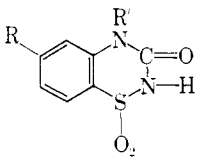
TABLE III

BENZOTHIADIAZINES



No.	R	R'	Yield, %	Recrystn. solvent[a]	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
27	H	*n*-Butyl	45	W	139–140	$C_{11}H_{14}N_2O_3S$	51.96	51.76	5.55	5.45	11.02	10.86
28	CH_3	*n*-Butyl	62.5	B	171–172[b]	$C_{12}H_{16}N_2O_3S$	53.72	53.70	6.01	6.07	10.44	10.57
29	H	Benzyl	50	M	205–207	$C_{14}H_{12}N_2O_3S$	53.33	58.56	4.20	4.44	9.27	9.68
30	H	Cyclohexylmethyl	37	E–H	202–204	$C_{14}H_{18}N_2O_3S$	57.13	56.94	6.17	5.99	9.52	9.33
31	H	Phenethyl	82.5	E–H	160	$C_{15}H_{14}N_2O_3S$	59.60	59.71	4.67	4.65	9.27	9.43
32	CH_3	Phenethyl	58	B	155–156	$C_{16}H_{16}N_2O_3S$	60.75	61.02	5.10	5.17	8.86	8.68
33	H	4-Pyridylethyl	20	D	249–252 dec.	$C_{14}H_{13}N_3O_3S$	55.44	55.16	4.32	4.95	13.86	13.99
34	H	2-Pyridylmethyl	59	D-H–Et	259–264 dec.	$C_{13}H_{11}N_3O_3S$	53.98	53.83	3.83	4.04	14.53	14.36
35	H	3-Pyridylmethyl	65	D	289–290 dec.	$C_{13}H_{11}N_3O_3S$	53.98	53.53	3.83	3.97	14.53	14.63
36	H	3-Piperidylmethyl[c]	20	W	332 dec.	$C_{13}H_{17}N_3O_3S$	52.87	52.98	5.80	6.02	14.23	14.15
37	H	4-Pyridylmethyl	92	D	300	$C_{13}H_{11}N_3O_3S$	53.98	53.82	3.83	4.03	14.53	14.41
38	CH_3	4-Pyridylmethyl	48	D-H–Et	297–307 dec.	$C_{14}H_{13}N_3O_3S$	55.44	54.39	4.32	4.64	13.86	13.72
39	H	*n*-Heptyl	89	B–H	92–93	$C_{14}H_{20}N_2O_3S$	56.74	56.60	6.80	7.14	9.45	9.24

[a] See Table I. [b] Lit.[2] m.p. 173–174°. [c] By catalytic reduction of **35** with PtO_2.

3-Oxo-4-(4-pyridylethyl)-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide (33).—A mixture of 21.5 g. (0.078 mole) of **21** and 4.65 g. (0.078 mole) of urea was heated for 1 hr. at 150–170° under a stream of nitrogen. The residue was heated with ethanol and cooled, and a colorless solid was filtered off, yield 6.0 g., m.p. 239–245°. Crystallization from methanol, then from a minimum amount of hot dimethylformamide to which ether was added to incipient turbidity gave 2.1 g., m.p. 253–256°. When heated at 200–205°, the product obtained analyzed for loss of vinylpyridine.

The Synthesis of N-Substituted 2-Aminoethanethiosulfuric Acids

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Almost all aminoalkylthiosulfuric acids whose pharmacological properties have been reported in the literature thus far have a primary amino group. A series of N-monosubstituted 2-aminoethanethiosulfuric acids was, therefore, synthesized to determine the effect of the presence of secondary amino groups in alkyl thiosulfates (Bunte salts) on their biological activity. The procedures employed in their synthesis were method A, used when the direct alkylation of the sodium salt of 2-aminoethanethiosulfuric acid was feasible, and method B, used mainly to prepare those Bunte salts in which the amino group is attached to a secondary carbon atom of an alkyl chain. This latter method involved the conversion of an N-alkylaminoethanol to the bromide hydrobromide which was allowed to react subsequently with one equivalent of sodium thiosulfate in aqueous or aqueous–ethanolic solution.

Experimental[1]

Method A. N-Alkylaminoethanethiosulfuric Acids.—To 0.25 mole of sodium hydroxide dissolved in 300 ml. of warm 95% ethanol was added rapidly with stirring a hot solution of 0.25 mole of 2-aminoethanethiosulfuric acid[2] in 25 ml. of water. To the mixture, which was then heated under reflux, there was added dropwise over 1.5 hr. 0.20 mole of the primary alkyl bromide. Heating and stirring were continued for 4.5 hr. after the complete addition of the halide. About 150 ml. of ethanol was then distilled from the mixture and replaced with an equal volume of water. The solution was neutralized with glacial acetic acid and cooled overnight causing the crystalline product to separate. The Bunte salt was collected by filtration, air-dried, and recrystallized several times to remove the contaminant resulting from dialkylation.

Method B. 2-(*sec*-Alkylamino)ethanols.—These compounds were prepared from 2-aminoethanol and *sec*-alkyl bromides by the method previously described[3] except that xylene was used as the solvent instead of benzene. A mixture of 0.5 mole of the alkyl bromide, 1.5 moles of 2-aminoethanol, and 150 ml. of xylene was heated under reflux with stirring for 21–37 hr. The two layers were separated and the lower layer containing mainly 2-aminoethanol was washed with three 20-ml. portions of benzene. The benzene extracts and the xylene layer were combined, washed with three 20-ml. portions of water, and dried over anhydrous magnesium sulfate. The solvents were removed on a steam bath by the use of an aspirator and the residue was distilled under reduced pressure through a Vigreux column. Yields ranged from 56–70%.

N-Alkylaminoethyl Bromide Hydrobromides.—These compounds were prepared according to the procedure of Cortese[4] by treating the corresponding N-alkylaminoethanol with 48% hydrobromic acid and by slowly distilling the water formed in the course of the reaction.

(1) Melting points are uncorrected and were determined on a Fisher-Johns melting point apparatus. The rate of heating influences the melting and decomposition points of aminoalkyl Bunte salts. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by Mr. Joseph Allcino, Metuchen, N. J.

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TABLE I

N-ALKYL- AND N-ARALKYLAMINOETHANETHIOSULFURIC ACIDS

$RNHCH_2CH_2SSO_3H$

R	M.p., °C.	% yield[a]	Method of synthesis	Recrystn. solvent	Molecular formula	Calcd., % C	Calcd., % H	Calcd., % N	Calcd., % S	Found, % C	Found, % H	Found, % N	Found, % S
Methyl	163–163.5	58.4	B[b]	H_2O–EtOH	$C_3H_9NO_3S_2$	21.04	5.29	8.18	37.45	20.94	5.28	7.88	37.17
Ethyl	183–184.5 dec.	56.7	B[c]	H_2O–EtOH	$C_4H_{11}NO_3S_2$	25.93	5.96	7.56	34.61	25.64	6.25	7.31	34.46
n-Propyl	173 dec.	80.3	B[d]	H_2O	$C_5H_{13}NO_3S_2$	30.13	6.57	7.03	32.18	30.26	6.97	6.90	32.62
n-Butyl	159–160	68.7	B[c]	H_2O	$C_6H_{15}NO_3S_2$	33.78	7.09	6.57	30.06	33.74	6.85	6.49	29.78
n-Pentyl	183–184 dec.	18.3	A	H_2O	$C_7H_{17}NO_3S_2$	36.98	7.54	6.16	28.21	37.11	7.44	6.32	28.47
n-Hexyl	182 dec.	26.5	A	H_2O	$C_8H_{19}NO_3S_2$	39.80	7.93	5.80	26.57	40.04	8.15	5.76	26.51
n-Heptyl	192–194 dec.	50.0	A	H_2O	$C_9H_{21}NO_3S_2$	42.32	8.29	5.49	25.11	42.65	8.55	5.68	24.99
n-Octyl	190–190.5 dec.	46.7	A	H_2O	$C_{10}H_{23}NO_3S_2$	44.58	8.60	5.20	23.80	44.91	8.90	5.20	23.74
n-Nonyl	194 dec.	20.0	A	10% EtOH	$C_{11}H_{25}NO_3S_2$	46.61	8.89	4.94	22.62	47.06	8.95	4.84	22.88
n-Decyl	190–192 dec.	37.6	A	10% EtOH	$C_{12}H_{27}NO_3S_2$	48.45	9.15	4.71	21.56	48.74	9.22	5.21	22.22
n-Undecyl	191–193	22.8	A	30% EtOH	$C_{13}H_{29}NO_3S_2$	50.12	9.39	4.50	20.59	50.39	9.37	4.22	20.67
n-Dodecyl	196–198 dec.	39.4	A	30% EtOH	$C_{14}H_{31}NO_3S_2$	51.65	9.60	4.30	19.70	51.81	9.80	3.94	19.11
n-Tridecyl	206.5–207 dec.	28.3	A	30% EtOH	$C_{15}H_{33}NO_3S_2$	53.05	9.79	4.13	18.89	53.43	9.82	4.04	18.96
n-Tetradecyl	207.5–208.5 dec.	21.3	A	50% EtOH	$C_{16}H_{35}NO_3S_2$	54.35	9.98	3.96	18.14	54.36	10.11	4.13	18.16
n-Pentadecyl	203.5 dec.	26.6	A	50% EtOH	$C_{17}H_{37}NO_3S_2$	55.54	10.15	3.81	17.44	55.93	9.88	3.94	17.57
n-Hexadecyl	199–200 dec.	15.6	A	50% EtOH	$C_{18}H_{39}NO_3S_2$	56.65	10.30	3.67	16.80	56.84	10.17	3.85	16.70
n-Heptadecyl	197–197.5 dec.	30.5	A	60% EtOH	$C_{19}H_{41}NO_3S_2$	57.67	10.44	3.54	16.21	57.31	10.27	3.65	16.51
n-Octadecyl	190–191 dec.	14.7	A	60% EtOH	$C_{20}H_{43}NO_3S_2$	58.63	10.58	3.42	15.65	58.69	10.61	3.47	15.49
Isopropyl	189 dec.	65.3	B[c]	H_2O	$C_5H_{13}NO_3S_2$	30.13	6.57	7.03	32.18	30.23	6.65	7.09	32.57
t-Butyl	230–231 dec.	47.1	B[f]	H_2O	$C_6H_{15}NO_3S_2$	33.78	7.09	6.57	30.06	33.69	6.85	6.40	30.24
2-Heptyl	169.5–170 dec.	56.0	B	H_2O	$C_7H_{17}NO_3S_2$	42.32	8.29	5.49	25.11	42.44	8.18	5.61	25.38
2-Octyl	178–179	72.2	B[g]	MeCN	$C_{10}H_{23}NO_3S_2$	44.58	8.60	5.20	23.80	44.69	8.49	5.49	23.52
3-Octyl	124	50.0	B	H_2O	$C_{10}H_{23}NO_3S_2$	44.58	8.60	5.20	23.80	44.47	8.74	5.21	23.75
4-Octyl	117.5–118	69.8	B	H_2O	$C_{10}H_{23}NO_3S_2$	44.58	8.60	5.20	23.80	44.66	8.37	5.16	24.07
Cyclooctyl	190 dec.	64.8	B	H_2O	$C_{10}H_{21}NO_3S_2$	44.91	7.91	5.24	23.98	44.87	7.92	5.11	24.39
2-Ethyl-1-hexyl	145–146	4.9	A[h]	EtOH	$C_{10}H_{23}NO_3S_2$	44.58	8.60	5.20	23.80	44.57	8.84	5.00	23.95
Isononyl	195–197	24.0	A	H_2O	$C_{11}H_{25}NO_3S_2$	46.61	8.89	4.94	22.63	46.56	9.02	4.86	22.67
2-Nonyl	187–188	55.8	B	H_2O	$C_{11}H_{25}NO_3S_2$	46.61	8.89	4.94	22.63	46.71	8.79	4.96	22.62
3-Nonyl	141–142	29.1	B	Me_2CHOH	$C_{11}H_{25}NO_3S_2$	46.61	8.89	4.94	22.63	46.41	8.91	5.04	22.58
4-Nonyl	99	45.5	B	EtOAc	$C_{11}H_{25}NO_3S_2$	46.61	8.89	4.94	22.63	47.07	9.05	4.94	22.41
2-Decyl	189 dec.	59.2	B	50% EtOH	$C_{12}H_{27}NO_3S_2$	48.45	9.15	4.71	21.56	48.48	9.22	4.75	21.60
3-Decyl	128–130	56.0	B	EtOAc	$C_{12}H_{27}NO_3S_2$	48.45	9.15	4.71	21.56	48.72	9.26	4.37	21.44
2-Undecyl	193–194 dec.	71.1	B	45% EtOH	$C_{13}H_{29}NO_3S_2$	50.12	9.38	4.50	20.59	49.84	9.21	4.45	20.77
Benzyl	197–197.5 dec.	92.5	B[i]	H_2O	$C_9H_{13}NO_3S_2$	43.70	5.28	5.66	25.93	43.89	5.54	5.80	25.72
Phenethyl	186–186.5 dec.	14.9	A	H_2O	$C_{10}H_{15}NO_3S_2$	45.95	5.79	5.36	24.54	45.92	5.84	5.32	24.42
Phenylpropyl	173–174 dec.	29.9	A	H_2O	$C_{11}H_{17}NO_3S_2$	47.97	6.22	5.09	23.29	48.13	6.39	5.12	23.42
Phenoxyethyl	190 dec.	6.5	A[j]	H_2O	$C_{10}H_{15}NO_4S_2$	43.30	5.45	5.05	23.12	43.64	5.42	5.02	22.91

[a] Yields of thiosulfuric acids prepared by method A are based on alkyl bromides and yields of those prepared by method B are based on N-alkylaminoethyl bromide hydrobromides. [b] Reported m. p. 160° (K. Schimmelschmidt, H. Hoffmann, and E. Mundlos, *Chem. Ber.*, **96**, 38 (1963)). [c] Starting amino alcohol obtained from Eastman Organic Chemicals. [d] Because the b.p. of N-*n*-propylaminoethanol is not sufficiently different from that of 2-aminoethanol for convenient separation of the two compounds by distillation, the alcohol was prepared by treating *n*-propylamine with ethylene oxide by the method of J. H. Biel, *J. Am. Chem. Soc.*, **71**, 1306 (1949). [e] Starting amino alcohol obtained from Pennsalt Chemicals Corp. [f] Starting amino alcohol obtained from Rohm and Haas Company. [g] Starting amino alcohol obtained from Universal Oil Products Company. [h] Reaction ran 8 days. [i] Starting amino alcohol obtained from Miles Chemical Company. [j] Reaction ran 2 weeks.

N-Alkylaminoethanethiosulfuric Acids.—An equimolar mixture of sodium thiosulfate pentahydrate and an N-alkylaminoethyl bromide hydrobromide in water or water–ethanol, depending on the solubility of the latter reactant, was heated near the reflux temperature for approximately 1 hr. Completion of the reaction was indicated by failure of sulfur to precipitate from an aliquot of the solution which was acidified with mineral acid. In most instances, the Bunte salt was sufficiently water insoluble to crystallize from solution upon cooling. Solutions containing a Bunte salt which was relatively water soluble were concentrated and the product was separated from sodium bromide by crystallization. Several recrystallizations were required in order to obtain a pure, halide-free product.

2-(Trimethylammonium)ethyl Thiosulfate.—A solution of 23.7 g. (0.15 mole) of (2-chloroethyl)trimethylammonium chloride and 37.3 g. (0.15 mole) of sodium thiosulfate pentahydrate in 35 ml. of water was heated at reflux for 1 hr. On cooling, the crystalline product separated from solution. Recrystallization once from water followed by several treatments of the product with boiling methanol to remove remaining sodium bromide afforded 20.6 g. (69.1%) of 2-(trimethylammonium)ethyl thiosulfate, m.p. 267–269° dec.

Anal. Calcd. for $C_5H_{13}NO_3S_2$: C, 30.13; H, 6.57; N, 7.03; S, 32.18. Found: C, 30.11; H, 6.74; N, 7.04; S, 31.97.

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Aminooxyacetic Acid Derivatives

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Aminooxyacetic acid, being a derivative of hydroxylamine, lends itself to reactions with carbonyl compounds.[1–8] Earlier work[4,5] has shown that certain oxime derivatives such as these have exhibited plant growth inhibition[4] or vitamin K activity[5]; furthermore, aminooxyacetic acid itself has been reported[8] to have antibacterial activity. The compounds described here were prepared in order that they might be investigated as poten-

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