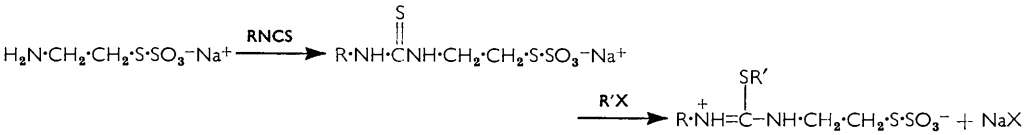
1228. N-*Linked Thiopseudourea Zwitterions*

By (the late) A. F. Ferris, O. L. Salerni, and B. A. Schutz

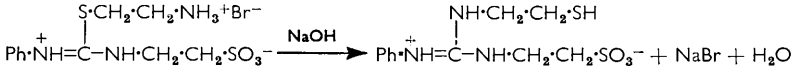
S-Linked thiopseudourea zwitterions have been prepared by the addition of thiourea to acrylic acids,[1] but no preparative method for the corresponding *N*-linked thiopseudourea zwitterions has been reported. We have synthesised the *N*-linked compounds by treating the sodium salts of certain amino-acids with alkyl or aryl isothiocyanates and subsequently alkylating the adduct.



The condensations were carried out in water–ethanol or in water–acetonitrile, and the intermediate amino-acid–isothiocyanate adduct was not isolated. The yields and m. p.s of a series of *N*-linked thiopseudourea zwitterions prepared from 2-aminoethylthiosulphuric acid and from taurine are given in the Table.

Extension of the method to other groups was limited by the difficulties in crystallising the zwitterions and in separating them from the by-product salt. All attempts to prepare zwitterions containing the carboxylic acid function from β-alanine failed for these reasons. Some of the products from 2-aminoethylthiosulphuric acid and taurine were uncrystallisable glasses. The zwitterion was usually separated from the by-product sodium salt by trituration in water or ethanol depending on the relative solubilities. Sodium bromide or iodide was separated from the zwitterion by selective crystallisation from water–ethanol or water–ethanol–acetone.

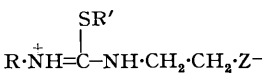
2-(2-Aminoethyl-3-phenyl-2-thiopseudoureido)ethanesulphonic acid, treated with an equivalent of base, rearranged to 2-[1-(2-mercaptoethyl)-2-phenyl-3-guanidino]ethanesulphonic acid.



The product, a gum, was converted by air oxidation into the solid disulphide, which was recovered in a 67% yield. "Transguanylation" rearrangements are commonly observed in compounds with the 2-aminoethyl-2-thiopseudourea structure.[2-5]

[1] H. Behringer and P. Zillikens, *Annalen*, 1951, **574**, 140.
[2] J. Y. Khym and D. G. Doherty, *J. Amer. Chem. Soc.*, 1957, **79**, 5663.
[3] D. G. Doherty, R. Shapira, and W. T. Burnett, jun., *J. Amer. Chem. Soc.*, 1957, **79**, 5667.
[4] J. Y. Khym, D. G. Doherty, and R. Shapira, *J. Amer. Chem. Soc.*, 1958, **80**, 3342.
[5] R. C. Clapp, L. Long, jun., and T. Hasselstrom, *J. Org. Chem.*, 1961, **26**, 1666.

2-(2-Alkyl-3-alkyl- or -aryl-thiopseudoureido)-ethylthiosulphuric or -ethanesulphonic acids



No.	R	R′	Z	Yield (%)	M. p.
1	Bu	Ph·CH_2	$-SSO_3^-$	80	157—158·5°
2	Bu^n	CH_2=CH·CH_2	$-SSO_3^-$	22	84—87
3	cyclo-C_6H_{11}	CH_2=CH·CH_2	$-SSO_3^-$	32	165·5—167
4	Ph	Me	$-SSO_3^-$	71	162·5—163·5 decomp.
5	Ph	Et	$-SSO_3^-$	75	160·5—161·5 decomp.
6	Ph	Pr^n	$-SSO_3^-$	88	162—163 decomp.
7	Ph	CH_2=CH·CH_2	$-SSO_3^-$	82	156—157
8	Ph	Bu^n	$-SSO_3^-$	60	129·5—131·5 decomp.
9	cyclo-C_6H_{11}	CH_2=CH·CH_2	$-SO_3^-$	83	230—231 decomp.
10	Ph	Ph·CH_2	$-SO_3^-$	93	244·5—245 decomp.
11	Ph	$Br^-H_3\overset{+}{N}\cdot CH_2\cdot CH_2$	$-SO_3^-$	68	209—213 decomp.

No.	Found (%) C	H	N	S	Empirical formula	Required (%) C	H	N	S
1	41·40	5·21	8·58	30·27	$C_{11}H_{16}N_2O_3S_3$	41·23	5·03	8·74	30·01
2	38·65	6·66	9·11	31·08	$C_{10}H_{20}N_2O_3S_3$	38·44	6·45	8·97	30·78
3	42·61	6·63	8·09	28·18	$C_{12}H_{22}N_2O_3S_3$	42·58	6·55	8·28	28·41
4	39·46	4·79	8·94	31·50	$C_{10}H_{14}N_2O_3S_3$	39·20	4·60	9·15	31·39
5	41·50	5·10	8·89	30·17	$C_{11}H_{16}N_2O_3S_3$	41·23	5·03	8·74	30·02
6	43·44	5·31	8·17	29·00	$C_{12}H_{18}N_2O_3S_3$	43·09	5·42	8·38	28·76
7	43·19	4·93	8·30	28·80	$C_{12}H_{16}N_2O_3S_3$	43·35	4·85	8·43	28·93
8	45·05	5·86	8·21	27·66	$C_{13}H_{20}N_2O_3S_3$	44·80	5·79	8·04	27·60
9	47·06	7·24	9·15	21·06	$C_{12}H_{22}N_2O_3S_2$	47·03	7·24	9·14	20·92
10	54·60	5·34	7·83	18·34	$C_{16}H_{18}N_2O_3S_2$	54·83	5·18	8·00	18·30
11	34·52	4·75	10·73	16·80	$C_{11}H_{18}BrN_3O_3S_2$ *	34·38	4·72	10·93	16·68

* Found: Br, 20·61; Calc.: 20·80%.

Experimental

All m. p.s are corrected.

2-(2-*Allyl*-3-*phenyl*-2-*thiopseudoureido*)*ethylthiosulphuric acid.* A suspension of 2-aminoethylthiosulphuric acid (15·7 g.) in ethanol (100 ml.) and sodium hydroxide (4·0 g.) in water (20 ml.) was treated with phenyl isothiocyanate (12·2 g.). The temperature rose from 24° to 36° and the mixture became homogeneous. After 1 hr., allyl chloride (9·2 g.) was added and the solution was refluxed for 3 hr. Evaporation of the solvents under reduced pressure gave a residue which was slurried with 50 ml. of anhydrous ethanol and filtered off, washed with ethanol (25 ml.), and dried under reduced pressure. The crude product (29·4 g.), triturated in 200 ml. of water, was filtered off and dried under reduced pressure, and afforded 2-(2-allyl-3-phenylthiopseudoureido)ethylthiosulphuric acid (24·6 g., 82%), m. p. 156—157° (decomp.). Recrystallisation of a sample (2·0 g.) from ethanol (200 ml.) gave an analytical sample (1·6 g.), m. p. 156—157°.

2-(2-*n*-*Butyl*-3-*phenyl*-2-*thiopseudoureido*)*ethylthiosulphuric acid.* When the preceding 2-aminoethylthiosulphuric acid–phenylisothiocyanate adduct was treated with n-butyl bromide (12·3 g.), no solid crystallised. A viscous gum separated on pouring the mixture into water (500 ml.). Upon trituration with anhydrous ethanol (50 ml.) the gum crystallised after several hours. The crude 2-(2-*n*-*butyl*-3-*phenyl*-2-*thiopseudoureido*)*ethylthiosulphuric acid* (18·7 g., 60%), which was filtered off and dried under reduced pressure, had m. p. 149—151·5° (decomp.). One recrystallisation from ethanol reduced the m. p. to 129·5—131·5°, but the m. p. was not changed after an additional recrystallisation.

2-(2-*Allyl*-3-*cyclohexyl*-2-*thiopseudoureido*)*ethylthiosulphuric acid.* Cyclohexyl isothiocyanate (12·7 g.) in 95% ethanol (100 ml.) was added to a solution of 2-aminoethylthiosulphuric acid

(15·7 g.) and sodium hydroxide (4·0 g.) in water (30 ml.). The mixture was refluxed 1 hr., cooled, treated with allyl chloride (9·2 g.), and refluxed for an additional 2 hr. When the mixture was evaporated under reduced pressure and the residue treated with anhydrous ethanol (75 ml.), sodium chloride (5·9 g., 102%) remained insoluble. Evaporation of the ethanol solution gave a glass which was redissolved in anhydrous ethanol. After several hours, 2-(2-*allyl*-3-*cyclohexyl*-2-*thiopseudoureido*)*ethylthiosulphuric acid* (7·9 g., 26%), m. p. 162—166°, precipitated and was filtered off, washed with ethanol, and dried under reduced pressure. Additional product (1·9 g., 6%) separated from the filtrate. An analytical sample, m. p. 165·5—167°, was obtained after two recrystallisations from ethanol (30 ml./g.).

2-(2-*Aminoethyl*-3-*phenyl*-2-*thiopseudoureido*)*ethanesulphonic acid hydrobromide.* A two-phase mixture containing taurine (12·5 g.), sodium hydroxide (4·0 g.), water (25 ml.), and acetonitrile (75 ml.) was stirred rapidly and treated with phenyl isothiocyanate (13·5 g.). After 30 min., the mixture became homogeneous, and 2-bromoethylamine hydrobromide (24·6 g.) was added. When the solution was refluxed for 2 hr., the mixture again separated into two phases. Evaporation of the solvents gave a thick syrup which was dissolved in anhydrous alcohol (150 ml.). A solid precipitated slowly after acetone (50 ml.) was added. After 3 hr., crude 2-(2-*aminoethyl*-3-*phenyl*-2-*thiopseudoureido*)*ethanesulphonic acid hydrobromide* (23·1 g.), m. p. 216—219° (decomp.), was filtered off and dried under reduced pressure. More (3·1 g., total 68%) was collected from the filtrate after 5 days. A portion of the product (19·0 g.) dissolved in warm water (80 ml.) was added to anhydrous ethanol (400 ml.) and acetone (50 ml.). The compound (9·6 g.), m. p. 209—213° (decomp.), that precipitated after 3 hr. was analysed.

Disulphide of 2-[1-(2-*mercaptoethyl*)-2-*phenyl*-3-*guanidino*]*ethanesulphonic acid.* Sodium hydroxide solution (5·6 ml., 10%) was added to 2-(2-aminoethyl-3-phenyl-2-thiopseudoureido)-ethanesulphonic acid (5·4 g.) in water (30 ml.). After 1 hr., evaporation of the solvent gave a syrup which was covered with ethanol (50 ml.) and left exposed to air for 2 weeks. Filtration of the crystallised material gave the *disulphide* (2·8 g., 67%), m. p. 207—215°. Recrystallisation from ethanol–water afforded an analytical sample (1·6 g.), m. p. 233—236° (Found: C, 43·5; H, 5·45; N, 13·9; S, 21·4. $C_{22}H_{32}N_6O_6S_4$ requires C, 43·7; H, 5·3; N, 13·9; S, 21·2%).

This work was supported by the U.S. Army Medical Research and Development Command, Department of the Army.

CHEMISTRY DIVISION, MIDWEST RESEARCH INSTITUTE,
KANSAS CITY, MISSOURI, U.S.A.

[*Received, May 6th,* 1965.]