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A SYNTHETIC APPROACH TO 1,3,4-THIADIAZOLIDINE-2-THIONES

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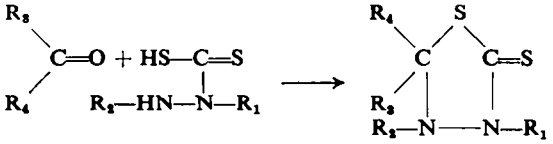
Abstract—The course of the reaction between dithiocarbazic acid and aldehydes and ketones has been examined. Aliphatic and π-deficient heterocyclic aldehydes and ketones form 1,3,4-thiadiazolidine-2-thiones. Aromatic and π-excessive heterocyclic aldehydes and ketones, however, form azines. A similar course occurs in the reaction between the hydrazones and carbon disulphide.

Alkyl dithiocarbazic acids (azine formation being excluded) form 3-alkyl-1,3,4-thiadiazolidine-2-thiones with aliphatic, aromatic as well as with heterocyclic aldehydes and ketones. These thiones can also be prepared from alkyl hydrazones and carbon disulphide. Aryl hydrazones, however, do not react with carbon disulphide.

RECENTLY, Grashey *et al.*[1,2] obtained 3,4-disubstituted 1,3,4-thiadiazolidine-2-thiones (III; $R_4 = H$) from reaction of carbon disulphide with the addition product of symmetrically disubstituted hydrazines and aldehydes.

Before these publications, the synthesis of the 1,3,4-thiadiazolidine-2-thione ring system (III) had only been achieved for the 4-aryl-1,3,4-thiadiazolidine-2-thiones (III; $R_1 = H$; $R_2 =$ aryl) obtained by reaction of 3-aryldithiocarbazic acids (II; $R_1 = H$; $R_2 =$ aryl) with aldehydes and ketones (I).[3,4]

Reactions of aldehydes and ketones with aliphatic dithiocarbazic acids (II; R_1 or $R_2 =$ alkyl) or with dithiocarbazic acid itself (II; $R_1 = R_2 = H$) had not been investigated. The 1,3,4-thiadiazolidine-2-thiones, unsubstituted in the 3- and 4-positions (III; $R_1 = R_2 = H$) or with an alkyl group in the 3- or 4-positions (III; R_1 or $R_2 =$ alkyl), are not known in the literature.



I II III

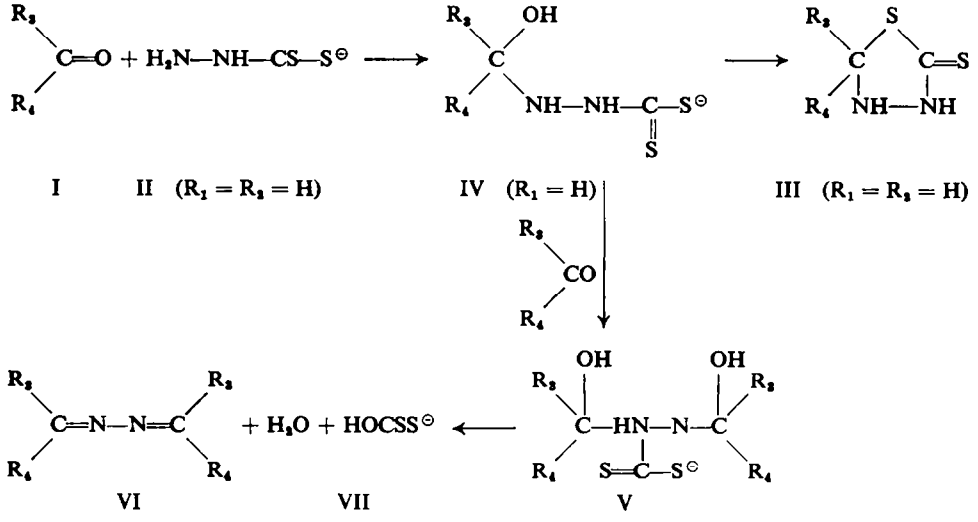
The reactions of dithiocarbazic acid and alkyldithiocarbazic acids with aldehydes and ketones are reported and a new preparation for 3-alkyl-1,3,4-thiadiazolidine-2-thiones is presented.

I. 5-R_3,R_4-1,3,4-*Thiadiazolidine-2-thiones*

(a) *Reaction of dithiocarbazic acid with aldehydes and ketones.* Although the 3-aryldithiocarbazic acids readily undergo ring closure with the most divergent kinds of

[1] R. Grashey, R. Huisgen, K. K. Sun and R. M. Mariarty, *J. Org. Chem.* **30**, 74 (1965).
[2] I. L. Karle, J. Karle and R. M. Mariarty, *Tetrahedron Letters* No. 47, 3579 (1964).
[3] J. F. Willems, *Fortschr. Chem. Forsch.* **4**, 631 (1964).
[4] E. Taeger and Zaki El-Hewehi, *J. Prakt. Chem.* [4] **18**, 255 (1962).

aldehydes and ketones the course of the reaction with dithiocarbazic acid itself depends on the aldehyde or the ketone used.



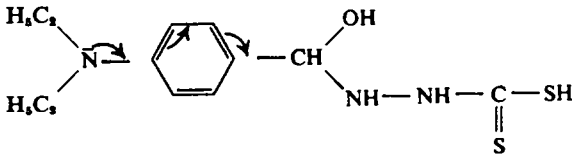
Aliphatic aldehydes and ketones react with an aqueous solution of ammonium dithiocarbazate at room temperature or by heating the mixture slightly. The 1,3,4-thiadiazolidine-2-thiones formed are precipitated from the solution by acidification (Table 1).

In the case of aromatic aldehydes and ketones, instead of the 1,3,4-thiadiazolidine-2-thiones, the corresponding azines (VI) are formed in practically quantitative yield. The azine formation occurs by addition of a second molecule of aldehyde or ketone to the intermediary N-substituted dithiocarbazate anion (IV) followed by elimination of water and the dithiobicarbonate anion (VII). This elimination is strongly favoured by substituents with high π-electron density which facilitate the formation of π-orbitals in the chain whereby the electrons between the chain and the aryl nuclei are withdrawn, stabilizing the azine system.

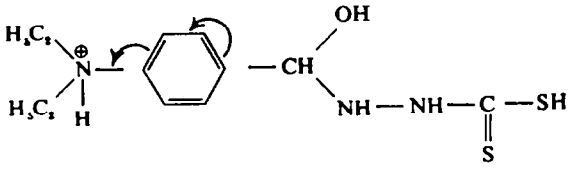
Electron attracting substituents make azine formation difficult so that ring closure dominates. This is clearly illustrated by the behaviour on the one hand of the pyridine aldehydes and on the other of 2-furaldehyde. With the former (π-deficient) a practically quantitative conversion into 1,3,4-thiadiazolidine-2-thiones occurs whereas from the latter (π-excessive), 2-furaldehyde-azine is obtained (Table 1).

The adverse influence of electron-attracting substituents on azine formation is illustrated by the reaction of dithiocarbazic acid with *p*-diethylaminobenzaldehyde hydrochloride and with *p*-diethylaminobenzaldehyde itself. The free base is immediately converted into the aldazine, but the reaction with the hydrochloride yields 5-(*p*-diethylaminophenyl)-1,3,4-thiadiazolidine-2-thione hydrochloride. As distinct from the diethylamine group (VIII), the diethylammonium group (IX), having an electron-attracting effect, counteracts azine formation.

The 5-(*p*-diethylaminophenyl)-1,3,4-thiadiazolidine-2-thione hydrochloride is, however, very unstable and during separation is converted into the *p*-diethylaminobenzaldehyde azine (VI; $R_3 = p(C_2H_5)_2N—C_6H_4$; $R_4 = H$) by splitting off hydrochloric acid, water and dithiocarbazic acid.

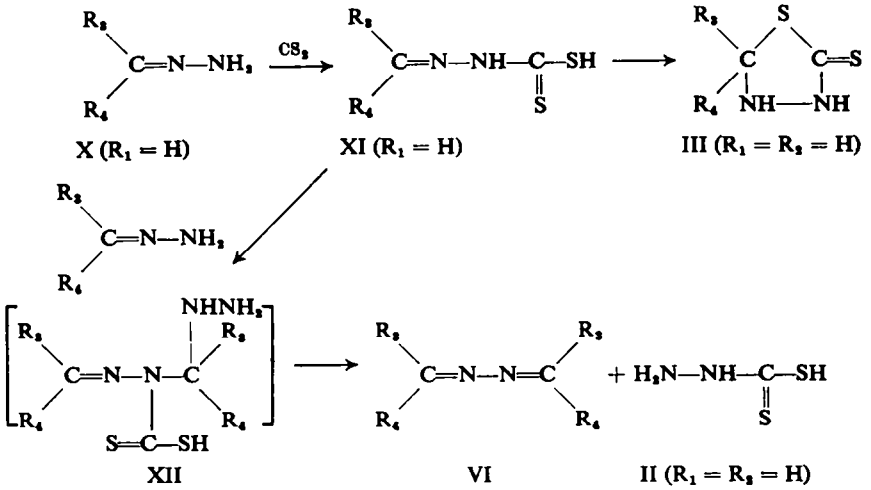


VIII



IX

(b) *Reaction of carbon disulphide with hydrazones.* During the study of this reaction, a new method was found for the preparation of 1,3,4-thiadiazolidine-2-thiones. The hydrazones of aliphatic aldehydes or ketones (X) react with carbon disulphide yielding 5-R_3,R_4-1,3,4-thiadiazolidine-2-thiones (III; $R_1 = R_2 = H$).



X ($R_1 = H$) XI ($R_1 = H$) III ($R_1 = R_2 = H$)

XII VI II ($R_1 = R_2 = H$)

This ring closure occurs only with aliphatic and π-deficient heterocyclic aldehydes or ketones (Table 1, method B). When R_3 or R_4 is a substituent with a high π-electron density the hydrazones are converted into azines. This conversion probably occurs via XII as an intermediate. In addition to the azine (VI), dithiocarbazic acid is found in the reaction medium.

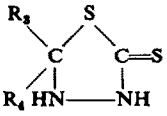
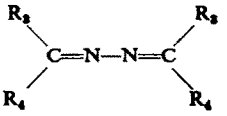
When R_3 or R_4 is a nitro-substituted phenyl group no azine formation is observed and 1,3,4-thiadiazolidine-2-thione ring closure does not occur or only with great difficulty. Only *o*-nitrobenzaldehyde hydrazone yields a small quantity of 5-(*o*-nitrophenyl)-1,3,4-thiadiazolidine-2-thione but *m*- and *p*-nitrobenzaldehyde hydrazones are recovered unchanged.

The hydrazones of nicotinaldehyde, picolinaldehyde and isonicotinaldehyde react

exothermally with carbon disulphide to form the corresponding 1,3,4-thiadiazolidine-2-thiones.

The reactions of carbon disulphide and hydrazones are listed in Table 1 under method B.

TABLE 1

Aldehyde or ketone (method A) Hydrazone (method B)		PRODUCT OBTAINED 						
			Yield in %				Yield in %	
R_3	R_4	m.p.	Method A[a]	Method B[a]	m.p.	Literature	Method A[a]	Method B[a]
H	H	98°	41					
CH_3	H	116°	92					
CH_3	CH_3	120–125°	68	21				
CH_3CH_2	CH_3	68°	27					
CF_3	CH_3	176°	17					
$CH_3CH_2CH_2CH_2$		126°	49					
$CH_3CH_2CH_2CH_2CH_2$		135–140°	85	80				
2-pyridyl	H	118–125°		98				
3-pyridyl	H	120–125°		85				
4-pyridyl	H	138–140°		86				
o-$O_2NC_6H_4$	H	140–150°		13[b]	205°	5	80	0
p-$O_2NC_6H_4$	H			0	260°	5	94	0
m-$O_2NC_6H_4$	H			0	190–192°	5	94	0
C_6H_5	CH_3				123–124°	6		97
C_6H_5	H				93°	7	100	80
o-ClC_6H_4	H				141°	8	86	70
p-ClC_6H_4	H				211°	9	100	
m-ClC_6H_4	H				141°	10	89	
o-HOC_6H_4	H				213°	11	84	95
p-HOC_6H_4	H				239–240°	12	84	
m-HOC_6H_4	H				205°	13	84	
3,4-$(OCH_2O)C_6H_3$	H				203°	14	95	
2-furyl	H				112–113°	7	95	40[c]

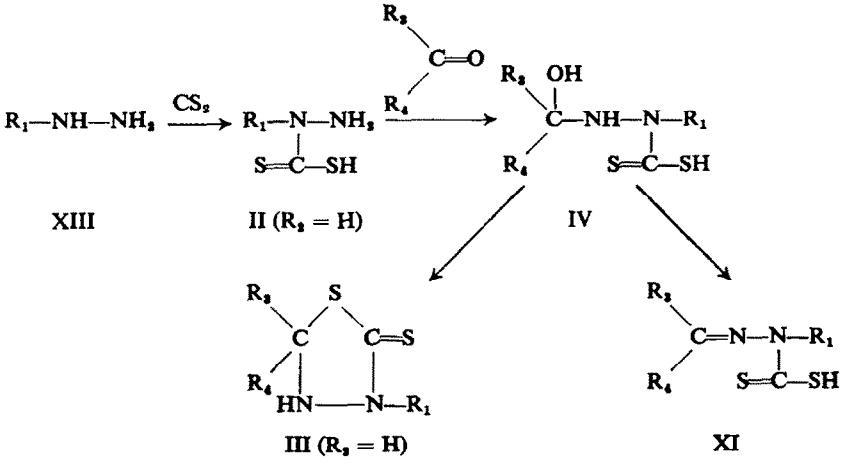
[a] method A: aldehyde or ketone and dithiocarbazic acid method B: hydrazones and carbon disulphide.
[b] 69% of unreacted *o*-nitrobenzaldehyde hydrazone.
[c] 50% of unreacted 2-furaldehyde hydrazone.

II. 5-R_3,R_4-3-*Alkyl*-1,3,4-*thiadiazolidine*-2-*thiones*

(a) *Reaction of* N-*alkyldithiocarbazates with aldehydes and ketones.* The reaction of alkylhydrazines (XIII) with carbon disulphide occurs with the most nucleophilic nitrogen atom (viz. the alkylated nitrogen in view of the electron-releasing properties

[5] K. Mijatake, *J. Pharm. Soc. Japan* **72**, 1162 (1952); *Chem. Abstr.* **47**, 6885a (1953).
[6] L. Horner, L. Hockenberger and W. Kirmse, *Chem. Ber.* **94**, 296 (1961).
[7] E. R. Blout and R. M. Gofstein, *J. Amer. Chem. Soc.* **67**, 16 (1945).
[8] G. Lock and K. Stach, *Ber. Dtsch. Chem. Ges.* **76**, 1252 (1943.
[9] M. Busch and W. Foerst, *J. Prakt. Chem.* (2), **119**, 302 (1928).
[10] T. Curtius, *J. Prakt. Chem.* (2) **85**, 178 (1912).
[11] T. Curtius and H. Franzen, *Ber. Dtsch. Chem. Ges.* **35**, 3234 (1902).
[12] H. Franzen and T. Eichler, *J. Prakt. Chem.* (2), **82**, 247 (1910).
[13] T. Curtius, *J. Prakt. Chem.* (2), **85**, 398 (1912).
[14] T. Curtius, *J. Prakt. Chem.* (2), **85**, 461–475 (1912).

of the alkyl group) resulting in the exclusive formation of 2-alkyldithiocarbazic acids (II; $R_2 = H$).

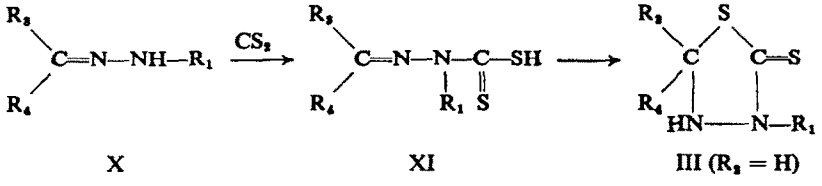


This reaction is analogous to the formation of 2-methylthiosemicarbazide from methylhydrazine and thiocyanic acid.[15]

When 2-alkyldithiocarbazic acids react with aldehydes and ketones, 3-alkylsubstituted 1,3,4-thiadiazolidine-2-thiones (III; $R_2 = H$) are formed. Since the products obtained show in their IR spectra specific NH-bands at 3·15 μ it may be concluded that products with open-chain structure (XI) are not formed in this reaction or only as intermediary products. Only in the 1,3,4-thiadiazolidine-2-thiones the NH-group occurs. Moreover, the relatively high stability of the silver salts of the products obtained points to the 1,3,4-thiadiazolidine-2-thione structure rather than to a dithiocarbazic acid derivative (XI).

Since azine formation is impossible in the reaction of N-alkyldithiocarbazic acids with carbonyl compounds, aliphatic, aromatic as well as heterocyclic aldehydes and ketones react to form the corresponding 3-alkyl-5-R_3,R_4-1,3,4-thiadiazolidine-2-thiones (Table 2, method A).

(b) *Reaction of carbon disulphide with* N-*alkyl hydrazones.* The N-alkylhydrazones

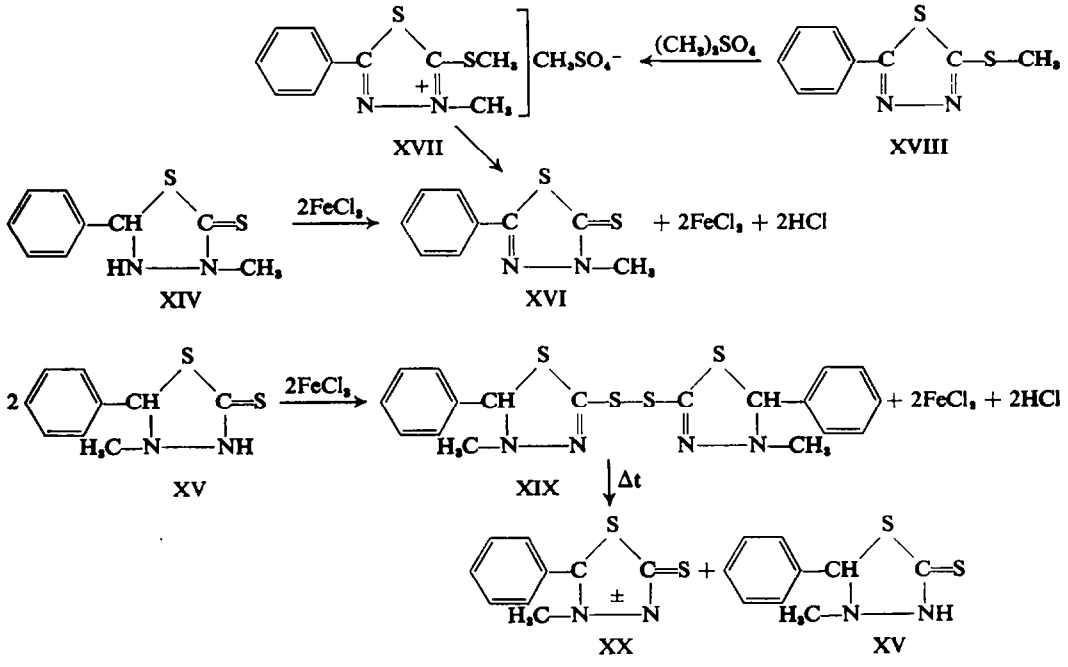


of aliphatic, aromatic and heterocyclic aldehydes or ketones readily undergo ring closure in carbon disulphide to form the corresponding 3-alkyl-5-R_3,R_4-1,3,4-thiadiazolidine-2-thiones (III; $R_2 = H$; Table 2—method B). The products formed are identical with those obtained from the carbonyl compounds and the alkyldithiocarbazic acids (method A). This is additional proof that the reaction of carbon disulphide with alkyl hydrazones occurs with the formation of a 2-alkyldithiocarbazic acid (II; $R_2 = H$)

[15] W. R. McBride, W. G. Finnegan and R. A. Henry, *J. Org. Chem.* **22**, 153 (1957).

and not a 3-alkyldithiocarbazic acid, otherwise the 4-substituted 5-R_3,R_4-1,3,4-thiadiazolidine-2-thiones (III; R_1 = H) would be formed according to the first method.

The 3-alkyl-5-R_3,R_4-1,3,4-thiadiazolidine-2-thiones can be titrated with alkali although these compounds contain no enolisable thioxo group. In order to examine the possibility of rearrangement of the alkyl group from $N_{(3)}$ to $N_{(4)}$, the position of the group in these compounds was determined. For this purpose the reaction product of benzaldehyde methylhydrazone and carbon disulphide was oxidized with iron(III) chloride. The reaction products and the consumption of iron(III) chloride depend on whether this oxidation is carried out on the 3-methyl-(XIV) or on the 4-methyl-(XV) 5-phenyl-1,3,4-thiadiazolidine-2-thione.

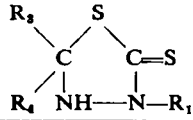


Experimentally it was found that two moles of iron (III) chloride are consumed per mole of alkyl-1,3,4-thiadiazolidine-2-thione. The oxidation product corresponds to the empirical formula $C_8H_8N_2S_2$ and is identical with the 3-methyl-5-phenyl-1,3,4-thiadiazoline-2-thione (XVI), independently prepared by desalkylation in pyridine of product (XVII), which was prepared by methylation of 2-methyl-thio-5-phenyl-1,3,4-thiadiazole (XVIII). This excludes the occasional sydnone (XX) formation by pyrolysis of the disulphide (XIX). As a result of this examination it may be assumed that all alkyl-1,3,4-thiadiazolidine-2-thiones possess the 3-alkyl structure, no matter whether they have been prepared by reaction of alkyldithiocarbazic acids and carbonyl compounds or by reaction of alkyl hydrazones and carbon disulphide. The 3-alkyl-1,3,4-thiadiazolidine-2-thiones prepared from alkyl hydrazones and carbon disulphide are listed in Table 2 under method B.

The methylhydrazones of 2,4-dinitrobenzaldehyde and *o*-nitrobenzaldehyde and

the β-hydroxyethylhydrazone of 2,4-dinitrobenzaldehyde do not react with carbon disulphide.

TABLE 2

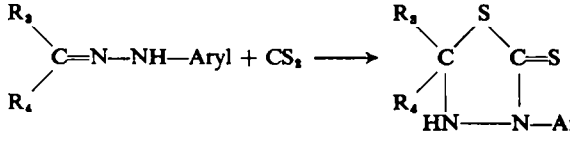


				Yield in %	
				Method	
R_3	R_4	R_1	m.p.	A[a]	B[a]
CH_3	CH_3	CH_3	82°	31	56
$CH_3CH_2CH_2CH_2CH_2$		CH_3	123–124°	35	85
CH_3	CH_3	CH_2CH_2OH	oil		25
$C_6H_5CH_2CH_2$	H	CH_3	60°		90
2-pyridyl	H	CH_3	97°		73
4-pyridyl	H	CH_3	116°		70
C_6H_5	H	CH_3	96°	14	96
C_6H_5	H	CH_2CH_2OH	90°		65
o-ClC_6H_4	H	CH_3	170°		30
o-HOC_6H_4	H	CH_3	140°		70
2-Furyl	H	CH_3	120°		52

[a] Method A: aldehyde or ketone and dithiocarbazic acid Method B: hydrazones and carbon disulphide.

III. 3-*Aryl*-5-R_3,R_4-1,3,4-*thiadiazolidine*-2-*thiones*

Attempts to cyclize arylhydrazones of aldehydes and ketones (X; R_1 = aryl) with carbon disulphide to form 3-aryl-5-R_3,R_4-1,3,4-thiadiazolidine-2-thiones (III; R_1 = aryl; R_2 = H) were unsuccessful.



X (R_1 = aryl) III (R_1 = aryl; R_2 = H)

The low electron density of the aryl substituted nitrogen atom prevents the nucleophilic attack on the carbon disulphide.

EXPERIMENTAL[*]

I. *Potassium*-N-*methyldithiocarbazate* (K-salt of II; $R_1 = CH_3$; $R_2 = H$)

To methylhydrazine (5 g; 0·108 mole) and 6% alcoholic KOH (100 ml), CS_2 (8·2 g; 0·108 mole) was added dropwise with stirring at room temp. The solution was kept overnight at room temp and the EtOH distilled off under red. press. The residue (14·5 g) was recrystallized from EtOH, yield 5 g, m.p.: 219–220°. (Found: C, 14·88; H, 3·21; N, 17·50–17·34; $C_2H_5N_2S_2K$ requires: C, 15·01; H, 3·15; N, 17·51%.)

II. *Synthesis of the hydrazones*

The hydrazones not described in literature were prepared as follows:

(a) *Isonicotinaldehyde methylhydrazone* (X; $R_1 = CH_3$, $R_2 = H$; R_4 = 4-pyridyl). Isonicotinaldehyde (10·7 g; 0·1 mole) dissolved in a solution of methylhydrazine sulphate (14·4 g; 0·1 mole) in

[*] All m.p.s were determined on a Kofler hot bench.

water (50 ml) was refluxed for 2 hr, made alkaline with NH_4OH and then extracted with $CHCl_3$. After evaporation of the $CHCl_3$, the residue was distilled, yield 8 g (60%); b.p. 130°/0·25 mm; m.p. 64–65° after recrystallization from CCl_4. (Found: C, 62·04; H, 6·72; $C_7H_9N_3$ requires: C, 62·27; H, 6·72%.)

(b) *Picolinaldehyde methylhydrazone* (X; $R_1 = CH_3$; $R_3 = H$; R_4 = 2-pyridyl) was prepared by a method similar to that described under (a), b.p. 135–140°/12 mm, yield 73%.

(c) 2,4-*Dinitrobenzaldehyde methylhydrazone* (X; $R_1 = CH_3$; $R_3 = H$; $R_4 = 2,4(O_2N)_2C_6H_3$). To a solution of methylhydrazine sulphate (7·2 g; 0·05 mole) in water (10 ml), a solution of 2,4-dinitrobenzaldehyde (9·8 g; 0·05 mole) in EtOH (50 ml) was added. The pH of the reaction mixture was adjusted to 7 by addition of pulverized sodium acetate and EtOH (100 ml) added in order to precipitate all inorganic salt. The mixture was filtered and the filtrate evaporated till crystallization began. The mixture was cooled and the crystals filtered off by suction, yield 3 g (27%), m.p. 97–99°. (Found: C, 42·54; H, 3·85; N, 24·57–24·55; $C_8H_8O_4N_4$ requires: C, 42·89; H, 3·60; N, 25·0%.)

(d) *Acetone methylhydrazone* (X; $R_1 = R_3 = R_4 = CH_3$). A solution of methylhydrazine sulphate (28·8 g; 0·2 mole) in water (35 ml) was added to acetone (100 ml) while stirring. The reaction mixture was refluxed for 15 min and dehydrated with anhydrous Na_2CO_3. The inorganic salts were filtered off and the filtrate evaporated, yield 8·5 g (50%).

(e) *Hydrocinnamaldehyde methylhydrazone* (X; $R_1 = CH_3$; $R_3 = H$; $R_4 = C_6H_5CH_2CH_2$). A solution of hydrocinnamaldehyde (11·5 g; 0·88 mole) in EtOH (100 ml) was added to 8·8M methylhydrazine in water (100 ml). The mixture was refluxed for 2 hr and the EtOH distilled off and the aqueous layer extracted with ether. The extract was dried over anhydrous Na_2SO_4 and the ether evaporated. The residue was distilled, yield 7 g (49%), b.p. 118°/2 mm.

(f) o-*Chlorobenzaldehyde methylhydrazone* (X; $R_1 = CH_3$; $R_3 = H$; R_4 = o-Cl-C_6H_4). This was prepared by a method similar to that described under (e), b.p. 114–119°/1·5 mm, yield 31%.

(g) o-*Nitrobenzaldehyde methylhydrazone* (X; $R_1 = CH_3$; $R_3 = H$; R_4 = o-$NO_2C_6H_4$). This was prepared by a method similar to that described under (e), b.p. 143°/0·5 mm, yield 55% ,m.p. 37–39° after recrystallization from hexane by cooling to −65°. (Found: C, 53·56; H, 4·90; N, 23·47–23·22; $C_9H_9O_2N_3$ requires: C, 53·68; H, 5·07; N, 23·48%.)

(h) *Benzaldehyde β-hydroxyethylhydrazone* (X; $R_1 = CH_2CH_2OH$; $R_3 = H$; $R_4 = C_6H_5$). This was prepared by a method similar to that described under (e), b.p. 162–163°/1 mm, yield 73%.

(i) 2,4-*Dinitrobenzaldehyde β-hydroxyethylhydrazone* (X; $R_1 = CH_2CH_2OH$; $R_3 = H$; $R_4 = 2,4(O_2N)_2C_6H_3$). This was prepared by a method similar to that described under (e) but extraction was unnecessary. The product crystallized on concentration of the solution, m.p. 117° after recrystallization from isopropyl alcohol, yield 81%. (Found: N, 22·27–21·58; $C_9H_{10}O_5N_4$ requires: N, 22·06%.)

III. *Synthesis of 1,3,4-thiadiazolidine-2-thiones*

(a) 1,3,4-*thiadiazolidine-2-thione* (III; $R_1 = R_2 = R_3 = R_4 = H$). A 37% formaldehyde solution (8·1 g; 0·1 mole) was added to an aqueous 1M solution of ammonium dithiocarbazate[16] (100 ml). After keeping the reaction mixture for 24 hr at room temp, 1,3,4-thiadiazolidine-2-thione was precipitated by acidification with 5N HCl. The sticky precipitate was purified by dissolving in 1N NaOH and precipitation with HCl, yield 5 g (41%), m.p. 98° (with dec). The product is instable. (Found: C, 19·83–20·61; H, 3·19–2·94; N, 18·08–18·26; $C_3H_4N_2S_2$ requires: C, 20·02; H, 3·36; N, 23·25%.)

(b) 5-*methyl*-1,3,4-*thiadiazolidine-2-thione* (III; $R_1 = R_2 = R_3 = H$; $R_4 = CH_3$). This was prepared by a method similar to that described under (a), m.p. 116°, yield 45%. (Found: C, 26·93–27·29; H, 4·23–4·57; N, 20·80; S, 47·55; $C_3H_6N_2S_2$ requires: C, 26·89; H, 4·51; N, 20·91; S, 47·86%.)

(c) 5,5-*Dimethyl*-1,3,4-*thiadiazolidine-2-thione* (III; $R_1 = R_2 = H$; $R_3 = R_4 = CH_3$). *Method* A. To ammonium dithiocarbazate (7·5 g; 0·06 mole) suspended with stirring in acetone (100 ml), water was added dropwise until a clear solution was obtained. After 5 min at room temp, a white precipitate formed and by boiling the reaction mixture precipitation was completed. The mixture was cooled and the precipitate filtered off by suction, yield 6 g (68%), m.p. 120–125°. A mixed m.p. of the product and an analytically pure specimen prepared according to method B was 120–125°.

Method B. Acetone hydrazone[17] (380 g; 5·3 moles) was added gradually with vigorous stirring

[16] S. M. Losanitch, *J. Chem. Soc.* 763 (1921).

[17] R. Von Rothenburg, *Ber. Dtsch. Chem. Ges.* **26**, 2060 (1893).

to CS_2 (500 ml). The reaction proceeded exothermally and after keeping the mixture overnight at room temp the crystalline product formed was filtered off by suction and washed with hexane, yield 162 g (21%), m.p. 120–125°. (Found: C, 32·64; H, 5·55; N, 18·68; $C_4H_8N_2S_2$ requires: C, 32·46; H, 5·45; N, 18·93%.)

(d) 5-*Ethyl*-5-*methyl*-1,3,4-*thiadiazolidine*-2-*thione* (III; $R_1 = H$; $R_3 = CH_3$; $R_4 = C_2H_5$). This was prepared by a method similar to that described under (a), m.p. 68°, yield 27%. (Found: C, 27·00; H, 6·61; N, 17·44; $C_5H_{10}N_2S_2$ requires: C, 27·07; H, 6·22; N, 17·29%.)

(e) 5-*Methyl*-5-*trifluoromethyl*-1,3,4-*thiadiazolidine*-2-*thione* (III; $R_1 = R_3 = H$; $R_3 = CH_3$; $R_4 = CF_3$). This was prepared by a method similar to that described under (a), m.p. 176°, yield 17%. (Found: N, 13·67–13·82; S, 31·97; $C_4H_5F_3N_2S_2$ requires: N, 13·87; S, 31·75%.)

(f) 5,5-*tetramethylene*-1,3,4-*thiadiazolidine*-2-*thione* (III; $R_1 = R_3 = H$; $R_3 + R_4 = (CH_2)_4$). This was prepared by a method similar to that described under (a), m.p. 126°, yield 49%. (Found: N, 16·26; $C_6H_{10}N_2S_2$ requires: N, 16·10%.)

(g) 5,5-*pentamethylene*-1,3,4-*thiadiazolidine*-2-*thione* (III; $R_1 = R_3 = H$; $R_3 + R_4 = (CH_2)_5$). *Method* A was similar to that described under (a), m.p. 153°, yield 85%. (Found: C, 44·45; H, 6·50; S, 33·89; $C_7H_{12}N_2S_2$ requires: C, 44·72; H, 6·43; S, 34·11%.)

Method B. To cyclohexanone hydrazone[18] (11·5 g; 0·11 mole) dissolved in $CHCl_3$ (30 ml), CS_2 (40 ml) was added. The reaction mixture was kept overnight and the crystalline product filtered off by suction and washed with n-hexane, yield 15 g (80%), m.p. 156° after recrystallization from $CHCl_3$–n-hexane 1:1. (Found: C, 44·67; H, 6·65; N, 15·14–15·03; $C_7H_{12}N_2S_2$ requires: C, 44·72; H, 6·43; N, 14·90%.)

(h) 5-(o-*Nitrophenyl*)-1,3,4-*thiadiazolidine*-2-*thione* (III; $R_1 = R_3 = R_3 = H$; $R_4 = o\text{-}O_2NC_6H_4$). This was prepared by the method described under (g), yield 13%, m.p. 140–150°. By evaporation of the $CHCl_3$–CS_2 filtrate 69% *o*-nitrobenzaldehyde hydrazone[19] was recovered. (Found: C, 40·19; H, 2·81; N, 17·30–17·37; $C_8H_7N_3O_2S_2$ requires: C, 39·87; H, 2·93; N, 17·44%.)

(i) 5-(4-*Pyridyl*)-1,3,4-*thiadiazolidine*-2-*thione* (III; $R_1 = R_3 = R_3 = H$; $R_4 = 4$-pyridyl). This was prepared by method B described under (g) starting from isonitocinaldehyde hydrazone,[20] yield 86%, m.p. 138–140°. (Found: C, 42·91; H, 3·69; $C_7H_7N_3S_2$ requires: C, 42·68; H, 3·58%.)

(j) 5-(2-*Pyridyl*)-1,3,4-*thiadiazolidine*-2-*thione* (III; $R_1 = R_3 = R_3 = H$; $R_4 = 2$-pyridyl). This was prepared by method B described under (g), starting from picolinaldehyde hydrazone,[21] yield 98%, m.p. 118–125°. (Found: C, 42·35; H, 3·45; $C_7H_7N_3S_2$ requires: C, 42·68; H, 3·58%.)

(k) 5-(3-*Pyridyl*)-1,3,4-*thiadiazolidine*-2-*thione* (III; $R_1 = R_3 = R_3 = H$; $R_4 = 3$-pyridyl). This was prepared by method B described under (g), starting from nicotinaldehyde hydrazone,[20] yield 85%, m.p. 120–125°. (Found: C, 42·53; H, 3·55; N, 21·65–21·41; $C_7H_7N_3S_2$ requires: C, 42·68; H, 3·58; N, 21·33%.)

(l) 3,5,5-*Trimethyl*-1,3,4-*thiadiazolidine*-2-*thione* (III; $R_1 = R_3 = R_4 = CH_3$; $R_3 = H$). *Method* A. Methylhydrazine sulphate (14 g; 0·1 mole) dissolved in water (40 ml) was made alkaline by addition 5N NaOH (60 ml) and CS_2 (7·6 g; 0·1 mole) was added dropwise with vigorous stirring which was continued until a completely clear solution was obtained. Acetone was added and the solution kept overnight at room temp and neutralized with HClaq, yield 5 g (31%), m.p. 78–79°; 82° (Found: C, 36·93; H, 6·33; N, 17·20–17·36; $C_5H_{10}N_2S_2$ requires: C, 37·07; H, 6·22; N, 17·29%.)

Method B was similar to that described under (c) starting from acetone methylhydrazone, yield 56%, m.p. 78–79°, 82°. (Found: C, 37·05; H, 6·16; N, 17·27–17·31; $C_5H_{10}N_2S_2$ requires: C, 37·07; H, 6·22; N, 17·29%.)

(m) 3-*Methyl*-5,5-*pentamethylene*-1,3,4-*thiadiazolidine*-2-*thione* (III; $R_1 = CH_3$; $R_2 = H$; $R_3 + R_4 = (CH_2)_5$). *Method* A. The procedure as described under (1), method A, starting from cyclohexanone yield 35%, m.p. 123–124° after recrystallization from hexane–$CHCl_3$. (Found: C, 47·82; H, 7·09; N, 13·82; $C_8H_{14}N_2S_2$ requires: C, 47·56; H, 6·99; N, 13·87%.)

Method B. The procedure as described under (1), method B, starting from cyclohexanone methylhydrazone,[22] yield 85%, m.p. 123–124°. The mixed m.p. of the product and a specimen prepared according to method A was 123–124°.

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[19] T. Curtius and A. Lublin, *Ber. Dtsch. Chem. Ges.* **33**, 2462 (1900).
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[22] R. H. Wiley and G. Irick, *J. Org. Chem.* **24**, 1926 (1959).

(n) *3-Methyl-5-phenylethyl-1,3,4-thiadiazolidine-2-thione* (III; $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = C_6H_5CH_2CH_2$). The procedure as described under (c), method B, starting from hydrocinnamaldehyde methylhydrazone yield 90%, m.p. 60°, (Found: N, 11·83; $C_{11}H_{14}N_2S_2$ requires: N, 11·77%.)

(o) *3-Methyl-5-phenyl-1,3,4-thiadiazolidine-2-thione* (III; $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = C_6H_5$). *Method* A. The procedure as described under (1), method A, starting from benzaldehyde yielded 14%, m.p. 96°. The mixed m.p. of the product and a specimen prepared according to method B was 96°.

Method B. The procedure described under (c), method B, starting from benzaldehyde methylhydrazone,[22] yielded 78%, m.p. 96° after recrystallization from EtOH. (Found: C, 51·56; H, 4·92; N, 13·43–13·41; $C_9H_{10}N_2S_2$ requires: C, 51·47; H, 4·80; N, 13·34%.)

(p) *3-Methyl-5-(o-chlorophenyl)-1,3,4-thiadiazolidine-2-thione* (III; $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = o\text{-}ClC_6H_4$). The procedure described under (c), method B, starting from *o*-chlorobenzaldehyde methylhydrazone yielded 30%, m.p. 170°. (Found: N, 11·45; $C_9H_9N_2S_2Cl$ requires: N, 11·46%.)

(q) *3-Methyl-5-(o-hydroxyphenyl)-1,3,4-thiadiazolidine-2-thione* (III; $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = o\text{-}HOC_6H_4$). The procedure described under (g), method B, starting from salicylaldehyde methylhydrazone,[23] yielded 67%, m.p. 140°. (Found: C, 47·79; H, 4·48; N, 12·47–12·58; $C_9H_{10}N_2OS_2$ requires: C, 47·93; H, 4·46; N, 12·40%.)

(r) *3-Methyl-5-(2-furyl)-1,3,4-thiadiazolidine-2-thione* (III; $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = 2\text{-}C_4H_3O$). The procedure, described under (g), method B, starting from 2-furaldehyde methylhydrazone,[23] was followed. The mixture should be heated gently to start the reaction, yield 52%, m.p. 120° after recrystallization from CCl_4. (Found: C, 42·17; H, 4·07; N, 13·81–13·76; $C_7H_8N_2OS_2$ requires: C, 42·00; H, 4·00; N, 14·00%.)

(s) *3-Methyl-5-(2-pyridyl)-1,3,4-thiadiazolidine-2-thione* (III; $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = 2\text{-}C_5H_4N$). The reaction, as described under (c), method B, starting from picolinaldehyde methylhydrazone, proceeds exothermally, yield 73%, m.p. 97° after recrystallization from $CHCl_3$–CCl_4, 1:1. (Found: N, 19·99–19·71; $C_8H_9N_3S_2$ requires: N, 19·92%.)

(t) *3-Methyl-5-(4-pyridyl)-1,3,4-thiadiazolidine-2-thione* (III; $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = 4\text{-}C_5H_4N$). The procedure described under (g), starting from isonicotinaldehyde methylhydrazone, yielded 73%, m.p. 116°. (Found: C, 45·51–45·67; H, 3·98–4·15; $C_8H_9N_3S_2$ requires: C, 45·54; H, 4·50%.)

(u) *3-Hydroxyethyl-5,5-dimethyl-1,3,4-thiadiazolidine-2-thione* (III; $R_1 = HOCH_2CH_2$; $R_2 = H$; $R_3 = R_4 = CH_3$). To acetone hydroxyethylhydrazone[23] (11·6 g; 0·1 mole) dissolved in $CHCl_3$ (20 ml), CS_2 (20 ml) was added with stirring. The reaction mixture was kept overnight at room temp and evaporated. The residue, a viscous oil which decomposes on distillation, yielded 5 g (25%). Microanalysis of the crude product gave the following results. (Found: C, 36·45–36·65; H, 6·77–6·93; N, 15·01–14·97; $C_8H_{16}N_2OS_2$ requires: C, 37·53; H, 6·30; N, 14·59%.)

(v) *3-Hydroxyethyl-5-phenyl-1,3,4-thiadiazolidine-2-thione* (III; $R_1 = HOCH_2CH_2$; $R_2 = R_3 = H$; $R_4 = C_6H_5$). The procedure described under (c), method B, starting from benzaldehyde hydroxyethylhydrazone yielded 65%, m.p. 90° after recrystallization from $CHCl_3$–CCl_4 1:1. (Found: N, 11·74; $C_{10}H_{12}ON_2S_2$ requires: N, 11·67%.)

IV. *3-Methyl-5-phenyl-1,3,4-thiadiazoline* (XVI)

Method 1. To 3-methyl-5-phenyl-1,3,4-thiadiazolidine-2-thione 19·5 g; (0·094 mole) dissolved in EtOH (500 ml) and heated to 60–70°, 1M $FeCl_3$aq (188 ml) was added dropwise by means of a burette until a positive reaction of thiocyanate ions (red colour) was obtained. During addition a precipitate was gradually formed and, after cooling, was separated from the solution by filtration, yield 17 g (88%). After recrystallization from acetone 15 g of XVI were obtained, m.p. 125°. (Found: mol. wt. 210–208; C, 51·80–51·42; H, 3·96–4·05; $C_9H_8N_2S_2$ requires: mol. wt. 208; C, 51·97; H, 3·88%.)

Method 2. 2-Methylthio-5-phenyl-1,3,4-thiadiazole[24] (62·5 g; 0·3 mole) dissolved in dimethyl sulphate (30 ml) was heated for 2 hr on a oil bath at 130°. The reaction mixture was cooled, treated with ether and the solid product is filtered off by suction. The precipitate (102 g) is washed with ether,

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[24] R. W. Young and K. H. Wood, *J. Amer. Chem. Soc.* **77**, 400 (1955).

dissolved in anhydrous EtOH and precipitated with acetone. In this way 48 g of 2-methylthio-3-methyl-5-phenylthiazolium methylsulphate (XVII) were obtained, m.p. 95–102, suspended in pyridine (100 ml) and the suspension refluxed for 1 hr. The reaction mixture was cooled, taken up in ether and the N-methylpyridinium methylsulphate filtered off. The filtrate was evaporated to dryness and the residue (26 g) recrystallized from EtOH using decolourizing carbon, yield 11 g, m.p. 125°. A mixed m.p. of the product and a specimen prepared according to method 1 was 125°.

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