of acetic acid, 3.3 g. (0.073 mole) of dimethylamine (13.2 ml. of 25% aqueous), and 2.2 g. (0.073 mole) of formaldehyde (5.95 ml. of 37% aqueous) at about 0° over a period of 1.5 hr. The reaction mixture was kept at room temperature for about 16 hr., and the clear yellow solution was diluted with 500 ml. of water. A small amount of yellow gum which precipitated was removed by filtration. The filtrate was made basic with 140 ml. of cold 10 *N* KOH. The solid which precipitated was filtered, washed with water until neutral, and dried. The product, m.p. 107–111°, suitable for the next step amounted to 12.5 g. (92%). For analysis it was recrystallized from 50 ml. of ether by the addition of 100 ml. of petroleum ether, and 7.1 g. of **11**: m.p. 109–111°, was obtained; λ_{max}^{MeOH} 295 mμ (ε 5730), 284 (7550), 276 (7660).

Anal. Calcd. for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 77.94; H, 9.43; N, 11.71.

5-Methyl-2-propylindole-3-acetonitrile (13).—A solution of 66.1 g. (0.287 mole) of 5-methyl-2-propylgramine (**11**) in the minimum volume of ether was added dropwise during 15 min. to 400 ml. of stirred methyl iodide at 3°. The mixture was stirred for 6 hr. at 0° and then allowed to warm to room temperature overnight. The pink solid was filtered and washed well with ether.

The dried methiodide was added to 183 g. of KCN in 1.4 l. of water. The mixture was heated to 80° in 20 min. with stirring and kept at that temperature for 2 hr. The mixture was cooled and the lumpy product was filtered and washed twice with water. To break up the solid, it was dissolved in 200 ml. of ethanol and added dropwise to 1 l. of stirred cold water. Product (57.7 g.) melting at 98–102° was obtained. Recrystallization from ether–petroleum ether gave 41.5 g. (68%) of **13**: m.p. 105–106°; λ_{max}^{MeOH} 296 mμ (ε 5730), 286 (7750), 277 (7880), 226 (33,200).

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 78.89; H, 7.45; N, 13.39.

Hydrolysis of **13** in aqueous-alcoholic KOH gave **5-methyl-2-propylindole-3-acetic acid (15)**, m.p. 144–149°, in 82% yield.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 73.03; H, 7.18; N, 6.20

The acid **15** in methanolic HCl was converted into **methyl 5-methyl-2-propylindole-3-acetate (17)**, m.p. 78–79°, in 91% yield; λ_{max}^{MeOH} 297 mμ (ε 6110), 287 (7700), 280 (7630), 225 (31,650).

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.24; H, 7.51; N, 5.65.

1-*p*-Chlorobenzyl-5-methyl-2-propylindole-3-acetic Acid (4).—Methyl 5-methyl-2-propylindole-3-acetate (**17**) was converted into the acid (**4**) by essentially the same process used for the preparation of the 2-ethylindole (**1**). The product **4**, m.p. 143–149°, was obtained in an over-all yield of 30%; λ_{Nuj}^{MeOH} 300 mμ (ε 5960); λ_{max}^{MeOH} 290 mμ (ε 7550), 273 (7650), 226 (36,800).

Anal. Calcd. for $C_{21}H_{22}ClNO_2$: C, 70.88; H, 6.23; Cl, 9.96; N, 3.94. Found: C, 70.80; H, 6.25; Cl, 9.90; N, 3.60.

1-*p*-Chlorobenzyl-5-methyl-2-phenylindole-3-acetic Acid (5).—A mixture of 9.9 g. (28 mmoles) of 80% N-*p*-chlorobenzyl-N-*p*-tolylhydrazine hydrochloride (**18**) and 5.0 g. (28 mmoles) of 3-benzoylpropionic acid (**21**) in 140 ml. of acetic acid was heated on the steam bath for 4 hr. The reaction solution was concentrated to dryness at reduced pressure. The residue in 200 ml. of methylene chloride was washed with one 200-ml. portion of 2 *N* HCl and three 100-ml. portions of water. The dried ($MgSO_4$) methylene chloride layer was concentrated, and the residue was crystallized from 150 ml. of methylene chloride by adding 300 ml. of petroleum ether. The solid (4 g., m.p. 180–195°) was recrystallized twice from 200 ml. of methylene chloride and 400 ml. of petroleum ether. The product (3.4 g., 31%, m.p. 204–207°) would not give completely satisfactory elemental analyses because of contamination with a small amount of solvent (CH_2Cl_2) which was not removed at 100° and reduced pressure. Recrystallization of this material from 80 ml. of hot acetone by adding 50 ml. of petroleum ether gave 2.9 g. of **5**, m.p. 205–208°, λ_{max}^{MeOH} 300 mμ.

Anal. Calcd. for $C_{24}H_{20}ClNO_2$: C, 73.94; H, 5.17; Cl, 9.09; N, 3.59. Found: C, 73.89; H, 5.13; Cl, 9.07; N, 3.86.

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Thio Analogs of Carisoprodol (N-Isopropyl-2-methyl-2-propyl-1,3-propanediol Dicarbamate)

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Two thio analogs of carisoprodol, 3-carbamoxy-2-methyl-2-propylpropyl N-isopropylthiocarbamate and 2-methyl-2-propyl-3-thiocarbamoxypropyl N-isopropylcarbamate, and two thio analogs of meprobamate, 3-carbamoxy-2-methyl-2-propylpropyl thiolcarbamate and 2-methyl-2-propylpropyl 1,3-bis(dithiocarbamate), were synthesized.

Carisoprodol, N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate (**1**), was first synthesized by Berger and Ludwig.[2] It has found wide application as a muscle relaxant.[3] Meprobamate, 2-methyl-2-propyl-1,3-propanediol dicarbamate (**2**), was first synthesized by Ludwig and Piech[4] and is a well-known tranquilizer. Recently,[5] the synthesis of two thio analogs (**3** and **4**) of meprobamate was published. We now wish to report the synthesis of 3-carbamoxy-2-methyl-2-propylpropyl N-isopropylthiocarbamate (**13**) and 2-methyl-2-propyl-3-thiocarbamoxypropyl N-isopropylcarbamate (**12**), thio analogs of carisoprodol, and 3-carbamoxy-2-

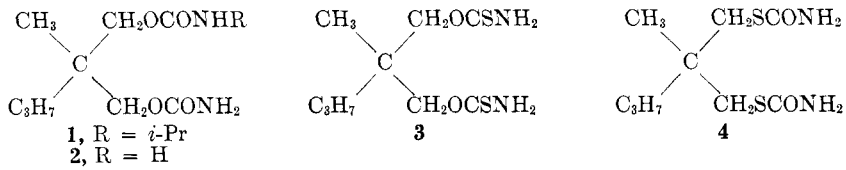
(1) To whom inquiries should be addressed.

(2) F. M. Berger and B. J. Ludwig, U. S. Patent 2,937,119 (May 17, 1960).

(3) F. M. Berger, "The Pharmacology and Clinical Usefulness of Carisoprodol," J. G. Miller, Ed., Wayne State University Press, Detroit, Mich., 1959.

(4) B. J. Ludwig and E. C. Piech, *J. Am. Chem. Soc.*, **73**, 5779 (1951).

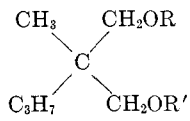
(5) B. J. Ludwig, F. J. Stiefel, L. S. Powell, and J. Diamond, *J. Med. Chem.*, **7**, 174 (1964); B. Loev and M. F. Kormendy, *J. Org. Chem.*, **28**, 3421 (1963).

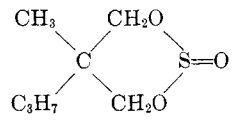


1, R = *i*-Pr
2, R = H

3

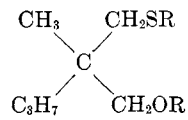
4

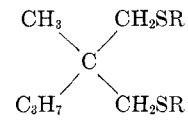




6

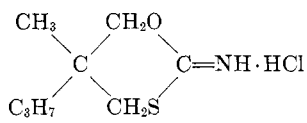
5, R = R′ = H
7, R = Ts; R′ = H
8, R = $CONH_2$; R′ = H
9, R = Ts; R′ = $CONH_2$
10, R = H; R′ = CONH-*i*-Pr
11, R = Ts; R′ = CONH-*i*-Pr
12, R = $CSNH_2$; R′ = CONH-*i*-Pr
13, R = $CONH_2$; R′ = CSNH-*i*-Pr
14, R = $CSNH_2$; R′ = H
15, R = CSNH-*i*-Pr; R′ = H
16, R = $CSNH_2$; R′ = CSNH-*i*-Pr





17, R = R′ = H
18, R = R′ = $CONH_2$
19, R = H; R′ = $CONH_2$
20, R = H; R′ = CONH-*i*-Pr

21, R = R′ = H
22, R = R′ = $CSNH_2$



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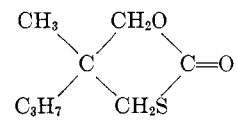

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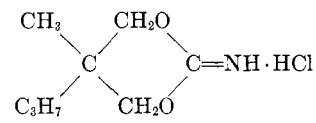

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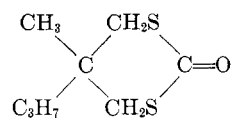

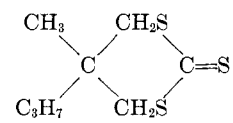

26 **27**

methyl-2-propylpropyl thiolcarbamate (**18**) and 2-methyl-2-propylpropyl 1,3-bis(dithiocarbamate) (**22**), thio analogs of meprobamate.

Derivatives of 3-Hydroxy-2-methyl-2-propylpropanethiol.—Attempts to prepare 1-chloro-2-methyl-2-propyl-3-hydroxypropane by reaction of 2-methyl-2-propyl-1,3-propanediol (**5**) with 1 equiv. of thionyl chloride in pyridine resulted in formation of the cyclic sulfite **6** in 56% yield.

Reaction of **5** with 1 equiv. of *p*-toluenesulfonyl chloride and pyridine in ether at 0°, afforded the monotosylate (**7**) in 95% yield. The desired hydroxythiol (**17**) was obtained from the monotosylate *via* reaction with potassium thiolacetate in dimethylformamide, followed by hydrolysis of the thiolacetate with alcoholic aqueous sodium hydroxide as described by Ludwig, *et al.*[5] Alternatively, **17** could be prepared by reaction of the monotosylate with sodium hydrosulfide in dimethylformamide. The former procedure afforded the best yields of the hydroxythiol.

An interesting aspect of the reaction between **7** and potassium thiolacetate was evidence that some intramolecular transesterification of the hydroxythiolacetate had occurred. The infrared absorption spectrum of the intermediate thiolester showed two carbonyl bands (5.75 and 5.90 μ) indicating the presence of both O-ester and S-ester. Evidence of an SH band at 3.85 μ suggested the presence of some 3-acetoxy-2-methyl-2-propylpropanethiol. Hydrolysis of the mixture of esters would yield the same product.

Treatment of **17** with cyanic acid in the manner used by Ludwig, *et al.*,[5] yielded an analytical sample of the thio analog of meprobamate, 3-carbamoxy-2-methyl-2-propylpropyl thiolcarbamate (**18**).

In order to obtain the unsymmetrically substituted carisoprodol analogs it was felt that a route through the cyclic carbonate intermediates would be best. The synthesis of 2-methyl-2-propyl-1,3-propanethiocarbonate (**24**) was accomplished in low yield by the slow addition of a solution of **17** and phosgene in ethyl acetate to pyridine in ethyl acetate.[6]

Refluxing of **17** with potassium thiocyanate in dimethylformamide, followed by treatment of the product with an ether solution of anhydrous HCl, yielded 2-methyl-2-propyl-1,3-propanethioiminocarbonate hydrochloride (**23**). Treatment of **23** with aqueous sodium hydrogen carbonate also afforded **24**.

Selective ring opening of **24** with ammonia or isopropylamine was not possible, thereby negating the use of **24** as an intermediate to the unsymmetrical carisoprodol analogs.

An alternate route to the carisoprodol analogs derived from **17** was then explored. It was found possible to prepare 2-methyl-2-propyl-3-tosyloxypropyl carbamate (**9**) by reaction of the monotosylate (**7**) with cyanic acid.[5] Tosylation of 2-methyl-2-propyl-3-hydroxypropyl carbamate (**8**), obtained from ring opening 5-methyl-5-propyl-2-*m*-dioxanone with ammonia,[2] afforded **9** in 65% yield.

(6) D. D. Reynolds, *J. Am. Chem. Soc.*, **79**, 4951 (1957).

The corresponding N-isopropylcarbamate derivative, 2-methyl-2-propyl-3-tosyloxypropyl N-isopropylcarbamate (**11**), was prepared by tosylation of 2-methyl-2-propyl-3-hydroxypropyl N-isopropylcarbamate (**10**), obtained by ring opening of 5-methyl-5-propyl-2-*m*-dioxanone with isopropylamine.[2]

Reaction of **9** with potassium thiolacetate in DMF, followed by refluxing the intermediate thiolacetate in methanolic HCl, yielded a colorless liquid showing the presence of a thiol band (3.90 μ) and absence of the thiolacetate band (5.95 μ) in the infrared. Chromatography of the crude product over Schlesinger silica gel afforded an analytical sample of the desired 3-carbamoxy-2-methyl-2-propylpropanethiol (**19**). In addition, some splitting of the carbamate linkage occurred, 3-hydroxy-2-methyl-2-propylpropanethiol being recovered from the chromatographic column.

In a like manner, 3-N-isopropylcarbamoxy-2-methyl-2-propylpropanethiol (**20**) was prepared in 32% yield from **11**. Sufficient quantities of neither **20** nor **19** were available for thorough investigation of their conversion to the carisoprodol analogs.

Derivatives of 2-Methyl-2-propyl-1,3-propanediol.—The two thioncarbamate analogs of carisoprodol derived from 2-methyl-2-propyl-1,3-propanediol (**12** and **13**) were obtained by treatment of 2-methyl-2-propyl-3-hydroxypropyl carbamate[2] (**8**) or 2-methyl-2-propyl-3-hydroxypropyl N-isopropylcarbamate[2] (**10**) with thiophosgene in methylene chloride, followed by treatment of the intermediate thiocarbonyl chlorides with isopropylamine or ammonia, respectively.

Attempts to utilize either 2-methyl-2-propyl-3-hydroxypropyl thioncarbamate (**14**) or 2-methyl-2-propyl-3-hydroxypropyl N-isopropylthioncarbamate (**15**) as intermediates to the carisoprodol analog, 2-methyl-2-propyl-3-thioncarbamoxypropyl N-isopropylthioncarbamate (**16**), failed. Treatment of **14**, obtainable by the method of Ludwig, *et al.*,[5] from the diol, with phosgene in tetrahydrofuran, afforded the iminocarbonate (**25**) as the hydrochloride, instead of the desired carbonyl chloride. Similar treatment of **15** failed to yield any of the desired carbonyl chloride. Infrared data indicated cyclization had occurred.

Derivatives of 2-Methyl-2-propyl-1,3-propanedithiol.—It was felt that the most promising route to the carisoprodol analogs derived from 2-methyl-2-propyl-1,3-propanedithiol (**21**) would be *via* the cyclic dithiocarbonate (**26**) or trithiocarbonate (**27**). Thus **21** was allowed to react with phosgene in methylene chloride containing antipyrine, according to the method of Ludwig and Piech.[4] A mixture of products was obtained, and the desired dithiocarbonate was isolated in 36% yield as a colorless oil by column chromatography. In addition to the desired cyclic carbonate, polymeric materials were produced. The low yields in the preparation of the dithiocarbonate negated its utility as an intermediate to the desired carisoprodol analogs.

Attempts to prepare the trithiocarbonate (**27**) from the dithiol and thiophosgene under a variety of conditions resulted in polymeric products. However, reaction of the dithiol with thiocyanic acid in ether, followed by treatment of the crude product with anhydrous HCl, yielded a mixture of the desired trithiocarbonate and the meprobamate analog (**22**). These products could be separated on a Florisil column.

Muscle Paralyzing Activity.—The thio analogs of carisoprodol prepared in this study were evaluated in CF-1 strain white mice for toxicity and muscle paralyzing activity following the procedure described by Berger.[7] The PD_{50} and LD_{50} values, respectively, for these compounds in mg./kg. after intraperitoneal administration were as follows: 2-methyl-2-propyl-3-thioncarbamoxypropyl N-isopropylcarbamate (**12**), 130, 448; 3-carbamoxy-2-methyl-2-propylpropyl N-isopropylthioncarbamate (**13**), 130, 482. Although these thio analogs are somewhat more potent than carisoprodol, they are considerably more toxic than the parent compound (PD_{50} 165, LD_{50} 980).

The additional thio analog of meprobamate prepared in this study in quantity sufficient for evaluation, 3-carbamoxy-2-methyl-2-propylpropyl thiolcarbamate (**18**), possessed PD_{50} and LD_{50} values of 173 and 720, respectively. This monothiolcarbamate analog of meprobamate is substantially less toxic than the corresponding monothioncarbamate derivative (PD_{50} 138, LD_{50} 345), the bis(thiolcarbamate) (212, 410), and the bis(thioncarbamate) (235, 460) described earlier by Ludwig, *et al.*,[5] and compares favorably with meprobamate (235, 800) in muscle paralyzing activity and lethality.

Experimental

2-Methyl-2-propyl-1,3-propane Cyclic Sulfite (6).—To a mixture of 33 g. (0.25 mole) of 2-methyl-2-propyl-1,3-propanediol (**5**) and 19.7 g. (0.25 mole) of pyridine cooled to 5° was added dropwise 29.5 g. (0.25 mole) of thionyl chloride with stirring. The temperature rose gradually to 75° during the addition. After heating at 70–90° for 2 hr., the solution was poured into 500 ml. of water containing 5 ml. of concentrated HCl. The heavy brown oil that separated was extracted with ether, washed with water, 5% $NaHCO_3$ solution, and then with water again. The ether extracts were dried ($MgSO_4$), and the oil was fractionated *in vacuo*. The fraction boiling at 110–112° (19 mm.) represented a 56% yield; $n^{27}D$ 1.4523; λ_{max}^{film} 3.35 (CH), 6.83 (CH_3), 8.40 (S=O), 10.3, 12.7 μ.

Anal. Calcd. for $C_7H_{14}O_3S$: C, 47.5; H, 8.21; S, 17.5. Found: C, 47.2; H, 7.92; S, 17.9.

2-Methyl-2-propyl-3-tosyloxypropanol (7).—To a solution of 13.2 g. (0.1 mole) of **5**, 7.9 g. (0.1 mole) of pyridine, and 25 ml. of anhydrous ether cooled to 5° was added 19.0 g. (0.1 mole) of *p*-toluenesulfonyl chloride dissolved in 50 ml. of anhydrous ether. The clear solution was placed in a refrigerator at 0° for 16 hr. The white precipitate of pyridine hydrochloride was filtered and the ethereal solution was washed with 5% aqueous HCl, water, and dried (Na_2SO_4). The solution was concentrated *in vacuo*, dissolved in the minimum amount of petroleum ether (b.p. 30–60°), and chromatographed on an alumina column (70 g., Merck, acid-washed). Elution of the column with ether yielded an analytical sample of **7** in 58% yield as a colorless oil; $n^{25}D$ 1.5107; λ_{max}^{film} 2.80 (OH), 3.35 (CH), 6.27 (aryl), 6.75 (CH_3), 7.40 (SO_2N), 8.55 (SO_2N), 9.13 (C–OH), 11.9, 12.3 (*para*-disubstituted benzene), 15.1 μ (covalent tosylate).

Anal. Calcd. for $C_{14}H_{22}O_4S$: C, 58.7; H, 7.75; S, 11.2. Found: C, 59.0; H, 7.89; S, 11.4.

A small amount of unreacted diol was removed from the column with methanol. A large-scale run, using 1 *M* quantities of diol, pyridine, and *p*-toluenesulfonyl chloride, stood for 3 days in the refrigerator at 0° and gave a crude yield of 95%. This crude product had an infrared absorption spectrum almost identical with that of the analytical sample obtained by alumina chromatography.

3-Hydroxy-2-methyl-2-propylpropanethiol (17) from 7. A. Using Potassium Thiolacetate.—A mixture of 14.4 g. (50.4 mmoles) of crude monotosylate **7** and 11.4 g. of anhydrous potassium thiolacetate (prepared by titration of distilled thiolacetic acid with 3 *N* KOH in methanol) in 60 ml. of dimethylformamide

(7) F. M. Berger, *J. Pharmacol. Exptl. Therap.*, **105**, 450 (1952).

(DMF) was heated at 95–100° under nitrogen with stirring for 2 hr. after which time the original blue color disappeared. After standing overnight under nitrogen, ether was added to the now almost solid mixture, and the salts were filtered. The ether was removed *in vacuo*, yielding 7.8 g. (81%) of the crude thiolester; the infrared absorption spectrum showed the absence of tosylate (7.40 μ).

The thiolester was hydrolyzed with 3.8 g. of NaOH, 25 ml. of water, and 60 ml. of ethanol by stirring for 3 hr. in a stoppered flask. The clear, yellow solution was chilled, acidified with 6 *N* HCl, and extracted with ether. The extracts were washed with water and dried ($MgSO_4$), and the product was distilled. A fraction boiling at 76–80° (0.5–0.6 mm.) weighed 3.65 g. (49%); $n^{26}D$ 1.4875; λ_{max}^{film} 2.95 (OH), 3.40 (CH), 3.90 (SH), 6.85 (CH_3), 7.30 (CH_3), 9.75 (C-OH), 10.7 μ (SH).

Anal. Calcd. for $C_7H_{16}OS$: C, 56.7; H, 10.9; S, 21.6. Found: C, 56.9; H, 10.9; S, 21.4.

Refluxing the monotosylate with potassium thiolacetate in DMF overnight, as in the preparation of the dithiol,[5] gave evidence that some 3-methyl-3-propylthietane was being formed (absorption at 8.55 μ in the infrared).

B. Using Sodium Hydrosulfide.—A solution of 10 g. (35 mmoles) of crude 2-methyl-2-propyl-3-tosyloxypropanol (**7**) in 75 ml. of DMF was added to 130 mmoles of anhydrous sodium hydrosulfide prepared from sodium in absolute ethanol by saturating the solution with H_2S. The mixture turned blue upon addition of **7**, and after stirring and heating at 110–138° for 1.5 hr., the color disappeared. The mixture was diluted with 100 ml. of water, acidified with 6 *N* HCl, and extracted with ether. The ether extracts were washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to yield 4.0 g. of crude product whose infrared absorption spectrum showed the absence of a tosyl band (7.40 μ). This crude liquid was fractionated to yield 1.48 g. (29%) of 3-hydroxy-2-methyl-2-propylpropanethiol, b.p. 66–68° (0.4 mm.). The infrared absorption spectrum was identical with that of the analytical sample, except for a weak band at 6.50 μ.

3-Carbamoxy-2-methyl-2-propylpropyl Thiolcarbamate (18).—To a mixture of 2.6 g. (17.5 mmoles) of 3-hydroxy-2-methyl-2-propylpropanethiol (**17**), 15 g. of 8 mesh "Drierite," 100 ml. of anhydrous, alcohol-free chloroform, and 3.2 g. (49 mmoles) of sodium cyanate cooled to +5° was added anhydrous HCl for 5 hr. while stirring. The slurry was filtered and concentrated under vacuum. The clear oily residue was dissolved in trichloroethylene, and a crude product melting at 60–66° was precipitated, using petroleum ether (b.p. 30–60°). After recrystallizing twice from chloroform–petroleum ether, a white solid resulted; m.p. 74–75°; λ_{max}^{Nujol} 2.95, 3.10 (NH_2), 5.72, 5.85 (C=O, carbamate), 6.00 (C=O, thiolcarbamate), 7.08 (C—N), 9.12, 9.25 μ (C—O—C).

Anal. Calcd. for $C_9H_{18}N_2O_3S$: C, 46.1; H, 7.68; N, 11.9. Found: C, 46.0; H, 7.43; N, 11.6.

A larger scale preparation from 3.8 g. of **17** afforded **18** in 43% yield.

2-Methyl-2-propyl-1,3-propanethiocarbonate (24).—To a solution of 3.0 g. (30.6 mmoles) of phosgene in 1.6 g. of ethyl acetate cooled to −15° was added 6 g. (40.6 mmoles) of freshly distilled 3-hydroxy-2-methyl-2-propylpropanethiol. This solution was added dropwise to a mixture of 4.83 g. (60.6 mmoles) of pyridine and 1.8 g. (20 mmoles) of ethyl acetate. The temperature was kept between 18–22° for 25 min. The slurry was then heated at 30–35° for 25 min., and then poured into 55 ml. (60 mmoles) of dilute HCl. The ethyl acetate solution was separated, washed with water, and dried (Na_2SO_4). Concentration *in vacuo* yielded 4.8 g. of a light yellow oil. This material was nitroprusside positive and Beilstein negative.

Column chromatography on Woelm neutral Al_2O_3 (activity 1) afforded an analytical sample of **24** as a colorless oil in 18% yield, after elution of the column with benzene, following prior elution with petroleum ether(b.p. 30–60°)–benzene (1:1). Gas–liquid chromatography on silicone gum rubber (methyl) GE-SE-30 at 75–250° gave one peak; n^{26D} 1.4982; λ_{max}^{Nujol} absence of SH (3.95), 3.38 (CH), 5.92 (C=O), 6.80, 7.16, 7.26 μ (CH_3).

Anal. Calcd. for $C_8H_{14}O_2S$: C, 55.1; H, 8.03; S, 18.4. Found: C, 54.7; H, 8.38; S, 18.3.

2-Methyl-2-propyl-1,3-propanethioiminocarbonate Hydrochloride (23).—To a solution of 2.4 g. (8.4 mmoles) of 2-methyl-2-propyl-3-tosyloxypropanol (**7**) in 50 ml. of DMF and a catalytic amount of potassium iodide was added 1.6 g. (10.8 mmoles) of potassium thiocyanate. This mixture was heated at reflux under nitrogen for 4.5 hr.; the solution was cooled to room temperature, poured into 500 ml. of water, and extracted with three 200-ml. portions of ether. The ether extracts were washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to an oil (1.1 g.). This was exposed for 10 min. in an ice bath to anhydrous HCl, ether was added, and more HCl was passed through the solution. Addition of more ether gave a semisolid upon scratching the flask. Recrystallization from ethanol–ether yielded a solid: m.p. 127–129°; λ_{max}^{Nujol} 3.30 (NH_2^+), 6.30 ($C{=}N_2^+$), 8.88 μ (C—O—C).

Anal. Calcd. for $C_8H_{16}ClNOS$: C, 45.8; H, 7.63; N, 6.68. Found: C, 45.7; H, 7.57; N, 6.70.

It was found that by suspension of **23** in ether and treatment with a saturated aqueous solution of $NaHCO_3$ hydrolysis to 2-methyl-2-propyl-1,3-propanethiocarbonate (**24**) occurred.

2-Methyl-2-propyl-3-tosyloxypropyl Carbamate (9). A. Preparation from 2-Methyl-2-propyl-3-tosyloxypropanol.—Anhydrous HCl was passed through a stirred solution of 4.8 g. (16.8 mmoles) of 2-methyl-2-propyl-3-tosyloxypropanol (**7**) in 50 ml. of methylene chloride containing 3 g. of 8 mesh "Drierite" and 1.27 g. (19.5 mmoles) of sodium cyanate for 2.5 hr. at 0°. The solution was capped and stirred overnight at room temperature. The mixture was filtered and the filtrate was concentrated *in vacuo* to yield a white solid which was recrystallized from ethyl acetate–petroleum ether (b.p. 30–60°), yield 78%, m.p. 116.5–117.5°.

Anal. Calcd. for $C_{15}H_{23}NO_5S$: C, 54.8; H, 6.98; N, 4.27. Found: C, 54.5; H, 7.05; N, 4.64.

B. Preparation from 2-Methyl-2-propyl-3-hydroxypropyl Carbamate.—To a solution of 10.1 g. (58 mmoles) of 2-methyl-2-propyl-3-hydroxypropyl carbamate (**8**) in 100 ml. of pyridine cooled to 0° was added 11 g. (58 mmoles) of tosyl chloride dissolved in 50 ml. of pyridine. The solution was allowed to stand overnight at room temperature and poured into 200 ml. of ice containing 170 ml. of concentrated HCl. The mixture was extracted with chloroform, the extracts were washed with 1 *N* HCl, water, saturated bicarbonate solution, water again, and dried ($MgSO_4$). The chloroform solution was concentrated *in vacuo* and afforded 12.4 g. (65%) of a white solid. Recrystallization of the solid from ethyl acetate–petroleum ether (b.p. 30–60°) yielded a white solid, m.p. 116–117°.

2-Methyl-2-propyl-3-tosyloxypropyl N-Isopropylcarbamate (11).—This compound was prepared by the second method used for 2-methyl-2-propyl-3-tosyloxypropyl carbamate (**9**). Compound **11** was a colorless sirup obtained in 70% crude yield. An analytical sample was obtained by column chromatography on Schlesinger silica gel. The crude material was put on the column with petroleum ether–benzene (1:1) and eluted with that solvent mixture. Nothing was eluted with petroleum ether–benzene (1:1) or benzene, but benzene–ether (1:1) elution yielded a colorless sirup after removal of the solvent, n^{23D} 1.4980.

Anal. Calcd. for $C_{18}H_{29}NO_5S$: C, 58.2; H, 7.87; N, 3.78; S, 8.63. Found: C, 58.2; H, 7.80; N, 3.68; S, 8.60.

Thin layer chromatography was performed on silica gel G in ether–benzene (55:80) as solvent; starting material, R_f 0.30; compound **11**, R_f 0.63.

3-Carbamoxy-2-methyl-2-propylpropanethiol (19).—A solution of 6 g. (18.3 mmoles) of 2-methyl-2-propyl-3-tosyloxypropyl carbamate (**9**) in 50 ml. of dimethylformamide containing 4.15 g. (36.5 mmoles) of potassium thiolacetate was heated at 125° for 2 hr. The solution was poured into 500 ml. of water and extracted with chloroform. The chloroform extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield 4.5 g. of crude thiolacetate (free from tosyl band in the infrared absorption spectrum). The thiolacetate, without further purification, was dissolved in 150 ml. of methanol, and anhydrous HCl was passed through the solution for 2 hr. while under reflux. The solution was concentrated *in vacuo*, dissolved in ether, washed free of chloride ions with water, dried ($MgSO_4$), and concentrated *in vacuo* to afford 2 g. (57%) of a colorless liquid. The infrared absorption spectrum showed the presence of an SH band at 3.90 μ and absence of a thiolacetate band at 5.95 μ.

The crude product was chromatographed on 20 g. of Schlesinger silica gel (90–200 mesh) by eluting the product from the column with petroleum ether(b.p. 30–60°)–benzene (1:1), benzene, benzene–ether (1:1), and finally ether. An analytical sample of **19** was isolated as a colorless oil (24%) from the ether eluate. Earlier eluates contained 3-hydroxy-2-methyl-2-propylpropanethiol formed by hydrolysis of the carbamate grouping.

Thin layer chromatography of the various eluted products on

silica gel G with ether as the developing solvent and with 1% iodine in methanol as a spotting spray helped to identify the two products isolated.

Anal. Calcd. for $C_8H_{17}NO_2S$: C, 50.2; H, 8.90; N, 7.33; S, 16.7. Found: C, 50.3; H 8.70; N, 7.12; S, 16.7.

Compound **19** had $n^{24}D$ 1.4947; R_f (silica gel G thin layer, ether solvent) 0.65; R_f, of 3-hydroxy-2-methyl-2-propylpropanethiol, 0.71; λ_{max}^{film} 2.90–3.10 (NH_2), 3.90 (SH), 5.8–5.90 (C=O, carbamate), 6.25 (NH), 10.7 μ (SH).

3-N-Isopropylcarbamoxy-2-methyl-2-propylpropanethiol (20).—This compound was prepared from **11** by the method used in the preparation of **19**. The crude reaction product was put on a Schlesinger silica gel column with petroleum ether–benzene (1:1) and eluted with benzene to afford analytically pure **20** in 32% yield, as a colorless oil. Further elution of the column with benzene–ether and finally ether yielded a mixture of **20** and 3-hydroxy-2-methyl-2-propylpropanethiol, as evidenced by silica gel G thin layer chromatography with benzene–ether (80:55) as developing solvent: **20**, R_f 0.45; hydroxythiol, R_f 0.30; λ_{max}^{film} 3.02 (NH), 5.90 (C=O, carbamate), 6.60 (NHR), 8.10 μ (C—O—C).

Anal. Calcd. for $C_{11}H_{23}NO_2S$: C, 56.6; H, 9.94; S, 13.7. Found: C, 56.8; H, 9.75; S, 13.1.

3-Carbamoxy-2-methyl-2-propylpropyl N-Isopropylthioncarbamate (13).—Preparations of **13**, using tetrahydrofuran as the solvent and acid acceptor, resulted in crystallization difficulties. The following procedure, which is very similar to the Ludwig and Piech method,[4] gave the best results and the purest product.

To a cold solution (5°) of 2.86 g. (25.1 mmoles) of freshly distilled thiophosgene in 10 ml. of anhydrous methylene chloride was added dropwise 4.34 g. (24.8 mmoles) of 2-methyl-2-propyl-3-hydroxypropyl carbamate (**8**) dissolved in 25 ml. of anhydrous methylene chloride containing 4.76 g. (25.3 mmoles) of antipyrine. The clear orange solution was stirred out of contact with light for 16 hr. The solution remained clear but became light yellow in color. The methylene chloride and any unreacted thiophosgene were removed under vacuum, yielding a yellow viscous oil which changed to crystalline antipyrine hydrochloride on the addition of anhydrous ether. The antipyrine hydrochloride was filtered, and the ether was removed under vacuum. A quantitative yield of the thiocarbonyl chloride resulted. The carbonyl chloride (4.0 g., 15.8 mmoles) was dissolved in 5 ml. of anhydrous ether, and allowed to react with 2 ml. of isopropylamine at room temperature for 2 hr. The isopropylamine hydrochloride was removed by filtration and the ether solution was concentrated *in vacuo*. The sticky residue solidified after standing at room temperature overnight: crude yield, 79%. Two recrystallizations from isopropyl acetate–petroleum ether (b.p. 30–60°) gave an analytical sample: m.p. 84–85°: λ_{max}^{Nujol} 2.88, 3.00 (NH), 5.90 (C=O, carbamate), 6.00 (NH), 6.60 (thioamide), 8.30 (C—O—C), 9.30 μ (C=S).

Anal. Calcd. for $C_{12}H_{24}N_2O_3S$: C, 52.2; H, 8.70; N, 10.2; S, 11.6. Found: C, 52.2; H, 8.45; N, 10.3; S, 11.6.

2-Methyl-2-propyl-3-thioncarbamoxypropyl N-Isopropylcarbamate (12).—A methylene chloride solution of 2.88 g. (13.2 mmoles) of 2-methyl-2-propyl-3-hydroxypropyl N-isopropylcarbamate (**10**) and 2.63 g. (14.0 mmoles) of antipyrine in 20 ml. of anhydrous methylene chloride was added dropwise to a chilled (5°), magnetically stirred solution of 1.51 g. (13.2 mmoles) of freshly distilled thiophosgene in 5 ml. of methylene chloride. After stirring for 18 hr. at room temperature, the volatile portion was removed under vacuum and a foamy yellow residue remained. After treatment with ether to precipitate antipyrine hydrochloride, and concentration of the ether solution, the acid chloride was obtained in an 88% crude yield. It was chilled in an ice bath, treated with 10 ml. of ammonium hydroxide for 2 hr., and washed free of chloride ion. The crude product was obtained in 81% yield. After recrystallizing twice, a product, m.p. of 91.5–93°, was obtained. A mixture with carisoprodol (89–91°) started to melt at approximately 70°; λ_{max}^{Nujol} 2.99, 3.08, 3.18 (NH), 6.00 (C=O, carbamate), 6.21 (NH_2), 6.55 (CONH, carbamate), 8.00 (C—O—C), 9.02, 9.13 μ (C=S, carbamate).

Anal. Calcd. for $C_{12}H_{24}N_2O_3S$: C, 52.2; H, 8.70; N, 10.2; S, 11.6. Found: C, 52.2; H, 8.48; N, 10.0; S, 11.4.

The ammonolysis could also be carried out by the use of anhydrous ammonia. In our laboratory a cleaner product resulted when aqueous ammonia was used.

2-Methyl-2-propyl-1,3-propaneiminocarbonate Hydrochloride (25).—To an ice-cold solution of 3.25 g. (33.2 mmoles) of phosgene in 3 g. of toluene was added 1.06 g. (5.5 mmoles) of 2-methyl-2-propyl-3-hydroxypropyl thioncarbamate dissolved in 6 ml. of tetrahydrofuran. A white precipitate separated immediately. This mixture was stirred overnight at room temperature. The solid was filtered off and washed with ether: m.p. 123–125°; 76% yield; λ_{max}^{Nujol} 3.20 (NH_2^+), 5.98 (C=N$^+$), 6.28 (NH_2^+), 8.80, 9.00 μ (C—O—C).

Anal. Calcd. for $C_8H_{16}ClNO_2$: C, 49.7; H, 8.30; Cl, 18.3; N, 7.25. Found: C, 50.6; H, 8.00; Cl, 18.2; N, 7.20.

2-Methyl-2-propyl-1,3-propanedithiocarbonate (26).—To a solution containing 6.85 g. (36.4 mmoles) of antipyrine, 30 ml. of methylene chloride, and 2.98 g. (18.2 mmoles) of freshly distilled 2-methyl-2-propyl-1,3-propanedithiol was added a cold solution of 1.82 g. (18.4 mmoles) of phosgene in 5 ml. of toluene. The solution was stirred overnight in a closed container and concentrated *in vacuo*, ether was added, and the antipyrine hydrochloride was filtered. Concentration of the ether solution *in vacuo* yielded a yellow oil, 3.1 g. Column chromatography of this material on Woelm neutral Al_2O_3 (activity grade 1) yielded an analytical sample of **26** as a colorless oil, 1.25 g. (36%) after elution with benzene. Gas–liquid chromatography on silicone rubber showed one peak: λ_{max}^{film} absence of SH (3.95 μ), 3.39 (CH), 6.10, 6.20 (C=O), 6.89, 7.08, 7.25 μ (CH_2).

Anal. Calcd. for $C_7H_{14}OS_2$: C, 50.4; H, 7.37; S, 33.7. Found: C, 50.1; H, 7.44; S, 33.8.

2-Methyl-2-propyl-1,3-propanetrithiocarbonate (27) and 2-Methyl-2-propylpropyl 1,3-Bis(dithiocarbamate) (22).—To a mixture of 11.3 g. (69.2 mmoles) of freshly distilled 2-methyl-2-propyl-1,3-propanedithiol and 10 g. of "Drierite" in 50 ml. of anhydrous ether was added an anhydrous solution of thiocyanic acid in ether (prepared from KSCN, 20.4 g., 210 mmoles, and 30 g. of phosphoric acid in 20 ml. of water, 10 g. of ice, and 100 ml. of ether). This mixture was placed in an ice bath and treated with anhydrous HCl for 1 hr., capped, and stirred magnetically overnight.

The reaction mixture was filtered and the ether was removed *in vacuo*, yielding a yellow oil (2.0 g.). Column chromatography of this oil on Florisil (60–200 mesh) afforded **27** as an analytically pure, low-melting solid (1.5 g.) upon elution of the column with petroleum ether (b.p. 30–60°) and benzene (1:1).

Final elution of the column with ether yielded a small amount of thick sirup which resisted all attempts to crystallize. This thick sirup was analyzed for the desired meprobamate analog (**22**).

Silica gel G thin layer chromatography of these two products was a valuable method for evaluation of their purity. With benzene–ether (80:55) as the developing solution, **27** had R_f 0.78, and compound **22**, 0.10. These compounds were easily detected as yellow spots after spraying of the plates with 1% iodine in methanol. These types of compounds were not readily detectable by the commonly used technique of sulfuric acid spraying and baking.

Compound 27 had λ_{max}^{film} absence of SH (3.95), 6.88, 7.10, 7.28 (CH_3), 9.49, 9.95 μ (C=S).

Anal. Calcd. for $C_7H_{14}S_3$: C, 46.6; H, 6.78; S, 46.6; mol. wt., 206. Found: C, 46.4; H, 6.70; S, 46.7; mol. wt. by vapor pressure osmometry in benzene solvent, 207.

Compound 22 had λ_{max}^{film} 3.05, 3.18 (NH_2), 2.40 (CH), 6.28 (NH_2), 6.85, 7.10, 7.35 (CH_3), 8.20 μ (C=S).

Anal. Calcd. for $C_9H_{18}N_2S_4$: C, 38.3; H, 6.39; N, 9.95; S, 45.4. Found: C, 38.9; H, 6.11; N, 9.31; S, 44.9.

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