tropic distillation with benzene. Addition of ethereal hydrogen chloride gave a white solid which was recrystallized several times from ethanol; yield, 1.2 g.

Acknowledgments.—We are greatly indebted to Messrs. M. E. Auerbach, K. D. Fleischer and staff for the chemical analyses, to Mr. A. E. Soria for preparation of a large amount of 1-(3-oxo-3-phenylpropyl)-4-phenyl-4-propionoxypiperidine and to Mrs. A. Pierson and Mrs. H. Lawyer for technical assistance in the pharmacological evaluations.

Dicarbamates and Thiolcarbamates

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Received February 23, 1962

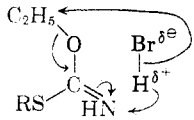
A number of thiolcarbamates structurally related to monocarbamates known to elicit muscle-relaxant and tranquilizing effects were synthesized for biological evaluation. One compound, phenoxypropylthiolcarbamate (compound 10, Table I), showed good taming effect in experimental animals. However, the thiolcarbamates in general possessed an offensive odor and consequently further work in this series was of limited value. Some dicarbamates were prepared but these were devoid of significant biological activity.

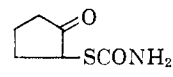
Several years ago we initiated a project in our Laboratory which had as its goal the synthesis and evaluation of substances for analgetic effects. A wide variety of thiazolin-2-ones[1,2] were prepared by the condensation of an α-halo ketone with ethyl xanthamidate. One of the compounds, 4-piperidinomethyl-2,3,4,5,6,7-hexahydrothiazolin-2-one,[3] exhibited good analgetic effects with rapid onset of action when tested in humans. However, a drug side effect (*i.e.*, reversible inflammation of the optic nerve) curtailed further investigations with this class of compounds.

In the course of the synthetic work in this series, it was observed that α-chlorocyclohexanone condensed with ethyl xanthamidate under relatively mild conditions to afford the corresponding thiazolin-2-one,

(1) G. deStevens, H. A. Luts, and J. A. Schneider, *J. Am. Chem. Soc.*, **79**, 1516 (1957).
(2) G. deStevens, A. Frutchey, A. Halamandaris, and H. A. Luts, *ibid.*, **79**, 5263 (1957).
(3) G. deStevens, A. L. Hopkinson, M. A. Connelly, P. Oke, and D. C. Schroeder, *ibid.*, **80**, 2201 (1958).

whereas the condensation with α-chlorocylopentanone could only be effected under forcing conditions. When the condensation was carried out under mild conditions, only 2-oxycyclopentylthiolcarbamate (I) was isolated. This substance was also obtained by acid hydrolysis of α-thiocyanocyclopentanone. The identity of the two substances supports the view that the thiol group rather than the imino group of ethyl xanthamidate undergoes condensation with the α-halo ketone. It thus appeared that under properly controlled conditions a facile one-step route to thiolcarbamates was in hand. It should be indicated that the hydrohalide formed in the initial step of this reaction is in turn responsible for hydrolysis of the intermediate ester to the amide.





I

In Table I is outlined a group of thiolcarbamates prepared by the general sequence shown. As a rule, the bromo compounds were much

$$RBr + HSC(OC_2H_5)=NH \longrightarrow RSCONHR + C_2H_5Br$$

more reactive than the corresponding chloro compounds unless the chloro group was activated. In addition, it was found in this series that the thiolcarbamates also could be obtained from the thiocyano derivative. The spectral properties of these substances further served to confirm the assigned structures. Besides the N–H absorption bands in the 3200 cm.$^{-1}$ to 3400 cm.$^{-1}$ region of the infrared, these compounds also elicited strong absorption at 1650–1665 cm.$^{-1}$ which is characteristic of the thiolcarbamoyl moiety.

Thiolcarbamates.—Some of the compounds listed in Table I were related to the well-known muscle relaxants[4]: *o*-$CH_3C_6H_4OCH_2CHOHCH_2OH$ (mephenesin), *o*-$CH_3OC_6H_4OCH_2CHOHCH_2OCONH_2$ (methocarbamol), and $C_6H_5(CH_2)_3OCONH_2$ (proformiphen).

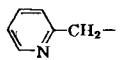
Compound 10 (see Table I) was administered intraperitoneally to mice (male CF-1) in a tragacanth suspension. Typical mephenesin-like effects were observed. Doses of 200 mg./kg. caused prostration, a weakened grasping reflex and abolition of the pinna reflex. Higher doses (*ca.* 500 mg./kg.) in addition to the above effects caused loss of righting reflexes as well as loss of corneal reflexes.

The LD_{50} in mice (I.P., 24 hr.) was estimated to be greater than

(4) For a review of the latest developments in muscle-relaxants, see W. Kunz in "Progress in Drug Research," Vol. II, E. Jucker, ed., Birkhäuser, Basle, 1960, pp. 262–265.

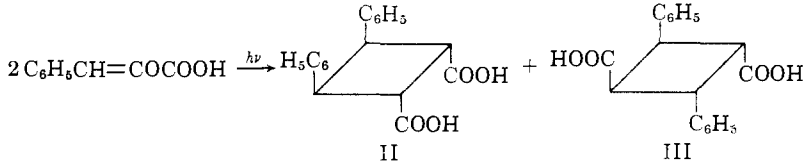
TABLE I

THIOLCARBAMATES RSCONHR'

No.	R	R'	M.p., °C.	Yield, %	Empirical formula	Calcd. % C	Calcd. % H	Calcd. % N	Found % C	Found % H	Found % N
1	$ClCH_2CH_2CH_2$—	H	105–107	36	C_4H_8ClNOS	31.39	5.22	9.13	31.37	5.28	9.41
2	$NC(CH_2)_4$—	H	85	34	$C_6H_{10}N_2OS$	45.26	6.37	17.70	44.98	6.26	17.49
3	$2,4(CH_3)_2C_6H_3CH_2$—	H	124–125	40	$C_{10}H_{13}NOS$			7.15			6.98
4		H	141–143	33	$C_7H_8N_2OS \cdot HCl$	40.80	4.45	13.72	40.51	4.52	13.80
5	$HOOC(CH_2)_2$—	C_6H_5	145–147	42	$C_{10}H_{11}NO_3S$	53.36	4.92	6.22	53.44	5.05	6.04
6	$C_6H_5CH{=}CHCH_2$—	CH_3	89–90	45	$C_{11}H_{13}NOS$	60.90	6.04	6.45	60.60	6.40	6.66
7	$C_6H_5CH{=}CHCH_2$—	H	174–175	66	$C_{10}H_{11}NOS$	62.17	5.74	7.25	61.97	5.80	7.12
8	$C_6H_5(CH_2)_3$—	H	194–195	65	$C_{10}H_{13}NOS$	61.50	6.71	7.18	61.48	6.89	6.78
9	$C_6H_5(CH_2)_3$—	CH_3	B.p. 162–164 0.5 mm.	42	$C_{11}H_{15}NOS$	60.45	6.92	6.41	61.00	6.95	6.46
10	$C_6H_5O(CH_2)_3$—	H	102–103	51	$C_{10}H_{13}NO_2S$	56.98	6.17		56.70	6.28	
11	$C_6H_5O(CH_2)_3$—	CH_3	B.p. 178–180 0.15 mm.	46	$C_{11}H_{15}NO_2S$	58.65	6.71	6.22	58.54	6.66	6.48
12	$2\text{-}ClC_6H_4O(CH_2)_3$—	H	90	45	$C_{10}H_{12}ClNO_2S$	48.87	4.93		49.08	5.10	
13	$2\text{-}CH_3OC_6H_4O(CH_2)_3$—	H	89–91 B.p.	42	$C_{11}H_{15}NO_3S$	54.75	6.27	5.81	54.79	6.37	6.00
14	$2\text{-}CH_3OC_6H_4O(CH_2)_3$—	CH_3	178–180 0.15 mm.	42	$C_{12}H_{17}NO_3S$	56.45	6.71		56.06	6.48	
15	$2\text{-}CH_3C_6H_4O(CH_2)_3$—	H	79–80	38	$C_{11}H_{15}NO_2S$	58.64	6.71	6.22	58.89	6.84	5.94
16	$4\text{-}CH_3OC_6H_4O(CH_2)_3$—	H	88–90	40	$C_{11}H_{15}NO_3S$	54.75	6.27	5.81	54.79	6.39	5.65

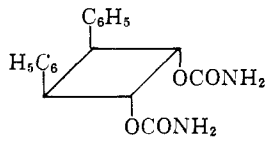
900 mg./kg. When this compound was administered to a normal unanesthetized cat (I.P., tragacanth suspension) in a single dose of 450 mg./kg., ataxia followed by prostration occurred in about 45 min. In addition, the pupils were mydriatic and the nictitating membrane was relaxed. This animal was fully recovered within 20 hr. The other compounds in Table I were tested similarly and found to be less active. However, compound 10 and related thiolcarbamates have a sharp noxious odor which was sufficiently disagreeable to prohibit further exploration in this series. Animals given adequate doses of these substances became permeated with their odor.

Dicarbamates.—The well-documented mild tranquilizing action of meprobamate prompted us to synthesize some dicarbamates for biological evaluation. One approach consisted of employing the cyclobutane ring as the central moiety. To this end the method of Bernstein and Quimby[5] was used for the preparation of β-truxinic acid (II) and α-truxillic acid (III). Lithium aluminum hydride reduction of the diethyl esters of acids II and III, respectively, gave the pre-

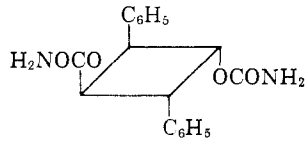


II III

viously described 1,2-bis(hydroxymethyl)-3,4-diphenylcyclobutane[6] and the new 1,3-bis(hydroxymethyl)-2,4-cyclobutane. These glycols were converted to the dicarbamates, IV and V.

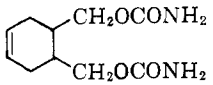


IV

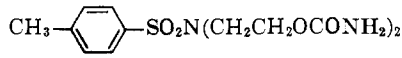


V

In the cyclohexene series *cis*-1,2-bis-(hydroxymethyl)-4-cyclohexene was converted also to the corresponding dicarbamate VI. Finally,



VI



VII

(5) H. I. Bernstein and W. C. Quimby, *J. Am. Chem. Soc.*, **65**, 4845 (1943).
(6) A. T. Blomquist and Y. C. Meinwald, *J. Am. Chem. Soc.*, **81**, 667 (1959).

the commercially available N-(2-hydroxyethyl)-N-2-(2-hydroxy-1-methylethyl)-*p*-toluenesulfonamide on treatment with sodium isocyanate and hydrogen chloride gave rise to the dicarbamate VII. These compounds were found to be devoid of tranquilizing effects when tested in rats according to the method previously described.

Experimental[7]

The substituted phenoxypropyl bromides used as intermediates for the preparation of compounds 12 through 16 in Table I were prepared according to the method outlined by Marvel and Tanenbaum.[8]

Compounds 1 through 11 were prepared from commercially available halides. Compounds 3, 4, 6 and 7 were synthesized from the corresponding chloro compounds, whereas the others were prepared from the bromo intermediates. N-Methyl ethyl xanthamidate used to prepare compounds 6, 9, 11 and 14 and N-phenyl ethyl xanthamidate used in the preparation of compound 5 were synthesized by a previously described procedure.[2,3]

General Procedure for the Preparation of Thiolcarbamates. 3-Phenoxypropylthiolcarbamate.—Ethyl xanthamidate (5.1 g., 0.05 mole) was added to 25 ml. of ethyl alcohol containing 10.5 g. (0.05 mole) of 3-phenoxypropyl bromide. After allowing the solution to reflux for 16 hr., the solvent was evaporated *in vacuo* at the steam bath. The resulting solid residue was collected on a filter and then recrystallized from ethyl alcohol.

3-Phenoxypropyl Isothiocyanate.—A solution of 4.2 g. of 3-phenoxypropyl bromide in 25 ml. of ethyl alcohol was treated with 6.0 g. of barium thiocyanate and the mixture was refluxed for 2 hr. The barium bromide was filtered off and the filtrate was concentrated *in vacuo*. Water was added to the oil and the mixture was extracted with ether. After drying the ether extract over magnesium sulfate, the extract was filtered and the filtrate was evaporated to yield a viscous yellow oil which was distilled *in vacuo*. The product boiled at 120–123° (0.2 mm.).

Anal. Calcd. for $C_{10}H_{11}NOS$: C, 62.35; H, 5.72. Found: C, 62.39; H, 5.80.

One gram of this isothiocyanate was allowed to react under reflux for 24 hr. with 30 ml. of ethyl alcohol:water (1:2) and 10 ml. of concd. hydrochloric acid. The solution was then chilled overnight. The precipitate was collected on a filter and recrystallized from ethyl alcohol. The resulting compound was found to be identical in all respects with the thiolcarbamate prepared by the general procedure described above.

1,2-Bis-(dicarbamoyloxymethyl)-3,4-diphenylcyclobutane (IV).—A solution of 3 g. (0.011 mole) of 1,2-bis(hydroxymethyl)-3,4-diphenylcyclobutane in 100 ml. of chloroform was chilled to −5°. Sodium cyanate (1.94 g., 0.045 mole) was added to the solution while hydrogen chloride was bubbled through the solution with vigorous stirring, the temperature being maintained at −5 to +5°. At the end of 2 hr. an additional 0.79 g. of sodium cyanate was added and hydrogen chloride was bubbled into the solution for another 2 hr. After standing at 0° for

(7) Melting points reported herein and in Table I are uncorrected.

(8) C. S. Marvel and A. J. Tannenbaum, "Org. Synth.," Coll. Vol. I, Gilman and Blatt, J. Wiley and Sons, New York, N. Y., 1932, pp. 435–436.

0.5 hr., the solution was filtered. A white solid material was collected which was combined with the solid obtained on concentrating the chloroform filtrate. The combined solids were added to 100 ml. of water and the aqueous mixture was extracted with ether. The aqueous mixture was filtered to yield 3.5 g. of crude product which was recrystallized twice from ethyl alcohol to give 2.0 g. of pure IV, m.p. 164–165°.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.77; H, 6.26; N, 7.90. Found: C, 67.32; H, 6.28; N, 7.98.

The following dicarbamates were prepared by the same procedure:

(a) **1,3-Bis-(carbamoyloxymethyl)-2,4-diphenylcyclobutane (V),** m.p. 162–164°, was obtained in 48% yield as a white crystalline powder after one recrystallization from alcohol: water.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.77; H, 6.26; N, 7.90. Found: C, 67.76; H, 6.38; N, 7.82.

1,3-Bis-(hydroxymethyl)-2,4-diphenylcyclobutane, recrystallized from methyl alcohol, melting at 100–101°, was obtained by lithium aluminum hydride reduction of the corresponding diester according to the method of Blomquist and Meinwald.[6]

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.77; H, 7.66.

(b) *cis*-**1,2-Bis-(dicarbamoyloxymethyl)-4-cyclohexane (VI)** was obtained in 65% yield as a white powder, m.p. 124–126°, after two recrystallizations from methyl alcohol–ethyl acetate.

Anal. Calcd. for $C_{10}H_{16}N_2O_4$: C, 52.62; H, 7.06; N, 12.27. Found: C, 52.57; H, 7.06; N, 12.49.

(c) **N-(2-Carbamoyloxyethyl)-N-(2-carbamoyloxy-1-methyl-ethyl)-*p*-toluenesulfonamide (VII),** m.p. 152–155°, was obtained in 60% yield.

Anal. Calcd. for $C_{14}H_{21}N_3O_6S$: C, 46.79; H, 5.89; N, 11.70. Found: C, 46.98; H, 5.83; N, 11.54.