437. *Congeners of Pyridine-4-carboxyhydrazide. Part I. Derivatives of 4-Cyanopyridine and 2-Cyanothiazole.*

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4-Cyanopyridine has been converted into the corresponding amidrazone, and several dipyridyl heterocyclic secondary products have been isolated. 2-Cyanothiazole and some derivatives have also been prepared.

The high antituberculosis activity of pyridine-4-carboxyhydrazide has led to the examination of many analogues and particularly to studies of the effect of nuclear and side-chain substitution. Hydrazides of several heterocyclic nuclei other than pyridine have also been described, variously substituted thiazole derivatives being amongst the most active in experimental infections.

One of the first pyridine derivatives that was prepared in these laboratories in 1952 for antitubercular studies was 4-amidinopyridine. This compound was biologically inactive *in vitro* against *Mycobacteria* but it seemed possible that *N*-amino-amidines (amidrazones) corresponding closely in structure to active hydrazides might be more interesting. Pyridine-4-carboxyamidrazone (I), which has recently been described by van der Burg,[1] and thiazole-2-carboxyamidrazone (I; R = 2-thiazolyl) were therefore prepared from the appropriate nitriles.

4-Cyanopyridine was most conveniently prepared by heating *iso*nicotinic acid with sulphamic acid, while the hitherto unknown 2-cyanothiazole was made by dehydration of the amide with phosphoric oxide. The thiazole nitrile was surprisingly reactive and was rapidly and smoothly converted in good yield into (I; R = 2-thiazolyl) on treatment with cold hydrazine hydrate (cf. 5-cyanotetrazole [2]). When the mixture was warmed, only 1 : 2(or 1 : 4)-dihydro-3 : 6-di-2′-thiazolyl-1 : 2 : 4 : 5-tetrazine (III; R = 2-thiazolyl) could be isolated. Attempts to oxidise this to the tetrazine (VII; R = 2-thiazolyl) were not successful.* Thiazole-2-thiocarboxyamide has also been prepared from 2-cyanothiazole.

4-Cyanopyridine was less reactive, and was therefore converted into the ethyl carboxyimidoate, which when treated with hydrazine yielded (I) and several other products,

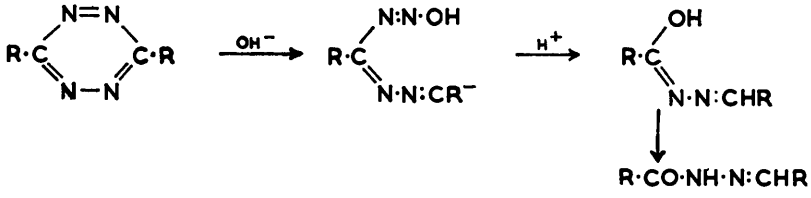
* This behaviour and the method of formation suggest the 1 : 4- rather than the 1 : 2-dihydro-structure (cf. Charronat and Fabiani [3]).

[1] van der Burg, *Rec. Trav. chim.*, 1955, **74**, 257.
[2] Lifschitz, *Ber.*, 1915, **48**, 415; Curtius, Darapsky, and Müller, *ibid.*, p. 1614.
[3] Charronat and Fabiani, *Compt. rend.*, 1955, **241**, 1783.

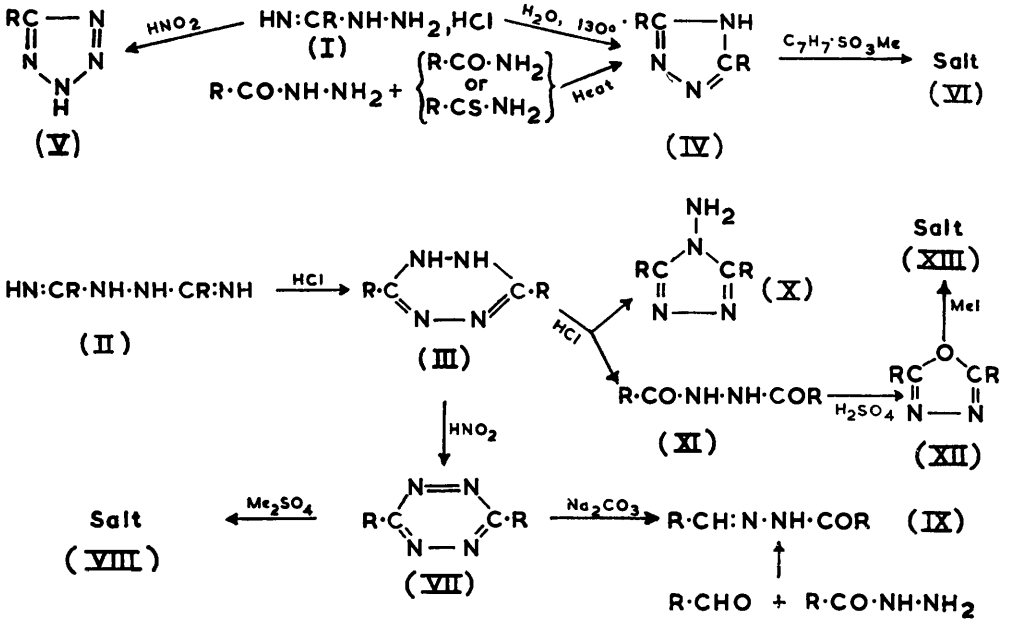
particularly 1 : 2-di(pyridine-4-carboxyimidoyl)hydrazine (II), 1 : 2-dihydro-3 : 6-di-4'-pyridyl-1 : 2 : 4 : 5-tetrazine (III), and 3 : 5-di-4'-pyridyl-1 : 2 : 4-triazole (IV). These compounds are all analogous to the phenyl and furyl derivatives obtained by Pinner and Caro[4] during their investigation of the reaction of imidoic esters with hydrazine.

The proportions of (I) and (II), which are presumably the primary products of the reaction, could be varied by varying the initial pH of the reaction. Separation was not difficult (see Experimental section).

Several closely allied compounds have been prepared by the traditional methods illustrated in the annexed Scheme. The dihydro-tetrazine (III), when oxidised in air, gave traces of the tetrazine (VII), but for preparative purposes nitrous acid was better. The tetrazine readily lost nitrogen hydrolytically in the presence of sodium carbonate to give the hydrazone (IX), which was also prepared from pyridine-4-carboxyhydrazide and 4-formylpyridine. The initial attack by hydroxyl ion might lead to an intermediate diazohydroxide with subsequent loss of nitrogen :



though this is not known with any certainty. When the pyridine nitrogen atoms are quaternary, the tetrazine ring is even more unstable, and the salt (VIII) evolves nitrogen when gently warmed in aqueous solution.

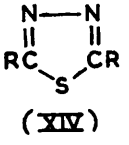


R = 4-pyridyl unless otherwise indicated in the text.

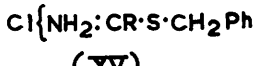
Since the amidrazone (I) and the dihydrotetrazine (III) respectively showed activity against the B.C.G. strain "*in vivo–in vitro*" and the H_{37} Rvstrain *in vivo*, alternative

[4] Pinner and Caro, *Ber.*, 1894, **27**, 3273; 1895, **28**, 465.
[5] McMillan, Leonard, Meltzer, and King, *J. Amer. Pharm. Assoc.*, 1953, **42**, 457.

methods of synthesis were examined. 4-Cyanopyridine was converted into pyridine-4-thiocarboxyamide [5] which was heated with alcoholic hydrazine hydrate. Eight products were isolated, all appearing to be secondary products. van der Burg [1] has shown that the amidrazone is formed in the first few minutes of this reaction, but is then rapidly decomposed. We detected none of this product, but obtained the derived 1 : 2-dihydro-3 : 6-di-4′-pyridyl-1 : 2 : 4 : 5-tetrazine (III), a trace of dipyridyltetrazine (VII), and 4-amino-3 : 5-di-4′-pyridyl-4 : 1 : 2-triazole (X). 2 : 5-Di-4′-pyridylthiadiazole (XIV) was isolated in 11% yield; it was the only product noted (22% yield) by McMillan *et al.*[5] in a similar experiment, and was also obtained as a by-product by van der Burg.[1]



(XIV)



(XV)
R = 4-pyridyl

Benzyl pyridine-4-thiocarboxyimidoate hydrochloride (XV), prepared from the nitrile by the standard method, was allowed to react with cold alcoholic hydrazine hydrate. Dibenzyl disulphide and the cyclic compounds (III), (VII), and (X) were the only products detected.

Experimental

Pyridine-4-carboxyamidrazone (I) *and* 1 : 2-*Dihydro*-3 : 6-*di*-4′-*pyridyl*-1 : 2 : 4 : 5-*tetrazine* (III).—4-Cyanopyridine (150 g.) in dry chloroform (1500 ml.) and ethanol (90 ml.) was treated with hydrogen chloride at 0° until a semi-solid upper layer separated. The vessel was sealed and kept at 0° for 24 hr., the contents were then added to 50% w/v sodium hydroxide solution (750 ml.) at 0° with vigorous stirring. The upper layer was separated, washed with water, and dried (K_2CO_3). Most of the solvent was removed under reduced pressure at 40—50°. The crude imidoate (*ca.* 200 g.) was added to ethanol (372 ml.), 100% hydrazine hydrate (83 ml.), water (105 ml.), and concentrated hydrochloric acid (114 ml.) at 5°. The mixture was kept at 0° for 2 hr. and the solid was collected. Recrystallisation from methanol containing 5% of ether gave the *amidrazone hydrochloride*, heavy pink prisms (17 g.), m. p. *ca.* 280° (decomp.) (Found: N, 31·7; Cl, 20·45. $C_6H_8N_4$,HCl requires N, 32·5; Cl, 20·5%). The original filtrate was heated at 100° for 3 hr. The *dihydrotetrazine* which separated crystallised from aqueous 75% acetic acid as orange needles, m. p. 275° (60 g.) (Found: C, 60·4; H, 4·45; N, 34·6. $C_{12}H_{10}N_6$ requires C, 60·5; H, 4·2; N, 35·3%).

Yields of amidrazone of 28% have been obtained in smaller-scale experiments, but with a correspondingly lower yield of the dihydrotetrazine.

1 : 2-*Di*(*pyridine*-4-*carboxyimidoyl*)*hydrazine* (II) *and* 3 : 5-*Di*-4′-*pyridyl*-1 : 2 : 4-*triazole* (IV).—Crude imidoate base (from 40 g. of 4-cyanopyridine) was treated at 0° with a neutral mixture of 100% hydrazine hydrate (16·5 ml.), ethanol (99 ml.), water (27·5 ml.), and concentrated hydrochloric acid (33 ml.). After 1 hr. at 0°, the solid was collected and stirred with an excess of 2N-ammonia, then crystallised from ethanol to give yellow plates of the *di-imine*, m. p. (decomp.) >280°. At 100° the plates were converted into an amorphous cream-coloured solid (5·2 g.) of the same m. p. (Found: C, 59·6; H, 4·6; N, 34·8. $C_{12}H_{12}N_6$ requires C, 60·0; H, 5·0; N, 35·0%).

The original filtrate was heated at 100° for 3 hr., the dihydrotetrazine (15·4 g.), identical with that described above, separating. This was removed, the filtrate was evaporated almost to dryness, and the solid was collected. 3 : 5-*Di*-4′-*pyridyl*-1 : 2 : 4-*triazole* formed colourless needles (1 g.), m. p. 283° (from ethanol) (Found: N, 31·4. $C_{12}H_9N_5$ requires N, 31·4%). This compound was also prepared by dissolving the crude hydrochloride of the above di-imine in hot water and boiling the solution for a short time until the triazole base separated. The *bismethotoluene*-p-*sulphonate* (VI) formed colourless prisms, m. p. 188° (from methanol–acetone) (Found: N, 11·4; S, 10·55. $C_{12}H_9N_5$,$2C_8H_{10}O_3S$ requires N, 11·8; S, 10·8).

Alternative Preparations of 3 : 5-*Di*-4′-*pyridyl*-1 : 2 : 4-*triazole* (IV).—In the following methods the crude triazole was purified by dissolution in cold 2N-sodium hydroxide, reprecipitation with 2N-acetic acid, and crystallisation from ethanol.

(*a*) Pyridine-4-carboxyhydrazide was heated with an equimolecular amount of pyridine-4-carboxyamide at 220—240° for 1 hr., or with pyridine-4-thiocarboxyamide at 140—150° for 30 min. The yields were 5% and 27% respectively.

(*b*) 1 : 2-Dihydro-3 : 6-di-4′-pyridyl-1 : 2 : 4 : 5-tetrazine (4·76 g.) was heated under reflux for 6 hr. in ethanol (50 ml.) containing potassium hydroxide (1·2 g.) which had been dissolved in the minimum of water. The solution was diluted with water and neutralised with 2N-acetic acid, to give the triazole (1·2 g.).

(*c*) Pyridine-4-carboxyamidrazone hydrochloride (4·0 g.) was heated with water (400 ml.) in a sealed vessel at 130° for 45 min. The solution was concentrated *in vacuo*, and the insoluble material was separated into the triazole (0·4 g.) and dihydrotetrazine * (0·2 g.) by means of 2N-sodium hydroxide.

5-4′-Pyridyl-1 : 2 : 3 : 4-tetrazole (V).—A solution of sodium nitrite (7·5 g.) in water (40 ml.) was rapidly added to pyridine-4-carboxyamidrazone (18·2 g.), dissolved in 2N-acetic acid (150 ml.), at 0°. After 2 hr. the crude *tetrazole* was collected and crystallised from pyridine, to give colourless prisms (10·5 g.), m. p. 262—263° (decomp.) (Found: C, 48·5; H, 3·5; N, 47·3. $C_6H_5N_5$ requires C, 49·0; H, 3·4; N, 47·6%).

3 : 6-Di-4′-pyridyl-1 : 2 : 4 : 5-tetrazine (VII).—A solution of the dihydrotetrazine (32 g.) in boiling aqueous 50% acetic acid (1·5 l.) was poured into the same cold solvent (6·5 l.). Sodium nitrite (9·4 g.) in a little water was slowly added to this mixture with constant stirring below 15°. After 10 min. the solution was neutralised with aqueous ammonia (*d* 0·88). The solid was crystallised from nitromethane and then from pyridine, to give deep magenta needles (21 g.) of the *tetrazine*, m. p. 258° (decomp.) (Found: C, 60·9; H, 3·5; N, 35·6. $C_{12}H_8N_6$ requires C, 61·0; H, 3·4; N, 35·6%). A dilute solution of the base in dry chlorobenzene was heated under reflux, and the calculated amount of dimethyl sulphate was added slowly. The red, crude *bismetho(methyl sulphate)* (VIII) (95%) was washed with dry ether, m. p. 200° (decomp.) (Found: N, 16·85; S, 13·3. $C_{12}H_8N_6,2C_2H_6O_4S$ requires N, 17·2; S, 13·1%). It could not be recrystallised, and decomposed readily in aqueous solution with evolution of nitrogen.

4-Formylpyridine Pyridine-4-carbonylhydrazone (IX).—(*a*) The above tetrazine was heated under reflux with 2N-sodium carbonate until solution was complete (*ca.* 5 min.). The solution was neutralised with acetic acid to give the *hydrazone* (56%), colourless needles (from water), m. p. 230° (Found: C, 64·4; H, 5·1; N, 24·0. $C_{12}H_{10}ON_4$ requires C, 63·7; H, 4·46; N, 24·8%).

(*b*) Pyridine-4-carbonylhydrazide and 4-formylpyridine heated under reflux for 1 hr. gave the same product, as prisms, m. p. 232° (from nitromethane).

Action of Dilute Acid on 1 : 2-Dihydro-3 : 6-di-4′-pyridyl-1 : 2 : 4 : 5-tetrazine (III).—The dihydrotetrazine (37 g.) was suspended in 2N-hydrochloric acid (370 ml.), to give a dark, insoluble hydrochloride. The suspension was heated under reflux for 8—9 min., and the resulting yellow solution was cooled, affording *4-amino-3 : 5-di-4′-pyridyl-4 : 1 : 2-triazole dihydrochloride* (X) (22 g.), colourless prisms, m. p. 312° (from 4N-hydrochloric acid) (Found: C, 46·1; H, 4·2. $C_{12}H_{10}N_6,2HCl$ requires C, 46·3; H, 4·0%), converted by 2N-ammonia into the *base*, 335—340° (decomp.) (Found: N, 34·9. $C_{12}H_{10}N_6$ requires N, 35·3%). The filtrate was evaporated to dryness, and the solid was extracted with hot acetone to remove a little hydrazine dihydrochloride, m. p. 195°. The residue was redissolved in water and treated with sodium hydrogen carbonate, to give colourless needles (15 g.) of 1 : 2-di(pyridine-4-carbonyl)-hydrazine (XI), m. p. 250° (Graf [6] gives m. p. 254°).

2 : 5-Di-4′-pyridyl-1 : 3 : 4-oxadiazole (XII).—1 : 2-Di(pyridine-4-carbonyl)hydrazine (108 g.) was added in portions with cooling below 35° to concentrated sulphuric acid (270 ml.). The solution was heated at 100° for 10 min., cooled, and poured on crushed ice. The mixture was neutralised with aqueous ammonia (*d* 0·88), to give the oxadiazole (32 g.), colourless needles, m. p. 185° (from water or methanol) (Found: C, 64·3; H, 3·49; N, 25·3. $C_{12}H_8ON_4$ requires C, 64·3; H, 3·6; N, 25·0%). When heated with methyl iodide in nitromethane it gave the *bismethiodide* (XIII) (57%) as orange needles, m. p. 278° (from aqueous acetone) (Found: N, 11·0; I, 48·9. $C_{12}H_8ON_4,2CH_3I$ requires N, 11·0; I, 49·7%).

Reaction between Pyridine-4-thiocarboxyamide and Hydrazine.—The thioamide (330 g.), ethanol (620 ml.), and 100% hydrazine hydrate (130 ml.) were warmed to 40°. When the vigorous evolution of hydrogen sulphide had subsided, the mixture was heated under reflux for 1 hr., cooled, and filtered. The filtrate was evaporated to dryness and the residue was leached

* Possibly a mixture of 1 : 2- and 1 : 4-dihydrotetrazines (cf. thiazole analogue, p. 2255).

[6] Graf, *J. prakt. Chem.*, 1933, **138**, 289.

out with boiling water (2·5 l.). The combined solid products were crystallised from aqueous 70% acetic acid, to give an acetate which dissociated at 100°, forming 1 : 2-dihydro-3 : 6-di-4′-pyridyl-1 : 2 : 4 : 5-tetrazine (III) (140 g.), m. p. 275°. The acetic acid filtrate was evaporated to dryness, and the solid was extracted with boiling pyridine (600 ml.), from which 2 : 5-di-4′-pyridyl-1 : 3 : 4-thiadiazole (XIV) separated as plates, m. p. 243° (30 g.). The residue crystallised from 2N-hydrochloric acid as flattened needles (35 g.) of 4-amino-3 : 5-di-4′-pyridyl-4 : 1 : 2-thiazole dihydrochloride (X), m. p. 312°.

The original aqueous extract was evaporated to dryness and the residue was fractionally crystallised from aqueous ethanol, to give small amounts of colourless plates, m. p. 227° (Found : C, 63·8; H, 4·6; N, 24·6. $C_{12}H_{10}ON_4$ requires C, 63·7; H, 4·5; N, 24·8%), and of colourless needles, m. p. 285° (Found : C, 59·9; H, 4·6; N, 29·3. $C_{12}H_{11}ON_5$ requires C, 59·7; H, 4·6; N, 29·0%).

Benzyl Pyridine-4-thiocarboxyimidoate (XV) *and its Reaction with Hydrazine.*—An ice-cooled solution of 4-cyanopyridine (5 g.) in toluene-ω-thiol (25 ml.) was saturated with dry hydrogen chloride and kept at room temperature for 5 days. The solid mass was powdered under dry ether and collected. The deliquescent crude thioester hydrochloride (9·9 g.) was added in portions with cooling to a solution of hydrazine hydrate (5 ml.) in ethanol (50 ml.), and the solution was made neutral with 2N-hydrochloric acid (*ca.* 15 ml.). It was kept for 1 week, and the solid precipitate was collected. The solid was readily separated into 1 : 2-dihydro-3 : 6-di-4′-pyridyl-1 : 2 : 4 : 5-tetrazine (III) (1·5 g.), m. p. 271°, a little of the magenta tetrazine (VII), and dibenzyl disulphide, m. p. 69—70°. Basification of the filtrate gave 4-amino-3 : 5-di-4′-pyridyl-1 : 2 : 4-triazole (X) (1·2 g.), m. p. 330° (decomp.).

2-*Cyanothiazole.*—An intimate mixture of thiazole-2-carboxyamide (64 g.) and phosphoric oxide (52 g.) was distilled under reduced pressure, while the bath temperature was slowly raised from 140° to 220°. The colourless distillate was redistilled (b. p. 98°/24 mm.), to give the *nitrile* (42 g.), m. p. 31° (Found : N, 25·4; S, 29·2. $C_4H_2N_2S$ requires N, 25·4; S, 29·1%).

Thiazole-2-carboxyamidrazone (I; R = 2-thiazolyl).—2-Cyanothiazole (10 g.) was mixed with 100% hydrazine hydrate (10 ml.) at 0°. When the reaction had subsided, the mixture solidified. It was broken up with water (10 ml.) and filtered off at 0°. The *amidrazone* (8 g.) formed colourless needles, m. p. 106° (from light petroleum, b. p. 80—100°) (Found : N, 39·55; S, 22·6. $C_4H_6N_4S$ requires N, 39·4; S, 22·55%).

1 : 2(or 1 : 4)-*Dihydro-3 : 6-di-2′-thiazolyl-1 : 2 : 4 : 5-tetrazine* (III; R = 2-thiazolyl).—100% Hydrazine hydrate (20 ml.) was added to 2-cyanothiazole (20 g.). The mixture was cooled at first to moderate the reaction, then heated on the steam-bath for 3 hr. The insoluble gummy product solidified after being washed with water and methanol. The *dihydrotetrazine* (7 g.) formed orange needles, m. p. 209° (decomp.) from aqueous pyridine (Found : N, 33·3; S, 25·6. $C_8H_6N_6S_2$ requires N, 33·6; S, 25·6%).

Thiazole-2-thiocarboxyamide.—2-Cyanothiazole (30 g.) was dissolved in ethanol (60 ml.) and treated with saturated ethanolic ammonia (240 ml.). The solution was saturated at 0° with hydrogen sulphide. After 2 hr. the *thioamide* was collected. It formed bright yellow plates (24 g.), m. p. 176°, from water (Found : N, 19·35; S, 44·8. $C_4H_4N_2S_2$ requires N, 19·4; S, 44·5%).

We thank Mr. C. F. Attridge for part of the experimental work, Mr. S. Bance, B.Sc., A.R.I.C., for the semimicro-analyses, Dr. H. J. Barber for his interest, and the Directors of May & Baker Ltd. for permission to publish these results.

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[*Received, December 16th,* 1955.]