Thermally Induced Isomerisation of Isoxazol-5-ylhydrazines

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The thermal isomerisation of isoxazol-5-ylhydrazines (I) led to 1-aminopyrazolin-5-ones (II), 4-aminopyrazolin-5-ones (III), and 1,2,4-triazin-6-ones (IV), in ratios depending on the nature of the substituents and the solvents used. A reaction mechanism involving a bicyclic intermediate, is suggested on the basis of the behaviour of isoxazolyl hydrazines methylated on the hydrazine moiety towards heating. Heating the methylated isoxazolylhydrazines (IXg and h) afforded the corresponding azirinecarbohydrazides (XII).

RECENTLY [1] we reported the thermally induced isomerisation of isoxazol-5-ylhydrazines (I), in hydrazine, to give 1-amino- (II) and 4-amino-pyrazolin-5-ones (III). On the basis of previous work [2] we suggested a mechanism involving a diradical intermediate. We now report studies on substituted isoxazol-5-ylhydrazines in various solvents or in the molten state carried out in order to discover whether the rearrangement involved hydrazine, and whether other products expected on the basis of the proposed reaction path could be isolated. We also hoped to obtain support for the suggested pathway.

Thermal cleavage reactions of isoxazoles are now assumed to occur along a reaction co-ordinate involving in-plane stretching of the N–O bond, which is intrinsically the weakest link of the system.[3]

As expected,[4] attempts to obtain evidence for the presence of a radical intermediate failed: no n.m.r. signal attributable to CIDNP, nor e.s.r. signal was detected during the reaction. However in the presence of peroxides the reaction was quicker and occurred at lower temperature, whereas it was unaffected by small amounts of water and organic acids. The rate was strongly dependent on the purity of the starting material.

As well as in anhydrous hydrazine, we studied the

[1] G. Adembri, F. Ponticelli, and P. Tedeschi, *J. Heterocyclic Chem.*, 1972, **9**, 1219.

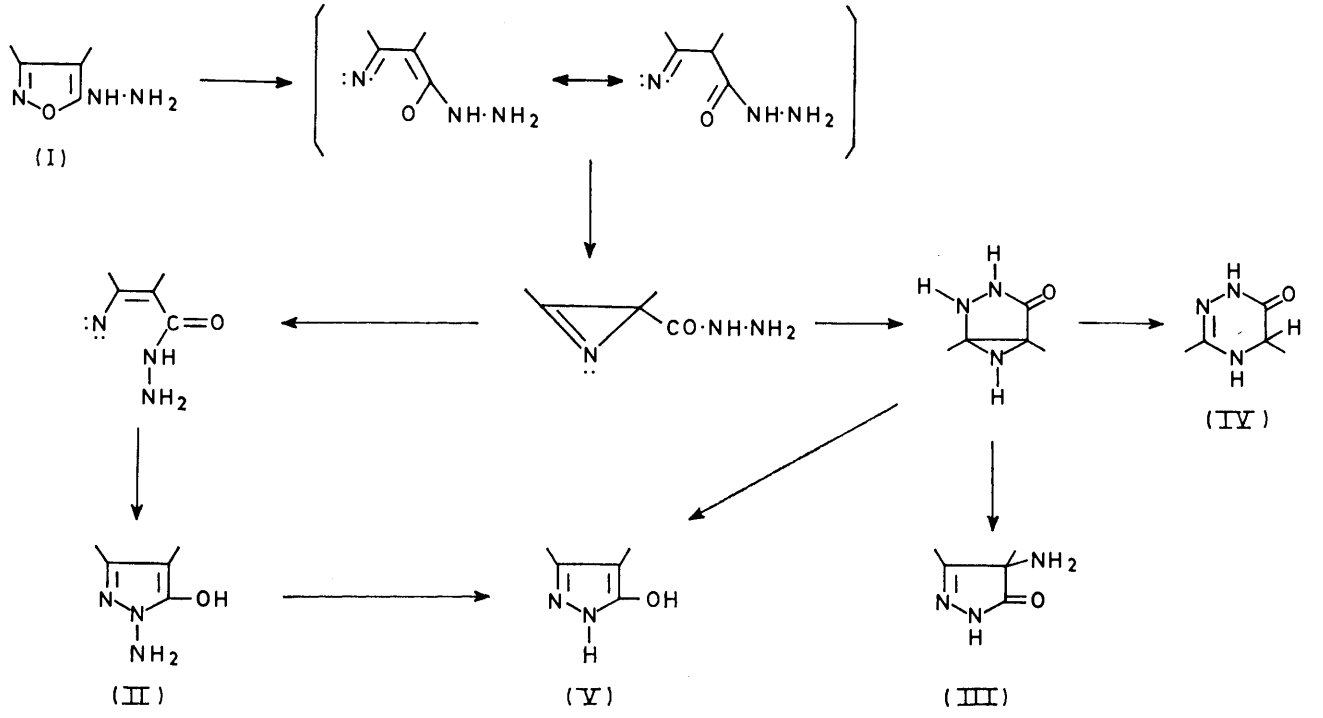
[2] (*a*) I. Adachi, K. Harada, and H. Kanō, *Tetrahedron Letters*, 1969, 4875; (*b*) T. Nishiwaki, T. Kitamura, and A. Nakano, *Tetrahedron*, 1970, **26**, 453; (*c*) T. Nishiwaki, A. Nakano, and H. Matsuoka, *J. Chem. Soc.* (*C*), 1970, 1825.

[3] A. Padwa, E. Chen, and A. Ku, *J. Amer. Chem. Soc.*, 1975, **97**, 6484.

[4] (*a*) N. M. Atherton, in 'Electron Spin Resonance,' Ellis Horwood, Chichester–Halsted Press, 1973, p. 182; (*b*) A. R. Lepley and G. L. Closs, in 'Chemically Induced Magnetic Polarization,' Wiley, New York, 1973, p. 130.

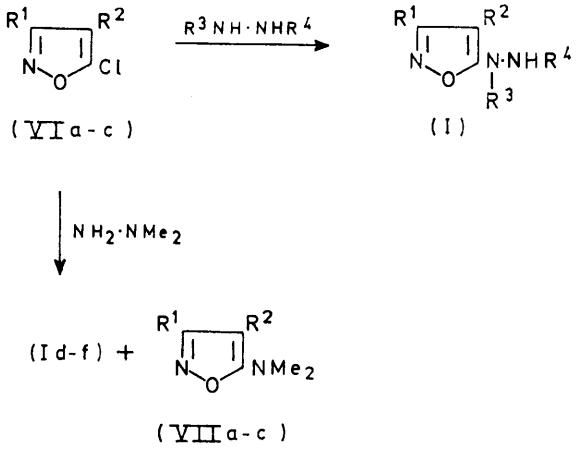
reaction in benzene, toluene, xylene, and dimethyl sulphoxide. From reactions in these solvents we were able to isolate also 1,2,4-triazin-6-ones (IV), expected on substituents on the nature and relative yields of products was also marked (see later).

The disappearance of the isoxazolylhydrazines and the



SCHEME 1

on the basis of the proposed path,[1] moreover the triazinone was sometimes the major product. The effect of



a; R^1 = Ph, R^2 = Me, R^3 = R^4 = H
b; R^1 = R^2 = Ph, R^3 = R^4 = H
c; R^1 = Me, R^2 = Ph, R^3 = R^4 = H
d; R^1 = Ph, R^2 = R^3 = Me, R^4 = H
e; R^1 = R^2 = Ph, R^3 = Me, R^4 = H
f; R^1 = R^3 = Me, R^2 = Ph, R^4 = H
g; R^1 = Ph, R^2 = R^3 = R^4 = Me
h; R^1 = R^2 = Ph, R^3 = R^4 = Me
i; R^1 = R^3 = R^4 = Me, R^2 = Ph

SCHEME 2

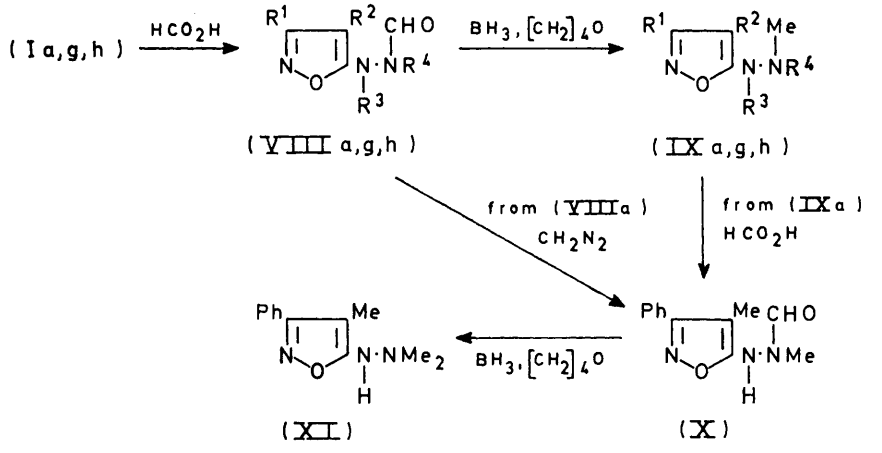
appearance of the products was followed by t.l.c. and by n.m.r. spectroscopy. Besides the main products (II)—(IV), minor compounds were detected; among these the pyrazolin-5-ones (V) were almost always present.

The thermal rearrangement can be rationalised in terms of an equilibration of a transient diradical intermediate with a 2*H*-azirine, which subsequently rearranges as shown in Scheme 1. Support for this suggestion was provided by the thermal isomerisation of isoxazolylhydrazines methylated on the hydrazine moiety.

The hydrazines (Ia—i) were conveniently prepared from 5-chloroisoxazoles (VI) and the appropriate hydrazines (Scheme 2). Reactions with methylhydrazine led only to a single product (Id—f) in high yield, whereas those with 1,1-dimethylhydrazine afforded a mixture of the hydrazine (Id—f) and 5-dimethylaminoisoxazole (VIIa—c). The hydrazines (IX) were obtained from the corresponding formyl derivatives (VIII); treatment of the hydrazines (I) with formic acid gave the 2-formyl derivatives only, and borane solutions reduced the CHO group to Me, without affecting the isoxazole ring. The dimethylhydrazine (XI) was achieved analogously by reduction of compound (X), obtainable by two procedures, the more convenient being the treatment of the formylhydrazine (VIIIa) with diazomethane. The structures of above compounds were assigned on the basis of spectral data.

Heating the hydrazines (IXg and h) gave the azirines

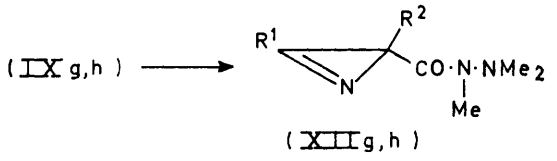
(XIIg and h) in high yield (Scheme 4). The i.r. spectra of the azirines were characterised by a medium intensity band at 1 740 cm^{-1}, due to C=N stretching [5] and a strong carbonyl band at *ca.* 1 640 cm^{-1}. U.v. spectra (solvent



SCHEME 3

methanol) were almost identical with that of 2,3-diphenylazirinecarboxamide.[6] The n.m.r. spectra showed three NMe signals, two of which coalesced on heating.

The isolation of the azirines (XII) can be considered to demonstrate that the azirines are intermediates in the rearrangement of compound (I). We believe that ring



SCHEME 4

expansion to the triazinones could occur by intramolecular attack of the hydrazine moiety with formation of a bicyclic aziridine by analogy with the mechanism proposed for the reaction of hydrazine with azirinecarboxamides.[6]

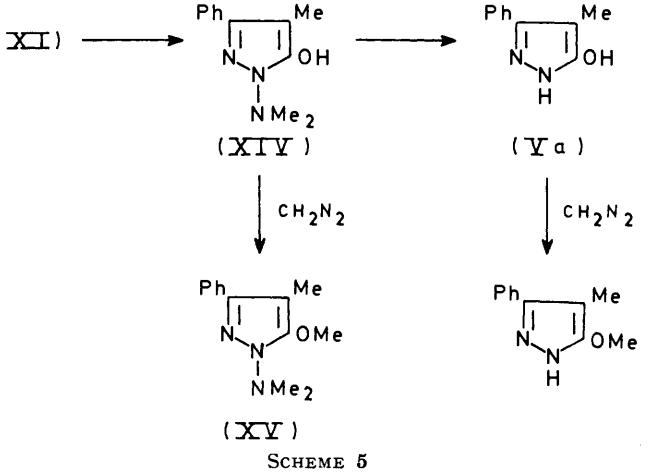
This interpretation is supported by the thermal isomerisation of the hydrazines (Id—f and g—i). Heating the hydrazines (Id—f) gave 4-amino-1-methylpyrazolones (IIId—f) and/or 1-methyltriazinones (IVd—f).[7] In agreement with the formation of a bicyclic intermediate, the hydrazines (Ig—i) yielded 1,2,5,6-tetrahydrotriazin-6-ones (XIII).[7]

In all cases, the methyl group (R^3) prevented the rearrangement to 1-aminopyrazolones (II). In contrast, introducing two methyl groups onto the terminal nitrogen atom of the hydrazino-group, only the rearrangement to 1-aminopyrazolones (II) was still possible. Thus, on heating the isoxazolylhydrazine (XI) in 1,1-dimethylhydrazine, we obtained a mixture of 1-dimethylaminopyrazolone (XIV) and the corresponding deaminated pyrazolone, which were easily separated by preparative t.l.c. of the methyl ethers (made by treatment with diazomethane).

[5] G. Smolinsky, *J. Org. Chem.*, 1962, **27**, 3557.
[6] T. Nishiwaki and T. Saito, *J. Chem. Soc.* (*C*), 1971, 2648.

The methyl ether (XV) was also prepared from 1-amino-5-methoxypyrazole (XVI) by reductive methylation with formaldehyde and sodium borohydride, formylation of the *N*-methyl derivative (XVII) to give compound (XVIII), and reduction of this with diborane solution.

The formation of the pyrazolone (Va) must be attributed to the decomposition of the 1-dimethylaminopyrazolone (XIV), since 1-aminopyrazolones (II), when heated, are deaminated to pyrazolones and, as expected, this tendency is more pronounced in the *N*-methyl derivatives. These results are also indicative of the position that the nitrogen atoms of the starting material assume in the products. Thus we can infer that the isoxazole ring nitrogen atom is that at the 4-position in the triazinones, and the amino-group nitrogen in the 4-aminopyrazolones; the amino-group nitrogen atom of 1-aminopyrazolones is the terminal nitrogen atom of the hydrazine moiety in the isoxazolylhydrazines.

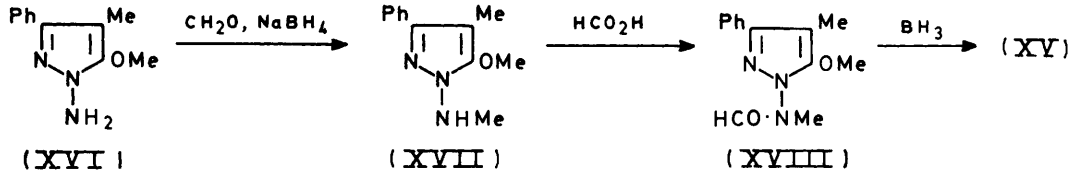


SCHEME 5

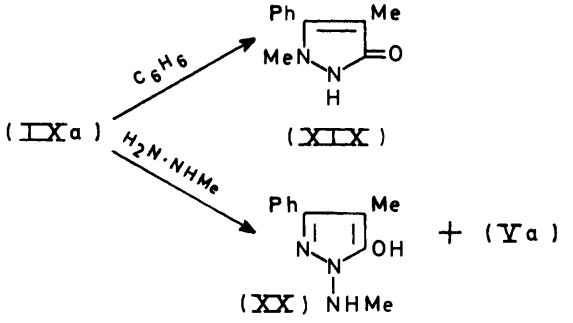
Thermal conrotatory opening of the aziridine ring in the bicyclic intermediate is not permitted by the

[7] A. Celli, A. Camparini, F. Ponticelli, and P. Tedeschi, *Chimica e Industria*, 1976, **58**, 221.

geometry of the system.[8] However, thermally disallowed valence isomerisation has been reported for other closely related systems.[9] It was suggested that the driving force for the process is provided by the relief of ring strain in the bicyclic intermediate and the gain in resonance energy of the dipolar intermediates.



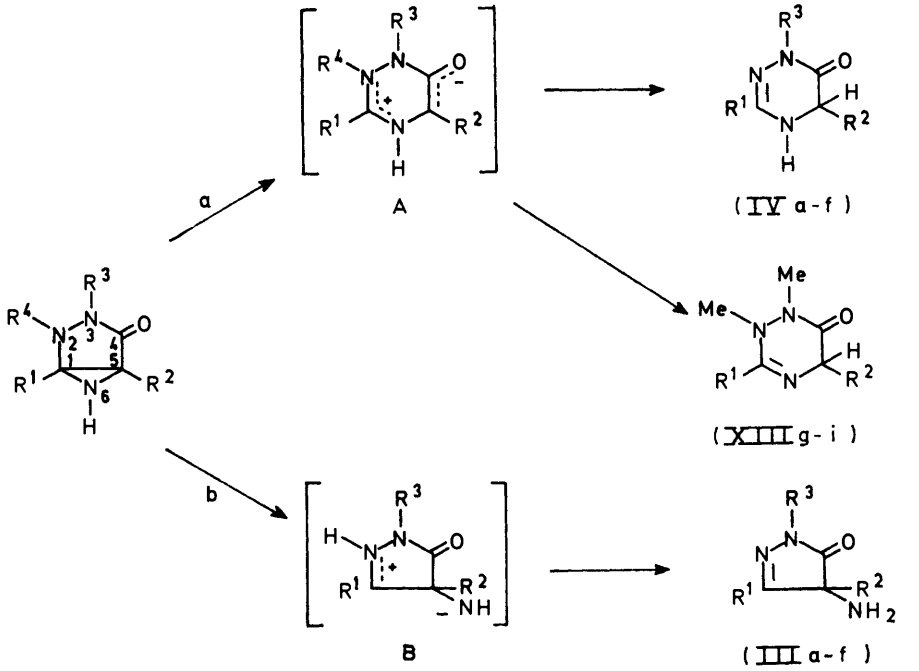
SCHEME 6



SCHEME 7

When the 2-methylisoxazolylhydrazine (IXa) rearranged in benzene, we obtained the pyrazolone (XIX), whereas in methylhydrazine a mixture of the 1-methylaminopyrazolone (XX) and its deamination product (Va) was isolated; the products were identified as methyl ethers. The formation of compound (XIX) suggests that the pyrazolone (V), often present in these reaction mixtures, can be formed by decomposition of the bicyclic intermediate as well as by deamination of the 1-aminopyrazolones (II).

The nature and position of the substituents exert a considerable influence on the relative yields of products. Although the number of compounds studied is not large, it is clear that in hydrocarbon solvents the 1-methylisoxazolylhydrazines (1d—f) give higher yields [especially of 4-aminopyrazolones (III)] than the unsubstituted compounds (Table 1). As regards substituents on the isoxazole ring, a methyl group increased the yield of 4-aminopyrazolones (III), whereas two phenyl groups increased



SCHEME 8

Rearrangement of the bicyclic intermediate can be achieved by either C–N or C–C bond cleavage of the aziridine ring followed by a hydrogen shift from the 2-

[8] R. Huisgen and H. Mader, *Angew. Chem. Internat. Edn.*, 1969, **8**, 604.

[9] (*a*) J. W. Lown and K. Matsumoto, *J. Org. Chem.*, 1971, **36**, 1405; (*b*) P. E. Hansen, and K. Undheim, *J.C.S. Perkin I*, 1975, 305.

that of the triazinone (IV). Two paths (a and b) for rearrangement of the bicyclic intermediate, involving a bond cleavage to give a dipolar intermediate A and/or B, are possible. Stabilisation of intermediate A by two phenyl groups (C–C bond cleavage) is competitive with that of intermediate B (C–N bond cleavage), favoured by

TABLE 1

Rearrangement products (% yields) of isoxazol-5-ylhydrazines in various solvents

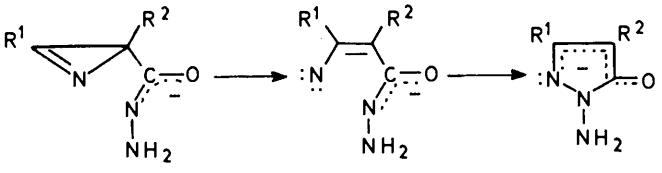
Isoxazol-5-yl-hydrazine	Solvent †	(II)	(III)	(IV)
(Ia)	A [a]	63		
	B	47	2	
	C	14	30	
	D	23	32	
(Ib)	A	68	4	
	B	34.6		5
	C		Trace	70
(Ic)	A [a]	43	12	
	B		Trace	15
	C		21.2	22
(Id)	C		90	
(Ie)	C		25	70
(If)	C		60	26

† A, hydrazine; B, di-n-butylamine; C, aromatic hydrocarbons; D, toluene–triethylamine (12 : 1 v/v).

[a] Ref. 1.

the higher electronegativity of the nitrogen atom. The isomerisation to the triazinones (IV) is completed by the hydrogen shift from N-2 to C-5. When the N-2 hydrogen atom is substituted by a methyl group the formation of the pyrazolones (III) and triazinones (IV) is disallowed; the only allowed path is that to the ylide A, followed by migration of the hydrogen atom from position 6 to C-5 with formation of triazinones (XIII).

The major production of 1-aminopyrazolones (II) in the presence of bases can be interpreted as an effect of the base on the azirine hydrazide intermediate. Thus the known mobility of hydrazide hydrogen atoms makes possible the formation of an anion, which promotes nucleophilic attack on the nitrene obtained by ring opening of the azirine.[10]



SCHEME 9

It has been suggested that bases stabilise the nitrene intermediate.[11] The same behaviour, to a lesser extent, is shown by basic solvents, or hydrocarbon solvents to which a base has been added.

Variation of substituents on the isoxazole ring has a considerable effect on the amounts of 1-aminopyrazolones (II).

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue.

[10] (*a*) T. Nishiwaki, *J.C.S. Chem. Comm.*, 1972, 565; (*b*) A. Padwa and P. H. J. Carlsen, *J. Org. Chem.*, 1976, **41**, 180.

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 357 spectrometer for Nujol mulls, unless otherwise stated. ^{1}H N.m.r. spectra (60 MHz) were recorded with a Hitachi-Perkin-Elmer R20 B instrument (Me_4Si as internal standard). U.v. spectra were measured for solution in methanol with a Perkin-Elmer 124 spectrophotometer. Spectroscopic data for compounds (1b and d—i), (VIIIa, g, and h), (IXa, g, and h), and (X) and (XI) are available as Supplementary Publication No. SUP 21967 (3 pp.).* Silica gel plates (Merck F_{254}) were used for analytical and preparative t.l.c.

5-Chloro-3,4-diphenylisoxazole (VIb).—To a stirred mixture of 3,4-diphenylisoxazolin-5-one (17 g, 0.071 7 mol) and phosphoryl chloride (52 ml, 0.568 mol), triethylamine (10.3 ml, 0.073 3 mol) was added dropwise with cooling (ice–water bath). The mixture was then heated at 120 °C for 2 h and the excess of phosphoryl chloride removed *in vacuo*. The residue was poured into ice–water, and the solid was filtered off, washed with water, dried, and extracted with boiling light petroleum (b.p. 40—70°). The extract was evaporated to give *compound* (VIb) (15 g, 81.9%). A sample obtained by two sublimations at 60 °C and 0.02 mmHg melted at 87—88° (Found: C, 70.5; H, 3.95; Cl, 14.0; N, 5.6. $C_{15}H_{10}ClNO$ requires C, 70.45; H, 3.95; Cl, 13.9; N, 5.5%); $\lambda_{max.}$ 230sh nm (log ε 4.02).

Preparation of Isoxazol-5-ylhydrazines (Ib *and* d—i).—A mixture of 5-chloroisoxazole and the appropriate hydrazine was heated as indicated in Table 2. The resulting solution was poured into ice–water and the crystalline product filtered off, washed with water, and purified as appropriate. Compound (Ig) was recovered by evaporation (to remove 1,2-dimethylhydrazine), treatment with 3N-hydrochloric acid, and extraction with light petroleum (b.p. 30—50 °C) (to remove starting material). Neutralisation of the aqueous layer, extraction with ether, and evaporation of the dried (Na_2SO_4) extracts gave an oil which was dissolved in boiling light petroleum (b.p. 30—50 °C). The solution, at room temperature, deposited a solid which was filtered off; the mother liquor was concentrated *in vacuo* and cooled at −10 °C to give compound (Ig).

Reaction of 5-Chloroisoxazoles (VIa—c) *with 1,1-Dimethylhydrazine. General Procedure.*—5-Chloroisoxazole (0.010 3 mol) and 1,1-dimethylhydrazine (10 ml, 0.131 6 mol) were heated in a sealed tube at 105—120 °C for 3 h. The resulting solution was evaporated *in vacuo* and the oily residue treated with water and extracted with ether. The ethereal solution was dried (Na_2SO_4) and evaporated.

(i) 5-Chloro-4-methyl-3-phenylisoxazole (VIa) at 120 °C afforded a mixture which was dissolved in light petroleum (b.p. 30—50 °C) and extracted first with 3N-hydrochloric acid and then with 6N-hydrochloric acid. Evaporation of the light petroleum layer yielded unchanged chloroisoxazole (VIa) (40%). Neutralisation of the 3N-hydrochloric acid solution, extraction with ether, and evaporation of the organic solvent afforded the isoxazolylmethylhydrazine (Id) (12%), identical (m.p. and i.r. spectrum) with the material already obtained. Analogous treatment of the 6N-hydrochloric acid solution yielded the 5-dimethylaminoisoxazole (VIIa) [12] (15%).

(ii) 5-Chloro-3,4-diphenylisoxazole (VIb) at 105 °C

[11] M. Komatsu, S. Ichijima, Y. Ohshiro, and T. Agawa, *J. Org. Chem.*, 1973, **38**, 4341.

[12] G. Adembri, E. Belgodere, G. Speroni, and P. Tedeschi, *Boll. sci. Fac. Chim. ind. Bologna*, 1965, **23**, 255.

afforded a mixture which was separated into two components by preparative layer chromatography with ether as developer. The fastest running band yielded *5-dimethylamino-3,4-diphenylisoxazole* (VIIb) (62%), m.p. 72—74° (from ethanol–water) (Found: C, 77.4; H, 6.15; N, 10.8. $C_{17}H_{16}N_2O$ requires C, 77.25; H, 6.1; N, 10.6%); $\lambda_{max.}$ 231 and 280 nm (log ε 4.24 and 3.95); δ ($CDCl_3$) 2.80 (NMe_2) and 7.15—7.22 (m, 2Ph). This product (yield 90%) was also obtained from the chloroisoxazole (VIb) and an excess of dimethylamine in benzene at 80 °C for 3 h.

The second band yielded the isoxazolylmethylhydrazine (Ie) (7%), identical (m.p. and i.r. spectrum) with the material already described.

at room temperature for 24 h and the excess of hydride destroyed with ethanol (6 ml). The solvents were removed *in vacuo*, concentrated hydrochloric acid (15 ml) was added slowly to the residue, and the solution was kept at ambient temperature for 18 h and neutralised with aqueous 25% sodium hydroxide. If the product was precipitated as a solid, it was collected by filtration. In the cases where the product was not precipitated, it was extracted with dichloromethane; the organic layer was washed with water, dried (Na_2SO_4), and evaporated. The crude compound was purified as described below.

(i) 1-*Methyl*-2-(4-*methyl*-3-*phenylisoxazol*-5-*yl*)*hydrazine* (IXa). The crude product was collected by filtration (yield

TABLE 2

Preparation of isoxazol-5-ylhydrazines (I)

Compound	Molar ratio of chloroisoxazole to hydrazine	Temp. (°C)	Time (min)	Yield (%)	M.p. (°C)	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N	Benzylidene deriv. m.p. (°C)
(Ib)	1 : 30	95	5	68	150—152 [c] (decomp.)	$C_{15}H_{13}N_3O$	71.9	5.0	16.5	71.7	5.2	16.7	135—137 [h]
(Id)	1 : 15	105 [a]	60	88.5	70 [d]	$C_{11}H_{13}N_3O$	65.2	6.6	20.75	65.0	6.45	20.7	97 [i]
(Ie)	1 : 25	Reflux	20	96.5	127 [e]	$C_{16}H_{15}N_3O$	72.6	5.85	15.7	72.45	5.7	15.85	174—175 [i]
(If)	1 : 25	Reflux	20	95	82 [f]	$C_{11}H_{13}N_3O$	65.1	6.25	20.65	65.0	6.45	20.7	70 [i]
(Ig)	1 : 8	100 [a]	360	55 [b]	34—36 [g]	$C_{12}H_{15}N_3O$	66.25	6.7	19.35	66.35	6.95	19.35	
(Ih)	1 : 6	100 [a]	90	97.1	93—95 [e]	$C_{17}H_{17}N_3O$	73.1	6.1	15.15	73.1	6.15	15.05	
(Ii)	1 : 8	100 [a]	120	74.3	89—90 [d]	$C_{12}H_{15}N_3O$	66.25	6.95	19.35	66.35	6.95	19.35	

[a] In a sealed tube. [b] Based on starting material consumed. [c] After recrystallisation from ethanol and from benzene. [d] After two recrystallisations from cyclohexane. [e] After recrystallisation from ethanol–water (1 : 1 v/v) and from light petroleum (b.p. 60—80 °C). [f] After recrystallisation from benzene–light petroleum (b.p. 40—70 °C) (1 : 2 v/v). [g] After recrystallisation from light petroleum (b.p. 30—50 °C). [h] From ethanol. [i] From light petroleum (b.p. 75—120 °C).

TABLE 3

N'-(Isoxazol-5-yl)formohydrazides

Compound	Cryst. solvent †	M.p. (°C)	Yield (%)	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
(VIIIa)	A	161	69.7	$C_{11}H_{11}N_3O_2$	60.9	5.2	19.3	60.8	5.1	19.35
(VIIIg)	B	75—76	79.9	$C_{13}H_{15}N_3O_2$	63.65	6.1	17.3	63.65	6.15	17.15
(VIIIh)	A	130—131	96.3	$C_{18}H_{17}N_3O_2$	70.5	5.5	13.6	70.35	5.6	13.7
(X)	C	96—98	54.1	$C_{12}H_{13}N_3O_2$	62.5	5.7	18.2	62.35	5.65	18.15

† A, ethanol; B, light petroleum (b.p. 40—70 °C); C, benzene–light petroleum (b.p. 40—70 °C) (1 : 1 v/v).

(iii) 5-Chloro-3-methyl-4-phenylisoxazole (VIc) at 110 °C afforded a mixture which was chromatographed on silica gel. 5-Dimethylamino-3-methyl-4-phenylisoxazole (VIIc)[12] (yield 62%) was eluted with light petroleum (b.p. 30—50 °C)–ether (9 : 1 v/v). Further elution with the same solvents gave the isoxazolylmethylhydrazine (If) (yield 21%), identical (m.p. and i.r. spectrum) with the material already obtained.

Preparation of the Formyl Derivatives (VIIIa, g, *and* h) *and* (X).—A mixture of the appropriate isoxazol-5-ylhydrazine (0.01 mol) and formic acid (10 ml) was heated at 85—90 °C for 30 min, cooled, and diluted with water to afford the formyl derivative which was purified as reported in Table 3.

Compound (X) was also obtained from the formyl derivative (VIIIa) (0.032 mol) in methanol (70 ml) and ethereal diazomethane (0.083 mol). The crude product was chromatographed over silica gel. Elution with ether gave a small amount of material which was discarded. Further elution with the same solvent afforded the formyl derivative (X) (yield 40%).

Reduction of the Formyl Derivatives (VIIIa, g, *and* h) *and* (X).—To the appropriate formyl derivative (0.01 mol) 1M-borane in tetrahydrofuran (20 ml) was added dropwise with stirring at 0 °C under nitrogen. The mixture was left

60%). The hydrochloride of (IXa), obtained by treating with gaseous hydrogen chloride a solution of (IXa) in dry ether, was crystallised from dry ethanol–ether, suspended in ether, and neutralised with N-sodium hydroxide to give the *isoxazolylmethylhydrazine* (IXa), which was recovered from ethereal solution. A sample obtained by crystallisation from cyclohexane melted at 95—98° (Found: C, 64.9; H, 6.3; N, 20.5. $C_{11}H_{13}N_3O$ requires C, 65.0; H, 6.45; N, 20.7%).

(ii) 1,1,2-*Trimethyl*-2-(4-*methyl*-3-*phenylisoxazol*-5-*yl*)*hydrazine* (IXg). This compound was collected as an oil (yield 57%), which was dissolved in dry ether and treated with gaseous hydrogen chloride to give the *hydrochloride*, m.p. 121—122° (from dry ethanol–ether) (Found: C, 58.2; H, 6.8; Cl, 13.3; N, 15.8. $C_{13}H_{18}ClN_3O$ requires C, 58.3; H, 6.8; Cl, 13.25; N, 15.7%).

(iii) 1-(3,4-*Diphenylisoxazol*-5-*yl*)-1,2,2-*trimethylhydrazine* (IXh). This *compound* was collected by extraction and, after two crystallisations from ethanol–water (1 : 1 v/v), melted at 98.5—100° (yield 65%) (Found: C, 73.95; H, 6.8; N, 14.5. $C_{18}H_{19}N_3O$ requires C, 73.7; H, 6.5; N, 14.3%).

(iv) 1,1-*Dimethyl*-2-(4-*methyl*-3-*phenylisoxazol*-5-*yl*)*hydrazine* (XI). This compound was collected by filtration

(yield 71%). A *sample* obtained by crystallisation first from ethanol–water (1 : 1 v/v) and then from cyclohexane, melted at 116—119° (Found: C, 66.4; H, 6.9; N, 19.15. $C_{12}H_{15}N_3O$ requires C, 66.35; H, 6.95; N, 19.35%).

5-Methoxy-4-methyl-1-methylamino-3-phenylpyrazole (XVII).—A solution of 1-amino-5-methoxy-4-methyl-3-phenylpyrazole (XVI) [1] (0.609 g, 0.003 mol) and aqueous formaldehyde (35%; 3 ml) in methanol (10 ml) was refluxed for 1 h. After cooling, sodium borohydride (0.4 g, 0.010 6 mol) was added slowly; the solution was kept at room temperature for 12 h, then evaporated *in vacuo*. The residue was extracted with dichloromethane; evaporation yielded *1-methylaminopyrazole* (XVII) (0.55 g, 84.4%). A sample obtained by crystallisation from cyclohexane had m.p. 83—85° (Found: C, 66.6; H, 6.95; N, 19.35. $C_{12}H_{15}N_3O$ requires C, 66.35; H, 6.95; N, 19.35%); $\nu_{max.}$ 3 255 cm^{-1} (NH); $\lambda_{max.}$ 249 nm (log ε 4.15); δ ($CDCl_3$) 2.10 (s, Me), 2.91 (s, NMe), 3.96 (s, OMe), 4.69br (exch., NH), and 7.25—7.71 (m, Ph).

5-Methoxy-4-methyl-1-(N-methylformamido)-3-phenylpyrazole (XVIII).—A solution of the 1-methylaminopyrazole (XVII) (0.5 g, 0.002 3 mol) in formic acid (5 ml) was heated at 90—95 °C for 40 min and neutralised with 2N-potassium carbonate, yielding the *formyl derivative* (XVIII) (0.45 g, 80%), which was collected by filtration and purified by sublimation at 65 °C and 0.01 mmHg; m.p. 73—75° (Found: C, 63.6; H, 6.2; N, 17.35. $C_{13}H_{15}N_3O_2$ requires C, 63.65; H, 6.15; N, 17.1%); $\nu_{max.}$ 1 690 cm^{-1} (CO); $\lambda_{max.}$ 244 nm (log ε 4.18).

1-Dimethylamino-5-methoxy-4-methyl-3-phenylpyrazole (XV).—To a solution of the formyl derivative (XVIII) (0.8 g, 0.003 3 mol) in dry dichloromethane (10 ml), tetrabutylammonium boronate [13] [0.006 6 mol in dichloromethane (5 ml)] was added with stirring at 0 °C under nitrogen. Methyl iodide (0.82 ml, 0.013 mol) was added dropwise, and the solution was refluxed (2 h) and then kept at room temperature overnight. Ethanol (1.5 ml) was added and the solvents were evaporated off *in vacuo*. The residue was dissolved in concentrated hydrochloric acid (8 ml); the solution was filtered and neutralised with 25% sodium hydroxide to yield the *1-dimethylaminopyrazole* (XV) (0.65 g, 86.2%), which was sublimed at 40 °C and 0.02 mmHg; m.p. 49—51° (Found: C, 67.75; H, 7.5; N, 18.3 $C_{13}H_{17}N_3O$ requires C, 67.5; H, 7.4; N, 18.2%); $\lambda_{max.}$ 248 nm (log ε 4.06); δ ($CDCl_3$) 2.10 (s, Me), 2.89 (s, NMe_2), 3.96 (s, OMe), and 7.25—7.71 (m, Ph).

Rearrangements of Isoxazol-5-ylhydrazines.—Conditions of reactions are reported in Table 4. The reaction mixtures were worked up as described below.

(a) *4-Methyl-3-phenylisoxazol-5-ylhydrazine* (Ia). (i) *In toluene.* After cooling, the solid was filtered off, dissolved in the minimum of N-sodium hydroxide, and acidified to pH 6 with concentrated hydrochloric acid to give (overnight in the refrigerator) 1-amino-4-methyl-3-phenylpyrazolin-5-one (IIa) [1] (0.06 g). Extraction of the mother liquors with chloroform afforded a second crop (0.01 g) of the same product (total 14%). The toluene solution was evaporated to dryness *in vacuo*, and the residue dissolved in chloroform and extracted with 1.5N-hydrochloric acid (3 × 10 ml). The combined acidic extracts were neutralised with 25% sodium hydroxide, cooled in the refrigerator, filtered, and extracted with chloroform. Evaporation of this extract afforded a residue which, on trituration with light petroleum (b.p. 30—50 °C), yielded *4-amino-4-methyl-3-phenylpyrazolin-5-one* (IIIa) (0.15 g, 30%). A sample obtained by crystallisation from benzene melted at 127—129° (Found: C, 63.4; H, 6.0; N, 22.3. $C_{10}H_{11}N_3O$ requires C, 63.5; H, 5.85; N, 22.2%); $\nu_{max.}$ ($CHCl_3$) 3 430 and 3 880br (NH and/or NH_2), and 1 725 cm^{-1} (CO); $\lambda_{max.}$ 216 and 290 nm (log ε 3.97 and 4.13); δ ($CDCl_3$) 1.46 (s, Me), 1.85br (exch., NH_2), 7.28—7.43 and 7.98—8.13 (m, Ph), and 9.45br (exch., NH). No 4,5-dihydro-5-methyl-3-phenyl-1,2,4-triazin-6(1*H*)-one (IVa) [7] was obtained. T.l.c. of the rest of the reaction mixture [chloroform–methanol (9 : 1 v/v)] showed the presence of a small amount of 4-methyl-3-phenylpyrazolin-5-one (VIa).

TABLE 4

Conditions of rearrangement of isoxazol-5-ylhydrazines

Compound	Solvent (ml) [a]	Temp. (°C)	Time (h)
(Ia)	PhMe (12)	100 [b]	2.5
	Bu^n_2NH (12)	100 [b]	2.5
(Ib)	N_2H_4 (4)	Reflux	2.5
	Xylene (15)	117 [b]	1.0
	Bu^n_2NH (15)	117 [b]	2.5
(Ic)	PhMe (12)	80	2.0
	Bu^n_2NH (12)	100	1.5
(Id)	PhMe (15)	Reflux	6.0
(Ie)	PhMe (15)	Reflux	1.5
(If)	Xylene (20)	Reflux	3.0
	$(CD_3)_2SO$ (7)	140	1.0
(Ig)	Xylene (12)	Reflux	10.0
(Ih)	PhMe (20)	Reflux	7.0
(Ii)	Xylene (20)	Reflux	2.0
(IXa)	PhH (25)	Reflux [b]	1.8
	$MeNH·NH_2$ (7.5)	82 [c]	2.5
(IXg)	None	132 [c]	1.8
(IXh)	None	150 [c]	1.0
(XI)	$Me_2N·NH_2$ (5.5)	102 [b,c]	5.0

[a] For 0.5 g of isoxazol-5-ylhydrazine. [b] Under nitrogen. [c] In a sealed tube.

The above rearrangement, carried out in the presence of triethylamine (1 ml) under the same conditions, gave the 1-aminopyrazolin-5-one (IIa) (yield 0.115 g, 23%) and the 4-aminopyrazolin-5-one (IIIa) (yield 0.160 g, 32%).

(ii) *In di-n-butylamine.* After cooling, the mixture was treated as above, yielding the 1-aminopyrazolin-5-one (IIa) (0.235 g, 47%) and the 4-aminopyrazolin-5-one (IIIa) (0.01 g, 2%).

(b) *3,4-Diphenylisoxazol-5-ylhydrazine* (Ib). (i) *In hydrazine.* The solvent was removed *in vacuo* and the residue treated with 3N-sodium hydroxide to give a solid (0.025 g) which consisted largely of 5-amino-3,4-diphenylisoxazole [14] (t.l.c.). The mother liquors were acidified to pH 6 with concentrated hydrochloric acid, cooled in a refrigerator, and filtered, to afford *1-amino-3,4-diphenylpyrazolin-5-one* (IIb) (yield 0.340 g, 68%), contaminated (t.l.c.) by a small amount of 3,4-diphenylpyrazolin-5-one (Vb). A sample of the former crystallised from ethanol melted at 184—186° (decomp.) (Found: C, 71.8; H, 5.2; N, 16.8. $C_{15}H_{13}N_3O$ requires C, 71.7; H, 5.2; N, 16.7%); $\nu_{max.}$ 3 335 and 3 185 (NH_2) and 2 650br cm^{-1} (OH); $\lambda_{max.}$ 240sh nm (log ε 4.14); δ [$(CD_3)_2SO$] 6.5br (exch., NH_2 and OH/NH) and 7.18—7.42 (m, 2 Ph). The aqueous mother liquors of (IIb) were extracted with chloroform, and the solvent was evaporated off to give a residue which, after repeated crystallisations from benzene, yielded *4-amino-3,4-diphenylpyrazolin-5-one* (IIIb) (0.02 g, 4%), m.p. 196—197° (Found: C.

[13] A. Brändström, U. Junggren, and B. Lamm, *Tetrahedron Letters*, 1972, 3173.

[14] R. Walter and P. G. Schickler, *J. prakt. Chem.*, 1897, **55**, 305.

71.5; H, 5.2; N, 16.9. $C_{15}H_{13}N_3O$ requires C, 71.7; H, 5.2; N, 16.7%); $\nu_{max.}$ ($CHCl_3$) 3 445, 3 385, and 3 300 (NH and/or NH_2), and 1 730 cm^{-1} (CO); $\lambda_{max.}$ 294 nm (log ε 4.13); δ [$(CD_3)_2SO$] 2.88 (s, exch., NH_2), 7.21—7.81 (m, 2 Ph), and 11.50 (s, exch., NH).

(ii) *In xylene*. After cooling, the solid was filtered off (yield 0.35 g, 70%) and identified (i.r.) as 4,5-dihydro-3,5-diphenyl-1,2,4-triazin-6(1*H*)-one (IVb).[6] T.l.c. of the mother liquors showed the presence of small amounts of the 4-aminopyrazolin-5-one (IIIb) and the pyrazolin-5-one (Vb).

(iii) *In di-n-butylamine*. The mixture was kept at room temperature (12 h) to afford a precipitate which was filtered off and dissolved in the minimum of N-sodium hydroxide (charcoal). Acidification to pH 6 with concentrated hydrochloric acid gave the 1-aminopyrazolin-5-one (IIb) (0.14 g). The di-n-butylamine solution was evaporated to dryness *in vacuo*, and the residue was treated with N-sodium hydroxide (5 ml) and extracted with ether. Acidification (pH 6) of the alkaline solution afforded a second crop (0.033 g) of the same product (total 34.6%), contaminated (t.l.c.) by a small amount of 3,4-diphenylpyrazolin-5-one (Vb). The ethereal solution was evaporated *in vacuo* and the residue, crystallised from benzene, afforded the 1,2,4-triazin-6-one (IVb) [6] (0.025 g, 5%).

(c) 3-*Methyl*-4-*phenylisoxazol*-5-*ylhydrazine* (Ic). (i) *In toluene*. The mixture was kept at room temperature (6 h) to afford a precipitate which was filtered off (0.230 g). T.l.c. analysis [chloroform–methanol (9 : 1 v/v)] showed the presence of the 1,2,4-triazin-6-one (IVc),[7] the 4-aminopyrazolin-5-one (IIIc),[1] and the pyrazolin-5-one (Vc). The ratios of products [(IVc) : (IIIc) : (Vc)] were determined by n.m.r. as 3 : 2.25 : 1. The toluene solution was extracted with 10% sodium hydroxide; the alkaline solution was neutralised and extracted with chloroform to afford, after evaporation and crystallisation from benzene, a second crop (0.023 g) of compound (IIIc) (total 21.2%).

(ii) *In di-n-butylamine*. The solution was evaporated *in vacuo* and the residue, in ether (5 ml), yielded the 1,2,4-triazin-6-one (IVc) (0.075 g, 15%). No 1-aminopyrazolin-5-one (IIc) was obtained, and t.l.c. of the rest of the mixture showed the presence of small amounts of the 4-aminopyrazolin-5-one (IIIc) and the pyrazolin-5-one (Vc), and a number of unidentified products.

(d) 1-*Methyl*-1-(4-*methyl*-3-*phenylisoxazol*-5-*yl*)*hydrazine* (Id). The solution was evaporated to dryness *in vacuo* and the residue, on trituration with light petroleum (b.p. 30—50 °C), yielded 4-*amino*-1,4-*dimethyl*-3-*phenylpyrazolin*-5-*one* (IIId) (0.45 g, 90%). A sample crystallised from cyclohexane melted at 118—119° (Found: C, 65.2; H, 6.4; N, 20.55. $C_{11}H_{13}N_3O$ requires C, 65.0; H, 6.45; N, 20.7%); $\nu_{max.}$ 3 350 and 3 285 (NH_2), and 1 705 cm^{-1} (CO); $\lambda_{max.}$ 218 and 300 nm (log ε 4.01 and 4.13); δ [$(CD_3)_2SO$] 1.32 (s, Me), 2.50br (exch., NH_2), 3.29 (s, NMe), 7.37—7.53 and 8.02—8.20 (m, Ph). No 4,5-dihydro-1,5-dimethyl-3-phenyl-1,2,4-triazin-6(1*H*)-one (IVd) [7] was found by t.l.c. of the rest of the reaction mixture.

(e) 1-*Methyl*-1-(3,4-*diphenylisoxazol*-5-*yl*)*hydrazine* (Ie). The solution was evaporated *in vacuo* and the residue separated into two components by preparative layer chromatography with ether as developer. The fastest running band gave 4-*amino*-1-*methyl*-3,4-*diphenylpyrazolin*-5-*one* (IIIe) (0.125 g, 25%), which, sublimed at 100 °C and 0.06 mmHg and crystallised from ethanol–water, melted at 149—150° (Found: C, 72.6; H, 5.8; N, 15.85. $C_{16}H_{15}N_3O$ requires C, 72.4; H, 5.7; N, 15.85%); $\nu_{max.}$ 3 365 and 3 300 (NH_2) and 1 710 cm^{-1} (CO); $\lambda_{max.}$ 220sh and 304 nm (log ε 4.09 and 4.08); δ ($CDCl_3$) 2.11br (exch., NH_2), 3.38 (s, NMe), and 7.16—7.80 (m, Ph). The second band yielded the 1,2,4-triazin-6-one (IVe) [7] (0.35 g, 70%).

(f) 1-*Methyl*-1-(3-*methyl*-4-*phenylisoxazol*-5-*yl*)*hydrazine* (If). (i) *In xylene*. The mixture was worked out as above yielding the 4-aminopyrazolin-5-one (IIIf) [1] (0.3 g, 60%) and the 1,2,4-triazin-6-one (IVf) [7] (0.13 g, 26%).

(ii) *In hexadeuteriodimethyl sulphoxide*. The reaction was monitored by n.m.r. spectroscopy. The ratios of products [(IIIf) : (IVf) : (If)] were determined as 12 : 6 : 1. When the above rearrangement was carried out in the same solvent at 120 °C in the presence of a small amount of benzoyl peroxide, the ratios of products [(IIIf) : (IVf) : (If)] were determined, after 40 min, as 4.7 : 1 : 8.6. No products were observed under the same conditions in hexadeuteriodimethyl sulphoxide alone or in the presence of small amounts of water and of benzoic acid.

(g) 1,2-*Dimethyl*-1-(4-*methyl*-3-*phenylisoxazol*-5-*yl*)*hydrazine* (Ig). The solvent was evaporated off *in vacuo* and the residue separated into five components by preparative layer chromatography with ether as developer. The fastest running band gave 1-*methyl*-2-*methylene*-1-(4-*methyl*-3-*phenylisoxazol*-5-*yl*)*hydrazine* (0.035 g, 7%), which was purified by crystallisation from light petroleum (b.p. 30—50 °C) and sublimation at 40 °C and 0.02 mmHg; m.p. 48—49° (Found: C, 66.8; H, 6.1; N, 19.5. $C_{12}H_{13}N_3O$ requires C, 66.95; H, 6.1; N, 19.5%); $\lambda_{max.}$ 228 and 284 nm (log ε 4.12 and 4.19); δ ($CDCl_3$) 2.13 (s, Me), 3.34 (s, NMe), 6.41 (AB system, *J* 10 Hz, CH_2), and 7.33—7.63 (m, Ph). This compound was also obtained (yield 60%) by refluxing the isoxazolylhydrazine (Id) (0.609 g, 0.003 mol) with aqueous formaldehyde (35%; 3 ml) for 30 min. The second band gave starting material (0.025 g, 5%). The third band gave 2-*methyl*-3-*phenyl*-2H-*azirine*-2-N-*methylcarboxamide* (0.095 g, 22%), after sublimation at 50 °C and 0.01 mmHg, m.p. 63—65° (Found: C, 70.0; H, 6.5; N, 14.8. $C_{11}H_{12}N_2O$ requires C, 70.2; H, 6.4; N, 14.9%); $\nu_{max.}$ (KBr) 3 280 (NH), 1 740 (C=N), and 1 635 cm^{-1} (CO); $\lambda_{max.}$ 247 nm (log ε 4.10); δ ($CDCl_3$) 1.52 (s, Me), 2.64 (d, *J* 6.5 Hz, s with D_2O, NHMe), 5.60br (exch., NH), and 7.32—7.84 (m, Ph). The fourth band yielded the 1,2,4-triazin-6-one (XIIIg) [7] (0.075 g, 15%) as an oil. The fifth band (0.165 g) was still a mixture [t.l.c. with chloroform–methanol (9 : 1 v/v)] and was not further examined.

(h) 1-(3,4-*Diphenylisoxazol*-5-*yl*)-1,2-*dimethylhydrazine* (Ih). The solvent was evaporated off *in vacuo* and the residue treated with ether to give the 1,2,4-triazin-6-one (XIIIh) [7] (0.300 g). A second crop (0.115 g, total 83%) was recovered from the mother liquors.

(i) 1-(3-*Methyl*-4-*phenylisoxazol*-5-*yl*)-1,2-*dimethylhydrazine* (Ii). The solution was evaporated *in vacuo*, and the oily residue was chromatographed on silica gel. Starting material (0.25 g, 50%) was eluted with ether. Further elution with ethanol gave the 1,2,4-triazin-6-one (XIIIi) [7] as an oil (0.20 g, 40%).

(j) 1-*Methyl*-2-(4-*methyl*-3-*phenylisoxazol*-5-*yl*)*hydrazine* (IXa). (i) *In benzene*. The solvent was evaporated off and the residue chromatographed on silica gel. Elution of the column with ether gave 4-*methyl*-5-*methylazo*-3-*phenylisoxazole* (0.113 g, 22.8%), which was sublimed at 60 °C and 0.02 mmHg; m.p. 79—81° (Found: C, 65.8; H, 5.4; N, 20.9. $C_{11}H_{11}N_3O$ requires C, 65.65; H, 5.5; N, 20.9%); $\lambda_{max.}$ 225 and 278 nm (log ε 4.12 and 4.09); δ ($CDCl_3$) 2.40

(s, Me), 4.11 (s, NMe), and 7.37—7.78 (m, Ph). The same product (m.p. and i.r. spectrum) was also obtained (55%) by adding to a solution of the isoxazol-5-ylhydrazine (IXa) in dioxan an excess of hydrogen peroxide (30%).

Further elution of the column with the same solvent gave 1,4-dimethyl-5-phenylpyrazolin-3-one (XIX) [1] (0.12 g, 26%). Further elution with ethanol gave 4-methyl-3-phenylpyrazolin-5-one (Va) (0.115 g, 26.9%).

(ii) *In methylhydrazine*. The solvent was evaporated off *in vacuo* and the residue treated with N-sodium hydroxide (6 ml) and extracted with ether. The extract was concentrated and chromatographed on silica gel. Elution of the column with ether gave *1-methylene-2-(4-methyl-3-phenylisoxazol-5-yl)hydrazine* (0.069 g, 13.9%). A sample obtained by crystallisation from cyclohexane, melted at 130—133° (Found: C, 65.5; H, 5.5; N, 20.9. $C_{11}H_{11}N_3O$ requires C, 65.65; H, 5.5; N, 20.9%); $\nu_{max.}$ 3 200 cm^{-1} (NH); $\lambda_{max.}$ 228 and 285 nm (log ε 4.16 and 4.15); δ ($CDCl_3$) 2.09 (s, Me), 6.68 (AB system, J_{AB} 11 Hz, CH_2), 7.34—7.64 (m, Ph), and 8.10br (exch., NH). The same product (m.p. and i.r. spectrum) was also obtained (yield 80%) from the isoxazol-5-ylhydrazine (Ia) (0.003 mol) and aqueous formaldehyde (35%; 3 ml) in methanol at reflux temperature for 30 min.

Further elution of the column with ether gave starting material (0.032 g, 6.4%).

The alkaline solution was acidified (pH 6) with concentrated hydrochloric acid and extracted with chloroform. The extract was evaporated and the residue (0.175 g) shown by t.l.c. to contain the pyrazolones (XX) and (Va), in a ratio determined by n.m.r. analysis as 3 : 1. Ethereal diazomethane (0.126 g, 0.003 mol) was added to a suspension of the above mixture in ether (10 ml). After 12 h the solution was evaporated and the residue separated into two components by preparative layer chromatography with chloroform–ether (3 : 1 v/v) as developer. The faster running band gave the 5-methoxy-1-methylaminopyrazole (XVII) identical (m.p. and i.r. spectrum) with the material described above. The second band yielded 5-methoxy-4-methyl-3-phenylpyrazole.[1]

(k) *1,1,2-Trimethyl-2-(4-methyl-3-phenylisoxazol-5-yl)hydrazine* (IXg). The mixture, treated with ether, deposited brown material, which was filtered off. Evaporation afforded *2-methyl-3-phenyl-2H-azirine-2-trimethylcarbohydrazide* (XIIg) (0.25 g, 50%) which, after sublimation at 70 °C and 0.02 mmHg, melted at 119—121° (Found: C, 67.3; H, 7.4; N, 18.1. $C_{13}H_{17}N_3O$ requires C, 67.5; H, 7.4; N, 18.2%); $\nu_{max.}$ (KBr) 1 750 (C=N) and 1 635 cm^{-1} (CO); $\lambda_{max.}$ 241 nm (log ε 4.12); δ ($CDCl_3$) 1.58 (s, Me), 2.00s and 2.10s (NMe_2),* 2.80 (s, NMe), and 7.46—7.90 (m, Ph).

(l) *1-(3,4-Diphenylisoxazol-5-yl)-1,2,2-trimethylhydrazine* (IXh). The mixture, treated with a small amount of ether, yielded *2,3-diphenyl-2H-azirine-2-trimethylcarbohydrazide* (XIIh) (0.355 g, 71%). A sample obtained by crystallisation from cyclohexane melted at 131—133° (Found: C, 73.7; H, 6.5; N, 14.35. $C_{18}H_{19}N_3O$ requires C, 73.7; H, 6.5; N, 14.3%); $\nu_{max.}$ 1 740 (C=N) and 1 630 cm^{-1} (CO); $\lambda_{max.}$ 218sh and 245 nm (log ε 4.21 and 4.24); δ [$(CD_3)_2SO$] 2.00s and 2.19s (NMe_2),† 2.81 (s, NMe), 7.25 (s, Ph), and 7.55—8.00 (m, Ph).

(m) *1,1-Dimethyl-2-(4-methyl-3-phenylisoxazol-5-yl)hydrazine* (XI). The solvent was evaporated off in an atmosphere of nitrogen; the residue, treated with N-sodium hydroxide, afforded starting material (0.116 g, 23.2%) which was filtered off. The alkaline solution was acidified (pH 6) with concentrated hydrochloric acid and extracted with chloroform. The extract was evaporated and the residue, dissolved in methanol–ether (1 : 1 v/v) (30 ml), treated with ethereal diazomethane (0.18 g, 0.004 3 mol). After 12 h the solution was evaporated and the residue separated into two components by preparative layer chromatography with chloroform as developer. The faster running band gave 1-dimethylamino-5-methoxypyrazole (XV) (0.096 g, 18%) identical (m.p. and i.r. spectrum) with the material described above. The second band yielded 5-methoxy-4-methyl-3-phenylpyrazole (0.052 g, 12%).

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* The two signals coalesced near 60 °C and gave a sharp singlet at *ca.* 80 °C.

† The two signals coalesced near 70 °C and gave a sharp singlet at *ca.* 90 °C.