New Compounds

2-(Purin-6-yl)-2-thiopseudourea Hydrochloride

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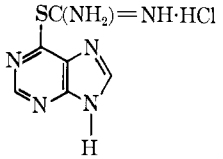
The reaction of 6-chloropurine with thiourea in refluxing ethanol has been reported to give 6-mercaptopurine monohydrate and 2,2-diamino-2H-thiazolo[3,4,5-*q*,*h*]purine.[2,3] Although 2-(purin-6-yl)-2-thiopseudourea hydrochloride (I) was postulated to be an intermediate in this reaction, this compound was not isolated and characterized. We have found that I can be prepared in 97% yield by allowing 6-chloropurine to react with thiourea in refluxing acetonitrile.



I

Experimental Section[4]

2-(Purin-6-yl)-2-thiopseudourea Hydrochloride (I).—A mixture of 6-chloropurine (0.47 g, 0.003 mole), thiourea (0.23 g, 0.003 mole), and acetonitrile (6 ml) was refluxed for 1 hr after which time the mixture was cooled with an ice–water bath. The resulting yellow precipitate was collected on a filter, washed with cold acetonitrile, and dried to give 0.67 g (97% yield) of I as a water-soluble yellow powder: mp 243° dec; infrared, ν_{max}^{KBr} 2941, 1656, 1590, 1565, 1408 sh, 1389, 1321, 1269, 1236, 1155, 1101, 994, 924, 848, 792, 694, and 638 cm^{-1}; far-infrared, ν_{max}^{KBr} 640, 616, 527, 484, and 454 cm^{-1}; ultraviolet, λ_{max}^{EtOH} 212 mμ (ϵ 14,100), 282 (10,400), and 330 (3000).

Anal. Calcd for $C_6H_7ClN_6S$: C, 31.24; H, 3.06; N, 36.43. Found: C, 31.42; H, 3.20; N, 36.00.

Conversion of I to 6-Mercaptopurine Monohydrate. A.—A solution of I (0.35 g, 0.0015 mole) in ethanol (5 ml) was refluxed for 1 hr. The yellow solid which precipitated after the solution had cooled was collected on a filter and dried to give 0.21 g (81% yield) of crude 6-mercaptopurine monohydrate, mp 269° dec. A single recrystallization from H_2O raised the melting point to 295–300° dec (lit.[2] mp 313–315° dec), no depression on admixture with an authentic sample, infrared spectrum essentially identical with that of an authentic sample.

B.—A solution of I (0.50 g, 0.0022 mole) in H_2O (6 ml) was titrated with 2 *N* NaOH to the phenolphthalein end point. The yellow solid which precipitated was collected on a filter and dried to give 0.27 g (73% yield) of 6-mercaptopurine monohydrate, mp 312° dec, no depression on admixture with an authentic sample.

(1) To whom inquiries should be directed.

(2) A. Bendich, P. J. Russell, Jr., and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).

(3) C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **31**, 1417 (1966).

(4) Melting points were determined with a Mel-Temp capillary melting point apparatus and are uncorrected. The elemental analysis was performed by Dr. G. Weiler and Dr. F. Strauss, Microanalytical Laboratory, Oxford, England. The infrared data were obtained with a Beckman IR 8 infrared spectrophotometer. The far-infrared data were obtained with a Perkin-Elmer Model 21 double-beam infrared spectrophotometer which was fitted with a CsBr prism and purged with nitrogen. The ultraviolet data were obtained with a Bausch and Lomb Spectronic 505 spectrophotometer.

Eugenolglycolic Acid Derivatives

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The bactericidal quality of eugenol and the exhibition by eugenolglycolic acid amides of hypnotic, sedative, anticonvulsive, and anesthetic activities[2] prompted us to use eugenolglycolic acid as the starting material for the synthesis of compounds of possible pharmacological interest, including amides, thioureas, hydrazides, hydrazones, and a thiosemicarbazide. Conventional methods of preparation have been used. Some of the compounds prepared are described in the experimental section and others are listed in Tables I–III.

Experimental Section[3]

Eugenolglycolic acid was prepared by us from eugenol and chloroacetic acid in the presence of alkali and was crystallized from benzene; mp 103° (lit.[4] mp 81, 75, 100°).

Preparation of Amides. A.—A cold solution of 2.22 g of eugenolglycolic acid in benzene was treated with 0.75 ml of $SOCl_2$. The solution was allowed to warm up gradually and, after the brisk evolution of HCl had subsided, it was refluxed for 1 hr. Excess $SOCl_2$ and benzene were then removed under reduced pressure, leaving behind a pale brown, pungent-smelling oil.

B.—The acid chloride was added dropwise to a solution of 0.01 mole of the amine in benzene containing 1 ml of pyridine to give the amide.

Preparation of Thioureas. A.—Eugenolglycolic acid chloride was added dropwise to a stirred solution of 0.38 g of ammonium thiocyanate in 4.0 ml of dry acetone. After the addition was complete, the mixture was refluxed for 15 min and then filtered to remove the NH_4Cl.

B.—To the filtrate, now containing eugenolglycolic acid isothiocyanate, was added dropwise a solution of 0.01 mole of the amine in acetone. The mixture was refluxed gently for 1 hr. On cooling, crystals of the thiourea separated out.

C.—Eugenolglycolic acid thiourea was prepared by refluxing 22.2 g of eugenolglycolic acid and 7.6 g of thiourea in toluene for 15 hr. The toluene was then removed under reduced pressure, leaving behind a residue which was recrystallized three times from ethanol to give white needles (see Table II).

Preparation of Hydrazides. A.—The primary hydrazide was prepared by converting the acid chloride to the ethyl ester and subsequently treating the ester with 80% hydrazine hydrate in the usual manner; white fluffy needles, mp 69° (10% EtOH), yield 87.6%.

Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.01; H, 6.83; N, 11.85. Found: C, 61.22; H, 6.90; N, 11.67.

B.—The *sym*-diacyl hydrazide was prepared by adding the acid chloride dropwise to 80% hydrazine hydrate and then refluxing for 0.5 hr; white needles, mp 124° (95% alcohol), yield 86.18%.

Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.27; H, 6.34; N, 6.29.

Hydrazo Hydrazones.—Molar proportions of the primary hydrazide and the carbonyl compound were refluxed in ethanol for 3 hr. Either crystals of the hydrazones separated on cooling the reaction mixture or the reaction mixture was worked up by customary procedures to yield the hydrazones.

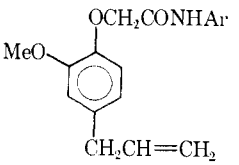
(1) To whom inquiries should be addressed: Department of Chemistry, The University of Mississippi, University, Miss. 38677.

(2) J. E. Thuillier, F. Litvan, and W. Stoll, U. S. Patent 2,911,440 (1959); *Chem. Abstr.*, **54**, 4498*b* (1960).

(3) Melting points were observed in capillary tubes and are corrected.

(4) M. Saarbach, *J. Prakt. Chem.*, **21**, 158 (1880); C. Gassmann and E. Krafft, *Ber.*, **28**, 1870 (1895); R. Clauser, *Chem. Zentr.*, **72**, 1049 (1901).

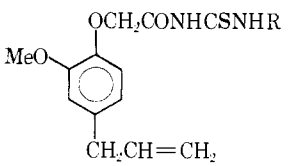
TABLE I



Ar	Mp, °C[a]	% yield	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
4-BrC_6H_4	91	78	$C_{18}H_{18}BrNO_3$	57.47	4.81	3.72	57.24	4.83	3.83
2-$CH_3C_6H_4$	71	57	$C_{19}H_{21}NO_3$	73.29	6.80	4.50	73.40	6.86	4.55
4-$OCH_3C_6H_4$	76	43	$C_{19}H_{21}NO_4$	69.71	6.47	4.28	69.74	6.41	4.14
2-$OC_2H_5C_6H_4$	56	48	$C_{20}H_{23}NO_4$	70.36	6.79	4.10	70.29	7.06	4.07
3-$OC_2H_5C_6H_4$	82	49	$C_{20}H_{23}NO_4$	70.36	6.79	4.10	70.19	6.95	4.21
4-$OC_2H_5C_6H_4$	76	30	$C_{20}H_{23}NO_4$	70.36	6.79	4.10	70.19	6.67	4.20
2-$NO_2C_6H_4$	102	76	$C_{18}H_{18}N_2O_5$	63.16	5.30	8.18	63.26	5.24	8.44
3-$NO_2C_6H_4$	91	78	$C_{18}H_{18}N_2O_5$	63.16	5.30	8.18	63.32	5.25	8.49
4-$NO_2C_6H_4$	118	81	$C_{18}H_{18}N_2O_5$	63.16	5.30	8.18	63.12	5.59	8.32
2-$CO_2HC_6H_4$	115	23	$C_{19}H_{19}NO_5$	66.84	5.61	4.10	66.80	5.60	4.18
3-$CO_2HC_6H_4$	156	29	$C_{19}H_{19}NO_5$	66.84	5.61	4.10	66.56	5.69	3.93
4-$CO_2HC_6H_4$	175	28	$C_{19}H_{19}NO_5$	66.84	5.61	4.10	67.10	5.68	4.24
$C_{10}H_7$[a]	78	65	$C_{22}H_{21}NO_3$	76.05	6.09	4.03	76.01	6.01	4.11
$C_{10}H_7$[b]	102	60	$C_{22}H_{21}NO_3$	76.05	6.09	4.03	75.99	6.16	4.00

[a] α-Naphthyl. [b] β-Naphthyl. [c] Crystallization solvent: 95% ethanol.

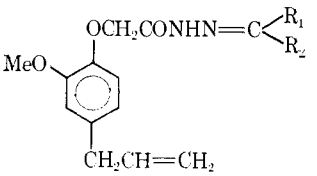
TABLE II



R	Mp, °C[a]	% yield	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H[b]	105	33	$C_{13}H_{16}N_2O_3S$	55.71	5.76	9.99	55.60	5.87	9.91
C_6H_5	192	42	$C_{19}H_{20}N_2O_3S$	64.03	5.66	7.86	64.26	5.65	7.73
2-BrC_6H_4	76	36	$C_{19}H_{19}BrN_2O_3S$	52.42	4.40	6.43	52.47	4.48	6.50
3-BrC_6H_4	197	59	$C_{19}H_{19}BrN_2O_3S$	52.42	4.40	6.43	52.60	4.52	6.45
4-BrC_6H_4	95	57	$C_{19}H_{19}BrN_2O_3S$	52.42	4.40	6.43	52.50	4.27	6.35
4-$CH_3C_6H_4$	195	66	$C_{20}H_{22}N_2O_3S$	64.85	5.99	7.56	65.03	5.91	7.45
4-$OC_2H_5C_6H_4$	183	68	$C_{21}H_{24}N_2O_4S$	62.99	6.04	6.99	63.16	6.36	7.24
3-$NO_2C_6H_4$	199	54	$C_{19}H_{19}N_3O_5S$	56.85	4.77	10.46	57.12	4.70	10.54
4-$NO_2C_6H_4$	129	38	$C_{19}H_{19}N_3O_5S$	56.85	4.77	10.46	56.87	4.85	10.39

[a] Crystallization solvent: 95% ethanol. [b] Prepared by method C under preparation of thioureas in the Experimental Section.

TABLE III



R_1	R_2	Mp, °C[a]	% yield	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
C_6H_5	H	88	62	$C_{19}H_{20}N_2O_3$	70.35	6.21	8.63	70.42	6.20	8.58
2-OHC_6H_4	H	213	76	$C_{19}H_{20}N_2O_4$	67.04	5.92	8.23	67.25	6.05	8.15
4-$NO_2C_6H_4$	H	117	66	$C_{19}H_{19}N_3O_5$	61.78	5.18	11.37	61.76	5.14	11.37
4-$OCH_3C_6H_4$	H	97[b]	59	$C_{20}H_{22}N_2O_4$	67.78	6.26	7.90	66.85	6.42	7.77
C_4H_3O[c]	H	120[b]	44	$C_{17}H_{18}N_2O_4$	64.97	5.77	8.91	64.78	6.01	9.09
C_6H_5	CH_3	126[d]	37	$C_{20}H_{22}N_2O_3$	70.98	6.55	8.27	71.03	6.52	8.27
C_6H_5	C_6H_5	159	78	$C_{25}H_{24}N_2O_3$	74.98	6.04	6.99	74.92	6.13	6.97
$C_6H_5CH=CH$	CH_3	118	64	$C_{22}H_{24}N_2O_3$	72.50	6.64	7.68	72.43	6.61	7.83
n-C_6H_{13}	CH_3	120	66	$C_{20}H_{30}N_2O_3$	69.34	8.73	8.08	69.55	8.99	8.21
4-$CH_3C_6H_4$	CH_3	134	70	$C_{21}H_{24}N_2O_3$	71.57	6.86	7.95	71.45	7.01	7.96
$C_{10}H_7$[e]	CH_3	125	71	$C_{24}H_{24}N_2O_3$	74.20	6.23	7.21	74.33	6.20	7.19

[a] Crystallization solvent unless specified otherwise: 95% ethanol. [b] Crystallization solvent: benzene–petroleum ether (60–80°). [c] 2-Furyl. [d] Crystallization solvent: methanol. [e] β-Naphthyl.

Eugenolglycolic Acid Thiosemicarbazide.—Eugenolglycolic acid chloride obtained from 2.22 g of eugenolglycolic acid was added dropwise to an ice-cold solution of 0.91 g of thiosemicarbazide in 4.0 ml of pyridine. The reaction mixture was allowed to stand at room temperature for 1 hr. It was then poured into H_2O and the product obtained was recrystallized from 50% EtOH to give white needles, mp 193°, yield 93.4%.

Anal. Calcd for $C_{13}H_{17}N_3O_3S$: C, 52.88; H, 5.81; N, 14.23. Found: C, 52.99; H, 5.92; N, 14.06.

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A Ready Synthesis of Pantothenoylcystine

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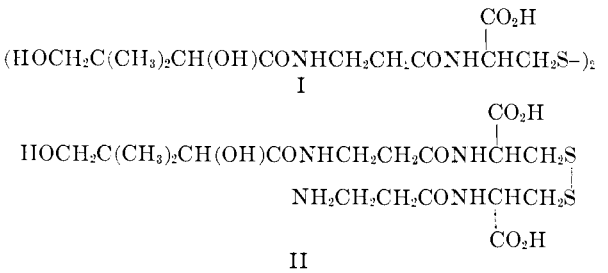
A new synthesis of the title compound I, which we feel will prove simpler in operation than that given by Baddiley and Mathias[2] for N-pantothenoyl-L-cysteine, is described.



I

II

Experimental Section[3]

N,N′-Bis(β-alanyl)-L-cystine.—Carbobenzyloxy-β-alanine[4] (22.3 g) was added portionwise with vigorous shaking during 20 min to a suspension of freshly ground PCl_5 (25 g) in dry ether (100 ml) at 0°. The mixture was filtered free of excess PCl_5 and concentrated *in vacuo* to an oil, dissolved in xylene (50 ml), and reconcentrated at low temperature and pressure (bath temp 40°). The resultant oil was dissolved in dry ether (50 ml) and added in six portions during 15 min with vigorous shaking to a solution of L-cystine (12 g) in 1 *N* NaOH (10 ml) at 0° in a stoppered flask. During the addition a further quantity of 1 *N* NaOH (130 ml) and water (100 ml) was added in portions. Shaking was continued for a further 15 min after addition was complete, and the mixture was acidified to congo red with 6 *N* HCl and extracted with ethyl acetate. The extracts were washed with water, dried overnight (Na_2SO_4), concentrated to 70 ml, and left at 0° when N,N′-bis(carbobenzyloxy-β-alanyl)-L-cystine crystallized; yield 24.3 g (75%), mp 118–125°.

The crude peptide (24.3 g) was dissolved in anhydrous liquid NH_3 (140 ml) and treated with stirring with small pieces of Na until a permanent blue color formed (required 5.8 g). The NH_3 was allowed to evaporate overnight and the residual solid dissolved in ice–water (60 ml) and was neutralized with HI (126 ml, 2 *N*, equivalent to 5.8 g of Na). The solution was cooled to 0° and treated slowly with aqueous H_2O_2 (20 vol, *ca.* 30 ml) until a test probe gave a negative nitroprusside reaction. After filtering, the solution was concentrated *in vacuo* then treated with ethanol when a viscous oil precipitated. This oil was washed free of NaI by decantation and dissolved in water (10 ml), and ethanol was added to turbidity when, on standing at 0° for several days, the peptide crystallized as feathery needles, yield 15.4 g, mp 201–202° dec. A further 3.0 g of the peptide was obtained from the ethanol washings: yield 71%, $[\alpha]^{20}D$ −126° (*c* 2.0, H_2O). This compound is reluctant to crystallize if it is very impure or if it is wet.

Anal. Calcd for $C_{12}H_{22}N_4O_8S_2$: C, 37.7; H, 6.2; N, 15.0; S, 16.8. Found: C, 37.7; H, 6.2; N, 15.0; S, 16.8.

N,N′-Bis(pantothenoyl)-L-cystine (I).—N,N′-Bis(β-alanyl)-L-cystine (9.55 g) in methanol (200 ml) was treated with 1 equiv of $NaOCH_3$ in methanol (37.0 ml, 1.37 *N*) and then with (−)-pantolactone (6.5 g). The solution was concentrated to an oil and held under N_2 at 100° for 3 hr. The resultant brittle foam is substantially pure disodium N,N′-bis(pantothenoyl)-L-cystine (I). Purification was effected by treating an aliquot (0.05) with the equivalent of 1 *N* HCl (2.5 ml) then partitioning the product between 1-butanol and water. The countercurrent distribution was effected by using 13 tap funnels each containing 1-butanol (20 ml), placing the material in the first funnel. The moving phase was water saturated with 1-butanol (10 ml) which passed through the system and was collected on issuing from the last funnel. This process was continued until 12 aqueous eluents had passed through the system and been collected. Examination of these eluents and of the contents of the tap funnels (homogenized by the addition of 5 ml of ethanol) by paper chromatography (1-butanol–acetic acid–water, 4:1:5) showed that the unreacted peptide was located in the first three aqueous eluents (R_f 0.11, detected by ninhydrin and by $NaCN-Na_2Fe(CN)_5NO$), while the monosubstituted peptide II was located in the first six eluents (R_f 0.20, detected by ninhydrin and by $NaCN-Na_2Fe(CN)_5NO$). Pure I was found to predominate in tap funnels 8–13 and in the last four eluents (R_f 0.3–0.5, elongated spot, detected only by $NaCN-Na_2Fe(CN)_5NO$). Concentration of these fractions gave the material as a resin, $[\alpha]^{20}D$ −77° (*c* 1.4, H_2O).

Anal. Calcd for $C_{24}H_{42}N_4O_{12}S_2$: C, 44.8; H, 6.6; N, 8.7; S, 10.0. Found: C, 44.7; H, 6.6; N, 8.6; S, 9.7.

(1) John Wyeth & Brother Ltd., Taplow, Maidenhead, Berkshire, England.

(2) J. Baddiley and A. P. Mathias, *J. Chem. Soc.*, 2803 (1954).

(3) Melting points were measured in open capillaries and are uncorrected. Microanalyses were performed by Drs. Weiler and Strauss, Oxford, England.

(4) R. H. Sifferd and V. du Vigneaud, *J. Biol. Chem.*, **108**, 753 (1935).