Substituted 3-Thiomorpholinones

H. LEHR, S. KARLAN, AND M. W. GOLDBERG

Research Laboratories, Hoffmann-La Roche Inc., Nutley, N. J.

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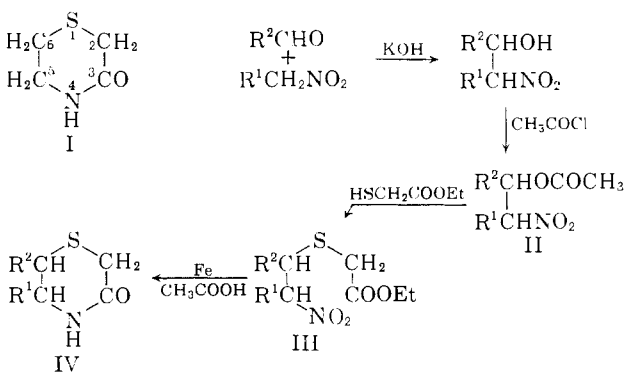
A series of substituted 3-thiomorpholinones was synthesized, using three different methods. The new compounds were tested for hypnotic activity and those with one or two alkyl groups in the 2-position were found to be active. Most of the 3-thiomorpholinones were oxidized to the corresponding sulfoxides and/or sulfones, which were found to be practically inactive.

The 3-thiomorpholinones, which form the subject of this communication, were synthesized in the hope of finding a new group of heterocyclic compounds with hypnotic or sedative activity. Only the unsubstituted 3-thiomorpholinone (I),[1] a few of its substitution products,[2] and some closely related 2,3-dihydro-4H-1,4-thiazin-3-ones[3] have so far been described.

The present paper describes a series of 3-thiomorpholinones, substituted in positions 2, 4, 5, or 6. Three methods were used for their synthesis.

Method A, condensation of ethyl thioglycolate with acetylated nitro alcohols (II), then reductive ring closure of the resulting ethyl nitroalkylmercaptoacetates (III), yielded 3-thiomorpholinones substituted in position 6, or 5 and 6 (IV).

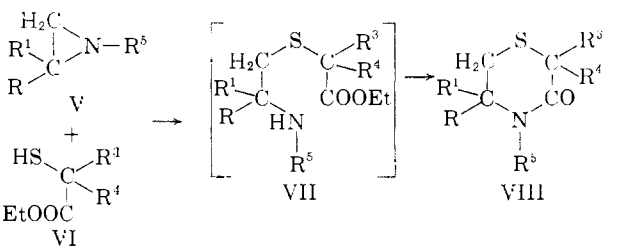


I II III IV

While homologs of ethyl thioglycolate, with one or two alkyl groups in the α-position, also could be condensed with acetylated nitro alcohols to the corresponding nitroalkylmercapto esters (III), the reduction of these nitro compounds, with ring closure to the corresponding 3-thiomorpholinones, failed in most cases. Only 2-ethyl-6-methyl-3-thiomorpholinone was obtained by this method, though in very low yield, by using ethyl α-mercaptobutyrate and 1-nitro-2-acetoxypropane.

Method B, condensation of α-mercapto esters (VI) with ethylenimine or its homologs (V), yielded 3-thiomorpholinones substituted in position 2, 4 or 5 (VIII).

The end products usually were obtained in one step. However, in some cases the intermediate aminoalkylmercapto esters (VII) could be isolated and then ring-closed to the corresponding 3-thiomorpholinones, either by heating for several hours at 150–180°, or by refluxing with sodium ethoxide in ethanol.

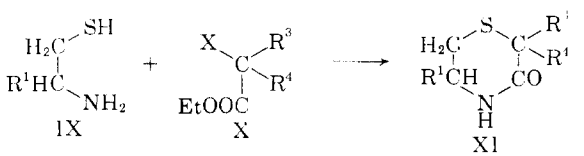


V VI VII VIII

When C-substituted ethylenimines (V, R = alkyl, R^1 = H or alkyl, R^5 = H) were used for the condensation with α-mercapto esters (VI), the position of these substituents in the 3-thiomorpholinone ring was uncertain, since the ring cleavage of the C-substituted ethylenimines can proceed in two ways, leading either to 5- or to 6-substituted 3-thiomorpholinones.

Since 6-methyl-3-thiomorpholinone (IV, R^1 = H, R^2 = CH_3), obtained unequivocally by method A from 1-nitro-2-acetoxypropane (II, R^1 = H; R^2 = CH_3) and ethyl thioglycolate, was not identical with the methyl-3-thiomorpholinone obtained by method B from 2-methylethylenimine (V, R = CH_3; R^1,R^5 = H) and ethyl thioglycolate (VI, R^3,R^4 = H), the latter compound represents the isomeric 5-methyl-3-thiomorpholinone (VIII, R = CH_3; R^1,R^3,R^4,R^5 = H). The ethylenimine ring, when condensed with α-mercapto esters, is therefore opened between the nitrogen atom and the unsubstituted methylene group.

Method C, condensation of β-mercaptoalkylamines (IX) with α-halo esters (X), yielded the corresponding 3-thiomorpholinones (XI), substituted in positions 2 and/or 5 in one step.



IX X XI

This method was useful in those cases where the α-mercapto esters were difficult to obtain. The mercaptoalkylamines (IX) were obtained from ethylenimine or its homologs by reaction with hydrogen sulfide. As with α-mercapto esters, C-substituted ethylenimines were cleaved by hydrogen sulfide between the nitrogen atom and the unsubstituted methylene group. Thus, condensation of ethyl α-bromoacetate (X, R^3,R^4 = H; X = Br) with 1-mercapto-2-aminopropane (IX, R^1 = CH_3), derived from 2-methylethylenimine, yielded 5-methyl-3-thiomorpholinone (XI, R^1 = CH_3; R^5,R^4 = H), identical with the compound obtained by method B from 2-methylethylenimine and ethyl thioglycolate.

(1) H. Bestian, *Ann.*, **566**, 210 (1950).

(2) (a) I. L. Knunyants and M. G. Linkova, *Bull. Acad. Sci., USSR*, 62 (1955); (b) F. S. Babichev and V. A. Shokol, *Ukrain. Khim. Zh.*, **22**, 215 (1956).

(3) G. S. Skinner, J. S. Elmslie, and J. D. Gabbert, *J. Am. Chem. Soc.*, **81**, 3756 (1959).

TABLE I

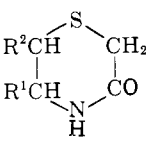
ETHYL NITROALKYLMERCAPTOACETATES

No.	Compound	B.p. °C.	B.p. mm.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	$CH_3CHCH_2NO_2$ $SCH_2COOC_2H_5$	114–115	0.5	$C_7H_{13}NO_4S$	40.57	6.32	41.00	6.10
2	$CH_3CHCH(CH_3)NO_2$ $SCH_2COOC_2H_5$	127–130	1	$C_8H_{15}NO_4S$	43.42	6.83	43.14	7.01
3	$CH_3CHCH(C_2H_5)NO_2$ $SCH_2COOC_2H_5$	133–135	1	$C_9H_{17}NO_4S$	45.94	7.28	45.28	7.25
4	$C_2H_5CHCH_2NO_2$ $SCH_2COOC_2H_5$	125–127	0.8	$C_8H_{15}NO_4S$	43.42	6.83	43.68	6.88
5	$C_2H_5CHCH(CH_3)NO_2$ $SCH_2COOC_2H_5$	132	1	$C_9H_{17}NO_4S$	45.94	7.28	46.17	6.56
6	$C_2H_5CHCH(C_2H_5)NO_2$ $SCH_2COOC_2H_5$	148–151	1.5	$C_{10}H_{19}NO_4S$	48.17	7.68	47.61	7.32
7	$CH_3(CH_2)_2CHCH_2NO_2$ $SCH_2COOC_2H_5$	136–137	0.8	$C_9H_{17}NO_4S$	45.94	7.28	45.56	7.15
8	$(CH_3)_2CHCHCH_2NO_2$ $SCH_2COOC_2H_5$	126–128	1	$C_9H_{17}NO_4S$	45.94	7.28	46.13	6.99
9	$(CH_3)_2CHCHCH(CH_3)NO_2$ $SCH_2COOC_2H_5$	135–137	1	$C_{10}H_{19}NO_4S$	48.17	7.68	48.38	7.76
10	$(CH_3)_2CHCHCH(C_2H_5)NO_2$ $SCH_2COOC_2H_5$	142–145	1	$C_{11}H_{21}NO_4S$	50.16	8.04	49.84	7.77
11	$Cl_3CCHCH_2NO_2$ $SCH_2COOC_2H_5$	162–163	0.8	$C_7H_{10}Cl_3NO_4S$	27.07	3.25	27.39	3.42
12	$CH_3CHCH_2NO_2$ $SCH(C_2H_5)COOC_2H_5$	127–129	0.8	$C_9H_{17}NO_4S$	[a]			
13	$CH_3CHCH_2NO_2$ $SC(C_2H_5)_2COOC_2H_5$	134–136	0.7	$C_{11}H_{21}NO_4S$	50.16	8.04	50.15	7.89
14	$CH_3CHCH(CH_3)NO_2$ $SCHCOOC_2H_5$ $CH_2COOC_2H_5$	182–183	1	$C_{12}H_{21}NO_6S$	46.89	6.89	47.10	6.40

[a] Reduced without prior purification to the corresponding 3-thiomorpholinone.

TABLE II

3-THIOMORPHOLINONES OBTAINED BY METHOD A[a]



No.	R^1	R^2	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	H	CH_3	58–60	C_5H_9NOS	45.77	6.92	46.02	7.03
2	H	C_2H_5	40–42	$C_6H_{11}NOS$	49.62	7.64	49.84	7.68
3	H	C_3H_7	43–45	$C_7H_{13}NOS$	52.80	8.23	52.88	8.11
4	H	$(CH_3)_2CH$	99–100	$C_7H_{13}NOS$	52.80	8.23	52.70	7.95
5	CH_3	CH_3	118–120	$C_6H_{11}NOS$	49.62	7.64	49.53	7.47
6	CH_3	C_2H_5	85–86	$C_7H_{13}NOS$	52.80	8.23	52.91	8.12
7	CH_3	$(CH_3)_2CH$	87–89	$C_8H_{15}NOS$	55.45	8.73	55.21	8.59
8	C_2H_5	CH_3	110–112	$C_7H_{13}NOS$	52.80	8.23	52.73	8.25
9	C_2H_5	C_2H_5	123–124	$C_8H_{15}NOS$	55.45	8.73	55.55	8.89
10	C_2H_5	$(CH_3)_2CH$	141–143	$C_9H_{17}NOS$	57.71	9.15	57.82	9.13

[a] One 2-substituted 3-thiomorpholinone was obtained by this method: 2-ethyl-6-methyl-3-thiomorpholinone, m.p., 73–74°. *Anal.* Calcd. for $C_7H_{13}NOS$: C, 52.80; H, 8.23. Found: C, 53.16; H, 7.92.

The α-mercapto esters used in methods A and B were prepared from the corresponding α-bromo acids by reaction with potassium ethyl xanthate, saponification of the resulting α-thionocarbethoxymercapto acids with ammonia,[4] and esterification in the usual manner. The intermediate β-nitroalkylmercapto esters, needed for the synthesis of 3-thiomorpholinones according to method A, were obtained by condensing the corresponding aldehydes and nitroalkanes to the desired nitro alcohols,[5] which were then acetylated and condensed with the appropriate α-mercapto ester in methanol, in the presence of sodium methoxide. The β-nitroalkylmercapto esters thus obtained (Table I) were reduced with iron filings in dilute acetic acid to the corresponding 3-thiomorpholinones. The reduction of the β-nitroalkylmercapto esters no. 11, 13 and 14 failed.

(4) E. Blilman, *Ann.*, **339**, 351 (1905); **348**, 120 (1906).

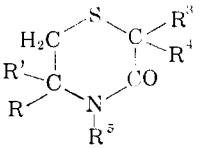
(5) B. M. Vanderbilt and H. B. Hass, *Ind. Eng. Chem.*, **32**, 34 (1940); J. B. Tindall, *ibid.*, **33**, 65 (1941).

The 3-thiomorpholinones synthesized in this study are summarized according to the method of preparation in Tables II, III and IV.

The 3-thiomorpholinones were oxidized with hydrogen peroxide in acetic acid–acetic anhydride to the corresponding sulfoxides and/or sulfones. Oxidation with 1 mole of hydrogen peroxide at −5 to +5° yielded sulfoxides only. The corresponding sulfones were obtained by using 2 moles of hydrogen peroxide at room temperature (25–30°). Table V lists the sulfoxides prepared in this study and Table VI summarizes the sulfones.

TABLE III

3-THIOMORPHOLINONES OBTAINED BY METHOD B

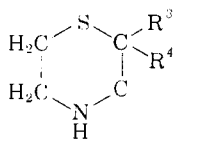


No.	R	R¹	R²	R³	R⁴	R⁵	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	H	H	H	H	H	H	90–91[a]	C_4H_7NOS				
2	H	H	CH_3	H	H	75–76[d]	[b]	C_5H_9NOS	45.77	6.92	45.91	6.73
3	H	H	H	H	H	CH_3		C_5H_9NOS	45.77	6.92	45.18	6.89
4	H	CH_3	H	H	H	H	128–130	C_5H_9NOS	45.77	6.92	45.59	6.77
5	H	H	C_2H_5	H	H	H	59–61[c]	$C_6H_{11}NOS$	49.62	7.64	49.87	7.03
6	H	H	H	H	H	C_2H_5	[c]	$C_6H_{11}NOS$	49.62	7.64	49.32	7.79
7	H	C_2H_5	H	H	H	H	108–110	$C_6H_{11}NOS$	49.62	7.64	49.71	7.93
8	H	H	C_3H_7	H	H	H	50–52	$C_7H_{13}NOS$	52.80	8.23	53.17	7.75
9	H	H	CH_3	CH_3	H	H	107–108	$C_6H_{11}NOS$	49.62	7.64	49.43	7.48
10	H	CH_3	CH_3	H	H	H	93–95	$C_6H_{11}NOS$	49.62	7.64	49.14	6.92
11	CH_3	CH_3	H	H	H	H	152–153	$C_6H_{11}NOS$	49.62	7.64	50.03	7.32
12	H	H	C_2H_5	C_2H_5	H	H	55–56	$C_8H_{15}NOS$	55.45	8.73	55.37	8.27
13	H	C_2H_5	C_2H_5	H	H	H	83–84	$C_8H_{15}NOS$	55.45	8.73	55.85	8.68
14	H	C_2H_5	CH_3	H	H	H	92–94	$C_7H_{13}NOS$	52.80	8.23	52.49	7.85
15	H	CH_3	C_2H_5	H	H	H	82–84	$C_7H_{13}NOS$	52.80	8.23	52.93	7.73
16	H	CH_3	C_3H_7	H	H	H	73–75	$C_8H_{15}NOS$	55.45	8.73	55.70	8.92
17	H	C_2H_5	C_3H_7	H	H	H	51–53	$C_9H_{17}NOS$	57.71	9.15	57.45	9.40
18	H	CH_3	CH_3	CH_3	H	H	127–128	$C_7H_{13}NOS$	52.80	8.23	53.23	7.88
19	CH_2	CH_3	CH_3	H	H	H	137–139	$C_7H_{13}NOS$	52.80	8.23	52.55	7.90
20	H	C_2H_5	CH_3	CH_2	H	H	102–103	$C_8H_{15}NOS$	55.45	8.73	55.60	8.72
21	CH_3	CH_3	C_2H_5	H	H	H	114–116	$C_8H_{15}NOS$	55.45	8.73	55.45	8.46
22	H	CH_3	C_2H_5	C_2H_5	H	H	53–55	$C_9H_{17}NOS$	57.71	9.15	57.55	8.70
23	H	C_2H_5	C_2H_5	C_2H_5	H	H	47–48	$C_{10}H_{19}NOS$	59.66	9.51	59.56	9.70
24	CH_3	CH_3	C_3H_7	H	H	H	91–93	$C_9H_{17}NOS$	57.71	9.15	57.61	9.24
25	CH_3	CH_3	CH_3	CH_3	H	H	172–174	$C_8H_{15}NOS$	55.45	8.73	55.70	8.51
26	CH_3	CH_3	C_2H_5	C_2H_5	H	H	73–75	$C_{10}H_{19}NOS$	59.66	9.51	59.75	9.65
27	H	H	CH_2COONa	H	H	H	*ca.* 260 dec.	$C_6H_8NNaO_3S$	36.54	4.08	36.90	4.24

[a] See footnote 1. [b] B.p. 110° (0.7 mm.). [c] B.p. 104° (0.5 mm.). [d] See footnote 2b.

TABLE IV

3-THIOMORPHOLINONES OBTAINED BY METHOD C

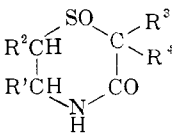


No.	R³	R⁴	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	H	$(CH_3)_2CH$	48–50[a]	$C_7H_{13}NOS$	52.80	8.23	53.08	8.21
2	H	C_6H_5	160–162[a]	$C_{10}H_{11}NOS$	62.11	5.74	62.07	5.75
3	C_2H_5	C_6H_5	164–166	$C_{12}H_{15}NOS$	65.12	6.83	65.37	6.75

[a] See footnote 2b.

TABLE V

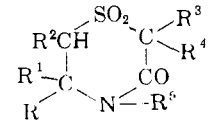
3-THIOMORPHOLINONE 1-OXIDES



No.	R¹	R²	R³	R⁴	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	H	H	H	H	141–143	$C_4H_7NO_2S$	36.08	5.30	35.91	4.90
2	CH_3	CH_3	H	H	149–152	$C_6H_{11}NO_2S$	44.70	6.88	44.84	6.97
3	CH_3	C_2H_5	H	H	180–182	$C_7H_{13}NO_2S$	47.97	7.48	48.29	7.50
4	H	$(CH_3)_2CH$	H	H	178–180	$C_7H_{13}NO_2S$	47.97	7.48	48.32	7.82
5	CH_3	$(CH_3)_2CH$	H	H	146–150	$C_8H_{15}NO_2S$	50.76	7.99	51.08	7.92
6	H	H	C_2H_5	C_2H_5	136–137	$C_8H_{15}NO_2S$	50.76	7.99	50.71	7.80

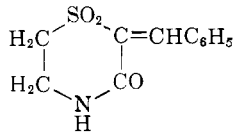
TABLE VI

3-THIOMORPHOLINONE 1,1-DIOXIDES

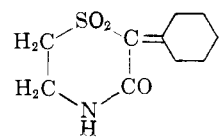


No.	R	R^1	R^2	R^3	R^4	R^5	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	H	H	H	H	H	H	171–173	$C_4H_7NO_3S$	32.21	4.73	32.41	4.52
2	CH_3	H	CH_3	H	H	H	167–170	$C_6H_{11}NO_3S$	40.66	6.26	41.08	5.89
3	H	H	C_2H_5	H	H	H	148–149	$C_6H_{11}NO_3S$	40.66	6.26	41.16	6.14
4	H	H	$(CH_3)_2CH$	H	H	H	195–197	$C_7H_{13}NO_3S$	43.96	6.85	44.13	7.19
5	CH_3	H	C_2H_5	H	H	H	132–134	$C_7H_{13}NO_3S$	43.96	6.85	44.22	7.20
6	H	H	CH_3	H	H	H	112–114	$C_5H_9NO_3S$	36.80	5.56	37.31	5.63
7	C_2H_5	H	CH_3	H	H	H	196–199	$C_7H_{13}NO_3S$	43.96	6.85	43.95	7.05
8	CH_3	H	H	H	H	H	157–159	$C_5H_9NO_3S$	36.80	5.56	37.06	5.15
9	C_2H_5	H	H	H	H	H	162–164	$C_6H_{11}NO_3S$	40.66	6.26	41.14	5.90
10	CH_3	CH_3	H	H	H	H	225–227	$C_6H_{11}NO_3S$	40.66	6.26	41.02	6.52
11	C_2H_5	H	$(CH_3)_2CH$	H	H	H	220–222	$C_9H_{17}NO_3S$	49.29	7.82	49.49	7.79
12	H	H	H	H	H	CH_3	156–158	$C_5H_9NO_3S$	36.80	5.56	37.07	5.84
13	C_2H_5	H	C_2H_5	H	H	H	144–146	$C_8H_{15}NO_3S$	46.81	7.37	47.27	7.30
14	CH_3	H	$(CH_3)_2CH$	H	H	H	142–144	$C_8H_{15}NO_3S$	46.81	7.37	47.08	7.18
15	H	H	H	H	H	C_2H_5	86–88	$C_6H_{11}NO_3S$	40.66	6.26	40.25	6.05
16	H	H	C_3H_7	H	H	H	160–161	$C_7H_{13}NO_3S$	43.96	6.85	43.95	6.99
17	H	H	H	CH_3	H	H	133–135	$C_5H_9NO_3S$	36.80	5.56	37.09	5.48
18	H	H	H	C_2H_5	H	H	142–144	$C_6H_{11}NO_3S$	40.66	6.26	41.05	6.08
19	H	H	H	C_3H_7	H	H	102–104	$C_7H_{13}NO_3S$	43.96	6.85	44.21	6.72
20	H	H	H	$CH(CH_3)_2$	H	H	146–147	$C_7H_{13}NO_3S$	43.96	6.85	44.30	6.56
21	H	H	H	C_6H_5	H	H	190–192	$C_{10}H_{11}NO_3S$	53.32	4.92	53.22	4.84
22	H	H	H	CH_3	CH_3	H	169–171	$C_6H_{11}NO_3S$	40.66	6.26	40.68	6.06
23	H	H	H	C_2H_5	C_2H_5	H	149–150	$C_8H_{15}NO_3S$	46.81	7.37	46.80	7.27
24	H	H	H	C_6H_5	C_2H_5	H	180–181	$C_{12}H_{15}NO_3S$	56.89	5.97	56.88	6.29
25	CH_3	H	H	CH_3	H	H	168–171	$C_6H_{11}NO_3S$	40.66	6.26	40.79	6.50
26	C_2H_5	H	H	CH_3	H	H	143–145	$C_7H_{13}NO_3S$	43.96	6.85	43.85	6.51
27	CH_3	CH_3	H	CH_2	H	H	215–216	$C_7H_{13}NO_3S$	43.96	6.85	44.30	6.74
28	CH_3	H	H	C_2H_5	H	H	185–187	$C_7H_{13}NO_3S$	43.96	6.85	44.10	6.95
29	CH_3	CH_3	H	C_2H_5	H	H	177–179	$C_8H_{15}NO_3S$	46.81	7.37	46.99	7.01
30	C_2H_5	H	H	C_2H_5	C_2H_5	H	121–122	$C_{10}H_{19}NO_3S$	51.47	8.21	51.56	7.62

The 2-methylene group in 3-thiomorpholinone 1,1-dioxide is reactive, as shown by the condensation with benzaldehyde and cyclohexanone, in the presence of piperidine, to 2-benzylidene-3-thiomorpholinone 1,1-dioxide (XII) and 2-cyclohexylidene-3-thiomorpholinone 1,1-dioxide (XIII), respectively.



XII



XIII

The pharmacological investigation of the new compounds, carrried out in our Pharmacology Department by Dr. L. O. Randall, revealed that only those 3-thiomorpholinones which carry one or two alkyl groups in position 2 exhibit hypnotic activity in animals (see Table VII). The most active compound was 2,2-diethyl-3-thiomorpholinone (Table VII, no. 7). This compound had in mice an LD_{50} of 2250 mg./kg. p.o., 652 mg./kg. i.p., and 137 mg./kg. i.v. The HD_{50} was 750 mg./kg. p.o., 166 mg./kg. i.p., and 74 mg./kg. i.v., giving therapeutic ratios of 3, 3.9 and 1.85, respectively. The duration of hypnosis was 13 min. p.o., 7 min. i.p. and 2 min. i.v. In rabbits the LD_{50} was 1500 mg./kg. p.o. and 185 mg./kg. i.v., and the HD_{50} 375 mg./kg. p.o. and 27.5 mg./kg. i.v., corresponding to therapeutic ratios of 4 and 6.7, respectively.

The sulfoxides and sulfones of this series were devoid of hypnotic activity, with the exception of 2,2-diethyl-3-thiomorpholinone 1,1-dioxide (Table VI, No. 23), which had in mice an LD_{50} of 4250 mg./kg. p.o. and an HD_{50} of 1250 mg./kg. p.o.

Experimental[6]

3-Thiomorpholinones. Method A.—All nitro alcohols, obtained by condensation of the appropriate aldehydes with nitroalkanes, are known compounds,[4] as are most of their acetates. The acetates, prepared by refluxing the nitro alcohols with excess acetyl chloride and fractionation *in vacuo*, were condensed with ethyl thioglycolate to the corresponding nitroalkylmercapto esters (Table I). In addition to ethyl thioglycolate, ethyl α-mercaptobutyrate,[7] ethyl α-mercapto-α,α-diethylacetate and diethyl thiomalate[8] were condensed with nitro alcohol acetates to the corresponding nitroalkylmercapto esters (no. 12, 13 and 14 in Table I). As a representative example, the preparation of **ethyl (1-ethyl-2-nitropropylmercapto)acetate** (no. 5 in Table I) is described. To a solution of 11.5 g. of sodium in 200 ml. of methanol was added gradually and with cooling 60 g. of ethyl thioglycolate in 100 ml. of methanol, then 80.5 g. of 2-nitro-3-acetoxypentane in 100 ml. of methanol. The stirred reaction mixture was kept for 1 hr. at −10° and for 18 hr. at room temperature. After removal of the solvent, the residue was treated with water and ether, the two layers were separated, and the aqueous layer was extracted once more with ether. The combined ether extracts were washed with 5% sodium carbonate solution and water, and dried over sodium sulfate. After removal of the solvent, the residue was fractionated *in vacuo*. Ethyl (1-ethyl-2-nitropropylmercapto)acetate was obtained as a colorless oil boiling at 132° (1 mm.); yield 98 g. (83.5%).

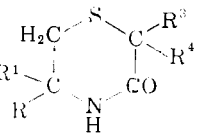
(6) All melting points are corrected.

(7) H. Bredereck, R. Gompper, and H. Seiz, *Chem. Ber.*, **90**, 1837 (1957).

(8) Esterification of commercially available thiomalic acid.

TABLE VII

PHARMACOLOGICAL DATA FOR 2-MONO- OR 2-DISUBSTITUTED 2-THIOMORPHOLINONES[a]



No.	R	R^1	R^3	R^4	LD_{50}, mg./kg.	HD_{50}[b], mg./kg.
1	H	H	H	H	4152	inact.
2	H	H	CH_3	H	3357	2778
3	H	H	C_2H_5	H	2750	1576
4	H	H	C_3H_7	H	2555	1187
5	H	H	CH_3	CH_3	3423	1411
6	H	CH_3	CH_3	H	1750	inact.
7	H	H	C_2H_5	C_2H_5	2250	750
8	H	C_2H_5	C_2H_5	H	2038	1500
9	H	C_2H_5	CH_3	H	326	inact.
10	H	CH_3	C_2H_5	H	2870	1576
11	H	CH_3	C_3H_7	H	1818	1114
12	H	C_2H_5	C_3H_7	H	589	inact.
13	H	CH_3	CH_3	CH_3	3458	*ca.* 2500
14	CH_3	CH_3	CH_3	H	808	inact.
15	H	C_2H_5	CH_3	CH_3	593	inact.
16	CH_3	CH_3	C_2H_5	H	3679	2424
17	H	CH_3	C_2H_5	C_2H_5	2170	921
18	H	C_2H_5	C_2H_5	C_2H_5	1792	1000
19	CH_3	CH_3	C_3H_7	H	3000	inact.
20	CH_3	CH_3	CH_3	CH_3	>4000	4000
21	CH_3	CH_3	C_2H_5	C_2H_5	3128	1576
22	H	H	CH_2COONa	H	>400	inact.
23	H	H	$(CH_3)_2CH$	H	1645	1028
24	H	H	C_6H_5	H	>4000	inact.
25	H	H	C_2H_5	C_6H_5	>4000	inact.

[a] All recorded values were obtained by oral administration to mice, with the exception of those for compound no. 22, which were obtained by intraperitoneal administration. [b] Fifty per cent hypnotic dose (mg./kg.). The animal is placed on its side and remains in that position for at least one minute.

All nitroalkylmercapto esters used in this study, their boiling points and microanalytical data are summarized in Table I. The yields ranged from 70 to 85%. Reduction of the nitroalkylmercapto esters with iron in dilute acetic acid yielded the corresponding 3-thiomorpholinones. As a typical example, the preparation of **5-methyl-6-ethyl-3-thiomorpholinone** (Table II, no. 6) is described.

Sixty grams of iron filings was suspended in 300 ml. of water containing 6 ml. of glacial acetic acid. The mixture was refluxed for 1 hr., 49 g. of ethyl (1-ethyl-2-nitropropylmercapto)-acetate, diluted with 50 ml. of ethanol, was added gradually to the boiling reaction mixture and refluxing was continued for 16 hr. After cooling, the mixture was made alkaline with sodium carbonate and filtered with the aid of Hyflo Super-Cel. The filtrate was concentrated *in vacuo* and chilled. The crystals were filtered off and extracted with three 100 ml. portions of ethyl acetate or acetone. The combined extracts were evaporated to dryness, and the residue was recrystallized from ethyl acetate–petroleum ether. 5-Methyl-6-ethyl-3-thiomorpholinone was obtained in the form of colorless crystals, melting at 85–86°; yield 12 g. (36.5%).

All 3-thiomorpholinones obtained by this method, are listed in Table II. The yields ranged from 36 to 51%. Reduction of the nitroalkylmercapto esters no. 11–14 (Table I) failed.

Method B.—The α-mercapto esters, used in this method, were obtained by condensation of α-bromo acids with potassium ethyl xanthate, then saponification with ammonia,[4] and esterification of the resulting α-mercapto acids in the usual manner. With the exception of ethyl α-mercaptovalerate and ethyl α-mercapto-α,α-diethylacetate, they are described in the literature. The preparation of the above-mentioned two esters is given as examples.

Ethyl α-Mercaptovalerate.—α-Bromovaleric acid (90 g.) was added to a solution of 69 g. of potassium carbonate in 450 ml. of water, followed by 80 g. of potassium ethyl xanthate. The mixture was allowed to stand at room temperature for 3 days. After acidification with concd. HCl, the solution was extracted with three 200 ml. portions of ether. The combined ether extracts were dried over sodium sulfate and evaporated to dryness. The oily residue (101 g.) was added to a mixture of 400 ml. of concd. aqueous ammonia and 750 ml. of ethanol, and the solution was kept for 5 days at room temperature. The mixture was extracted once with 500 ml. of ether to remove the xanthogenamide formed, acidified, and extracted 3 times with 200 ml. portions of ether. The combined extracts were dried over sodium sulfate and evaporated to dryness. The residue, after fractionation *in vacuo*, yielded α-mercaptovaleric acid as a colorless oil, boiling at 115–116° (10 mm.); yield 42 g. (62%).

α-Mercaptovaleric acid (33 g.) was dissolved in 100 ml. of ethanol, 10 ml. of concd. H_2SO_4 was added, and the mixture was refluxed under nitrogen for 18 hr. Most of the ethanol was removed *in vacuo*, the residue neutralized with 10% sodium carbonate, and extracted with ether. Fractionation *in vacuo* yielded ethyl α-mercaptovalerate, boiling at 82° (15 mm.); yield 23 g. (58%).

Anal. Calcd. for $C_7H_{14}O_2S$: C, 51.82; H, 8.70. Found: C, 51.74; H, 8.73.

Ethyl α-Mercapto-α,α-diethylacetate.—Sodium (23 g.) was dissolved in 1 l. of absolute ethanol. To the cooled solution was added gradually 195 g. of α-bromo-α,α-diethylacetic acid. Toward the end of the addition, the sodium salt was partly precipitated. To the suspension was added 190 g. of potassium ethyl xanthate and the reaction mixture was stirred for 16 hr. at room temperature. The potassium bromide was filtered off, and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in 300 ml. of water and acidified with concd. HCl. The partly crystallizing oily layer was extracted twice with 500 ml. portions of ether, and the combined extracts were dried over sodium sulfate. After removal of the solvent, the residue was treated with petroleum ether, and the α-(thionocarbethoxymercapto)-α,α-diethylacetic acid was filtered off and dried *in vacuo*; yield 160 g. (68%). A sample after recrystallization from dil. ethanol melted at 115–116°.

α-(Thionocarbethoxymercapto)-α,α-diethylacetic acid (160 g.) was dissolved in 400 ml. of concd. aqueous ammonia in a 500-ml. erlenmeyer flask. When the solution was completed, more aqueous ammonia was added to fill the flask to the neck. After standing at room temperature for 3 days, the solution was extracted three times with 300 ml. of ether to remove the xanthogenamide formed. The aqueous solution was acidified with cooling in a nitrogen atmosphere, the separated oil was extracted 3 times with 500 ml. portions of ether, and the combined ether extracts were dried over sodium sulfate. After removal of the solvent, the residue was fractionated *in vacuo* under nitrogen. α-Mercapto-α,α-diethylacetic acid was obtained as a colorless oil, boiling at 128–130° (13 mm.) and solidifying to white needles, m.p. 35–37°; yield 84 g. (84%).[9]

α-Mercapto-α,α-diethylacetic acid (84 g.) was dissolved in 250 ml. of ethanol, 25 ml. of concd. sulfuric was added and the mixture refluxed under nitrogen for 18 hr. Most of the ethanol was distilled off, and the residue neutralized with 10% sodium carbonate solution. The oil was extracted twice with 250 ml. of ether and the combined extracts were dried over sodium sulfate. After removal of the solvent, the residue was fractionated *in vacuo*. Ethyl α-mercapto-α,α-diethylacetate was obtained as a colorless liquid, boiling at 85–88° (15 mm.); yield 82 g. (82%).

Anal. Calcd. for $C_8H_{16}O_2S$: C, 54.51; H, 9.15; Found: C, 54.35; H, 9.40.

2,2-Diethyl-3-thiomorpholinone (Table III, no. 12).—Ethyl α-mercapto-α,α-diethylacetate (82 g.) was mixed with cooling with 24 g. of ethyleneimine. The mixture was kept at 60° for 3 hr., and then for 3 days at room temperature. Fractional distillation *in vacuo* yielded 89 g. (87%) of ethyl α-(β-aminoethylmercapto)-α,α-diethylacetate boiling at 115–125° (0.8 mm.). After redistillation, the colorless oil boiled at 123° (1 mm.).

Anal. Calcd. for $C_{10}H_{21}NO_2S$: C, 54.76; H, 9.65. Found: C, 54.92; H, 9.68.

The *hydrochloride*, prepared in the usual manner, melted at 73–75° after recrystallization from ether–petroleum ether.

Anal. Calcd. for $C_{10}H_{22}ClNO_2S$: C, 46.95; H, 8.67. Found: C, 46.91; H, 8.48.

(9) L. Field and R. O. Beauchamp Jr., *J. Am. Chem. Soc.*, **74**, 4707 (1952), obtained α-mercapto-α,α-diethylacetic acid from α-bromo-α,α-diethylacetic acid in 21.6% yield, boiling at 85–118° (1 mm.) and melting, after redistillation, at 26–28.5°.

Ethyl α-(β-aminoethylmercapto)-α,α-diethylacetate (76 g.) was heated in an oil bath at 150–180° for 6 hr. Fractional distillation *in vacuo* yielded 38 g. of unreacted starting material and 16 g. of a viscous oil boiling at 138–150° (0.7 mm.) which solidified in the cold (12.1 g.). The 38 g. of unreacted ethyl α-(β-aminoethylmercapto)-α,α-diethylacetate was reheated for 5 hr. at 150–180°. On chilling, crystals deposited, which were filtered off, washed with pentane and air-dried (15.5 g.). The filtrate was again heated for 6 hr. at 150–180° and yielded an additional crop of crystals (4.8 g.). Total yield was 32.4 g. (42.6%). After recrystallization from pentane, 2,2-diethyl-3-thiomorpholinone was obtained in form of white needles melting at 55–57°.

By an alternate route, 89 g. of ethyl α-(β-aminoethylmercapto)-α,α-diethylacetate was added to a solution of 9.4 g. of sodium in 200 ml. of ethanol and the mixture refluxed for 30 min. After removal of the solvent, the residue was acidified with hydrochloric acid, and the separated oil extracted twice with 250 ml. portions of ether. The combined ether extracts were washed with water, and dried over sodium sulfate. After removal of the solvent, the residue was recrystallized from pentane. The 2,2-diethyl-3-thiomorpholinone melted at 55–56.5°; yield 50 g. (62%).

2-Methyl-3-thiamorpholone (Table III, no. 2).—Ethyl α-mercaptopropionate (11 g.) and 5 g. of ethylenimine were mixed under cooling. The mixture was kept at 60° for 2 hr., and then at room temperature for 3 days. On chilling, crystals deposited, which were filtered off and washed with a minimum of ice-cold ethanol; yield 7 g. (65%). After recrystallization from benzene–petroleum ether, 2-methyl-3-thiomorpholinone melted at 75–76°.

All 3-thiomorpholinones obtained by this method are listed in Table III. The yields ranged from 62–70%.

Method C.—The α-halo esters used in this method are known compounds, with the exception of ethyl α-bromo-α-phenylbutyrate. Its preparation is given below.

One hundred grams of ethyl α-phenylbutyrate was dissolved in 125 ml. of carbon tetrachloride. N-Bromosuccinimide (92 g.) and 1 g. of benzoyl peroxide were added, and the mixture heated on the water bath. After a few min. a vigorous reaction took place. The mixture was refluxed for 2 hr., the succinimide was filtered off, and the filtrate evaporated to dryness. Fractional distillation of the residue yielded 86 g. (61%) of ethyl α-bromo-α-phenylbutyrate, boiling at 149–151° (20 mm.). It was used without further purification for the preparation of the corresponding 3-thiomorpholinone.

2-Ethyl-2-phenyl-3-thiomorpholinone (Table IV, no. 3).—β-Mercaptoethylamine[10] (19.5 g.) was dissolved in 250 ml. of dry toluene, 5.2 g. of sodium was added, and the stirred mixture refluxed for 16 hr. under nitrogen. To the suspension was added 68 g. of ethyl α-bromo-α-phenylbutyrate and the mixture refluxed for 18 hr. After filtration, the solution was concentrated *in vacuo*. The crystals were collected, washed with benzene, and air dried; yield 12 g. (22%). After recrystallization from benzene–petroleum ether, 2-ethyl-2-phenyl-3-thiomorpholinone melted at 164–166°.

Table IV lists the 3-thiomorpholinones obtained by this method. The yields ranged from 22–62%.

2,2-Diethyl-3-thiomorpholinone 1-Oxide (Table V, no. 6).—Three grams of 2,2-diethyl-3-thiomorpholinone was dissolved in a mixture of 9 ml. of glacial acetic acid and 2 ml. of acetic anhydride. The solution was cooled to −5°, and 1.8 ml. of 30% hydrogen peroxide was added very slowly, so that the temperature did not rise above +5°. After the addition was completed, the mixture was left in the cooling bath for 5 hr., and then kept in the refrigerator for 7 days. After this time, the solvent was removed *in vacuo* at a bath temperature of 35°. Recrystallization from acetone yielded 2 g. (60%) of 2,2-diethyl-3-thiomorpholinone 1-oxide, melting at 136–137°. All 3-thiomorpholinone 1-oxides (Table V) were prepared by this method. The yields ranged from 40 to 60%.

2,2-Diethyl-3-thiomorpholinone 1,1-Dioxide (Table VI, no. 23).—2,2-Diethyl-3-thiomorpholinone (7 g.) was dissolved in a mixture of 20 ml. of glacial acetic acid and 5 ml. of acetic anhydride, and 10 ml. of 30% hydrogen peroxide was added slowly, the reaction mixture being kept at 0°. After the addition was completed, the mixture was kept for 5 hr. in the cooling bath, and then left at room temperature for 5 days. The solvent was removed *in vacuo*, and the residue was recrystallized from ethanol. 2,2-Diethyl-3-thiomorpholinone 1,1-dioxide was obtained in the form of white needles melting at 149–150°; yield 6.7 g. (80.7%).

All 3-thiomorpholinone 1,1-dioxides (Table VI) were prepared by this method. The yields ranged from 62 to 86%.

2-Cyclohexylidene-3-thiomorpholinone 1,1-Dioxide (XIII).—3-Thiomorpholinone 1,1-dioxide (2 g.) was dissolved in 15 ml. of cyclohexanone, 5 drops of piperidine was added, and the mixture refluxed for 7 hr. After cooling, 1.2 g. of unreacted 3-thiomorpholinone 1,1-dioxide was filtered off. The filtrate was taken to dryness, the pasty residue was treated repeatedly with acetone, and the end-product recrystallized from ethanol. 2-Cyclohexylidene-3-thiomorpholinone 1,1-dioxide was obtained in the form of white needles, melting at 215–217°.

Anal. Calcd. for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.59. Found: C, 52.71; H, 6.57.

2-Benzylidene-3-thiomorpholinone 1,1-Dioxide (XII).—Three grams of 3-thiomorpholinone 1,1-dioxide was dissolved in 100 ml. of pyridine, 2.5 g. of benzaldehyde and 10 drops of piperidine were added, and the mixture was refluxed for 7 hr. After removal of the solvent *in vacuo*, the residue was treated with ether. The yellow, amorphous product was recrystallized three times from ethanol. 2-Benzylidene-3-thiomorpholinone 1,1-dioxide was obtained in form of white crystals melting at 199–201°.

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67. Found: C, 55.29; H, 4.71.

Acknowledgments.—The authors are indebted to Dr. A. Steyermark and his staff for the microanalyses and to Mr. F. Jenkins for technical assistance.

(10) E. J. Mills, Jr., and M. T. Bogert, *J. Am. Chem. Soc.*, **62**, 1173 (1940).