The Anticonvulsant Activities of Some Substituted Acetonaphthones

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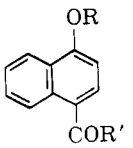
A series of 4-acyl-1-naphthoxy alcohols and ketones has been prepared and shown to possess activity as anticonvulsants. 1-(4-Acetyl-1-naphthoxy)-2-propanol is an effective anticonvulsant in mice and rats in doses far below the toxic level. A method is described for the preparation of 4-acetyl-1-naphthol on a large scale.

Baisse[2] has reported that the ketone, 1-ethoxy-4-hydroxyacetylnaphthalene sodium hemisuccinate (I, R = C_2H_5, R′ = CH_2OH) possessed anesthetic activity comparable to that of 21-hydroxypregnane-3,20-dione sodium succinate (hydroxydione).[3] In the course of a search for an anesthetic resembling hydroxydione in pharmacological activity[4] but possessing a nonsteroidal structure, we prepared a number of substituted acetophenones, naphthyl ketones, and a few ketonic ethers of eugenol and isoeugenol. Although little hypnotic activity was observed in these ketones, certain naphthyl members[5] displayed appreciable anticonvulsant properties.

As little systematic investigation of nonsteroidal ketones as anticonvulsants has been reported since the work of Merritt and Putnam,[6] a number of substituted naphthalenes, in particular naphthyl ethers bearing a carbonyl group in the aliphatic side chain (I, R = CH_2CO–alkyl, R′ = alkyl or aryl, *cf.* Table I), and the corresponding secondary alcohols (I, R = CH_2CHOH-alkyl, R′ = alkyl or aryl, *cf.* Table II), were therefore examined for anticonvulsant activity.



I

The naphthols required for the present investigation were, in general, prepared as described in the literature. Properties of those which have not been described previously are given in the Experimental section. The large quantity of 4-acetyl-1-naphthol required for this work was obtained conveniently by the acylation of 1-naphthol with acetic acid below 25° using boron trifluoride as catalyst.[7] The material so obtained comprised 2-acetyl- (4–10%) and 4-acetyl-1-naphthol (90–96%). The less acidic 2-acetyl isomer[8] could be separated by fractional precipitation at pH 9.2. The mixture of naphthols could, however, be used directly for the preparation of 1-(4-acetyl-1-naphthoxy)-2-propanol (see below). We found that the acylation of 1-naphthol with propionic acid and boron trifluoride, under the same conditions, gave a mixture of 2-propionyl- (*ca.* 60%) and 4-propionyl-1-naphthol (*ca.* 40%). The formation of a greater proportion of the 2-acyl isomer with propionic rather than with acetic acid is of interest, as Buu-Hoï and Seailles[9] report the formation of 2-acyl-1-naphthols, at 65–85° using boron trifluoride with propionic acid or long-chain alkyl carboxylic acids. Fawaz and Fieser[10] also obtained the 2-acyl isomers with long-chain alkyl carboxylic acids and boron trifluoride etherate at 100°.

Most of the naphthoxy ketones were prepared by heating the appropriate naphthol and halo ketone in acetone with potassium carbonate and potassium iodide.[11] Some other aliphatic halides, *e.g.*, propargyl bromide and 4-chloro-2-butanol, were reacted in a similar manner.

In many cases the reaction of naphthols with epoxides using alkali as catalyst gave only moderate yields of naphthoxy alcohols. Further, naphthols sensitive to strong base would not react under these conditions. The 4-acyl-1-naphthols were, however, sufficiently acidic to react with the appropriate epoxides using sodium acetate as catalyst, and by this procedure the naphthoxy alcohols were obtained in excellent yield. An added advantage of using sodium acetate was that pure 1-(4-acetyl-1-naphthoxy)-2-propanol could be prepared directly from the mixture of 2- and 4-acetyl-1-naphthols mentioned above, since 2-acetyl-1-naphthol was not sufficiently acidic to react under these conditions. Other catalysts such as potassium bicarbonate, sodium formate, and sodium benzoate were used in special cases (see Experimental section).

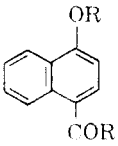
In some cases it was more convenient to obtain the naphthoxy alcohol by reduction of the naphthoxy ketone, or the latter by oxidation of the former. These methods also confirmed the direction of opening of the epoxides.

Testing for Anticonvulsant Activity.—Male albino mice (17–22 g.) were used after being deprived of food overnight. The compounds tested were administered orally 0.5–2.0 hr. before the convulsant, the optimum time for protection being 0.5–1.0 hr. for secondary alcohols and 2 hr. for ketones. In the early experiments arachis oil served as the vehicle for administration, but for most of the work described here mucilage

(1) To whom inquiries should be addressed.
(2) J. Baisse, *Compt. rend.*, **245**, 755 (1957).
(3) Viadril®.
(4) S. K. Fidor, M. S. Kodet, B. M. Bloom, E. J. Angello, S. Y. P'an, and G. D. Laubach, *J. Pharmacol. Exptl. Therap.*, **119**, 299 (1957); F. J. Murphy, N. P. Quadagni, and F. DeBon, *J. Am. Med. Assoc.*, **168**, 1412 (1955).
(5) *Cf.* W. H. Hunter, R. J. Boscott, P. H. Sherman, and C. R. Worthing, British Patent Application, 12334/60, 24505/60, and 34590/60; U. S. Patent 3,078,286.
(6) H. H. Merritt and T. J. Putnam, *Arch. Neurol. Psychiat.*, **39**, 1003 (1938); T. J. Putnam and H. H. Merritt, *ibid.*, **45**, 505 (1941).
(7) *Cf.* A. V. Topchiev, S. V. Zavgorodnii, and Y. M. Paushkin, "Boron Trifluoride and its Compounds as Catalysts in Organic Chemistry," Pergamon Press Limited, London, 1959, p. 298; K. Kindler, H. Oelschläger, and P. Henrich, *Arch. Pharm.*, **287**, 210 (1954).
(8) T. Bisanz and B. Dybowska [*Roczniki Chem.*, **33**, 975 (1959)] report 10.3 and 8.4 as the p*K* values of 2- and 4-acetyl-1-naphthol in 48% v./v. ethanol, respectively.
(9) N. G. Buu-Hoï and J. Seailles, *J. Org. Chem.*, **20**, 606 (1955).
(10) G. Fawaz and L. F. Fieser, *J. Am. Chem. Soc.*, **72**, 996 (1950).
(11) C. D. Hurd and P. Perletz, *ibid.*, **68**, 38 (1946).

TABLE I

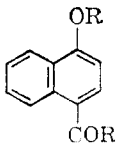
4-ACYL 1-NAPHTHOXY KETONES



Compound no.	R	R'	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	M.p., °C.	Relative potency against strychnine; compound 16 = 1.0	LD_{50}, g./kg.	Approximate therapeutic index
1	CH_2COMe	Me	$C_{15}H_{14}O_3$	74.4	74.2	5.83	5.82	123–124	0.75	>10.2	>28
2	CH_2COEt	Me	$C_{16}H_{16}O_3$	75.0	75.2	6.29	6.31	111–112	0.75	9.5	26
3	$CHMeCOMe$	Me	$C_{16}H_{16}O_3$	75.0	75.2	6.29	6.33	94	<0.10	>10.2	
4	CH_2COPr-*n*	Me	$C_{17}H_{18}O_3$	75.5	76.2	6.71	6.67	84	0.47	7.3	13
5	$CHMeCOEt$	Me	$C_{17}H_{18}O_3$	75.5	75.7	6 71	6.62	97	<0 10	10 2	
6	CH_2COCMe_3	Me	$C_{18}H_{20}O_3$	76.0	76.2	7.09	7.09	130	0.11	>10.2	>4.2
7	$-CH(CH_2)_4CO-$	Me	$C_{18}H_{18}O_3$	76.6	76.8	6.43	6.45	153	<0.10	>10.2	
8	$CH_2CO(CH_2)_3Me$	Me	$C_{18}H_{20}O_3$	76.0	76.1	7.09	7.14	63	0.16	10.2	6.0
9	$CH_2CO(CH_2)_5Me$	Me	$C_{20}H_{24}O_3$	76.9	77.1	7.74	7.74	68	<0.10	>10.2	
10	CH_2COPh	Me	$C_{20}H_{16}O_3$	78.9	79.0	5.30	5.28	145.5	<0.10	>10.2	
11	CH_2COMe	Et	$C_{16}H_{16}O_3$	75.0	75.3	6.29	6.32	102	0.40	10.2	15
12	CH_2COEt	Ph	$C_{21}H_{18}O_3$	79.2	79.2	5.70	5.59	75	<0.10	>10.2	
13	CH_2COEt	CH_2OMe	$C_{17}H_{18}O_4$	71.3	71.4	6.34	6.39	75	1.10	4.6	19
14	CH_2COMe	Me(2-Cl)	$C_{15}H_{13}ClO_3$	65.1	65.4	4.77	4.87	68	<0.10	6.9	

TABLE II

ACYL-1-NAPHTHOXY ALCOHOLS



Compound no.	R	R'	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	M.p., °C.	Relative potency against strychnine; compound 16 = 1	LD_{50}, g./kg.	Approximate therapeutic index
15	CH_2CH_2OH	Me	$C_{14}H_{14}O_3$	73.0	73.0	6.13	6.05	113	2.0	10.2	75
16	$CH_2CH(OH)Me$	Me	$C_{15}H_{16}O_3$	73.7	73.8	6.60	6.73	116	1.0	9.3	34
17	$CH_2CH(OH)Et$	Me	$C_{17}H_{18}O_3$	75.5	75.1	6.71	6.84	88–89	1.0	3.0	11
18	$(CH_2)_2CH(OH)Me$	Me	$C_{15}H_{18}O_3$	74.4	74.7	7.02	7.18	87	0.26	2.1	2.0
19	$CH_2C{\equiv}CCH_2OH$	Me	$C_{16}H_{14}O_3$	75.6	75.7	5.55	5.54	106	0.43	1.6	2.6
20	$CH_2CH(OH)CH_2(OH)$	Me	$C_{15}H_{16}O_4$	69.2	69.3	6.20	6.31	110	0.25	4.7	4.4
21	$CH_2CH(OH)CH_2OPr$-*i*	Me	$C_{18}H_{22}O_4$	71.5	71.5	7.33	7.25	93	0.49	5.1	9.3
22	$CH_2C{\equiv}CH$	Me	$C_{15}H_{12}O_2$	80.3	80.5	5.39	5.41	112	0.13	>10.2	>4.9
23	$CH_2CH(OH)Me$	Et	$C_{16}H_{18}O_3$	74.4	75.0	7.02	7.02	98	0.34	>10.2	>13
24	$CH_2CH(OH)Me$	CH_2OH	$C_{15}H_{16}O_4$	69.2	69.1	6.20	5.97	144	0.73	6.9	19
25	$CH_2CH(OH)Me$	CH_2OMe	$C_{16}H_{18}O_4$	70.0	70.0	6.61	6.39	91	2.1	4.2	33
26	$CH_2CH(OH)Me$	CH_2OEt	$C_{17}H_{20}O_4$	70.8	70.8	6.99	6.95	82	1.3	5.1	25
27	$CH_2CH(OH)Me$	CH_2OPr-*n*	$C_{18}H_{22}O_4$	71.5	71.4	7.33	7.31	76	1.1		
28	$CH_2CH(OH)Me$	CH_2OBu-*n*	$C_{19}H_{24}O_4$	72.1	72.3	7.65	7.62	81	0.83	>10.2	>31
29	$CH_2CH(OH)Me$	CH_2OAc	$C_{17}H_{18}O_5$	67.5	67.9	6.00	6.02	122	1.1	>5.1	>21
30	$CH_2OH(OH)Me$	CH_2Cl	$C_{15}H_{15}ClO_3$	64.6	64.6	5.39	5.44	142	<0.10	>2.6	
31	Et	$(CH_2)_2COMe$	$C_{17}H_{18}O_3$	75.5	75.8	6.71	6.72	80	<0.20	3.3	
32	$CH_2CH(OH)Me$	H	$C_{14}H_{14}O_3$	73.0	73.1	6.13	5.99	113	0.69		

of tragacanth was used. Because of the low solubility of most of the compounds tested, care was taken to reduce the solids to a uniform state of comminution in order to minimize variations in potency for a given compound. The challenging doses of the convulsants, strychnine sulfate (1.9–2.2 mg./kg.) and pentylenetetrazole (90–110 mg./kg.), were administered intraperitoneally. The exact dose used in any test was adjusted to give 90–95% mortality in controls taken from the same bath of mice under test. Figures for protection against convulsants afforded by the compounds under test are based upon mortality figures assessed 24 hr. after challenge.

Certain compounds were also investigated for anticonvulsant activity in male albino rats (150–250 g.). Strychnine sulfate (3.5 mg./kg., i.p.) or pentylenetetrazole (90 mg./kg., i.p.) was used as the convulsant. Some of the compounds were also examined for their

TABLE III

OTHER NAPHTHALENE DERIVATIVES

Compound no.	1st substituent	Other substituents	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	M.p., °C.	Relative potency against strychnine; compound 16 = 1.0	LD_{50}, g./kg.	Approximate therapeutic index
33	1-OCH_2COMe		$C_{13}H_{12}O_2$	78.0	78.2	6.04	6.04	37[a]	0.27	4.5	4.5
34	2-OCH_2COMe		$C_{13}H_{12}O_2$	78.0	78.4	6.04	6.09	78[b]	<0.10	2.9	
35	1-OCH_2COMe	5,6,7,8-Tetrahydro	$C_{13}H_{16}O_2$	76.4	76.4	7.90	7.85	42	0.15	2.7	1.5
36	2-OCH_2COMe	5,6,7,8-Tetrahydro	$C_{13}H_{16}O_2$	76.4	76.4	7.90	7.77	36[c]	0.30	3.7	4.1
37	1-OCH_2COEt		$C_{14}H_{14}O_2$	78.5	78.6	6.59	6.70	[d]	0.10	4.5	1.7
38	1-$OCH(CH_2)_4CO$		$C_{16}H_{16}O_2$	80.0	79.9	6.71	6.79	90	<0.10	10.2	
39	2-OCH_2COPh	5,6,7,8-Tetrahydro	$C_{18}H_{18}O_2$	81.2	81.7	6.81	6.85	79–80	0.10	>10.2	>3.8
40	2-OCH_2COMe	6-COMe	$C_{15}H_{14}O_3$	74.3	74.1	5.83	5.83	135	<0.10	5.4	
41	1-OCH_2COMe	4-Cl	$C_{13}H_{11}ClO_2$	66.6	67.1	4.69	4.66	82	<0.10	7.3	
42	1-OCH_2COMe	2-Cl	$C_{13}H_{11}ClO_2$	66.6	66.8	4.69	4.88	[e]	<0.10	5.4	
43	1-OCH_2COMe	2-OMe	$C_{14}H_{14}O_3$	73.0	73.1	6.13	6.23	33[f]	<0.10	3.5	
44	1-OCH_2COMe	2-COEt	$C_{16}H_{16}O_3$	75.0	75.3	6.29	6.24	[g]	<0.10	4.9	
45	1-$OCH_2CH(OH)Me$		$C_{13}H_{14}O_2$	77.2	77.4	6.93	6.82	64–65[h]	0.30	>10.2	>11
46	1-$OCH_2CH(OH)CH_2(OH)$		$C_{13}H_{14}O_3$	71.5	71.5	6.47	6.39	98[i]	0.30	6.9	7.7
47	1-$OCH_2C{\equiv}CH$		$C_{13}H_{10}O$	85.7	85.9	5.53	5.57	[j]	0.10	3.5	1.3
48	1-$OCH_2CH(OH)Me$	4-$OCH_2CH(OH)Me$	$C_{16}H_{26}O_4$	69.6	70.3	7.30	7.19	108	0.33	5.0	6.1
49	1-CH_2CH_2COMe		$C_{14}H_{14}O$	84.8	84.8	7.12	7.20	[k]	<0.14	4.2	

[a] Described as an oil by R. Stoermer [*Ann.*, **312,** 311 (1900)]. [b] Ref. 11 and footnote *a* give m.p. 75–77°, 78°. [c] S. Sabetay [*Bull. soc. chim. France*, **45,** 534 (1929)] gives m.p. 37.5°. [d] Oil, b.p. 122° (0.1 mm.), $n^{26}D$ 1.5903. [e] Oil, b.p. 112° (0.05 mm.), $n^{25}D$ 1.6008. [f] Initially obtained as an oil, b.p. 140° (0.4 mm.), $n^{16}D$ 1.5995. [g] Oil, b.p. 140° (0.1 mm.), $n^{25}D$ 1.5978. [h] M.p. 59–63°: J. F. Kerwin, G. C. Hall, F. J. Milnes, I. H. Witt, R. A. McLean, E. J. Fellows, and G. E. Ullyot, *J. Am. Chem. Soc.*, **73,** 4162 (1951); D. R. Boyd and E. R. Marle, *J. Chem. Soc.*, **105,** 2135 (1914). [i] M.p. 99–100°: British Drug Houses, Ltd., W. Bradley and J. Forrest, British Patent 628,497; F. M. Berger, *J. Pharmacol. Exptl. Therap.*, **93,** 470 (1948); E. Bua and E. Tibaldi, *Farm. sci. e tec.* (Pavia), **6,** 448 (1951); T. Kariyone, H. Yamada, M. Takahashi, T. Omiya, K. Okamoto, and Y. Kashihara, *J. Pharm. Soc. Japan*, **72,** 1545 (1952); and T. Omiya, *Folia Pharmacol. Japan*, **49,** 159 (1953). [j] Oil, b.p. 100° (0.2 mm.), $n^{15}D$ 1.6243. [k] Oil, b.p. 120° (0.4 mm.), $n^{13}D$ 1.6008; lit. [F. Mayer and A. Siegeitz, *Ber.*, **55,** 1835 (1922)] b.p. 186–187° (12 mm.).

ability to prevent hind-leg extensor spasm to maximum electroshock (100–140 v., 48 c./sec., 10 msec. pulse, 1 sec. duration) in female albino rats (150–250 g.)

A few selected compounds were tested for their blockade of the flexor, crossed extensor, or linguomandibular reflexes in cats under chloralose (80 mg./kg., i.p.), or for their relaxation of the muscular rigidity in cats in which precollicular decerebration had been performed under nitrous oxide–halothane anesthesia.

Pharmacological Results. A. Protection against Strychnine in Mice.—The activities of compounds tested in mice for their protection against the toxicity caused by strychnine are given in Tables I–III in terms of the relative potency values derived from ED_{50} figures. The potency of 1-(4-acetyl-1-naphthoxy)-2-propanol (compound **16**), was taken as 1.0. Therapeutic indices (LD_{50}/ED_{50}) for protection against strychnine are also given.

Data for various compounds known to possess anticonvulsant activity and those for **16** are compared in Table IV. It is evident that the therapeutic index for compound **16** in mice is much more favorable than for any of the other anticonvulsants tested.

B. Anticonvulsant Activity in Rats.—Anticonvulsant data for 2-methyl-2-propylpropane-1,3-diol dicarbamate (meprobamate), phenobarbital sodium, 2-(4-chloro phenyl)-3-methyl-1,2,3,4-tetrahydro-1,3-thiazin-4-one 1,1-dioxide (chlormethazanone),[12] and **16** are presented in Table V; also shown are the activities against pentylenetetrazole and electroshock extensor spasm together with the corresponding therapeutic indices.

The therapeutic index (>190) of **16** for protection against strychnine toxicity is far greater than that of the other compounds with which it was compared. Compound **16** also displayed the highest therapeutic index for protection against electroshock extensor spasm. It was, however, less effective than chlormethazanone and meprobamate against pentylenetetrazole toxicity.

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TABLE IV

PROTECTIVE ACTION AGAINST STRYCHNINE TOXICITY OF VARIOUS ANTICONVULSANTS, ADMINISTERED ORALLY, IN MICE

Compound	ED_{50} for antistrychnine activity, g./kg.	LD_{50}, g./kg.	Approximate therapeutic index, LD_{50}/ED_{50}
Meprobamate	0.38	1.77	5
Mephenesin[a]	0.47	1.58	3
Phenobarbitone Na	0.058	0.180	3
Chlormethazanone	0.27	1.35	5
Methocarbamol[b]	0.54	4.20	8
Chlorethiazole[c]	0.38	2.11	6
Styramate[d]	0.21	1.25	6
Carisoprodol[e]	>0.58	4.61	<8
Compound 16	0.27	9.30	34

[a] 3-*o*-Toloxypropane-1,2-diol. [b] 3-(*o*-Methoxyphenoxy)propane-1,2-diol 1-carbamate. [c] 5-(2-Chloroethyl)-4-methylthiazole. [d] 2-Hydroxy-2-phenylethyl carbamate. [e] *N*-Isopropyl-2-methyl-2-propylpropane-1,3-diol dicarbamate.

C. Duration of the Anticonvulsant Effect in Rats.—In mice, few compounds were found to give protection against convulsants for longer than 5 hr., although at the high dose of 2 g./kg. of **16** provided 40% protection against strychnine when the mice were challenged 24 hr. after dosage. In rats several of the potent naphthoxy ketones and alcohols showed long lasting anticonvulsant activity. Compound **2,** for instance, at a dose of 1125 mg./kg. (one-eighth of its LD_{50}) still gave 50% protection against strychnine 60 hr. after dosage; after 96 hr., protection was no longer significant. Compound **16**, which was examined in most detail, showed a similarly long duration of effect; the protective action of a dose of 270 mg./kg. ($^1/_{25}$th of its LD_{50}) decreased

TABLE V

PROTECTIVE ACTION OF VARIOUS ANTICONVULSANTS AGAINST STRYCHNINE AND PENTYLENETETRAZOLE TOXICITY AND ELECTROSHOCK EXTENSOR SPASM IN RATS

Durations of action are maximum times for just significant protection ($P < 5\%$). Unless otherwise stated, the ED_{50} values are based on activity 1 hr. after administration.

			Protection against strychnine				Protection against pentylenetetrazole				Protection against electroshock extensor spasm			
Compound	Route	LD_{50}, mg./kg.	ED_{50}, mg./kg.	Therapeutic index	Duration—Hr.	Duration—Dose, mg./kg.	ED_{50}, mg./kg.	Therapeutic index	Duration—Hr.	Duration—Dose, mg./kg.	ED_{50}, mg./kg.	Therapeutic index	Duration—Hr.	Duration—Dose, mg./kg.
Meprobamate	p.o.	1600	>800	<2	4	460	41	39	<8	64	49	33		
Phenobarbitone Na	p.o.	210[a]	20	10.5			11	19	40	25	6.5	32	48	25
Chlormethazanone	p.o.	1450	20[b]	73	48	54	21	69			44	33		
Compound 16	p.o.	>7500	40	>190	80	270	270	>28	16	270	140	>53	32	270
Compound 16	i.p.	1000	220[c]	4.5	96	40	80	12.5	40	40	30	33	32	40

[a] R. W. Schaffarzick [*Science*, **116**, 663 (1952)] gives the oral LD_{50} as 660 mg./kg. [b] Tested at optimum time = 24 hr. after administration. [c] Tested at optimum time = 64 hr. after administration.

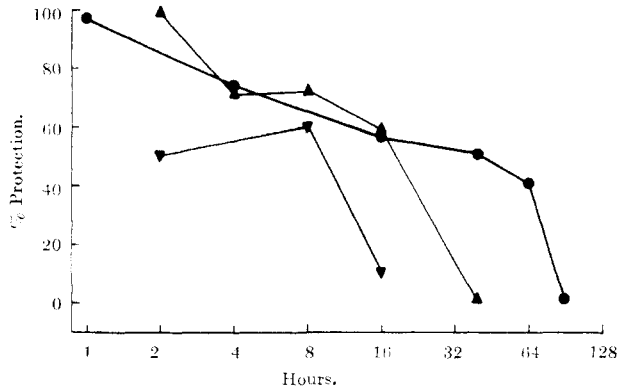

Fig. 1.—Time-course of the protective action of compound 16 (270 mg./kg.) against strychnine toxicity (●——●), pentylenetetrazole toxicity (▼——▼), and maximum electroshock extensor spasm (▲——▲), after oral administration to rats.

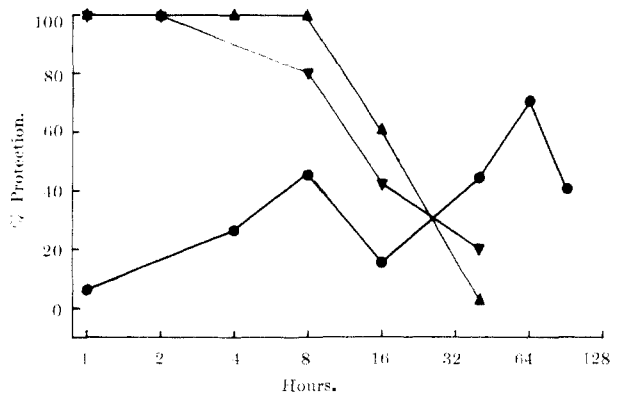

Fig. 2.—Time-course of anticonvulsant action of compound 16 (270 mg./kg.) after intraperitoneal administration to rats. For key, see Fig. 1.

gradually from nearly 100% after 1 hr. to 40% after 64 hr., followed by a further fall to zero 96 hr. after administration (see Fig. 1). The protection afforded by this dose against pentylenetetrazole toxicity and electroshock extensor spasm was somewhat shorter in duration. The long lasting effect would appear to be due at least partly to slow absorption of the compound (or an active metabolite)[13] from the alimentary tract of rats, since 36% of the administered dose could be detected[14] in the stomach and intestines at 24 hr., and 14% at 48 hr. after dosage.

The duration of the protective effect of chlormethazanone was determined against strychnine, and of phenobarbitone against pentylenetetrazole and maximum electroshock. At the doses used, which were two to four times the ED_{50} levels, the effects lasted 40–48 hr. Meprobamate gave only weak protection to rats against strychnine toxicity, even at a dose of half of its LD_{50}. However, it displayed stronger anticonvulsant action against pentylenetetrazole.

Chlormethazanone displayed an unexpected latency of effect against strychnine but not against pentylenetetrazole or electroshock. Its maximum protective effect against strychnine occurred 24 hr. after oral administration. A somewhat similar time-course was displayed by **16** after intraperitoneal, but not after oral, administration (see Fig. 2). No protection was afforded against strychnine challenge 1 hr. after injection. The protective action developed slowly, reached a maximum at 64 hr., and was still just significant 96 hr. after administration. On comparison of its activity by oral and intraperitoneal routes, it was found that when the activity was assessed at the times of maximum effect (1 and 64 hr., respectively), **16** was considerably more potent by the former than by the latter route of administration.

On the other hand, intraperitoneal administration considerably enhanced the muscle relaxant activity of **16**; a dose of 270 mg./kg., which by the oral route caused only slight symptoms of muscle weakness, on intraperitoneal injection produced prostration and muscle flaccidity. The activities against pentamethylenetetrazole and electroshock were correspondingly increased by this route, but the time courses of these protective effects were similar to those after oral administration, optimum activity occurring 1 hr. after administration.

D. The Activities of Analogs of Compound 16 in Rats.—In rats, as in mice, compounds possessing hydroxy or alkoxy substituents on the acetyl grouping of **16** displayed potency superior to that of the parent compound in protecting against strychnine toxicity. Relative potencies were: methoxy (**25**) > ethoxy (**26**) > *n*-propoxy (**27**) > hydrogen (**16**) > *n*-butoxy (**28**) > hydroxy-substituted (**24**). The relative potencies against electroshock extensor spasm showed a similar structure-activity relationship. The acute toxicities of these compounds ran in parallel with their anticonvulsant properties, however, so that the therapeutic in-

(13) The only metabolite of **16** identified with certainty was 4-acetyl-1-naphthol (obtained after hydrolysis of the urine with hydrochloric acid under conditions which did not affect **16** itself), which was inactive as a strychnine antagonist.

(14) Determination on the basis of the presence in the molecule of a Zimmermann-reactive keto group [N. H. Callow, R. K. Callow, and C. W. Emmens, *Biochem. J.*, **32**, 1312 (1938)].

dexes were not significantly superior to that of **16**. It was noticeable that the methoxy- and ethoxyacetyl derivatives (**25**, **26**) displayed greater sedative and muscle relaxant properties than their higher anticonvulsant potencies indicated.

In rats, the alkoxyacetyl derivatives did not, however, bestow such long-lasting protection against strychnine as did **16**. For instance, the methoxyacetyl compound (**25**) was less active than **16** when the animals were challenged with strychnine 40 hr. after oral dosage (270 mg./kg.), even though 1 hr. after administration the former was found to be appreciably more potent than **16**.

E. The Effects on Polysynaptic Spinal Reflexes in Anesthetized Cats.—In chloralosed cats, the activity of the soluble hemisuccinate ester of **16** in blocking polysynaptic spinal reflexes was compared with that of mephenesin. For significant reduction of the flexor reflex, the minimum effective intravenous dose of the ester was about 30 mg./kg.; that for mephenesin was 10–15 mg./kg. Comparable doses for the crossed extensor reflex were 10 and 5 mg./kg., respectively. Blockade of the linguo-mandibular reflex was observed at roughly the same dose levels. On a molecular basis, therefore, the hemisuccinate ester of **16** displayed a potency approximately equal to that of mephenesin in depressing polysynaptic spinal reflexes. Both mephenesin and the ester were more effective in blocking spinal reflexes involving many synapses (such as the crossed extensor and linguo-mandibular reflexes) than those of a shorter pathway (*e.g.*, the flexor reflex).

Doses of 40–80 mg./kg. of the hemisuccinate ester of **16** produced slight relaxation of the rigidity in decerebrate cats; the hemisuccinate ester of the corresponding methoxy derivative (**25**) was more active in this respect.

Intragastric doses of up to 500 mg./kg. of **16** itself did not relax decerebrate rigidity within 3 hr. of administration.

F. Miscellaneous Pharmacological Effects.—In general, oral administration of the naphthoxy ketones and alcohols in mice produced minimum symptoms at doses below 1–2 g./kg. Higher doses caused varying degrees of decreased motor activity, ataxia, muscle weakness, and prostration. Outstanding exceptions were the tetrahydro compounds (**36, 39**) which produced hyperactivity with hyperthemia, and **3**, **14**, and **44** which caused either myoclonus or convulsions. Compounds which possessed high anticonvulsant potency (*e.g.*, **15–17**, **24**, **25**, **29**) usually displayed some muscle relaxation in mice at dose levels of 20–100 mg./kg. The series was generally notable for the low toxicity and incidence of few gross symptomological effects displayed by its members; some compounds (*e.g.*, **1**, **5**, and **10**) produced virtually no observable biological effect at doses of 5–10 g./kg.

Discussion

In an examination of various naphthoxy ketones for anticonvulsant action, 4-acetyl-1-naphthoxyacetone (**1**) was found to possess a high therapeutic index in mice.

The preparation of a number of 1-naphthoxyacetones (Table III) lacking the acyl group in the 4-position gave a series of compounds that were less active and of greater toxicity than **1**. Thus 1-naphthoxyacetone (**33**) displayed only feeble anticonvulsant properties when tested against strychnine toxicity in mice. The activity was decreased on lengthening the ketone chain (**37**, **38**), by nuclear substituents such as chlorine or methoxyl (**41–43**), by reduction to the corresponding tetrahydro derivative (**35**), by change of position of the ethereal linkage (**34**), or by replacement of the ethereal oxygen atom by a methylene group (**49**). The related (1-naphthoxy)-2-propanol (**45**) proved to be little, if any, more active than the ketone (**33**), but was considerably less toxic to mice. Further substitution of a hydroxyl group to give the mephenesin analog (**46**), previously reported (Table III, footnote *i*) as a muscle relaxant, led to no increase in anticonvulsant activity.

In view of the promise shown by 4-acetyl-1-naphthoxyacetone (**1**) and 1-(4-acetyl-1-naphthoxy)-2-propanol (**16**) as anticonvulsants in mice, these two compounds formed the basis for further studies. The optimum position for the acyl group was on position 4 of the naphthalene nucleus, as was shown by the low activity of the other isomers (**40**, **44**, and the 2-acetyl analogs, not reported here). We therefore attempted to define the optimal structures to form the ether chain in position 1 and the acyl group in position 4 of the naphthalene nucleus.

In the series of ketonic ethers (Table I) lengthening of the ketone from acetone (**1**) to butanone (**2**) gave little loss in anticonvulsant properties, but further increase up to the octanone (**9**) was accompanied by a progressive decline in activity. Similarly, branch chain or cyclic ketonic ether analogs of **1** exhibited little or no activity (**3**, **5–7**).

In the series of compounds derived from 1-(4-acetyl-1-naphthoxy)-2-propanol (**16**) alteration of the propanol side chain was not examined in any great detail. The corresponding ethanol (**15**) was very active and of low toxicity, but lengthening the chain to give the butanol (**18**) resulted in a more toxic, less active compound and indicated that the optimum distance between the oxygen functions was two methylene groups, since the isomeric butanol (**17**) that satisfied this requirement was equal to **16** in potency, though more toxic. The introduction of an acetylenic function in the side chain led only to loss of activity (**19**, **22**).

We thus established that for anticonvulsant activity, an unbranched alkoxy group with two to four carbon atoms carrying an alcoholic or ketonic oxygen function on the carbon atom β to the ether linkage was required in position 1 of the naphthalene nucleus. Further addition of hydroxyl or ether groups lowered activity (**20**, **21**), as did omission of the alcoholic grouping (**22** and also 1-ethoxy-4-acetonaphthone, not reported).

We chose the 2-hydroxypropoxy side chain of **16** as the basic structure from which to examine the effects of variation in the 4-acyl substituent. The replacement of acetyl by propionyl (**23**) led to a considerable loss in activity, and further derivatives based on 4-benzoyl-1-naphthol were completely inactive. The high activity of **16** in rats against strychnine challenge and extensor spasm induced by maximum electroshock was retained on increasing the length of the alkoxy group, up to *n*-butoxy, in the 1-(4-alkoxyacetyl-1-napthoxy)-2-propanols (**25–28**). The methoxy- and ethoxyacetyl derivatives (**25**, **26**) were more potent than **16** in these tests and displayed, furthermore, appreciable

muscle relaxant properties. Unfortunately their toxicities increased in parallel to their anticonvulsant activities.

The magnitude of the therapeutic index of **16** in mice and rats was no doubt partly attributable to its low toxicity, to which slowness of absorption from the alimentary tract contributed to some extent. For instance, 2 hr. after an oral dose (560 mg./kg.) 86% of the compound could still be detected[14] in the stomach and intestines of rats, although within 1 hr. of dosing the animals were fully protected against strychnine toxicity. Whether **16** is active *per se* or as a result of metabolic conversion, the active entity is clearly a potent anticonvulsant in rats. In limited metabolic studies 4-acetyl-1-naphthol was isolated[13] from the urine of dogs, rats, and humans receiving **16**.

Possible support for some metabolic conversion of **16** into an active form as an anticonvulsant agent against strychnine was given by the finding that optimum activity against strychnine, but not against pentylenetetrazole or electroshock, occurred some 64 hr. after intraperitoneal injection in rats (but not mice). A somewhat similar latency of antistrychnine action was displayed by chlormethazanone after oral injection in rats; as with **16** administered intraperitoneally, the effects against pentylenetetrazole and electroshock did not show this latency. In the case of chlormethazanone this effect could be attributed to the slow penetration to the site of strychnine action, though there is no evidence for such a hypothesis. This argument could not be advanced in the case of **16** administered intraperitoneally, however, since this compound showed no delay in onset of antistrychnine activity after oral dosage.

It is possible that the delayed protection of rats against strychnine convulsions and toxicity afforded by **16** after intraperitoneal administration may arise not from a true anticonvulsant action but from some acceleration of detoxification of strychnine in the body. A similar delayed antagonism of the pharmacological actions of strychnine by 2-(*p*-chlorophenyl)-3-methyl-2,3-butanediol (phenaglycodol), meprobamate, carisoprodol, or phenobarbital,[15] and of a number of other agents by several drugs[16] has been reported. This aspect of the action of compound **16**, therefore, merits further study.

Whatever the mechanism of the delayed protective action against strychnine toxicity after intraperitoneal injection, however, it appears that **16** (or its metabolites) may give rise in the rat to two active forms. One form, which appears rapidly after oral but not after intraperitoneal injection, possesses high specificity for those nervous pathways (presumably in the spinal cord) on which strychnine acts. The other form, which could be the unchanged compound, since it appears to act almost immediately after either oral or intraperitoneal administration, may be responsible for the marked muscle relaxation, sedation, and central depression (which are seen particularly after intraperitoneal injection), and for the protection against pentylenetetrazole and electroshock. This form of **16** may be considered to be acting less specifically and at higher levels of the central nervous system. Indeed, intravenous injections of the hemisuccinate ester of **16** produced effective anesthesia in rabbits.

The desmethyl compound (**15**), which was a more potent strychnine antagonist than **16** in rats and mice when administered orally, failed to show any protection against strychnine at 1, 18, or 70 hr. after intraperitoneal injection. No other members of the series were tested for this dichotomy of anticonvulsant action after intraperitoneal injection.

There is some evidence that the specific antistrychnine acting form of **16** occurs in dogs as well as in rats. Beagle dogs which had been given daily oral doses of 250–1000 mg./kg. of **16** for 3 months showed complete protection against strychnine toxicity at 1 hr. and appreciable protection at 20 hr. after their last dose.

In man, **16** or its hemisuccinate, administered orally or intravenously, respectively, could not be shown to be effective in preventing or reducing epileptic attacks nor in relieving various conditions of muscular spasticity.

Experimental[17]

2-Bromo-3-pentanone[18] and 4-chloro-2-butanol[19] was prepared by published methods. The higher alkylchloromethyl ketones were prepared by the action of the appropriate alkyl cadmium on chloroacetyl chloride according to the method of Bunnett and Tarbell.[20] The following 1-naphthols were prepared as described in the literature: 4-benzoyl,[21] 4-chloroacetyl,[22] 2-chloro,[23] 4-chloro,[24] and formyl.[25] 6-Acetyl-2-naphthol was prepared in 50% yield by the acetylation of 2-naphthol-1-sulfonic acid using acetyl chloride and aluminum chloride[26]; and 5,6,7,8-tetrahydro-2-naphthol as described by Gutsche and Peter.[27]

2- and 4-Acetyl-1-naphthol.—Boron trifluoride was passed into a stirred suspension of 1-naphthol (600 g.) in acetic acid (600 g.) maintained at 10–20°. Passage of the gas was continued until the mixture was saturated at a final temperature of 0–5°. The reaction mixture changed during this time to a viscous orange gum, which gradually set to a bright yellow solid when allowed to stand overnight at room temperature. The solid was introduced into a well stirred solution of 5% sodium acetate (12 l.), and when adequately dispersed, the product was filtered off and washed with water to give a mixture of 2- and 4-acetyl-1-naphthol as a bright yellow solid (750 g.) which could be used directly for the preparation of 1-(4-acetyl-1-naphthoxy)-2-propanol. The solid was dissolved with stirring in aqueous 3% potassium hydroxide (20 l.), and the pH adjusted to 9.2 with 50% acetic acid. The solid that precipitated was filtered and found to be almost pure 2-acetyl-1-naphthol (30 g., 3.9% based on 1-naphthol), m.p. 98° (lit.[28] m.p. 98°). The filtrate was acidified with concentrated hydrochloric acid, the precipitated solid was filtered, washed free of acid, and dried at 60° *in vacuo*, yield 700 g., m.p. 195–196°. This material was refluxed for 1 hr. with benzene (3 l.), and the mixture was cooled and filtered to give 4-acetyl-1-naphthol (620 g., 80% based on 1-naphthol), m.p. 197° (lit.[28] m.p. 198°).

2- and 4-Propionyl-1-naphthol.—The acylation of 1-naphthol

(15) R. Kato, *Arzneimittel-Forsch.*, **11**, 797 (1961); R. Kato, E. Chiesara, and P. Vassanetti, *Biochem. Pharmacol.*, **11**, 913 (1962).

(16) H. Remmer, *Arch. Exptl. Pathol. Pharmakol.*, **235**, 279 (1959); R. Kato, *Experientia*, **16**, 427 (1960); A. H. Conney, C. Davison, R. Gastel, and J. J. Burns, *J. Pharmacol. Exptl. Therap.*, **130**, 1 (1960).

(17) Melting points were determined in open capillaries using an electrically heated block and are uncorrected.

(18) A. Pauly, *Ber.*, **34**, 1771 (1901).

(19) F. Sondheimer and R. B. Woodward, *J. Am. Chem. Soc.*, **75**, 5438 (1953).

(20) J. F. Bunnett and D. S. Tarbell, *ibid.*, **67**, 1944 (1945).

(21) R. D. Desai and R. M. Desai, *J. Sci. Ind. Res.* (India), **14B**, 498 (1955).

(22) J. Houben, *Ber.*, **59**, 2878 (1926); J. Houben and W. Fischer, *ibid.*, **60**, 1759 (1927).

(23) H. Franzen and G. Stäube, *J. prakt. Chem.*, **211**, 383 (1921).

(24) J. W. Airan and S. V. Shah, *J. Univ. Bombay*, **10** (Pt. 5), 131 (1942).

(25) R. Adams and I. Levine, *J. Am. Chem. Soc.*, **45**, 2373 (1923).

(26) Bayer Farbenfabriken A.G., British Patent 734,879.

(27) G. D. Gutsche and H. H. Peter, *Org. Syn.*, **37**, 80 (1957).

(28) H. Lederer, *J. prakt. Chem.*, **243**, 49 (1952).

with propionic acid and boron trifluoride using the above method gave a mixture of 2- and 4-propionyl-1-naphthols. The isomers were separated by extraction with a boiling mixture of carbon tetrachloride and benzene (1:1), in which the 4-propionyl isomer was insoluble, thus obtaining 2-propionyl-1-naphthol (20%), m.p. 85–87° (lit.[29] m.p. 85°), and 4-propionyl-1-naphthol (10%), m.p. 190° (lit.[30] m.p. 188°).

4-Acetoxyacetyl-1-naphthol.—A mixture of 4-chloroacetyl-1-naphthol (1.1 g.), acetic acid (3 g.), redistilled triethylamine (2.5 g.), sodium iodide (0.2 g.), and acetone (25 ml.) was refluxed for 17 hr. on a steam bath. The mixture was filtered, and the filtrate was evaporated on a steam bath. The residual oil when poured into water precipitated a solid (1 g.), m.p. 157–160°, which was crystallized from ethyl acetate to give 4-acetoxyacetyl-1-naphthol, m.p. 164–166°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.8; H, 4.95. Found: C, 69.0; H, 4.69.

4-Methoxyacetyl-1-naphthol.—The alkoxyacetonitriles required for this and related naphthols were conveniently prepared by heating the alkoxymethyl chlorides[31] with cuprous cyanide.[32] A mixture of methoxyacetonitrile (32.1 ml.), 1-naphthol (60.8 g.), zinc chloride (82.7 g.), and ether (140 ml.) was saturated with hydrogen chloride at 0° and was allowed to stand at this temperature overnight. The solid ketimine hydrochloride was filtered and hydrolyzed by heating with water (1 l.) for a few minutes, when 4-methoxyacetyl-1-naphthol crystallized. The solution was cooled, and the product was filtered, washed with water, and crystallized from ethanol to give the naphthol (55 g.), m.p. 184–186°.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.2; H, 6.13. Found: C, 72.2; H, 5.48.

The same procedure was used to prepare the following compounds.

4-Ethoxyacetyl-1-naphthol had m.p. 175–177°. *Anal.* Calcd. for $C_{14}H_{14}O_3$: C, 73.0; H, 6.13. Found: C, 73.2; H, 6.14.

4-*n*-Propoxyacetyl-1-naphthol had m.p. 156–158°. *Anal.* Calcd. for $C_{15}H_{16}O_3$: C, 73.8; H, 6.60. Found: C, 74.2; H, 6.59.

4-*n*-Butoxyacetyl-1-naphthol had m.p. 150–152°. *Anal.* Calcd. for $C_{16}H_{18}O_3$: C, 74.4; H, 7.02. Found: C, 74.3; H, 6.95.

4-Acetyl-2-chloro-1-naphthol. (**A**).—Powdered aluminum chloride (2 g.) was added to a stirred solution of 4-acetyl-1-naphthol (37.2 g.) in dioxane (800 ml.). Sulfuryl chloride (27 g.) was added over 5–10 min., the mixture was stirred at 25–30° for 2 hr. and then poured into water (2 l.). The precipitated solid was filtered, dried, and crystallized from benzene to give 4-acetyl-2-chloro-1-naphthol (31 g), m.p. 139–140°. Recrystallization from benzene gave the pure compound, m.p. 143–144°.

Anal. Calcd. for $C_{12}H_9ClO_2$: C, 65.3; H, 4.07; Cl, 16.1. Found: C, 65.0; H, 4.16; Cl, 16.02.

(**B**).—The acylation of 2-chloro-1-naphthol with acetic acid and boron trifluoride gave a 12% yield of 4-acetyl 2-chloro-1-naphthol, m.p. 141–142°.

2-Methoxy-1-naphthol, m.p. 54–56°, was prepared[33] in 77% yield by the general method reported by Hawthorne.[34]

The preparation of naphthoxy ketones from halo ketones and naphthols is best illustrated by the preparation of 4-acetyl-1-naphthoxyacetone.

4-Acetyl-1-naphthoxyacetone (**1**).—A mixture of 4-acetyl-1-naphthol (41 g., 0.22 mole), chloroacetone (28 g., 0.30 mole), anhydrous potassium carbonate (69 g., 0.50 mole), potassium iodide (4.5 g.), and acetone (250 ml.) was refluxed with vigorous stirring for 24 hr. About half of the acetone was removed by distillation, and the residue was poured into water (1 l.). Sodium hydroxide solution (20 ml., 20%) was added to dissolve any unchanged naphthol, and the brown solid was filtered and washed free of alkali to give the crude product (51 g.). This material was crystallized from acetone to give 4-acetyl-1-naphthoxyacetone in colorless needles (46 g.), m.p. 123–124°.

(29) R. D. Desai, A. Hamid, and H. P. Shroff, *Proc. Indian Acad. Sci. Sect. A.*, **13**, 33 (1941).

(30) R. D. Desai and A. Hamid, *ibid.*, **13**, 132 (1941).

(31) J. W. Farren, H. R. Fife, F. E. Clarke, and C. E. Garland, *J. Am. Chem. Soc.*, **47**, 2419 (1925).

(32) D. Gauthier, *Compt. rend.*, **143**, 831 (1906); C. D. Hurd and G. W. Fowler, *J. Am. Chem. Soc.*, **61**, 249 (1939).

(33) P. H. Sherman and C. R. Worthing, to be published.

(34) M. F. Hawthorne, *J. Org. Chem.*, **22**, 1001 (1957).

Hydration of Compound 47.—The catalyst[35] was prepared from red mercuric oxide (2.5 g.), boron trifluoride etherate (1 ml.), trichloroacetic acid (0.05 g.), and methanol (5 ml.). 1-(4-Acetyl-1-naphthoxy)-2-propyne (5 g.) in methanol (550 ml.) was added, the mixture was stirred vigorously for 20 hr. at room temperature and filtered, and the filtrate was evaporated *in vacuo* to 100 ml. and was poured into 2 *N* H_2SO_4 (200 ml.). The precipitate was filtered, washed with water, and crystallized twice from ethanol to give 4-acetyl-1-naphthoxyacetone (3.0 g.), m.p. 123–124° (not depressed on admixture with authentic material).

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.4; H, 5.83. Found: C, 74.2; H, 5.76.

1-(4-Acetyl-1-naphthoxy)-2-propanol (**16**).—A mixture of crude 4-acetyl-1-naphthol (177 g., containing 10% 2-acetyl-1-naphthol), sodium acetate (82 g.), and water (1 l.) was stirred at 55° while 1,2-epoxypropane (270 ml.) was added slowly so as to maintain gentle reflux. The temperature was raised to about 80° over a period of 4 hr. during which time a brown oil separated. The mixture was cooled, aqueous sodium hydroxide (300 ml., 10%) was added, and stirring was continued until the oil solidified. The solid was filtered, washed with water, and dried to give the crude product (209 g.). Crystallization from methanol gave the pure alcohol (137 g., 70% based on 4-acetyl-1-naphthol), m.p. 116°.

The alkaline filtrate was boiled with charcoal, filtered, and acidified to give 2-acetyl-1-naphthol (17 g.), m.p. and m.m.p. 97°.

Oxidation of Compound 16.—A stirred solution of 1-(4-acetyl-1-naphthoxy)-2-propanol (2.44 g.) in acetone (60 ml.) was treated at 20° with a solution of chromium trioxide[36] (2.5 ml., 8 *N*) until the red color of the solution persisted. The acetone solution was decanted from the precipitated chromic sulfate and was poured into water (200 ml.). The precipitated solid was filtered off and washed with water. The dried product (0.5 g.) was crystallized twice from ethanol to give the pure compound, m.p. 122–124° (not depressed on admixture with authentic 4-acetyl-1-naphthoxyacetone).

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.4; H, 5.83. Found: C, 74.1; H, 5.84.

Most of the compounds in Table II were prepared by the method given for **16**. The following cases required special conditions.

1-(4-Acetoxyacetyl-1-naphthoxy)-2-propanol (Compound 29).—A mixture of 4-acetoxyacetyl-1-naphthol (9 g.), sodium formate (2.53 g.), 1,2-epoxypropane (42 ml.), and water (15 ml.) was stirred and heated under reflux on a steam bath for 17 hr. The oil that separated was extracted into chloroform, which then was washed with 2 *N* aqueous sodium hydroxide and with water, was dried ($MgSO_4$) and evaporated. The resulting solid (5 g., m.p. 117–120°) was crystallized from a mixture of ethyl acetate and petroleum ether (b.p. 60–80°) to give **29** (3 g.), m.p. 122°.

1-(4-Hydroxyacetyl-1-naphthoxy)-2-propanol (Compound 24). (**A**).—A mixture of 4-acetoxyacetyl-1-naphthol (7.3 g.), sodium benzoate (4.3 g.), 1,2-epoxypropane (34 ml.), and water (100 ml.) was stirred under reflux on a steam bath for 24 hr. The oil that separated was extracted with chloroform, the chloroform solution was washed with 2 *N* aqueous sodium hydroxide and with water, and was dried ($MgSO_4$) and evaporated. The resulting solid (5.6 g., m.p. 127–130°) was crystallized from methanol giving **24**, m.p. 144°.

(**B**).—Hydrolysis of 1-(4-acetoxyacetyl-1-naphthoxy)-2-propanol (**29**) with methanolic HCl gave **24**, m.p. 144–145° (not depressed on admixture with the material prepared by method A).

1-(4-Formyl-1-naphthoxy)-2-propanol (**Compound 32**).—A mixture of 4-formyl-1-naphthol (8.6 g.), potassium bicarbonate (1 g.), 1,2-epoxypropane (15 g.), and water (120 ml.) was stirred for 17 hr. at 60° under nitrogen. The mixture was poured into aqueous sodium hydroxide (200 ml., 2%) when a green oil separated and slowly solidified. The product was washed with water, dried, and crystallized from benzene giving **32** (2 g.), m.p. 105°. Recrystallization from petroleum ether (b.p. 80–100°) gave the pure compound, m.p. 113°.

3-(4-Acetyl-1-naphthoxy)-1,2-epoxypropane.—A solution of sodium hydroxide (12 g.) in water (150 ml.) was added over 45

(35) F. Sondheimer, N. Danieli, and Y. Mazur, *ibid.*, **24**, 1278 (1959).

(36) C. Djerassi, R. R. Engle, and A. Bowers, *ibid.*, **21**, 1547 (1956); *cf.* K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

min. to a stirred mixture of 4-acetyl-1-naphthol (55.8 g.) and epichlorohydrin (41.6 g.) at 70°. The mixture was stirred at this temperature for another hour, during which time a gummy solid separated. The product crystallized on cooling and was filtered off to give the epoxide (46 g.), m.p. 102–103°. Crystallization from ethanol gave the pure compound, m.p. 104–105°.

Anal. Calcd. for $C_{15}H_{14}O_3$: C, 74.4; H, 5.83. Found: C, 74.5; H, 5.91.

3-(4-Acetyl-1-naphthoxy)-1-isopropoxy-2-propanol (Compound 21).—A mixture of 3-(4-acetyl-1-naphthoxy)-1,2-epoxypropane (23.5 g.), stannic chloride (3 ml.), and 2-propanol (225 ml.) was refluxed for 1 hr., most of the solvent was distilled, and the residue was diluted with ether (200 ml.). The ether solution was filtered to remove inorganic material, washed with dilute aqueous sodium bicarbonate, filtered again, dried (magnesium sulfate), and evaporated. The resulting solid (19.7 g.), m.p. 89–91°, was crystallized from ether giving **21**, m.p. 93°.

Reduction of 1-Naphthoxyacetone.—A solution of 1-naphthoxyacetone (15 g.) in methanol (15 ml.) was stirred at 5° and was treated with a solution of potassium borohydride (2.1 g.) in water (30 ml.). The mixture was stirred for an additional 2 hr. by which time a solid had separated. The solid was filtered, washed with water, dried, and crystallized from petroleum ether (b.p. 60–80°) to give 1-(1-naphthoxy)-2-propanol (13 g.), m.p. 64–65°, not depressed on admixture with **45** prepared from 1-naphthol, 1,2-epoxypropane, and sodium hydroxide.[37]

(37) See footnote *h*, Table II.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.2; H, 6.93. Found: C, 77.4; H, 6.82.

Compound 16 Hydrogen Succinate.—A mixture of **16** (11 g.), succinic anhydride (5 g.), and pyridine (25 ml.) was allowed to stand at 40° for 24 hr. The solution was poured into a mixture of ice and dilute acetic acid, and the precipitated solid was filtered off. The solid was dissolved in dilute aqueous sodium bicarbonate, the solution was treated with charcoal, filtered, and acidified in the cold with 2 *N* hydrochloric acid. The precipitated solid was filtered off, washed free of acid with water, and dried to give the hemisuccinate (13.5 g.), m.p. 162–163°. Crystallization from aqueous methanol gave the pure ester (13 g.), m.p. 163°.

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.3; H, 5.81. Found: C, 66.0; H, 5.84.

Compound 25 Hydrogen Succinate.—A similar procedure was used to prepare the hemisuccinate from compound **25** (10 g.), succinic anhydride (4 g.), and pyridine (25 ml.). After one crystallization from toluene and two from ethyl acetate, the pure ester, m.p. 100–103°, was obtained.

Anal. Calcd. for $C_{20}H_{22}O_7$: C, 64.2; H, 5.92. Found: C, 64.1; H, 5.92.

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Thiocarbamate Derivatives of 2-Methyl-2-propyl-1,3-propanediol[1]

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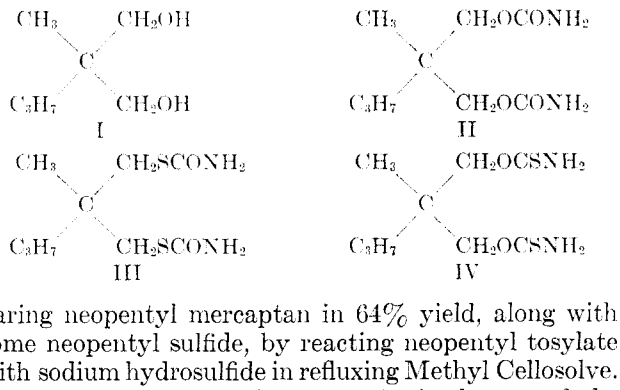
Two sulfur analogs of meprobamate, 2-methyl-2-propyl-1,3-propanedithiol dicarbamate and 2-methyl-2-propyl-1,3-propanediol bis(thiocarbamate), have been prepared. The dithioldicarbamate was obtained by carbamylation of the dithiol, made available from the diol *via* the ditosylate and bis(thiolacetate) derivatives. The isomeric bis(thiocarbamate) was synthesized by ammonolysis of the intermediate bis(S-methylxanthate) derivative of 2-methyl-2-propyl-1,3-propanediol. 2-Methyl-2-propyl-1,3-propanediol monothiondicarbamate, the monothion analog of meprobamate, was also prepared. These sulfur analogs possess muscle paralyzing activity comparable with that of meprobamate but are somewhat more toxic than this compound.

The first synthesis of meprobamate (II) was reported in 1951 by Ludwig and Piech.[2] This compound has achieved wide medical usage, particularly as a tranquilizing agent.[3] We now wish to report the synthesis of the bis(thiolcarbamate) (III) and bis(thioncarbamate) (IV) derivatives of 2-methyl-2-propyl-1,3-propanediol.

Thiolcarbamate Derivatives.—Our first efforts were directed toward converting diol I to the corresponding 2-methyl-2-propyl-1,3-propanedithiol (VII), the key intermediate in the preparation of III. Since sulfonates are generally more reactive than the corresponding halides toward nucleophilic reagents, the disulfonate derivatives Va and Vb were selected as the most desirable intermediates for the conversion of I to VII.

Some difficulty was anticipated in cleaving the carbon–oxygen bond of V because of its neopentyl-like structure. Bordwell, *et al.*,[4] were successful in preparing neopentyl mercaptan in 64% yield, along with some neopentyl sulfide, by reacting neopentyl tosylate with sodium hydrosulfide in refluxing Methyl Cellosolve. Employing their procedure, we obtained none of the desired dithiol (VII); instead we isolated a sulfur-containing compound and assigned to it the structure 3-methyl-3-propylthietane (IX) on the basis of its elemental analysis, molar refraction, and infrared spectrum.[5]



(1) Presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1–4, 1963.

(2) B. J. Ludwig and E. C. Piech, *J. Am. Chem. Soc.*, **73**, 5779 (1951).

(3) F. M. Berger, *Intern. Record Med. Gen. Pract. Clin.*, **169**, 184 (1956).

(4) F. G. Bordwell, B. M. Pitt, and M. Knell, *J. Am. Chem. Soc.*, **73**, 5004 (1951).

(5) S. Searles, Jr., and E. F. Lutz, *ibid.*, **80**, 3168 (1958), reported the synthesis of 3,3-diethylthietane in 43.8% yield from 2,2-diethyl-1,3-propylene carbonate and potassium thiocyanate at 190–195°. Since the completion of this work, infrared spectra have been published for 3,3-dialkylthietanes (Univ. Micro., 61-995, H. R. Hays). Compound IX shows absorption at 1258 and 1180 cm.$^{-1}$ attributable to the thietane structure.