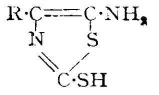
412. *Studies in the Azole Series. Part X. Some 5-Amino-2-mercapto-4-alkylthiazoles and 2 : 4-Dithio-5-alkylhydantoins.*

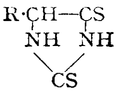
By A. H. Cook, Sir Ian Heilbron, and E. S. Stern.

Reaction of various aliphatic α-amino-nitriles with carbon disulphide gives 5-amino-2-mercapto-4-alkylthiazoles which are readily isomerised to dithiohydantoins on warming with alkali.

In previous papers in this series (Cook, Heilbron, and Levy, Part II, *J.*, 1947, **1598**; Part III, this vol., p. 201) it was observed that the stability of 5-amino-2-mercaptothiazoles (I) varies greatly with the substituent in the 4-position. Thus (I; R = Ph) was readily obtainable from α-aminobenzyl cyanide and was quite stable when pure, though it rearranged to the isomeric dithiohydantoin (II; R = Ph) on boiling with alkali. Aminopropionitrile, on the other hand, in reaction with carbon disulphide gave the dithiohydantoin (II; R = Me) immediately, the intermediate thiazole only being isolated when the reaction was carried out in the presence of a carbonyl compound, *e.g.*, in acetone, whereupon the Schiff's base was produced. The present paper describes thiazoles of the type (I) in which R is a higher alkyl group; the substituents chosen were the *n*-hexyl, the 1-ethylamyl, and the ω-carbethoxy-*n*-butyl groups.

It was found that on reaction of the appropriate α-amino-nitrile with carbon disulphide comparatively low-melting *aminomercaptothiazoles* [I; R = *n*-C_6H_{13}, Bu^n·CHEt, or CO_2Et·Bu^n, respectively] were produced; these were quite stable when pure but on warming with alkali or even on prolonged standing in solution they isomerised to the corresponding *dithiohydantoins* (II). The thiazole (I; R = *n*-C_6H_{13}) condensed readily with carbonyl compounds giving *Schiff's bases* (III; R = H, R′ = *n*-C_6H_{13}, or R = R′ = Me); the thiazoles (I) condensed with glyoxal (Part II, *loc. cit.*) and the purple colour obtained served to distinguish them from the isomeric dithiohydantoins (II). Acetylation of (I; R = *n*-C_6H_{13} and R = Bu^n·CHEt) proceeded with great ease in acetic anhydride, and as the *acetyl* derivatives failed to react with carbonyl compounds they must be the 5-acetamido-compounds. Methylation, on the other hand, by contrast with the phenyl analogue (I; R = Ph), usually failed to give a solid methylthio-derivative though 5-*acetamido*-2-*methylthio*-4-n-*hexylthiazole* was suitable for the characterisation of the parent thiol compound.


(I.)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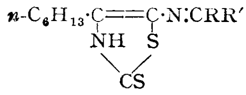
(III.)

The structure of the dithiohydantoins (II; R = *n*-C_6H_{13} and R = Bu^n·CHEt) was established by desulphurisation with aqueous chloroacetic acid (Johnson *et al.*, *J. Amer. Chem. Soc.*, 1912, **34**, 1041) to the corresponding hydantoins, which were independently prepared by the method of Henze and Speer (*J. Amer. Chem. Soc.*, 1942, **64**, 522).

The above thiazoles were selected because the products appeared to bear some structural relationship to biotin; accordingly, several of the resulting thiazoles and dithiohydantoins were tested for biotin activity at the laboratories of the Distillers Co. Ltd., Great Burgh, Epsom, by Mr. J. S. Harrison, to whom the authors are much indebted. These tests showed no growth-promoting effect for either *L. casei* or *Sacch. cerevisiæ*; a slight growth-inhibitory effect could not be reversed by addition of biotin and appears to be due to the general toxicity of these compounds.

Experimental.

Heptaldehyde had b. p. 53°/19 mm., $n_D^{20°}$ 1·4113, and the cyanohydrin had b. p. 140°/19 mm., n_D^{19} 1·4351.

1-Amino-*n*-octyl cyanide (cf. Erlenmeyer and Sigel, *Annalen*, 1875, **177**, 125) was obtained by treating the above cyanohydrin (15 g.) in ethanol (15 c.c.) with liquid ammonia (30 c.c.) overnight at room temperature. The *hydrochloride* (15 g.), precipitated from ether, crystallised from ethyl acetate in needles, m. p. 141—142° (Found: C, 54·4; H, 9·6; N, 15·5. $C_8H_{17}N_2Cl$ requires C, 54·4; H, 9·7; N, 15·85%). Regeneration of the base yielded an oil which on distillation gave an unidentified *oil*, b. p. 100°/10^{-3} mm., $n_D^{18°}$ 1·4500 (Found: C, 74·8; H, 11·5; N, 11·8%); on treatment with ethereal hydrochloric acid this gave the hydrochloride described above.

5-*Amino-2-mercapto*-4-n-*hexylthiazole* (as I).—The above hydrochloride (48 g.) was neutralised with sodium hydrogen carbonate, and the base extracted into light petroleum (b. p. 40—60°); addition of carbon disulphide (24 g.) in light petroleum afforded, after standing for 6 hours at 0° under nitrogen, 5-*amino-2-mercapto*-4-n-*hexylthiazole* (21 g.) which crystallised from ethyl acetate–light petroleum in pale yellow needles, m. p. 113° (Found: C, 50·4; H, 7·4; N, 12·7; S, 29·6. $C_9H_{16}N_2S_2$ requires C, 50·0; H, 7·5; N, 13·0; S, 29·6%). Light absorption: $\lambda_{max.}$ in ethanol = 3340 A., ϵ = 11200; in 20% aqueous ammonia $\lambda_{max.}$ = 3040 A., ϵ = 5500. Acetylation of the thiazole (2 g.) with acetic anhydride (10 c.c.) gave 5-*acetamido-2-mercapto-4-hexylthiazole* (2 g.), which crystallised from ether–benzene in needles, m. p. 175° (Found: C, 51·6; H, 7·0; N, 10·65. $C_{11}H_{18}ON_2S_2$ requires C, 51·1; H, 7·0; N, 10·85%). Light absorption: maximum in ethanol at 3370 A., ϵ = 16,000.

Treatment of the acetyl compound (1 g.) in 2N-sodium hydroxide (10 c.c.) with methyl sulphate (0·5 g.) at 0° yielded 5-*acetamido-2-methylthio*-4-n-*hexylthiazole* (1·2 g.), which formed needles from ethyl acetate–light petroleum, m. p. 85·5° (Found: C, 53·2; H, 7·4; N, 10·4; S, 24·1. $C_{12}H_{20}ON_2S_2$ requires C, 52·9; H, 7·4; N, 10·3; S, 23·5%). Light absorption in ethanol: $\lambda_{max.}$ = 2500, 2560, and 2990 A., ϵ = 3600, 3600, and 12,000 respectively.

5-n-*Heptylideneamino-2-mercapto*-4-n-*hexylthiazole* (III; R = H, R′ = *n*-C_6H_{13}) was obtained from the thiazole (I; R = *n*-C_6H_{13}) by addition of heptaldehyde. It crystallised from ethyl acetate–light petroleum in very pale yellow needles, m. p. 113° (Found: C, 61·7; H, 8·95; N, 8·7; S, 21·0. $C_{16}H_{28}N_2S_2$ requires C, 61·4; H, 9·0; N, 8·5; S, 20·5%). Light absorption maxima in ethanol: 2280, 2400, and 3370 A.; ϵ = 6500, 6300, and 12,500. respectively. This substance (8·5 g.) was also obtained by treating (A), from the distilled α-amino-*n*-octyl cyanide (10 g.), with carbon disulphide (5 g.) in light petroleum.

Treatment of the thiazole (I; R = *n*-C_6H_{13}) with acetone, or addition of carbon disulphide to α-amino-*n*-octyl cyanide in acetone, afforded 2-*mercapto*-5-iso*propylideneamino*-4-n-*hexylthiazole* (III; R = R′ = Me), m. p. 99—100° (Found: N, 10·6; S, 25·5. $C_{12}H_{20}N_2S_2$ requires N, 10·9; S, 25·0%).

The thiazole (I; R = *n*-C_6H_{13}) (2 g.) with pyridine (10 c.c.) on refluxing for 10 minutes gave a *bis-compound* (1·8 g.) (cf. the behaviour of I, R = Ph; Part II of this series), soluble in aqueous sodium hydroxide and in excess of pyridine but insoluble in ammonia. It crystallised from dioxan–water in yellow needles, m. p. 212—215° (decomp.) (Found: C, 50·6; H, 6·9; N, 12·9; S, 29·6. $C_{18}H_{30}N_4S_4$ requires C, 50·2; H, 7·0; N, 13·0; S, 29·8%). Light absorption in ethanol: $\lambda_{max.}$ = 2230, 2650, 3370 A.; ϵ = 13,500, 21,500, and 5600, respectively.

2 : 4-*Dithio*-5-n-*hexylhydantoin* (II; R = *n*-C_6H_{13}).—Treatment of the thiazole (I; R = C_6H_{13}) (5 g.) with hot 2N-sodium hydroxide for 10 minutes or with hot saturated aqueous potassium carbonate (20 c.c.) for 1 hour under nitrogen afforded on acidification 2 : 4-*dithio*-5-n-*hexylhydantoin* (4·8 g.), a colourless solid which very rapidly became yellow, and on crystallisation from ethyl acetate had m. p. 233—234° (decomp.) (Found: C, 49·3; H, 7·0; S, 29·5. $C_9H_{16}N_2S_2$ requires C, 50·0; H, 7·5; S, 29·6%). Light absorption maxima in ethanol: 2420 and 3220 A.; ϵ = 6500 and 15,000, respectively; in 20% aqueous ammonia: maximum at 3340 A., ϵ = 8500. This dithiohydantoin was also obtained by treating 1-amino-*n*-octyl cyanide (5 g.) and carbon disulphide (2·5 g.) with a suspension of potassium carbonate (4·2 g.) in ethanol (35 c.c.) for 3 hours at 60° under nitrogen. It was soluble in ammonia and carbonate solution but insoluble in bicarbonate or 1N-sodium acetate. Acetylation of (II; R = *n*-C_6H_{13}) (0·5 g.) with acetic anhydride (5 c.c.) and sulphuric acid (0·1 c.c.) gave the *monoacetyl* compound (0·4 g.),separating from ethyl acetate–light petroleum in needles, m. p. 155° (Found: C, 50·3; H, 7·0; S, 25·3. $C_{11}H_{18}ON_2S_2$ requires C, 51·1; H, 7·0; S, 24·8%). Dithio-*n*-hexylhydantoin (0·8 g.) with chloroacetic acid (0·8 g.) in water (5 c.c.) on refluxing for 30 minutes under nitrogen gave 4-*n*-hexylhydantoin (0·6 g.), m. p. 146°, undepressed by authentic material prepared by Henze and Speer's method (*loc. cit.*).

2-Ethyl-*n*-hexanal had b. p. 160°, $n_D^{22°}$ 1·4152 (cf. Weizmann *et al.*, *Chem. and Ind.*, 1937, **56**, 587). The *cyanohydrin* had b. p. 86·5°/0·05 mm., $n_D^{19°}$ 1·4419 (Found: C, 69·8; H, 11·1; N, 9·0. $C_9H_{17}ON$ requires C, 69·5; H, 11·0; N, 9·0%). Treatment of the cyanohydrin (15 g.) with liquid ammonia (25 c.c.) in ethanol (15 c.c.) and standing overnight afforded 1-amino-2-ethyl-*n*-hexyl cyanide, the *hydrochloride* (8·5 g.) of which crystallised from ethyl acetate in needles, m. p. 139° (Found: C, 56·6; H, 10·0; N, 15·0. $C_9H_{19}N_2Cl$ requires C, 56·65; H, 10·0; N, 14·7%).

5-*Amino-2-mercapto*-4-1′-*ethyl*-n-*amylthiazole*.—Regeneration of the preceding base from the hydrochloride (3 g.), extraction with light petroleum, and reaction with carbon disulphide (2 g.) afforded 5-*amino-2-mercapto*-4-1′-*ethyl*-n-*amylthiazole* (1 g.) which crystallised from ethyl acetate–light petroleum in pale yellow needles, m. p. 79° (decomp.) (Found: C, 52·5; H, 8·0; N, 11·7. $C_{10}H_{18}N_2S_2$ requires C, 52·1; H, 7·9; N, 12·2%). Light absorption maximum in ethanol at 3390 A., ϵ = 11,500, and in 20% ammonia at 3040 A., ϵ = 7500. Acetylation with acetic anhydride gave the 5-*acetamido*-derivative, crystallising from ethyl acetate–light petroleum in very pale yellow needles, m. p. 200—201° (decomp.) (Found: C, 52·5; H, 7·3; N, 9·7. $C_{12}H_{20}ON_2S_2$ requires C, 52·9; H, 7·4; N, 10·3%). Light absorption maximum in ethanol at 3310 A., ϵ = 14,500.

2 : 4-*Dithio*-5-1′-*ethyl*-n-*amylhydantoin* was obtained by alkali treatment of the thiazole; the colourless compound on crystallisation from ethyl acetate gave pale yellow needles, m. p. 258° (decomp.) (Found: C, 52·3; H, 8·1; S, 26·8. $C_{10}H_{18}N_2S_2$ requires C, 52·1; H, 7·9; S, 27·8%). The dithiohydantoin (0·15 g.) on refluxing with 20% aqueous chloroacetic acid (2 c.c.) gave 5-1′-*ethyl*-n-*amylhydantoin* (0·1 g.), m. p. 145—146° (Found: C, 60·3; H, 8·9; N, 13·7. $C_{10}H_{18}O_2N_2$ requires C, 60·6; H, 9·15; N, 14·1%), identical with a sample prepared by the method of Henze and Speer (*loc. cit.*).

ω-Carbethoxy-*n*-valeraldehyde, prepared by the method of Baker *et al.* (*J. Org. Chem.*, 1947, **12**, 163), had b. p. 93°/1 mm., $n_D^{23°}$ 1·4305; the *cyanohydrin* had b. p. 138°/0·01 mm., $n_D^{21°}$ 1·4471 (Found: C, 58·5; H, 8·3. $C_9H_{15}O_3N$ requires C, 58·35; H, 8·15%). Treatment of the cyanohydrin (12 g.) in ethanol (20 c.c.) with liquid ammonia (20 c.c.) gave α-amino-ω-carbethoxyhexonitrile, which was isolated as its oxalate.

5-*Amino*-2-*mercapto*-4-ω-*carbethoxy*-n-*butylthiazole* was obtained by regeneration of the base from the above oxalate and reaction with carbon disulphide. It crystallised from ethyl acetate–light petroleum in very pale yellow needles, m. p. 65° (decomp.) (Found: C, 46·1; H, 6·2; N, 10·8. $C_{10}H_{16}O_2N_2S_2$ requires C, 46·1; H, 6·2; N, 10·8%).

2 : 4-*Dithio*-5-ω-*carbethoxy*-n-*butylhydantoin*, obtained by treatment of the thiazole with a suspension of potassium carbonate in ethanol at 60° for 3 hours under nitrogen, crystallised from ethyl acetate–light petroleum and had m. p. 199—200° (Found : C, 46·65; H, 6·8; N, 11·1. $C_{10}H_{16}O_2N_2S_2$ requires C, 46·1; H, 6·2; N, 10·8%).

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