Substituted 2-Mercaptoisobutyramides and 2-Ethyl-2-mercaptobutyramides

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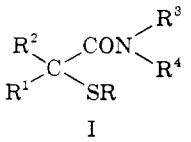
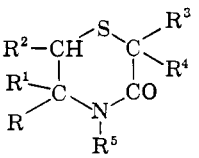
The synthesis of a series of S- and N-substituted 2-mercaptoisobutyramides, 2-ethyl-2-mercaptobutyramides, and the corresponding sulfones is described. The substituted 2-ethyl-2-mercaptobutyramides were found to be more potent as central nervous system depressants than the substituted 2-mercaptoisobutyramides, which, in turn, were more potent than the sulfones. With regard to the sedative, hypnotic, and anticonvulsant activity in mice, and the ataxia inducing effect in cats, dogs, and monkeys, the most potent compound was 2-ethyl-2-propargylmercaptobutyramide (Table VI, No. 17).

In our search for new, non-barbiturate hypnotics or sedatives, we synthesized a group of 2-mercapto-2,2-dialkylacetamides of the general structure I, carrying various substituents on the mercapto and amido groups.



I



II

These compounds are derivatives of the unknown 2-mercaptoisobutyramide (I, $R^1 = R^2 = CH_3$; $R = R^3 = R^4 = H$) and the recently synthesized 2-ethyl-2-mercaptobutyramide (I, $R^1 = R^2 = C_2H_5$; $R = R^3 = R^4 = H$),[1] and represent an "open form" of the substituted 3-thiomorpholinones (II), described in an earlier communication.[2] A number of simpler compounds of type I, in which R^1 is alkyl and R^2 is H, are known.[3] However, only three S-substituted derivatives of 2-mercaptoisobutyramide (I, $R^1 = R^2 = CH_3$; $R = C_2H_5$, C_3H_7, C_4H_9; $R^3 = R^4 = H$) have been described,[3] which had been obtained from 2-bromoisobutyramide by condensation with the appropriate mercaptan. The corresponding sulfones are also known. S-Substituted derivatives of 2-ethyl-2-mercaptobutyramide have not yet been described.

Since mercaptans, particularly unsaturated mercaptans, are generally less readily available than the corresponding halides, we used as starting materials for the synthesis of our new compounds 2-mercaptoisobutyric acid and 2-ethyl-2-mercaptobutyric acid, and condensed these mercapto acids with the appropriate halide.[4] The resulting S-substituted acids were converted to the corresponding acid chlorides, which upon reaction with ammonia or amines yielded the desired end products. Some of the substituted 2-mercaptoamides were oxidized by conventional methods to the corresponding sulfones.

Table I lists the new S-substituted 2-mercaptoisobutyric and 2-ethyl-2-mercaptobutyric acids prepared by us. Their acid chlorides, which are also included in this table, were used without further purification for the preparation of the desired amides. The S-substituted mercapto amides, derived from 2-mercaptoisobutyramide, are summarized in Table II, and those derived from 2-ethyl-2-mercaptobutyramide in Table III. The sulfones are listed in Table IV.

Pharmacology.—The detailed pharmacological methods for assaying the substituted 2-mercaptoamides are given in the publication by Randall, *et al.*[5] The inclined screen method in mice estimates sedation and measures the dose (PD_{50}) at which half the mice roll off an inclined screen. Hypnosis is defined by the dose (HD_{50}) which causes loss of righting reflex in half the mice. The LD_{50} is the dose at which half the mice die. The anti-strychnine effect is measured as the minimum effective dose (MED) for preventing convulsions (0.63 mg./kg. i.v. infusion of strychnine). The anticonvulsant activity is measured as the dose (ED_{50}) which prevents convulsions from pentylenetetrazole (125 mg./kg., s.c.) or electroshock (hind limb extension) in half the mice. Gross behavioral effects are observed in cats, dogs, and monkeys after oral administration of large doses.

The S-substituted 2-mercaptoisobutyramides (Table V) had relatively weak activity as sedatives, hypnotics, and anticonvulsants in mice and as ataxia inducing agents in cats. Considerably greater activity was observed in the S-substituted 2-ethyl-2-mercaptobutyramides (Table IV). High sedative, hypnotic, and anticonvulsant activity was reached in the propargyl (17), allyl (12), methyl (1), ethyl (3), and propyl (8) derivatives. All of these had sedative, hypnotic, and anticonvulsant effects well below the lethal dose in mice. At moderate dose levels, they caused ataxia and weakness rather than hypnosis in cats. The propargyl (17) and allyl (12) derivatives induced ataxia in dogs and monkeys at moderate doses and sleep at higher doses. The propargyl derivative (17) caused ataxia and sleep in dogs at 80 mg./kg. p.o. with a duration of 3–4 days. The allyl derivative (12) caused ataxia and sleep in dogs at 80 mg./kg. p.o. with a duration of 24 hr. The monkey showed marked ataxia at these same dose levels. The sulfones (Table VII) showed very little activity as central nervous system depressants.

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

(2) H. Lehr, S. Karlan, and M. W. Goldberg, *J. Med. Chem.*, **6**, 136 (1963).

(3) A. Pomerantz and R. Connor, *J. Am. Chem. Soc.*, **61**, 3386 (1939).

(4) Some S-substituted 2-mercaptoisobutyric acids, including the methyl, ethyl, propyl, and isopropyl derivatives, were prepared by this method by E. Larson and L. Monies, *Trans. Chalmers Univ. Technol.* (Gothenburg, Sweden), **47**, 9 (1945); *Chem. Abstr.*, **40**, 2795 (1946). These 2-alkylmercaptoisobutyric acids were used for the preparation of compounds No. 1–6 listed in Table II.

(5) L. O. Randall, G. A. Heise, W. Schallek, R. E. Bagdon, R. Banziger, A. Boris, R. A. Moe, and W. B. Abrams, *Current Therap. Res.*, **3**, 405 (1961).

TABLE I

S-SUBSTITUTED 2-MERCAPTO ACIDS, $R_2C(SR^1)COOH$

No.	R	R^1	B.p., °C. (mm.)	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H	Acid chloride B.p., °C. (mm.)	Yield, %
1	CH_3	C_4H_9	150 (15)	73	$C_8H_{16}O_2S$	54.51	9.15	54.51	9.02	101–103 (15)	84
2	CH_3	$CH_2CH{=}CH_2$	125 (7)	86	$C_7H_{12}O_2S$	52.47	7.55	52.17	7.62	91–94 (15)	88.5
3	CH_3	$CH_2CH{=}CH{-}CH_3$	107 (0.2)	83	$C_8H_{14}O_2S$	55.14	8.10	55.10	7.80	99–102 (15)	90
4	CH_3	$CH_2C{\equiv}CH$	[a]	87	$C_7H_{10}O_2S$	53.14	6.37	53.58	6.40	98–101 (13)	89.5
5	C_2H_5	CH_3	133 (10)	70	$C_7H_{12}O_2S$	51.82	8.70	52.16	8.34	77–79 (8)	90
6	C_2H_5	C_2H_5	157 (18)	80	$C_8H_{16}O_2S$	54.51	9.15	54.57	9.02	109–112 (15)	89.5
7	C_2H_5	C_3H_7	106 (0.2)	78	$C_9H_{18}O_2S$	56.80	9.53	56.67	9.70	124–126 (18)	92
8	C_2H_5	C_4H_9	125 (0.2)	85	$C_{10}H_{20}O_2S$	[b]				116–118 (7)	84
9	C_2H_5	$CH_2CH{=}CH_2$	110 (0.3)	82.5	$C_9H_{16}O_2S$	57.41	8.57	57.71	8.36	121–125 (16)	91
10	C_2H_5	$CH_2CH{=}CH{-}CH_3$	127 (0.3)	61	$C_{10}H_{18}O_2S$	59.37	8.97	59.62	8.77	127–130 (15)	95
11	C_2H_5	$CH_2C{\equiv}CH$	115 (0.1)	77	$C_9H_{14}O_2S$	58.03	7.58	58.41	7.38	98–101 (13)	92

[a] M.p. 37–38°. [b] Converted to the acid chloride without prior purification.

TABLE II

SUBSTITUTED 2-MERCAPTOISOBUTYRAMIDES, $(CH_3)_2C(SR^1)CONHR^2$

No.	R^1	R^2	M.p., °C.	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	CH_2	H	110–112	36.5	$C_5H_{11}NOS$	45.08	8.33	45.42	8.35
2	CH_3	CH_3	45–46	49	$C_6H_{13}NOS$	48.94	8.90	48.76	8.82
3	C_2H_5	H	91–92	75.5	$C_6H_{13}NOS$	[a]			
4	n-C_3H_7	H	93–94	78	$C_7H_{15}NOS$	[a]			
5	i-C_3H_7	H	84–85	96	$C_7H_{15}NOS$	52.13	9.38	52.11	9.07
6	i-C_3H_7	CH_3	39–40	55	$C_8H_{17}NOS$	54.81	9.78	54.63	9.33
7	C_4H_9	H	107–108	96.5	$C_8H_{17}NOS$	[a]			
8	$CH_2CH{=}CH_2$	H	75–76	94	$C_7H_{13}NOS$	52.80	8.23	52.91	7.72
9	$CH_2CH{=}CH_2$	CH_3	59–60	85.5	$C_8H_{15}NOS$	55.45	8.73	55.51	8.33
10	$CH_2CH{=}CH{-}CH_3$	H	91–93	62	$C_8H_{15}NOS$	55.45	8.73	55.76	8.63
11	$CH_2CH{=}CH{-}CH_3$	CH_3	42–43	68	$C_9H_{17}NOS$	57.71	9.15	57.87	8.78
12	$CH_2C{\equiv}CH$	H	75–76	82	$C_7H_{11}NOS$	53.47	7.05	53.29	7.22
13	$CH_2C{\equiv}CH$	CH_3	64–66	50	$C_8H_{13}NOS$	55.78	7.61	55.90	6.95

[a] See footnote 3.

TABLE III

SUBSTITUTED 2-ETHYL-2-MERCAPTOBUTYRAMIDES, $(C_2H_5)_2C(SR^1)CONR^2R^3$

No.	R^1	R^2	R^3	M.p., °C.	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	CH_3	H	H	101–103	86.5	$C_7H_{15}NOS$	52.13	9.38	51.93	9.43
2	CH_3	CH_3	H	55–56	90	$C_8H_{17}NOS$	54.81	9.78	55.23	9.64
3	C_2H_5	H	H	54–55	93	$C_8H_{17}NOS$	54.81	9.78	55.14	9.73
4	C_2H_5	C_6H_{11}	H	72–73	91	$C_{14}H_{27}NOS$	65.31	10.57	65.35	10.38
5	C_2H_5	$CH_2CH{=}CH_2$	H	[b]	83.5	$C_{12}H_{23}NOS$	61.35	9.83	61.62	10.10
6	C_2H_5	C_2H_5	C_2H_5	[c]	87	$C_{12}H_{25}NOS$	62.28	10.89	62.53	10.78
7	C_2H_5	CH_2CH_2 / CH_2CH_2 CH_2		[d]	85	$C_{13}H_{25}NOS$	64.15	10.35	64.15	10.00
8	C_3H_7	H	H	43–44	76.5	$C_9H_{19}NOS$	57.10	10.12	57.16	10.09
9	C_3H_7	CH_3	H	[e]	82	$C_{11}H_{23}NOS$	59.06	10.41	58.98	10.31
10	C_4H_9	H	H	35–36	75	$C_{10}H_{21}NOS$	59.06	10.41	59.14	10.41
11	C_4H_9	CH_3	H	[f]	79	$C_{11}H_{23}NOS$	60.78	10.66	60.97	10.35
12	$CH_2CH{=}CH_2$	H	H	39–40	83	$C_9H_{17}NOS$	57.71	9.15	58.04	9.03
13	$CH_2CH{=}CH_2$	CH_3	H	46–48	83	$C_{10}H_{19}NOS$	59.66	9.51	59.88	9.46
14	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	H	[g]	76	$C_{12}H_{21}NOS$	63.39	9.31	63.43	9.21
15	$CH_2CH{=}CH{-}CH_3$	H	H	66–68	91	$C_{10}H_{19}NOS$	59.66	9.51	59.80	9.16
16	$CH_2CH{=}CH{-}CH_3$	CH_3	H	[h]	56.5	$C_{11}H_{21}NOS$	61.35	9.83	61.11	10.13
17	$CH_2C{\equiv}CH$	H	H	79–81	94	$C_9H_{15}NOS$	58.35	8.16	58.60	7.99
18	$CH_2C{\equiv}CH$	CH_3	H	69–71	82	$C_{10}H_{17}NOS$	60.26	8.60	60.74	8.47

[a] B.p. 125° (1.5 mm.). [b] B.p. 98–99° (0.3 mm.). [c] B.p. 116–118° (0.3 mm.). [d] B.p. 130° (7 mm.). [e] B.p. 113° (0.5 mm.). [f] B.p. 132° (1.5 mm.). [g] B.p. 129° (1 mm.).

TABLE IV

SULFONES

$R_2C(CONR^2R^3)(SO_2R^1)$

No.	R	R^1	R^2	R^3	M.p., °C.	Yield, %	Formula	—Calcd., %— C	H	—Found, %— C	H
1	CH_3	C_2H_5	H	H	90–91	71	$C_6H_{13}NO_3S$	[a]			
2	CH_3	C_3H_7	H	H	83–84	67	$C_7H_{15}NO_3S$	[a]			
3	CH_3	C_4H_9	H	H	76–77	84.5	$C_8H_{17}NO_3S$	[a]			
4	C_2H_5	C_2H_5	H	H	99–100	64	$C_8H_{17}NO_3S$	46.36	8.27	46.34	8.39
5	C_2H_5	C_2H_5	C_6H_{11}	H	73–74	89	$C_{14}H_{27}NO_3S$	58.09	9.41	58.30	9.56
6	C_2H_5	C_2H_5	C_2H_5	C_2H_5	48–50	87	$C_{12}H_{25}NO_3S$	54.72	9.57	54.61	9.41
7	C_2H_5	C_2H_5	CH_2CH_2 / CH_2CH_2	CH_2	42–43	49	$C_{13}H_{25}NO_3S$	56.70	9.15	56.65	9.35
8	C_2H_5	C_3H_7	H	H	58–60	64	$C_9H_{19}NO_3S$	48.84	8.65	49.07	8.42

[a] See footnote 3.

TABLE V

PHARMACOLOGY OF SUBSTITUTED 2-MERCAPTOISOBUTYRAMIDES LISTED IN TABLE II

	—Mice—						—Cats—	
Compound no.	Toxicity LD_{50}, mg./kg.	Inclined screen PD_{50}, mg./kg. p.o.	Hypnosis HD_{50}, mg./kg.	Anti-strychnine MED mg./kg. p.o.	Anti-pentylenetetrazole ED_{50}, mg./kg. p.o.	Anti-maximal electroshock ED_{50}, mg./kg. p.o.	Dose, mg./kg.	Symptoms
1	>1600 i.p.	450	700 i.p.	>500	267	667	300	Ataxia
2	>1600 i.p.	>500	700 i.p.	500				
3	1750 p.o.	225	1071 p.o.	400				
4	2733 p.o.	400	1800 p.o.					
	862 i.p.		200 i.p.	500	600	600		
5	2250 p.o.	200	500 p.o.	400	667		100	Ataxia
	800 i.p.		342 i.p.					
6	635 i.p.	250	420 i.p.	400			100	Ataxia
7	>4000 p.o.	>500	1900 p.o.		>800	667		
8[a]	2000 p.o.	300	740 p.o.					
	1400 i.p.		386 i.p.	400	600	400	50	Ataxia
							100	Ataxia
								Paralysis
9		300		500			100	Ataxia
	>85 i.p.		386 i.p.				200	Paralysis
10		500	1250 p.o.	500	>800		100	Ataxia
	>800 i.p.		344 i.p.					
11	1475 p.o.	362	900 p.o.				100	Weakness
	552 i.p.		261 i.p.	500	800			
12	1300 p.o.	350	658 p.o.	500	600		50	Weakness
	1030 i.p.		413 i.p.				100	Ataxia
13	1542 p.o.	450	900 p.o.	500			100	Ataxia
	1325 i.p.		511 i.p.					

[a] Dog, 160 mg./kg. p.o., sleep, ataxia.

Experimental[6]

Substituted 2-Mercaptoisobutyramides (Table II).—The preparation of 2-allylmercaptoisobutyramide (8) is described as a representative example.

To a cooled solution of 52.2 g. of sodium in 1500 ml. of ethanol was added 136 g. of 2-mercaptoisobutyric acid.[7] Allyl bromide (143.5 g.), diluted with 100 ml. of ethanol, was then added gradually, and the mixture stirred for 18 hr. at room temperature under nitrogen. After removal of the solvent *in vacuo*, the residue was dissolved in water and the solution acidified and extracted with ether. The ether extract was dried over sodium sulfate. After removal of the solvent, the residue was fractionated *in vacuo*, yielding 156 g. (86%) of 2-allylmercaptoisobutyric acid, boiling at 25° (7 mm.) (Table I, 2). The acid was converted to the acid chloride by refluxing for 2 hr. with 250 ml. of thionyl chloride. Fractionation *in vacuo* yielded 154 g. (88.5%) of 2-allylmercaptoisobutyryl chloride, boiling at 91–94° (15 mm.).

A solution of 149 g. of 2-allylmercaptoisobutyryl chloride in 500 ml. of absolute ether was added slowly to an ice-cooled solution of 53 g. of ammonia in 1000 ml. of absolute ether. After standing overnight at room temperature, the solvent was removed *in vacuo* and the residue recrystallized from ligroin (60–90°). The pure 2-allylmercaptoisobutyramide melted at 75–76°; yield, 125 g. (94%).

By an alternate procedure, 50 g. of 2-allylmercaptoisobutyryl chloride was added, while stirring and cooling, to 500 ml. of concd. aqueous ammonia and ammonia gas passed through the mixture for 6 hr. After standing for 18 hr. in the refrigerator, the 2-allylmercaptoisobutyramide was filtered off, dried *in vacuo*, and recrystallized from ligroin (60–90°); m.p. 75–76°; yield 35 g. (78.5%).

Substituted 2-Ethyl-2-mercaptobutyramides (Table III).—The preparation of 2-ethyl-2-ethylmercaptobutyramide (3) is described as a representative example.

Method A.—To a cooled, stirred solution of 30.3 g. of sodium in 900 ml. of ethanol was slowly added 97.5 g. of 2-ethyl-2-mercaptobutyric acid[2] in a nitrogen atmosphere. Ethyl bromide (79 g.), diluted with 100 ml. of ethanol, was then added gradually,

(6) All melting points were determined in a Thomas–Hoover melting point apparatus and are corrected.

(7) E. Biilman, *Ann.*, **348**, 129 (1906).

TABLE VI

PHARMACOLOGY OF SUBSTITUTED 2-ETHYL-2-MERCAPTOBUTYRAMIDES LISTED IN TABLE III

	Mice						Cats	
Compound no.	Toxicity LD_{50}, mg./kg.	Inclined screen PD_{50}, mg./kg. p.o.	Hypnosis HD_{50}, mg./kg.	Anti-strychnine MED mg./kg. p.o.	Anti-pentylene-tetrazole-ED_{50}, mg. kg. p.o.	Anti-maximal electroshock ED_{50}, mg. kg. p.o.	Dose, mg./kg.	Symptoms
1	575 i.p.	75	167 i.p.	>200	300	300	50	Ataxia
								Weakness
2	2089 p.o.	250	920 p.o.	500	>400		100	Ataxia
	575 i.p.		315 i.p.					Weakness
3	1125 p.o.	75	225 p.o.	200	83	300	25	Weakness
	285 i.p.		90 i.p.				50	Ataxia
	110 i.v.		30 i.v.				100	Paralysis
4	675 i.p.		None	>1000	>800	>800		
5	800 i.p.	400	800 i.p.	500				
8	1576 p.o.	100	839 p.o.	500	533	333	50	Weakness
							100	Ataxia
	419 i.p.		138 i.p.					Paralysis
9	1900 p.o.	200	825 p.o.	400			50	No effect
	1185 i.p.		233 i.p.		800	800	100	Paralysis
10	488 i.p.	>500	304 i.p.		600	600		
11	713 i.p.	450	194 i.p.					
12[a]	891 p.o.	100	417 p.o.	>200	300	600	25	Ataxia
	450 i.p.		187 i.p.				50	Paralysis
							100	Loss of righting reflex, head drop
13	1000 p.o.	300	782 p.o.	500			200	Ataxia
								Weakness
14	715 i.p.	450	630 i.p.	500				
15	2733 p.o.	>500	1350 p.o.		>800	667		
	825 i.p.		206 i.p.					
16	2090 p.o.	250	829 p.o.	>400				
	950 i.p.		213 i.p.					
17[b]	610 p.o.	75	210 p.o.	200	83	148	50	Ataxia
	367 i.p.		109 i.p.				100	Loss of righting reflex
18		200		400	>800	250	50	Ataxia
	581 i.p.		300 i.p.				100	Ataxia

[a] Monkey, 80 mg./kg. p.o., ataxia; 160 mg./kg. p.o., sleep. Dog, 40 mg./kg. p.o., ataxia; 80 mg./kg. p.o., sleep. [b] Monkey, 40 mg./kg. p.o., ataxia, 80 mg./kg. p.o. marked ataxia. Dog, 40 mg./kg. p.o., ataxia; 80 mg./kg. p.o., sleep.

TABLE VII

PHARMACOLOGY OF SULFONES LISTED IN TABLE IV

	Mice						Cats	
Compound no.	Toxicity LD_{50}, mg./kg.	Inclined screen, PD_{50}, mg./kg. p.o.	Hypnosis HD_{50}, mg./kg.	Anti-strychnine MED, mg./kg. p.o.	Anti-pentylene-tetrazole ED_{50}, mg. kg. p.o.	Anti-maximal electroshock ED_{50}, mg. kg. p.o.	Dose, mg./kg.	Symptoms
1	>4000 p.o.	>1000	None	667	>800			
2	>800 i.p.	>500	None		533	>800		
3	>800 i.p.	>500	None		272			
4	1750 p.o.	300	538 p.o.	>800	100	600		
5	>800 p.o.		None	>800	>800	>800		
6	225 p.o.		None		>800	>800		
7	387 i.p.		None		>800	>800		
8	1333 p.o.	250	625 p.o.	500	167	533	100	Weakness

and the reaction mixture stirred for 18 hr. at room temperature. After removal of the solvent *in vacuo*, the residue was dissolved in water and the solution was acidified and extracted with ether. The ether extract was dried over sodium sulfate. After removal of the solvent, the residue was fractionated *in vacuo*, yielding 93 g. (80%) of 2-ethyl-2-ethylmercaptobutyric acid, boiling at 157° (18 mm.) (Table I, 6). The acid was converted to the acid chloride by refluxing for 2 hr. with 140 ml. of thionyl chloride. Fractionation *in vacuo* yielded 92 g. (89.5%) of 2-ethyl-2-ethylmercaptobutyrylchloride, boiling at 109–112° (15 mm.).

A solution of 87 g. of 2-ethyl-2-ethylmercaptobutyrylchloride in 400 ml. of absolute ether was added gradually to an ice-cooled solution of 30 g. of ammonia in 500 ml. of absolute ether. After standing for 6 hr. at room temperature, water was added and the organic layer was separated and dried over sodium sulfate. After removal of the solvent, the residue was recrystallized from petroleum ether. The pure 2-ethyl-2-ethylmercaptobutyramide melted at 54–56°; yield 73 g. (93%).

Method A was used for the preparation of all other compounds listed in Table III.

Method B.—This was used only for the preparation of 2-ethyl-2-ethylmercaptobutyramide. Ethyl mercaptan (22 g.) was

added to a solution of 7.1 g. of sodium in 150 ml. of ethanol. To the mixture was added a solution of 60 g. of 2-bromo-2-ethylbutyramide[8] in 100 ml. of ethanol and the reaction mixture refluxed for 16 hr. under nitrogen. The precipitated sodium bromide was filtered off and the solvent removed *in vacuo*. The residue was dissolved in 300 ml. of acetone, filtered from additional sodium bromide, and the filtrate evaporated to dryness. The residue was recrystallized from petroleum ether, yielding 27 g. (54%) of 2-ethyl-2-ethylmercaptobutyramide, melting at 54–55°.

Sulfones (Table IV).—The preparation of 2-ethyl-2-ethylsulfonylbutyramide (4) is described as a representative example. 2-Ethyl-2-ethylmercaptobutyramide (27 g.) was dissolved in 100 ml. of a mixture of acetic acid–acetic anhydride (5:1). To the ice-cooled solution was added, in portions, 40 ml. of 30% hydrogen peroxide. After the addition was completed, the mixture was kept in the cooling bath for 3 hr. and then at room temperature for 3 days. The solvent was removed *in vacuo*, and the residue treated repeatedly by dissolving in benzene and removing the solvent *in vacuo*. Recrystallization from benzene–petroleum ether yielded 20.4 g. (64%) of 2-ethyl-2-ethylsulfonylbutyramide, melting at 99–100°.

(8) G. Fuchs, *Angew. Chem.*, **17**, 1505 (1904).

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Strong Analgesics: Some N-(Piperidinoalkyl)-anilides

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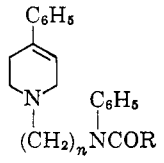
A number of N-(piperidinoalkyl) anilides have been prepared and tested for analgesic activity. One of these compounds, 1-[2-(N-phenylpropionamidoethyl)]-4-phenyl-4-piperidinol, was approximately fifty times as potent as meperidine. Several others also possessed strong analgesic activity.

One of the unsuccessful methods tried for the synthesis of 1-(2-anilinoethyl)-4-phenyl-4-propionoxypiperidine, a potent analgesic,[1] was a preferential O-acylation of 1-(2-anilinoethyl)-4-phenyl-4-piperidinol dihydrochloride using propionic anhydride as the acylating agent. The crystalline product, isolated in low yield, was found to be a mixture of N-[2-(4-phenyl-1,2,3,6-tetrahydropyridino)ethyl]-propionanilide (I, n = 2, R = C_2H_5) and N-[2-(4-hydroxy-4-phenylpiperidino)-ethyl]-propionanilide (II, n = 2, R = C_2H_5). Pure samples of each of these compounds were prepared and tested for analgesic activity, but only II (n = 2, R = C_2H_5) proved to be a potent analgesic, having about 50 times the activity of meperidine.



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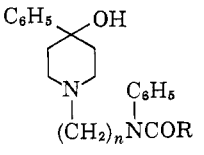

II

On the basis of these observations, it seemed desirable to prepare additional compounds based on structures I and II in which n and R were varied, and saturated analogs of I, quaternaries, O-acyl derivatives, 3-methyl derivatives, and compounds in which the anilide benzene ring was substituted. Melting points and analytical data for the compounds prepared are listed in Table I.

Most of the compounds of series I and II were prepared by N-alkylation of either 4-phenyl-1,2,3,6-tetrahydropyridine, 4-phenyl-4-piperidinol, or 3-methyl-4-phenyl-4-piperidinol[1] with the appropriate anilinoalkyl bromide followed by acylation with the appropriate acid chloride or anhydride. A *m*-hydroxyanilide, 1-[2-N-(3-hydroxyphenyl)propionamidoethyl]-4-phenyl-4-piperidinol, was prepared from *m*-benzyloxyaniline as described in the Experimental section.

All modifications of structure II (n = 2, R = C_2H_5) decreased activity. Saturation of the Δ^3 double bond was the only modification which appreciably increased activity in structure I (n = 2, R = C_2H_5).

It is of interest to note that N(1-methyl-2-piperidinoethyl)propionanilide, reported[2] while this work was in progress, possessed about $^1/_{50}$ of the activity of II (n = 2, R = C_2H_5).

Experimental[3]

1-(2-Anilinoethyl)-4-phenyl-4-piperidinol.—A mixture of 4-phenyl-4-piperidinol[4] (26.6 g., 0.15 mole), 2-anilinoethyl bromide hydrobromide[5] (47.8 g., 0.17 mole), 60 ml. of triethylamine, and 300 ml. of chloroform was refluxed for 24 hr., cooled and washed well with water. The chloroform solution was dried over sodium sulfate and concentrated to a red oil which completely crystallized after standing for 1 week. It was recrystallized from cyclohexane using decolorizing charcoal; m.p. 101–103°, 26 g. (58.5%).

A small portion was converted to the **dihydrochloride** and recrystallized from ethanol–ether; m.p. 158.6–160.4°.

Anal. Calcd. for $C_{19}H_{24}N_2O \cdot 2HCl$: Cl, 19.2; O, 4.33. Found: Cl, 19.15; O, 4.37.

1-(3-Anilinopropyl)-4-phenyl-4-piperidinol.—This compound was prepared by the procedure described for 1-(2-anilinoethyl)-4-phenyl-4-piperidinol, using 3-anilinopropylbromide hydrobromide,[6] m.p. 91–93°, yield 65%.

(1) P. M. Carabateas and L. Grumbach, *J. Med. Pharm. Chem.*, **5**, 913 (1962).

(2) W. B. Wright, H. A. Brabander, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **81**, 1518 (1959).

(3) All melting points were taken in a modified Hershberg apparatus and are corrected.

(4) C. J. Schmidle and R. C. Mansfield, *J. Am. Chem. Soc.*, **78**, 1702 (1956).

(5) W. M. Pearlman, *ibid.*, **70**, 871 (1948).

(6) B. Elpern, P. M. Carabateas, and L. Grumbach, *J. Org. Chem* **26**, 4728 (1961).