The 2-Thiopseudourea Moiety, a New Local Anesthesiophore[1]

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Twenty 2-thiopseudoureas and related 2-aminothiazoles are shown to be four- to twentyfold more surface anesthetic and two- to sixfold more anesthetic by infiltration in guinea pigs than lidocaine hydrochloride. Although most of the tabulated 2-thiopseudoureas are more toxic than lidocaine, nevertheless, 19 of them have substantially greater margins of safety (RA/RT = 1.3–2.8). A higher degree of anesthesiophoric specificity is noted for the 2-thiopseudourea moiety (**12**) compared with the similar guanidine moiety (**13**). Furthermore, wholly aliphatic-substituted 2-thiopseudoureas (**21–23** and **25**) are potent local anesthetics, and thus represent a significant deviation from the generally held concept of the essential structural requirements for local anesthetics. Thus, the 2-thiopseudourea moiety, $-SC(=N-)N<$, is a new and potent local anesthesiophore. Longer duration of anesthesia, but also greater irritancy, are generally associated with these 2-thiopseudoureas compared with lidocaine. The preparation of these anesthetics is described. Twenty-five of them are new compounds.

Such a variety of organic structures are anesthetics[2] that it is not surprising to learn of a new agent in this area. It does seem significant, however, to report the anesthesiophoric character of a class of compounds such as 2-thiopseudoureas.

Most of the synthetic effort to produce local anesthetics in the past has been guided by the concept that the essential structural requirements are a lipophilic end containing an aromatic nucleus, a hydrophilic end consisting of a tertiary amino group, and an intermediate alkyl or substituted-alkyl chain.[2] An objective of this report is to show significant deviation from this concept for certain anestethic 2-thiopseudoureas. A further objective is to demonstrate the 2-thiopseudourea moiety, $-SC(=N-)N<$, as a new and potent local anesthesiophore.

Local anesthetic properties associated with 2-thiopseudourea and related compounds have been reported previously, but none of these investigations attributed these properties to the 2-thiopseudourea moiety. Ballowitz[3] described 2-amino-6-ethoxybenzothiazole as equal to procaine in sensory and motor nerve block, but inferior to cocaine on mucous membranes. Subsequently, Bhargava and co-workers[4] prepared and tested a number of 2-(dialkylaminoacetylamino)thiazoles and -benzothiazoles as well as 5-(dialkylaminoacetylamino)-2-iminothiazolidinones and -2,4-thiazolidinediones. The most active of these have a 1.5–5 times faster onset of anesthesia compared with procaine. Lately "N-(2-pseudothiouroniumethyl)-*endo*-perhydro-4,7-methanoisoindole" was alleged[5] to be anesthetic.

(1) Presented in part at the 133rd Meeting of the American Association for the Advancement of Science, Washington, D. C., Dec 1966.

(2) A. Burger in "Medicinal Chemistry," A. Burger, Ed., 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1960, Chapter 20; J. M. Ritchie, P. J. Cohen, and R. D. Dripps in "The Pharmacological Basis of Therapeutics," L. S. Goodman and A. Gilman, Ed., 3rd ed, The Macmillan Co., New York, N. Y., 1965, Chapter 20.

(3) K. Ballowitz, *Arch. Exptl. Pathol. Pharmakol.*, **163**, 687 (1931); *Chem. Abstr.*, **26**, 2509 (1931).

(4) P. N. Bhargava and P. R. Singh, *J. Indian Chem. Soc.*, **37**, 241 (1960); P. N. Bhargava and K. A. Jose, *ibid.*, **37**, 314 (1960); P. N. Bhargava and G. C. Singh, *ibid.*, **38**, 77 (1961); P. N. Bhargava and K. U. Prasad, *ibid.*, **38**, 165 (1961); P. N. Bhargava and P. Ram, *ibid.*, **38**, 167 (1961); P. N. Bhargava, P. Ram, and K. I. Singh, *ibid.*, **39**, 396 (1962); P. N. Bhargava and S. C. Sharma, *ibid.*, **39**, 319 (1962); P. N. Bhargava and P. R. Singh, *J. Sci. Ind. Res.* (India), **20C**, 209 (1961); **21C**, 158 (1962); P. N. Bhargava and S. C. Sharma, *Bull. Chem. Soc. Japan*, **35**, 1926 (1962); P. N. Bhargava and P. Ram, *ibid.*, **38**, 339 (1965).

(5) J. W. Bolger, U. S. Patent 3,124,595 (1964).

Experimental Section

Materials.—Melting points were determined on a Fisher-Johns block and are corrected. Ultraviolet spectra were obtained with a Beckman DU spectrophotometer. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

5-Phenylpentyl chloride,[6] **N-(2-chloroethyl)-N-ethylaniline,**[7] **2-chloro-2-phenylacetophenone,**[8] **1-cyclohexyl-3-isopropyl-2-thiourea,**[9] **and 1-methyl-3-(2-methylbenzyl)-2-thiourea**[10] were prepared as previously described.

1-Cyclohexyl-3,3-tetramethylene-2-thiourea.—Pyrrolidine (14.2 g, 0.2 mole) was added portionwise to cyclohexyl isothiocyanate (28.2 g, 0.2 mole). When the exothermic reaction subsided, the product was crystallized twice from ethyl acetate; yield 30.4 g (72%), mp 135–136°.

Anal. Calcd for $C_{11}H_{20}N_2S$: C, 62.39; H, 9.62. Found: C, 62.32; H, 9.51.

1(2)-Benzyl-2(1),3-dicyclohexylguanidine Hydrochloride (13).—Benzylamine hydrochloride (8.9 g, 62 mmoles), dicyclohexyl carbodiimide (12.6 g, 62 mmoles), and 60 ml of dry pyridine were refluxed for 1 hr and concentrated *in vacuo* to dryness. The tacky residue was triturated with anhydrous ether and crystallization occurred; yield 21.8 g, mp 175–185°. This product was recrystallized once from 95% ethanol; yield 15.0 g (70%), mp 195–196°. Analyses are given in Table I.

Preparation of 2-Thiopseudourea Salts (1–12 and 14–24).—The general procedure was to reflux a 1-propanol solution of the appropriate alkyl or aralkyl halide and 2-thiourea for 3–4 hr, concentrate *in vacuo* to dryness, and crystallize the product. Ocassionally water aided crystallization. Usually one or two recrystallizations gave 2-thiopseudourea salts of analytical purity. Other solvents employed in the place of 1-propanol were: (a) ethanol for **5**, (b) 2-propanol for **7** and **8**, and (c) benzene for **10** and **11**. Compounds **9** and **12** were prepared in acetone solution refluxed about 16 hr. Compound **21** was prepared in methyl iodide solution at room temperature for 16 hr, **22** in refluxing (16 hr) ethyl bromide solution, and **23** in refluxing (30 min) allyl bromide solution. The melting points, yields, recrystallization solvents, molecular formulas, and elemental analyses are given in Table I.

Preparation of 2-Aminothiazolium Salts (25–28).—The general procedure was to reflux an ethanol solution of the appropriate α-chlorocarbonyl compound and symmetrical 1,3-dialkyl-2-thiourea for 3–4 hr, concentrate, and crystallize the product. Usually one or two recrystallizations gave samples of analytical purity (see Table I).

4,5-Diphenyl-4-hydroxy-3-methyl-2-methylamino-2-thiazolinium Chloride (29).—2-Chloro-2-phenylacetophenone (11.5 g, 50 mmoles), 1,3-dimethyl-2-thiourea (5.2 g, 50 mmoles), and

(6) A. Iliceto, A. Fava, and A. Simeone, *Gazz. Chim. Ital.*, **90**, 600 (1960); *Chem. Abstr.*, **55**, 14335 (1961).

(7) H. Dehnert, German Patent 650,259 (1937); *Chem. Abstr.*, **32**, 952 (1938).

(8) A. M. Ward in "Organic Syntheses", Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p 159.

(9) E. Schmidt, and W. Striewsky, *Ber.*, **74B**, 1285 (1941); *Chem. Abstr.*, **36**, 4804 (1942).

(10) A. Berger and E. Borgaes, U. S. Patent 3,090,810 (1963).

Table I

2-Thiopseudourea Salts and Related Anesthetics

No.	Mp, °C	Yield, %	Recrystn solvent(s)	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	126–128	53	Acetone	$C_{12}H_{18}N_2S\cdot HCl$	55.69	7.40	10.82	55.64	7.38	10.72
2	106–108	66	Acetone–MeOH	$C_{10}H_{14}N_2S\cdot HCl$	52.05	6.55	12.14	52.15	6.63	12.15
3[a]	177–180	..	*n*-PrOH	$C_{10}H_{12}N_2S\cdot HCl$	52.51	5.73	12.25	52.78	5.93	12.09
4	128–129	26	Acetone–MeOH	$C_{12}H_{18}N_2OS\cdot HCl$	52.45	6.97	10.19	52.41	6.97	10.20
5	118–121	80	Acetone	$C_{10}H_{14}N_2OS\cdot HBr$	41.24	5.19	9.62	41.38	5.42	9.72
6	127–128	71	Acetone–MeOH	$C_{11}H_{17}N_2S\cdot HCl$	50.85	6.98	16.17	50.85	7.05	15.97
7[b]	185–187	92	*n*-BuOH	$C_{13}H_{19}N_2O_2S\cdot HBr$	43.58	4.50	11.73	43.67	4.56	11.68
8[c]	190–191	78	*i*-PrOH	$C_8H_9ClN_2S\cdot HCl$	40.52	4.25	11.81	40.74	4.37	11.89
9[d]	Oil	..	...	$C_{16}H_{26}N_2S\cdot HCl$	61.02	8.64	8.90	60.87	8.85	8.85
10	151–153	92	Acetone–CH_2Cl_2	$C_{17}H_{26}N_2S\cdot HCl$	62.46	8.32	8.57	62.58	8.48	8.31
11	125–127	72	Acetone	$C_{18}H_{26}N_2S\cdot HCl$	63.78	8.03	8.27	63.70	8.09	
12	158–160	64	Acetone–MeOH	$C_{20}H_{30}N_2S\cdot HCl$	65.46	8.51	7.63	65.60	8.57	7.75
13	195–196	70	95% EtOH	$C_{21}H_{31}N_3\cdot HCl$	68.64	9.22	12.01	68.80	9.44	12.32
14	134–136	75	Acetone–ether	$C_{20}H_{29}N_3O_2S\cdot HCl$	58.31	7.34	10.20	58.30	7.52	10.09
15	163–165	70	EtOAc–MeOH	$C_{20}H_{29}N_3O_2S\cdot HCl$	58.31	7.34	10.20	58.68	7.37	9.91
16	101–103	75	EtOAc–petr ether[e]	$C_{22}H_{31}N_2S\cdot HBr$	60.12	8.03	6.37	60.14	8.05	6.14
17	148–150	59	Acetone–EtOH	$C_{18}H_{24}N_2S\cdot HCl$	64.17	7.48	8.31	63.95	7.36	8.10
18[f]	136–138	96	Acetone	$C_{17}H_{26}N_2S\cdot HCl$	63.63	6.60	8.73	63.58	6.75	8.53
19	97–98	86	EtOAc–acetone	$C_{17}H_{20}N_2S\cdot HBr$	55.89	5.79	7.67	55.85	5.74	7.66
20[g]	120–121	73	EtOAc–acetone	$C_{16}H_{18}N_2S\cdot HI$	48.25	4.81	7.03	48.71	4.99	7.02
21	143–144	68	EtOAc–acetone	$C_{14}H_{26}N_2S\cdot HI$	43.98	7.12	7.33	44.35	7.33	7.24
22[h]	172–174	75	Acetone–MeOH	$C_{13}H_{28}N_2S\cdot HBr$	51.57	8.37	8.02	51.61	8.25	8.13
23	157–158	72	...	$C_{16}H_{28}N_2S\cdot HBr$	53.18	8.09	7.75	53.29	8.23	7.50
24	188–190	62	Acetone–CH_2Cl_2	$C_{13}H_{37}N_3S\cdot 2HCl$	55.32	9.53	10.19	55.11	9.40	10.13
25[i]	223–224	38	Acetone	$C_{15}H_{23}N_2S\cdot HCl$	59.88	8.37	9.31	60.03	8.57	9.17
26[k]	185–186	89	Acetone	$C_{13}H_{20}N_2S\cdot HCl$	60.69	7.13	9.44	60.74	7.09	9.64
27[l]	238–240	48	*i*-PrOH	$C_6H_{16}N_2S\cdot HBr$	49.84	5.47	8.94	50.20	5.74	9.02
28[l,m]	233–235	63	Acetone–MeOH	$C_{17}H_{14}N_2S\cdot HCl$	64.85	4.80	8.90	64.90	5.07	8.80
29	146–148[k]	87	EtOAc–MeOH	$C_{17}H_{16}N_2OS\cdot HCl$	60.98	5.72	8.37	61.16	5.83	8.53

[a] O. Wichterle and J. Cerny, *Chem. Listy*, **49**, 1038 (1955), report mp 170–171°; H. Nishimura, *Yakugaku Zasshi*, **84**, 930 (1964), reports mp 185–187°. [b] J. W. Griffin and D. H. Hey, *J. Chem. Soc.*, 3334 (1952), report mp 174.5–177°. [c] G. S. Dawes and F. N. Fastier, *Brit. J. Pharmacol.*, **5**, 323 (1950). [d] Hydrate has mp 33–36°. [e] D. F. Percival and R. M. Herbst, *J. Org. Chem.*, **22**, 925 (1957), report mp 119.5–120.5°. [f] Polymorphic form has mp 157–158°. [g] λ_{max} 261 mμ (ε 8700) in 0.1 *N* HCl. [h] λ_{max} 262 mμ (ε 10,400) in 0.1 *N* HCl. [i] λ_{max} 257 mμ (ε 11,400) in 0.1 *N* HCl. [k] λ_{max} 290–296 mμ (ε 11,800) in 0.1 *N* HCl. [k] Fast melt on preheated block; slow heating gives mp 184–186°. [l] Prepared by Dr. Arthur Berger. [m] Prepared by Dr. Nicholas J. Kartinos. [n] Bp 35–60°.

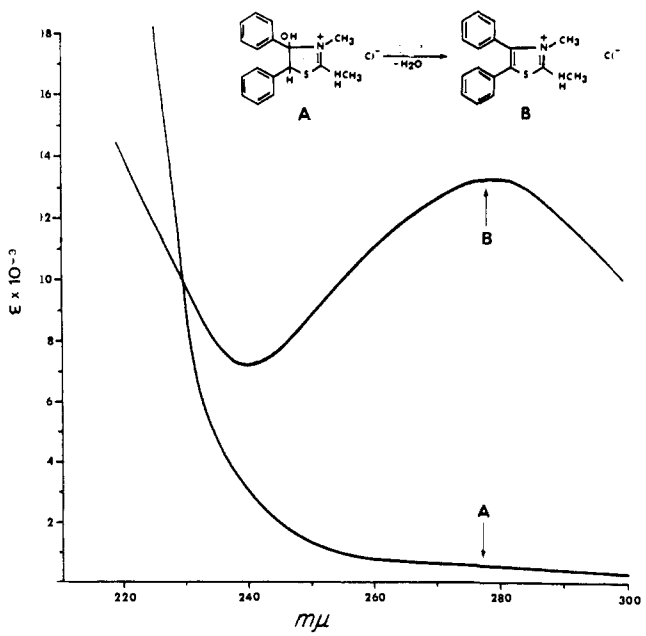


Figure 1.—Ultraviolet absorption spectra of a 3.22×10^{-5} *M* solution of the 4-hydroxy-2-thiazoline **29** in 0.1 *N* HCl (curve A, no change after 24 hr at room temperature), and after heating at 100° for 3 hr (curve B) which dehydrates **29** to the corresponding thiazole.

100 ml of acetone were refluxed for 1 hr. Crystallization began after 30 min of reflux. Concentration of the mixture gave 14.6 g (87%) of product, mp 142–147°. This product was dissolved in 45 ml of hot methanol and diluted with 90 ml of ethyl acetate. This solution was concentrated to about 60 ml when crystallization started. After refrigeration, **29** was collected by filtration and dried; yield 10.2 g (61%), mp 146–148°. See Table I. The ultraviolet absorption spectrum of **29** is given in Figure 1, curve A. Dehydration at 100° of **29** to a thiazole in dilute 0.1 *N* HCl solution is shown spectrophotometrically in Figure 1, curve B.

Methods.—Local anesthetic potency and duration were measured on corneas and in intradermal wheals of guinea pigs by the method of Galysh, *et al.*,[11] a modification of earlier methods.[12,13] The potency results are given in Tables II and III. The surface EC_{50} is the concentration (mg/ml) of anesthetic agent in normal saline which abolishes the corneal reflex in 50% of the corneas tested 5 min after instillation of two or three drops. The infiltration EC_{50} is the concentration (mg/ml) of 0.25 ml of anesthetic solution which causes a loss of response to painful stimuli in 50% of the wheals tested at the time of peak action, *i.e.*, 5 min following intradermal injection. The EC_{50} was estimated by the least-squares method from a three- to five-point plot of response *vs.* concentration. Ten sites per concentration were each tested three times, and the responses were pooled. Two or more such EC_{50} determinations were made and averaged to

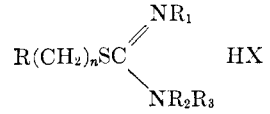
(11) F. T. Galysh, R. N. Morris, and B. M. Regan, unpublished data presented in part at the 133rd Meeting of the American Association for the Advancement of Science, Washington, D. C., Dec 1966.

(12) M. R. A. Chance and H. Lobstein, *J. Pharmacol. Exptl. Therap.*, **82**, 204 (1944).

(13) E. Bülbring and I. Wajda, *ibid.*, **85**, 78 (1945).

TABLE II

2-THIOPSEUDOUREA SALTS AS LOCAL ANESTHETICS

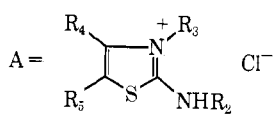


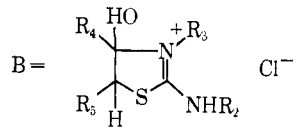
No.	R	n	R_1	R_2	R_3	X	Surf EC_{50}, mg/ml	Infil EC_{50}, mg/ml	Toxicity LD_{50}, mg/kg iv	RA Surf	RA Infil	RT iv	RA (infil)/ RT(iv)
1	C_6H_5	5	H	H	H	Cl	1.1	0.41	36	8.4	1.8	0.9	2.0
2	C_6H_5	3	H	H	H	Cl	3.1	0.58	31	3.0	1.3	1.0	1.3
3	$C_6H_5CH{=}CH$	1	H	H	H	Cl	3.3	0.53	58	2.8	1.4	0.6	2.5
4	$2\text{-}C_2H_5OC_6H_4$	3	H	H	H	Cl	0.90	0.33	27	10	2.2	1.2	1.9
5	C_6H_5O	3	H	H	H	Br	4.3	0.79	57	2.1	0.9	0.6	1.7
6	$C_6H_5N(C_2H_5)$	2	H	H	H	Cl	2.0	0.64	49	4.6	1.2	0.7	1.8
7	Phthalimido	4	H	H	H	Br	27	0.95	52	0.34	0.8	0.6	1.3
8	$2\text{-}ClC_6H_4$	1	H	H	H	Cl	3.8	0.72	43	2.4	1.0	0.7	1.4
9[a]	C_6H_5	1	$n\text{-}C_4H_9$	H	$n\text{-}C_4H_9$	Cl	0.44	0.12	5.9	21	6.2	5.4	1.1
10	C_6H_5	1	$c\text{-}C_6H_{11}$	H	$i\text{-}C_3H_7$	Cl	0.60	0.12	8.1	15	6.2	3.9	1.6
11	C_6H_5	1	$c\text{-}C_6H_{11}$		$-(CH_2)_4-$	Cl	0.69	0.19	17	13	4.0	1.9	2.2
12	C_6H_5	1	$c\text{-}C_6H_{11}$	H	$c\text{-}C_6H_{11}$	Cl	0.38	0.22	14	24	3.4	2.2	1.5
13	$C_6H_5CH_2NHC(=N\text{-}c\text{-}C_6H_{11})NH\text{-}c\text{-}C_6H_{11}\cdot HCl$						...	1.8	25	...	0.4	1.3	0.3
14	$4\text{-}NO_2C_6H_4$	1	$c\text{-}C_6H_{11}$	H	$c\text{-}C_6H_{11}$	Cl	0.92	0.29	18	10	2.5	1.8	1.4
15	$3\text{-}NO_2C_6H_4$	1	$c\text{-}C_6H_{11}$	H	$c\text{-}C_6H_{11}$	Cl	1.0	0.19	16	9.2	3.9	2.1	1.9
16	C_6H_5	3	$c\text{-}C_6H_{11}$	H	$c\text{-}C_6H_{11}$	Br	0.41	0.23	15	22	3.2	2.1	1.5
17	1-Naphthyl	1	$i\text{-}C_3H_7$	H	$i\text{-}C_3H_7$	Cl	0.74	0.15	8.0	12	4.9	4.0	1.2
18	C_6H_5	1	CH_3	H	$2\text{-}CH_3C_6H_4CH_2$	Cl	0.58	0.17	15	16	4.4	2.2	2.0
19	H	2	$C_6H_5CH_2$	H	$C_6H_5CH_2$	Br	1.1	0.22	10	8.4	3.4	3.2	1.1
20	H	1	$C_6H_5CH_2$	H	$C_6H_5CH_2$	I	1.6	0.44	24	5.7	1.7	1.3	1.3
21	H	1	$c\text{-}C_6H_{11}$	H	$c\text{-}C_6H_{11}$	I	1.5	0.28	26	6.1	2.6	1.2	2.1
22	H	2	$c\text{-}C_6H_{11}$	H	$c\text{-}C_6H_{11}$	Br	1.0	0.20	17	9.2	3.7	1.9	1.9
23	$CH_2{=}CH$	1	$c\text{-}C_6H_{11}$	H	$c\text{-}C_6H_{11}$	Br	0.91	0.22	26	10	3.4	1.2	2.8
24	$(C_2H_5)_2N$	2	$c\text{-}C_6H_{11}$	H	$c\text{-}C_6H_{11}$	HCl_2	1.4	0.16	7.2	6.6	4.6	4.4	1.0
Lidocaine hydrochloride							9.2	0.74	32	1.0	1.0	1.0	1.0

[a] F. J. Bandelin, private communication, 1960, first reported this compound's "good anesthetic activity."

TABLE III

2-AMINOTHIAZOLIUM AND 2-AMINO-4-HYDROXY-2-THIAZOLINIUM CHLORIDES AS LOCAL ANESTHETICS





No.	Type	R_2	R_3	R_4	R_5	Surf EC_{50}, mg/ml	Infil EC_{50}, mg/ml	Toxicity LD_{50}, mg/kg iv	RA infil	RT iv	RA/RT
25	A	$c\text{-}C_6H_{11}$	$c\text{-}C_6H_{11}$	H	H	2.7	0.40	13	1.8	2.4	0.8
26	A	$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	C_6H_5	H	>50	1.2	28	0.6	1.2	0.5
27[a]	A	CH_3	CH_3	$2,4\text{-}(CH_3)_2C_6H_3$	H	3.1	0.56	38	1.3	0.8	1.6
28	A	$-(CH_2)_2-$		C_6H_5	C_6H_5	1.1	0.31	17	2.4	1.9	1.3
29	B	CH_3	CH_3	C_6H_5	C_6H_5	2.1	0.42	33	1.8	1.0	1.8

[a] Hydrobromide salt.

obtain the values given in the tables. Standard errors were generally about 10% of the estimated EC_{50}.

Acute toxicity was estimated[11] in male CF-1 mice. Five 0.15 log graded doses were injected intravenously into ten mice per dose, and the median lethal dose, LD_{50}, was determined 7 days later. Standard errors were generally about 10% of the estimated LD_{50}.

Relative activity, RA, is the ratio of the infiltration EC_{50}'s of the standard, lidocaine hydrochloride, to the candidate anesthetic. Similarly, relative toxicity, RT, is the ratio of the intravenous LD_{50}'s of standard to candidate. The ratio, RA/RT, gives the safety margin of the candidate anesthetic relative to lidocaine, whose RA, RT, and RA/RT are, by definition, unity.

Irritation was measured[11] in the rabbit by the trypan blue method[14] following intradermal injection of the anesthetic agent dissolved in normal saline.

(14) J. O. Hoppe, E. B. Alexander, and L. C. Miller, *J. Am. Pharm. Assoc., Sci. Ed.*, **39**, 147 (1950).

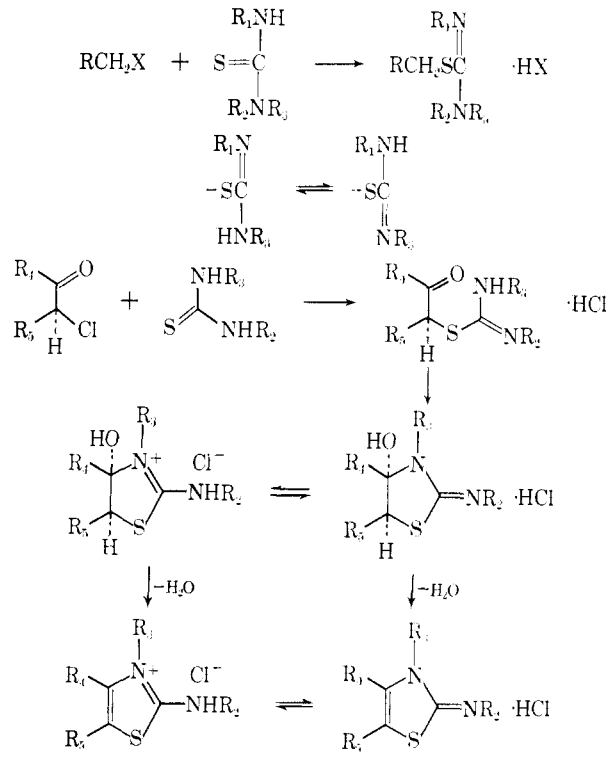
Results and Discussion

Chemistry.—The familiar reaction between a 2-thiourea and an organic halide to form a 2-organo-2-thiopseudouronium halide (Scheme I) requires no elaboration except to point out the possible existence of nonequivalent tautomers when R_1 differs from R_3, and R_2 is hydryl as in **10** and **18**.

The reaction between a 2-thiourea and an α-halocarbonyl compound has been postulated[15b] to give first an α-thiopseudoureidocarbonyl compound which cyclizes to a 2-imino-4-hydroxythiazolidine which, in

(15) (a) P. M. Kochergin and M. N. Shchukina, *J. Gen. Chem. USSR*, **26**, 483 (1956), English translation of *Zh. Obshch. Khim.*, **26**, 458 (1956); (b) *J. Gen. Chem. USSR*, **26**, 3233 (1956), English translation of *Zh. Obshch. Khim.*, **26**, 2905 (1956).

Scheme I



turn, dehydrates to a 2-imino-4-thiazoline (Scheme I). This postulate follows from the isolation (a) of α-imidazomercapto ketones from the reactions of several α-halo ketones with 2-mercapto-4(5)-phenylimidazole[15a] (a 2-thiourea enol) and (b) of 3-hydroxyimidazo[2,1-*b*]-thiazolines from the reactions between 2-mercapto-4(5)-arylimidazoles and α-bromoacetaldehyde.[15b] The isolated products of (a) and (b) are intermediates in the preparation of the corresponding imidazo[2,1-*b*]-thiazoles.[15]

Subsequently, 1,3-diaryl- or 1-acyl-3-aryl-2-thioureas and α-halo ketones (in the presence of triethylamine) were shown to give 2-imino-4-hydroxythiazolidines.[16] No α-thiopseudoureido ketone intermediates were isolated in this study.

Still later the reactions between 2-haloacetophenones and ethylenethiourea in acetone at room temperature were reported to yield 2-(2-imidazolinomercapto)-acetophenones or the corresponding enols.[17] In this study no 3-hydroxy-3-aryl-5,6-dihydroimidazo[2,1-*b*]-thiazolidines were believed to have been isolated.

From the reaction between 2-chloro-2-phenylacetophenone and 1,3-dimethyl-2-thiourea in boiling acetone we obtained 4,5-diphenyl-4-hydroxy-3-methyl-2-methylamino-2-thiazolinium chloride (**29**). Elemental analyses and ultraviolet absorption spectra (Figure 1) confirm this 4-hydroxy-2-thiazoline structure.[18] Compound **29** has neither a phenylcarbonyl group (absence of strong and specific absorption near 240 mμ) nor a phenylcarbonyl enol group (absence of uv absorption characteristic of a *cis*- or *trans*-stilbene chromophore).

Neither the results of Shchukina and co-workers, Fefer and King, nor ours have demonstrated the isolation of *both* postulated intermediates in the discrete reaction between one α-halocarbonyl compound and one 2-thiourea.

The 2-aminothiazoles **25**–**28** were prepared without attempting to isolate intermediates. Their structures are based on elemental analyses and ultraviolet absorption spectra[19] (Table I).

Pharmacology. All but one of the 23 2-thiopseudoureas listed in Table II are two- to twentyfold more surface anesthetic than lidocaine, and 20 of these are more anesthetic (RA 1.2–6.2) by infiltration. Most of these, however, are more toxic than lidocaine, but not **1**, **3**, and **5**–**8** (RT 0.6–0.9). Nevertheless 19 tabulated 2-thiopseudoureas have substantially greater margins of safety (RA/RT = 1.3–2.8) compared with lidocaine. The range of substituents on sulfur (alkyl, aminoalkyl, phenylalkyl, ethoxy-, chloro-, and nitrophenylalkyl, phenoxy-, anilino-, and phthalimidoalkyl) and on nitrogen (hydryl, alkyl, cyclohexyl, and benzyl) in these tabulated anesthetics is sufficiently diverse to indicate an anesthesiophoric character for the 2-thiopseudourea moiety. The anesthetic 2-aminothiazoles and the 2-amino-4-hydroxy-2-thiazoline in Table III show, moreover, the 2-thiopseudourea anesthesiophore is also operative in ring structures.

Duration of anesthesia on guinea pig corneas and in wheals[11] is equal to or greater than lidocaine for all the tabulated 2-thiopseudoureas; however, these are all more irritating[10] intradermally in the rabbit than lidocaine.

2-Benzyl-1,3-dicyclohexyl-2-thiopseudourea hydrochloride (**12**), compared with the corresponding guanidine **13**, is eight times more anesthetic by infiltration and just twice as toxic. Thus, a higher degree of anesthesiophoric specificity is apparently inherent in the 2-thiopseudourea moiety.

Compounds **21**–**23** and **25** are three to ten times more surface anesthetic than lidocaine and also substantially more anesthetic by infiltration (RA 1.8–3.7). These four are S-substituted by a one- to three-carbon alkyl or alkenyl while N,N′-disubstituted by cyclohexyl. Thus, these structure–activity relationships represent a significant deviation from the generally held concept that the essential structural requirements for local anesthetics are an aromatic nucleus and a tertiary amino group joined by an alkyl chain.

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(16) (a) K. M. Murav'eva and M. N. Shchukina, *Dokl. Akad. Nauk SSSR*, **126**, 1274 (1959); *Chem. Abstr.*, **54**, 498 (1960); (b) *Zh. Obshch. Khim.*, **30**, 2327, 2334 (1960); *Chem. Abstr.*, **55**, 9376*a*, 9376*g* (1961).

(17) M. Fefer and L. C. King, *J. Org. Chem.*, **26**, 828 (1961).

(18) Essentially the same ultraviolet absorption spectrum above 220 mμ was observed in methanol for **29** as for 4,5-diphenyl-2-ethylamino-2-thiazoline prepared according to H. G. Soderbaum, *Ber.*, **28**, 1900 (1895).

(19) W. Wilson and R. Woodger, *J. Chem. Soc.*, 2943 (1955); M. Selin, M. Selin, O. Teto, G. Drillien, and P. Rumpf, *Bull. Soc. Chim. France*, 3527 (1965); J. L. M. Loontjens, *Bull. Soc. Chim. Belges*, **75**, 380 (1966).