on standing a few hours. The methylhydrazone of indole-3-carboxaldehyde was obtained in large colorless crystals from ethanol, but turned pink after a few hours. Chromatography removed the color, but it returned rapidly. The methylhydrazone of 2-hydroxy-1-naphthaldehyde (m.p. 70–73° crude) decomposed upon attempted recrystallization and could not be obtained pure. Most of the pure aliphatic methyl and dimethylhydrazones were tested with acidic ethanolic 2,4-dinitrophenylhydrazine reagent and gave immediate precipitation of the corresponding 2,4-dinitrophenylhydrazone.

Pyridine-3-carboxaldehyde methylhydrazone. Nine grams (0.085 mole) of the aldehyde were cooled in a dry-ice acetone bath during the addition of 4.0 g. (0.087 mol.) of methylhydrazine. The reaction mixture was heated on a water bath for one hour and fractionated to give 8.4 g., 73.9%, of product, b.p. 107°/0.2 mm. The distillate solidified in the receiver.

Cyclohexanone methylhydrazone Nine and eight tenths grams (0.1 mol.) of cyclohexanone were cooled in a dry-ice acetone bath as 4.6 grams (0.1 mol.) of methylhydrazine were added dropwise. The mixture was heated to reflux for 0.5 hr., 25 ml. of water were added and the product extracted with 100 ml. of ether. The ether extracts were dried over magnesium sulfate, the ether removed, and the residue fractionated to give 9.8 g., 77.7%, of the product, b.p. 117°/50 mm. Unless ether-extracted from an aqueous solution, the product foams uncontrollably on distillation.

1-Methyl-2-phenoxyacetylhydrazine. A mixture of 6.8 g. (0.0377 mole) of ethyl phenoxyacetate and 3 g. (0.0653 mol.) of methylhydrazine was allowed to stand at room temperature 24 hr. The crystals which formed were collected and recrystallized twice from toluene–petroleum ether to give 5.1 g. 75.2%, of the product, m.p. 86–89°. This compound is recovered unchanged after attempted reaction with 3-nitrobenzaldehyde or 5-nitrosalicylaldehyde establishing the 1,2-structure.

Anal. Calcd. for $C_9H_{12}O_2N_2$: N, 15.55. Found: N, 15.57.

1-Methyl-1,2-di(1-naphthoyl)-hydrazine. A solution of 4 g. (0.021 mol.) of 1-naphthoyl chloride in 50 ml. of benzene was cooled to approximately 10° prior to the dropwise addition of 1 g. (0.217 mol.) of methylhydrazine. The solvent was then removed and the residue recrystallized from toluene-petroleum ether to give 2.9 g., 78%, of the product, m.p. 185°.

Isatin, 1-methyl-1-phenoxyacetylhydrazone. To 1.75 g. (0.01 mol.) of isatin methylhydrazone in 25 ml. of benzene was added dropwise 1.7 g. of phenoxyacetyl chloride. This mixture was heated at 60° on a water bath for 15 min. and evaporated to dryness. After being washed with 10% sodium bicarbonate and water, the red residue was recrystallized from methanol-water to give 1.74 g., 56.3%, of the product, m.p. 201–202°.

N-Phenoxyacetyl citronellal methylhydrazone. To 3.0 g. (0.0165 mol.) of citronellal methylhydrazone dissolved in 15 ml. of toluene was added 3.0 g. (0.0176 mol.) of phenoxyacetyl chloride. Evaporation of the solvent and recrystallization of the residue from ethanol gave 1.8 g., 34.6%, of the product, m.p. 137–139°.

The infrared absorption data were obtained using chloroform or carbon tetrachloride solutions or potassium bromide pellets and a Baird double beam recording spectrophotometer. The ultraviolet absorption data were obtained using a Beckman DK-2 recording ultraviolet spectrophotometer using methanol (Baker, purified) as solvent.

Acknowledgment. The authors wish to acknowledge partial support of this research through grant C-2457 from the National Cancer Institute of the National Institutes of Health and to the Research Corporation and the Brown-Forman Company for grants for the purchase of the infrared spectrophotometer.

LOUISVILLE, KY.

[CONTRIBUTION FROM THE LABORATORIES OF LEPETIT S.P.A.]

5,5-Disubstituted Dihydro-1,3-oxazine-2,4-diones. Research on Compounds Active on Central Nervous System. XII[1a]

EMILIO TESTA, LUIGI FONTANELLA, GIANFRANCO CRISTIANI, AND GIANGUALBERTO GALLO[1b]

Received June 15, 1959

A number of 5,5-dialkyl-, alkyl- aryl-, alkyl-cycloalkyl-, and polymethylene-, dihydro-1,3-oxazine-2,4-diones (I)[1c] have been synthesized by treating the suitable α,α-disubstituted β-hydroxypropionic acids (V) with sodium cyanate and hydrochloric acid to give α,α-disubstituted β-carbamyloxypropionic acids (VI); the latter are cyclized to I by treatment with thionyl chloride and pyridine. From compounds I the corresponding 3-methyl derivatives (XI) have been obtained as well as some dihydro-1,3-oxazine-2,4-dithiones (XII) which by oxydation with hydrogen peroxide yield the original oxazine-2,4-diones (I). Some examples of the ring opening of compounds I by alkaline hydrolysis and by reduction with $LiAlH_4$ present evidence for the assigned structure I. The 5,5-disubstituted dihydro-1,3-oxazine-2,4-diones and some derivatives thereof show promising activity on central nervous system (CNS).

As a part of our studies on CNS-acting substances we have synthesized a number of 5,5-disubstituted dihydro-1,3-oxazine-2,4-diones (I) which represent a class of compounds[1d] of potentially great pharmacological interest. Actually, oxazinediones I are structurally related to some heterocyclic rings, whose basic features are common to a number of clinically useful hypnotic, narcotic, sedative, and anticonvulsant agents; namely barbiturates, glutarimides, and oxazolidinediones. Furthermore,

(1) (a) E. Testa, L. Fontanella, and G. F. Cristiani, *Ann.*, **626**, 114 (1959).

(1) (b) Physical chemical department of Lepetit S.p.A.

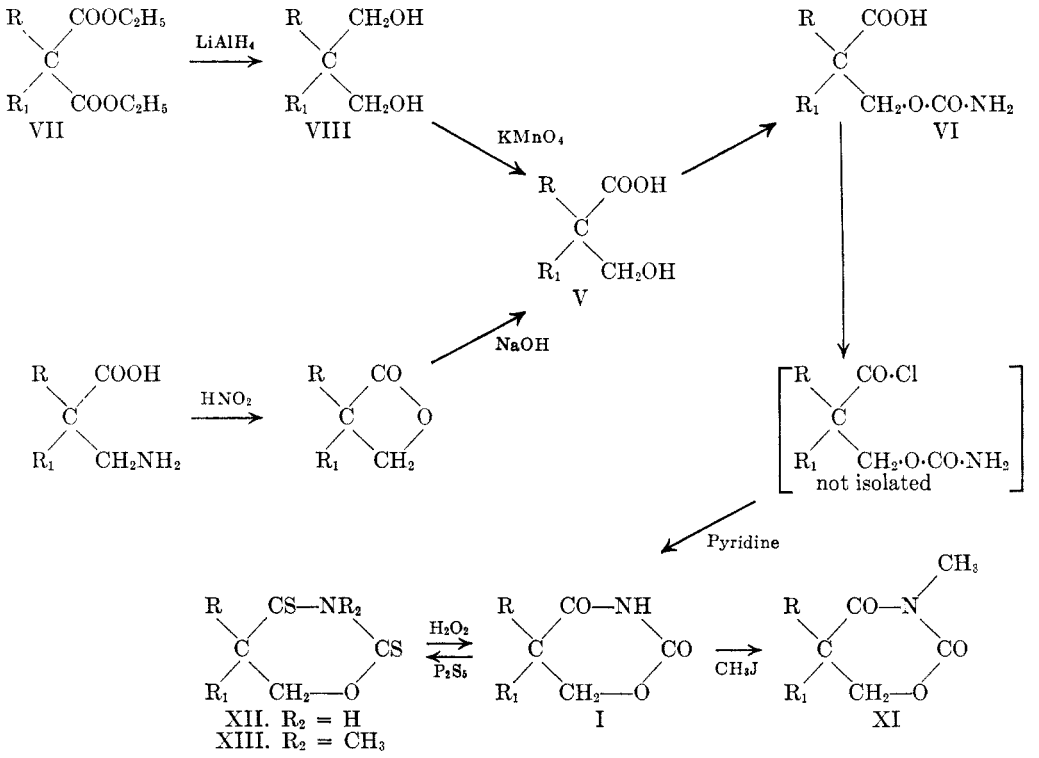
(1) (c) It is to note that the described new heterocyclic compounds may also be named tetrahydro-1,3-oxazine-2,4-diones.

(1) (d) Recently R. S. Safir and R. J. Lopresti briefly described various 5,6-substituted dihydro-1,3-oxazine-2,4-diones (U. S. Patent **2,797,217**) with possible sedative action on CNS.

oxaziniediones I are cyclic carbamates and may be related to meprobamate and its derivatives.

A member of this series, 5-ethyl-5-phenyldihydro-1,3-oxazine-2,4-dione has been described by R. Fusco and one of us[2] and has also been prepared in its optically active forms. In a preliminary pharmacological screening the expected sedative action of Ii has been confirmed[3] and the promising results obtained prompted us to carry on further work on this subject.

Oxaziniediones I have been synthesized according to the following scheme:



Most of the key intermediate α,α-disubstituted hydroxypropionic acids (V) have been already described by us[2,4] and by others.[5-10] We have prepared V by two different ways. The compounds V lacking an aryl substituent in the α-position have been obtained by reduction with lithium aluminum hydride of α,α-disubstituted diethyl malonate (VII) followed by partial oxidation with alkaline $KMnO_4$ of the resulting 2,2-disubstituted 1,3-propanediols (VIII) (Method A). This procedure which was first described by J. B. Ludwig[7] for the preparation of the α,α-diethyl derivative, has been now slightly modified and found to be of general value for the synthesis of α,α-dialkyl-β-hydroxypropionic acids. When compounds VIII bear in the α- position a phenyl substituent the above method produces the desired V only in trace amounts together with large quantities of starting products VIII and of substances obtained by further oxidative degradation of the molecule. Therefore we obtained the α-alkyl tropic acids by diazotizing the suitable α,α-disubstituted-β-aminopropionic acid (IX) and hydrolyzing the resulting α,α-disubstituted β-lactone (X) according to a general method previously described by us[4] (Method B).

Because of difficulties occurring in the preparation of some of the amino acids IX through an acid hydrolysis of their ethyl esters[4,11] (Method C-1), we have found it more convenient in some instances to perform the hydrolysis on the α,α-disubstituted 2-azetidinones (Method C-2) obtained by cyclizing the ethyl esters of aminoacids.[12,13] This two-stage hydrolysis affords smoothly and in high yields some compounds IX. From the α,α-disubstituted β-hydroxypropionic acids (V) by reaction with finely powdered sodium cyanate and hydrogen chloride in dry chloroform medium the corre-

(2) R. Fusco and E. Testa, *Farmaco Ed. sci.*, **12**, 823 (1957).

(3) G. Maffii, Personal communication.

(4) E. Testa, L. Fontanella, G. F. Cristiani, and F. Fava, *Ann.*, **619**, 47 (1958).

(5) J. L. Green and H. J. Hagenmeyer, *J. Am. Chem. Soc.*, **77**, 3016 (1955).

(6) V. Neustädter, *Ann.*, **351**, 304 (1907).

(7) B. J. Ludwig, *J. Am. Chem. Soc.*, **72**, 5329 (1950).

(8) A. Vecchi and G. Melone, *J. Org. Chem.*, **24**, 109 (1959).

(9) H. E. Zaugg, *J. Am. Chem. Soc.*, **72**, 3001 (1950).

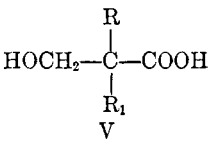
(10) F. F. Blicke and H. Raffelson, *J. Am. Chem. Soc.*, **74**, 1730 (1952).

(11) E. Testa, L. Fontanella, and F. Fava, *Farmaco Ed sci.*, **13**, 152 (1958).

(12) E. Testa, L. Fontanella, G. F. Cristiani, and F. Fava, *Ann.*, **614**, 158 (1958).

(13) E. Testa and L. Fontanella, *Ann.*, **625**, 95 (1959).

TABLE I



V

Compound	R	R_1	Procedure	Yield, % Theory	M.P.	Formula
Va[5]	CH_3—	CH_3—	A	67	125–127	$C_5H_{10}O_3$
Vb[6]	CH_3—	C_2H_5—	A	73	B.p. 110°/1 mm.	$C_6H_{12}O_3$
Vc	CH_3	n-C_3H_7—	A	66	49–51 B.p. 107°/0.5 mm.	$C_7H_{14}O_3$[a]
Vd[7]	C_2H_5—	C_2H_5—	A	55	60–62	$C_7H_{14}O_3$
Ve	n-C_3H_7—	n-C_3H_7—	A	51	93–95 B.p. 100–115°/0.6 mm.	$C_9H_{18}O_3$[b]
Vf	n-C_4H_9—	n-C_4H_9—	A	30	B.p. 150–155°/0.8 mm.	$C_{11}H_{22}O_3$[c]
Vg	—CH_2—CH_2—	—CH_2—CH_2—	A	82	94–95 (from benzene)	$C_7H_{12}O_3$[d]
Vh[8]	C_6H_5—	CH_3—	B(C-1)	52	86–87	$C_{10}H_{12}O_3$
Vi[2,4]	C_6H_5—	C_2H_5—	B(C-1)	74	96–98	$C_{11}H_{14}O_3$
Vl[4]	C_6H_5	n-C_3H_7—	B(C-1)	68.7	104–107	$C_{12}H_{16}O_3$
Vm[4]	C_6H_5—	iso-C_3H_7—	B(C-2)	50	138–140	$C_{12}H_{16}O_3$[e]
Vn[4]	C_6H_5—	n-C_4H_9—	B(C-2)	57	91–92	$C_{13}H_{18}O_3$[f]
Vo[4,10]	C_6H_5—	C_6H_5·CH_2—	B(C-2)	44	191–193	$C_{16}H_{16}O_3$
Vp[10]	C_6H_5—	C_6H_{11}—[g]	B(C-2)	43.5	146–148	$C_{15}H_{20}O_3$
Vq[4,9]	C_6H_5—	C_6H_5—	B(C-1)	12	161–163	$C_{15}H_{14}O_3$

[a] *Anal.* Calcd.: C, 57.51; H, 9.65. Found: C, 57.59; H, 9.88. [b] *Anal.* Calcd.: C, 62.03; H, 10.41. Found: C, 61.91; H, 10.18. [c] *Anal.* Calcd.: C, 65.28; H, 10.81. Found: C, 65.15; H, 10.75. [d] *Anal.* Calcd.: C, 58.31; H, 8.39. Found: C, 58.11; H, 8.64. [e] The intermediate β-amino-α-phenyl-α-iso-propyl-propionic acid previously described[4] as crude product has now been purified. M.p. 275–277°C. (from water). *Anal.* Calcd. for $C_{12}H_{17}NO_2$: N, 6.76. Found: N, 6.44. [f] *Anal.* Calcd.; C, 70.23; H, 8.16. Found: C, 70.15; H, 8.15. [g] Cyclohexyl.

sponding carbamates (VI) have been obtained.[2] VI are white stable crystalline compounds, partially soluble in $CHCl_3$ and ether, and may be recrystallized from water. Surprisingly, the reaction does not occur when potassium cyanate is substituted for sodium cyanate. The α,α-disubstituted-β-carbamyloxypropionic acids (VI) have been treated with thionyl chloride to give the corresponding acid chlorides, which were not isolated but cyclized to the desired dihydro-oxazinediones by means of anhydrous pyridine. In some cases the ring closure of compounds VI has been accomplished in one stage by directly adding thionyl chloride to the carbamate in anhydrous pyridine.

The 5,5-disubstituted dihydro-1,3-oxazine-2,4-diones (I) are stable compounds which may be distilled in vacuo whithout decomposition. Except the 5-phenyl-5-*n*-butyl-derivative, which is a liquid, they are white crystalline substances.

Oxaziediones I have been transformed into the corresponding *N*-methyl-derivatives (XI) by the method of Davies *et al.*[14] successfully applied previously by one of us[15] to the *N*-alkylation of some five-membered heterocyclic compounds. The 3,5,5-trisubstituted dihydro-1,3-oxazine-2,4-diones (XI) are colorless oils and may be distilled *in vacuo* without decomposition; many of the products crystallize on standing.

Some of the 5,5-disubstituted dihydro-1,3-oxazine-2,4-diones and the 3-methyl-5-phenyl-5-ethyl-dihydro-1,3-oxazine-2,4-dione (XIII) have been converted into the corresponding dihydro-1,3-oxazine-2,4-dithiones (XII and XIII) by reaction with phosphorus pentasulfide. Compounds XII and XIII on treatment with alkaline hydrogen peroxide yield the original oxaziediones. Attempts to introduce only one sulfur atom in the molecule of compounds I or XI were unsuccessful.

We have performed some degradative studies on 5-phenyl-5-ethyl-dihydro-1,3-oxazine-2,4-dione (Ia) to reach the evidence that no rearrangement occurred during the cyclization process and the structure assigned to compounds I is correct. In fact, by alkaline hydrolysis of the above derivative α-ethyltropic acid has been obtained[2]; by $LiAlH_4$ reduction of the same product 2-methylamino-2-phenyl-1-butanol (XIV) has been isolated.

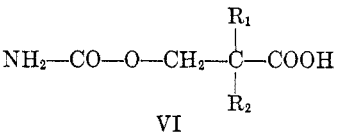
Compound XIV has also been synthesized from ethyl β-amino-α-ethyl-α-phenylpropionate[16] (XV) by reaction with ethyl chloroformate followed by reduction with $LiAlH_4$ of ethyl β-carbethoxyamino-α-ethyl-α-phenylpropionate (XIV). Compound XIV obtained by synthesis is identical with the $LiAlH_4$ reduction product of 5-phenyl-5-ethyl-dihydro-1,3-oxazine-2,4-dione.

(14) J. S. H. Davies and W. H. Hook, *J. Chem. Soc.*, 30 (1950).

(15) E. Testa and R. Ettorre, *Arch. Pharm.*, **290**, 532 (1957).

(16) E. Testa, L. Fontanella, and G. F. Cristiani, *Farmaco Ed. sci.*, **13**, 437 (1958).

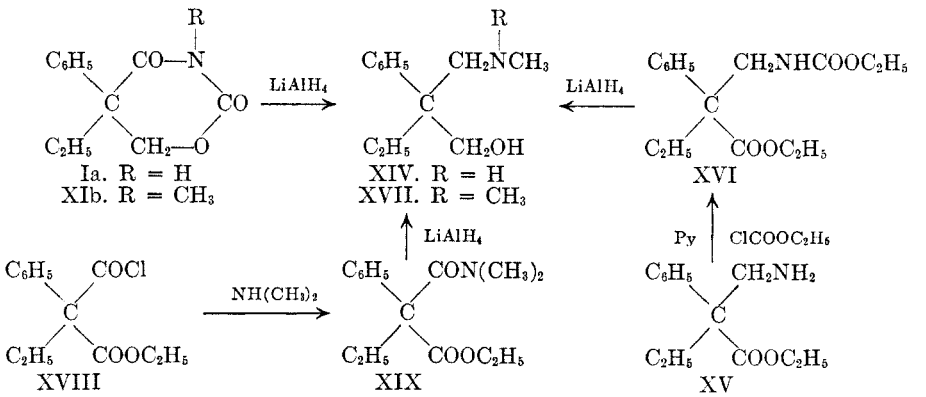
TABLE II



VI

Compound	R_1	R_2	Yield	M.P.	Formula (M.W.)	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VIa	CH_3—	CH_3—	27.5	173–174	$C_6H_{11}NO_4$ (161.15)	44.71	6.88	8.69	44.85	7.10	8.65
VIb	CH_3—	C_2H_5—	62	139–140	$C_7H_{13}NO_4$ (175.18)	47.99	7.48	7.99	48.01	7.52	8.08
VIc	CH_3—	n-C_3H_7—	37	138–140	$C_8H_{15}NO_4$ (189.21)	50.78	7.99	7.40	50.85	8.10	7.68
VId	C_2H_5—	C_2H_5—	49.5	128–129	$C_8H_{15}NO_4$ (189.21)	50.78	7.99	7.40	50.88	7.88	7.45
VIe	n-C_3H_7—	n-C_3H_7—	83	184–185	$C_{10}H_{19}NO_4$ (217.26)	55.28	8.81	6.45	55.48	9.01	6.47
VIf	n-C_4H_9—	n-C_4H_9—	69.2	169–171	$C_{12}H_{23}NO_4$ (245.31)	58.75	9.45	5.71	58.63	9.41	5.34
VIg	—CH_2—CH_2—CH_2—CH_2—		27	186–187	$C_8H_{13}NO_4$ (187.18)	51.32	7.00	7.48	51.71	6.99	7.32
VIh	C_6H_5—	CH_3—	70	136–137	$C_{11}H_{13}NO_4$ (223.22)	59.18	5.87	6.27	59.15	6.12	6.30
VIi	C_6H_5—	C_6H_5—	85.8	169–170	$C_{12}H_{15}NO_4$ (237.25)	60.74	6.37	5.90	60.55	6.29	5.94
VIl	C_6H_5—	n-C_3H_7	79.5	157–159	$C_{12}H_{17}NO_4$ (251.27)	62.13	6.82	5.57	62.15	6.81	5.79
VIm	C_6H_5	iso-C_3H_7—	91	146–148	$C_{13}H_{17}NO_4$ (251.27)	62.13	6.82	5.57	61.98	6.77	5.53
VIn	C_6H_5	n-C_4H_9—	91	167–168	$C_{14}H_{19}NO_4$ (265.3)	63.37	7.22	5.28	63.28	7.25	5.58
VIo	C_6H_5	C_6H_5·CH_2—	96	178–180	$C_{17}H_{17}NO_4$ (299.31)	68.21	5.72	4.68	68.25	5.75	4.66
VIp	C_6H_5—	C_6H_{11}—[a]	85	175–180	$C_{16}H_{21}NO_4$ (291.34)	65.95	7.26	4.81	65.75	7.23	4.75
VIq	C_6H_5—	C_6H_5—	97	193–195	$C_{16}H_{15}NO_4$ (285.19)	67.38	5.30	4.91	67.31	5.47	4.90

[a] Cyclohexyl.

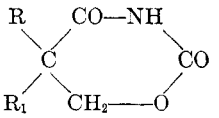


Therefore Ia behaves toward $LiAlH_4$ reduction like a carbamate[17]; in analogous manner its *N*-methyl derivative (XIb) yields by reduction with $LiAlH_4$ 2-dimethylaminomethyl-2-phenyl-1-butanol (XVII). The structure of XVII was also confirmed by synthesis[18] from α-carbethoxy-α-phenylbutyryl chloride (XVIII),[2] first converted to XIX, which was then reduced to XVII with $LiAlH_4$. To provide further evidence of the structure assigned to the series of compounds V, VI, I, and XI and to better

(17) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publ. Inc., New York, 1956, p. 636.

(18) We are indebted to Dr. A. Vecchi for the communication of the method of synthesis and for providing us with a sample of compound XVII.

TABLE III



I

Compound	R_1	R_2	Procedure	Yield, % Theory	M.P.	Formula	Analysis					
							Calcd.			Found		
							C	H	N	C	H	N
Ia	CH_3—	CH_3—	A	45.7	124–127[a]	$C_6H_9NO_3$ (143.14)	50.34	6.33	9.78	50.24	6.20	9.89
Ib	CH_3—	C_2H_5—	B	42.7	83–85[a]	$C_7H_{11}NO_3$ (157.16)	53.49	7.05	8.91	53.38	7.02	8.88
Ic	CH_3—	n-C_3H_7—	A	41	60–62 (from CH_3—COO-C_2H_5 and petroleum ether)	$C_8H_{13}NO_3$ (171.19)	56.12	7.65	8.18	56.30	7.49	8.13
Id	C_2H_5—	C_2H_5—	A	56.2	97–98[b]	$C_8H_{13}NO_3$ (171.19)	56.12	7.65	8.18	56.08	7.58	8.85
Ie	n-C_3H_7—	n-C_3H_7—	A	71.6	95–97[a]	$C_{10}H_{17}NO_3$ (199.24)	60.27	8.60	7.03	60.41	8.62	6.91
If	n-C_4H_9—	n-C_4H_9—	B	81	92–95[a]	$C_{12}H_{21}NO_3$ (227.29)	59.24	9.31	6.16	59.12	9.25	6.14
Ig	—CH_2—CH_2—	CH_2—CH_2—	A	35.7	105 (from benzene-petroleum-ether)	$C_8H_{11}NO_3$ (169.17)	56.79	6.55	8.28	56.81	6.75	8.27
Ih	C_6H_5—	CH_3—	A	78	134–135[c]	$C_{11}H_{11}NO_3$ (205.20)	64.38	5.40	6.83	64.31	5.25	6.83
Ii	C_6H_5—	C_2H_5—	A	69.3	130–132[c]	$C_{12}H_{13}NO_3$ (219.23)	65.74	5.97	6.38	65.95	5.92	6.44
Il	C_6H_5—	n-C_3H_7—	B	65	118–120[c]	$C_{13}H_{15}NO_3$ (233.26)	66.93	6.48	6.03	66.75	6.58	6.03
Im	C_6H_5—	iso-C_3H_7—	B	66	174–175[c]	$C_{13}H_{15}NO_3$ (233.26)	66.93	6.48	6.03	66.91	6.55	6.15
In	C_6H_5—	n-C_4H_9	B	80.5	B.p. 175–180/0.2 mm.	$C_{14}H_{17}NO_3$ (247.28)	67.99	6.92	5.66	67.81	5.75	5.70
Io	C_6H_5—	C_6H_5·CH_2—	B	53.2	141–145[c]	$C_{17}H_{15}NO_3$ (281.30)	72.58	5.37	4.98	72.29	5.35	5.02
Ip	C_6H_5—	C_6H_{11}—[d]	B	50.5	164–165[c]	$C_{16}H_{19}NO_3$ (273.32)	70.30	7.01	5.12	70.18	7.08	5.11
Iq	C_6H_5—	C_6H_5—	A	91	220–221[e]	$C_{16}H_{13}NO_3$ (267.27)	71.89	4.90	5.24	72.01	4.97	5.09

[a] From ligroin. [b] From ethyl ether. [c] From abs. ethanol. [d] Cyclohexyl. [e] From ethyl acetate.

characterize the new described products, their infrared spectra between 4000 and 650 cm.$^{-1}$ have been measured. The infrared spectra have been carried out using a Perkin Elmer Model 12 C single-beam spectrophotometer fitted with a NaCl prism. The substances were examined as such when liquid and in a Nujol mull when solid. For each basic structure the most typical bands have been selected and assigned as arising from the vibration of chemical bonds of the structures.[20] The upper and lower limits of the frequencies of the members of the four series and the types of the vibrations from which the bands take origin are given in Table VI.

A preliminary pharmacological screening have shown that oxaziniediones I and their *N*-methyl-derivatives XI possess the foreseen sedative action; furthermore some member of this series show an interesting exciting activity on CNS. The results of the pharmacological investigation on the described 5,5-disubstituted dihydro-1,3-oxazine-2,4-diones and derivatives will be published elsewhere by G. Maffii *et al.*

EXPERIMENTAL

α,α-DISUBSTITUTED β-HYDROXYPROPIONIC ACIDS (V)

(A) *α,α-Dialkyl and α,α-tetramethylene derivatives* (Va–g). 2,2-Dimethyl-1,3-propandiol.[21] In a 3-l. flask fitted with a mechanical stirrer, a thermometer, a reflux condenser, and a dropping funnel, 42.5 g. of lithium aluminum hydride and 400 ml. of anhydrous ether were placed. Into the stirred suspension, 150 g. of diethyl α,α-dimethylmalonate[22] were slowly dropped. After the addition was over, the mixture

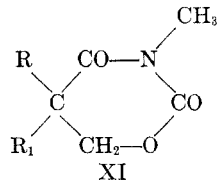
(19) K. Ronco, B. Prijs, and H. Erlenmeyer, *Helv. Chim. Acta*, **39**, 2094 (1957).

(20) L. K. Bellamy, *The Infra-red Spectra of Complex Molecules*, Methuen and Co., London (1958).

(21) R. W. Shortridge, R. A. Craig, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Am. Chem. Soc.*, **70**, 946 (1948).

(22) L. C. Thorne, *J. Chem. Soc.*, **39**, 543 (1881).

TABLE IV

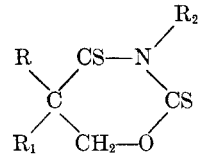


XI

Compound	R	R_1	Yield, % Theory	B.P./Mm. (a–g) M.P. (h–q)	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XIa	CH_3—	CH_3—	71.5	75–80/0.4[a]	$C_7H_{11}NO_3$ (157.16)	53.49	7.05	8.91	53.31	7.25	9.22
XIb	CH_3—	C_2H_5—	82.5	125–130/1[a]	$C_8H_{13}NO_3$ (171.19)	56.12	7.65	8.18	55.98	7.41	8.25
XIc	CH_3—	n-C_3H_7—	53.5	106–107/0.6	$C_9H_{15}NO_3$ (185.22)	58.36	8.16	7.56	58.42	8.29	7.60
XId	C_2H_5—	C_2H_5—	33.1	90–95/0.4[a]	$C_9H_{15}NO_3$ (185.22)	58.36	8.16	7.56	58.28	8.15	7.76
XIe	n-C_3H_7—	n-C_3H_7—	68.5	85–90/0.4[a]	$C_{11}H_{19}NO_3$ (213.27)	61.94	8.98	6.57	62.08	9.15	6.65
XIf	n-C_4H_9—	n-C_4H_9—	71.5	115–125/0.6[a]	$C_{13}H_{23}NO_3$ (241.32)	64.70	9.61	5.80	64.71	9.58	5.90
XIg	—CH_2—CH_2—CH_2—CH_2—		70.5	140–145/0.5 M.p. 43–44°	$C_9H_{13}NO_3$ (183.20)	59.00	7.15	7.65	58.90	7.25	7.65
XIh	C_6H_5—	CH_3—	68	90–92[b]	$C_{12}H_{13}NO_3$ (219.23)	65.74	5.97	6.39	65.58	5.91	6.37
XIi	C_6H_5—	C_2H_5—	47	73–76	$C_{13}H_{15}NO_3$ (233.26)	66.93	6.48	6.00	66.87	6.45	6.07
XIl	C_6H_5—	n-C_3H_7—	73.5	65–66[b]	$C_{14}H_{17}NO_3$ (247.28)	67.99	6.93	5.66	67.85	6.85	5.62
XIm	C_6H_5—	iso-C_3H_7—	94	94–96[b]	$C_{14}H_{17}NO_3$ (247.28)	67.99	6.93	5.66	68.05	6.80	5.51
XIn	C_6H_5—	n-C_4H_9—	79.5	82–84[b]	$C_{15}H_{19}NO_3$ (261.31)	68.94	7.24	5.36	68.75	7.08	5.07
XIo	C_6H_5—	C_6H_5·CH_2—	84	102–105[b]	$C_{18}H_{17}NO_3$ (295.32)	73.20	5.80	4.74	73.18	5.75	4.59
XIp	C_6H_5—	C_6H_{11}[c]	74.3	133–135[b]	$C_{17}H_{21}NO_3$ (286.34)	71.30	7.39	4.89	71.25	7.43	4.72
XIq	C_6H_5—	C_6H_5—	70.5	123–124[b]	$C_{17}H_{16}NO_3$ (281.38)	72.56	5.37	4.98	72.51	5.35	4.92

[a] Kügelrohr technique of Ronco and Cows.[19] [b] From ligroin. [c] Cyclohexyl.

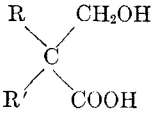
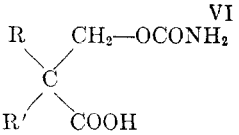
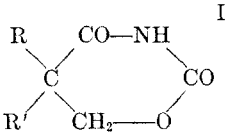
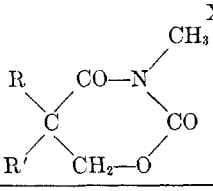
TABLE V



Compound	R	R_1	R_2	Reaction Time, Min.	Yield, % Theory	Formula	M.P.	Analysis Calcd. N	Calcd. S	Found N	Found S
XIIc	CH_3—	n-C_3H_7—	H	75	60.5	$C_8H_{13}NOS_2$ (203.31)	51–55[a]	6.89	31.54	6.85	31.25
XIId	C_2H_5—	C_2H_5—	H	75	57	$C_8H_{13}NOS_2$ (203.34)	80–82[a]	6.89	31.54	6.76	31.30
XIIe	n-C_3H_7—	n-C_3H_7—	H	75	51.5	$C_{10}H_{17}NOS_2$ (231.31)	74–76[a]	6.05	27.71	6.36	27.50
XIIh	C_6H_5—	CH_3—	H	45	24.5	$C_{11}H_{11}NOS_2$ (237.33)	136–138[b]	5.93	27.02	5.87	26.87
XIIIi	C_6H_5—	C_2H_5—	CH_3	360	64	$C_{13}H_{15}NOS_2$ (265.38)	83–84[c]	5.28	24.16	5.32	24.55

[a] From ligroin. [b] From benzene. [c] From methanol.

TABLE VI

Structure	Frequency Range, Cm.$^{-1}$	Vibration
V 	3470–3300	Alcoholic OH stretching
	2740–2520	Acid OH stretching
	1710–1690	C=O stretching
	1268–1200	Acid C—O stretching
	1055–1022	Alcoholic C—O stretching
VI 	3470–3400	Asymmetric NH stretching
	3370–3280	Symmetric NH stretching
	2770–2550	Acid OH stretching
	1735–1700	C=O stretching
	1610–1585	NH_2 deformation (Amide II)
	1270–1220	Acid C—O stretching
	1100–1054	Alcoholic C—O stretching
I 	3230–3090	NH stretching
	1765–1740	(2) C=O stretching
	1735–1700	(4) C=O stretching
	1248–1210	(2-1) C—O stretching
	1090–1042	(6-1) C—O stretching
XI 	1760–1740	(2) C=O stretching
	1700–1690	(4) C=O stretching
	1305–1278	(2-1) C—O stretching
	1102–1060	(6-1) C—O stretching

was refluxed 3 hr., cooled to 0°, and cautiously treated with 220 ml. of water, 110 ml. of 10% hydrochloric acid and eventually with 110 ml. of concentrated hydrochloric acid. The mixture was extracted with ethyl ether and the mother liquor concentrated in vacuo to a volume of about 200 ml. The residue was first extracted once with the ether previously used, then twice with fresh ethyl ether. The combined extracts were dried over Na_2SO_4 and evaporated to a small volume: 46 g. of diol were obtained, which were slurried in benzene, filtered, dried, and employed for the following steps without further purification. M.p. 125–127°.

α,α-Dimethyl-*β*-hydroxypropionic acid[5] (Va). To a stirred suspension of 46 g. of crude 2,2-dimethyl-1,3-propanediol in 11.5 g. of sodium hydroxide and 560 ml. of water, 114 g. of potassium permanganate in 1870 ml. of water were slowly added at room temperature. After completion of the addition (about 2 hr.), the mixture was warmed on water bath until the pink color of the solution faded, then it was cooled, filtered, and washed with water. The filtrate was acidified with hydrochloric acid to *p*H 4.0–5.0 and evaporated to dryness *in vacuo*. The residue was treated with ethyl ether, dried, and concentrated; an oil was obtained, which crystallized on rubbing. The crude product (43 g.) was dissolved in 100 ml. of hot benzene, filtered and the filtrate treated with petroleum ether. After standing some hours in the refrigerator, 35 g. (67%) of crystals were obtained. The m.p. (123–125°) remained unchanged after a further recrystallization from ligroin.

Anal. Calcd. for $C_5H_{10}O_3$: C, 50.84; H, 8.53. Found: C, 50.89; H, 8.56.

α,α-Disubstituted β-hydroxypropionic acids (Vb–g) were prepared exactly as described for Va; their properties and yields are reported in Table I.

(B) *α-Substituted α-phenyl-β-hydroxypropionic acids (α-substituted tropic acids)* (Vh–q). *α*-Substituted *β*-amino-*α*-phenyl-*β*-hydroxypropionic acids:

C-1. *By hydrolysis of the ethyl esters.* The ethyl esters were hydrolyzed with concentrated hydrochloric acid according to the procedure described in previous papers.[4,11]

C-2. *By cyclization to 3-substituted 3-phenyl-2-azetidinones followed by acid hydrolysis.* Example for *β*-amino-*α*-benzyl-*α*-phenylpropionic acid (Vo).

Sixty g. of 3-benzyl-3-phenyl-2-azetidinone (obtained in 84.8% yield from ethyl *β*-amino-*α*-benzyl-*α*-phenylpropionate, as formerly described by us[13]) were refluxed for 4 hr. with 1200 ml. of concentrated hydrochloric acid, then allowed to stand overnight. The precipitate was collected by filtration: 74.5 g. (100% of the theoretical amount) were obtained consisting of the hydrochloride of *β*-amino-*α*-benzyl-*α*-phenylpropionic acid melting at 263–265° (dec.).

Anal. Calcd. for $C_{16}H_{17}NO_2.HCl$: Cl, 12.15. Found: Cl, 12.38.

The above hydrochloride (70 g.) was suspended in 200 ml. of water, treated with the molar equivalent of 50% sodium hydroxide solution and stirred 2 hr. The mixture was filtered, washed with cold water, and dried on water bath: yield 58 g., m.p. 278–280°.

Cyclization of α-substituted β-amino-α-phenylpropionic acid (IX) *to α,α-disubstituted β-lactones* (X) *followed by alkaline hydrolysis to α-substituted β-hydroxy-α-phenylpropionic acids* (Vh–q). This process was carried out exactly as formerly described by us and co-workers[4]; the properties and yields of the acids Vh–q are reported in Table I.

The previously unreported intermediate *α-cyclohexyl-α-phenyl-β-propiolactone* (Xp) was synthesized from *β*-amino-*α*-cyclohexyl-*α*-phenylpropionic acid[11] exactly as formerly described.[4] M.p. 97–98° (from light petroleum).

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.06; H, 8.05.

α,α-DISUBSTITUTED *β*-CARBAMYLOXYPROPIONIC ACIDS (VIa–q)

α,α-Dimethyl-β-carbamyloxypropionic acid (VIa). A solution of 24 g. of *α,α*-dimethyl-*β*-hydroxypropionic acid (Va) in 400 ml. anhydrous chloroform was cooled to 0° and treated with 18 g. of finely powdered sodium cyanate. A stream of hydrogen chloride was bubbled into the mixture

while stirring at 0° to +5°; after 2 hr. 9 g. of sodium cyanate were added and hydrogen chloride was bubbled into the mixture for an additional 2 hr. under stirring at 0° to +5°. The gas stream was then discontinued, the mixture allowed to stand 30 min. at 0°, and filtered. The collected precipitate was dried on water bath, suspended in 350 ml. of water, and extracted with about 750 ml. of ether. The ether extract was evaporated *in vacuo* and the residue recrystallized from water: yield 9 g. of crystals melting at 173–174°. By evaporating to dryness the chloroform mother liquors, treating the residue with 25 ml. of ether, filtering, and evaporating, 4 g. of starting compound (Va) were obtained.

Anal. Calcd. for $C_6H_{11}NO_4$: C, 44.71; H, 6.88; N, 8.69. Found: C, 45.01; H, 7.15; N, 8.86.

The α,α-disubstituted β-carbamyloxypropionic acids VIb–q, prepared as described for VIa, are collected in Table II.

It is to note that in most cases (VIb,d,e,h,m–p) the compound VI will go into the chloroform solution and may be isolated after evaporation of the solvent through a crystallization from water.

5,5-DISUBSTITUTED DIHYDRO-1,3-OXAZINE-2,4-DIONES (Ia–q)

Method (A). *5,5-Dimethyldihydro-1,3-oxazine-2,4-dione* (Ia). Eight g. of β-carbamyloxy-α,α-dimethylpropionic acid (VIa) and 18 ml. of thionyl chloride were refluxed for 1 hr. The excess of thionyl chloride was then removed in vacuo, the residue treated with benzene and evaporated to dryness; this last procedure was repeated three times. To the oil obtained, 10 ml. of pyridine were added while cooling in an ice salt bath to avoid the temperature's rising above 35–40°. The mixture was allowed to stand at room temperature for 1 hr., poured into 25 g. ice and made acidic to Congo red with hydrochloric acid. The resinous precipitate was extracted with six 50-ml. portions of ether; the ether extract was washed with water, dried over Na_2SO_4, and concentrated to a final volume of 50 ml. After one night at 0° the precipitate was collected by suction: yield 2.8 g., m.p. 125–127°. By evaporating to dryness the mother liquor and crystallizing the residue from ligroin an additional crop of 0.3 g. was obtained.

Anal. Calcd. for $C_6H_9NO_3$: C, 50.34; H, 6.33; N, 9.78. Found: C, 50.24; H, 6.20; N, 9.99.

By the same method compound Ic–e,g–i,q, were prepared; their properties and yields are reported in Table III.

Method (B).[22a] *5-Ethyl-5-methyldihydro-1,3-oxazine-2,4-dione* (Ib). To 11.7 g. of α-ethyl-α-methyl-β-carbamyloxypropionic acid (VIb) in 55.8 ml. of thionyl chloride 5.7 ml. of anhydrous pyridine were added in about 10 min. while stirring and avoiding the temperature's exceeding 25°. The crystalline VIb slowly dissolved and the solution became clear and yellow. After completion of the addition the mixture was refluxed 1 hr., then evaporated to dryness *in vacuo*. The residue was treated twice with benzene and the solvent removed *in vacuo* each time. The residue was slurried in water, extracted with ethyl ether, the ether extract washed with water, sodium carbonate, and finally water, and dried over Na_2SO_4. By concentrating to a small volume 6.1 g. of Ib crystallized on standing. The product was recrystallized from ligroin: yield 4.5 g.; m.p. 83–85°.

Anal. Calcd. for $C_7H_{11}NO_3$: N, 8.91. Found: N, 8.88.

Compounds Ib,f,l–p were prepared by the same method; their properties and yields are reported in Table III.

5,5-DISUBSTITUTED 3-METHYLDIHYDRO-1,3-OXAZINE-2,4-DIONES (XIa–q)

3-Methyl-5-ethyl-5-phenyldihydro-1,3-oxazine-2,4-dione (XIi). A mixture of 5 g. of Ii, 2.55 g. of anhydrous potassium carbonate, 5 g. of methyl iodide in 50 ml. of anhydrous acetone was refluxed 10 hr., then cooled, and filtered. The filtrate was evaporated to dryness *in vacuo* and the oily residue was crystallized from 150 ml. of light petroleum. After one night in the refrigerator the precipitate was collected and dried. Yield 2.5 g., m.p. 73–76°.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 6.00. Found: N, 6.07.

The other compounds (XI) were prepared with the same method; in most cases they were oily and were purified by distillation with the technique of Ronco *et al.*[19] The properties and yields of XIa–q are recorded in Table IV.

5,5-DISUBSTITUTED DIHYDRO-1,3-OXAZINE-2,4-DITHIONES (XIIc–e,h, AND XIIi)

5-Methyl-5-n-propyldihydro-1,3-oxazine-2,4-dithiones (XIIc). Five g. of 5-methyl-5-*n*-propyldihydro-1,3-oxazine-2,4-dione (Ic) were thoroughly mixed with 10 g. of powdered phosphorus pentasulfide and the mixture was heated on an oil bath at 165–170° for 75 min. After cooling the reaction mixture was slurried with ether, filtered, and the operation repeated until the ether was colorless. The collected ether filtrates were treated with charcoal, filtered, and the solvent was removed *in vacuo*. The oily residue was crystallized from ligroin (30 ml.): yield 3.6 g., m.p. 51–55°.

Anal. Calcd. for $C_8H_{13}NOS_2$: N, 6.89; S, 31.54. Found: N, 6.85; S, 31.25.

By this method compound XIId, e, and h and compound XIIi were prepared; their properties and yields are reported in Table V.

OXIDATION OF 5,5-DISUBSTITUTED DIHYDRO-1,3-OXAZINE-2,4-DITHIONES (XII AND XIII) TO THE CORRESPONDING 1,4-DIONES (I AND XI)

5-Methyl-5-n-propyldihydro-1,3-oxazine-2,4-dithiones (XIIc). To a suspension of 600 mg. of 5-methyl-5-*n*-propyldihydro-1,3-oxazine-2,4-dithione (XIIc) in 15 ml. of water, enough 10% sodium hydroxide solution was added to obtain a clear solution, then 30 ml. of 30% hydrogen peroxide were added while cooling in an ice water bath. The mixture was heated on a water bath until discolorated, then cooled, acidified with 10% hydrochloric acid, and extracted with ethyl ether. The ether extract was dried and evaporated *in vacuo:* 350 mg. of a crystalline compound melting at 59–60° were obtained. The mixed melting point with an authentic sample of Ic was not depressed. The infrared spectra of samples of Ic obtained both by cyclization of VIc and by oxidation of the corresponding dithio compound XIIc were identical.

ALKALINE HYDROLYSIS OF 5-ETHYL-5-PHENYLDIHYDRO-1,3-OXAZINE-2,4-DIONE (Ii)

A mixture of 800 mg. of Ii, 10 ml. of ethanol, and 10 ml. of 50% potassium hydroxide were refluxed for 0.5 hr., the solvent was removed *in vacuo* and the residue extracted with ethyl ether. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ethyl ether. The latter ether extract was evaporated to dryness and the oily residue was crystallized from benzene-light petroleum. The crystalline product melting at 93–94° was identical (mixed melting point, infrared spectra) with an authentic sample of α-ethyl-α-phenyl-β-hydroxypropionic acid (α-ethyltropic acid)[2] (Vi).

2-METHYLAMINOMETHYL-2-PHENYL-1-BUTANOL (XIV) BY REDUCTION OF 5-ETHYL-5-PHENYLDIHYDRO-1,3-OXAZINE-2,4-DIONES (Ii) WITH $LiALH_4$

In a 1-l. flask fitted with a dropping funnel, a thermometer, and a reflux condenser, 4 g. of $LiAlH_4$ in 100 ml. of anhydrous ethyl ether were placed. To the suspension 7.5 g. of Xi in 300 ml. of anhydrous ethyl ether were slowly added while cooling. When the addition was over (about 1 hr.), the mix-

(22a) We are indebted to Dr. A. Passera for the development of this procedure.

ture was refluxed for 4 hr., then allowed to stand overnight. A 10% ammonium chloride solution (100 ml.) was cautiously added, then the mixture was filtered. The solid residue was slurried with ethyl ether and filtered. The collected ether filtrates were washed with water and concentrated to a final volume of 250 ml. and extracted with two 50-ml. portions of 10% hydrochloric acid. The acidic extract was made alkaline with a saturated solution of sodium carbonate and extracted with ethyl ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, filtered, concentrated, and the residue distilled *in vacuo*. The fraction boiling at 102° with a pressure of 0.4 mm. was collected and crystallized on standing: yield 3.1 g., m.p. 41–42°.

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.56; H, 9.91; N, 7.25. Found: C, 74.61; H, 9.95; N, 7.20.

The infrared spectrum was identical with an authentic sample of XIV prepared by another way as described below. The mixed melting points of samples of XIV obtained by the two different methods were not depressed.

2-METHYLAMINOMETHYL-2-PHENYL-1-BUTANOL (XIV) FROM ETHYL β-AMINO-α-ETHYL-α-PHENYLPROPIONATE (XV)

β-Carbethoxyamino-α-ethyl-α-phenylpropionic acid (XVI). In a flask fitted with a mechanical stirrer, a thermometer, and a dropping funnel, 20 g. of ethyl β-amino-α-ethyl-α-phenylpropionate[16] (XV) and 100 ml. of anhydrous pyridine were placed. The mixture was cooled to 0°, then 20 g. of ethyl chloroformate were slowly added while stirring. When the addition was complete, the mixture was further stirred at 0° for 1 hr. then cautiously poured into 350 ml. of ice water, acidified with 10% sulfuric acid and extracted with ethyl ether. The ether extract was washed with water until neutral, dried over sodium sulfate, filtered, and concentrated to dryness. The residue was distilled *in vacuo* collecting the fraction boiling at 150° with a pressure of 0.4 mm. Yield 23.1 g.

Anal. Calcd. for $C_{16}H_{23}NO_4$: C, 65.50; H, 7.90; N, 4.77. Found: C, 65.76; H, 7.87; N, 5.00.

2-Methylaminomethyl-2-phenyl-1-butanol (XIV). To a suspension of 15 g. of $LiAlH_4$ in 150 ml. of anhydrous ethyl ether 10 g. of XVI in 100 ml. of anhydrous ethyl ether were slowly added at low temperature. The mixture was refluxed 3 hr., allowed to stand overnight, then cautiously treated with 100 ml. of 10% ammonium chloride. The mixture was filtered, treated with ethyl ether and the ether layer extracted with two 30 ml. portions of 10% hydrochloric acid. The ether layer was discarded; the acid extract was made alkaline with a saturated solution of sodium carbonate, then extracted three times with ether. The combined ether extracts were washed with water, dried over sodium sulfate, concentrated, and the residue was distilled with the technique of Ronco *et al.*[19] Yield 2.77 g. of XIV, b.p. 90° (air bath) with a pressure of 0.2 mm. The distilled product solidified on standing, m.p. 41–42.5°.

2-DIMETHYLAMINOMETHYL-2-PHENYL-1-BUTANOL (XVII) BY REDUCTION OF 3-METHYL-5-ETHYL-5-PHENYLDIHYDRO-1,3-OXAZINE-2,4-DIONE (XIi)

Twenty g. of XIi were reduced with 10 g. of $LiAlH_4$ by the same method described above for the reduction of Ii: 12.55 g. of XVII were obtained, b.p. 95–96° with a pressure of 0.4 mm.; XVII solidified on standing, m.p. 68.5–69°.

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.30; H, 10.00; N, 6.74.

The infrared spectrum was identical with an authentic sample of the product prepared by another way described hereunder.[18] The mixed melting point of samples of XVII obtained by the two different methods was not depressed.

2-DIMETHYLAMINOMETHYL-2-PHENYL-1-BUTANOL (XVII) FROM α-CARBETOXY-α-PHENYL BUTYRYL CHLORIDE (XVIII)[18]

N,N-Dimethyl-α-carbetoxy-α-phenylbutyramide (XIX). A 17.5% benzene solution of dimethylamine (100 ml.) was added to 30 g. of α-carbetoxy-α-phenylbutyryl chloride (XVIII).[2] After 15 min. the solution was treated with water, acidified with hydrochloric acid, and extracted with ethyl ether. The ether extract was evaporated to dryness and the residue crystallized from ligroin. Yield 28 g., m.p. 52–55°.

2-Dimethylaminomethyl-2-phenyl-1-butanol (XVII). Into a suspension of 17.4 g. of $LiAlH_4$ in 150 ml. of anhydrous ethyl ether a solution of 15 g. of XIX in 90 ml. of anhydrous ethyl ether was gradually dropped without exceeding 25–27°. The mixture was refluxed 1.5 hr. and poured cautiously after cooling into 2 volumes of cold water. The mixture was extracted with ethyl ether and the organic layer evaporated to dryness *in vacuo*. The residual oil was distilled *in vacuo* collecting the fraction boiling at 95–96° with 0.4 mm. Yield 9 g. of XVII. The product crystallized on standing, m.p. 68–69°.

Acknowledgment. We are grateful indebted to Prof. R. Fusco for the very useful discussions on this subject during the experimental work and to Miss. Dr. A. Wittgens for the assistance in the compilation of the manuscript.

MILAN, ITALY

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF AYERST, MCKENNA & HARRISON LTD.]

New Analeptics: 1-(Diphenylmethyl)-2-methyl-2-thiopseudourea Analogs

STANLEY O. WINTHROP AND GREGORY GAVIN

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1-(Diphenylmethyl)pseudoureas, guanidines, and amidines have been prepared as potential analeptics. Analogs of 1-(diphenylmethyl)-2-methyl-2-thiopseudourea where the diphenylmethyl moiety has been replaced by other groupings are also reported. Certain of these compounds possess appreciably analeptic activity.

In a previous paper[1] some 1-(diphenylmethyl)-2-alkyl-2-thiopseudoureas were described and reported to possess analeptic activity. The first member of the series proved to be the most potent with respect to increasing the spontaneous activity of the rat. Since this compound is structurally quite unlike any of the known analeptic drugs, it was of interest to prepare certain of its analogs for pharma-

(1) S. O. Winthrop, S. Sybulski, G. Gavin, and G. A. Grant, *J. Am. Chem. Soc.*, **79**, 3496 (1957).