302. *Preparation and Hydrolysis of Some Derivatives of 1 : 3 : 4-Thiadiazole.*

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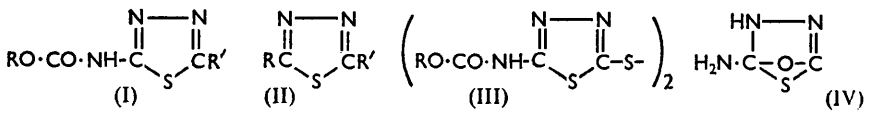
Some 5-alkoxycarbonylamino-1 : 3 : 4-thiadiazole-2-sulphonamides have been prepared and their reactions and those of certain intermediates studied.

Our object was the preparation of a series of 5-alkoxycarbonylamino-1 : 3 : 4-thiadiazole-2-sulphonamides (I; R = alkyl, R′ = $SO_2{\cdot}NH_2$) for study as carbonic anhydrase inhibitors.[1]

2-Amino-5-mercapto-1 : 3 : 4-thiadiazole (II; R = NH_2, R′ = SH), required as starting material, was originally prepared by Guha [2] by heating ethanolic potassium thiosemicarbazidedithiocarboxylate under pressure. We find that this thiadiazole is formed in excellent yield when thiosemicarbazide is heated with carbon disulphide and an equivalent of potassium hydroxide, or with ethyl potassium xanthate in ethanol or ethylene glycol. A small quantity of 2 : 5-dimercapto-1 : 3 : 4-thiadiazole (II; R = R′ = SH) is formed as by-product, presumably by hydrolysis of the thiosemicarbazide to hydrazine and reaction of the latter with carbon disulphide. Conversion of the amino-thiol (II; R = NH_2, R′ = SH) into the alkoxycarbonylamino-thiols (I; R = alkyl, R′ = SH) was effected by reaction with the alkyl chloroformate in pyridine: with excess of the chloroformate, disubstitution products (I; R = alkyl, R′ = $S{\cdot}CO_2R$) were formed, but with the exception of the benzyl derivative these passed into the alkoxycarbonyl-amino-thiols on crystallisation from ethanol or aqueous ethanol.



Conversion of the alkoxycarbonylamino-thiols (I; R = alkyl, R′ = SH), and also of the foregoing dibenzyl derivative, into the corresponding sulphonyl chlorides (R′ = SO_2Cl) was readily achieved by chlorination under fairly critical conditions (cf. refs. 1, 3, 4). Chlorination of the *n*-hexyl derivative (I; R = C_6H_{13}, R′ = SH) in 70% acetic acid at 0—5° gave the sulphonyl chloride and a small quantity of the disulphide (III; R = C_6H_{13}). Use of 50% acetic acid at −2° to 0° led to the formation of the disulphide which, however, was converted into the sulphonyl chloride by chlorine in 70% acetic acid at 15°. In anhydrous dioxan at 10°, only the chloro-derivative (I; R = C_6H_{13}, R′ = Cl)

[1] Roblin and Clapp, *J. Amer. Chem. Soc.*, 1950, **72**, 4890; Miller, Dessert, and Roblin, *ibid.*, p. 4893.
[2] Guha, *ibid.*, 1922, **44**, 1510.
[3] Schiller and Otto, *Ber.*, 1876, **9**, 1638; Zincke and Frohneberg, *Ber.*, 1909, **42**, 2728; Douglass and Johnson, *J. Amer. Chem. Soc.*, 1938, **60**, 1486; Lee and Dougherty, *J. Org. Chem.*, 1940, **5**, 81.
[4] Findlay and Dougherty, *J. Amer. Chem. Soc.*, 1946, **68**, 1666.

was obtained (cf. Findlay and Dougherty [4]). The sulphonyl chloride was also prepared by reaction of the thiol with iodobenzene dichloride or with *tert.*-butyl hypochlorite, the latter reagent yielding products essentially free from the disulphide. With sodium hypochlorite in alkaline solution or with chlorine in alkaline *tert.*-butyl alcohol the thiol yielded the disulphide as the major product. Incidentally, the pure sulphonyl chlorides slowly decomposed at room temperature with evolution of sulphur dioxide, and rapidly at their melting points, the nuclear chloro-compounds (I; R = alkyl, R′ = Cl) being obtained in almost theoretical yields.

The sulphonyl chlorides were converted smoothly into the required sulphonamides (I; R′ = SO_2·NH_2) by aqueous or liquid ammonia or by suspensions of ammonium carbonate or hydrogen carbonate in benzene. Hydrazine removed the sulphonyl group from the sulphonyl chloride (I; R = C_6H_{13}, R′ = SO_2Cl) with formation of 2-*n*-hexyloxycarbonylamino-1 : 3 : 4-thiadiazole (I; R = C_6H_{13}, R′ = H).

The *n*-hexyloxy-amide (I; R = C_6H_{13}, R′ = SO_2·NH_2) was stable in aqueous-ethanolic N-hydrochloric acid, but was converted by 4N-acid into the 5-hydroxy-derivative (I; R = C_6H_{13}, R′ = OH), also obtained from the corresponding sulphonamide and sulphonyl chloride by treatment with acetic anhydride. 5-Acetamido-1 : 3 : 4-thiadiazole-2-sulphonamide (" Diamox ") (II; R = NHAc, R′ = SO_2·NH_2) behaved differently with 4N-hydrochloric acid, being converted into the amine hydrochloride (II; R = NH_3Cl, R′ = SO_2·NH_2). In acetic anhydride it passed into the hydroxy-derivative (II; R = NHAc, R′ = OH), also formed in low yield when 1-phenyl-5-thiodiurea (Ph·NH·CO·NH·NH·CS·NH_2) was subjected to short treatment with the same reagent,[5] and it was hydrolysed to 2-amino-5-hydroxy-1 : 3 : 4-thiadiazole (II; R = NH_2, R′ = OH).

2-Amino-5-hydroxy-1 : 3 : 4-thiadiazole of m. p. 177° was prepared by Freund and Schander [6] by heating 2-thiodiurea (NH_2·CO·NH·NH·CS·NH_2) with concentrated hydrochloric acid but Guha used acetic anhydride for the cyclisation, obtaining an acetyl derivative which gave a base, m. p. 235°, apparently isomeric with Freund and Schander's material. Its structure was investigated by Janniah and Guha [8] who converted the base of m. p. 177° into an acetyl derivative which gave the product, m. p. 235°, on hydrolysis. The last compound was insoluble in alkali and did not react with mercuric chloride, but formed derivatives with phenyl *iso*cyanate and *iso*thiocyanate and with benzaldehyde, on which basis it was assigned the constitution (IV).

Attempts to repeat Freund and Schander's preparation surprisingly proved unsuccessful, but there seems little doubt that their product is authentic 2-amino-5-hydroxy-1 : 3 : 4-thiadiazole, which we have additionally obtained by the action of acetic anhydride on 1-ethoxycarbonylthiosemicarbazide.[9] Guha's base of m. p. 235°, in contrast, is formulated by us as 2-amino-5-methyl-1 : 3 : 4-thiadiazole (II; R = NH_2, R′ = Me). Reaction of 2-thiobiurea with formic acid and with propionic anhydride similarly yielded 2-amino-1 : 3 : 4-thiadiazole (II; R = NH_2, R′ = H) and its 5-ethyl homologue (R′ = Et), respectively.

Experimental

Ultraviolet absorptions refer to EtOH solutions unless otherwise stated.

*2-Amino-5-mercapto-*1 : 3 : 4-*thiadiazole* (II; R = NH_2, R′ = SH).—To thiosemicarbazide (182 g.) suspended in anhydrous ethanol (700 ml.) were added anhydrous sodium carbonate (106 g.) and carbon disulphide (184 g.). The mixture was warmed with stirring under reflux for 1 hr., then heated on the steam-bath for 4 hr. The solvent was largely removed, and the residue dissolved in water (800 ml.) and just acidified with concentrated hydrochloric acid (*ca.* 160 ml.) to give the product (216 g.), m. p. 232° (decomp.).

[5] Cf. Guha and Chakraborty, *J. Indian Chem. Soc.*, 1929, **6**, 99.
[6] Freund and Schander, *Ber.*, 1896, **29**, 2506.
[7] Guha, *J. Amer. Chem. Soc.*, 1923, **45**, 1036.
[8] Janniah and Guha, *ibid.*, 1930, **52**, 4860; *J. Indian Inst. Sci.*, 1933, *A*, **16**, 19.
[9] Fromm and Nehring, *Ber.*, 1923, **56**, 1374.

2-Alkoxycarbonylamino-5-mercapto-1 : 3 : 4-thiadiazole.—The preparative method is exemplified as follows: 2-Amino-5-mercapto-1 : 3 : 4-thiadiazole (66·5 g.) in pyridine (180 ml.) was stirred and treated dropwise below 40° with ethyl chloroformate (55·2 g.) during 1 hr. The mixture was diluted, then acidified with hydrochloric acid with cooling, and the *product* collected and crystallised from water (see Table 1).

Preparation of Sulphonyl Chlorides (I; R′ = SO_2Cl).—The preparative method is exemplified as follows: Finely powdered 2-ethoxycarbonylamino-5-mercapto-1 : 3 : 4-thiadiazole (50 g.) in 70% acetic acid (600 ml.) was treated with stirring at 0—5° with a slow steam of chlorine

TABLE 1. *The alkoxycarbonylamino-thiols and -sulphonamides, etc.* (I).

				Found (%)				Required (%)			
R	X	M. p.	Formula	C	H	N	S	C	H	N	S
Me	SH	192—194° [a]	$C_4H_5O_2N_3S_2$	25·4	2·6	21·4	—	25·1	2·6	22·0	—
	$SO_2{\cdot}NH_2$	223—224 [a]	$C_4H_6O_4N_4S_2$	20·6	2·3	22·8	26·3	20·2	2·5	23·5	26·9
Et	SH	204—205 [a]	$C_5H_7O_2N_3S_2$	29·0	3·4	19·9	31·5	29·2	3·4	20·5	31·2
	SO_2Cl	148—149 [b]	$C_5H_6O_4N_3ClS_2$	22·4	2·4	15·2	23·4	22·1	2·2	15·5	23·6
	$SO_2{\cdot}NH_2$	226 [a]	$C_5H_8O_4N_4S_2$	24·2	3·2	—	25·1	23·8	3·4	—	25·4
Pr^n	SH	186—187 [c]	$C_6H_9O_2N_3S_2$	33·0	4·5	18·7	—	32·9	4·1	19·2	—
	$SO_2{\cdot}NH_2$	221—222 [a]	$C_6H_{10}O_4N_4S_2$	27·1	4·0	20·8	24·1	27·1	3·8	21·0	24·1
Bu^n	SH	188—190 [c]	$C_7H_{11}O_2N_3S_2$	36·2	4·8	18·3	—	36·0	4·8	18·0	—
	$SO_2{\cdot}NH_2$	197—198 [a]	$C_7H_{12}O_4N_4S_2$	29·8	4·1	20·2	22·8	30·0	4·3	20·0	22·8
n-C_5H_{11}	SH	189—190 [c]	$C_8H_{13}O_2N_3S_2$	39·0	5·2	16·7	26·0	38·9	5·3	17·0	25·9
	$SO_2{\cdot}NH_2$	193 [a]	$C_8H_{14}O_4N_4S_2$	32·8	5·1	18·9	21·4	32·6	4·8	19·0	21·8
n-C_6H_{13}	SH	171—173 [c]	$C_9H_{15}O_2N_3S_2$	41·4	5·4	16·1	24·3	41·4	5·8	16·1	24·5
	SO_2Cl	128—130 [b]	$C_9H_{14}O_4N_3ClS_2$	32·8	4·3	—	Cl 10·2	33·0	4·3	—	Cl 10·8
	$SO_2{\cdot}NH_2$	187—189 [a]	$C_9H_{16}O_4N_4S_2$	35·0	5·0	18·1	20·7	35·1	5·2	18·2	20·8
CH_2Ph	$S{\cdot}CH_2Ph$	179—180 [c]	$C_{18}H_{15}O_4N_3S_2$	54·3	4·2	11·1	16·5	53·9	3·8	10·5	16·0
	$SO_2{\cdot}NH_2$ [d]	217—218 [c]	$C_{10}H_{10}O_4N_4S_2$	38·0	3·3	17·9	20·4	38·2	3·2	17·8	20·4

[a] From H_2O. [b] From $(CH_2Cl)_2$–light petroleum (b. p. 60—80°). [c] From aq. EtOH. [d] Vaughan, Eichler, and Anderson, *J. Org. Chem.*, 1956, **21**, 720.

TABLE 2. *Chlorinations of 2-alkoxycarbonylamino-5-mercapto-1 : 3 : 4-thiadiazoles.*

Reagent	Solvent	Temp.	Time (hr.)	Yields (%) Sulphonyl chloride	Disulphide
Et ester					
Cl_2	70% AcOH	0— 5°	1·75	72	—
,, ...	70% Dioxan	10—15	1·5	50	—
,, ...	70% Bu^{t}OH	10—15	1·75	66	—
n-*Hexyl ester*					
Cl_2	70% AcOH	10—15	1·75	70	—
,, ...	70% ,,	—3— 0	1·75	60	30
,, ...	50% ,,	—2— 0	1·5	—	75
,, ...	70% Bu^{t}OH	10—15	1·75	69—77	—
,, ...	,, ,, (alkaline)	15	1·5	0	98
,, ...	70% Dioxan	10	1·0	60	—
,, ...	50% ,,	10	1·0	Mainly unchanged	
,, ...	100% ,, [a]	10	1·25	0	0
Bu^{t}OCl	90% ,,	10—15	2·5	79	—
,, ...	70% ,,	15	3·5	53	—
NaOCl	75% AcOH	5	3·0	52	44
$PhICl_2$	70% Dioxan	10—15	3·5	70 [b]	—

[a] See text. [b] Estimated yield, converted directly into sulphonamide.

for 1·75 hr. The solids (47·5 g.) were collected, washed with ice-cold water, and air dried. The *sulphonyl chlorides* crystallised from ethylene dichloride–light petroleum (b. p. 60—80°). For this and variants see Table 2.

Di-(2-n-hexyloxycarbonylamino-1 : 3 : 4-thiadiazol-5-yl) Disulphide (III; R = C_6H_{13}).—(*a*) Treatment of 2-*n*-hexyloxycarbonylamino-5-mercapto-1 : 3 : 4-thiadiazole (130 g.) in 50% acetic acid (500 ml.) with chlorine for 1½ hr. at −2° to 0° yielded the *disulphide* (98 g.), m. p.

187—192° (Found: C, 41·8; H, 5·5; N, 16·2; S, 24·3. $C_{18}H_{28}O_4N_6S_4$ requires C, 41·5; H, 5·4; N, 16·2; S, 24·6%), after crystallisation from ethylene dichloride or aqueous ethanol.

(*b*) The thiol (50 g.) in 40% *tert.*-butyl alcohol (600 ml.) containing sodium hydroxide (7 g.) was treated with chlorine for 1½ hr. at 15°, giving the disulphide (49 g.).

The disulphide (15 g.) in 70% acetic acid (500 ml.) was treated with stirring at 15° with chlorine for 2 hr., giving the sulphonyl chloride (10 g.).

Di-(2-*methoxycarbonylamino*-1 : 3 : 4-*thiadiazol*-5-*yl*) *disulphide* (III; R = Me) had m. p. 246—248° (Found: C, 25·3; H, 2·3; N, 22·2; S, 33·4. $C_8H_8O_4N_6S_4$ requires C, 25·3; H, 2·1; N, 22·1; S, 33·7%), after crystallisation from aqueous ethanol.

Preparation of the Sulphonamides (I; R′ = $SO_2{\cdot}NH_2$).—The crude water-washed sulphonyl chlorides were added to aqueous ammonia (*d* 0·880) or to liquid ammonia, and the sulphonamides purified from water (see Table 1).

2-*Chloro*-5-n-*hexyloxycarbonylamino*-1 : 3 : 4-*thiadiazole* (I; R = C_6H_{13}, R′ = Cl).—(*a*) 5-*n*-Hexyloxycarbonylamino-1 : 3 : 4-thiadiazole-2-sulphonyl chloride (5 g.) in carbon tetrachloride (30 ml.) was heated with copper bronze (0·1 g.) under reflux for 2 hr. The mixture was taken to dryness, and the solids were extracted with boiling ethanol. Dilution of the extract with water yielded the *chloro-derivative* (2 g.), needles, m. p. 144°, $\lambda_{max.}$ 255 mμ (ε 8909) (Found: C, 40·9; H, 5·1; N, 15·9; Cl, 13·3. $C_9H_{14}O_2N_3ClS$ requires C, 41·0; H, 5·4; N, 15·9; Cl, 13·5%), after purification from aqueous ethanol.

(*b*) The foregoing sulphonyl chloride (1·0 g.) was melted carefully in a free flame and kept molten by intermittent heating for 5 min.; evolution of sulphur dioxide occurred. The residue was crystallised from ethanol to yield the chloro-derivative (0·68 g.).

(*c*) 2-*n*-Hexyloxycarbonylamino-5-mercapto-1 : 3 : 4-thiadiazole (15 g.) in anhydrous dioxan (250 ml.) was treated with chlorine for 75 min. at 10°. The product (7·2 g.), isolated by pouring the mixture into iced water (500 ml.), was purified from ethanol, to yield the chloro-derivative.

2-*Chloro*-5-*ethoxycarbonylamino*-1 : 3 : 4-*thiadiazole*, m. p. 184—185° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 28·9; H, 2·9; N, 20·0; Cl, 17·4. $C_5H_6O_2N_3ClS$ requires C, 28·9; H, 2·9; N, 20·0; Cl, 17·1%), was prepared in 74% yield, by fusion of 5-ethoxycarbonylamino-1 : 3 : 4-thiadiazole-2-sulphonyl chloride in a free flame for about 2 min., whereafter evolution of sulphur dioxide had ceased.

2-*Acetamido*-5-*chloro*-1 : 3 : 4-*thiadiazole* separated from ethyl acetate in needles, m. p. 245—246° (Found: C, 27·3; H, 2·3; N, 24·0. $C_4H_4ON_3ClS$ requires C, 27·0; H, 2·3; N, 23·7%).

2-n-*Hexyloxycarbonylamino*-1 : 3 : 4-*thiadiazole* (I; R = C_6H_{13}, R′ = H).—5-*n*-Hexyloxycarbonylamino-1 : 3 : 4-thiadiazole-2-sulphonyl chloride (16·4 g.) was added portionwise with stirring at 20° to 50% hydrazine hydrate solution (60 g., 12 mol.). After 12 hr. at room temperature excess of hydrazine was removed under reduced pressure. Acidification with dilute hydrochloric acid furnished the *product* (10·1 g.), m. p. 95—96° (from ethanol) (Found: C, 47·4; H, 6·2; N, 18·8; S, 14·0. $C_9H_{15}O_2N_3S$ requires C, 47·2; H, 6·6; N, 18·3; S, 14·0%), not depressed on admixture with a sample prepared by reaction of *n*-hexyl chloroformate with 2-amino-1 : 3 : 4-thiadiazole in pyridine.

Action of Hydrochloric Acid and Acetic Anhydride on the Sulphonamides.—(*a*) 5-Acetamido-1 : 3 : 4-thiadiazole-2-sulphonamide (8·5 g.) in concentrated hydrochloric acid (70 ml.) was boiled under reflux for 3½ hr. and the solution taken to dryness under reduced pressure. Crystallisation of the residue from ethanol–ether gave 5-amino-1 : 3 : 4-thiadiazole-2-sulphonamide hydrochloride (5 g.), m. p. 199—200° (decomp.), whose m. p. was not depressed on admixture with authentic material.

(*b*) The acetamido-sulphonamide (2·5 g.) was boiled with acetic anhydride (50 ml.) for 8½ hr. After removal of acetic anhydride under reduced pressure the solids were crystallised from a large volume of ethanol, to yield 2-*acetamido*-5-*hydroxy*-1 : 3 : 4-*thiadiazole* (1·0 g.), m. p. 304° (decomp.) (Found: C, 30·5; H, 3·2; N, 26·6; S, 19·8. $C_4H_5O_2N_3S$ requires C, 30·2; H, 3·2; N, 26·4; S, 20·1%). The last compound was also obtained by the action of acetic anhydride on 1-phenyl-5-thiobiurea and on 1-ethoxycarbonyl thiosemicarbazide as below.

(*c*) A suspension of 1-phenyl-5-thiobiurea (10 g.) in acetic anhydride (40 ml.) containing anhydrous sodium acetate (2 g.) was heated with stirring over a free flame until the vigorous exothermic reaction commenced. The solvent was removed under reduced pressure and the residue extracted with 50% ethanol, to yield 2-acetamido-5-hydroxy-1 : 3 : 4-thiadiazole (1·3 g.). The alcohol-soluble fraction yielded *s*-diphenylurea (1·5 g.) and acetanilide (1·5 g.).

(*d*) 1-Ethoxycarbonylthiosemicarbazide (22·5 g.) and anhydrous sodium acetate (5 g.) in acetic anhydride (75 ml.) similarly yielded 2-acetamido-5-hydroxy-1 : 3 : 4-thiadiazole (3·65 g.), m. p. 305° (decomp.).

(*e*) 2-Acetamido-5-hydroxy-1 : 3 : 4-thiadiazole (1·8 g.) was heated under reflux with aqueous-ethanolic 4N-hydrochloric acid (45 ml.) until the solids had dissolved and then for a further 30 min., yielding prismatic needles (1·0 g.) of 2-amino-5-hydroxy-1 : 3 : 4-thiadiazole, m. p. 177° (decomp.), $\lambda_{max.}$ 253 mμ (ε 4893) (Found: C, 21·0; H, 2·8; N, 35·5; S, 26·8. Calc. for $C_2H_3ON_3S$: C, 20·5; H, 2·6; N, 35·9; S, 27·3%). The *benzylidene derivative* (from aqueous ethanol) had m. p. 182° (decomp.) (Found: C, 52·6; H, 3·5; N, 20·4. $C_9H_7ON_3S$ requires C, 52·6; H, 3·4; N, 20·5%).

(*f*) 5-Ethoxycarbonylamino-1 : 3 : 4-thiadiazole-2-sulphonamide (5 g.) was converted into *2-ethoxycarbonylamino-5-hydroxy*-1 : 3 : 4-*thiadiazole* (1·6 g.), m. p. 263—265° (from aqueous ethanol), $\lambda_{max.}$ 255 mμ (ε 7562) (Found: C, 32·1; H, 3·7; N, 22·0; S, 16·4. $C_5H_7O_3N_3S$ requires C, 31·7; H, 3·7; N, 22·2; S, 16·9%), by hot concentrated hydrochloric acid.

(*g*) 5-*n*-Hexyloxycarbonylamino-1 : 3 : 4-thiadiazole-2-sulphonamide (4 g.) was recovered unchanged after being heated with N-ethanolic hydrochloric acid (40 ml.) for 2½ hr. When it (10 g.) was heated with ethanolic 3N-hydrochloric acid (200 ml.) for 10 hr., 2-n-*hexyloxycarbonylamino-5-hydroxy*-1 : 3 : 4-*thiadiazole* (3·4 g.), m. p. 242° (decomp.), $\lambda_{max.}$ 255 mμ (ε 7832) (Found: C, 44·6; H, 6·4; N, 16·7; S, 12·9. $C_9H_{15}O_3N_3S$ requires C, 44·1; H, 6·2; N, 17·1; S, 13·1%), was obtained (after crystallisation from aqueous ethanol).

(*h*) When the last-mentioned sulphonamide (5 g.) was boiled under reflux with acetic anhydride (40 ml.) for 7½ hr., sulphur dioxide was evolved and 2-*n*-hexyloxycarbonylamino-5-hydroxy-1 : 3 : 4-thiadiazole (1·4 g.), m. p. 240° (decomp.), was obtained. The same compound (2·4 g.) was formed when 5-*n*-hexyloxycarbonylamino-1 : 3 : 4-thiadiazole-2-sulphonyl chloride (6·55 g.) was heated under reflux with acetic anhydride (40 ml.) for 5 hr.

2-*n*-Hexyloxycarbonylamino-5-hydroxy-1 : 3 : 4-thiadiazole was unchanged by boiling ethanolic 3·5N-hydrochloric acid for 20 hr.

Reactions of 2-Thiodiurea.—(*a*) 2-Thiodiurea (10 g.), m. p. 218° (decomp.), $\lambda_{max.}$ 240 mμ (ε 13,530 in H_2O), was gently heated under reflux with concentrated hydrochloric acid (100 ml.) for 15 min., then the acid was removed under reduced pressure. Water (20 ml.) was added, and the solids were collected and washed with cold water (20 ml.). The *product* (5·4 g.), a polymorphic form of the starting material, crystallised from water in prisms, m. p. 204° (decomp.), $\lambda_{max.}$ 240 mμ (ε 13,150 in H_2O) (Found: C, 18·2; H, 4·7; N, 41·6. $C_2H_6ON_4S$ requires C, 17·9; H, 4·5; N, 41·8%). When this product (6 g.) had been heated with concentrated hydrochloric acid (30 ml.) on the steam-bath for 40 min., thiosemicarbazide hydrochloride (3·5 g.), m. p. 186° (decomp.), separated on cooling.

(*b*) 2-Thiodiurea (58 g.) in suspension in acetic acid (100 ml.) and acetic anhydride (200 ml.) was heated under reflux for 1 hr. 2-Acetamido-5-methyl-1 : 3 : 4-thiadiazole (47 g.), m. p. 295—297° (Found: C, 38·2; H, 4·2; N, 27·0. Calc. for $C_5H_7ON_3S$: C, 38·2; H, 4·5; N, 26·7%), was obtained after crystallisation from acetic acid. The foregoing compound (55 g.) was heated on the steam-bath with concentrated hydrochloric acid (100 ml.) for 5 hr., then the acid was removed under reduced pressure. The solids, crystallised from ethanol–ethyl acetate, furnished 2-amino-5-methyl-1 : 3 : 4-thiadiazole hydrochloride hemihydrate, needles, m. p. 108—110° (Found: C, 22·0, 22·3; H, 4·4, 4·8. Calc. for $C_3H_6N_3ClS,\frac{1}{2}H_2O$: C, 22·4; H, 4·4%). The base separated from ethanol in prisms, m. p. 235° (decomp.) (Found: C, 31·2; H, 4·5; N, 36·0. Calc. for $C_3H_5N_3S$: C, 31·3; H, 4·4; N, 36·5%). Reacetylation of the base yielded the original acetyl derivative.

2-n-*Hexyloxycarbonylamino-5-methyl*-1 : 3 : 4-*thiadiazole* separated from aqueous ethanol in flat needles, m. p. 144—145° (Found: C, 49·8; H, 7·4; N, 17·1. $C_{10}H_{17}O_2N_3S$ requires C, 49·4; H, 7·1; N, 17·3%).

5-*Methyl*-1 : 3 : 4-*thiadiazol-2-ylurea* had m. p. 297—298° (decomp.) (Found: C, 30·1; H, 3·7; N, 35·0. $C_4H_6ON_4S$ requires C, 30·4; H, 3·8; N, 35·4%), after crystallisation from ethylene glycol.

2-Thiodiurea (20 g.) was heated under reflux for 1 hr. with propionic acid (75 ml.) and propionic anhydride (50 ml.). After removal of the solvents under reduced pressure, the solids yielded 2-*ethyl-5-propionamido*-1 : 3 : 4-*thiadiazole*, needles, m. p. 225—226° (from ethyl acetate) (Found: C, 46·0; H, 6·1; N, 23·4; S, 17·9. $C_7H_{11}ON_3S$ requires C, 45·4; H, 6·0; N, 22·7; S, 17·3%).

2-Thiodiurea (13·4 g.), heated with 98—100% formic acid (75 ml.) for 20 hr. on the steam-bath, yielded 2-formamido-1 : 3 : 4-thiadiazole, m. p. 221° (decomp.) (from water), identical with authentic material.

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