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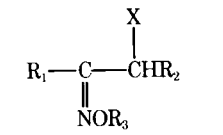
New Derivatives of 2-Alkoxyiminoalkylmercaptans as Potential Radioprotective Agents

SOU-YIE CHU, NORMAN L. HINES, and DOMINICK A. COVIELLO [x]

Abstract □ 2-Alkoxyiminoalkylmercaptans were treated with appropriate reagents by established procedures to prepare the corresponding "Bunte salts," 2-(2-alkoxyiminoalkylthio)-2-imidazolines, 2-(2-alkoxyimino)alkyl dithiocarbonates, and ethyl 2-alkoxyiminoalkyl trithiocarbonates. Selected compounds were screened for radioprotective activity, and none was found to have significant activity.

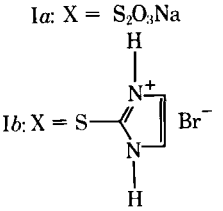
Keyphrases □ 2-Alkoxyiminoalkylmercaptan derivatives—synthesized as potential radioprotective agents □ Radioprotective activity—2-alkoxyiminoalkylmercaptan derivatives synthesized and screened □ Antiradiation agents, potential—synthesis and screening of 2-alkoxyiminoalkylmercaptan derivatives

The grouping of atoms N—C—C—S is apparently a good pharmacophore for antiradiation activity, since cysteamine (2-mercaptoethylamine) derivatives are among the most effective prophylactics against radiation damage. Since 2-alkoxyiminoalkyl bromides can be prepared by reacting *O*-alkyl ethers of aldoximes and ketoximes with *N*-bromosuccinimide (1), it was felt that they could be readily converted to 2-alkoxyiminomercaptan derivatives (I) incorporating the radioprotective pharmacophore. The bromides were reacted with sodium thiosulfate, ethylenethiourea, sodium *O*-ethyl dithiocarbonate, and sodium ethyl trithiocarbonate to yield "Bunte salts" (I*a*), 2-(2-alkoxyiminoalkylthio)-2-imidazolines (I*b*), ethyl *S*-(2-alkoxyimino) alkyl dithiocarbonates (I*c*), and ethyl 2-alkoxyiminoalkyl trithiocarbonates (I*d*), respectively, by established procedures (2–5). The yields and physical data of the compounds prepared are shown in Table I.



I

I*a*: X = S_2O_3Na



I*b*: X = S, Br^-

I*c*: X = $SCOSC_2H_5$

I*d*: X = $SCS_2C_2H_5$

Compounds III, XII, XVI, XX, XXI, XXV, and XXVIII were evaluated for radioprotective activity[1]. The test method was described (6) previously.

EXPERIMENTAL

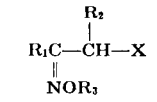
Bunte Salts—The preparation of sodium *S*-(3-ethoxyimino-2-butyl)thiosulfate illustrates the general procedure.

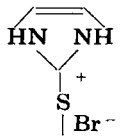
A solution of 24.8 g (0.1 mole) of sodium thiosulfate pentahydrate in 50 ml of water was mixed with a solution of 19.4 g (0.1 mole) of 3-bromobutanone oxime *O*-ethyl ether in 30 ml of 95% ethanol. The mixture was stirred while heating with steam at reflux for 25 min. The resulting homogeneous solution was then evaporated to dryness under reduced pressure. The residue was extracted with 40 ml of ether, and the solution was cooled in the refrigerator overnight. The white amorphous crystals that formed were collected and dried in air to yield 4.4 g of the title compound. The mother liquor was taken to dryness on the flash evaporator, and the residue was taken up in 95% ethanol and treated with ether. The 7.2 g of product that precipitated melted at 162–164° dec.; total yield, 11.6 g (56.3%). Minor changes in the workup were all that distinguished the preparative methods for the various Bunte salts.

2-(2-Alkoxyiminoalkylthio)-2-imidazolinium Bromides—The general procedure was as follows. A mixture of ethylenethiourea (2.04 g, 0.02 mole) and bromoacetone oxime *O*-ethyl ether (3.96 g, 0.022 mole) in 15 ml of dimethylformamide was stirred at room temperature for 3 hr. Twenty-five milliliters of ether was added, and the resulting solution was cooled in an ice bath. A solid crystallized in white lustrous plates and was collected and washed with 10 ml of dimethylformamide–ether (1:1). The product weighed 5.0 g (air dried), mp 109–112°. From the mother liquor, 0.65 g of product was obtained by adding more ether and chilling the mixture. The total yield was 5.65 g (100%). The crude product

[1] At Walter Reed Army Institute of Research, Washington, D.C.

Table I—2-Alkoxyiminomercaptan Derivatives



Compound	R_1	R_2	R_3	X	Boiling Point or Melting Point (with Decomposition)	Yield, %	Composition	Refractive Index
I	CH_3	H	C_2H_5		180–185°	94	$C_5H_{10}NNaO_4S_2$	—
II	CH_3	CH_3	C_2H_5		162–164°	56	$C_6H_{12}NNaO_4S_2$	—
III	H	C_2H_5	C_2H_5		128–130°	70.5	$C_6H_{12}NNaO_4S_2$	—
IV	—$(CH_2)_3$—		C_2H_5		220–222°	71	$C_7H_{12}NNaO_4S_2$	—
V	—$(CH_2)_4$—		C_2H_5		154–157°	44	$C_8H_{14}NNaO_4S_2$	—
VI	CH_3	C_2H_5	C_2H_5	S_2O_3Na	139–140°	54	$C_7H_{16}NNaO_5S_2$[a]	—
VII	C_6H_5	H	C_2H_5		135–136°	25	$C_{10}H_{12}NNaO_4S_2$	—
VIII	CH_3	H	CH_3		164–165°	97	$C_4H_8NNaO_4S_2$	—
IX	C_6H_5	H	CH_3		156–158°	92	$C_9H_{12}NNaO_5S_2$[a,b]	—
X	—$(CH_2)_3$—		CH_3		185–190°	76	$C_6H_{10}NNaO_4S_2$	—
XI	CH_3	CH_3	CH_3		151–153°	53	$C_5H_{12}NNaO_5S_2$[a]	—
XII	CH_3	H	C_2H_5		117–119°[c]	89	$C_8H_{16}BrN_3OS$	—
XIII	C_6H_5	H	C_2H_5		133–135°[c]	57	$C_{13}H_{18}BrN_3OS$	—
XIV	CH_3	H	CH_3		168–170°	90	$C_7H_{14}BrN_3OS$	—
XV	C_6H_5	H	CH_3		175–176°	86	$C_{12}H_{16}BrN_3OS$	—
XVI	C_6H_5	H	C_2H_5	$SCOSC_2H_5$	132–134°/0.1 torr	35	$C_{13}H_{17}NO_2S_2$	n_D^{27} 1.5852
XVII	C_6H_5	H	C_2H_5	$SCS_2C_2H_5$	174–176°/0.1 torr	41	$C_{13}H_{17}NOS_3$[d]	$n_D^{21.5}$ 1.6354
XVIII	C_6H_5	H	CH_3	$SCOSC_2H_5$	128–130°/0.025 torr	56	$C_{12}H_{15}NO_2S_2$[e]	n_D^{22} 1.5998
XIX	C_6H_5	H	CH_3	$SCS_2C_2H_5$	145–147°/0.025 torr	42	$C_{12}H_{15}NOS_3$[f]	$n_D^{21.5}$ 1.6477
XX	CH_3	CH_3	C_2H_5	$SCOSC_2H_5$	78–80°/0.02 torr	68	$C_9H_{17}NO_2S_2$	$n_D^{29.5}$ 1.5232
XXI	CH_3	CH_3	C_2H_5	$SCS_2C_2H_5$	90–92°/0.02 torr	31	$C_9H_{17}NOS_3$	$n_D^{21.5}$ 1.5815
XXII	CH_3	CH_3	CH_3	$SCOSC_2H_5$	75–77°/0.025 torr	54	$C_8H_{15}NO_2S_2$	n_D^{22} 1.5350
XXIII	CH_3	CH_3	CH_3	$SCS_2C_2H_5$	85–87°/0.025 torr	51	$C_8H_{15}NOS_3$[g]	n_D^{22} 1.5934
XXIV	CH_3	H	C_2H_5	$SCOSC_2H_5$	154–156°/26 torr	60	$C_8H_{15}NO_2S_2$[h]	n_D^{27} 1.5294
XXV	CH_3	H	C_2H_5	$SCS_2C_2H_5$	96–98°/0.03 torr	52	$C_8H_{15}NOS_3$	$n_D^{21.5}$ 1.6239
XXVI	CH_3	H	CH_3	$SCOSC_2H_5$	72–74°/0.02 torr	58	$C_7H_{13}NO_2S_2$	n_D^{22} 1.5420
XXVII	CH_3	H	CH_3	$SCS_2C_2H_5$	93–95°/0.02 torr	56	$C_7H_{13}NOS_3$[i]	n_D^{22} 1.6044
XXVIII	—$(CH_2)_3$—		C_2H_5	$SCOSC_2H_5$	100–102°/0.03 torr	59	$C_{10}H_{17}NO_2S_2$	$n_D^{29.5}$ 1.5460

[a] Analyzed as the monohydrate. [b] Calc. for: C, 35.87; N, 4.65. Found: C, 35.22; N, 4.26. [c] Melt without decomposition. [d] Calc. for: C, 52.17. Found: C, 53.09. [e] Calc. for: C, 53.53; S, 23.79. Found: C, 52.88; S, 23.33. [f] Calc. for: S, 33.68. Found: 32.11. [g] Calc. for: N, 3.91. Found: 5.71. [h] Calc. for: S, 28.96. Found: 29.98. [i] Calc. for: S, 43.05. Found: 42.76.

Table II—Analytical Data for 2-Alkoxyiminomercaptan Derivatives

	Analysis							
	Calculated				Found			
Compound	C	H	N	S	C	H	N	S
I	25.53	4.28	5.95	27.26	25.38	4.41	5.87	27.36
II	28.91	4.85	5.62	25.72	28.67	4.74	5.67	25.61
III	28.91	4.85	5.62	25.72	28.97	4.91	5.76	25.48
IV	32.18	4.63	5.36	24.54	32.11	4.83	5.53	24.42
V	34.90	5.13	5.09	23.29	34.84	5.28	5.22	23.19
VI	29.89	5.73	4.98	22.79	30.04	5.81	5.11	22.73
VII	40.40	4.07	4.71	21.57	40.25	4.10	4.65	21.63
VIII	21.72	3.65	6.33	28.99	21.64	3.80	6.25	28.84
IX	35.87	4.01	4.65	21.28	35.22	3.80	4.26	21.05
X	29.15	4.08	5.66	25.93	29.21	4.18	5.78	25.90
XI	23.71	4.78	5.53	25.32	23.49	4.59	5.59	25.44
XII	34.05	5.71	14.89	11.36	34.18	5.64	14.79	11.31
XIII	45.35	5.27	12.21	9.31	45.41	5.39	12.27	9.30
XIV	31.35	5.26	15.67	11.96	31.46	5.51	15.53	11.90
XV	43.64	4.88	12.72	9.71	43.85	5.01	12.70	9.75
XVI	55.12	6.00	4.94	22.61	55.09	6.00	5.08	22.68
XVII	52.17	5.68	4.68	32.10	53.09	5.79	4.59	32.05
XVIII	53.53	5.57	5.20	23.79	52.88	5.66	5.33	23.33
XIX	50.52	5.26	4.87	33.68	50.61	5.34	4.67	32.11
XX	45.91	7.23	5.94	27.23	46.11	7.34	6.09	27.24
XXI	43.20	6.77	5.60	38.40	43.52	6.32	5.56	38.33
XXII	43.42	6.78	6.33	28.96	43.90	6.89	5.98	29.00
XXIII	40.51	6.33	3.91	40.51	40.56	6.49	5.71	40.50
XXIV	43.43	6.79	6.33	28.96	43.49	6.52	6.32	29.98
XXV	40.51	6.32	5.91	40.51	40.54	6.47	5.98	40.35
XXVI	40.58	6.28	6.76	30.91	41.79	6.11	6.61	30.54
XXVII	37.66	5.82	6.28	43.05	37.56	5.71	6.26	42.73
XXVIII	48.58	6.96	5.67	25.91	48.75	6.83	5.93	26.06

was then crystallized from 15 ml of isopropyl alcohol to yield 5 g (89%) of white plates, mp 117–119°.

Ethyl 2-Methoxyiminoalkyl Trithiocarbonates—Into a 100-ml round-bottom flask was placed 4 g (0.025 mole) of sodium ethyl trithiocarbonate in 20 ml of acetone, and 5.7 g (0.025 mole) of the *O*-methyl ether of ω-bromoacetophenone oxime in 10 ml of acetone was added with stirring. A white solid precipitate formed immediately and the solution became warm. The addition of 80 ml of water caused an oil to separate while the original precipitate went into solution. The oil was extracted with 15-ml portions of ether, and the extracts were combined and dried over anhydrous sodium sulfate. The ether was removed by distillation, and the remaining oil was distilled under reduced pressure.

Ethyl *S*-(2-Methoxyimino) Alkyl Dithiocarbonates—Into a round-bottom flask was placed 3.65 g (0.025 mole) of sodium *O*-methyl dithiocarbonate in 20 ml of acetone. To the stirred solution was added 5.7 g (0.025 mole) of the *O*- ethyl ether of ω-bromoacetophenone oxime in 10 ml of acetone. A white solid precipitate formed immediately and the solution became warm. When 80 ml of water was added, an oil separated while the original precipitate went into solution. The oil was then extracted with three 15-ml portions of ether. The extracts were combined and dried over anhydrous sodium sulfate. The ether was removed by distillation, and the remaining oil was distilled under reduced pressure.

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Suppression of Benzoic Acid Adsorption on Sulfamethazine by Polyvinylpyrrolidone: Effect of Contact Time

R. N. NASIPURI and SALEH A. H. KHALIL ˣ

Abstract □ The suppressive effect of polyvinylpyrrolidone on benzoic acid adsorption by sulfamethazine was found to be time dependent. First-order plots showed that benzoic acid apparently diffused from the bulk to the sulfonamide surface through the polymeric "protective" film; therefore, the effect was dependent on the polymer–sulfonamide ratio. An increase in the polymer concentration slowed down the rate of benzoic acid migration. This effect cannot be attributable solely to an increase in bulk viscosity since nonpolymeric viscosity-imparting agents, *e.g.*, glycerol and syrup, did not appreciably inhibit adsorption.

Keyphrases □ Benzoic acid—suppression of adsorption on sulfamethazine by polyvinylpyrrolidone, effect of contact time □ Sulfamethazine—adsorption of benzoic acid, suppression by polyvinylpyrrolidone, effect of contact time □ Polyvinylpyrrolidone—suppression of benzoic acid adsorption on sulfamethazine, effect of contact time □ Adsorption—benzoic acid on sulfamethazine, suppression by polyvinylpyrrolidone, effect of contact time

Protective colloids have been used to inhibit some surface phenomena such as crystal growth and adsorption of solutes onto solid surfaces. Polyvinylpyrrolidone appears to be exceptionally effective for these purposes. For example, the polymer was effective in suppressing the crystal growth of sulfathiazole (1) and inhibiting the interconversion of two forms of sulfaline (sulfamethoxypyrazine) (2). The suppressive effect of polyvinylpyrrolidone on cyanocobalamin adsorption by talc was reported (3). Recently, the authors found that, in the presence of as little as 5 mg % of this polymer, benzoic acid adsorption on sulfamethazine was completely inhibited (4, 5).

Table I—Lag Period (in Hours)[a] at Various Sulfamethazine–Polyvinylpyrrolidone Concentrations

Polyvinylpyrrolidone Concentration, g %	Sulfamethazine Concentration, g %				
	0.1	0.4	1	4	10
0.02	2	1	1	1	1
0.04	4	2	2	2	1
0.10	8	6	4	4	2
0.20	10	10	6	4	4
0.50	20	12	8	6	4
1.00	24	16	12	8	8

[a] Average of four runs (±0.2 hr).

The effect of time on the suppressive effect of protective polymers has received little attention. The present report concerns the effect of contact time on the suppressive role of polyvinylpyrrolidone on benzoic acid adsorption by sulfamethazine.

EXPERIMENTAL

Materials—Sulfamethazine[1], BP grade, was used; the powder had a mean volume–surface diameter of 32.6 μm. Benzoic acid[2] was of BP quality and the polyvinylpyrrolidone[3] sample had an av-

[1] Sulfadimidine, Imperial Chemical Industries Ltd., Cheshire, England.
[2] British Drug Houses Ltd., Poole, England.
[3] Plasdone K 29–32, GAF Corp., New York, N.Y.