[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WASHINGTON UNIVERSITY]

The Synthesis of Some Dialkylaminoalkyl Arylthiourethans and Thioureas[1]

BY THOMAS F. WOOD AND JOHN H. GARDNER

A number of dialkylaminoalkyl arylurethans have been shown to exert pronounced local anesthetic action. One of these, diothane hydrochloride, has been introduced into practical use and a considerable number of others have been described but not manufactured commercially. Since a number of thio-analogs of the alkamine ester anesthetics have shown very considerable physiological activity,[2] a study of related thiourethans has been made in the present investigation.

In addition to the well-known hypnotic action of urea derivatives, Wenker showed that certain N-dialkylaminoalkyl-N'-arylureas have anesthetic properties,[3] a finding which has been confirmed in this Laboratory.[4] Consequently, two thio-analogs of these compounds have been prepared and studied.

Materials.—β-Diethylaminoethanol, γ-diethylaminopropanol and phenyl isothiocyanate were purchased from the Eastman Kodak Co. β-4-Morpholinoethanol was obtained from the Carbide and Carbon Chemical Corporation. *p*-Dimethylaminophenyl isothiocyanate was prepared by the method of Slotta and Dresser.[5] β-4-Morpholinoethylamine was prepared by the method of Hultquist and Northey.[6]

Thiourethans.[7]—The sodium derivatives of the amino alcohols were prepared by warming the alcohols with the theoretical amount of sodium sand suspended in xylene. These condensed rapidly with the theoretical amount of phenyl or *p*-dimethylaminophenyl isothiocyanate to give the sodium derivative of the thiourethan. In the cases of β-diethylaminoethyl and β-4-morpholinoethyl phenylurethans, the sodium derivatives separated as white crystalline material and were filtered out, dissolved in water and converted to the hydrochloride with hydrochloric acid. The other sodium derivatives formed colloidal suspensions in xylene. They were dissolved directly in dilute hydrochloric acid as the hydrochlorides. The free bases were liberated from the solutions of the hydrochlorides by treatment with sodium carbonate. Those which crystallized were filtered out and purified. The others were extracted with ether, the ether solutions dried over anhydrous magnesium sulfate and the ether evaporated. The products were converted into the hydrochlorides for analysis. The yields and properties are given in Table I.

Thiourethan Hydrochlorides.—The hydrochlorides of the phenylthiourethans were prepared by treating benzene solutions of the bases with the calculated quantity of hydrogen chloride in absolute ether. The products were purified by crystallization from suitable solvents. For the preparation of the hydrochlorides of the *p*-dimethylaminophenylthiourethans, the bases were dissolved in absolute alcohol and treated with the calculated amount of hydrogen chloride in absolute ether. Absolute ether was then added until the hydrochlorides were completely precipitated. The products were sufficiently pure for analysis without further purification. The yields, melting points and analyses are given in Table I.

N-(β-4-Morpholinoethyl)-N'-phenylthiourea.—To 15 g. of β-4-morpholinoethylamine there was added slowly a solution of 15.5 g. of phenyl isothiocyanate in 40 cc. of dry benzene. Exothermic condensation took place rapidly and, on cooling, the mixture solidified to a white crystalline mass. This was filtered and washed with cold benzene and crystallized from alcohol; yield, 25 g. (82%), m. p. 136°.

Anal. Calcd. for $C_{13}H_{19}ON_3S$: S, 12.08. Found: S, 11.82, 11.88.

The hydrochloride was precipitated as a white crystalline mass by the addition of the theoretical amount of a solution of hydrogen chloride in absolute ether to the base in dry benzene. The compound was so hygroscopic that an accurate determination of yield, melting point or analysis was impossible.

N-(β-4-Morpholinoethyl)-N'-*p*-dimethylaminophenylthiourea.—To 1.0 g. of β-4-morpholinoethylamine there was added a solution of 1.1 g. of *p*-dimethylphenyl isothiocyanate in 20 cc. of benzene. Reaction occurred immediately with evolution of heat and, on cooling, the solution deposited the thiourea in the form of slender white needles. Precipitation was completed by the addition of petroleum ether; yield, 1.5 g. (79%), m. p. 174° from alcohol. The product was converted into the hydrochloride for analysis.

To a solution of the base in 5:1 benzene–absolute alcohol there was added the theoretical amount of a solution of hydrogen chloride in absolute ether. The hydrochloride was precipitated by the addition of absolute ether and chilling; m. p. 168–169°.

Anal. Calcd. for $C_{15}H_{25}ON_4ClS$: Cl, 10.29. Found: Cl, 10.41, 10.51.

Pharmacological Report.—For the preliminary pharmacological data, we are indebted to L. W. Rowe and A. Simond of the Research and Biological Laboratories of Parke, Davis and Company. The compounds were tested for local anesthetic action by the rabbit cornea and the frog sensory nerve methods as first proposed by Sollmann.[8]

(1) Presented before the Division of Medicinal Chemistry, American Chemical Society, Detroit, Michigan, September 10, 1940. Original manuscript received March 21, 1941.

(2) L. S. Fosdick and H. L. Hansen, THIS JOURNAL, **55**, 2872 (1933); *J. Pharmacol.*, **50**, 323 (1934); C. F. Lischer and C. N. Jordan, THIS JOURNAL, **59**, 1623 (1937); S. A. Karjala and S. M. McElvain, *ibid.*, **55**, 2966 (1933).

(3) H. Wenker, *ibid.*, **60**, 158 (1938).

(4) J. A. Campbell, "Derivatives of Dialkylaminoalkylureas," Dissertation, Washington University, 1937.

(5) K. H. Slotta and H. Dressler, *Ber.*, **63**, 895 (1930).

(6) M. E. Hultquist and E. H. Northey, THIS JOURNAL, **62**, 447 (1940).

(7) General method of M. Rozhdestvenskii, *J. Russ. Phys.-Chem. Soc.*, **41**, 1488 (1909); *Chem. Zentr.*, **81**, I, 910 (1910).

(8) T. Sollmann, *J. Pharmacol.*, **11**, 1, 17, 69 (1918).

TABLE I

THIOURETHANS AND HYDROCHLORIDES

Thiourethan	Yield, %	M. p., °C.	Yield, %	M. p., °C.	Formula	Hydrochlorides S Found	S Calcd.	Cl Found	Cl Calcd.
β-Diethylaminoethyl phenyl	62	Oil	49	121–2	$C_{18}H_{21}ON_2ClS$	11.10 10.96	11.10	12.17 12.13	12.28
β-Diethylaminoethyl *p*-dimethylaminophenyl	40	76	83	162–3d	$C_{19}H_{26}ON_3ClS$			10.86 10.90	10.69
γ-Diethylaminopropyl phenyl	41	76–77	66	98–100d	$C_{14}H_{23}ON_2ClS$			11.82 11.93	11.72
β-4-Morpholinoethyl phenyl	58	109	61	156–6.5	$C_{18}H_{19}O_2N_2ClS$	10.66 10.70	10.59	11.85 11.80	11.71
β-4-Morpholinoethyl *p*-dimethylaminophenyl	57	97	81	166	$C_{19}H_{24}O_2N_3ClS$			10.39 10.20	10.25

TABLE II

ANALGESIC, HYPNOTIC, ANESTHETIC AND TOXICITY TESTS

Phenylthiourethan hydrochloride = R Phenylthiourea hydrochloride = R_1	Mice, M. L. D. mg./g.	Intraperitoneally analgesic effect	Local anesthetic tests: Rabbit cornea—1% concn. at 1 min.	duration, min.	irritation	Frog sensory nerve[a] Anesthesia complete at min. 1%	0.5%	0.25%
β-Diethylaminoethyl-R	0.18	Slight?	Good	5	Slight	5	10	13
β-Diethylaminoethyl-*p*-dimethylamino-R	.10	None	Good[b]	14	Slight	8	15[c]	..
γ-Diethylaminopropyl-R	.15	Slight?	Good	8	Some	7	8	12
β-4-Morpholinoethyl-R	.35	None	Good	2	Some	7	10	..
β-4-Morpholinoethyl-*p*-dimethylamino-R	.20	Slight?	Some	3	Slight	8	11?	..
N-(β-4-Morpholinoethyl)-N′-R_1	.35	Slight?	None	..	....	..[d]	...	..
N-(β-4-Morpholinoethyl)-N′-*p*-dimethylamino-R_1	.40	Slight?	Slight?	..	....	..[d]	...	..
Procaine hydrochloride	.45			15		3	5.5	11
Cocaine hydrochloride	.10					..	2.5	9

[a] Averages of two determinations. [b] 0.5% concn. good at 2 min., duration 7 min. [c] Almost complete. [d] Not complete at 15 min.

They were also tested for possible analgesic or hypnotic action by gross observation of effects upon white mice following varied dosage given intraperitoneally. For analgesic tests the pain stimulus used was pinching of the tail, ears, and feet before and after administration of a dose of the compound. The toxicity tests were done on white mice injected intraperitoneally. The data are collected in Table II.

The pharmacological data may be summarized with the statements that the thiourethans showed pronounced local anesthetic activity, but were all considerably weaker than procaine hydrochloride, with appreciably greater toxicity. None of the compounds had any definite effects as analgesics or hypnotics.

Summary

1. Five new dialkylaminoalkyl arylthiourethans and two new dialkylaminoalkyl aryl thioureas have been prepared.

2. The thiourethans show fairly strong local anesthetic effects but no hypnotic or analgesic effects.

3. The thioureas are without anesthetic or hypnotic effects to any measurable degree.

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[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Changes in the Pressure of Monomolecular Films of Stearic Acid Due to Added Drops of Benzene

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It has been indicated[2] that it is possible to obtain a measurement of the pressure against which a liquid, such as benzene, will spread on a water surface by measuring the minimum pressure which will prevent the spreading. When benzene is dropped on a film of stearic acid which is under a lower pressure than the spreading pressure, each drop penetrates the film, spreads on the water and increases the film pressure. The increase in film pressure will be greater the larger the amount of benzene added, until the increased pressure equals the spreading pressure of the benzene. Addition of larger amounts of benzene will not cause the pressure to increase above this spreading pressure. Drops of benzene which are below a certain volume evaporate before the pressure has increased

(1) Samuel Avery Research Fellow, 1940–1941.

(2) E. R. Washburn and Chris P. Keim, THIS JOURNAL, **62**, 1747, 2318 (1940).