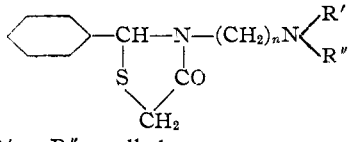
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

4-Thiazolidones. IV. The Preparation of Some 3-Alkylaminoalkyl-2-aryl Derivatives

BY ALEXANDER R. SURREY

The observation[1] that several of the 2-aryl-3-dialkylaminoalkyl-4-thiazolidones (I) showed promising local anesthetic activity suggested that



I, R′ = R″ = alkyl
II, R′ = H, R″ = alkyl, cycloalkyl, aralkyl

it would be of interest to study the activity of some 2-aryl-3-alkylaminoalkyl derivatives (II). A series of these compounds has been synthesized and is reported in the present communication.

TABLE I

ALKYLAMINOPROPIONITRILES,[2] $RNHCH_2CH_2CN$

R	Yield %	B. p. °C.	mm.	$n^{25}D$	Analyses, % Nitrogen Calcd.	Found
n-Hexyl	91	130–134	12	1.4410	18.15	18.02
n-Octyl	91	117–120	1	1.4452	7.67	7.65[a]
Benzyl	92	119–124	0.7–0.8	1.5296	8.75	8.69[a]
Cyclopentyl	82	115–116	7	1.4685	10.01	10.10[a]

[a] Titration of basic nitrogen.

TABLE II

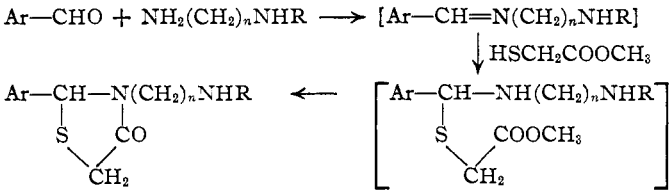
N-ALKYL PROPANEDIAMINES-1,3[2] $RNHCH_2CH_2CH_2NH_2$

R	Yield, %	B. p. °C.	mm.	$n^{25}D$	Analyses, % Nitrogen Calcd.	Found
n-Amyl	70	106–109[a]	18	1.4470	19.43	19.22
n-Hexyl	70	110	9	1.4481	17.72	17.69
n-Octyl	70	143–146	12	1.4512	15.00	14.86
Benzyl	77	98–102	1	1.5321	17.08	17.05
Cyclopentyl	73	90–95	8	1.4757	19.70	19.58

[a] Reference 2. The boiling point 102–103° at 15 mm. and analysis for picrate are reported.

The compounds described in Table III were prepared by essentially the same procedure reported for the tertiary aminoalkyl derivatives.[1] The appropriate benzaldehyde and secondary–primary diamine (see Tables I and II) were condensed to form the corresponding Schiff base which in turn was allowed to react with methyl thioglycolate (see flow sheet). With the exception of

FLOW SHEET



(1) Surrey, THIS JOURNAL, **71**, 3015 (1949).

(2) Prepared according to the procedure of Tarbell, Shakespeare, Claus and Bunnett, THIS JOURNAL, **68**, 1217 (1946).

benzylidene-*n*-propyl-(and *n*-butyl)-aminopropylamine, none of the Schiff bases was isolated. Attempts to purify several of them by vacuum distillation resulted in considerable decomposition.

It has been reported that trimethylene-1,3-diamines[3] and 1,3-dianilinopropane[4] react with aldehydes to yield hexahydropyrimidines. In these instances, both amino groups were either primary or secondary. With a primary–secondary diamine, as is the case in the present series, the reaction with aldehydes does not give the heterocyclic compound but rather a Schiff base as shown by the ultraviolet absorption spectrum[5] (see Fig. 1) and molecular refraction of benzylidene-*n*-propylaminopropylamine.

In order to determine the effect of substitution in the 5-position of the thiazolidone nucleus, 3-(3-butylaminopropyl)-5-ethyl-2-phenyl-4-thiazolidone hydrochloride was prepared according to the above described procedure by the reaction of benzylidene-*n*-propylaminopropylamine with methyl α-mercapto-*n*-butyrate. In addition, two of the thiazolidones, 2-(4-chlorophenyl)-3-(3-pentylaminopropyl)-4-thiazolidone and 3-(3-butylaminopropyl)-2-phenyl-4-thiazolidone were oxidized to the corresponding 1-dioxides with potassium permanganate. Good yields of the desired products were obtained when the reaction was carried out in acetic acid solution at 5–10°.

Pharmacology.—The anesthetic activity of the present series of 2-aryl-3-alkylaminoalkyl-4-thiazolidones was investigated by the Pharmacology Division of this Institute.[6] The results of this study showed that most of the compounds possessed a high degree of activity in producing sciatic nerve block in guinea pigs and spinal anesthesia in rabbits. Good results were also obtained in intracutaneous wheal tests in man. It was observed that increasing the length of the terminal N-alkyl group increased the local anesthetic activity. The optimum was reached at 5–6 carbon atoms after which the solubility decreased rather sharply. Substitution of the 4-butoxy for the 3,4-methylenedioxy group in the benzene ring increased the tissue irritation properties of the compound.

(3) Bergmann, Herman and Zimkin, *J. Org. Chem.*, **13**, 353 (1948).

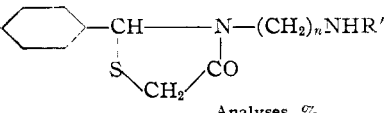
(4) (a) Veer, *Rec. trav. chim.*, **57**, 989 (1938); (b) Scholtz, *Ber.*, **32**, 2251 (1899).

(5) The author wishes to thank Dr. F. C. Nachod for the data on the absorption spectra reported.

(6) The author is indebted to Dr. F. P. Luduena and Dr. J. O. Hoppe under whose supervision the pharmacological investigation was carried out. The details of this study will be published elsewhere.

TABLE III

3-ALKYLAMINOALKYL-2-ARYL-4-THIAZOLIDONE HYDROCHLORIDES



R	R′	Yield,[a] %	M. p., °C.	Formula[b]	Analyses, % Sulfur Calcd.	Sulfur Found	Chlorine[c] Calcd.	Chlorine[c] Found
			$n = 2$					
3,4-O_2CH_2	2-Hydroxyethyl	16	152.2–155.4	$C_{14}H_{18}N_2O_4S$	9.24	9.38	10.22	10.02
3,4-O_2CH_2	Cyclohexyl	77	186.3–187[d]	$C_{18}H_{24}N_2O_3S$	8.32	8.28	9.20	8.99
			$n = 3$					
3,4-O_2CH_2	2-Hydroxyethyl	57	140.1–141.3	$C_{15}H_{20}N_2O_4S$	8.88	8.98	9.82	9.75
4-OC_4H_9-*n*	*n*-Propyl	81	84.2–85.4	$C_{19}H_{30}N_2O_2S$	7.92	8.00	8.77	8.46
3,4-O_2CH_2	*n*-Propyl	80	173.3–174.5	$C_{16}H_{22}N_2O_3S$	8.94	8.64	9.89	9.80
3,4-O_2CH_2	*i*-Propyl	57	169.3–171.4	$C_{16}H_{22}N_2O_3S$	8.94	8.90	9.89	9.72
H	*n*-Butyl	85[e]	168–170	$C_{16}H_{24}N_2OS$	9.75	9.72	10.78	10.59
3,4-O_2CH_2	*n*-Butyl	49	189.4–190.8	$C_{17}H_{24}N_2O_3S$	8.60	8.49	9.50	9.33
3-OCH_3-4-OC_2H_5	*n*-Butyl	54	96–99	$C_{19}H_{30}N_2O_3S$	7.96	7.87	8.80	8.65
4-NO_2	*n*-Butyl	80	205–205.6	$C_{16}H_{23}N_3O_3S$	8.57	8.67	9.48	9.45
4-NH_2	*n*-Butyl	78	192.6–193.2	$C_{16}H_{25}N_3OS$	9.32	9.23	10.31	10.26
3,4-O_2CH_2	*i*-Butyl	57	149.9–150.3[f]	$C_{17}H_{24}N_2O_3S$	8.60	8.65	9.51	9.36
3,4-O_2CH_2	*n*-Amyl	90	179.8–181.1	$C_{18}H_{26}N_2O_3S$	8.29	8.10	9.19	9.16
3,4-O_2CH_2	*n*-Hexyl	60	172.7–173	$C_{19}H_{28}N_2O_3S$	8.00	8.09	8.84	8.67
3,4-O_2CH_2	*n*-Octyl	42	132.3–134	$C_{21}H_{32}N_2O_3S$	7.47	7.25	8.27	8.24
3,4-O_2CH_2	Cyclopentyl	25	170.4–171.8	$C_{18}H_{24}N_2O_3S$	8.33	8.14	9.21	8.98
4-OCH_3	Cyclohexyl	22	152–153.8	$C_{19}H_{28}N_2O_2S$	8.33	8.33	9.21	9.09
3,4-O_2CH_2	Cyclohexyl	95	146–148	$C_{19}H_{26}N_2O_3S$	8.06	8.00	8.92	8.81
3,4-O_2CH_2	Benzyl	10	176.7–178.2	$C_{20}H_{22}N_2O_3S$	7.87	7.99	8.73	8.46
			$n = 6$					
3,4-O_2CH_2	Cyclohexyl	30	128.7–130.2[g]	$C_{22}H_{32}N_2O_3S$	7.27	7.38	8.04	7.90

[a] The majority of the yields reported are based on single experimental runs. [b] The formulas of the bases are listed. [c] Ionic chlorine. [d] Melting point of base, 99–100°. *Anal.* Calcd.: N (basic nitrogen), 4.02. Found: N, 4.02. [e] Based on purified Schiff base. [f] Melting point of base, 81.3–82.4°. *Anal.* Calcd.: S, 9.53. Found: S, 9.51. [g] Melting point of base, 98.4–100.2°. *Anal.* Calcd.: S, 7.92. Found: S, 7.55 (dry basis); H_2O, 1.86.

Experimental[7]

N-Cyclohexylhexamethylenediamine-1,6.—The procedure employed was that described by Pearson, Jones and Cope[8] for the preparation of N-cyclohexylethylenediamine. The product distilled at 115–118° (0.7–0.8 mm.); $n^{25}D$ 1.4756.

Anal. Calcd. for $C_{12}H_{26}N_2$: N, 14.13. Found: N, 14.35.

3-(6-Cyclohexylaminohexyl)-2-(3,4-methylenedioxyphenyl)-4-thiazolidone.—The following is an example of the general procedure employed for the preparation of most of the compounds listed in Table III.

A mixture of 18.5 g. of N-cyclohexylhexamethylenediamine-1,6 and 14 g. of piperonal in 100 ml. of Skellysolve E was refluxed until no more water was collected in a separator connected to the apparatus. Methyl thioglycolate (10 g.) was then added and refluxing was continued at a gentle rate until no more methanol was collected in the separator. After cooling, the solvent[9] was decanted from the oil which separated and the latter was dissolved in ether and extracted with 1 *N* hydrochloric acid. The acid extracts were combined, basified, and the oil extracted with ether. The ether was dried over Drierite and removed by distillation. The residue (24 g.) was dissolved in 120 ml. of acetone, filtered with Norite and to the filtrate was added alcoholic hydrogen chloride solution. The solid (1 g.) which separated melted at 223–226° (uncor.) and did not depress the melting point of a sample of dihydrochloride prepared from N-cyclohexylhexamethylenediamine-1,6.

Ether was added to the acetone filtrate and a crystalline solid separated on standing (9 g.). It was recrystallized once from isopropyl alcohol, dissolved in hot water and the solution basified. The solid base was collected, washed with water and then recrystallized from a mixture of ethanol and ether.[10]

2-(4-Butoxyphenyl)-3-(3-propylaminopropyl)-4-thiazolidone Hydrochloride.—A mixture of 26.7 g. of 4-butoxybenzaldehyde and 17.4 g. of N-propylpropanediamine-1,3 in 100 ml. of dry benzene was refluxed until no more water separated. After removing the solvent *in vacuo*, the crude Schiff base was dissolved in 100 ml. of Skellysolve E and the reaction was continued according to the general procedure described above.

3-(3-Butylaminopropyl)-2-(4-nitrophenyl)-4-thiazolidone Hydrochloride.—Fifteen grams of 4-nitrobenzaldehyde and 13 g. of N-butylpropanediamine-1,3 in 100 ml. of dry benzene[11] were refluxed for one and one-half hours while removing the water as it formed. Methyl thioglycolate (11 g.) was added and refluxing was continued for three and one-half hours. After standing overnight some tarry material had separated. Additional benzene was added to the reaction mixture and the benzene solu-

(7) All melting points are corrected unless otherwise indicated.

(8) Pearson, Jones and Cope, THIS JOURNAL, **68**, 1225 (1946).

(9) In most instances the solvent was distilled off under reduced pressure.

(10) Where the preparation of a particular compound was repeated, the isolation of the product could be simplified considerably by seeding the reaction mixture with the solid base where available or with the hydrochloride after the addition of alcoholic hydrogen chloride and acetone. The solid base or hydrochloride was obtained in this manner directly from the reaction mixture.

(11) When Skellysolve E was used as a solvent excessive decomposition occurred.

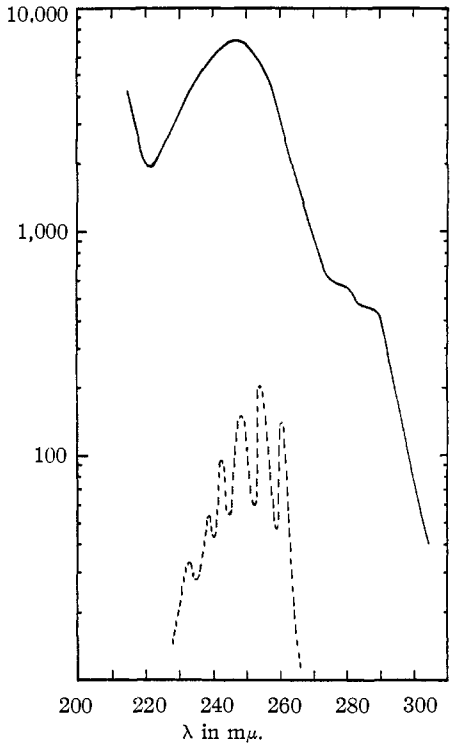


Fig. 1.—Absorption curves of benzylidene-*n*-propylminopropylamine in 95% ethanol: —, benzene in 95% ethanol: ---, as constructed from data of Campbell, Linden, Godshalk and Young, THIS JOURNAL, **69**, 881 (1947).

tion was extracted with 1 *N* hydrochloric acid. The solid hydrochloride which separated from the combined acid extracts was recrystallized from isopropyl alcohol and triturated with acetone; yield, 14 g.

2-(4-Aminophenyl)-3-(3-butylaminopropyl)-4-thiazolidone Hydrochloride.—A mixture of 7 g. of 3-(3-butylaminopropyl)-2-(4-nitrophenyl)-4-thiazolidone, 28 g. of iron filings, 50 ml. of ethanol, 25 ml. of water and 1 ml. of glacial acetic acid was refluxed with efficient stirring for three hours. The solution was made alkaline with sodium carbonate, more ethanol added, and the resulting solution was filtered hot. After removing the ethanol by distillation, the amino compound was extracted with chloroform. The crude base, after removal of the solvent, was converted to the hydrochloride.

Benzylidene-3-propylaminopropylamine.—This compound was prepared from benzaldehyde and N-propylpropanediamine-1,3 by refluxing the reactants in benzene and removing the water as it formed. After washing the benzene solution with sodium bicarbonate solution and then water, the product distilled at 107° (0.3 mm.); $n^{27}D$ 1.5272, d^{27} 0.9697.

Anal. Calcd. for $C_{13}H_{20}N_2$: N, 13.72; mol. ref., 65.24. Found: N, 13.70; mol. ref., 64.80.[12]

(12) The molecular refraction calculated for the isomeric hexahydropyrimidine is 63.65.[3]

Benzylidene-3-butylaminopropylamine.—The compound distilled at 113–117° (0.4–0.5 mm.).

Anal. Calcd. for $C_{14}H_{22}N_2$: N, 12.85. Found: N, 12.97.

3-(3-Butylaminopropyl)-5-ethyl-2-phenyl-4-thiazolidone Hydrochloride.—A mixture of 13.4 g. of methyl α-mercaptobutyrate[13] and 21.8 g. of benzylidene-3-butylaminopropylamine in 100 ml. of Skellysolve E was treated according to the general procedure described above. The crude base (26 g.) was dissolved in 250 ml. of acetone, filtered with Norite and the calculated amount of alcoholic hydrogen chloride was added. After adding dry ether to the solution, 12 g. (34%) of solid hydrochloride separated. Two recrystallizations from ethyl acetate followed by drying at 95° for two hours gave a product melting at 125.2–126.5°.

Anal. Calcd. for $C_{18}H_{28}N_2OS\cdot HCl$: S, 8.98; Cl^-, 9.93. Found: S, 9.07; Cl^-, 10.21.

2-(4-Chlorophenyl)-3-(3-pentylaminopropyl)-4-thiazolidone-1-dioxide Hydrochloride.—A solution of 8.6 g. of potassium permanganate in 300 ml. of water was added dropwise with stirring at 5–10° to a solution of 8.5 g. of 2-(4-chlorophenyl)-3-(3-pentylaminopropyl)-4-thiazolidone in 30 ml. of glacial acetic acid. The addition required thirty minutes. Sodium bisulfite solution was added to the reaction mixture and the colorless solution treated with an excess of ammonium hydroxide. The solution was extracted with chloroform, dried, and the solvent was removed by distillation. The residue (7 g.) was converted to the hydrochloride, which after recrystallization from ethanol melted at 198.5–200°.

Anal. Calcd. for $C_{17}H_{25}ClN_2O_3S\cdot HCl$: S, 7.83; Cl^-, 8.66. Found: S, 7.93; Cl^-, 8.60.

3-(3-Butylaminopropyl)-2-phenyl-4-thiazolidone-1-dioxide Hydrochloride.—This compound was recrystallized from ethanol; m. p. 158.8–160.4°.

Anal. Calcd. for $C_{16}H_{24}N_2O_3S\cdot HCl$: S, 8.88; Cl^-, 9.82. Found: S, 9.15; Cl^-, 9.55.

Summary

A series of 3-alkylaminoalkyl-2-aryl-4-thiazolidones has been prepared by the reaction of methyl thioglycolate with several benzylidene-alkylaminoalkylamines. Methyl α-mercaptobutyrate has been employed for the preparation of 3-(3-butylaminopropyl)-5-ethyl-2-phenyl-4-thiazolidone. Two of the thiazolidones were oxidized with potassium permanganate to yield the 1-dioxides.

Most of the compounds reported showed high local anesthetic activity in the production of sciatic nerve block in guinea pigs and spinal anesthesia in rabbits.

RENSSELAER, NEW YORK RECEIVED MAY 9, 1949

(13) The ester was obtained by refluxing the corresponding acid in methanol with concentrated sulfuric acid. The product was taken up in ether and the ether solution was washed with water, sodium bicarbonate solution and again with water. After drying, the ether was distilled off. Calcd. for $C_5H_{10}O_2S$: SH, 24.6. Found: SH, 23.6.