dry benzene was added and the mixture refluxed for 3 hr. on the steam bath. The cooled mixture was diluted with benzene, filtered with charcoal, and evaporated under reduced pressure. The residue (*ca.* 2.8 g.) was dissolved in 8 ml. of commercial absolute ethanol and to this solution was added 1.6 g. of *d*-tartaric acid. This was dissolved by heating until the solution was clear. After standing in the refrigerator, there was obtained 3.9 g. (60%) of a yellow crystalline solid, m.p. 140–142°. Upon recrystallization from commercial absolute ethanol, fine yellow granules separated, m.p. 142–144°.

β-Dimethylaminoethyl cinnoline-4-carboxylate. After cooling the acid chloride mixture as prepared above, a solution of 5.5 g. of dimethylaminoethanol in 10 ml. of dry benzene was added and the mixture heated and stirred on the steam bath for 2 hr. The cooled mixture was diluted with ether, treated with charcoal, and filtered. After evaporation of the solvents, there was obtained 4.86 g. (70%) of a red sirup, boiling at 165–173° at 0.073 mm.

Monopicrate, m.p. 194–196°, yellow needles from methanol.

Anal. Calcd. for $C_{19}H_{18}N_6O_9$: C, 48.10; H, 3.82; N, 17.72. Found: C, 48.35; H, 3.92; N, 17.89.

Preparation of the tertiary aminoalkyl cinnoline-4-carboxamides. The procedure is illustrated with the synthesis of *N*-γ-dimethylaminopropyl cinnoline-4-carboxamide. After cooling the acid chloride mixture as prepared above, 4.2 g. of γ-dimethylaminopropylamine in 10 ml. of dry benzene was added over a period of 10 min. with stirring while the reaction mixture was kept in an ice bath. The mixture was stirred for 1 hr. at room temperature. The mixture was diluted, treated with charcoal, and filtered. After evaporation of the solvents there was obtained 3.5 g. (72%) of a red sirup, boiling at 202–205° at 0.07 mm.

4-Chlorocinnoline. This compound was prepared by the method of Leonard and Boyd.[7] Since this compound is unstable,[8] it was prepared in small quantities and used immediately. It was not necessary to purify the 4-chlorocinnoline by recrystallization but it was used directly upon recovery from the dried ether solution, m.p. 74–76°.

Preparation of aminoalkoxy ethers. The procedure is illustrated with the synthesis of 4-β-dimethylaminoethoxycinnoline.

To a solution of 4.3 g. of β-dimethylaminoethanol in 34 ml. of anhydrous benzene was added 0.57 g. of metallic sodium. The reaction mixture was refluxed on a steam bath until all the sodium had dissolved. In this instance 1 hr. heating was required. After cooling the reaction mixture in an ice bath, 3.4 g. of 4-chlorocinnoline was added and the mixture refluxed for 4 hr. on a steam bath, whereupon the solution became dark red. After allowing the reaction mixture to cool, it was diluted with dry ether, filtered with charcoal, and the solution evaporated.[9] The ether residue was distilled under reduced pressure. There was obtained 3.7 g. (83%) of a red sirup, bp. 162–167° at 0.05 mm. which after standing solidified to a pale yellow solid, m.p. 70–73°C., which after recrystallization from petroleum ether (b.p. 60–90°) gave pale yellow plates, m.p. 74–76°.

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ALBUQUERQUE, N. M.

(7) N. J. Leonard and S. N. Boyd, Jr., *J. Org. Chem.*, **11**, 423 (1946).

(8) M. Busch and K. Klett, *Ber.*, **25**, 2849 (1892).

(9) The ethers were very water soluble and, thus, it was necessary to avoid the use of water in the isolation procedure in order to obtain satisfactory yields.

[CONTRIBUTION FROM WYETH LABORATORIES, INC., RESEARCH AND DEVELOPMENT DIVISION]

A New Class of Local Anesthetics: Hydroxyalkyliminobisacetamides[1]

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A series of hydroxyalkyliminobisacetamides and their esters was prepared and examined for local anesthetic action. The compounds derived from *N*-α,α-trimethylphenethylamine showed a high degree of activity, some examples being 4000 times as active as procaine. Structure-activity relationships were studied in the course of this investigation.

During an investigation of the synthesis and pharmacology of basically substituted derivatives of acetamide several hydroxyalkylaminoacetamides[2] possessed appreciable local anesthetic activity. A more critical study of one of these, *N*-methyl-*N*-α,α - dimethylphenethyl - 2 - hydroxyethylaminoacetamide (I), revealed that this action was not due to the acetamide, but to a trace of commingled 2 - hydroxyethyliminobis[*N* - methyl - *N* - (α,α-dimethylphenethyl)acetamide] (II).

$$HOCH_2CH_2NHCH_2CON(CH_3)C(CH_3)_2CH_2C_6H_5$$

$$\text{I}$$

The preparation of the latter compound and its subsequent testing showed it to be an extremely potent local anesthetic, at least 4000 times as active as procaine.[3]

To establish the structural requirements for activity in this series a study was made of the effect of variation in sections of the molecule on activity. The compounds prepared had the general formula III, wherein X is alkyl, cycloalkyl, or

$$HO.X.N\begin{cases} CH_2\text{—}CONRR^1 \\ CH_2CONR^2R^3 \end{cases} \qquad \begin{aligned} &\text{II. } X = CH_2CH_2\text{—} \\ &R = R_2 = CH_3 \\ &R_1 = R_3 = C(CH_3)_2CH_2C_6H_5 \end{aligned}$$

$$\text{III}$$

(1) Presented in part before the Medicinal Chemistry Section, Delaware Valley Regional Meeting, Philadelphia, Feb. 25, 1960, abstracts p. 21.

(2) W. F. Bruce and J. Seifter, U. S. Patents: (a) **2,778,834** (1957); (b) **2,856,427** (1958).

(3) J. M. Glassman, G. H. Hudyma, and J. Seifter, *J. Pharm. Exptl. Therap.*, **119**, 150 (1957).

TABLE I

HYDROXYALKYLAMINOACETAMIDES

R—NHCH$_2$CON(R′)(CH$_3$)

No.	R	R′	HCl Salt M.P.	Formula	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
1	$HOCH_2CH_2$	$C_6H_5CH_2C(CH_3)_2$	[a]	$C_{15}H_{24}N_2O_2$	10.60	10.90		
2	$C_6H_5CHOHCH_2$	$C_6H_5CH_2C(CH_3)_2$	201–202	$C_{21}H_{28}ClN_2O_2$	7.43	7.34	9.42	9.50
3	$C_6H_5CHOHC(CH_3)_2$	$C_6H_5CH_2C(CH_3)_2$	189–190	$C_{21}H_{29}ClN_2O_2$	6.92	6.75	8.77	8.55
4	$HOCH_2C(CH_3)_2$	$C_6H_5CH_2C(CH_3)_2$	169–170	$C_{17}H_{29}ClN_2O$	8.00	8.26	10.82	11.01
5	$(HOCH_2)_3C$	$C_6H_5CH_2C(CH_3)_2$	175–176	$C_{17}H_{29}ClN_2O_4$	7.80	7.77	9.88	9.58
6	$HOCH(CH_3)CH_2$	$C_6H_5CH_2$	134–135	$C_{13}H_{21}ClN_2O_2$	10.25	10.20	13.12	13.47

[a] Free base (from petroleum ether): m.p. 76–77°.

aralkyl, R, R^1, R^2, R^3 represent lower alkyl or aralkyl, and where RR^1 may or may not equal R^{2}R^3.

The symmetrically substituted compounds (RR^1 = R^{2}R^3) were prepared by treatment of an amino alcohol with two equivalents of a chloroacetamide. The asymmetrically substituted compounds were obtained in two steps by treatment of an amino alcohol with one equivalent of chloroacetamide to yield the hydroxyalkylaminoacetamide which was then converted to the iminoacetamide by further treatment with one equivalent of a second chloroacetamide.

These alkylations were generally carried out in refluxing butanol in the presence of excess potassium carbonate. In the case of several sterically hindered amino alcohols, *e.g.*, 2-amino-2-methylpropanol, it was necessary to use a higher boiling solvent such as anisole to obtain the bis compounds. The required chloroacetamides were prepared by literature methods.

As a result of these studies a number of structure-activity relationships became apparent. Of the iminoacetamides which we examined, those in which the amido nitrogen was derived from aliphatic amines had relatively little local anesthetic action and were more toxic than those derived from aralkylamines. The use of a sterically hindered amine, *N* - α,α - trimethyl - β - phenethylamine (mephentermine), produced the highest degree of local anesthetic activity found in these bisacetamides; substitution of *N*-α-dimethylphenethylamine for mephentermine in one amide group halved the activity. In the alkanolamine portion, use of a sterically hindered base such as 2-amino-2-methylpropanol produced the opposite effect, markedly reducing activity. A more critical factor, however, was the number of methylene groups separating the hydroxyl from the tertiary amino group. Activity dropped sharply with the addition of even one methylene. Thus the 3-hydroxypropyl derivative (Table III, No. 4) shows only 1/500 the effectiveness of the homologous 2-hydroxyethyl compound (Table III, No. 1).

The effect of altering the chemical type was also examined. Replacement of hydroxyl by amino or chloro, quaternarization of the tertiary amine, reduction of the amide groups to tertiary amines, all resulted in nearly complete loss of activity (Table VI). Ester formation with either aliphatic or aromatic acids yielded active compounds (Table V), but in no instance was the activity increased by this change.

A portion of the results of pharmacologic studies of the hydroxyalkyliminobisacetamides has been presented elsewhere.[4,5] The more detailed pharmacology of these materials will appear in a forthcoming publication from these laboratories.

EXPERIMENTAL

Since the preparation of all chloroacetamides, hydroxyalkylaminoacetamides, hydroxyalkyliminoacetamides, and their esters was carried out in essentially the same manner, one example of each is given.

N-Methyl-N-α,α-dimethylphenethylchloroacetamide. To a solution of 140 g. (0.86 mole) of *N*-methyl-*N*-α,α-dimethylphenethylamine in 500 ml. of toluene was added, with stirring, and at −20°, 45 g. (0.40 mole) of chloroacetyl chloride. The rate of addition was such that the temperature remained below −15°. The reaction was stirred 1 hr. in the cold and allowed to come to room temperature. The solid amine hydrochloride was removed by filtration and washed with a little toluene. The filtrate was dried, concentrated under reduced pressure, and the residue distilled to give 67.5 g. (70.5%) of product, b.p. 140–141° (0.5 mm.).

Anal. Calcd. for $C_{13}H_{18}ClNO$: Cl, 14.83; N, 5.85. Found: Cl, 14.51; N, 5.62.

N-Methyl-N-α,α-dimethylphenethyl-2-hydroxyethylaminoacetamide.[6] To a well stirred mixture of 6.1 g. (0.1 mole) of ethanolamine and 30 g. of anhydrous powdered sodium carbonate in 300 ml. of boiling 1-butanol, was added slowly 23.9 g. (0.1 mole) of *N*-methyl-*N*-α,α-dimethylphenethylchloroacetamide in 50 ml. 1-butanol. The reaction mixture was refluxed for 12 hr., cooled, and filtered. The solution was concentrated and the residue crystallized from hexane. There was obtained 16.6 g. (63%), m.p. 74.5–76.5°.

Anal. Calcd. for $C_{15}H_{24}N_2O_2$: C, 68.30; H, 9.16; N, 10.58. Found: C, 67.94; H, 8.90; N, 10.90.

The hydrochloride had a m.p. of 163–164°.

Anal. Calcd. for $C_{15}H_{25}ClN_2O_2$: N, 9.32; Cl, 11.78. Found: N, 9.15; Cl, 11.59.

2-Hydroxyethyliminobis[N-methyl-N(α,α-dimethylphen-

(4) D. H. Baeder, J. M. Glassman, G. M. Hudyma, and J. Seifter, *Proc. Soc. Exptl. Biol. Med.*, **89**, 645 (1955).

(5) J. M. Glassman, G. M. Hudyma, and J. Seifter, *J. Pharm. Exptl. Therap.*, **119**, 150 (1957).

(6) J. Seifter, R. S. Hanslick, and M. E. Freed, U. S. Patent **2,780,646** (1957).

TABLE II

HYDROXYALKYLIMINOBISACETAMIDES

R—N($CH_2CONR^1R^2$)$_2$

No.	R	R^1	R^2	B.P.	Formula	Carbon		Hydrogen		Nitrogen		Duration of Activity[a]	(% Soln.)
						Calcd.	Found	Calcd.	Found	Calcd.	Found		
1	$HOCH_2CH_2$	CH_3CH_2	CH_3CH_2	203–205/1 mm.	$C_{14}H_{29}N_3O_3$	58.20	57.90	10.17	9.83	14.61	14.35	Neg.	0.1
2	$HOCH_2CH_2$	$CH_3(CH_2)_2CH_2$	$CH_3(CH_2)_2CH_2$	208–210/0.5 mm.	$C_{22}H_{45}N_3O_3$	66.21	65.89	11.30	11.08	10.50	10.24	25 min.	0.01
3	$CH_3CHOHCH_2$	$CH_3(CH_2)_2CH_2$	$CH_3(CH_2)_2CH_2$	200–205/0.1 mm.	$C_{23}H_{47}N_3O_3$	66.75	66.40	11.40	11.62	10.13	10.26	Neg.	0.1
4	$HOCH_2CH_2$	$(CH_3)_2CHCH_2$	$(CH_3)_2CHCH_2$	170–171/0.5 mm.	$C_{22}H_{45}N_3O_3$	66.21	66.58	11.30	11.18	10.50	10.26	Neg.	0.1
5	$HOCH_2CH_2CH_2$	$(CH_3)_2CHCH_2$	$(CH_3)_2CHCH_2$	190–192/0.5 mm.	$C_{23}H_{47}N_3O_3$	66.75	67.1	11.40	11.25	9.33	9.63	Neg.	0.1
6	$HOCH_2C(CH_3)_2$	$CH_3(CH_2)_2CH_2$	$CH_3(CH_2)_2CH_2$	155–160/0.5 mm.	$C_{23}H_{49}N_3O_3$	67.3	67.7	11.5	11.3	9.35	9.52	Neg.	0.1
7	$HOCH_2C(CH_3)_2$	CH_3CH_2	$CH_3(CH_2)_2CH_2$	170–175/0.5 mm.	$C_{20}H_{41}N_3O_3$	64.80	64.42	11.12	10.87	11.30	11.20	Neg.	0.1
8	$HOCH_2CH_2$	$CH_3(CH_2)_3CH_2$	$CH_3(CH_2)_3CH_2$	230–235/1 mm.	$C_{26}H_{53}N_3O_3$	68.40	68.1	11.98	11.75	9.22	8.91	25 min.	0.01
9	$HOCH_2CH_2$	C_6H_{11}	C_6H_{11}	[b]	$C_{30}H_{54}ClN_3O_3$	[c]				7.82	7.50	Neg.	0.1
10	$HOCH_2CH_2$	$CH_3(CH_2)_4CH_2$	$CH_3(CH_2)_4CH_2$	194–196/0.5 mm.	$C_{30}H_{61}N_3O_3$	70.5	70.18	12.00	11.85	8.25	8.15	48 min.	0.1

[a] Compounds were not tested at concentrations greater than 0.1%. Compounds were tested by application to the corneas of rabbits. [b] Hydrochloride, m.p. 215–216°. [c] Cl, Calcd. 6.62; found, 6.41.

ethyl)acetamide].[6] To a stirred mixture of 23.9 g. (0.1 mole) of *N*-methyl-*N*-α,α-dimethylphenethylchloroacetamide and 20 g. of potassium carbonate in 250 ml. of boiling butanol was added a solution of 3.1 g. (0.05 mole) of freshly distilled ethanolamine. After 20 hr. under reflux the reaction mixture was cooled and filtered. The filtrate was washed with aqueous 5% sodium carbonate, then with water, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue recrystallized from benzene-hexane, yielding 33.2 g. (71%) of product, m.p. 104–105°.

Anal. Calcd. for $C_{28}H_{41}N_3O_3$: C, 71.90; H, 8.84; N, 8.98. Found: C, 71.93; H, 8.80; N, 9.0.

The hydrochloride twice crystallized from methanol-acetone melted at 146–147°.

Anal. Calcd. for $C_{28}H_{42}ClN_3O_3$: N, 8.35; Cl, 7.04. Found: N, 8.20; Cl, 6.87.

2-Hydroxyethyliminobis[N-methyl-N(α,α-dimethylphenethyl)acetamide], nicotinic acid ester.[6] A solution of 2 g. (0.004 mole) of product and 0.1 g. (0.004 mole) of nicotinic anhydride in 50 ml. of dry benzene was heated under reflux for 16 hr. Nicotinic acid was removed from the cooled mixture by filtration and the filtrate concentrated under vacuum. The residue was dissolved in acetone and filtered. The acetone solution was treated with dry hydrogen chloride and the precipitate collected on a filter, washed with acetone, and dried: 2.15 g. (83%), m.p. 158–159°.

Anal. Calcd. for $C_{34}H_{46}Cl_2N_4O_4$: N, 8.68; Cl, 11.05. Found: N, 8.74; Cl, 11.33.

2-Chloroethyliminobis[N-methyl-N(α,α-dimethylphenethyl)acetamide]. A solution of 20 g. (0.042 mole) of product in 100 ml. of dry chloroform was treated with a solution of 5 g. (0.04 mole) of thionyl chloride in 25 ml. of chloroform. The reaction mixture was stirred for 3 hr. The solvent was removed and the residue crystallized from ethanol-ether, weighed 16.5 g. (79%), m.p. 155–156°.

Anal. Calcd. for $C_{23}H_{41}Cl_2N_3O_2$: N, 8.04; Cl, 13.58. Found: N, 7.80; Cl, 13.35.

2-Aminoethyliminobis[N-methyl-N(α,α-dimethylphenethyl)acetamide]. 2-Chloroethyliminobis[*N*,-methyl-*N*-(α,α-dimethylphenethylacetamide] hydrochloride, 3 g. (0.006 mole), in 20 ml. of methanol containing 3 g. anhydrous ammonia was sealed in a pressure-tube and heated for 18 hr. at 90°. The bomb was cooled and the contents transferred to a beaker. The tube was rinsed out with a little methanol and the combined methanol solution filtered free of ammonium chloride. The methanol and the excess ammonia were removed by evaporation and the residue dissolved in 50 ml. of 2-propanol. A further precipitate formed; this was removed by filtration. The solution was treated with dry hydrogen chloride. On addition of dry ether (about 150 ml.) a crystalline product formed; yield, 1.3 g. (40.5%), m.p. 231–232°.

Anal. Calcd. for $C_{28}H_{44}Cl_2N_4O_2$: N, 10.40; Cl, 13.15. Found: N, 10.71; Cl, 13.40.

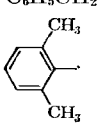
N,N-Bis[N-methyl-N(α,α-dimethylphenethyl)aminoethyl]-2-hydroxyethylamine. A solution of 9.4 g. (0.02 mole) of 2 - hydroxyethyliminobis[N - methyl - N(α,α - dimethylphenethyl)acetamide] in 150 ml. of anhydrous ether was added slowly to a stirred suspension of 1.8 g. (0.05 mole) of lithium aluminum hydride in 300 ml. of dry ether. After addition was complete the reaction was refluxed for 25 hr. The reaction mixture was decomposed by the cautious addition of 8 ml. of water. After filtration, the ethereal solution was dried over anhydrous sodium sulfate. The dried solution was treated with hydrogen chloride. An oil separated from the ether. The ether was removed by decantation and the oil, on trituration with acetone, solidified. After recrystallization from methanol-acetone 3.2 g. (29.3%) product, m.p. 229–230° dec. was obtained. The infrared spectra showed no indication of amide impurities.

Anal. Calcd for $C_{28}H_{48}Cl_3N_3O$: N, 7.66; Cl_3 19.40. Found: N, 7.70, Cl, 19.47.

TABLE III

HYDROXYALKYLIMINOBISACETAMIDES

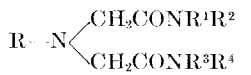
$R—N(CH_2CONR^1R^2)_2$

No.	R	R^1	R^2	M.P.	Formula	Carbon		Hydrogen		Nitrogen		Activity, Min.	(% Soln.)
						Calcd.	Found	Calcd.	Found	Calcd.	Found		
1	$HOCH_2CH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	104–104.5[a]	$C_{28}H_{41}N_3O_3$	71.9	71.93	8.80	8.92	9.0	8.73	25	0.0005
2	$HOCH(CH_3)CH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	113–114[a]	$C_{29}H_{43}N_3O_3$	72.45	72.11	8.95	8.92	8.74	8.68	28	0.0001
3	$HOCH_2CH(C_2H_5)$	CH_3	$C_6H_5CH_2C(CH_3)_2$	144–145[b]	$C_{30}H_{46}ClN_3O_3$	67.72	67.15	8.70	8.36	7.88	7.61	37	0.0005
4	$HOCH_2CH_2CH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	164–165[b]	$C_{29}H_4Cl_4N_3O_3$	[b,f]				8.13	8.30	82	0.1
5	$HO(CH_2)_5CH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	[c]	$C_{32}H_{49}N_3O_3$	73.60	73.31	9.44	9.35			Neg.	0.1
6	$(HOCH_2)_3C$	CH_3	$C_6H_5CH_2C(CH_3)_2$	157–158[a]	$C_{30}H_{45}N_3O_5$	68.30	68.02	8.58	8.31	7.98	7.76	24	0.001
7		CH_3	$C_6H_5CH_2C(CH_3)_2$	108–108.5[a]	$C_{32}H_{47}N_3O_3$	73.75	74.0	9.06	9.01	8.05	8.00	75	0.0025
8	$C_6H_5CHOHCH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	182–183[b]	$C_{34}H_{46}ClN_3O_3$	70.40	69.93	7.98	8.10	7.23	7.10	24	0.001
9	$C_6H_5CHOHC(CH_3)_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	203–204[b]	$C_{34}H_{46}ClN_3O_3$	[g]				6.91	6.93	Neg.	0.1
10	$HOCH_2CH_2$	CH_3	C_6H_{11}	[d]	$C_{20}H_{37}N_3O_3$	65.5	65.65	10.5	10.3	11.42	11.18	Neg.	0.1
11	$HOCH_2CH_2$	H	$C_6H_5CH_2CH_2$	72–73[b]	$C_{22}H_{29}N_3O_3$	69.0	69.15	7.64	7.60	10.95	10.87	Neg.	0.1
12	$HOCH_2CH_2$	$CH_3(CH_2)_2CH_2$	$C_6H_5CH_2$	118 [b]	$C_{25}H_{36}ClN_3O_3$	66.7	66.2	8.4	8.7	[h]		29	0.001
13	$HOCH(CH_3)CH_2$	$CH_3(CH_2)_4CH_2(CH_3)$	$C_6H_5CH_2$	[e]	$C_{35}H_{55}N_3O_3$	74.30	74.43	9.78	9.76	7.43	7.20	44	0.1
14	$HOCH(CH_3)CH_2$	H		193–194[b]	$C_{19}H_{24}ClN_3O_3$					9.72	9.49	Neg.	0.1

[a] Base. [b] Hydrochloride. [c] B.p. 250–260°/2 μ. [d] B.p. 190–195°/1 mm. [e] B.p. 195–200°/0.05 mm. [f] Cl, Calcd. 6.85; found, 6.87. [g] Cl, Calcd. 5.83; found, 5.93. [h] Cl, Calcd. 7.15; found, 7.38.

TABLE IV

UNSYMMETRIC HYDROXYALKYLIMINOBISACETAMIDES



No.	R	R^1	R^2	R^3	R^4	M.P.	Formula	Nitrogen Calcd.	Nitrogen Found	Duration Activity, Min.	(% Soln.)
1	$HOCH_2CH_2$	CH_3CH_2	CH_3CH_2	$CH_3(CH_2)_2CH_2$	$CH_3(CH_2)_2CH_2$	[a]	$C_{18}H_{37}N_3O_3$	12.2	11.9	29	0.1
2	$HOCH_2CH_2$	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	$CH_3(CH_2)_2CH_2$	$(CH_3)_2CHCH_2$	[b]	$C_{20}H_{37}N_3O_3$			21	0.1
3	$HOCH_2CH_2$	CH_3CH_2	CH_3CH_2	CH_3	$C_6H_5CH_2C(CH_3)_2$	121–122	$C_{21}H_{35}N_3O_3$	11.21	10.99	Neg.	0.1
4	$HOCH_2CH_2$	$CH_3(CH_2)_3CH_2$	$CH_3(CH_2)_3CH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	92–93	$C_{27}H_{47}N_3O_3$	9.10	8.93	63	0.1
5	$HOCH_2CH_2CH_2$	$(CH_3)_2CHCH_2$	$(CH_3)_2CHCH_2$	CH_3	C_6H_{11}	[c]	$C_{22}H_{43}N_3O_3$	[f]		Neg.	0.1
6	$HOCH_2CH_2$	CH_3	$C_6H_5CH_2CH(CH_3)$	CH_3	$C_6H_5CH_2C(CH_3)_2$	(Hygro)	$C_{27}H_{40}N_3O_3Cl$	8.53	8.40	55	0.001
7	$HOCH_2CH_2$	H	$C_6H_5CH_2CH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	158[d]	$C_{25}H_{36}N_3O_3Cl$	9.02	8.90	Neg.	0.1
8	$HOCH_2CH_2$	H	$HOCH_2CH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	42[d]	$C_{19}H_{32}N_3O_4Cl$	[g]		Neg.	0.1
9	$HOCH_2CH_2$	H	$CH_3(CH_2)_4CH_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	[e]	$C_{24}H_{41}N_3O_3$	10.0	9.7	9	0.05

[a] B.p. 203–205/1 mm. (base). [b] B.p. 198–200/0.5 mm. (base). [c] B.p. 205–208/1 mm. (base). [d] Hydrochloride. [e] 260°/1 mm. (base). [f] *Anal.* Calcd.: C, 66.52; H, 10.91. Found: C, 66.57; H, 10.87. [g] Cl, Calcd. 8.8; found, 8.5.

TABLE V

ESTERS OF HYDROXYALKYLAMINOBISACETAMIDES

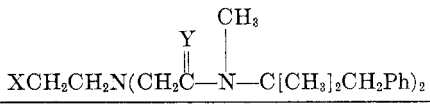
$XCH_2CH_2N(CH_2CONR^1R^2)_2$

No.	X	R^1	R^2	M.P.[a]	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Duration of Activity, Min.	(% Soln.)
1	CH_3CO_2	CH_3	$C_6H_5CH_2C(CH_3)_2$	169–170	$C_{30}H_{44}N_3O_4Cl$	66.02	66.07	8.06	8.03	7.50	7.22	32	0.001
2	$CH_3(CH_2)_{10}CO_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	143–145	$C_{40}H_{64}N_3O_4Cl$		[b]			6.13	5.90	38	0.01
3	p-$CH_3C_6H_4CO_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	168–169	$C_{36}H_{47}N_3O_4Cl$		[c]			8.58	6.67	42	0.001
4	p-$NO_2C_6H_4CO_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	168–169	$C_{35}H_{45}N_4O_6Cl$		[d]			8.58	8.62	27	0.0005
5	CH_3CO_2	$CH_3(CH_2)_2CH_2$	$CH_3(CH_2)_2CH_2$	[e]	$C_{24}H_{47}N_3O_4$	65.0	64.8	10.7	10.5			32	0.01
6	m-$ClC_6H_4CO_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	87–88[f]	$C_{35}H_{44}N_3O_4Cl$	69.40	69.46	7.32	7.48	6.93	6.78	Active[g]	0.1
7	m-pyrCO$_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	158–159	$C_{34}H_{46}N_4O_4Cl_2$		[h]			8.68	8.52	35	0.0005
8	p-$CH_3OC_6H_4CO_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	126–127	$C_{36}H_{48}N_3O_5Cl$	67.70	67.73	7.58	7.90	6.58	6.80	Active[g]	0.1
9	p-$NH_2C_6H_4CO_2$	CH_3	$C_6H_5CH_2C(CH_3)_2$	199–200	$C_{35}H_{48}N_4O_4Cl_2$	63.90	63.80	7.34	7.53	8.51	8.25	Active[g]	0.1

[a] Hydrochloride. [b] Cl, Calcd., 5.20; found, 5.41. [c] Cl, Calcd., 5.71; found, 5.92. [d] Cl, Calcd., 5.44; found, 5.20. [e] B.p. 212–214°/0.05 mm. (base). [f] Base from 2-propanol-petroleum ether. [g] Tested only qualitatively. [h] Cl, Calcd., 11.05; found, 11.11.

TABLE VI

MISCELLANEOUS DERIVATIVES



No.	X	Y	M.P.	Formula	Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found	Duration of Activity, Min.	(% Soln.)
1	Cl	O	155–156[a]	$C_{28}H_{41}N_3O_2Cl_2$	13.50	13.16	8.04	7.75	43[b]	0.1
2	NH_2	O	231–232[a]	$C_{28}H_{44}N_4O_2Cl_2$	13.15	13.40	10.40	10.71	Neg.	0.1
3	$HO(CH_3I)$	O	122–123	$C_{29}H_{44}N_3O_3I$	20.85[c]	20.90	6.92	6.60	Neg.	0.1
4	HO	2H	239–240[a]	$C_{28}H_{43}N_3OCl_3$	19.40	19.47	7.66	7.70	Neg.	0.1

[a] Hydrochloride. [b] The compound *per se* may not be active; this degree of activity can be attributed to a trace of the highly active *N,N*-bis(*N*-methyl-*N*-ω-phenyl-*tert*-butylacetamido)-2-hydroxyethylamine present in the chloro compound either as an initial impurity or formed *in situ* by hydrolysis of the 2-chloroethylamine group. [c] Iodine.

A trimethiodide was prepared by heating the free base of the above trihydrochloride with methyl iodide in acetone. After crystallization from acetone it melted at 154–155°.

Anal. Calcd. for $C_{31}H_{54}IN_3O$: N, 4.85, I, 43.90. Found: N, 4.60; I, 43.82.

2-Hydroxyethyliminobis[N-methyl-N(α,α-dimethylphenethyl)acetamide methiodide. 2-Hydroxyethyliminobis[N-methyl-(α,α-dimethylphenethyl)acetamide], 5 g. (0.011 mole), was heated under reflux with 25 ml. of methyl iodide for 30 min. The solution was concentrated and the residue taken up in 30 ml. of ethyl acetate. On standing in the cold crystallization occurred and the product was collected on a filter, washed with ether, and dried; yield, 5.7 g. (86.4%), m.p. 122–123°.

Anal. Calcd. for $C_{29}H_{44}IN_3O_3$: N, 6.92, I, 20.85. Found: N, 6.60; I, 20.90.

PHILADELPHIA 1, PA.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

Tranquilizing Agents. Xanthen- and Thioxanthen-$\Delta^{9,\gamma}$-propylamines[1] and Related Compounds

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The Grignard reaction of a 3-chloro-*N,N*-dialkylpropylamine with xanthen-9-ones and thioxanthen-9-ones gave a series of 9-(3-dialkylaminopropyl)xanthen-9-ols and thioxanthen-9-ols. Dehydration of these compounds gave the corresponding xanthen- and thioxanthen-$\Delta^{9,\gamma}$-propylamines, some of which were potent tranquilizers. Substantial differences in dehydration of the xanthen-9-ols and thioxanthen-9-ols were observed and are explained. The characteristic changes in the ultraviolet spectra, used to follow these reactions, are described. Several open chain analogs were prepared to study structure-activity relationships.

The well known efficacy of chlorpromazine in the treatment of neuropsychiatric disorders has led to the syntheses of a great number of 10-phenothiazinepropylamines,[2] many of which are new tranquilizing drugs. We wish to report the chemistry of a series of xanthen- and thioxanthen-$\Delta^{9,\gamma}$-propylamines (III) (Table II) with potent tranquilizing activity. Our basic idea for these compounds originated from consideration of the structures of azacyclonol[3] and chlorpromazine.[4] This suggested the preparation of 9-(3-dialkylaminopropyl)xanthen-9-ol and thioxanthen-9-ol analogs (I) (Table I) for pharmacological investigation as potential tranquilizing agents. Dehydration of these compounds yielded the unsaturated analogs (III).

The general method for the preparation of the tertiary alcohols of type I was the Grignard reaction of a 3-chloro-*N,N*-dialkylpropylamine with a xanthen-9-one or thioxanthen-9-one. A modification of Marxer's procedure for 3-(dialkylaminopropyl)-diphenylcarbinols[5] was used. The reaction of the

(1) Since 1957, Chemical Abstracts numbering of the thioxanthene ring system has been changed to conform with that of the isosteric xanthene molecule. The current nomenclature is used throughout this paper.

(2) J.-P. Bourquin, G. Schwarb, G. Gamboni, R. Fischer, L. Ruesch, S. Guldimann, V. Theus, E. Schenker, and J. Renz, *Helv. Chim. Acta*, **41**, 1061, 1072 (1958); **42**, 259 (1959).

(3) (a) Frenquel is the trademark of Wm. S. Merril Co. for azacyclonol—*i.e.*, α-(4-piperidyl)diphenylcarbinol hydrochloride; (b) F. Rinaldi, L. H. Rudy and H. E. Himwich, *Am. J. Psychiatry*, **112**, 343 (1955).

(4) Thorazine is the trademark of Smith Kline and French Laboratories for chlorpromazine—*i.e.*, 2-chloro-10-(3-dimethylaminopropyl)phenothiazine hydrochloride.

(5) A. Marxer, *Helv. Chim. Acta*, **24**, 209E (1941).