330. *Miscellaneous Thiazoles.*

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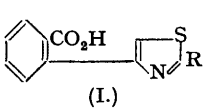
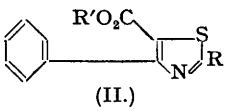
Derivatives of 4-o-*carboxyphenylthiazole* (I) and *4-phenylthiazole-5-carboxylic acid* (II) prepared by standard methods could not be cyclised to indonothiazoles (III). Phenyldithiobiuret and α-halogeno-ketones react together to give *azamethin* bases (IV). A few new *thiazyl sulphides* have been prepared. 2-Chloroacetylfuran and 2-*bromoacetylfuran* have been obtained crystalline and converted into derivatives of 4-(2′-*furyl*)*thiazole* (VI). 2-Chloroacetylpyrrole condenses normally with thiourea and normally with thioacetamide in the presence of alkali to give derivatives of 4-(2-*pyrryl*)*thiazole* (VII), but abnormally with alkyl dithiocarbamates to give *di*-(2-*pyrroylmethyl*) *sulphide* (VIII).

THE formation of polycarbocyclic thiazoles by intramolecular ring closure of 4-arylthiazole-5-acetic acids has been reported recently (Knott, *J.*, 1945, 455). In attempts to prepare indonothiazoles (III) by analogous methods two types of intermediate were required, namely, a 4-o-*carboxyphenylthiazole* (I) and a *4-phenylthiazole-5-carboxylic acid* (II; R′ = H). (I) was readily prepared from *o*-carboxyphenacyl bromide and (II; R′ = Et) from ethyl α-bromobenzoylacetate or the chloro-analogue (Hirst, Macbeth, and Traill, *Proc. Roy. Irish Acad.*, 1925, **37***B*, 47). Hydrolysis of (II; R = Me, R′ = Et) gave the required acid, but where R = NH_2 simultaneous loss of carbon dioxide gave 2-amino-4-phenylthiazole. Ethyl α-bromobenzoylacetate condensed with ethyl and *iso*propylthioncarbamates to give *ethyl 2-hydroxy-4-phenylthiazole-5-carboxylate* (II; R = OH, R′ = Et); the simultaneous loss of the alkyl group was also observed by Hantzsch and Hubacher (*Annalen*, 1890, **259**, 250) whilst employing chloroacetone.



(I.)



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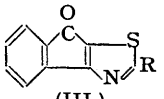
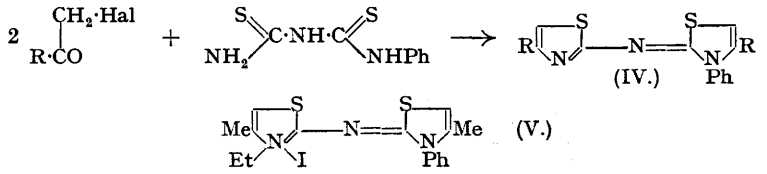


(III.)

All cyclisation experiments on the acids or esters were unsuccessful.

The condensation of dithiomalonamides with α-halogeno-ketones has been described by Lehr, Guex, and Erlenmeyer (*Helv. Chim. Acta*, 1944, **27**, 972) who thus obtained dithiazolylmethanes. Some time ago an analogous reaction was applied to phenyldithiobiuret which condensed very readily with chloroacetone and phenacyl bromide to give *azamethin* bases (IV). Where R = Me (IV) formed an *ethiodide* which is [2-(4-*methyl*-3-*ethylthiazole*)][2-(3-*phenyl*-

4-*methylthiazole*)]*azamethincyanine iodide* (V). This pale yellow dye does not sensitise a photographic silver chloride emulsion.



(IV.)

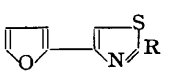
(V.)

Using the method of Buchman, Reims, and Sargent (*J. Org. Chem.*, 1941, **6**, 764) for the direct formation of 2-alkylthiothiazoles by the condensation of chloroacetone and methyl dithiocarbamate, *2-alkylthio-4-phenylthiazoles* and *2-benzylthio-4-phenylthiazole* have been prepared.

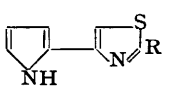
As intermediates for photographic sensitising dyes, 4-(2′-furyl)-* and 4-(2′-pyrryl)-thiazoles containing a reactive substituent in the 2-position were required.

2-Chloroacetylfuran, one of the intermediates for the preparation of the above thiazoles, has been obtained as an oil by Gilman and Burtner (*J. Amer. Chem. Soc.*, 1935, **57**, 911), and by Burger and Harnest (*ibid.*, 1943, **65**, 2382); it has now been found to crystallise readily at room temperature as did also *2-bromoacetylfuran*. 2-Chloroacetylpyrrole, the second required intermediate, was obtained in 20% yield from pyrrole and chloromethyl cyanide by Blicke, Faust, Gearien, and Warzynski (*J. Amer. Chem. Soc.*, 1943, **65**, 2465). Using this method with slight variations, a 35% yield was obtained.

The halogeno-acetylfuran condensed normally with thiourea, thioacetamide, and methyl dithiocarbamate to give the *2-amino-*, *2-methyl-*, and *2-methylthio-*derivatives of 4-(2′-furyl)-thiazole (VI; R = NH_2, Me, SMe).



(VI.)



(VII.)

$(C_4H_4N\cdot CO\cdot CH_2)_2S$

(VIII.)

2-Chloroacetylpyrrole condensed normally with thiourea giving the hydrochloride of *2-amino-4-(2′-pyrryl)thiazole* (VII; R = NH_2) as sole product. With thioacetamide, however, condensation in alcohol gave a deep red solution, and the resultant product was difficult to purify. The formation of dye was prevented, however, in the presence of alkali carbonate and the main reaction product was the expected *4-(2′-pyrryl)-2-methylthiazole* (VII; R = Me) although an appreciable amount of a crystalline solid was obtained, which was not volatile in steam. With methyl dithiocarbamate the chloro-ketone gave chiefly a purple dye in the absence of alkali. The addition of alkali carbonate again prevented dye formation, but the product obtained was identical with the by-product obtained in the thioacetamide condensation. It is *di-(2-pyrroylmethyl) sulphide* (VIII). The same product was obtained from the chloro-ketone and ethyl dithiocarbamate, ammonium dithiocarbamate, or sodium sulphide. The mechanism of this abnormal reaction is probably analogous to the formation of substituted diquinolyl sulphides from chloroquinolines and thiourea (Rosenhauer, Hoffmann, and Heuser, *Ber.*, 1929, **62**, 2730; Renfrew, *J. Amer. Chem. Soc.*, 1946, **68**, 1433) and of other diheterocyclyl sulphides from heterocyclyl chlorides and thiourea (Surrey and Lindwall, *J. Amer. Chem. Soc.*, 1940, **62**, 1697; Watt, *J. Org. Chem.*, 1939, **4**, 436).

Experimental

(Analyses are by Drs. Weiler and Strauss, Oxford: m. ps. are not corrected.)

4-o-Carboxyphenyl-2-methylthiazole (I; R = Me).—*o*-Carboxyphenacyl bromide (1·22 g.; 0·005 mol.) (Gabriel and Michael, *Ber.*, 1877, **10**, 1551) and thioacetamide (0·375 g.; 0·005 mol.) gave the hydrobromide on refluxing together for 15 minutes in *iso*propyl alcohol (2·5 c.c.). The *base*, m. p. 143—147°, formed colourless needles from aqueous methyl alcohol (Found: S, 14·5. $C_{11}H_9O_2NS$ requires S, 14·65%). *2-Amino-4-o-carboxyphenylthiazole* (I; R = NH_2), obtained similarly from thiourea (0·38 g.), formed soft needles, m. p. 174° (decomp.), from alcohol. The needles contained solvent of crystallisation removed by drying at 115°/20 mm. (Found: S, 14·7. $C_{10}H_8O_2N_2S$ requires S, 14·55%).

4-Phenyl-2-methylthiazole-5-carboxylic Acid (II; R = Me, R′ = H).—Thioacetamide (0·75 g.; 0·01 mol.), ethyl α-bromobenzoylacetate (2·6 g.; 0·01 mol.), and *iso*propyl alcohol (10 c.c.) were refluxed

* Since this paper was written, B.P. 571,077 has appeared describing the condensation of 2-bromoacetylfuran (obtained by bromination of 2-acetylfuran) with thioacetamide to give 4-(2′-furyl)-2-methylthiazole.

for 15 minutes, diluted with aqueous sodium carbonate, and the precipitated oil taken up in ether which was dried, the ether then being removed. The oil could not be crystallied. It was dissolved in alcohol (5 c.c.) and shaken with 10% aqueous hydroxide (2 c.c.), then allowed to stand for 3 hours. The *acid* obtained on acidification formed pink tablets, m. p. 216° (decomp.), from alcohol (Found: S, 14·45. $C_{11}H_9O_2NS$ requires S, 14·65%).

Ethyl 2-Amino-4-phenylthiazole-5-carboxylate.—This, obtained similarly from ethyl α-bromobenzoylacetate and thiourea, formed thick, pale yellow needles, m. p. 173° (Hirst *et al.*, *loc. cit.*, give m. p. 173°) from methyl alcohol (Found: S, 12·65. Calc. for $C_{12}H_{12}O_2N_2S$: S, 12·9%). The ester (1·0 g.) was dissolved in hot alcohol (20 c.c.), 10% aqueous sodium hydroxide (2 c.c.) was added, and after 30 minutes at 50° the solution was neutralised with dilute acetic acid, giving colourless needles of 2-amino-4-phenylthiazole, m. p. 151°, not depressed on admixture with authentic specimen obtained from phenacyl bromide and thiourea (Found: S, 17·95. Calc. for $C_9H_8N_2S$: S, 18·2%).

Ethyl 2-Hydroxy-4-phenylthiazole-5-carboxylate (II; R = OH, R′ = Et).—Ethyl α-bromobenzoylacetate (2·6 g.; 0·01 mol.), ethyl thioncarbamate (1·05 g.; 0·01 mol.) or *iso*propyl thioncarbamate (1·19 g.), and *iso*propyl alcohol (5 c.c.) were boiled together for a few minutes. The liquor clouded and deposited pale yellow needles, which then formed colourless needles from alcohol, m. p. 202°, soluble in ammonia (Found: S, 12·9. $C_{12}H_{11}O_3NS$ requires S, 12·85%).

Azamethin[2-(4-*phenylthiazole*)][2-(3:4-*diphenyl*-2:3-*dihydrothiazole*)] (IV; R = Ph).—Phenacyl bromide (0·4 g.; 0·002 mol.) was added to a hot solution of phenyldithiobiuret (0·215 g.; 0·01 mol.) in absolute ethyl alcohol (10 c.c.) and refluxed for 15 minutes. To this solution was then added anhydrous sodium carbonate (1·1 g.) and the mixture refluxed for a further 15 minutes. Addition of water (100 c.c.) precipitated the *base* as a solid which formed colourless needles (0·4 g.), m. p. 228—230°, from benzene–light petroleum (Found: C, 70·7; H, 4·1; N, 9·85. $C_{24}H_{17}N_3S_2$ requires C, 70·0; H, 4·15; N, 10·2%). The *dihydrobromide* was obtained if the carbonate addition was omitted and the mixture concentrated after 1 hour. From *iso*propyl alcohol it formed yellow prisms, m. p. 152° (Found: HBr, 28·25. $C_{24}H_{17}N_3S_2,2HBr$ requires HBr, 28·25%).

Azamethin[2-(4-*methylthiazole*)][2-(3-*phenyl*-4-*methyl*-2:3-*dihydrothiazole*)] (IV; R = Me).—By proceeding as above but using phenyldithiobiuret (1·07 g.) and chloroacetone (0·92 g.), the *base* was obtained as faintly yellow needles, m. p. 170—171°, from alcohol (Found: S, 22·25. $C_{14}H_{13}N_3S_2$ requires S, 22·35%).

[2-(4-*Methyl*-3-*ethylthiazole*)][2-(3-*phenyl*-4-*methylthiazole*)]*azamethincyanine Iodide* (V).—The base (IV; R = Me) (1 g.) and ethyl iodide (1 c.c.) were heated for 8 hours in a sealed tube on the steam-bath. From methanol the *ethiodide* formed yellow needles, m. p. 190—192° (Found: S, 14·7. $C_{16}H_{18}N_3IS_2$ requires S, 14·45%).

2-*Alkylthio- and* 2-*Benzylthio*-4-*phenylthiazoles*.—Molar quantities of phenacyl bromide and the dithiocarbamic ester were refluxed for 15 minutes in ethyl alcohol. The hydrobromides were obtained on concentration. 2-Methylthio-4-phenylthiazole was obtained in colourless needles, m. p. 24°, from benzene (Levi, *Gazzetta*, 1931, **61**, 719, describes it as an oil) (Found: S, 30·8. Calc. for $C_{10}H_9NS_2$: S, 30·95%). The *hydrobromide* formed colourless prisms, m. p. 194—196°, from *iso*propyl alcohol. The crystals contain the solvent, removed at 115° (Found: S, 22·3. $C_{10}H_{10}NBrS_2$ requires S, 22·25%). 2-*Ethylthio*-4-*phenylthiazole* was obtained as a viscous oil, b. p. 300° (partial decomp.) (Found: S, 29·9. $C_{11}H_{11}NS_2$ requires S, 28·3%). The *hydrobromide* formed colourless needles, m. p. 167—169°, from *iso*propyl alcohol. The crystals contain solvent removed at 115° (Found: S, 21·35. $C_{11}H_{12}NBrS_2$ requires S, 21·25%). 2-*Benzylthio*-4-*phenylthiazole* formed glassy crystals, m. p. 56—57°, from benzene–light petroleum (Found: S, 22·5. $C_{16}H_{13}NS_2$ requires S, 22·65%). Its hydrobromide had m. p. 192°.

2-*Halogenoacetylfurans*.—The method employed was essentially that of Burger *et al.* (*loc. cit.*). The furoyl chloride was treated with ethereal diazomethane until the powerful lachrymatory action of the chloride could not be detected on removing a spot of the reaction mixture. Dry hydrogen chloride or bromide was used to decompose the diazo-compound. 2-Chloroacetylfuran, b. p. 125°, solidified after distilling twice. From benzene–light petroleum it formed colourless leaflets, m. p. 30·5°, in 86% yield (Found: Cl, 24·25. Calc. for $C_6H_5O_2Cl$: Cl, 24·55%) (Burger *et al.* report b. $p._4$ 93—108°; Gilman *et al.* b. $p._{27}$ 127—129°). 2-*Bromoacetylfuran*, b. $p._{22}$ 126°, formed colourless leaflets, m. p. 34°, from benzene–light petroleum in 87% yield (Found: Br, 42·15. $C_6H_5O_2Br$ requires Br, 42·4%).

2-*Amino*-4-(2′-*furyl*)*thiazole*.—Thiourea (0·38 g.; 0·005 mol.) and chloroacetylfuran (0·722 g.; 0·005 mol.) were dissolved in hot ethyl alcohol (5 c.c.), anhydrous sodium carbonate (0·026 g.; 0·025 mol.) was added, and the mixture refluxed for 5 minutes. On addition of water the thiazole separated. From benzene–light petroleum it formed glistening flat needles, m. p. 124·5°, in 95% yield (Found: S, 19·45. $C_7H_6ON_2S$ requires S, 19·3%).

4-(2′-*Furyl*)-2-*methylthiazole*.—Thioacetamide (7·5 g.; 0·1 mol.) and 2-bromoacetylfuran (18·9 g.; 0·1 mol.) were covered with ethyl alcohol (20 c.c.) and warmed gently. Heat was suddenly evolved and after cooling, the required *hydrobromide* separated, the precipitation being completed by addition of ether. It formed pale brown needles, m. p. 194—196°, from methanol–ether in 87% yield (Found: Br, 32·6; S, 12·85. C_8H_8ONBrS requires Br, 32·5; S, 13·05%). The *base* was obtained as an oil, b. $p._{22}$ 128°, possessing a strong thiazole odour * (Found: S, 19·35. C_8H_7ONS requires S, 19·4%).

2-*Methylthio*-4-(2′-*furyl*)*thiazole*.—Obtained as for the 2-methyl analogue, the *hydrobromide* (70% yield) formed tiny plates, m. p. 208—210° (decomp.), from ethyl alcohol–ether (Found: Br, 28·9. $C_8H_8ONBrS_2$ requires S, 28·95%). The *base* was obtained as a heavy oil, b. $p._{22}$ 177°, with an odour like that of mushrooms (Found: S, 32·4. $C_8H_6ONS_2$ requires S, 32·55%).

2-*Chloroacetylpyrrole*.—The procedure according to Blicke *et al.* (*loc. cit.*) was followed, but the reaction mixture of the ketimine hydrochloride was allowed to stand for 18 hours before filtration, the hydrolysis solution made neutral to Congo-red with sodium acetate before being heated, and the required product extracted from the resin by repeated refluxing with carbon tetrachloride. With these variations, a 36% yield was obtained.

* B.P. 571,077 gives b. $p._{15}$ 120—130° but no analysis.

2-*Amino*-4-(2′-*pyrryl*)*thiazole*.—Obtained like the furyl analogue, the *base* formed creamy needles, m. p. 160°, from hot water (Found : N, 24·9; S, 19·4. $C_7H_7N_3S$ requires N, 24·45; S, 19·4%). The hydrochloride, m. p. 200° (decomp.), formed greenish needles from alcohol.

4-(2′-*Pyrryl*)-2-*methylthiazole*.—Thioacetamide (1·5 g.; 0·02 mol.) and 2-chloroacetylpyrrole (2·87 g.; 0·02 mol.) were dissolved in warm ethyl alcohol (10 c.c.) and excess of anhydrous sodium carbonate (1·0 g.) was added. The whole was refluxed for 30 minutes, the flask being shaken well every time a red coloration developed. On dilution with water an oil was precipitated which solidified. The solid (3·2 g.) was subjected to steam distillation giving 2·5 g. of the steam-volatile thiazole, obtained as glassy aggregates, m. p. 94—95°, from methanol (Found : S, 19·85. $C_8H_8N_2S$ requires S, 19·55%). It can also be purified by distillation (b. $p._{20}$ 171°) or by recrystallisation of the crude condensate from methanol. The residue from the steam distillation (0·5 g.) formed colourless needles, m. p. 179°, from acetone.

Di-(2-*pyrroylmethyl*) *Sulphide*.—(*a*) 2-Chloroacetylpyrrole (1·435 g.; 0·01 mol), and methyldithiocarbamate (1·07 g.; 0·01 mol.) or ethyl dithiocarbamate (1·21 g.), were dissolved in warm ethyl alcohol (5 c.c.) and, after the addition of anhydrous sodium carbonate (1·0 g.) to avoid dye formation, the whole was refluxed for 30 minutes. The precipitate obtained on dilution with water gave needles on recrystallisation from alcohol, m. p. 179—180°, which fluoresced yellow in ultra-violet light. They were identical with the by-product from the thioacetamide condensation.

(*b*) Equimolecular amounts of 2-chloroacetylpyrrole and ammonium dithiocarbamate were refluxed in alcohol for 10 minutes. Ammonium chloride was precipitated. On dilution with water the sulphide was precipitated, m. p. 179°, mixed m. p. with (*a*) 179°.

(*c*) 2-Chloroacetylpyrrole (2 mol.) and sodium sulphide (1 mol.) gave the sulphide after being refluxed for 10 minutes in alcohol. The *product* had m. p. 179° and did not depress the m. p. of the specimens obtained under (*a*) and (*b*) (Found : C, 58·25; H, 4·8; N, 11·2; S, 12·95. $C_{12}H_{12}O_2N_2S$ requires C, 58·05; H, 4·85; N, 11·3; S, 12·95%).

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[*Received, January 17th*, 1947.]