# The Synthesis of Pantherine and Related Compounds

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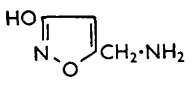
One of the active principles of *Amanita muscaria*, 5-aminomethyl-3-hydroxyisoxazole (I) has been synthesised from 3-bromo-5-methylisoxazole by way of 3-methoxyisoxazole-5-acetic acid (XIII), and from 3-methoxyisoxazole-5-carboxylic acid (XXa) by reduction of its amide with diborane. Analogues of (I) with methyl and ethyl substituents in the 4-position have been prepared similarly from 3-hydroxy-4,5-dimethylisoxazole and 4-ethyl-3-hydroxy-5-methylisoxazole by the first method. Homologues of (I) with longer basic side chains in the 5-position were made by the Curtius reaction from 3-methoxyisoxazole-5-propionic acid (XXIIb), and by diborane reduction of amides of 3-methoxyisoxazole-5-acetic acid (XIII) and 3-methoxy-4-methylisoxazole-5-acetic acid (XXIb). 3-Hydroxyisoxazoles with the basic side chain in the 4-position were prepared from 3-hydroxy-5-methylisoxazole-4-carboxylic acid (XXXIIb) and ethyl 2-(trifluoroacetamidomethyl) acetoacetate (XXV).

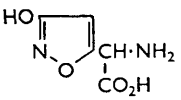
THE common fungus *Amanita muscaria* has long been known to cause mental disturbance when eaten.[1,2] This has frequently been attributed to muscarine, one of its major pharmacologically active constituents, although Lewin pointed out many years ago [1] that this assumption was almost certainly incorrect. That this is so can be demonstrated readily by boiling aqueous extracts of the plant for a short time; their effects on the central nervous system are reduced while the muscarinic activity remains constant.[3]

The presence in the plant of muscarinic substances has rendered the search for substances active in the central nervous system difficult in the past. We developed a method [4] for detecting the centrally acting substances by use of the common house-fly *Musca domestica* which was unaffected by muscarine but in which prolonged unconsciousness was produced when it was fed with extracts of the fungus. By this means and by subsequent testing in mammals we isolated [5] a substance highly active in the central nervous system, shown by mass and n.m.r. spectroscopy to be 5-aminomethyl-3-hydroxyisoxazole (I).

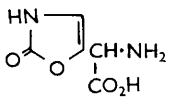
Onda and his co-workers [6] have isolated from the related fungus *Amanita pantherina* an insecticidal substance they named ' pantherine,' which they believed to



(I)

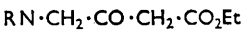


(II)



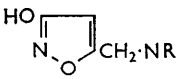
(III)

be an amino-acid or peptide, but which now appears to be identical with (I), the decarboxylation product of ibotenic acid (II), the insecticidal constituent of *A. strobiliformis* isolated by Takemoto and his co-workers.[7] Eugster and his collaborators [8] have also reported the isolation of pantherine, ibotenic acid, and muscazone (III) from *A. muscaria*, and the synthesis of pantherine.[9] We wish to record our work in this field and our independent synthesis of pantherine and related compounds.

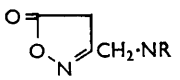


(IV)

R = phthaloyl.



(V)



(VI)

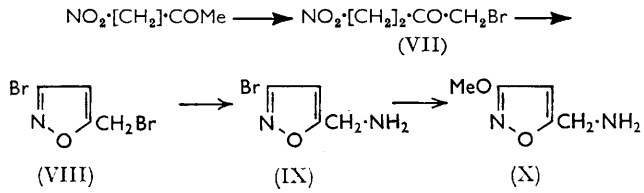
Our earliest approach to the synthesis of pantherine was from the keto-ester (IV) and hydroxylamine; it

† *Present address:* Lilly Research Centre, Windlesham, Surrey.

[1] L. Lewin, ' Phantastica, Narcotic and Stimulating Drugs,' Routledge and Kegan Paul Ltd., London, 1931, p. 123.
[2] J. Ramsbottom, ' Mushrooms and Toadstools,' Collins Ltd., London, 1954, p. 44.
[3] G. A. Mogey, private communication.
[4] K. Bowden, A. C. Drysdale, and G. A. Mogey, *Nature*, 1965, **206**, 1359.
[5] K. Bowden and A. C. Drysdale, *Tetrahedron Letters*, 1965, 727.
[6] M. Onda, M. Fukushima, and M. Akagawa, *Chem. and Pharm. Bull. (Japan)*, 1964, **12**, 751.
[7] T. Takemoto, T. Yokobe, and T. Nakajima, *J. Pharm. Soc. Japan.*, 1964, **84**, 1232.
[8] C. M. Eugster, G. F. R. Müller, and R. Good, *Tetrahedron Letters*, 1965, 1813.
[9] A. R. Gagneux, F. Häfliger, C. H. Eugster, and R. Good, *Tetrahedron Letters*, 1965, 2077.

was hoped to obtain the 3-hydroxyisoxazole (V) and subsequently, by hydrolysis, the primary amine (I). However, only the isomeric isoxazol-5-one (VI) was isolated from the condensation carried out under a variety of conditions.

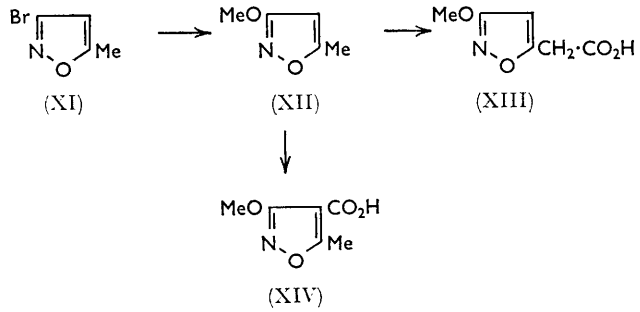
Another route investigated by us involved the possible utilisation of 5-aminomethyl-3-bromoisoxazole (IX), the preparation of which has been reported by Fusco and Rossi [10] from 4-nitro-3-butan-2-one (Scheme).




SCHEME

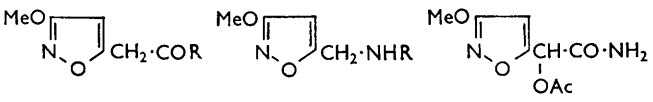
It was hoped this bromo-compound would furnish the 3-methoxyisoxazole (X) which might be converted into the desired compound (I). We encountered difficulties in repeating the work of these authors; in our hands the bromo-ketone (VII) was obtained only in poor yields. A related approach to the synthesis of (I) from 3-chloro-5-hydroxymethylisoxazole, prepared by Bravo *et al.*,[11] did not convert this compound into 5-bromomethyl-3-chloroisoxazole under a variety of conditions.

The synthesis of pantherine was finally achieved from 3-bromo-5-methylisoxazole (XI), which was converted into 3-methoxy-5-methylisoxazole (XII). This was readily lithiated with butyl-lithium; and the lithio-derivative on carbonation yielded a mixture of 3-methoxyl-isoxazole-5-acetic acid (XIII) and 3-methoxy-5-methyl-isoxazole-4-carboxylic acid (XIV). The acid (XIII) was subsequently prepared by Japanese workers [12] in poor yield.




This mixture of acids was readily separated by silica gel chromatography and the major component shown by n.m.r. to have structure (XIII) [$\tau$ 6·25 (2H, s, 5-$CH_2$) 6·06 (3H, s, 3-OMe), and 4·09 (1H, s, 4-H), in deuteriochloroform]. The minor product (XIV) showed peaks at $\tau$ 7·32 (3H, s, 5-Me) and 5·84 (3H, s, 3-OMe). These assignments are in agreement with those for similar 3-hydroxy- and 3-methoxy-isoxazoles studied by Katritzky and his co-workers.[13]

It seemed that pantherine should be readily available from (XIII), but the conventional Schmidt reaction and the modified procedure according to Weinstock [14] did not give the aminomethylisoxazole (X), possibly because of the decarboxylation of the starting material. Alternative procedures for the conversion of (XIII) to (X) were examined. Acott and Beckwith [15] have shown that primary amides may be converted into *N*-acylamines by means of lead tetra-acetate in acetic acid. With this in mind the acid (XIII) was converted into the amide (XVa) *via* the acid chloride (XVb), or better *via* the ester (XVc). However, the amide (XVa) gave with lead tetra-acetate in acetic acid, not the expected acylamine (XVIa) but a substance we believe to have the structure (XVII).




R
a; $NH_2$
b; Cl
c; OMe
d; $NH{\cdot}NH_2$
e; $N_3$
f; NHMe

R
a; Ac
b; $CO_2Et$

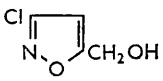
The molecular weight of the compound (XVII) was 214 (mass spectrum) and the n.m.r. spectrum (deuteriodimethyl sulphoxide) had peaks at $\tau$ 7·84 (3H, s, OAc), 6·08 (3H, s, OMe), 4·0 (1H, s, 5-CH), 3·64 (1H, s, 4-H), and 2·18br and 2·42br (each 1H, s, $NH_2$). This interesting reaction was not pursued further, but would provide possible starting material for the synthesis of ibotenic acid (II).

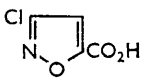
Finally the required aminomethylisoxazole (X) was obtained by conversion of the ester (XVc) into the hydrazide (XVd) and thence to the acid azide (XVe) by the procedure of Honzl and Rudinger.[16] Rearrangement of the azide in boiling toluene–ethanol gave a good yield of the urethane (XVIb), which was readily hydrolysed by aqueous alcoholic potassium hydroxide to the amine (X), isolated as its hydrochloride.

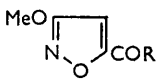
Another successful approach to the synthesis of this compound was by the oxidation of the alcohol (XVIII) with potassium permanganate [11] to 3-chloroisoxazole-5-carboxylic acid (XIX), which yielded the methoxy-acid (XXa) without extensive breakdown of the ring system. The primary amide (XXd) was obtained from the acid by way of the acid chloride (XXb), or better, from the ester (XXc), and was reduced with diborane to the primary amine (X). Treatment of this compound with

[10] R. Fusco and S. Rossi, *Rend. Ist. Lombardo*, 1960, *A* **94**, 729.
[11] P. Bravo, G. Gaudiano, A. Quilico, and A. Ricca, *Gazzetta*, 1961, **91**, 47.
[12] Y. Kishida, T. Hiraoka, J. Ide, A. Terador, and N. Nakamura, *Chem. and Pharm. Bull.* (*Japan*), 1966, **14**, 89.
[13] A. J. Boulton A. R. Katritzky, A. Majid Hamid, and S. Øksne, *Tetrahedron*, 1964, **20**, 2835.
[14] J. Weinstock, *J. Org. Chem.*, 1961, **26**, 3511.
[15] B. Acott and A. L. J. Beckwith, *Chem. Comm.*, 1965, 161.
[16] J. Honzl and J. Rudinger, *Coll. Czech. Comm.*, 1961, **26**, 2333.

hydrogen bromide in acetic acid gave pantherine (I) (45%), isolated by use of Deacidite FF resin.


(XVIII)

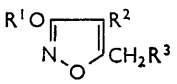

(XIX)


(XX)

R
a; OH
b; Cl
c; OMe
d; $NH_2$

The synthesis of pantherine by carbonation of 3-methoxy-5-methylisoxazole was extended to the synthesis of certain congeners. Øksne and Katritzky [17] showed that α-substituted β-keto-esters give 3-hydroxyisoxazoles with hydroxylamine. By this method we prepared 3-methoxy-4,5-dimethylisoxazole (XXIa) which, on lithiation with n-butyl-lithium followed by carbonation, gave 3-methoxy-4-methylisoxazole-5-acetic acid (XXIb) as the sole product. The structure of this compound was confirmed by its n.m.r. spectrum [τ 8·2 (3H, s, 4-Me), 6·33 (2H, s, 5-$CH_2$), and 6·04 (3H, s, 3-OMe)].

The assignment of the peak at τ 8·2 to the 4-methyl group was supported by the presence of this peak in compound (XXIa).


(XXI)

| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| a; | Me | Me | H |
| b; | Me | Me | $CO_2H$ |
| c; | Me | Me | $NH{\cdot}CO_2Et$ |
| d; | Me | Me | $NH_2$ |
| e; | H | Me | $NH_2$ |
| f; | H | Et | $NH_2$ |
| g; | Me | Me | $CO{\cdot}NMe_2$ |

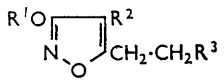
The acid (XXIb) was subjected to a sequence of reactions as used in the synthesis of pantherine from (XIII) and by this means the compound (XXId) was made. Whilst basic hydrolysis of the urethane (XXIc) gave only a moderate yield (46%) of (XXId), acid hydrolysis proceeded with concomitant cleavage of the methoxy-group to give the pantherine analogue (XXIe) in good yield (66%). Acid cleavage of the methoxy-group of the amine (XXId) proceeded cleanly to give an excellent yield of the hydroxy-compound (XXIe).

The ethyl analogue (XXIf) of pantherine was prepared in a similar manner starting with 4-ethyl-3-hydroxy-5-methylisoxazole.[13]

As we were interested in the effect of changes in the side chain of pantherine on biological activity, the aminoethyl homologue (XXIIa) was prepared by subjecting the known 3-methoxyisoxazole-5-propionic acid [18] (XXIIb) to the successful Curtius procedure developed for the synthesis of pantherine. However, instead of using ethanol during the rearrangement of the azide we found it preferable to use benzyl alcohol and obtain the urethane (XXIIc). This was readily cleaved by hydrogen bromide in acetic acid to give the hydroxyisoxazole (XXIIa).

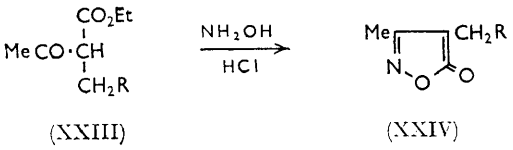
[17] S. Øksne and A. R. Katritzky, *Proc. Chem. Soc.*, 1961, 387.
[18] I. Thiele and H. Landers, *Annalen*, 1909, **369**, 300.

The secondary amine (XXIIe) was prepared by the reduction with diborane of the amide (XVf), which in turn was treated with hydrogen bromide in acetic acid to yield the required hydroxyisoxazole. Similarly the 4-methyl homologue (XXIIf) was prepared from the amide (XXIg) by diborane reduction and hydrolysis of the product (XXIIg) with hydrogen bromide in acetic acid.


(XXII)

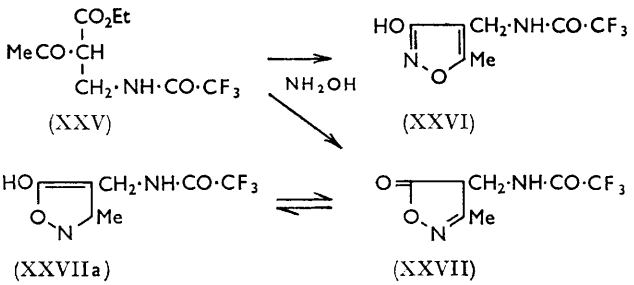
| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| a; | H | H | $NH_2$ |
| b; | Me | H | $CO_2H$ |
| c; | Me | H | $NH{\cdot}CO_2{\cdot}CH_2Ph$ |
| d; | Me | H | NHMe |
| e; | H | H | NHMe |
| f; | H | Me | $NMe_2$ |
| g; | Me | Me | $NMe_2$ |

As we were interested in homologues of pantherine with the basic side chain in the 4-position, the compound (XXIII) was prepared by the reaction of ethyl β-dimethylaminocrotonate with phthalimidomethyl bromide, a procedure we have found to be superior to the normal amidomethylation process [19] for unsubstituted β-keto-esters. The keto-ester (XXIII) with hydroxylamine did not give the required isoxazole under basic conditions and in the presence of acid the reaction gave the isoxazole-5-one (XXIV).


(XXIII) (XXIV)

R = phthalimido

Continuing the study of the use of keto-esters for the preparation of isoxazoles we prepared the compound (XXV) by the reaction of ethyl β-dimethylaminocrotonate with trifluoroacetamidomethyl chloride. With hydroxylamine in the presence of sodium ethoxide it gave an easily separable mixture of the isoxazoles (XXVI) and (XXVII).

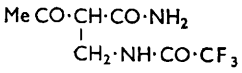

(XXV) (XXVI) (XXVIIa) (XXVII)

The minor product was shown to be (XXVI) by hydrogenation in the presence of palladium–charcoal to the β-keto-amide (XXVIII). Mild hydrolysis of (XXVI) gave the required isoxazole (XXIXa), which was isolated as the toluene-*p*-sulphonate, as the parent base proved difficult to crystallise.

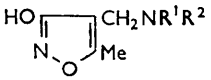
The n.m.r. spectrum of (XXVI) (deuterioacetone) was

[19] H. E. Zaugg and W. B. Martin, *Org. Reactions*, 1934, **14**, 52.

rather unusual in that the protons of the 4-methylene group gave rise to a doublet at $\tau$ 5·7 and 5·78. The



(XXVIII)



(XXIX)

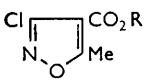
| | $R^1$ | $R^2$ |
|---|---|---|
| a; | H | H |
| b; | H | Me |
| c; | Me | Me |

amide, hydroxyl, and 5-methyl protons gave signals at $\tau$ 1·34, 2·68, and 7·68, respectively. A similar spectrum was observed for the isomeric compound (XXVII). The 4-methylene protons again gave rise to a doublet at $\tau$ 5·8 and 5·88, but the protons of the OH and NH groups gave a single broad peak at $\tau$ 1·25, whilst the 3-methyl protons gave a singlet at $\tau$ 7·68.

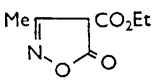
The appearance as doublets of the methylene signals in compounds (XXVI) and (XXVII) may be due to either (i) restricted rotation about the amide bond or (ii) coupling of the methylene protons with the adjacent NH group. Using (XXVII) as an example, we showed that the correct explanation was (ii); irradiation of the broad NH peak at 525 c./sec. from tetramethylsilane caused the methylene doublet at $\tau$ 5·8 and 5·88 to collapse to a singlet peak at $\tau$ 5·82. Confirmation was obtained by examining the compound (XXVI) in deuterium oxide; the n.m.r. spectrum showed the methylene signals as a singlet peak, $\tau$ 5·78, owing to the absence of coupling in the $CH_2ND$ system.

The n.m.r. spectrum of (XXVII) indicates that in solution the compound exists in the tautomeric enol form (XXVIIa). However, the infrared spectrum of the compound indicates that in the solid state it exists partly in the keto-form (XXVII), since there are bands at 1703 and 1730 cm.$^{-1}$ attributable to the trifluoroacetamide carbonyl [20] and lactone carbonyl groups, respectively, of structure (XXVII).

The procedures outlined above were capable of producing only primary amines of the structure (XXIXa), and a general method was required for the preparation of the substituted amines (XXIXb and c). An obvious intermediate for these compounds was the acid (XIV) but this was available only as the minor by-product in the preparation of pantherine. We found that dichloro-



(XXX) a; R = Et
b; R = H

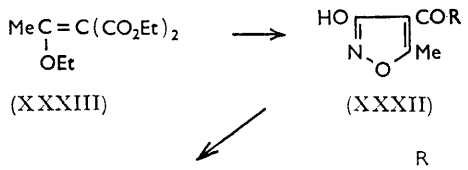


(XXXI)

formaldehyde oxime with ethyl β-dimethylaminocrotonate gave the unusual 3-chloroisoxazole (XXXa), which with concentrated potassium hydroxide in methanol yielded the required acid (XIV). Mild hydrolysis of (XXXa) gave the corresponding chloro-acid (XXXb).

[20] L. J. Bellamy, 'The Infra-red Spectra of Complex Molecules,' Methuen, London, 1960.
[21] P. P. T. Shah, *J. Amer. Chem. Soc.*, 1931, **53**, 1836.

Another approach to the synthesis of the acid (XIV) was the use of diethyl acetylmalonate. This ester reacts with hydroxylamine [17] to give the isoxazol-5-one (XXXI) as the main product. We considered it possible that if the ketone group were blocked by conversion into an acetal, the corresponding 3-hydroxyisoxazole (XXXIIa) might be formed under suitable conditions with hydroxylamine. Attempts to form an acetal from diethyl acetylmalonate and either ethylene glycol or ethyl orthoformate failed, but the enol ether (XXXIII)[21] with hydroxylamine, under appropriate conditions, gave the ester (XXXIIa).



(XXXIII)

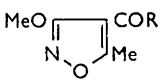
(XXXII)

(XXXIV)

| | R |
|---|---|
| a; | OEt |
| b; | OH |
| c; | Cl |
| d; | $NH_2$ |
| e; | $NEt_2$ |
| f; | piperidino |
| g; | morpholino |

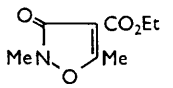
The structure of the ester (XXXIIa) was confirmed by its n.m.r. spectrum [$\tau$ 8·58 (3H, t, $CH_3{\cdot}CH_2$), 5·58 (2H, q, $O{\cdot}CH_2$), 7·40 (3H, s, 5-Me), and 2·0 (1H, s, OH)]. Hydrogenation of (XXXIIa) gave ethyl 2-carbamoylacetoacetate (XXXIV), whilst hydrolysis with aqueous sodium hydroxide yielded the acid (XXXIIb), which was converted into the acid chloride (XXXIIc) with thionyl chloride; this served as a source of the amides (XXXIId—g).

Methylation of the ester (XXXIIa) with dimethyl sulphate–potassium carbonate gave the methoxyisoxazole (XXXVa) and a small amount of the *N*-methyl isomer (XXXVI).



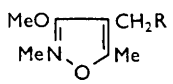
(XXXV)

| | R |
|---|---|
| a; | OEt |
| b; | Cl |
| c; | $NH_2$ |
| d; | NHMe |
| e; | NHEt |



(XXXVI)

| | R |
|---|---|
| f; | $NMe_2$ |
| g; | $NEt_2$ |
| h; | piperidino |
| i; | morpholino |



(XXXVII)

| | R |
|---|---|
| a; | $NMe_2$ |
| b; | NHMe |
| c; | $NH_2$ |

The ester (XXXVa) was hydrolysed to the acid (XIV) in the same manner as the parent (XXXIIa) and converted into the acid chloride (XXXVb). This was used for the preparation of the amides (XXXVc—i).

Reduction of the dimethylamide (XXXVf) with diborane [22] gave a solid which absorbed in the infra-red at 2430 and 2250 cm.$^{-1}$; this indicates [23] the presence of

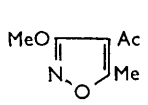
[22] H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, 1964, **86**, 3566.
[23] H. C. Brown, 'Hydroboration,' Benjamin, New York, 1962, p. 182.

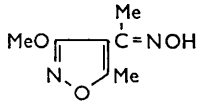
organoborane links. This boron complex, which was stable to cold dilute sodium hydroxide and hydrochloric acid, was decomposed by warming with dilute hydrochloric acid for 15 minutes to give the hydrochloride of the amine (XXXVIIa). The n.m.r. spectrum of the compound had four singlet peaks at $\tau$ 7·55 (3H, 5-Me), 7·1 (6H, $NMe_2$), 6·0 (3H, OMe), and 5·85 (2H, 4-$CH_2$).

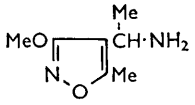
Treatment of compound (XXXVIIa) with hydrogen bromide in acetic acid in the usual manner produced the hydroxyisoxazole (XXIXc), the n.m.r. spectrum of which had three singlet peaks, $\tau$ 7·55 (3H, 5-Me), 7·08 (6H, $NMe_2$), and 5·85 (2H, 4-$CH_2$). The tertiary amine (XXXVIIa) readily gave a quaternary compound with methyl iodide.

By the reduction procedure employed in the preparation of the amine (XXXVIIa), the amines (XXXVIIb and c) were prepared from the corresponding amides, and the hydroxyisoxazole (XXIXb) was obtained by cleavage of the methoxy-group in compound (XXXVIIb) in the usual way.

A 3-hydroxyisoxazole with a branched chain in the 4-position was obtained starting from the acid chloride (XXXVb) which, reacted with diethyl ethoxymagnesium malonate[24] gave 4-acetyl-3-methoxy-5-methylisoxazole (XXXVIII). This ketone formed a crystalline oxime (XXXIX) with hydroxylamine, which was reduced by aluminium amalgam in moist ether to give 4-(1-aminoethyl)-3-methoxy-5-methylisoxazole (XL).

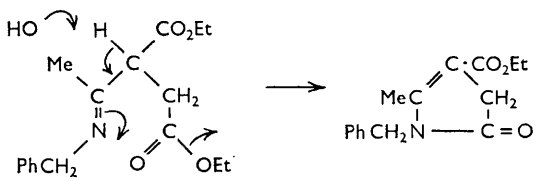

(XXXVIII)


(XXXIX)


(XL)

The structure of the branched-chain amine (XL) was confirmed by the n.m.r. spectrum (deuterium oxide) [$\tau$ 8·45 (3H, d, CH·C$H_3$), 7·67 (3H, s, 5-Me), 6·05 (3H, s, OMe), and 5·52 (1H, q, C$H$·$CH_3$)].

Analogues with longer side chains in the 4-position were required for biological studies; an acetyl succinate $AcCH(CH_2{\cdot}CO_2Et)CO_2Et$ (XLI) was used to this end. The compound did not react with hydroxylamine in the presence of base and attempts to block the keto-group by reaction with ethyl orthoformate or ethylene glycol to obtain a compound suitable for conversion into a hydroxamic acid were also unsuccessful. However, a Schiff base (XLII) was formed with benzylamine; the

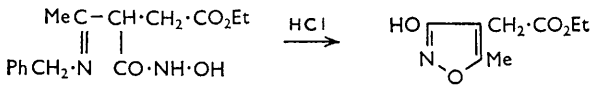

(XLII) (XLIII)

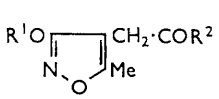
structure of this compound was confirmed by its infrared spectrum and hydrolysis to the compound (XLI) with water.

When the Schiff base was added to hydroxylamine in aqueous alkali, the cyclic condensation product (XLIII) was formed,[25] in preference to a nucleophilic attack by hydroxylamine on the carbonyl group.

The required hydroxamic acid (XLIV) was eventually obtained when the Schiff base (XLII) was heated with hydroxylamine in anhydrous methanol; it readily cyclised when mixed with hydrochloric acid to give the 3-hydroxyisoxazole (XLV).

The structure of the isoxazole (XLV) was confirmed by its infrared and n.m.r. spectra [$\tau$ 8·74 (3H, t, $CH_2{\cdot}CH_3$), 7·76 (3H, s, 5-Me), 6·65 (2H, s, 4-$CH_2$), and 5·80 (2H, q, $CH_2{\cdot}CH_3$)]. The ester (XLV) was hydrolysed by dilute sodium hydroxide solution to the acid (XLVIa), which was isolated as a syrup, and formed a crystalline amide (XLVIb) with ammonia. This amide could not be reduced to the primary amine. When it was treated with lithium aluminium hydride for 48 hours, highly volatile products were formed which were lost in the work-up. Attempts to reduce the amide with diborane in tetrahydrofuran led to no recognisable product.

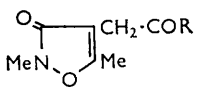

(XLIV) (XLV)


(XLVI)

| | $R^1$ | $R^2$ |
|---|---|---|
| a; | H | OH |
| b; | H | $NH_2$ |
| c; | Me | OEt |
| d; | Me | $NH_2$ |
| e; | Me | OH |

Apart from the primary amide (XLVIb), we could not prepare any amide from the acid (XLVIa), which decomposed rapidly when treated with either thionyl chloride or oxalyl chloride even at low temperature. Attempts to prepare the amides by direct reaction with the amines, with the exception of ammonia, failed.

The products of methylation of the hydroxy-ester (XLV) depended on the methylating agent. With diazomethane the *O*-methyl ether (XLVIc) was the main product, whereas with dimethyl sulphate the product was mostly *N*-methyl compound (XLVIIa).


(XLVII)

a; R = OEt
b; R = $NH_2$

Both the *O*- and *N*-methyl derivatives of (XLV) formed crystalline amides with ammonia, with the structures (XLVId) and (XLVIIb), respectively, but neither of these amides was successfully reduced by either lithium aluminium hydride or diborane to the corresponding amine.

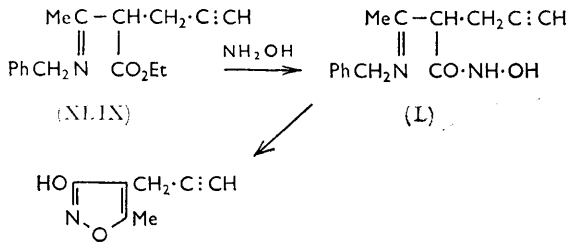
The methoxy-acid (XLVIe) was prepared by hydrolysis

[24] H. G. Walker and C. R. Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 1386.
[25] C. A. Grob and P. Ankli, *Helv. Chim. Acta*, 1949, **32**, 2010.

of the ester (XLVIc) with aqueous sodium hydroxide, but this compound, like the corresponding hydroxy-acid (XLVIa), decomposed when treated with either thionyl chloride or oxalyl chloride.

The methoxy-ester (XLVIc) did not react with primary or secondary amines to form substituted amides, and these were sought by other methods. When dimethylamine was added to the mixed anhydrides obtained from the acid (XLVIe) and either toluene-*p*-sulphonyl chloride [26] or pivaloyl chloride [27] no amides were isolated. Again, the use of dicyclohexylcarbodiimide [28] as a condensing agent for the acid (XLVIe) with amines was unsuccessful.

Another route towards the synthesis of 4-substituted hydroxyisoxazoles starting from ethyl 2-prop-2-ynylacetoacetate,[29] Me·CO·CH($CO_2$Et)·$CH_2$·C:CH (XLVIII), was examined. This compound formed a Schiff base (XLIX), which further reacted with hydroxylamine to give the hydroxamic acid (L); this, on treatment with



(XLIX) (L) (LI)

dilute hydrochloric acid, cyclised to 3-hydroxy-5-methyl-4-prop-2-ynylisoxazole (LI). The n.m.r. spectrum of this compound showed peaks at τ 8·10 (1H, t, C:CH), 7·83 (3H, s, 5-Me), and 6·95 (2H, d, 4-$CH_2$). This synthesis determined unambiguously the structure of compound (LI), which was also obtained by the direct reaction of hydroxylamine with the keto-ester (XLVIII) itself.

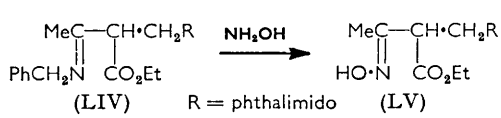
Methylation of the hydroxyisoxazole (LI) with diazomethane gave a mixture consisting mainly (g.l.c.) of the *O*-methyl derivative (LII), with a little of the *N*-methyl

(LII) (LIII)

compound (LIII). These were separated by distillation under reduced pressure to give the *O*-methyl ether (LII) as a viscous oil [τ 8·10 (1H, t, C:CH), 7·83 (3H, s, 5-Me), 6·95 (2H, d, 5-Me), and 5·94 (3H, s, OMe)]. On hydrogenation the isoxazole (LII) absorbed three molar proportions of hydrogen and gave a product which slowly evolved ammonia.

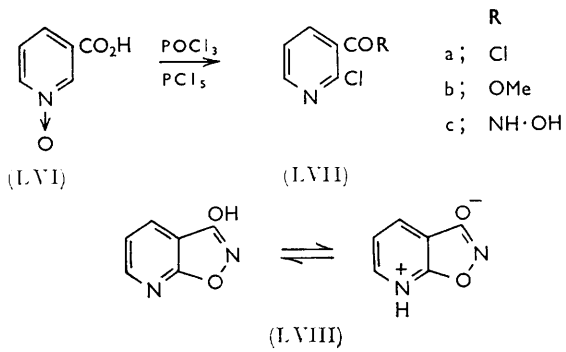
Attempted hydration of the acetylenic bond in compound (LII) using dilute sulphuric acid–mercuric sulphate caused extensive decomposition of the molecule and no product was isolated. Oxidation of the terminal group by the Brown hydroboration method [30] also did not give a definable product.

During further work on the utilisation of Schiff bases for the preparation of isoxazoles, ethyl 2-phthalimidomethylacetoacetate (XXIII) was treated with benzylamine to give the Schiff base (LIV), but this with hydroxylamine yielded the oxime (LV) and not the expected hydroxamic acid. Possibly the bulk of the phthalimidomethyl group may shield the ethoxycarbonyl group from the hydroxylamine, which then displaces benzylamine by nucleophilic attack. In acidic media the oxime cyclised to 3-methyl-4-phthalimidomethylisoxazol-5(4*H*)-one (XXIV).



(LIV) R = phthalimido (LV)

Finally, a bicyclic hydroxyisoxazole with the amino-group incorporated into a second ring was synthesised from nicotinic acid *N*-oxide (LVI), which when heated with phosphoryl chloride and phosphorous pentachloride forms 2-chloronicotinyl chloride [31] (LVIIa). The methyl ester (LVIIb) prepared from this is converted into the hydroxamic acid (LVIIc) by heating with hydroxylamine. This hydroxamic acid cyclised in aqueous sodium hydroxide to 3-hydroxypyrido[3,2-*d*]isoxazole (LVIII).



(LVI) (LVII) (LVIII)

## EXPERIMENTAL

*Isolation of Pantherine from* A. muscaria—Freshly collected plants were freeze-dried whole, powdered quickly, and stored in air-tight bottles. On the average, 1 kg. of fresh plants gave 45 g. of dried powder. This material (50 g.) was stirred mechanically with water (700 ml.) for 30 min., and the mixture was added to boiling water (700 ml.). Stirring was continued while the mixture was heated to boiling during 10 min. The mixture was cooled quickly in ice, with stirring and filtered through cloth, and the filtrate was clarified by centrifugation. The filtrates were added to Deacidite FF resin (base form; from 250 g. of the hydrochloride) and the mixture was

[26] D. Theoderopoulos and J. Gazopoulos, *J. Org. Chem.*, 1962, **27**, 2091.
[27] M. Zaoral, *Coll. Czech. Chem. Comm.*, 1962, **27**, 1273.
[28] T. C. Sheehan and G. P. Hess, *J. Amer. Chem. Soc.*, 1955, **77**, 1067.
[29] G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 1953, 3052.
[30] H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, 1959, **81**, 1512.
[31] G.P. 582,319 (*Chem. Abs.*, 1933, **27**, 5152).

stirred gently for 4 hr. at room temperature. The supernatant liquors were decanted and the resin was washed by decantation with carbon dioxide-free water until the pH of the washings approached 7. Sufficient distilled water was added to cover the resin, which was gently stirred and cooled in an ice bath, and glacial acetic acid was added dropwise until the pH of the supernatant solution reached 6. The resin was filtered off and washed twice with carbon dioxide-free water, and after addition of distilled water, the supernatant solution was brought to pH 2·8 by the gradual addition of glacial acetic acid. The solution was filtered from the resin, which was extracted twice with distilled combined washings and the filtrate obtained at pH 2·8 were combined and freeze-dried to give the concentrated extract (0·5 g.).

This material was further purified by dissolving it in the minimum amount of water and passing the solution down a small column of cellulose phosphate powder (Whatman P.70). The column was washed with water until the filtrates no longer gave a colour with ninhydrin. The retained material was eluted from the column with N-ammonium hydroxide and, after removal of the excess of ammonia, the eluate was freeze-dried to give the semi-purified material (100 mg.).

The material was then crystallised from alcohol or sublimed at 110—140° (bath)/$10^{-4}$ mm., to give pure pantherine (50 mg.), m. p. 172—174° (decomp.), τ ($D_2O$) 4·15 (1H, s, 4-H) and 5·82 (2H, s, 5-$CH_2$), *m/e* ($^{12}C$ = 12·000000) 114·0427 ($C_4H_6N_2O_2$), 113·0352 ($C_4H_5N_2O_2$), 97·0165 ($C_4H_3NO_2$), 97·043 ($C_4H_5N_2O$), 86·0241 ($C_3H_4NO_2$), 86·0478 ($C_3H_6N_2O$), 83·0369 ($C_4H_5NO$), 71·037 ($C_3H_5NO$), 69·0213 ($C_3H_3NO$), 55·0423 ($C_3H_3O$), 55·0059 ($C_2HNO$), 43·0058 (CHNO), 43·0184 ($C_2H_3O$), 43·0422 ($C_2H_5N$), and 41·0027 ($C_2HO$). With ninhydrin the compound gave a characteristic yellow spot that slowly turned purple.

*3-Methoxyisoxazole-5-acetic Acid* (XIII) *and 3-Methoxy-5-methylisoxazole-4-carboxylic Acid* (XIV).—n-Butyl-lithium in hexane (110 ml.; 2M) was added during 20 min. with stirring, below −65°, to 3-methoxy-5-methylisoxazole (22·6 g.) in dry tetrahydrofuran (100 ml.). The mixture was stirred at −75° for a further 1 hr., then poured on to a stirred slurry of dry carbon dioxide (*ca.* 1 kg.) and ether (1 l.). The carbon dioxide evaporated overnight and the product was extracted with 2N-sodium hydroxide solution (3 × 100 ml.). The basic solution was acidified with dilute hydrochloric acid and the mixture of the required acids was extracted with ether (3 × 100 ml.). The ethereal solution was dried ($MgSO_4$) and the solvent was removed *in vacuo* to yield the product (25 g.), which gave the mixture of acids as needles (21·7 g.) [from ethyl acetate–light petroleum (b. p. 60—80°)].

This material was dissolved in benzene–acetic acid (8 : 1) and chromatographed on a column of silica gel (450 g.; 100—200 mesh; 90 × 4 cm.). Fractions (25 ml.) were collected. Fractions 1—7 were negative, 8—17 contained traces of material, and 18—38 contained 3-methoxy-5-methylisoxazole-4-carboxylic acid (3·0 g.). Fractions 39—42 contained a mixture of acids, and 43—71 gave 3-methoxyisoxazole-5-acetic acid (14·55 g.). The fractions were assayed using thin-layer Silica Gel G plates of 250 μ thickness developed with benzene–acetic acid (8 : 1); the acids were detected with Bromocresol Blue spray. 3-Methoxy isoxazole-5-acetic acid had $R_F$ 0·23 and 3-methoxy-5-methylisoxazole-4-carboxylic acid $R_F$ 0·36. *3-Methoxy-5-methylisoxazole-4-carboxylic acid* gave prisms, m. p. 195—197° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 45·85; H, 4·6; N, 9·1. $C_6H_7NO_4$ requires C, 45·9; H, 4·5; N, 8·9%).

*3-Methoxyisoxazole-5-acetic acid* had m. p. 105—108° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 45·9; H, 4·5; N, 9·1. $C_6H_7NO_4$ requires C, 45·9; H, 4·5; N, 8·9%).

*Methyl 3-Methoxyisoxazole-5-acetate* (XVc).—A solution of 3-methoxyisoxazole-5-acetic acid (5·2 g.) in methanolic hydrogen chloride (100 ml.; 3%) was heated under reflux for 6 hr. and then set aside overnight. Removal of the solvent *in vacuo* gave an oil which was taken up in ether, washed with sodium hydrogen carbonate solution, and dried ($MgSO_4$), to give the crude product. The *ester* distilled at 80°/0·1 mm. (4·5 g.) and solidified when cool (Found: C, 49·1; H, 5·4; N, 8·3. $C_7H_9NO_4$ requires C, 49·1; H, 5·3; N, 8·2%), τ ($CDCl_3$) 6·18 (3H, s, CO·OMe), 5·98 (3H, s, 3-OMe), and 3·98 (1H, s, 4-H).

*3-Methoxyisoxazole-5-acetohydrazide* (XVd).—To hydrazine hydrate (3·0 g.) in methanol (20 ml.) was added a solution of methyl 3-methoxyisoxazole-5-acetate (6·5 g.) in methanol (20 ml.), and the mixture was heated under reflux for 4 hr. The solvent was removed *in vacuo* and the last traces of hydrazine were removed in a vacuum desiccator (conc. $H_2SO_4$) overnight. The product (6·3 g.) gave the *hydrazide* (6·0 g.) as needles, m. p. 100—101° (from ethyl acetate) (Found: C, 42·0; H, 5·4; N, 24·8. $C_6H_9N_3O_3$ requires C, 42·1; H, 5·3; N, 24·55%).

*5-(Ethoxycarbonylamino)methyl-3-methoxyisoxazole* (XVIb).—A suspension of 3-methoxyisoxazole-5-acetohydrazide (5·13 g.) in dry tetrahydrofuran (50 ml.) was treated with dry hydrogen chloride in dry tetrahydrofuran (50 ml.; 1·75N). The mixture was cooled to −40° and t-butyl nitrite (4—5 ml.) in tetrahydrofuran (20 ml.) was added with mechanical stirring during 10 min.; the temperature was allowed to rise to 10°. The solvent was removed (25°/15 mm.) and the yellow oily azide was dissolved in ethyl acetate (100 ml.) and washed with brine containing 1% sodium hydrogen carbonate (50 ml.), and then dried ($MgSO_4$). Removal of the solvent at 25°/15 mm. gave the azide, which was dissolved in toluene (50 ml.) and heated at 100° until evolution of nitrogen ceased (30 min.). Ethanol (10 ml.) was added, and the mixture was heated under reflux for 2 hr. Removal of volatile materials at 25°/15 mm. gave the crude product, which was distilled to give the *urethane* (4·1 g.) as an oil, b. p. 128—130°/0·2 mm. (Found: C, 47·9; H, 6·2; N, 13·8. $C_8H_{12}N_2O_4$ requires C, 48·0; H, 6·0; N, 14·0%).

*5-Aminomethyl-3-methoxyisoxazole* (X).—(*a*) A solution of 5-(ethoxycarbonylamino)methyl-3-methoxyisoxazole (4 g.) in ethanol (12 ml.) containing potassium hydroxide (2·5 g.) was heated under reflux for 8 hr. The reaction mixture was set aside overnight, dissolved in water (20 ml.), and acidified with dilute hydrochloric acid. The solution was evaporated to dryness under reduced pressure and extracted with hot ethanol. Removal of the ethanol left the crude product as pale yellow plates which gave the amine hydrochloride as plates (2·8 g.), m. p. 175—177° (decomp.) (from propan-2-ol–ether) (Found: C, 36·6; H, 5·5; N, 17·1. Calc. for $C_5H_9ClN_2O_2$: C, 36·5; H, 5·5; N, 17·0%).

(*b*) 3-Methoxyisoxazole-5-carboxamide (4·6 g.) in dry tetrahydrofuran (100 ml.) was refluxed for 48 hr. with tetrahydrofuran (100 ml.) containing diborane generated externally from sodium borohydride (37·8 g.) in diglyme (100 ml.) and boron trifluoride etherate (23 ml.) in diglyme

by the method of Brown and Zweifel.[30] The complex formed was decomposed with hydrochloric acid and the solution was evaporated to dryness *in vacuo*. The residue was taken up in water, treated with an excess of 50% aqueous potassium hydroxide, and extracted with ether. The ethereal extracts were dried, filtered, and treated with dry hydrogen chloride. The hydrochloride of the base (from methanol) was identical with the product of method (*a*).

*5-Aminomethyl-3-hydroxyisoxazole* (I).—A solution of 5-aminomethyl-3-methylisoxazole hydrochloride (1·0 g.) in acetic acid (10 ml.) containing hydrogen bromide (4·5 g.) was heated under reflux for 1 hr. The solvent was removed *in vacuo* and the hygroscopic residue was dissolved in water (10 ml.). The solution was filtered and the filtrate was poured on to a column of Deacidite FF ion-exchange resin (30 g., OH form). The resin was washed with deionised water until the washings were neutral; it was then transferred to a beaker and the pH brought to 3 with acetic acid (pH meter). The resin was filtered off and washed with ethanol, and the combined filtrate and washings were evaporated to dryness at 20°/0·2 mm. The crystalline residue gave 5-aminomethyl-3-hydroxyisoxazole (0·3 g.), m. p. 170—172° (decomp.) (from methanol–tetrahydrofuran) as almost colourless prisms (Found: C, 41·9; H, 5·35; N, 24·4; O, 28·2. Calc. for $C_4H_6N_2O_2$: C, 42·1; H, 5·3; N, 24·55; O, 28·0%).

*3-Methoxyisoxazole-5-carboxylic Acid* (XXa).—3-Chloroisoxazole-5-carboxylic acid (2·5 g.) was heated under reflux with a mixture of potassium hydroxide (15 g.), water (7·5 ml.), and methanol (43 ml.) for 4 hr. under nitrogen. The mixture was cooled, an excess of concentrated hydrochloric acid was added, and the result was repeatedly extracted with ether. The ethereal extract was dried ($Na_2SO_4$) and evaporated to give an oil which solidified. The crude material sublimed at 80°(bath)/$10^{-4}$ mm. to give *3-methoxyisoxazole-5-carboxylic acid* (2·0 g.), m. p. 134—136° (Found: C, 42·0; H, 3·5; N, 9·8. $C_5H_5NO_4$ requires C, 42·0; H, 3·5; N, 9·8%).

*3-Methoxyisoxazole-5-carboxamide* (XXd).—(*a*) 3-Methoxyisoxazole-5-carboxylic acid (0·5 g.) was heated under reflux with purified thionyl chloride (5 ml.) for 2 hr. After removal of volatile materials at 25°/15 mm., the crude acid chloride was dissolved in dry benzene (10 ml.) and added during 30 min. to boiling benzene into which ammonia was passed. Passage of ammonia was continued for 30 min. after the addition was complete. The mixture was filtered hot and the filtrates were evaporated to dryness *in vacuo*. The residue (0·3 g.) gave *3-methoxyisoxazole-5-carboxamide* (0·1 g.), m. p. 174—175° [from ethyl acetate–light petroleum (b. p. 40—60°)] (Found: C, 42·2; H, 4·3; N, 19·5. $C_5H_6N_2O_3$ requires C, 42·3; H, 4·3; N, 19·7%).

(*b*) 3-Methoxy-isoxazole-5-carboxylic acid (1 g.) was heated under reflux with methanolic hydrogen chloride (30 ml.; 3%) for 3 hr. The residue after removal of solvent gave *methyl 3-methoxyisoxazole-5-carboxylate* (XXc) (0·9 g.), m. p. 72—73° [from light petroleum (b. p. 40—60°)] (Found: C, 45·8; H, 4·5; N, 9·1. $C_6H_7NO_4$ requires C, 45·9; H, 4·5; N, 8·9%). The ester (0·8 g.) was added to aqueous ammonia (40 ml.; *d* 0·88) with stirring and the mixture was stirred a further 30 min. at room temperature. The crude amide was filtered off, washed with a little cold water, and dried (0·55 g.). It may be purified readily by sublimation at 50° (bath)/$10^{-3}$ mm. to give the amide, m. p. 174°.

*3-Methoxy-4-methylisoxazole-5-acetic Acid* (XXIb).—A solution of 3-methoxy-4,5-dimethylisoxazole (25·4 g.) in dry tetrahydrofuran (650 ml.) was cooled to −75° under nitrogen and mechanically stirred during the addition (20 min.) of n-butyl-lithium in hexane (123 ml.; 2·0M); the temperature was held at −70 to −75°. Stirring and cooling were continued for 1 hr. and the clear yellow solution was then poured on to a slurry of dry carbon dioxide (2 kg.) in ether (1 l.). The *acid* was isolated as in the preparation of 3-methoxyisoxazole-5-acetic acid, as prisms (21·4 g.), m. p. 99—101° (Found: C, 49·2; H, 5·45; N, 8·4. $C_7H_9NO_4$ requires C, 49·1; H, 5·3; N, 8·2%).

*Methyl 3-Methoxy-4-methylisoxazole-5-acetate*.—3-Methoxy-4-methylisoxazole-5-acetic acid (20 g.) was esterified with methanolic hydrogen chloride (400 ml.; 3%) by heating under reflux for 6 hr., and the product was isolated as in the preparation of methyl 3-methylisoxazole-5-acetate. The *ester* distilled as an oil, b. p. 78—80°/0·1 mm. (17·9 g.), which solidified when cool (Found: C, 52·1; H, 6·1; N, 7·8. $C_8H_{11}NO_4$ requires C, 51·9; H, 6·0; N, 7·6%).

*3-Methoxy-4-methylisoxazole-5-acetohydrazide*.—The compound was prepared from methyl 3-methoxy-4-methylisoxazole-5-acetate (17 g.) with hydrazine hydrate (6·9 g.) in methanol (10 ml.) by heating under reflux for 4 hr. The product was isolated as described for the preparation of 3-methoxyisoxazole-5-acetohydrazide and gave the *hydrazide* (12·4 g.) as prisms, m. p. 118·5—120° (from methanol) (Found: C, 45·6; H, 6·1; N, 22·6. $C_7H_{11}N_3O_3$ requires C, 45·4; H, 6·0; N, 22·7%).

*5-(Ethoxycarbonylamino)methyl-3-methoxy-4-methylisoxazole* (XXIc).—The azide was prepared from 3-methoxy-4-methylisoxazole-5-acetohydrazide (10 g.) in dry tetrahydrofuran (110 ml.) by adding dry hydrogen chloride in tetrahydrofuran (93 ml.; 1·75N) at −40° followed by t-butyl nitrite (8 ml.) in tetrahydrofuran (20 ml.). The temperature was allowed to rise to 0° and the solvent was removed *in vacuo*. The crude product was purified as in the preparation of the previous azide, then rearranged in toluene at 100°; the product reacted with ethanol to give the *urethane* (9·9 g.), b. p. 135—140°/0·4 mm., which solidified when cool, m. p. 41—43·5° (Found: C, 50·6; H, 6·7; N, 13·2. $C_9H_{14}N_2O_4$ requires C, 50·5; H, 6·6; N, 13·1%).

*5-Aminomethyl-3-methoxy-4-methylisoxazole Hydrochloride*.—The urethane (12·8 g.) in methanol (39 ml.) containing potassium hydroxide (7·6 g.) was heated under reflux for 8 hr. The *amine hydrochloride* was isolated as in the preparation of 5-aminomethyl-3-methoxyisoxazole hydrochloride and gave plates (4·94 g.), m. p. 200—202° (decomp.) (from propan-2-ol) (Found: C, 40·2; H, 6·1; N, 15·65. $C_6H_{11}ClN_2O_2$ requires C, 40·3; H, 6·2; N, 15·7%).

*5-Aminomethyl-3-hydroxy-4-methylisoxazole* (XXIe).—A solution of 5-aminomethyl-3-methoxy-4-methylisoxazole (1·0 g.) in glacial acetic acid containing hydrogen bromide (10 ml.; 45%) was heated under reflux for 1 hr. The solution was cooled and the amine hydrobromide (0·76 g.), m. p. 227—229° (decomp.), was filtered off. The hydrobromide was converted into the free base by means of Deacidite FF ion-exchange resin in the manner described for the preparation of 5-aminomethyl-3-hydroxyisoxazole to give *5-aminomethyl-3-hydroxy-4-methylisoxazole* as prisms, m. p. 205—206° (from water–methanol) (Found: C, 46·8; H, 6·3; N, 21·7. $C_5H_8N_2O_2$ requires C, 46·9; H, 6·3; N, 21·9%), τ ($D_2O$) 8·07 (3H, s, 4-Me) and 5·73 (2H, s, 5-$CH_2$).

*5-Aminomethyl-3-hydroxy-4-methylisoxazole Hydrobromide*.—The compound was prepared directly from 5-(ethoxy-

carbonylamino)methyl-3-methoxy-4-methylisoxazole (11·6 g.) in glacial acetic acid containing hydrogen bromide (100 ml.; 45%) by heating under reflux for 2 hr. The mixture was then cooled to room temperature, and the crystalline solid was filtered off and gave the *hydrobromide* as prisms (7·2 g.), m. p. 234—235° (decomp.) (from glacial acetic acid) (Found: C, 28·5; H, 4·3; N, 13·2. $C_5H_9BrN_2O_2$ requires C, 28·7; H, 4·3; N, 13·4%).

*4-Ethyl-3-methoxy-5-methylisoxazole.*—A stirred solution of 4-ethyl-3-hydroxy-5-methylisoxazole (50·4 g.) in ether (850 ml.) was treated at 0° with an ethereal solution of diazomethane prepared from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (191 g.) and the resulting solution was left overnight at 0°. The excess of diazomethane was destroyed with a few drops of glacial acetic acid, and the ethereal solution was washed with aqueous potassium carbonate (2 × 100 ml.) and dried ($MgSO_4$). After removal of the solvent the remaining reddish oil was distilled with a Vigreux column (6 in.) to give *4-ethyl-3-methoxy-5-methylisoxazole* (32·3 g.), b. p. 78—81°/13 mm. The product was homogeneous (g.l.c. with a 20 ft. × 3/8 in. S.E. 30 column) (Found: C, 59·3; H, 7·9; N, 9·8. $C_7H_{11}NO_2$ requires C, 59·55; H, 7·85; N, 9·9%), τ ($CDCl_3$) 8·94 (3H, t, $J \sim 7$ c./sec., $CH_2{\cdot}CH_3$), 7·8 (5H, m, 5-$CH_3$ and 4-$CH_2$), and 6·1 (3H, s, 3-OMe).

A higher-boiling fraction obtained during the distillation, possibly 4-ethyl-2,5-dimethylisoxazol-3-one, was not investigated further.

*4-Ethyl-3-methoxyisoxazole-5-acetic Acid.*—The acid was prepared from 4-ethyl-3-methoxy-5-methylisoxazole (5·0 g.) and n-butyl-lithium (22 ml.; 1·9M) in tetrahydrofuran by the procedure detailed above for the preparation of homologues. The *acid* gave needles, m. p. 75—77° [from light petroleum (b. p. 80—100°)] (Found: C, 52·1; H, 6·3; N, 7·7. $C_8H_{11}NO_4$ requires C, 51·9; H, 6·0; N, 7·6%), τ ($CDCl_3$) 8·9 (3H, t, $J \sim 7$ c./sec., $CH_2{\cdot}CH_3$), 7·68 (2H, q, $J \sim 7$ c./sec., $CH_2{\cdot}CH_3$), 6·3 (2H, s, 5-$CH_2$), 6·02 (3H, s, 3-OMe), and −1·25 (1H, s, $CO_2H$).

The *methyl ester*, prepared with methanolic hydrogen chloride, had b. p. 88—90°/0·3 mm. (Found: C, 54·4; H, 6·7; N, 7·2. $C_9H_{13}NO_4$ requires C, 54·3; H, 6·6; N, 7·0%). The *acid hydrazide*, prepared as described above, had m. p. 121·5—122·5° (from propan-2-ol) (Found: C, 48·4; H, 6·7; N, 21·1. $C_8H_{13}N_3O_3$ requires C, 48·2; H, 6·6; N, 21·1%). The urethane was obtained as described above for the preparation of homologues; 5·2 g. of product b. p. 130—134°/0·4 mm. were obtained from 5 g. of acid hydrazide. The urethane (3·9 g.) heated under reflux with hydrogen bromide in glacial acetic acid (48 ml.; 45%) for 1 hr. gave *5-aminomethyl-4-ethyl-3-hydroxyisoxazole hydrobromide* as needles (2·16 g.), m. p. 210—212° (decomp.) (from propan-2-ol) (Found: C, 32·4; H, 4·9; N, 12·6. $C_6H_{11}BrN_2O_2$ requires C, 32·3; H, 5·0; N, 12·6%), τ ($D_2O$) 8·9 (3H, t, $J \sim 8$ c./sec., $CH_2{\cdot}CH_3$), 7·6 (2H, q, $J \sim 8$ c./sec., $CH_2{\cdot}CH_3$), and 5·7 (2H, s, 5-$CH_2$).

*Methyl 3-Methoxyisoxazole-5-propionate.*—A solution of 3-methoxyisoxazole-5-propionic acid (1·09 g.) was esterified by heating under reflux with methanolic hydrogen chloride (75 ml.; 3%) for 3 hr. and the product was isolated in the usual way. The *ester* gave blades (0·75 g.), m. p. 58—59° [from light petroleum (b. p. 40—60°)] (Found: C, 51·7; H, 6·0; N, 7·4. $C_8H_{11}NO_4$ requires C, 51·9; H, 6·0; N, 7·6%).

*3-Methoxyisoxazole-5-propionohydrazide.*—The compound was prepared in the usual manner from the ethyl ester and hydrazine hydrate in methanol by heating under reflux for 4 hr. The *acid hydrazide* gave prisms, m. p. 123—125° (from benzene) (Found: C, 45·6; H, 6·1; N, 22·6. $C_7H_{11}N_3O_3$ requires C, 45·4; H, 6·0; N, 22·7%).

*5-(2-Benzyloxycarbonylamino)ethyl-3-methoxyisoxazole* (XXIIc).—A suspension of 3-methoxyisoxazole-5-propionohydrazide (5 g.) in dry tetrahydrofuran (55 ml.) was cooled to −40° and dry hydrogen chloride in tetrahydrofuran (46·5 ml.; 1·75N) was added with stirring. This was followed by the addition of 3-methylbutyl nitrite (5·4 ml.) in dry tetrahydrofuran during 40 min.; the temperature rose to −25°. The resulting solution was stirred for a further 30 min., while the temperature rose to 0°. The solvent was removed *in vacuo* at 20° and the pale yellow residue was dissolved in ethyl acetate (100 ml.) and washed with brine containing 1% sodium hydrogen carbonate (100 ml.). The ethyl acetate solution was then dried ($MgSO_4$). The solvent was removed *in vacuo* at 20° to yield the azide as a pale yellow solid, which was dissolved in dry toluene (100 ml.) and heated under reflux until the evolution of nitrogen ceased (15 min.). Benzyl alcohol (30 ml.) was added, and the mixture was heated under reflux for 2 hr. Removal of the solvent *in vacuo* left a pale brown oil which solidified when cool. The *product* (4·2 g.) was obtained as needles, m. p. 59—61° [from light petroleum (b. p. 80—100°)] (Found: C, 60·7; H, 5·8; N, 10·2. $C_{14}H_{16}N_2O_4$ requires C, 60·9; H, 5·8; N, 10·1%).

*5-(2-Aminoethyl)-3-hydroxyisoxazole* (XXIIa). — The amine was obtained from the benzyl carbamate (XXIIc) (11·75 g.) by heating under reflux for 30 min. with hydrogen bromide in glacial acetic acid (125 ml.; 45%). After removal of the acetic acid *in vacuo*, the product was passed over Deacidite FF ion-exchange resin (250 g.; OH form) as described for the purification of homologues, and gave the *amine* as blades (3·0 g.), m. p. 158—160° (decomp.) (from aqueous tetrahydrofuran) (Found: 47·0; H, 6·4; N, 21·9. $C_5H_8N_2O_2$ requires C, 46·9; H, 6·3; N, 21·9%), τ ($D_2O$) 6·6—7·3 (4H, envelope, 5-$CH_2{\cdot}CH_2$) and 4·4 (1H, s, 4-H).

*Ethyl 3-Methoxyisoxazole-5-acetate.*—3-Methoxyisoxazole-5-acetic acid (3·5 g.), esterified by heating under reflux with ethanolic hydrogen chloride (60 ml.; 3%) gave the *ester* (3·4 g.), b. p. 84—86°/0·4 mm., m. p. 24—25·5° (Found: C, 51·8; H, 6·1; N, 7·6. $C_8H_{11}NO_4$ requires C, 51·9; H, 6·0; N, 7·6%).

*3-Methoxyisoxazole-5-acetamide* (XXd).—(*a*) 3-Methoxyisoxazole-5-acetic acid (0·5 g.) in ether (20 ml.) containing oxalyl chloride (1·5 g.) was heated under reflux for 2 hr. The ether and the excess of oxalyl chloride were removed *in vacuo* at room temperature to give the acid chloride as an unstable brown oil which was dissolved in ether (25 ml.). The solution was saturated with ammonia, left at room temperature for 12 hr., washed with aqueous sodium hydrogen carbonate and water, and dried ($MgSO_4$). Removal of the ether left the *amide* which gave large blades (0·3 g.), m. p. 101—103° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 46·1; H, 5·2; N, 17·9. $C_6H_8N_2O_3$ requires C, 46·2; H, 5·2; N, 18·0%), τ ($CDCl_3$) 6·3 (2H, s, 5-$CH_2$), 5·99 (3H, s, 3-OMe), and 4·02 [1H, s (broadened), 4-H].

(*b*) Methyl 3-methoxyisoxazole-5-acetate (4·4 g.) was stirred with aqueous ammonia (100 ml., *d* 0·88) for 1 hr. at room temperature. The solution was set aside overnight, and evaporated to dryness *in vacuo*. The residue gave plates (4·3 g.), m. p. 100—103° (from ethyl acetate), identical with the material obtained from the acid chloride.

*Ethyl* 3-*Chloro*-5-*methylisoxazole*-4-*carboxylate* (XXXa).—A solution of dichloroformaldehyde oxime (34·2 g.) in dry tetrahydrofuran (50 ml.) was added to ethyl β-dimethylaminocrotonate (57·1 g.) and the mixture was left at room temperature for 3 days. It was then poured into ice–water (200 ml.) and the oil was extracted into ether (3 × 100 ml.). The ethereal solution was dried ($MgSO_4$) and evaporated, to give a pungent oil which was distilled to give ethyl acetoacetate, b. p. 60—70°/15 mm. and a second fraction, b. p. 112—120°/15 mm., which when redistilled gave *ethyl* 3-*chloro*-5-*methylisoxazole*-4-*carboxylate* (23·0 g.), b. p. 116—118°/15 mm. (Found: C, 44·6; H, 4·4; Cl, 18·4; N, 7·3. $C_7H_8ClNO_3$ requires C, 44·3; H, 4·3; Cl, 18·7; N, 7·4%), τ ($CDCl_3$) 8·7 (3H, t, $J$ = 7 c./sec., $CH_2{\cdot}CH_3$), 7·3 6(3H, s, 5-Me), and 5·75 (2H, q, $J$ = 7 c./sec., $CH_2{\cdot}CH_3$).

3-*Chloro*-5-*methylisoxazole*-4-*carboxylic Acid* (XXXb).—To a solution of the ester (XXXa) (3·2 g.) in ethanol (15 ml.) was added potassium hydroxide (1·9 g.) in water (3 ml.), and the mixture was left overnight at room temperature. It was then diluted with water (25 ml.) and extracted with ether (2 × 25 ml.), and the aqueous solution was acidified with dilute hydrochloric acid. The solid which separated was extracted with ether (4 × 25 ml.) and the ethereal extract was washed with water (25 ml.) and dried ($MgSO_4$). Removal of the solvent left a crystalline solid which gave the *acid* as needles (2·4 g.), m. p. 132—134° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 37·3; H, 2·65; Cl, 21·8; N, 8·5. $C_5H_4ClNO_3$ requires C, 37·2; H, 2·5; Cl, 21·95; N, 8·7%), τ ($CDCl_3$) 7·24 (3H, s, 5-Me) and −2 (1H, s, $CO_2H$).

3-*Methoxy*-5-*methylisoxazole*-4-*carboxylic Acid* (XIV).—A solution of the chloro-acid (XXXb) (6·62 g.) was heated under reflux on a boiling-water bath for 24 hr. in methanol (20 ml.) containing water (4 ml.) and potassium hydroxide (7·3 g.). Initially a vigorous reaction occurred and much solid separated. The next day the reaction mixture was diluted with water (25 ml.) and extracted with ether (2 × 25 ml.); the aqueous portion was acidified with dilute hydrochloric acid. The precipitated solid was extracted with ether (3 × 25 ml.) and dried ($MgSO_4$). Removal of the solvent left a brown solid which gave 3-methoxy-5-methylisoxazole-4-carboxylic acid, m. p. 197° [from ethyl acetate–light petroleum (b. p. 60—80°) (charcoal)], identical with that obtained by the lithiation procedure already described (Found: C, 45·9; H, 4·4; N, 8·55. Calc. for $C_6H_7NO_4$: C, 45·9; H, 4·5; N, 8·9%).

*Ethyl* 2-(*Trifluoroacetamidomethyl*)*acetoacetate* (XXV).—A solution of *N*-hydroxymethyltrifluoroacetamide (90 g.) in dry ether (1 l.) was cooled and stirred at 0° during the addition of phosphorus pentachloride (125 g.) in portions. The mixture was heated under reflux for 10 min., cooled to room temperature, and left for 48 hr.; the solvent and phosphoryl chloride were removed in a rotary evaporator at 15 mm. Toluene (2 × 50 ml.) was added and each time removed on the evaporator. The residue was dissolved in dry tetrahydrofuran (200 ml.) and filtered to give solution *A*. To a solution of ethyl 3-dimethylaminocrotonate (107·7 g.) in dry tetrahydrofuran (600 ml.) cooled to −5° was added solution *A*. The mixture was left at room temperature for 3 days then diluted with dry ether (1 l.). The crystalline solid which separated was collected, washed well with ether, and dissolved in water (600 ml.). After a few minutes an oil separated which was extracted into ether (3 × 200 ml.). The ethereal solution was washed with brine and dried ($MgSO_4$). Removal of the solvent left an oil (105 g.) which was distilled under reduced pressure to give the *product* (102 g.), b. p. 98—102°/0·2 mm., m. p. 35—36° (Found: C, 42·3; H, 4·6; F, 22·3; N, 5·4. $C_9H_{12}F_3NO_4$ requires C, 42·4; H, 4·7; F, 22·35; N, 5·5%), τ ($CDCl_3$) 8·72 (3H, t, $J$ ~ 7 c./sec., $CH_2{\cdot}CH_3$), 7·7 (3H, s, Ac), 6·02—6·32 (3H, envelope, CH and $CH_2{\cdot}NH$), 5·78 (2H, q, $J$ ~ 7 c./sec. $O{\cdot}CH_2$), and 2·4br (1H, s, NH).

3-*Hydroxy*-5-*methyl*-4-*trifluoroacetamidomethylisoxazole* (XXVI) *and* 3-*Methyl*-4-*trifluoroacetamidomethylisoxazol*-5(4H)-*one* (XXVII).—A solution of hydroxylamine hydrochloride (5·6 g.) in ethanol (25 ml.) was added to a solution of sodium ethoxide (10·88 g.) in ethanol (200 ml.) at 0°. Ethyl 2-(trifluoroacetamidomethyl)acetoacetate (20·4 g.) in ethanol (80 ml.) was then added. The temperature was held at 0—10° for 3 hr., and the mixture was acidified with concentrated hydrochloric acid and set aside at room temperature overnight. Ether (200 ml.) was added and the mixture was filtered. The filtrates were evaporated to dryness at 30°/15 mm. and the residue was triturated with water (80 ml.). Crystals were filtered off and gave 3-*hydroxy*-5-*methyl*-4-*trifluoroacetamidomethylisoxazole* (3·0 g.), m. p. 212° (from ethanol, then ethyl acetate) (Found: C, 37·4; H, 3·2; F, 25·4; N, 12·5. $C_7H_7F_3N_2O_3$ requires C, 37·5; H, 3·2; F, 25·35; N, 12·5%).

The aqueous filtrate from the trituration was evaporated under reduced pressure (15 mm.); a second crop of crystalline material separated (9 g.). This gave 3-*methyl*-4-*trifluoroacetamidomethylisoxazol*-5(4H)-*one* (7·0 g.), m. p. 123° (from ethyl acetate) (Found: C, 37·5; H, 3·27; F, 25·25; N, 12·4. $C_7H_7F_3N_2O_3$ requires C, 37·5; H, 3·2; F, 25·35; N, 12·5%).

4-*Aminomethyl*-3-*hydroxy*-5-*methylisoxazoletoluene*-p-*sulphonate*.—A solution of 3-hydroxy-5-methyl-4-trifluoroacetamidomethylisoxazole (10 g.) in water (100 ml.) containing sodium hydroxide (3·8 g.) was stirred at 0° for 30 min. and then kept at 2° overnight. The clear yellow solution was extracted with ether (100 ml.) and then evaporated to 30 ml. *in vacuo* at room temperature. The solution was applied to a column of Amberlite IRA 401 ion-exchange resin (200 ml. wet resin; OH form) and the resin was washed until the eluate was neutral. The resin was transferred to a beaker and the pH of the aqueous phase was adjusted to 3 with dilute acetic acid. The resin was filtered off and the filtrates were evaporated to dryness *in vacuo* to yield crude 4-aminomethyl-3-hydroxy-5-methylisoxazole (3·6 g.). This was dissolved in methanol (25 ml.) and the theoretical amount of toluene-*p*-sulphonic acid was added in methanol (25 ml.). The solution was boiled with charcoal and filtered and the filtrates were treated with ethyl acetate to yield the *tosylate* as blades (7 g.), m. p. 215—220°. A sample crystallised from propan-2-ol had m. p. 220° (Found: C, 48·2; H, 5·3; N, 9·3; O, 26·6. $C_{12}H_{16}N_2O_5S$ requires C, 48·0; H, 5·4; N, 9·3; O, 26·65%), τ ($D_2O$) 7·66 and 7·68 [each 3H, (poorly resolved), 5-Me and $CH_3{\cdot}C_6H_4{\cdot}$], 6·1 (4-$CH_2$), and 2·5 (4H, m $CH_3{\cdot}C_6H_4$).

*Hydrogenation of* 3-*Hydroxy*-5-*methyl*-4-*trifluoroacetamidomethylisoxazole*.—A solution of the isoxazole (0·5 g.) in ethanol (25 ml.) was hydrogenated over 10% palladium–charcoal (0·1 g.) at 45 lb./in.$^2$ for 2 hr. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo* to yield a crystalline solid which gave 2-*trifluoroacetylmethylacetoacetamide* as blades (0·4 g.), m. p. 161—162° (from aqueous ethanol) (Found: C, 37·2; H, 3·9; F, 25·1; N, 12·4. $C_7H_9F_3N_2O_3$ requires C, 37·2; H, 4·0; F, 25·2; N, 12·4%).

*Ethyl* 2-(*phthalimidomethyl*)*acetoacetate* (XXIII).—To a solution of *N*-bromomethylphthalimide (12 g.) in dry tetrahydrofuran (50 ml.) was added ethyl β-dimethylaminocrotonate (7·85 g.) at room temperature, and the mixture was set aside 3 days during which crystalline material separated. This was filtered off, added to water (25 ml.) and warmed to 50° for 10 min.; an oil separated which solidified when cool. The solid (12 g.) gave *ethyl* 2-(*phthalimidomethyl*)*acetoacetate* (10 g.), m. p. 74—76° [from light petroleum (b. p. 60—80°) or methanol], as needles (Found: C, 62·4; H, 5·4; N, 4·8. $C_{15}H_{15}NO_5$ requires C, 62·3; H, 5·2; N, 4·8%), τ ($CDCl_3$) 8·74 (3H, t, $J \sim 7$ c./sec., $CH_2{\cdot}CH_3$), 7·62 (3H, s, Ac), 5·52—5·9 (5H, complex $CH_2{\cdot}CH_3$, CH, and $CH_2{\cdot}N$), and 2·05 (4H, s, $C_6H_4$).

3-*Methyl*-4-*phthalimidomethylisoxazole*-5(4H)-*one* (XXIV).—A mixture of ethyl 2-(phthalimidomethyl)acetoacetate (14·5 g.) and hydroxylamine hydrochloride (4·2 g.) in ethanol (250 ml.) was heated under reflux for 24 hr. The solution was evaporated to dryness *in vacuo* and the residue gave the *isoxazolone* as pale yellow prisms (11 g.), m. p. 173° (decomp.) (from ethanol) (Found: C, 60·4; H, 3·9; N, 10·8. $C_{13}H_{10}N_2O_4$ requires C, 60·5; H, 3·9; N, 10·85%), τ [$(CD_3)_2SO$] 7·63 (3H, s, 3-Me), 5·55 (2H, s, 4-$CH_2$), and 2·15 (4H, m, $C_6H_4$).

3-*Methoxyisoxazole*-5-(2-*acetoxy*)*acetamide* (XVII).—A solution of 3-methoxyisoxazole-5-acetamide (4·0 g.) in glacial acetic acid (65 ml.) and acetic anhydride (2·0 ml.) containing lead tetra-acetate (13·0 g.) was warmed at 80° until an aliquot portion gave no precipitate with water and a negative test with starch–potassium iodide paper (5 hr.). The acetic acid was removed at 15 mm., and a pale yellow gum was obtained. It was dissolved in water (20 ml.) and extracted into ethyl acetate (3 × 20 ml.). The organic phase was dried ($MgSO_4$) and evaporated to give a gum which was dissolved in ethyl acetate (20 ml.). The solution was passed down a column (1 × 30 cm.) of silica gel (50 g.; 100—200 mesh), with the same solvent as eluent. Early fractions gave a gum that would not crystallise; later fractions yielded a product which crystallised on trituration with light petroleum (b. p. 60—80°). This material gave the *product* as needles (0·5 g.), m. p. 124·5—125·5° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 44·9; H, 4·7; N, 12·9; O, 37·3. $C_8H_{10}N_2O_5$ requires C, 44·9; H, 4·7; N, 13·1; O, 37·4%).

3-*Hydroxy*-5-*methyl*-4-*prop*-2-*ynylisoxazole* (LI).—(*a*) To a solution of hydroxylamine prepared at 0° from hydroxylamine hydrochloride (7·65 g.) and aqueous sodium hydroxide (80 ml.; 15%) was added ethyl 2-prop-2-ynylacetoacetate (16·8 g.) in portions. The mixture was shaken until the smell of ester disappeared (*ca.* 1 hr.), then acidified at 0° with concentrated hydrochloric acid. The mixture was set aside at 0° overnight and the crystals were filtered off and gave *prisms*, m. p. 92—94° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 61·2; H, 5·3; N, 10·2. $C_7H_7NO_2$ requires C, 61·3; H, 5·15; N, 10·2%).

(*b*) Ethyl 2-prop-2-ynylacetoacetate (10 g.) and benzylamine (7·0 g.) were heated together under reflux in toluene (20 ml.) for 2 hr., during which time water (1·05 ml.) was evolved. Benzylamine was removed from the mixture by passing it down a short column of neutral alumina to give the Schiff base as a light yellow oil (15 g.) which contained no starting materials (g.l.c.). The Schiff base (2·57 g.) was added to a solution of hydroxylamine prepared from hydroxylamine hydrochloride (0·75 g.) and sodium (0·25 g.) in methanol (30 ml.). The mixture was heated under reflux for 1 hr., cooled, and filtered, and the filtrates were concentrated to give an oil which crystallised when triturated with dioxan (1 ml.). The product gave 3-*benzylimino*-2-*prop*-2-*ynylbutyrohydroxamic acid* (L) (1·4 g.), m. p. 153—155° (from ethyl acetate) (Found: C, 68·5; H, 6·9; N, 11·6. $C_{14}H_{16}N_2O_2$ requires C, 68·8; H, 6·6; N, 11·5%). The hydroxamic acid (1·22 g.) dissolved in N-hydrochloric acid (10 ml.) deposited a crystalline solid after 10 min. The mixture was set aside at 0° for 2 hr., and the solid (0·42 g.) was collected to yield 3-hydroxy-5-methyl-4-prop-2-ynylisoxazole, m. p. 91—93°.

*Ethyl* 4-*Benzylimino*-3-*ethoxycarbonylpentanoate* (XLII).—Ethyl acetylsuccinate (21·6 g.) and benzylamine (10·7 g.) were heated together under reflux in toluene (50 ml.) for 3 hr. during which time water (1·6 ml.) was evolved. The solution was concentrated under reduced pressure to a pale yellow oil (30 g.) which was passed down a short column of alumina to give the *Schiff base* (28 g.) (Found: C, 67·1; H, 7·7; N, 4·5. $C_{17}H_{23}NO_4$ requires C, 66·9; H, 7·6; N, 4·6%).

1-*Benzyl*-4-*ethoxycarbonyl*-5-*methylpyrrol*-2(3H)-*one* (XLIII).—The Schiff base (XLII) (3·0 g.) was added to a solution of hydroxylamine hydrochloride (0·7 g.) and sodium hydroxide (1·2 g.) in water (20 ml.). The reaction mixture was kept at 0° for 1 hr. and then acidified with concentrated hydrochloric acid. The crystalline material (1·5 g.) obtained from the cooled solution gave the *pyrrolone* (1·0 g.), m. p. 110—111° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: C, 69·4; H, 6·4; N, 5·6%); *M* (Rast), 249. $C_{15}H_{17}NO_3$ requires C, 69·5; H, 6·6; N, 5·4%; *M*, 259].

*Ethyl* 3-*Benzylimino*-2-*phthalimidomethylbutyrate* (LIV).—Ethyl 2-phthalimidomethylacetoacetate (8·7 g.) and benzylamine (3·6 g.) were heated together in xylene (50 ml.) for 2 hr. during which time water (0·5 ml.) was evolved. The mixture was cooled and the precipitate of phthalimide (2·3 g.) was filtered off. Concentration of the filtrate gave a second crystalline precipitate (4·5 g.) which gave the *Schiff base* (LIV), m. p. 160—162° (from ethanol) (Found: C, 69·7; H, 6·1; N, 7·4. $C_{22}H_{22}N_2O_4$ requires C, 69·8; H, 5·9; N, 7·4%). The Schiff base, heated with methanolic hydroxylamine, gave the oxime (LV), m. p. 139—141·5° and this, heated in glacial acetic acid under reflux, ring-closed to 3-methyl-4-phthalimidomethylisoxazol-5(4H)-one (XXIV) identical with that obtained previously.

*Ethyl* 3-*Hydroxy*-5-*methylisoxazole*-4-*acetate* (XLV).—To a solution of hydroxylamine prepared from hydroxylamine hydrochloride (7·64 g.) and sodium (2·53 g.) in methanol (150 ml.) was added the Schiff base (XLII) (30 g.) and the mixture was heated under reflux for 2 hr. and filtered. The filtrates were concentrated to give an oil which later crystallised. Trituration with a little ethanol gave material (21 g.) which gave the *hydroxamic acid* (XLIV), m. p. 120—122° (from ethyl acetate) (Found: C, 61·7; H, 7·0; N, 9·7. $C_{15}H_{20}N_2O_4$ requires C, 61·7; H, 6·9; N, 9·6%). The hydroxamic acid (14·6 g.) was dissolved in water (30 ml.) and the solution was kept at 30° during the addition of concentrated hydrochloric acid (7·5 ml.). The solution was kept at 30° for 30 min. and then cooled to 0° when the product came out of solution. It gave *ethyl* 3-*hydroxy*-5-*methylisoxazole*-4-*acetate* (6·2 g.), m. p. 78—79° (from ethyl acetate) (Found: C, 52·1; H, 6·1; N, 7·6. $C_8H_{11}NO_4$ requires C, 51·9; H, 6·0; N, 7·6%). The ester (5·0 g.) dissolved in aqueous ammonia (25 ml.; *d* 0·88) was set aside at room temperature for 24 hr. and then the excess of

ammonia was removed *in vacuo*. The residue was acidified with concentrated hydrochloric acid and evaporated to dryness. The residue was extracted with absolute ethanol to give the *amide* (XLVIb) (2·3 g.), m. p. 160—162° (Found: C, 46·1; H, 5·3; N, 17·9. $C_6H_8N_2O_3$ requires C, 46·15; H, 5·2; N, 17·9%).

*3-Methoxy-5-methylisoxazole-4-acetamide* (XLVId).—To a solution of ethyl 3-hydroxy-5-methylisoxazole-4-acetate (9·25 g.) in ether (100 ml.) was added diazomethane (2·0 g.) in ether–ethanol. The mixture was set aside at room temperature overnight and then concentrated to give a brown oil which was decolourised by passing it through a neutral alumina column. The product was a pale yellow oil (8·1 g.) which showed only one peak on g.l.c. and decomposed when distilled at 15 mm. The product (2·5 g.) was mixed with aqueous ammonia (10 ml.; *d* 0·88) and stirred for 3 hr. at room temperature, after which time it had dissolved. The solution was set aside for 16 hr. at room temperature and evaporated to dryness under reduced pressure. The *amide* (XLVId) (1·3 g.) was obtained by crystallisation from acetone, m. p. 113—115° (Found: C, 49·3; H, 5·8; N, 16·2. $C_7H_{10}N_2O_3$ requires C, 49·4; H, 5·9; N, 16·5%).

*Ethyl 3-Hydroxy-5-methylisoxazole-4-carboxylate* (XXXIIa) *and 4-Ethoxycarbonyl-3-methylisoxazol-5(4H)-one* (XXXI).—To a solution of hydroxylamine prepared from hydroxylamine hydrochloride (7·6 g.) and sodium (4·6 g.) in methanol (100 ml.) was added rapidly the enol ether (XXXIII) (23 g.) with stirring at −5°. The mixture was then kept at −5° for 15 min. and acidified with concentrated hydrochloric acid. It was filtered and the filtrates were concentrated *in vacuo*. The residue gave 4-ethoxycarbonyl-3-methylisoxazol-5(4*H*)-one (5·0 g.), m. p. 164—165° [from light petroleum (b. p. 60—80°)] (Found: C, 49·3; H, 5·4; N, 8·0. Calc. for $C_7H_9NO_4$: C, 49·1; H, 5·3; N, 8·2%). The filtrates from the crystallisation when concentrated gave *ethyl 3-hydroxy-5-methylisoxazole-4-carboxylate* (8·4 g.), m. p. 91° (Found: C, 49·2; H, 5·4; N, 8·2. $C_7H_9NO_4$ requires C, 49·1; H, 5·3; N, 8·2%). Hydrogenation of this ester in ethanol at room temperature and pressure over Adams catalyst gave ethyl 2-carbamoylacetoacetate (XXXIV), m. p. 113° (Found: C, 48·3; H, 6·6; N, 8·2. Calc. for $C_7H_{11}NO_4$: C, 48·55; H, 6·4; N, 8·1%).

*3-Hydroxy-5-methylisoxazole-4-carboxylic Acid* (XXXIIb).—The ethyl ester (10 g.) was dissolved in aqueous sodium hydroxide (100 ml. of 10%) and the solution was warmed on the steam-bath for 1 hr. The mixture was cooled in ice and acidified with concentrated hydrochloric acid; the solid was filtered off and gave the *acid* (7·0 g.), m. p. 240° (decomp.) (Found: C, 41·8; H, 3·6; N, 9·8. $C_5H_5NO_4$ requires C, 42·0; H, 3·5; N, 9·8%), which (7·0 g.) was heated under reflux for 40 min. with thionyl chloride (70 ml.). The excess of thionyl chloride was then removed under reduced pressure. The crude acid chloride was boiled twice with light petroleum (b. p. 60—80°) and after removal of the petroleum was dissolved in benzene (40 ml.) and slowly added to aqueous ammonia (30 ml., *d* 0·88) with vigorous stirring. The aqueous layer was separated and extracted with ethyl acetate (30 ml.), and the combined organic solutions were dried ($Na_2SO_4$) and concentrated *in vacuo* to give a solid which gave the *amide* (XXXIId) (5·0 g.), m. p. 237° (decomp.) (from ethyl acetate) (Found: C, 42·4; H, 4·1; N, 19·5. $C_5H_6N_2O_3$ requires C, 42·3; H, 4·3; N, 19·7%).

The *amides* listed in Table 1 were prepared from the acid chloride in a similar manner.

TABLE 1

Amides from (XXXIIb)

| | M. p. | Solvent | Yield (%) | Found C | Found H | Found N | Required C | Required H | Required N |
|---|---|---|---|---|---|---|---|---|---|
| (XXXIIe) | 141° | Et·OAc | 48 | 54·7 | 7·2 | 14·0 | 54·5 | 7·1 | 14·1 |
| (XXXIIf) | 184 | MeOH | 38 | 57·4 | 6·9 | 13·5 | 57·1 | 6·7 | 13·3 |
| (XXXIIg) | 173 | $H_2O$ | 46 | 51·0 | 5·8 | 13·4 | 50·9 | 5·7 | 13·2 |

*3-Methoxy-5-methylisoxazole-4-carboxylic Acid* (XIV).—4-Ethoxycarbonyl-3-hydroxy-5-methylisoxazole (10 g.), anhydrous potassium carbonate (10 g.), and dimethyl sulphate (7·5 g.) were heated together under reflux in dry acetone (130 ml.) for 3 hr. The mixture was filtered and the filtrates were concentrated to give an oil which was added to aqueous sodium hydroxide (50 ml.; 10%). The mixture was boiled until homogenous. The solution was cooled and acidified with concentrated hydrochloric acid to give 3-methoxy-5-methylisoxazole-4-carboxylic acid (4·0 g.), identical with that obtained by the methods already described.

The *amides* listed in Table 2 were prepared from the acid by way of the acid chloride by the method described for the amides of the acid (XXXIIb).

TABLE 2

Amides from (XIV)

| | M. p. | Solvent | Yield (%) | Found C | Found H | Found N | Required C | Required H | Required N |
|---|---|---|---|---|---|---|---|---|---|
| (XXXVc) | 157° | Et·OAc | 72 | 46·3 | 5·05 | 18·0 | 46·1 | 5·2 | 17·9 |
| (XXXVd) | 95 | *a* | 90 | 49·6 | 6·1 | 16·2 | 49·4 | 5·9 | 16·5 |
| (XXXVf) | 65 | *a* | 95 | 52·4 | 6·8 | 15·25 | 52·2 | 6·6 | 15·2 |
| (XXXVe) | 61 | *a* | 80 | 52·3 | 6·8 | 15·4 | 52·2 | 6·6 | 15·2 |
| (XXXVg) | 28 | *b* | 74 | 56·5 | 7·6 | 13·2 | 56·6 | 7·6 | 13·2 |
| (XXXVh) | 62 | *a* | 56 | 59·0 | 7·3 | 12·4 | 58·9 | 7·2 | 12·5 |
| (XXXVi) | *c* | | 16 | 53·0 | 6·1 | 12·2 | 53·1 | 6·2 | 12·4 |

[a] Light petroleum (b. p. 60—80°). [b] B. p. 90°/0·4 mm. [c] B. p. 112°/0·4 mm.

*4-Dimethylaminomethyl-3-methoxy-5-methylisoxazole* (XXXVIIa).—The dimethylamide (3·7 g.) in dry tetrahydrofuran (10 ml.) was added slowly to a solution of diborane (50 ml.; 0·7M) at 0° with stirring under nitrogen. The solution was then heated and stirred under reflux for 1 hr. It was then cooled and acidified with 6N-hydrochloric acid. The tetrahydrofuran was distilled off and sodium hydroxide was added until the aqueous phase was saturated. It was then extracted twice with ether, and the ether extract was dried ($Na_2SO_4$) and concentrated to give an oil which solidified. The compound contained boron and its infrared spectrum indicated the presence of $RBH_2$ bonds. The complex was decomposed by heating with 2N-hydrochloric acid (50 ml.) on the steam-bath for 15 min.; the mixture was then cooled, made alkaline with sodium hydroxide, and extracted with ether. The dried ethereal extract was treated with a solution of hydrogen chloride in ethanol–ether and the *hydrochloride* (2 g.) was crystallised from ethanol–ether, m. p. 175° (Found: C, 46·3; H, 7·1; Cl, 17·1; N, 13·7. $C_8H_{15}ClN_2O_2$ requires C, 46·5; H, 7·3; Cl, 17·15; N, 13·55%). The base gave a *methiodide*, m. p. 220° (Found: C, 34·9; H, 5·6; I, 40·8; N, 8·8. $C_9H_{17}IN_2O_2$ requires C, 34·6; H, 5·5; I, 40·6; N, 9·0%).

*4-Dimethylaminomethyl-3-hydroxy-5-methylisoxazole* (XXIXc).— 4-Dimethylaminomethyl-3-methoxy-5-methylisoxazole (0·55 g.) was heated under reflux for 1 hr. with hydrogen bromide in acetic acid (6·5 ml.; 45%). Ether

was added to the cooled solution and a crystalline precipitate was obtained which gave the *hydrobromide* (0·6 g.), m. p. 194° (decomp.) (from ethanol) (Found: C, 35·2; H, 5·4; Br, 33·8; N, 11·7. $C_7H_{13}BrN_2O_2$ requires C, 35·5; H, 5·5; Br, 33·7; N, 11·8%).

*3-Methoxy-5-methyl-4-methylaminomethylisoxazole* (XXXVIIb).—The methylamide (7·0 g.) in dry tetrahydrofuran (120 ml.) was added slowly to diborane in tetrahydrofuran (120 ml.; 0·7M). The mixture was heated under reflux and stirred under dry nitrogen for 3 hr., then cooled and acidified with 6N-hydrochloric acid. The tetrahydrofuran was removed and the solution was made strongly alkaline with solid sodium hydroxide and extracted with ether. The ethereal extracts were dried ($NaSO_4$) and added to ethanolic hydrogen chloride. The *hydrochloride* (3·5 g.) crystallised from ethanol–ethyl acetate, m. p. 182° (Found: C, 43·8; H, 6·9; Cl, 18·4; N, 14·4. $C_7H_{13}ClN_2O_2$ requires C, 43·6; H, 6·8; Cl, 18·4; N, 14·5%). The hydrochloride yielded *3-hydroxy-5-methyl-4-methylaminomethylisoxazole hydrobromide*, m. p. 194° (decomp.) when heated with hydrogen bromide in acetic acid for 1 hr. (Found: C, 32·5; H, 5·1; Br, 35·7; N, 12·4. $C_6H_{11}BrN_2O_2$ requires C, 32·3; H, 5·0; Br, 35·8; N, 12·6%).

*4-Aminomethyl-3-methoxy-5-methylisoxazole* (XXXVIIc).—The amine was prepared by heating the primary amide under reflux with diborane in tetrahydrofuran for 5 hr. The *hydrochloride* (22%) had m. p. 229° (decomp.) (Found: C, 40·5; H, 6·4; Cl, 19·7; N, 15·5. $C_6H_{11}ClN_2O_2$ requires C, 40·3; H, 6·2; Cl, 19·9; N, 15·7%).

*4-(1-Aminoethyl)-3-methoxy-5-methylisoxazole* (XL).—Carbon tetrachloride (0·2 ml.) was added to a mixture of magnesium (1·46 g.) and ethanol (1·5 ml.) in ether (20 ml.). Diethyl malonate (8·8 g.) was added, and the mixture was heated under reflux for 2 hr. To this was added dropwise the acid chloride prepared from 3-methoxy-5-methylisoxazole-4-carboxylic acid (8 g.), and the mixture was heated under reflux for a further 30 min. The mixture was then cooled, acidified with dilute sulphuric acid, and extracted several times with ether. The combined ether layers were concentrated to an oil which was added to a solution of concentrated sulphuric acid (2·5 ml.) in acetic acid (20 ml.) and water (15 ml.). The mixture was heated under reflux for 4 hr., cooled, made alkaline with an excess of sodium hydroxide, and extracted with ether (4 × 30 ml.). The ether extracts were concentrated to give the crude ketone (XXXVIII) (5·0 g.), m. p. *ca.* 30°. The crude ketone was added to a solution of hydroxylamine hydrochloride (2·3 g.) and sodium acetate (2·7 g.) in aqueous ethanol (20 ml.; 50%). The mixture was boiled for 45 min. and when cooled gave the oxime (XXXIX) (4·5 g.), m. p. 153° (from ethanol). The oxime (2·0 g.) in methanol (25 ml.) was added to a mixture of aluminium amalgam [from aluminium (4 g.) and aqueous mercuric chloride (100 ml.; 5%)] and methanol (25 ml.). Water (25 ml.) was added and the mixture was stirred for 16 hr. at 20° and then filtered. The filtrates were concentrated to yield an oil which was added to ethanolic hydrogen chloride; the *hydrochloride* of (XL) (1·3 g.) was precipitated by addition of an excess of ether; m. p. 203° (from ethanol–ether) (Found: 43·9; H, 7·0; Cl, 14·4; N, 18·3. $C_7H_{13}ClN_2O_2$ requires C, 43·6; H, 6·8; Cl, 14·5; N, 18·4%).

*3-Methoxy-5-(2-methylaminoethyl)isoxazole*.—A solution of methyl 3-methoxyisoxazole-5-acetate (3·0 g.) in ethanol (100 ml.) containing methylamine (20 g.) and water (10 ml.) was left at room temperature for 3 days. The solvent was removed *in vacuo* to yield a gum which gave *3-methoxyisoxazole-5-(N-methyl)acetamide* as blades (2·1 g.), m. p. 79—80° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: 49·5; H, 5·9; N, 16·6. $C_7H_{10}N_2O_3$ requires C, 49·4; H, 5·9; N, 16·5%), τ ($CDCl_3$) 7·15 and 7·22 (3H, d, NH·C*H*$_3$), 6·36 (2H, s, 5-$CH_2$), 6·02 (3H, s, 3-OMe), 4·08 (1H, s, 4-H), and 3·3br (1H, s, NH). The amide (1·7 g.) in tetrahydrofuran (50 ml.) was reduced with diborane generated externally from sodium borohydride (1·7 g.) and boron trifluoride etherate (11·5 ml.) in diglyme to give *3-methoxy-5-(2-methylaminoethyl)isoxazole hydrochloride* as needles (0·4 g.), m. p. 117—119° (from propan-2-ol–ether) (Found: C, 43·8; H, 7·0; Cl, 18·6; N, 14·6. $C_7H_{13}ClN_2O_2$ requires C, 43·6; H, 6·8; Cl, 18·4; N, 14·5%), τ ($D_2O$) 7·22 (3H, s, NMe), 6·38—6·92 (4H, m, $CH_2$·$CH_2$), 6·02 (3H, s, 3-OMe), and 3·88 (1H, s, 4-H).

*3-Hydroxy-5-(2-methylaminoethyl)isoxazole Hydrobromide*.—A solution of 3-methoxy-5-(2-methylaminomethyl)isoxazole hydrochloride (0·32 g.) in glacial acetic acid containing hydrogen bromide (5 ml.; 45%) was heated under reflux for 30 min. The mixture was evaporated to dryness and the gummy residue triturated with propan-2-ol, when it crystallised. The solid gave prisms (0·25 g.), m. p. 118·5—121·5° (decomp.) [from propan-2-ol—ether (charcoal)] (Found: C, 32·2; H, 4·8; Br, 35·65; N, 12·4. $C_6H_{11}N_2O_2$ requires C, 32·3; H, 5·0; Br, 35·8; N, 12·6%), τ ($D_2O$) 7·18 (3H, s, C*H*$_3$·NH), 6·38—7·0 (4H, m, $CH_2$·$CH_2$), and 3·92 (1H, s, 4-H).

*5-(2-Dimethylaminoethyl)-3-hydroxy-4-methylisoxazole* (XXIIf).—Ethyl 3-methoxyisoxazole-5-acetate with dimethylamine in ethanol gave *3-methoxy-4-methylisoxazole-5-(NN-dimethyl)acetamide* (XXIg) as needles, m. p. 89—91° [from light petroleum (b. p. 60—80°)] (Found: C, 54·5; H, 6·9; N, 13·9. $C_9H_{14}N_2O_3$ requires C, 54·5; H, 7·1; N, 14·1%), τ ($CDCl_3$) 8·18 (3H, s, 4-Me), 6·9 and 7·5 (each 3H, s, $NMe_2$ with restricted rotation), 6·3 (2H, s, 5-$CH_2$), and 6·02 (3H, s, 3-OMe). Reduction of the dimethylamide with diborane by heating under reflux in tetrahydrofuran for 2 hr. and isolation of the product in the usual way gave *5-(2-dimethylaminoethyl)-3-methoxy-4-methylisoxazole hydrochloride*, which gave needles, m. p. 196° (from propan-2 ol–ether) (Found: C, 49·1; H, 8·0; N, 13·1. $C_9H_{17}ClN_2O_2$ requires C, 49·0; H, 7·8; N, 12·7%). The methoxyisoxazole, when heated under reflux with glacial acetic acid containing hydrogen bromide (45%) for 1 hr., gave *5-(2-dimethylaminoethyl)-3-hydroxy-4-methylisoxazole hydrobromide* as plates, m. p. 162—164° (from propan-2-ol) (Found: C, 38·3; H, 6·2; Br, 31·7; N, 11·2. $C_8H_{15}BrN_2O_2$ requires C, 38·3; H, 6·0; Br, 31·8; N, 11·2%), τ ($D_2O$) 8·1 (3H, s, 4-Me), 7·02 (6H, s, $NMe_2$), and 6·62 (4H, m, $CH_2$·$CH_2$).

*2-Chloronicotinohydroxamic Acid* (LVIIc).—Nicotinic acid *N*-oxide (14 g.), phosphorus pentachloride (42·4 g.), and phosphoryl chloride (40 ml.) were heated together for 90 min. The excess of phosphoryl chloride was removed *in vacuo*. Methanol (100 ml.) was added slowly to the residue, and the solution was concentrated to an oil to which water (100 ml.) was added. The mixture was extracted with ether (3 × 50 ml.) and the ethereal extract was dried ($K_2CO_3$) and concentrated to give the methyl ester as an oil (5·0 g.) which solidified on standing. The ester (5·0 g.) was added to a solution of hydroxylamine hydrochloride (2·25 g.) and sodium hydroxide (2·55 g.) in water (25 ml.) and the mixture was stirred at room temperature until no oily drops remained. Acidification of the cold solution with hydrochloric acid gave the *hydroxamic acid* (4·0 g.),

m. p. 177° (from water) (Found: C, 41·9; H, 3·0; Cl, 20·4; N, 16·2. $C_6H_5ClN_2O_2$ requires C, 41·8; H, 2·9; Cl, 20·6; N, 16·2%).

3-*Hydroxypyrido*[3,2-d]*isoxazole* (LVIII).—The hydroxamic acid (1·3 g.) was heated under reflux with aqueous sodium hydroxide (13 ml.; 10%) for 30 min. The mixture was cooled and acidified with an excess of hydrochloric acid to give the *pyridoisoxazole* (0·5 g.), m. p. 247° (from ethanol) (Found: C, 52·7; H, 3·0; N, 20·4. $C_6H_4N_2O_2$ requires C, 52·95; H, 3·0; N, 20·6%).

*Addendum*

3-*Methoxy*-5-*methylisoxazole*.—A solution of 3-bromo-5-methylisoxazole (32·4 g.) in methanol (220 ml.) containing water (40 ml.) and potassium hydroxide (85·5 g.) was heated under reflux for 24 hr. in an atmosphere of nitrogen. The solution was diluted with water (1 l.) and extracted with ether (4 × 250 ml.). The ethereal solution was dried ($MgSO_4$) and the solvent was removed to yield a pale brown oil which gave the *product* as a liquid (13·0 g.), b. p. 78°/30 mm. Gas–liquid chromatography using a 6 ft × 1/8 in. column of 10% S.E. 30 showed one impurity (*ca.* 1% of the peak area). A homogeneous sample was obtained for microanalysis by preparative g.l.c. on a column (80 × 3/4 in.) containing 20% U.C.-W 98 on 60/80 P support maintained at 100° with helium flow at 400 ml./min. Difficulty was experienced in obtaining consistent microanalytical results with this compound owing to its volatility (Found: C, 52·45; H, 6·3; N, 12·55. $C_5H_7NO_2$ requires C, 53·1; H, 6·2; N, 12·4%).

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