2,3-diphenylbutane. Similar results were obtained with *p*-chlorobenzal chloride.

Previous work has shown that methylmagnesium iodide reacts with benzal chloride to give stilbene dichloride.

From these results it is clear that solutions of methylmagnesium iodide and methylmagnesium chloride differ widely in their action on benzal chloride.

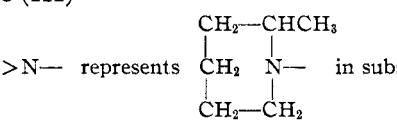
URBANA, ILLINOIS RECEIVED FEBRUARY 23, 1933
PUBLISHED JULY 6, 1933

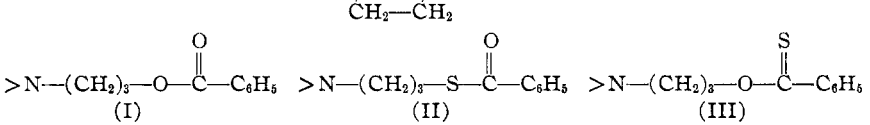
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

2-Methylpiperidinopropyl Thiol- and Thionbenzoates

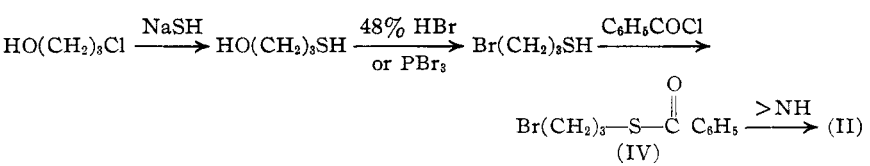
BY S. A. KARJALA AND S. M. MCELVAIN

Since practically all of the local anesthetics containing an ester structure are derived from oxygen acids, it seemed desirable to undertake the preparation of compounds derived from certain thio acids in order that the pharmacological effect of this exchange of oxygen for sulfur might be ascertained. Of the simpler types of aminoalkyl benzoates which have been prepared in this Laboratory the methylpiperidinopropyl benzoates[1] have been found to be the most efficient. On account of the rather considerable pharmacological work which has been done[2] on 2-methylpiperidinopropyl benzoate (I) it was decided to prepare the sulfur analogs of this anesthetic. The present paper reports the preparation and properties of 2-methylpiperidinopropyl thiolbenzoate (II) and the corresponding thionbenzoate (III)





The thiolbenzoate (II) was prepared by the following series of reactions

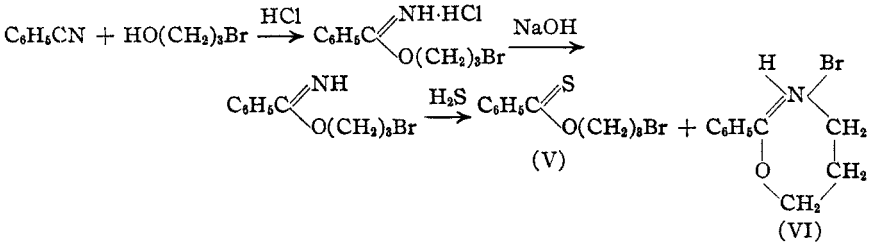


(1) McElvain, THIS JOURNAL, **49**, 2835 (1927).

(2) (a) Coles and Rose, *J. Lab. Clin. Med.*, **15**, 239 (1929); (b) *ibid.*, **15**, 731 (1930); (c) Meeker, *Surg., Gynecol. Obstet.*, **50**, 997 (1930).

The thiolbenzoate was isolated as the hydrochloride which melted at 137–138°.

The preparation of the thionbenzoate (III) was at first rather difficult due to the readiness with which the thion structure rearranged into the thiol structure. For example, in the attempted preparation of bromopropyl thionbenzoate (V) through the following series of reactions

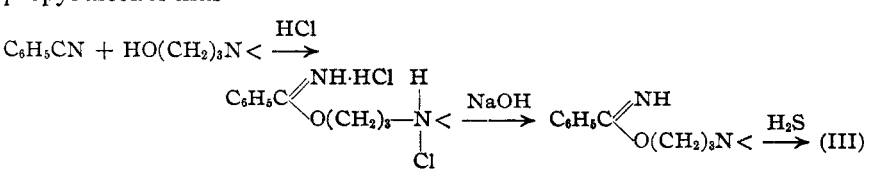


(V) (VI)

a yellow oil which was found to be about 66% of the thion form (V) and 34% of the thiol form (IV) was obtained. Distillation of this product so reduced the thion content that after the third distillation the product contained only about 7% of the thion form. Details of the method which was developed for the estimation of thion sulfur are given in the experimental part of the paper. Along with the bromopropyl thiobenzoates, a small amount of 2-phenyl-4,5-dihydro-1,3-oxazine hydrobromide (VI) was obtained. When trimethylene chlorohydrin was used instead of the bromohydrin a mixture of the chloropropyl thiobenzoates, which before distillation contained about 85% of the thion form, was obtained.

Both the crude chloro- and bromopropyl thionbenzoates when condensed with 2-methylpiperidine yielded the thiolbenzoate (II) instead of the expected thion compound (III). This was true regardless of whether the condensation was brought about in a short time at elevated temperatures or over a longer period of time at room temperatures. Indeed, it is probable that the most economical method of preparation of the thiolbenzoate is through the condensation of the crude (85% thion sulfur) chloropropyl thionbenzoate with 2-methylpiperidine.

The thion benzoate (III) was finally prepared from 2-methylpiperidinopropyl alcohol thus

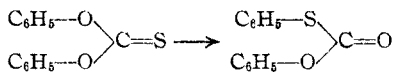


The thionbenzoate was isolated as the hydrochloride which crystallized in beautiful yellow clusters and melted at 149–149.5°. The over-all yield of the hydrochloride from the above reactions was 32% of the theoretical.

The thion sulfur content of this product was found to be 95%, a value which probably represents the limit of accuracy of the method of estimation (see Table I in Experimental Part).

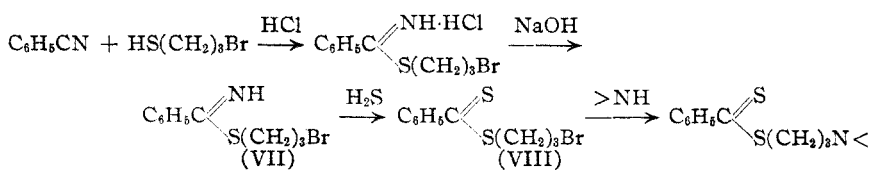
2-Methylpiperidinopropyl thionbenzoate hydrochloride readily rearranges into the corresponding thiol compound when heated for ten minutes at 175°. The rearrangement is practically complete as shown by the fact that one recrystallization of the heated product from an alcohol–ether mixture gave the pure thiol benzoate, melting at 137–138°.

The ease with which the thion compounds, which are now reported, rearrange is striking. In contrast with ethyl thionbenzoate, which may be repeatedly distilled (b. p. 240–243°) without any noticeable alteration of the thion structure, the chloro- and bromopropyl thionbenzoates (b. p. 180–182° (19 mm.) and 147–149° (1 mm.), respectively) are rearranged to a considerable extent by much lower distillation temperatures. Schönberg[3] and co-workers have found that diphenyl thion carbonate rearranges into the thiol carbonate when heated at 280° for ninety minutes



These are much more drastic conditions than are necessary to bring about the rearrangement of the 2-methylpiperidinopropyl thionbenzoate hydrochloride. It is not unlikely that the halogen which is present in these easily rearranged compounds is responsible for their proneness to rearrangement, since Wheeler and Barnes[4] have shown that alkyl halides cause the rearrangement of certain thioncarbamic, thioncarbanilic and thioncarbazinic esters, even at room temperature.

An attempt was made to prepare the 2-methylpiperidinopropyl dithiobenzoate through the following series of reactions



These reactions proceeded satisfactorily up to the condensation of the bromopropyl dithiobenzoate (VIII) with 2-methylpiperidine. When the conditions were such as to cause any reaction between these substances there was such a large amount of decomposition products that no tertiary amine could be isolated. It may be noted that the free imino ester (VII) changes somewhat less readily than its oxygen analog into the cyclic 2-phenyl-4,5-dihydro-1,3-thiazine hydrobromide, the sulfur analog of VI.

(3) Schönberg, *et al.*, *Ber.*, **63**, 178 (1930); *Ann.*, **483**, 107 (1930).
(4) Wheeler and Barnes, *Am. Chem. J.*, **22**, 141 (1899); **24**, 60 (1900).

Experimental

γ-Hydroxypropyl Mercaptan.—This product was prepared by the procedure reported by Bennett[5] for the preparation of β-hydroxyethyl mercaptan. The product which boiled at 81–82° (10 mm.)[6] was obtained in 40–65% yields. During its distillation there was a considerable amount of polymer formed even when the distillation was carried out in an atmosphere of nitrogen. This polymer was in part the disulfide as shown by the fact that an additional quantity of the mercaptan could be recovered from it after it had been reduced with zinc and sulfuric acid.

γ-Bromopropylmercaptan.—A mixture of 54 g. of γ-hydroxypropyl mercaptan and 250 cc. of 48% hydrobromic acid was distilled slowly through a 45-cm. Vigreux column in an atmosphere of nitrogen and the distillate collected in a separatory funnel. The lower layer of the distillate was drawn off, dried with anhydrous sodium sulfate, and distilled. The yield of the bromo-mercaptan, boiling at 55–56° (12 mm.), was 34 g. (37%).

The following procedure, using phosphorus tribromide, gives somewhat higher yields of the bromo-mercaptan: to 37 g. of the hydroxy-mercaptan contained in a 500-cc. 3-necked flask fitted with a stirrer, dropping funnel, a thermometer and an outlet tube, and cooled to −5°, was added slowly 36.5 g. of phosphorus tribromide. After this addition the reaction mixture was allowed to come to room temperature overnight. Water was then added, the bromo-mercaptan layer separated, washed once with water, dried with anhydrous sodium sulfate, and finally distilled. The yield of the bromo-mercaptan was 32 g. (53%).

Anal.[7] Calcd. for C_3H_7SBr: S, 20.64. Found: S, 20.79.

γ-Bromopropyl Thiolbenzoate.—A mixture of 20 g. of bromopropyl mercaptan, 28 g. of benzoyl chloride and a solution of 24 g. of sodium carbonate in 150 cc. of water was stirred for four to five hours at 40–50°. The mixture was then extracted with ether and the ethereal solution dried with sodium sulfate and distilled. After three distillations the bromopropyl thiolbenzoate was obtained as a colorless liquid, b. p. 148–149° (1 mm.); n_D^{25} 1.5950; d_{25}^{25} 1.4170; yield, 25 g. (75%).

Anal. Calcd. for $C_{10}H_{11}SOBr$: S, 12.36. Found: S, 12.33.

γ-(2-Methylpiperidino)-propyl Thiolbenzoate Hydrochloride.—Ten grams (1 mole) of bromopropyl thiolbenzoate and 7.6 g. (2 moles) of 2-methylpiperidine were mixed and heated at 100° for one hour. The reaction mixture was then diluted with ether, the precipitated 2-methylpiperidine hydrochloride filtered off, and the tertiary amine precipitated from the ethereal solution with dry hydrogen chloride. The resulting hydrochloride was recrystallized from an alcohol–ether mixture and was obtained as pale tan crystals which melted at 137–138°. The yield was 10 g. (85%).

Anal. Calcd. for $C_{16}H_{24}NOSCl$: S, 10.22; Cl, 11.33. Found: S, 10.06; Cl, 11.16.

γ-Chloropropylbenzimino Ester Hydrochloride.—This compound was prepared from benzonitrile and trimethylene chlorohydrin by the procedure which has been used[8] for the preparation of β-chloroethylbenzimino ester hydrochloride. The product melted at 122–123°, and the yield was practically quantitative.

Anal.[9] Calcd. for $C_{10}H_{12}ONCl \cdot HCl$: Cl, 15.22. Found: Cl, 15.05.

γ-Bromopropylbenzimino Ester Hydrochloride.—This compound was prepared as was the corresponding chloro compound using trimethylene bromohydrin[10] instead of

(5) Bennett, *J. Chem. Soc.*, **119**, 422 (1921).

(6) *Cf.* Rajahn and Lenine, *Arch. Pharm.*, **263**, 619 (1925).

(7) Sulfur analyses were made by the method of Rosser and Woodward, *J. Chem. Soc.*, 2357 (1932).

(8) Gabriel and Neumann, *Ber.*, **25**, 2384 (1892).

(9) For ionic chlorine. Carried out by the modified Volhard procedure, Treadwell–Hall, "Analytical Chemistry," John Wiley and Sons, New York, Sixth Ed., 1924, Vol. II, p. 604.

(10) Frühling, *Monatsh.*, **3**, 697 (1882).

trimethylene chlorohydrin. It melted at 115–116°. Since it was not possible to determine only the ionic halogen[9] in this compound, the total halogen was determined by a sodium peroxide fusion.

Anal. Calcd. for $C_{10}H_{18}NOBrCl$: Cl-Br, 41.4. Found: Cl-Br, 42.2.

γ-Bromopropyl Thionbenzoate.[11]—An excess of cold 2 *N* sodium hydroxide was added to 87 g. of the bromopropylimino ester hydrochloride and the free base immediately taken up in ether. This ethereal solution, which became turbid rapidly, was dried for a short time with sodium sulfate and then treated with hydrogen sulfide. The gas was passed into the solution, cooled by an ice–salt mixture, at a rapid rate until the ether was saturated with hydrogen sulfide; then the flow of gas was reduced and allowed to continue slowly for about twenty hours. During the addition of the gas a considerable quantity of crystals separated from the ether solution. After the flow of gas had been stopped these crystals were filtered off and the ethereal filtrate washed ten times with 100-cc. portions of water. The ether solution was dried over sodium sulfate and the ether removed by distillation under diminished pressure. The remaining yellow oil weighed 14 g. This crude thionbenzoate boiled at 148–150° (1 mm.).

Anal. Calcd. for $C_{10}H_{11}OSBr$: S, 12.36. Found: S, 12.26.

2-Phenyl-4,5-dihydro-1,3-oxazine Hydrobromide.—The crystals which separated from the ethereal solution in the above preparation of the thionbenzoate were recrystallized from an alcohol–ether mixture. The product melted at 139–140°. Generally the yield of this material was about 20 g. from a run of the size described above.

Anal. Calcd. for $C_{10}H_{12}ONBr$: Br, 33.06. Found: Br, 32.98.

γ-Chloropropyl Thionbenzoate.—This compound was prepared in the same manner as the bromopropyl thionbenzoate described above except that trimethylene chlorohydrin was used instead of trimethylene bromohydrin. It boiled at 145–146° (1 mm.) and the yield was 68% of the theoretical.

Anal. Calcd. for $C_{10}H_{11}OSCl$: S, 14.95. Found: S, 14.80.

Determination of Thion Sulfur.—Matsui[11] has shown that ethyl thionbenzoate is readily decomposed by silver nitrate into silver sulfide and ethyl benzoate. It was found in the present work that both the thion and thiol esters gave precipitates of silver sulfide when heated with a solution of silver nitrate on a steam-bath for a few hours. However, no traces of silver sulfide were formed when the thiol ester was allowed to stand for twelve hours with silver nitrate in the dark and at room temperature, but the thion esters gave immediate and after a time practically complete precipitates of silver sulfide under these conditions. On the basis of this difference in behavior toward silver nitrate the following procedure was used for the estimation of thion sulfur. A sample of the sulfur compound was dissolved in 25 cc. of alcohol and then treated with 10 cc. of 0.5 *N* silver nitrate solution. The resulting mixture was allowed to stand in the dark at room temperature for twelve hours. The precipitate was then filtered off, washed free from soluble silver salts, transferred to a 250-cc. beaker, and heated on a steam-bath with sufficient concentrated nitric acid to make the solution 6 *N*. In the cases of the halogen substituted esters some silver halide was formed, so the nitric acid solution was cooled, filtered, and the insoluble silver halide washed well with water. The filtrate was then titrated with standard ammonium thiocyanate solution using a ferric alum indicator. Table I shows the results of analyses of a number of thio esters.

It is evident from the values reported in Table I that this method of determination of thion sulfur gives an approximate estimate of the amount of this structure. Such deviations from the theoretical as are shown by compounds 1, 7 and 8 are well within the

(11) *Cf.* Matsui, *Mem. Coll. Sci. Eng. Kyōtō Imp. Univ.*, **3**, 247 (1912); *Chem. Abstracts*, 1612 (1912).

TABLE I

THION SULFUR CONTENT OF VARIOUS THIO ESTERS

	Compound	Total S, %	% S as C = S	% Thion structure
1	$C_6H_5C(S)OC_2H_5$[a]	19.28	18.53	96
2	$C_6H_5C(S)O(CH_2)_3Cl$ (undistilled)	14.95	12.65	85
3	$C_6H_5C(S)O(CH_2)_3Br$ (undistilled)	12.36	8.13	66
4	No. 3 once distilled	12.36	3.66	30
5	No. 3 twice distilled	12.36	2.56	21
6	No. 3 thrice distilled	12.36	0.83	7
7	$C_6H_5C(O)S(CH_2)_3Br$	12.36	0.26	2
8	$C_6H_5C(S)O(CH_2)_3N<\cdot HCl$	10.22	9.72	95

[a] This product was prepared by the method described by Matsui, Ref. 11. It boils at 121-124° (20 mm.) or 240–243° at atmospheric pressure, and was distilled under the latter conditions before it was subjected to analysis for thion sulfur.

limits of error of the method. The extent of rearrangement of the bromopropyl thionbenzoate during distillation is readily followed by this procedure.

Reaction of the Halogeno-propyl Thionbenzoates with 2-Methylpiperidine.—Both the chloro- and bromopropyl thionbenzoates reacted readily with 2-methylpiperidine when the reactants were heated together for twenty minutes at 130°. When the reaction mixture was worked up in the usual manner the tertiary amine hydrochloride isolated was 2-methylpiperidinopropyl thiolbenzoate, m. p. 137–138°, which was obtained above by the reaction of γ-bromopropyl thiolbenzoate with 2-methylpiperidine. In the case of the chloropropyl thionbenzoate the yield of the piperidinopropyl thiolbenzoate was 60% of the theoretical. Because of the readiness with which this crude chloropropyl thionbenzoate is prepared, this procedure for the preparation of the thiolbenzoate is more advantageous than that described above in which γ-bromopropyl thiolbenzoate is used.

γ-(2-Methylpiperidino)-propyl Thionbenzoate Hydrochloride.—A mixture of 20.6 g. (1 mole) of benzonitrile and 31 g. (1 mole) of γ-(2-methylpiperidino)-propyl alcohol (prepared from trimethylene chlorohydrin and 2-methylpiperidine) was treated with dry hydrogen chloride and allowed to warm up from the heat of reaction until all of the tertiary amine hydrochloride had gone into solution. The reaction flask was then placed in cold water and the hydrogen chloride addition continued until the heavy viscous sirup was completely saturated with the gas. This took about thirty hours. Since the resulting reaction mixture would not crystallize, it was placed in a vacuum desiccator to remove the excess hydrogen chloride. The product thus obtained was then dissolved in water, treated with an excess of 2 *N* sodium hydroxide and extracted with ether. The ethereal solution, after drying with sodium sulfate, was placed in a flask cooled in an ice-bath and then saturated with hydrogen sulfide. After saturation the hydrogen sulfide addition was continued slowly for twenty-four hours. The ether solution was then washed with eight 100-cc. portions of water and, after drying with anhydours sodium sulfate, treated with dry hydrogen chloride. A brown oil precipitated which after washing with ether readily crystallized from an alcohol–ether mixture in beautiful yellow clusters and melted at 149–149.5°. The yield was 20 g. (32% of the theoretical). This compound was found to be practically pure thion form (No. 8, Table I).

Anal. Calcd. for $C_{16}H_{24}ONSCl$: S, 10.22. Found: S, 10.26.

Rearrangement of γ-(2-Methylpiperidino)-propyl Thionbenzoate Hydrochloride.—A 1-g. sample of this yellow thion compound was placed in a test-tube and heated in an oil-bath at 175° for ten minutes. On cooling, the melt appeared as a pale brown, vis-

cous sirup which when taken up in absolute alcohol and this solution carefully diluted with ether yielded the characteristic pale tan crystals of the thiol form, m. p. 137–138°. That the conversion was practically quantitative was shown not only by the weight of the product obtained but also by the fact that the pure thiol form was obtained directly without further recrystallizations.

γ-Bromopropyl Thiolbenzimino Ester Hydrochloride.—A mixture of 31 g. of γ-bromopropyl mercaptan and 21 g. of benzonitrile was cooled in an ice-bath and saturated with dry hydrogen chloride. The mixture soon solidified to a pinkish-red mass. The mass was broken up in a mortar under ether, washed thoroughly and dried. Recrystallization from acetone gave a product melting at 157–158°. The yield was 52.5 g. (88%).

Anal. Calcd. for $C_{10}H_{13}SNClBr$: S, 10.88. Found: S, 10.93.

γ-Bromopropyl Dithiobenzoate.—This compound was prepared from the bromopropyl thiolbenzimino ester hydrochloride by the method of Sakurada.[12] The product was obtained in 67% yields as pale yellow needles, melting at 112–114°. It should be pointed out that the ether should be removed under diminished pressure from the γ-bromopropyl dithiobenzoate after the hydrogen sulfide treatment, since temperatures even as low as the boiling point of ether are sufficient to cause polymerization of the dithiobenzoate to a deep red, ether insoluble oil.

Anal. Calcd. for $C_{10}H_{11}S_2Br$: S, 23.27. Found: S, 23.18.

2-Phenyl-4,5-dihydro-1,3-thiazine Hydrobromide.—This compound was not formed as readily from the free γ-bromopropyl thiolbenzimino ester during the treatment with hydrogen sulfide as was the oxazine from free γ-bromopropylbenzimino ester. However, when an ether solution of the free thiolbenzimino ester was allowed to stand or was evaporated on a steam-bath an oil separated which after recrystallization from an alcohol–ether mixture, melted at 171–172°.

Anal. Calcd. for $C_{10}H_{12}NSBr$: Br, 30.97. Found: Br, 30.91.

Reaction of γ-Bromopropyl Dithiobenzoate with 2-Methylpiperidine.—A solution of 10 g. (1 mole) of the bromopropyl dithiobenzoate and 7.2 g. (2 moles) of 2-methylpiperidine in 25 cc. of dry benzene was refluxed for twenty hours. There was no apparent indication of reaction. The benzene was then removed by distillation and the residue heated to 150° in an oil-bath for thirty minutes. The reaction mixture was converted by this treatment into a black insoluble tar from which nothing definite could be extracted.

In another attempted condensation a mixture of 4.25 g. of the dithio ester and 3 g. of 2-methylpiperidine was warmed slightly in a steam-bath until a homogeneous solution resulted. This solution was then allowed to stand at room temperature for three days. After a few hours a solid material began to crystallize from the solution. The reaction mixture was finally treated with ether, whereupon it dissolved completely. Dry hydrogen chloride precipitated only 2-methylpiperidine hydrochloride from the ethereal solution. After this was filtered off, 3.34 g. of the original bromopropyl dithiobenzoate was recovered from the ethereal filtrate by evaporation.

Pharmacological Report.—The hydrochlorides of 2-methylpiperidinopropyl thiolbenzoate (II) and 2-methylpiperidinopropyl thionbenzoate (III) are being studied pharmacologically by Mr. Charles L. Rose of the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana. A summary of a preliminary report of this study is given in Table II. Anesthesia values were determined by application of a 1% solution of the

(12) Sakurada, *Mem. Coll. Sci. Kyōtō*, **10**, 79 (1926).

anesthetic to the rabbit's cornea and also by intracutaneous injection of this solution into guinea pigs. Toxicity was determined by intravenous injection into white rats. For comparison the corresponding values[2b] for 2-methylpiperidinopropyl benzoate hydrochloride (I) are included in the table.

TABLE II

PHARMACOLOGICAL DATA

Compound	Average duration of corneal anesthesia, min.	Average duration of intracutaneous anesthesia, min.	Intravenous toxicity (mg./kg.) M. L. D.
I	22	44	20
II	1	50	16
III	38	77	22

Discussion of the Pharmacological Data.—The most striking feature of these data is the rather considerable difference in the pharmacological behavior of the thiol (II) and thion (III) structures. The former compound shows practically no mucous surface anesthesia, but is a quite efficient anesthetic when injected. The thion compound, on the other hand, has a powerful action when it is applied to the rabbit's cornea (cocaine in similar concentration shows an average duration of anesthesia of twenty-four minutes) as well as when it is injected intracutaneously. This compound is noticeably more efficient than its oxygen analog (I). It should be noted also that this thion compound has a toxicity that is distinctly lower than those of its isomer and analog.

Summary

2-Methylpiperidinopropyl thiol and thionbenzoates have been prepared and their pharmacological properties are compared with those of their oxygen analogs.

The halogeno-propyl thionbenzoates which were prepared in the course of this work and the methylpiperidinopropyl thionbenzoate have been found to be very susceptible to rearrangement into the corresponding thiol forms.

A method of estimating the amount of the thion structure in the presence of the thiol structure is described.

MADISON, WISCONSIN RECEIVED FEBRUARY 24, 1933
PUBLISHED JULY 6, 1933