naphthylamine derivatives were treated with nitrosyl sulfuric acid. D'Amico and coworkers[10] have also reported the tendency of aromatic amines to nitrosate on nitrogen in aqueous medium and on carbon in alcoholic medium. The nmr spectrum of N-nitroso-N-ethyl-1-naphthylamine is also of interest. In CCl_4 it shows two CH_3 triplets centered at 1.0 and 1.27 ppm and two CH_2 quartets centered at 3.93 and 4.5 ppm. This observation, which indicates the presence of two steric configurations resulting from restricted rotation about a partial N=N double bond



is in accord with previous observations on other nitrosamines,[11] and serves further to confirm the N-nitroso structure of this material.

The stability of the nitroso compounds III was examined by uv spectroscopy and was found to vary considerably with the nature of the side chain. The most labile compound was N,N-diethyl-N′-4-nitroso-1-naphthylethylenediamine (VIa). This material could be isolated in crude form by direct filtration of an anhydrous reaction mixture, but could be purified by recrystallization only in small amounts and with substantial losses due to its instability. The inherent instability of the dialkylaminoethyl side chain is further illustrated by the failure to obtain any of the desired products from naphthylamines containing a dimethylaminoisopropyl, diisopropylaminoethyl, or allylcyclohexylaminoethyl side chain. A cyclic terminal amine conferred additional stability; for example, 1-{2-[(4-nitroso-1-naphthyl)amino]ethyl}piperidine (**17**, Table IV) was converted to V to the extent of 98% in 2 hr at pH 3, but only to the extent of 86% after 24 hr at pH 7. In general, compounds in which the side chain interruption was greater than two carbon atoms were more stable. Thus, N,N-diethyl-N′-(4-nitroso-1-naphthyl)-1,3-propanediamine (VIb) was converted to V to the extent of 42% at pH 3 in 2 hr and 86% at pH 7 in 24 hr. 1-{2,2-Dimethyl-3-[(4-nitroso-1-naphthyl)amino]propyl}piperidine (**14**, Table III) also showed greater neutral stability, being converted to V only to the extent of 48% after 24 hr at pH 7. 1-{3-[(4-Nitroso-1-naphthyl)amino]propyl}-piperidine (**6**, Table II) exhibited a similar picture showing excellent 24-hr stability in alkaline methanol, somewhat less stability in acidic methanol, and extremely poor stability in both acidic and basic aqueous systems. The instability of these materials is undoubtedly connected with the presence of a terminal amine in the side chain. Thus N-ethyl-4-nitroso-1-naphthylamine (**21**, Table V) remained essentially unchanged even after 7 days in neutral, acidic, or basic methanol.

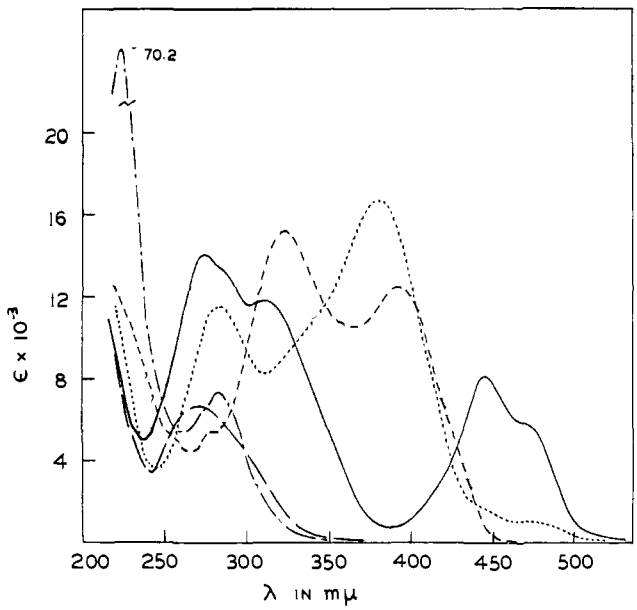


Figure 1.—Uv spectra of 1-{3-[(4-nitroso-1-naphthyl)amino]-propyl}piperidine (**6**): — in MeOH, --- in MeOH plus 1 drop of 5 *N* HCl/cell, ---- in methanol plus 1 drop of 12 *N* KOH/cell; N-nitroso-N-ethyl-1-naphthylamine in MeOH -·-; and N-nitroso-N-ethylaniline in MeOH ——.

It is interesting to note that replacement of naphthalene by quinoline affords a much more stable system. No difficulty was experienced in the preparation of 8-[(2-diethylaminoethyl)amino]-6-methoxy-5-nitrosoquinoline (VIII), and in fact hydrolysis of similar compounds[12] requires reflux in methanolic potassium hydroxide.

The N-methyl derivative of VIa could not be isolated. Its extreme lability resulted in an immediate precipitate of V from the reaction mixture, and this was the only isolable product. This is in agreement with results of experiments on N,N-dimethyl- and N,N-diethyl-1-naphthylamine in which the 4-nitroso derivatives could be isolated only in the crude form and rapidly decomposed to V upon attempted purification.

The facile lability of III provides a simple preparative route to substituted 1,4-nitrosonaphthols. Thus, 6-methoxy-4-nitroso-1-naphthol and 8-chloro-4-nitroso-1-naphthol were readily prepared from N,N-diethyl-N′-(6-methoxy-1-naphthyl)ethylenediamine and N,N-diethyl-N′-(8-chloro-1-naphthyl)ethylenediamine, respectively.

The nitrosonaphthylamine derivatives described in the present communication were tested in mice against a Puerto Rican strain of *S. mansoni*[13a] by Dr. Paul E. Thompson and coworkers of these laboratories. Drugs were given in a powdered diet for 14 days or by gavage in 10 ml/kg of aqueous 1% hydroxyethyl- or carboxymethylcellulose for 5 or 10 days. Drug amounts are expressed as free base. Only the N,N-dialkyl-N′-(4-nitroso-1-naphthyl)alkylenediamines (Tables II–IV)

(9) L. Blangey, *Helv. Chim. Acta*, **21**, 1579 (1938).

(10) J. J. D'Amico, C. C. Tung, and L. A. Walker, *J. Am. Chem. Soc.*, **81**, 5957 (1959).

(11) G. J. Karabatsos and R. A. Taller, *ibid.*, **86**, 4373 (1964).

(12) R. C. Elderfield and C. Ressler, *ibid.*, **72**, 4059 (1950), describe the nitrosation of analogous aminoquinolines.

(13) (a) For a description of test methods see P. E. Thompson, J. E. Meisenhelder, and H. Najarian, *Am. J. Trop. Med. Hyg.*, **11**, 31 (1962); (b) D. Rosi, G. Peruzzotti, E. W. Dennis, D. A. Berberian, H. Freele, B. F. Tullar, and S. Archer, *J. Med. Chem.*, **10**, 867 (1967).

exhibited schistosomicidal activity. The degree of activity among them was extremely variable, reflecting the dependence of activity upon the nature of the side chain but not allowing any definitive structure–activity conclusions to be drawn. Compounds **3**, **5**, **6**, **11**, **14**, and **15** exhibited activity of an order equal or superior to hycanthone[13b] at doses ranging from 130 to 300 mg/kg. Surprisingly, VIa was devoid of activity, presumably as a result of its extreme instability.

4-Nitroso-1-napthol (V) is a likely metabolite of the N-(dialkylaminoalkyl)-4-nitroso-1-naphthylamines. Although this material killed adult *S. mansoni in vitro* at 50 μg/ml, it was active in mice only at toxic levels and had little or no effect in monkeys. Therefore, it is presumed not to be solely responsible for the therapeutic efficacy of the nitrosonaphthylamines.

Several representative N,N-dialkyl-N′-(4-nitroso-1-naphthyl)alkylenediamines were selected for trial against the Puerto Rican strain of *S. mansoni* in rhesus monkeys.[13a] Compound **5** as the hydrated hydrochloride salt showed significant antischistosomal activity, but was poorly tolerated as reflected by emesis, diarrhea, and inappetance. A series of insoluble salts of this material was prepared (*cf.* Experimental Section) in an effort to overcome the gastrointestinal intolerance. In general these salts retained activity, but were not superior to the hydrochloride. The most promising compound studied was 1-{3-[(4-nitroso-1-naphthyl)amino]propyl}piperidine (**6**). Gavage doses of 25 mg/kg administered twice daily for 5 or 10 days to rhesus monkeys infected with *S. mansoni* usually effected a cure or strongly suppressed egg production. However, the relatively narrow therapeutic index of this material (intolerance variably reflected by diarrhea, weight loss, and inappetance) indicated that additional studies were not warranted at this time.

Experimental Section[14,15]

N,N-Dialkyl-N′-(4-nitroso-1-naphthyl)alkylenediamines (III) (Tables II–IV).—To a solution of 25.6 g (0.1 mole) of N,N-diethyl-N′-1-naphthyl-1,3-propanediamine[7] in 150 ml of EtOH containing 25 ml of concentrated HCl (0.292 mole) cooled to 0–5° was added a solution of 6.9 g (0.1 mole) of $NaNO_2$ in the minimum amount of H_2O. A green solid formed rapidly. The mixture was stirred briefly and poured into Et_2O. The solvents were decanted and the residue was recrystallized from *i*-PrOH and chilled in an ice bath to give 17.3 g of N,N-diethyl-N′-(4-nitroso-1-naphthyl)-1,3-propanediamine dihydrochloride monohydrate (**5**, Table II) as green crystals, mp 135–136°. The base (VIb) was prepared by dissolving the salt in H_2O, making the solution basic with NH_4OH, extracting with Et_2O, drying, removing the solvent at room temperature, and recrystallizing the residue from *i*-PrOH to give a green-brown solid, mp 89.5–92°. *Anal.* ($C_{17}H_{28}N_4O$) C, H, N.

N,N-Diethyl-N′-(4-nitroso-1-naphthyl)-1,3-propanediamine Salt with 1,5-Naphthalenedisulfonic Acid.—To a stirred aqueous solution of 3.76 g (0.01 mole) of VIb dihydrochloride monohydrate (**5**) was added an aqueous solution of 3.68 g (0.01 mole) of disodium 1,5-naphthalenedisulfonate dihydrate. A solid formed slowly. After several hours the solid was removed by filtration and dried *in vacuo* to give 4.0 g (67%) of the salt as a tan solid, mp 185° with gradual shrinkage and charring with indefinite decomposition. *Anal.* ($C_{27}H_{34}N_4O_7S_2 \cdot H_2O$) H, N; C: calcd, 54.81; found, 55.44; H_2O: calcd, 3.05; found, 3.47.

N,N-Diethyl-N′-(4-nitroso-1-naphthyl)-1,3-propanediamine Salt with 2,2′-Thiobis(4,6-dichlorophenol).—An aqueous solution of 3.56 g (0.01 mole) of 2,2′-thiobis(4,6-dichlorophenol) containing 20 ml of 1.01 *N* NaOH was added to an aqueous solution of 3.76 g (0.01 mole) of VIb dihydrochloride monohydrate. A yellow solid formed immediately. The mixture was stirred briefly and filtered, and the solid was dried *in vacuo*. Stirring with warm MeCN gave 5.1 g (78%) of the salt as a yellow solid, mp 150° dec. *Anal.* ($C_{29}H_{29}Cl_4N_3O_3S \cdot 0.5H_2O$) C, H, N, H_2O. The following salts of VIb were prepared similarly. The acid component, yield, melting point, and analytical values follow.

Fluorescein, 78%, mp 121° gradual decomposition to 153°. *Anal.* ($C_{37}H_{35}N_3O_5 \cdot 1.33H_2O$) H, N, H_2O; C: calcd, 69.25; found, 68.73.

3-Hydroxy-7-sulfo-2-naphthoic acid, 70%, mp 156–160° dec. *Anal.* ($C_{25}H_{29}N_3O_5S \cdot 0.5H_2O$) H, N, H_2O; C: calcd, 59.77; found, 59.29.

4,4-Methylenebis(1-hydroxy-2-naphthoic acid), 56%, mp 145° gradually decomposes to 165°. *Anal.* ($C_{39}H_{39}N_3O_7 \cdot 0.5H_2O$) C, H, N, H_2O.

5,5′-Methylenebis(6-hydroxy-2-naphthoic acid), 70%, mp 190–200° dec. *Anal.* ($C_{40}H_{39}N_3O_7 \cdot 0.75H_2O$) C, H, N, H_2O.

4,4′-Methylenebis(7-bromo-3-hydroxy-2-naphthoic acid), 51%, mp 183–187° dec. *Anal.* ($C_{40}H_{37}Br_2N_3O_7 \cdot 1.5H_2O$) C, H, N, H_2O.

4,4′-Biphenyldisulfonic acid, 80%, decomposed by 170°. *Anal.* ($C_{28}H_{33}N_3O_7S_2 \cdot 2.5H_2O$) C, H, N, H_2O.

N-Ethyl-4-nitroso-1-naphthylamine (21, Table V).—To a suspension of 8.6 g (0.05 mole) of N-ethyl-1-naphthylamine in 80 ml of EtOH containing 9 ml of concentrated HCl was added at 5° an aqueous solution of 3.5 g (0.05 mole) of $NaNO_2$. The mixture colored deep purple and then became deep green. The mixture was stirred for 1 hr and filtered. The green filtrate was poured into iced water, made basic with NaOH, and extracted with Et_2O. The extracts were dried ($MgSO_4$) and treated with 25 ml of a 30% solution prepared by bubbling dry HCl into *i*-PrOH. The green solid which formed was removed by filtration and dried *in vacuo* to give 8.3 g (70%) of product, mp >310°.

The hydrochloride was dissolved in H_2O and the solution was made basic with NH_4OH. The gum which formed solidified on standing and was removed by filtration and recrystallized twice from C_6H_6 to give the base, mp 123–126°.[16] *Anal.* ($C_{12}H_{12}N_2O$) C, H, N.

2-[(4-Nitroso-1-naphthyl)amino]ethanol (22, Table V).—To a solution of 18.7 g (0.1 mole) of 2-(1-naphthylamino)ethanol in 150 ml of EtOH was added 17 ml of concentrated HCl (0.02 mole). A solid formed, the suspension was cooled to 4°, and to it was added dropwise an aqueous solution of 6.9 g (0.1 mole) of $NaNO_2$. The mixture was stirred for 1 hr and filtered to give 14.2 g of green solid. Recrystallization twice from MeOH gave 2.1 g (8.3%) of product, mp >300°.

N-(3-Methoxypropyl)-4-nitroso-1-naphthylamine (23, Table V).—To a solution of 10.8 g (0.05 mole) of N-(3-methoxypropyl)-1-naphthylamine in EtOH containing 6.5 ml of concentrated HCl cooled to 5° was added dropwise an aqueous solution of 3.5 g (0.05 mole) of $NaNO_2$. The mixture was stirred briefly, filtered to remove a small amount of beige solid, and poured into Et_2O to give 8.7 g of a green solid. Recrystallization from *i*-PrOH gave 3.0 g (22%) of product, mp 135–136° dec.

1-{3-[(5,6,7,8-Tetrahydro-4-nitroso-1-naphthyl)amino]propyl}-piperidine (VII).—To a solution of 13.6 g (0.05 mole) of 1-{3-[(5,6,7,8-tetrahydro-1-naphthyl)amino]propyl}piperidine[17] in a mixture of 200 ml of EtOH, 100 ml of MeOH, and 50 ml of H_2O containing 13 ml of concentrated HCl cooled to 5–10° was added an aqueous solution of 3.5 g (0.05 mole) of $NaNO_2$. After stirring for about 1 hr, the mixture was poured into H_2O, made basic with NaOH, and extracted with Et_2O. Gaseous HCl was bubbled into the dried extracts. A green gum formed which gradually solidified. Recrystallization twice from *i*-PrOH gave 2.2 g (13%) of product, mp 163.5–165° dec. *Anal.* ($C_{18}H_{27}N_3O \cdot HCl$) C, H, N.

6-Methoxy-4-nitroso-1-naphthol.—To a solution of 6.8 g (0.025 mole) of N,N-diethyl-N′-(6-methoxy-1-naphthyl)ethylenediamine[7] in EtOH containing 6.5 ml of concentrated HCl was added at 5–10° an aqueous solution of 1.73 g (0.025 mole) of $NaNO_2$. The ice bath was removed and the mixture was allowed

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

(15) 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.

(16) E. Koch, *Ann.*, **243**, 310 (1887), reports mp 143°.

(17) L. M. Werbel, E. F. Elslager, M. W. Fisher, Z. B. Gavribs, and A. A. Phillips, *J. Med. Chem.*, **11**, 911 (1968).

to warm to room temperature overnight. Filtration gave a brown solid which was dissolved in aqueous NaOH, filtered, and acidified with HCl to give a yellow solid. Recrystallization from 95% EtOH gave 1.9 g (37%) of product, mp 219–221° dec. *Anal.* ($C_{11}H_9NO_3$) C, H, N.

8-Chloro-4-nitroso-1-naphthol.—The reaction of nitrous acid with N,N-diethyl-N′-(8-chloro-1-naphthyl)ethylenediamine[7] as above gave 42% of product as a pale yellow solid, mp >300°. *Anal.* ($C_{10}H_6ClNO_2$) C, H, N.

8-[(2-Diethylaminoethyl)amino]-6-methoxy-5-nitrosoquinoline (VIII).—To a solution of 7.4 g (0.027 mole) of 8-[(2-diethylaminoethyl)amino]-6-methoxyquinoline[12] in 95% EtOH containing 7 ml of concentrated HCl at 5° was added an aqueous solution of 1.87 g (0.027 mole) of $NaNO_2$. The mixture was stirred for several hours, diluted with H_2O, and made basic with NaOH. The green-brown solid which resulted was removed by filtration, dried, and recrystallized from C_6H_6 to give 4.1 g (50%) of the product as a yellow solid, mp 135.5–137°. *Anal.* ($C_{16}H_{22}N_4O_2$) C, H, N.

N-(3-Methoxypropyl)-1-naphthylamine.—A mixture of 144 g (1.0 mole) of 1-naphthol, 95 g (1.06 mole) of 3-methoxypropylamine, and 174 g (1.0 mole) of $Na_2S_2O_4$ in 600 ml of H_2O was heated in a bomb for 8 hr at 150°. The mixture was removed from the bomb, made strongly basic with NaOH, and extracted with Et_2O. The extracts were dried (Na_2SO_4), the solvent was removed *in vacuo*, and the residue distilled to give 95.4 g (44%) of the product, bp 126–128° (0.2 mm). *Anal.* ($C_{14}H_{17}NO$) C, H, N.

N-(2-Ethylbutyl)-1-naphthylamine.—A mixture of 42.9 g (0.3 mole) of 1-naphthylamine and 30.0 g (0.3 mole) of 2-ethylbutyraldehyde in 400 ml of C_6H_6 containing 1.0 g of *p*-toluenesulfonic acid was heated under reflux for 3 hr. H_2O was removed with a water take-off head. The mixture was concentrated to dryness and hydrogenated over 0.5 g of PtO_2 in 250 ml of EtOH for 16 hr at an initial temperature of 25° and a hydrogen pressure of 3.87 kg/cm². The catalyst was removed by filtration and the solvent was removed *in vacuo*. Distillation of the residue gave 23.4 g (34%) of the product, bp 106–108° (0.09 mm). *Anal.* ($C_{16}H_{21}N$) C, H, N.

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2,2-Dimethyl-3-vinylcyclobutaneacetic Acid, a Fungistatic Agent Derived from Pinene[1a]

R. L. SETTINE,[1b] J. B. LEWIS,[1c] RUTH MAYNE,[1d] AND G. W. HEDRICK[1c]

Department of Chemistry, The University of Mississippi, University, Mississippi, Naval Stores Laboratory, Olustee, Florida, and Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture, New Orleans, Louisiana

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Pure 2,2-dimethyl-3-vinylcyclobutaneacetic acid was prepared by pyrolysis of pinolic acid and some acyl esters followed by selective epoxidation of the ethylidene homolog which was produced along with the vinyl compound. Tests indicate that 2,2-dimethyl-3-vinylcyclobutaneacetic acid is comparable to 10-hendecenoic acid in its fungistatic activity against *Aspergillus niger*, *Aspergillus oryzae*, and *Aspergillus flavus*.

10-Hendecenoic acid and its salt are reported to have unusually good fungistatic action.[2] Because both 10-hendecenoic acid and a recently described acid, 2,2-dimethyl-3-vinylcyclobutaneacetic acid,[3] contains a terminal vinyl group it was believed that the latter acid may also be an effective fungistatic agent. Tests on *Aspergillus niger*, *Aspergillus oryzae*, and *Aspergillus flavus* suggest that the test material is as fungistatic as 10-hendecenoic acid. Since di-*n*-hexyl pinate[4] and lauryl pinonate[5] are not fungistats, the fungicidal properties of the vinylcyclobutane derivative must be due to the vinyl group rather than the dimethylcyclobutaneacetic acid moiety which is present in all three compounds. In addition to the biological activity the acid has a more pleasant odor than 10-hendecenoic acid.

This report covers new information on the synthesis and isolation of the vinylcyclobutaneacetic acid and results of fungistatic tests of the acid compared with 10-hendecenoic acid.

Pyrolysis of pinolic acid, 2,2-dimethyl-3-(1-hydroxyethyl)cyclobutaneacetic acid, or its acetate gave a mixture of 2,2-dimethyl-3-vinyl- and 2,2-dimethyl-3-ethylidenecyclobutaneacetic acids.[3] A comparison of this mixture with 10-hendecenoic acid gave somewhat discouraging results.[6]

In the present work, the ratio of vinyl to ethylidene compounds was considerably less than previously reported. To improve the yield of desired product, the pyrolyses of some esters other than the acetate were investigated (Table I). Pivalic and 3,3-dimethylhexanoic acid esters gave substantially better yields than the other esters. Separation of products was effected by selective epoxidation of the olefin mixture with *m*-chloroperbenzoic acid (MCPA) in ether. The vinyl compound was less readily attacked than the ethylidene derivative and distillation of the partially epoxidized mixture gave dimethylvinylcyclobutaneacetic acid free of the ethylidene derivative.

Thoi[7] and Trave[8] and other workers have given the name *cis-dl*-pinolic acid to the solid isomer, mp 105°

(1) (a) Presented at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967; (b) The University of Mississippi; (c) Naval Stores Laboratory; (d) Agricultural Research Service.

(2) K. S. Markley, "Fatty Acids," Part I, 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1960, p 122.

(3) J. D. Park, R. L. Settine, and G. W. Hedrick, *J. Org. Chem.*, **27**, 902 (1962).

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(5) H. B. Summers, G. W. Hedrick, F. C. Magne, and R. Y. Mayne, *ibid.*, **51**, 549 (1959).

(6) R. Mayne, unpublished results, 1961.

(7) Le-van Thoi, *Ann. Chim.* (Rome), **10**, 35 (1931).

(8) R. Trave, *Chim. Ital.*, **85**, 908 (1958).