[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

Sulfur Studies. XIX. Alkyl Esters of Phenylthiocarbamic Acid[1]

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Recent interest in phenylcarbamic acid esters has led to the development of several valuable local anesthetics. The field of the analogous phenylthiocarbamic acid esters has not been widely explored.

This paper deals with the preparation of a series of alkyl phenyl thiourethans, and a study of their pharmacological properties. A few substituted phenyl thiourethans are included in the study. The thiourethans were prepared in general by the action of phenyl isothiocyanate on the appropriate alcohols. In all cases, the phenyl thiourethans were crystalline solids with definite melting points. The reaction is straightforward, giving good yields.

The method of preparation had to be modified in a few cases. Alcohols which are easily dehydrated give *sym*-diphenylthiourea, and not the expected thiourethan. When heated with phenyl isothiocyanate the water apparently hydrolyzes the isothiocyanate to give aniline which combines with an excess of the reagent to form diphenyl thiourea. Allyl alcohol, *t*-butyl alcohol, ethylene glycol, propylene glycol, tetraethylhexanediol, and pinacol all gave *sym*-diphenylthiourea instead of the corresponding phenylthiourethan. This difficulty was overcome by allowing the sodium alcoholate to react with phenyl isothiocyanate in an appropriate solvent. Examples are given below in the case of *t*-butyl phenyl thiourethan and allyl phenyl thiourethan.

Experimental

Alkyl Phenyl Thiourethans.—The phenyl (or substituted phenyl) isothiocyanate (1 mole) was heated on a steam-bath under reflux with the appropriate aliphatic alcohol (10 moles) for a period of ten to sixteen hours. At the end of this time, the excess alcohol was evaporated on a steam-bath. On cooling, the thiourethan separated as a crystalline substance. In cases where the alcohol is appreciably water-soluble, the thiourethan may be precipitated by adding water to the cool reaction mixture. The precipitated thiourethan was filtered, and then recrystallized from either petroleum ether or a water–alcohol mixture.

This method was modified somewhat for higher boiling alcohols, such as heptyl, octyl and nonyl. The molar ratio of alcohol to isothiocyanate was decreased from 10:1 in such cases, and only a slight excess of alcohol (10–20%) was used. The change was necessitated by the difficulty encountered in evaporating the excess alcohol. In addition, the period of heating was extended to three or four days.

***t*-Butyl Phenyl Thiourethan.**—*t*-Butyl alcohol (44 g., 0.6 mole) was heated on a steam-bath under reflux with sodium (4.6 g., 0.2 mole) until all of the sodium had dissolved (about two hours). Then, phenyl isothiocyanate (27 g., 0.2 mole) was added. The flask was cooled. After thirty minutes, the reaction mixture was poured into ice-cold water (300 cc.), and made acidic with hydrochloric acid. The insoluble thiourethan was filtered with suction, washed with cold water, and dried in the air. It was recrystallized twice from petroleum ether (60–90°). The melting point of the thiourethan was 86.5°. The yield was 31% of the theoretical.

Allyl Phenyl Thiourethan.—Sodium (4.6 g., 0.2 mole) was dissolved in allyl alcohol (40.6 g., 0.7 mole). The initial reaction was quite vigorous, and the flask had to be cooled. Phenyl isothiocyanate (27 g., 0.2 mole) was added when all of the sodium had dissolved. Anhydrous ether (200 cc.) was added, and the chilled solution was saturated with dry hydrogen chloride. The precipitate of thiourethan and sodium chloride was filtered, and then extracted with dry acetone. The acetone solution was evaporated almost to dryness. Ice water was added. The oily thiourethan solidified on cooling in an ice–salt bath. The dry waxy solid was recrystallized from petroleum ether (30–60°) with just enough benzene added to keep it in solution at 40°. By slowly cooling the solution below 40°, with constant stirring, the substance crystallized. The second recrystallization was carried out with the aid of seed crystals. The thiourethan melted at 75–77°. The yield was 35% of the theoretical.

Substituted Phenyl Isothiocyanates.—Four substituted phenyl isothiocyanates were prepared for study: *p*-tolyl, *p*-nitrophenyl, *p*-carboxyphenyl and 2,4-dichlorophenyl isothiocyanates. *p*-Tolyl isothiocyanate was prepared by the method of Dains, Brewster and Olander.[3]

p-Nitrophenyl isothiocyanate,[4] *p*-carboxyphenyl isothiocyanate,[5] and 2,4-dichlorophenyl isothiocyanate[6] were prepared by the action of thiophosgene on the appropriate substituted anilines.

Pharmacological Properties.—These alkyl phenyl thiourethans were found to be pharmacologically inactive as hypnotics. This pharmacological inactivity is doubtless due in part to the extreme insolubility of these compounds in water. The pharmacological studies were carried out by the Wm. S. Merrell Co., of Cincinnati, Ohio, through the courtesy of Dr. Robert S. Shelton, to which the authors are deeply grateful.

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(3) Dains, Brewster and Olander, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. I, 1932, p. 437.

(4) Browne and Dyson, *J. Chem. Soc.*, 3285 (1931).

(5) Browne and Dyson, *ibid.*, 178 (1934).

(6) Dyson, George and Hunter, *ibid.*, 3041 (1926).

TABLE I

ALKYL ARYL THIOURETHANS, ArNHCSOR

	Thiourethan	Formula	M. p., °C.	Yield, %	%, S Calcd.	%, S Found
1	Methyl phenyl	$C_6H_5NHCSOCH_3$	92–93	63	19.17	19.16
2	Ethyl phenyl	$C_6H_5NHCSOC_2H_5$	70–72	60	17.69	17.81
3	*n*-Propyl phenyl	$C_6H_5NHCSOC_3H_7$-*n*	45–46	64	16.42	16.39
4	*i*-Propyl phenyl	$C_6H_5NHCSOC_3H_7$-*i*	84–85	75	16.42	16.51
5[a]	*n*-Butyl phenyl	$C_6H_5NHCSOC_4H_9$-*n*	51–53	50	15.32	15.46
6	*i*-Butyl phenyl	$C_6H_5NHCSOC_4H_9$-*i*	74–76	90	15.32	15.46
7[a]	*t*-Butyl phenyl[b]	$C_6H_5NHCSOC_4H_9$-*t*	86.5	31	15.32	15.01
8[a]	*n*-Amyl phenyl	$C_6H_5NHCSOC_5H_{11}$-*n*	49–50	55	14.36	14.51
9[a]	*i*-Amyl phenyl	$C_6H_5NHCSOC_5H_{11}$-*i*	44–46	80	14.36	14.38
10[a]	*n*-Heptyl phenyl	$C_6H_5NHCSOC_7H_{15}$-*n*	34	30	12.76	14.38
11[a]	*n*-Octyl phenyl	$C_6H_5NHCSOC_8H_{17}$-*n*	41–43	41	12.09	11.95
12[a]	*n*-Nonyl phenyl	$C_6H_5NHCSOC_9H_{19}$-*n*	45–47	32	11.48	11.61
13[a]	2-Phenylethyl phenyl	$C_6H_5NHCSO(CH_2)_2C_6H_5$	89.5	50	12.47	12.62
14[a]	3-Phenylpropyl phenyl	$C_6H_5NHCSO(CH_2)_3C_6H_5$	74	53	11.82	11.93
15[a]	Allyl phenyl[b]	$C_6H_5NHCSOCH_2CH{=}CH_2$	75–77	35	16.60	16.30
16	Ethyl 4-tolyl	(4)$CH_3C_6H_4NHCSOC_2H_5$	85	60		
17	Ethyl 4-nitrophenyl	(4)$NO_2C_6H_4NHCSOC_2H_5$	175	75		
18	Ethyl 2,4-dichlorophenyl	(2,4)$Cl_2C_6H_3NHCSOC_2H_5$	79	65		
19	Ethyl 4-carboxyphenyl	(4)$COOHC_6H_4NHCSOC_2H_5$	212	79		
20	Ethyl allyl	$CH_2{=}CHCH_2NHCSOC_2H_5$	B. p. 115–119 at 14 mm.			

[a] These compounds have not hitherto been reported. [b] Specific preparations given.

Summary

1. The phenyl thiourethans of a number of aliphatic alcohols have been prepared and found to be pharmacologically inactive as hypnotics.

2. Several thiourethans have been prepared for the first time by the action of isothiocyanates on sodium alcoholates. This method is of particular value where water is easily removed from the alcohol.

3. In cases where the alcohol is easily dehydrated, the water thus formed reacts with the phenyl isothiocyanate giving *sym*-diphenylthiourea instead of the anticipated alkylthiourethan.

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Anhydro ("Cyclized") Vitamin A[1]

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Vitamin A, when treated with anhydrous alcoholic hydrochloric acid, is changed into a substance with three absorption bands in the ultraviolet and with slight biological activity.[2] Edisbury, *et al.*,[3] first studied this reaction and noted that apparently the same substance could be obtained by breaking up with water the antimony trichloride reaction product of vitamin A. Although the reaction was first thought to be one of cyclization, the properties described below for the material indicate that the reaction is one of dehydration, and for this reason we prefer to call the product "anhydro vitamin A" instead of "cyclized vitamin A."

(1) Presented before the Division of Biological Chemistry at the Memphis meeting of the American Chemical Society, April, 1942.

(2) N. D. Embree, *J. Biol. Chem.*, **128**, 187 (1939).

(3) J. R. Edisbury, A. E. Gillam, I. M. Heilbron and R. A. Morton, *Biochem. J.*, **26**, 1164 (1932).

Dehydration of Vitamin A.—The method described by Edisbury, *et al.*,[3] for the dehydration of vitamin A is satisfactory. A concentrate of vitamin A (in the alcohol form) is allowed to stand for fifteen minutes at room temperature in 100 parts or more of *N*/30 anhydrous alcoholic hydrogen chloride, after which the solution is neutralized, dissolved in ether and washed free of inorganic reagents. A dark orange-brown color, formed upon the addition of the acid, disappears upon neutralization. At temperatures above 30° the reaction is faster but the formation of products other than anhydro vitamin A is increased. At lower temperatures the reaction is slowed up considerably; *e. g.*, at −60° no dehydration took place in several days. An increase in the acid concentration has about the same general effect as an increase in temperature.

The material can be concentrated most simply by