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ISOXAZOLES—II

MANNICH BASES

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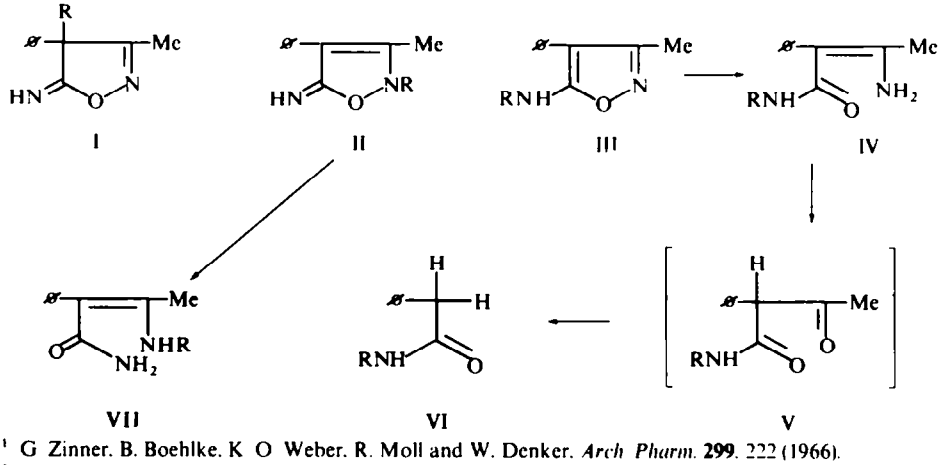
Abstract—The structure and the spectra of several aminoalkylisoxazoles are presented. Proof is given that aminomethylation (Mannich reaction) of isoxazoles can involve different nucleophilic centres.

THE recent report of the synthesis of a Mannich base of a 4,4-diethylisoxazolin-3,5-dione[1] prompts us to record the results of our own research. By treatment of an ethanol solution of a group of aminoisoxazoles, isoxazolinones and aminoisoxazolinones with formaldehyde and a secondary amine we obtained in most cases crystalline addition compounds (Mannich bases) the structures of which were established by degradation experiments and by physico-chemical methods.[2–4]

In Table 1 the physical constants are reported of a selected group of Mannich bases, all of them piperidine derivatives, and of a 4-dialkylaminoalkylisoxazole which was synthesized for comparison.[5] To simplify the discussion the examples have been divided into 5 sub-groups which will be discussed separately.



[1] G Zinner, B. Boehlke, K O Weber, R. Moll and W. Denker, *Arch Pharm.* **299**, 222 (1966).

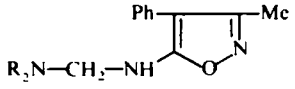
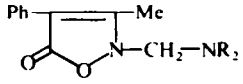
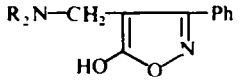
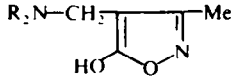
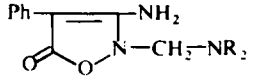
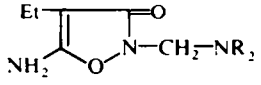
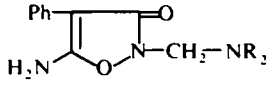
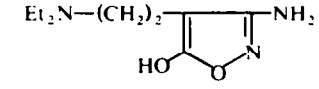
[2] For a general discussion on the IR and UV spectra of a group of aminoisoxazolinones and for leading Refs on this subject, see preceding communication [3]

[3] W Barbieri, L. Bernardi, S Coda, V. Colò and G. Palamidessi, *Tetrahedron* **23**, 4395 (1967).

[4] These bases were found to be rather unstable and, particularly in the presence of acids, they easily dissociated to give the starting isoxazoles. In other cases complete decomposition occurred on attempting recrystallization and for these reasons in some cases only the spectroscopic methods could safely be used as structural proof

[5] It can be easily seen how the instability[4] of these substances is reflected in the experimental mol. wt determined osmometrically at 37°: in most cases low values due to dissociation were found, except when anhydrous aprotic solvents could be employed

TABLE

No	Compound[a,b]	M.p.	Formula	Mol. wt.	Apparent mol. wt.[c]	λ_{max}; mμ in EtOH
1		94 95	$C_{16}H_{21}N_3O$	271·3	206 E 273 A	260
2		101-102	$C_{16}H_{20}N_2O_2$	272·3	152 E 287 B	283
3		175–177	$C_{15}H_{18}N_2O_2$	258·3	213 E 182 M	230
4		163 166	$C_{10}H_{16}N_2O_2$	196·2	195 E	243[f]
5		97 99	$C_{15}H_{19}N_3O_2$	273·3	248 E	260, 270[d]
6		158 160	$C_{11}H_{19}N_3O_2$	225·3	211 E	247
7		146–148	$C_{15}H_{19}N_3O_2$	273·3	208 E	259
8		164 166	$C_9H_{17}N_3O_2$	—	-	238

[a] Only one of the tautomer formulae is reported.

[b] NR_2 is the 1-piperidyl radical ($C_5H_{10}N$).

[c] E = EtOH 95%; M = MeOH; B = benzene; A = acetone.

[d] The 260 mμ maximum is probably due to some 3-amino-4-phenylisoxazolin-5-one formed by dissociation of 5 in EtOH sol.

[e] s = strong; m = medium; v = very; w = weak; b = broad.

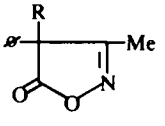
[f] log ε 3·78

I

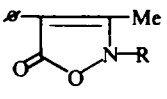
	IR absorption bands[a] (cm^{-1})						
KBr	3250 w					1640 s	
CH_2Cl_2	3400 m					1650 s	
KBr					1720 s	1615 m	1595 mw
CH_2Cl_2					1735 s	1618 m	1595 m
KBr	2400 sb					1625 sb	1580 m
CH_2Cl_2						1620 sb	
KBr	2500 sb					1620 sb	
CH_2Cl_2				1800 w	1730 w	1630 s	
KBr	3520 vw	3320 vw	3080 s		1720 s	1640 s	1580 s
CH_2Cl_2	3480 s	3300–3200 b			1735 s	1630 vs	
KBr	3300 s	3100 s				1650 s	1575
CH_2Cl_2	3500 m	3400 m			1700 vw	1650 vs	
KBr	3500 vw	3260 w	3080 s			1620 vs	1575 vs
CH_2Cl_2	3500 m	3400 m				1650 vs	1620 sb
KBr	3350 s	3200 s	2300 sb			1635 sb	

(a) 3-*Alkyl*-4-*aryl*-5-*aminoisoxazoles*. The Mannich bases of this group are exemplified by 3-methyl-4-phenyl-5-(1-piperidylmethyl)aminoisoxazole (No. 1). Of the three possible formulae (I, II, III; R = $C_5H_{10}N—CH_2$) I can be excluded on the ground of the UV spectrum but the IR spectrum, which shows a medium band at 3400 cm^{-1}, does not allow a clear distinction between II and III: the λ_{max} value (UV spectrum) would, however, suggest structure II as the less probable.[6] Structure III was confirmed by degradation experiments. Compd 1 was reduced in ethanol with a Pt catalyst[7] until 1 mole of hydrogen had been absorbed: careful work up of the solution afforded a compound $C_{16}H_{23}N_3O$ whose IR spectrum (KBr) suggested the probable presence of a secondary amide (1650 and 1540 cm^{-1}; amide I and amide II band) thus favouring IV (and III) over VII (and II). The reduction product was hydrolysed with H_2SO_4, the acid solution was extracted to eliminate all non-basic substances,[8] basified and continuously extracted with ether. From the ether extract both phenylacetamide and a *basic secondary amide* (CH_2Cl_2: 3440 cm^{-1} band; NH stretching—KBr: 1660 and 1550 cm^{-1}; amide I and amide II bands) were isolated. This same basic amide was obtained by condensation of phenylacetamide with formaldehyde and piperidine and it was therefore formulated as VI. The isolation of VI, which obviously takes origin from the ketoamide V, by "acid hydrolysis", settles the structure of IV and allows the assignment of formula III to the Mannich base.

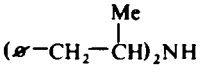
(b) 3-*Alkyl*-4-*arylisoxazolin*-5-*ones*. 2-(1-Piperidylmethyl)3-methyl-4-phenylisoxazolin-5-one (No. 2) exemplifies the results of the Mannich reaction run on one of the title compounds. Of the two structures VIII and IX (R = $C_5H_{10}N—CH_2$) which can be conceived for this Mannich base, VIII can be discarded on spectroscopic evidence. In fact the IR spectrum presents a 1735 cm^{-1} CO stretching band, which



VIII



IX



X

is typical of a 2H-isoxazolin-5-one such as IX.[3, 10] The UV spectrum is also in accord with structure IX.[11–13]

(c) *Isoxazolin*-5-*ones*. As examples of this class of compounds, the Mannich bases of 3-phenylisoxazolin-5-one (No. 3) and 3-methylisoxazolin-5-one (No. 4) were

[6] Cf. the spectrum of 2-methyl-4-phenyl-5-aminoisoxazolin-3-one in alkaline solution.[3]

[7] L. Panizzi, *Gazz. Chim. Ital.* **76**, 44 (1946).

[8] Mostly-2-phenyl-3-oxobutyramide, identified by IR spectrum and mixed m.p. with an authentic sample.[9]

[9] L. Almirante, A. Bianchi and V. Zamboni, *Ann Chim.* **46**, 623 (1956).

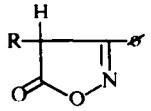
[10] Structure VIII would require a much higher CO stretching band (about 1800 cm^{-1}).

[11] Cf.[12] 2,3-Dimethyl-4-phenylisoxazolin-5-one: λ_{max} 283 mμ.

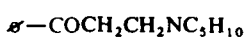
[12] A. Quilico and G. Speroni, *The Chemistry of Heterocyclic Compounds Five and Six-membered Compounds with Nitrogen and Oxygen* (Edited A. Weissberger) p. 214. Interscience, New York, N.Y. (1962).

[13] Catalytic reduction in neutral solution gave a complex mixture from which was isolated, thanks to its low solubility, the hydrochloride of di-(1-phenyl)-isopropylamine (X) (Unknown stereoisomer). The structure of X was confirmed by its synthesis via catalytic reduction of 2 moles of benzyl methyl ketone and 1 mol NH_3. The formation of X is in accord with structure IX, although it cannot be used as a definite proof of it.

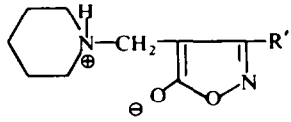
investigated. The structure of 3-phenyl-4-(1-piperidylmethyl)isoxazolin-5-one (XI; R = $C_5H_{10}N—CH_2$) for No. 3 was deduced by the spectroscopic data and by degradation experiments: the analogous structure of 3-methyl-4-(1-piperidylmethyl)-isoxazolin-5-one to No. 4 was assigned on spectral analogy. Hydrogenation of



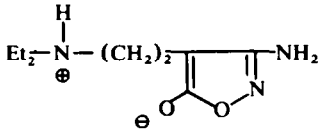
XI



XII



XIII



XIV

No. 3 in ethanol containing one equiv HCl[14] gave the hydrochloride of β-N-piperidinopropiophenone (XII), identified by the IR spectrum and mixed m.p. with an authentic sample.[15] The structure of 3-phenyl-4-1-piperidylmethyl)isoxazolin-5-one (XI) assigned to No. 3 remains, therefore, confirmed.

It is, however, understood that formula XI represents only one of the possible tautomeric structures: a more detailed picture can be drawn if we take into account the IR spectra. As reported in Table 1, the spectrum (solid state) of No. 3 presents a broad complex band in the 2600–2200 cm^{-1} region which can be assigned to an $NH^{(+)}$ vibration. In the 6 μ region the peculiar CO stretching bands of the 2H- and 4H-isoxazolin-5-ones (1735 cm^{-1} and 1790 cm^{-1}, resp.)[3] are conspicuously absent, whereas a strong band at 1620 cm^{-1} (isoxazole ring) is present: all these facts point to the internal salt structure XIII (R′ = Ph) for No. 3.[16–19] To confirm these results an isoxazolin-5-one having a basic chain in the 4 position (No. 8)[20] was synthesized from ethyl diethylaminoethylcyanoacetate and hydroxylamine: in this case also, a salt-like structure is feasible and in fact the IR spectrum presents the same features of the spectrum of No. 3 (bands at 2300 and 1635 cm^{-1}; absence of absorption bands at 1700–1800 cm^{-1}). The structure XIV can therefore be assigned[21,22] to No. 8.

[14] In absence of HCl, only a red, amorphous, intractable substance was isolated.

[15] C. Mannich and K. Curtaz, *Arch. Pharm.* **264**, 741 (1926).

[16] The UV spectrum is also in accord with such a structure.[17]

[17] Cf.[18] 3-Phenyl-4-methyl-5-methoxyisoxazole: λ_{max} 228 mμ.

[18] A. J. Boulton and A. R. Katritzky, *Tetrahedron* **12**, 41 (1961).

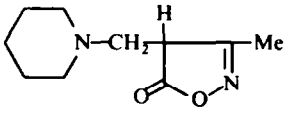
[19] Cf. A. R Katritzky, S. Øksne and A. J. Boulton, *Tetrahedron* **18**, 777 (1962).

[20] Structural proof rests on the synthetic procedure adopted. Compd. 8 was found to be different from the isomer 4-(diethylaminoethyl)-5-aminoisoxazolin-3-one (compd. 4 of Ref. 3) whose structure had been confirmed by degradation.

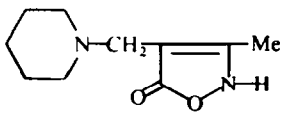
[21] Of course this only means that structures XIII and XIV are preponderant, but it does not exclude other tautomeric structures (e.g. XI) which could eventually be favoured by a change of state or solvent.

[22] The UV spectrum of No. 8 is in accord with the proposed formula XIV. A 3-aminoisoxazolin-5-one structure, on the contrary, would require a higher absorption maximum.[3]

The IR spectrum of No. 4 is similar to the one of Nos. 3 and 8 and therefore the structure XIII (R′ = Me) can be assigned to it. However, the presence of weak bands at 1800 and 1730 cm^{-1} and also the position and the intensity of the UV absorption maximum suggest that, besides XIII (R′ = Me) the tautomeric 4H and 2H structures XV and XVI, are also present.

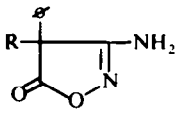


XV

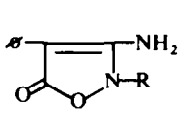


XVI

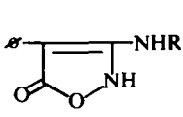
(d) *3-Aminoisoxazolin-5-ones.* Compound No. 5, 2-(1-piperidylmethyl)3-amino-4-phenylisoxazolin-5-one is here reported as a representative of Mannich bases related to this class of isoxazolones. Of the four possible formulae that can be assigned to the product of the Mannich reaction, XVII, XVIII, XIX and XX (R = $C_5H_{10}N—CH_2$), and XVII and XX can be discarded easily, because they are not in accord with the UV spectrum (λ_{max} 270 mμ). Moreover the IR spectrum of No. 5 presents a band



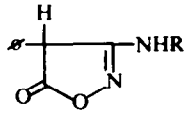
XVII



XVIII

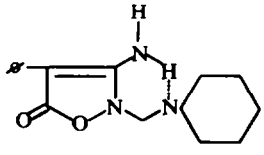


XIX

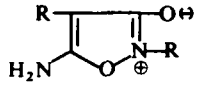


XX

(CH_2Cl_2) at 1735 cm^{-1} which has been found to be related to a 2H-isoxazolin-5-one structure such as XVIII and XIX. A choice among these formulae could be reached by examining the 3 μ region of the IR spectrum which presents, in CH_2Cl_2 solution, a strong sharp band at 3480 cm^{-1}, a strong broad band at 3300–3200 cm^{-1}, a weak shoulder at 3520 cm^{-1} and a weak band at 3400 cm^{-1}. The features of this spectrum are very similar to the one presented by the spectra of 2-dialkylaminoalkyl-3-aminoisoxazolin-5-ones and which we have shown to be due to a strong intramolecular hydrogen bond between the NH_2 and the tertiary amino group. Accordingly, the strong 3480 and 3300–3200 cm^{-1} bands have been assigned to a hydrogen bonded NH_2 and the two weak bands to a free NH_2. We therefore have assigned to compd No. 5 the formula XVIII, which is best expressed by the intramolecular hydrogen bonded structure XXI.



XXI



XXII

(e) *5-Aminoisoxazolin-3-ones.* The Mannich bases of these isoxazolones are exemplified by compds Nos. 6 and 7. The structure XXII was assigned to them on

spectroscopic grounds since both the UV spectrum and the IR spectrum are strictly similar to the spectra of 2-alkyl-5-aminoisoxazolin-3-ones.[3,23]

CONCLUSIONS

The nucleophilic reactivity toward alkyl halides of C_4 in isoxazolin-5-ones has been previously reported;[3] the present aminomethylation experiments confirm the nucleophilicity of this atom. In fact in some cases the attack on C_4 was found to be prevalent, whereas in other cases only N_2 was affected.[24] Although at present it is difficult to predict the course of the Mannich reaction on other isoxazole derivatives since the outcome seems to be bound to subtle changes in the substrate.[26] the structure of the products, however, could be easily determined by comparing the UV and IR spectra with the spectroscopic data of the model substances we have reported in this note.

EXPERIMENTAL

M.ps are uncorrected. The IR spectra were recorded on a Perkin-Elmer M 237 double grating spectrophotometer. Samples were prepared as solution in CH_2Cl_2 and examined in 1 mm cells with NaCl windows and as dispersions in pressed KBr discs. Mol wts were determined at 37° with a Mechrolab M 301 A osmometer.

3-Methyl-4-phenyl-5-(1-piperidylmethyl)aminoisoxazole (No. 1)

To 3-methyl-4-phenyl-5-aminoisoxazole[10] (1·75 g) and piperidine (1·1 ml) dissolved in EtOH (8 ml) was slowly added a standard[29] soln of formaldehyde (4 ml) at 0°. The soln was kept overnight at 33°, the solvent was eliminated *in vacuo*, the residue was washed with water and crystallized from AcOEt–pet. ether to give 1·6 g of No. 1. (Found: C, 70·6; H, 7·75; N, 15·5. $C_{16}H_{21}N_3O$ requires: C, 70·8; H, 7·8; N, 15·5%.)

Hydrogenation of 3-methyl-4-phenyl-5-(1-piperidylmethyl)aminoisoxazole

A soln of No. 1 (4 g) in MeOH (80 ml) containing PtO_2 (0·6 g) was hydrogenated at +15° and atm press until 1 mole of H_2 was absorbed. The solvent was eliminated *in vacuo*, the residue was treated with cyclohexane–pet. ether and the flask was kept in the refrigerator for 7 days. cis-N-(1-*piperidylmethyl*) 2-*phenyl*-3-*aminocrotonamide* (1·2 g) was collected by filtration and recrystallized from cyclohexane–pet. ether, m.p. 98–100°. (Found: C, 70·2; H, 8·5. $C_{16}H_{23}N_3O$ requires: C, 70·3; H, 8·5%.) This compound was dissolved in 10% H_2SO_4 (60 ml) and treated at 60° for 1 hr. After cooling the soln was extracted for 12 hr with ether in order to remove non-basic compounds.[30] The acid soln was next basified with NaOH and extracted

[23] The IR-spectrum shows the presence of a free NH_2 (3500 and 3400 cm^{-1} bands) and the 1650 cm^{-1} band due to an isoxazole ring mode: the 1-piperidylmethyl substituent must therefore be attached at N_2. For a discussion concerning the dipolar rather than the 2-alkyl-3-one structure see ref. 3.

[24] According to the literature[25] aminomethylation of 1-R-2-pyrazolin-5-ones affords C_4 derivatives exclusively.

[25] B. Pathak and T. N. Ghosh, *J. Indian Chem. Soc.* **26**, 371 (1949).

[26] An empirical rule can be set as follows. It is known that isoxazolin-5-ones are either in the 2H or 4H tautomeric form.[27] Our data suggest that N_2 aminomethylation is prevalent (Nos. 2 and 5) in 2H-isoxazolin-5-ones such as 3-methyl-4-phenylisoxazolin-5-one[28] and 3-amino-4-phenylisoxazolin-5-one.[3] Likewise C_4 aminomethylation prevails (Nos. 3 and 4) in the case of isoxazolin-5-ones which are mostly in the 4H form such as 3-methyl- and 3-phenylisoxazolin-5-one.[27] When neither form is important as in the case of 3-methyl-4-phenyl-5-aminoisoxazole the aminomethylation occurs at the amino group (No. 1).

[27] A. R. Katritzky and J. M. Lagowsky, *Advances in Heterocyclic Chemistry* (Edited A. R. Katritzky) Vol. 2; p. 37. Academic Press, New York (1963).

[28] W. Barbieri, unpublished results.

[29] The standard solution was prepared by diluting 5 ml of commercial formaldehyde with 20 ml of EtOH.

[30] 2-Phenyl-3-oxobutyrramide, m.p. 130° (lit.[10] m.p. 130°) (0·4 g) was isolated from the Et_2O extract.

with Et_2O overnight. The Et_2O extract was evaporated and the residue was treated with 1N HCl (10 ml). The insoluble part was filtered off (phenylacetamide. 0·3 g) and the soln was basified and extracted with Et_2O. From the Et_2O extract, *N-(1-piperidylmethyl)phenylacetamide*. m.p. 110–112° (0·2 g) was isolated on concentration. (Found: C, 72·4; H, 8·6; N, 11·9. $C_{14}H_{18}N_2O$ requires: C, 72·4; H, 8·7; N, 12·1%.)

N-(1-Piperidylmethyl)phenylacetamide

Phenylacetamide (2 g) and methylolpiperidine[31] (2·2 ml) were kept at 0° for 2 hr, then K_2CO_3 (0·5 g) was added and the mixture was left overnight at room temp. EtOH (2 ml) was added and the suspension was warmed at 80° for 1 hr. AcOEt was next added to the cooled suspension and the insoluble residue discarded. The solvent was eliminated *in vacuo* and the residue was treated with the minimum amount of 1N HCl: the soln was filtered, basified with Na_2CO_3 and extracted with Et_2O. N-(1-Piperidylmethyl) phenylacetamide (0·8 g), m.p. 110–112°, identical to that obtained by degradation of No. 1, was obtained by concentration of the Et_2O extract.

2-(1-Piperidylmethyl)3-methyl-4-phenylisoxazolin-5-one (No. 2).

To 3-methyl-4-phenylisoxazolin-5-one[33] (1·75 g) and piperidine (1·1 ml) in EtOH (8 ml) was slowly added at 0° a standard formaldehyde soln (4 ml). After 2 hr the soln was heated to 33° and kept at this temp for 14 hr. The solvent was eliminated *in vacuo* and the residue was treated with Et_2O (300 ml). The insoluble residue was discarded and the ether soln was concentrated and diluted with pet. ether to give No. 2 (1·6 g) that was next crystallized from benzene–pet. ether. (Found: C, 70·3; H, 7·5. $C_{16}H_{20}N_2O_2$ requires: C, 70·6; H, 7·4%.)

Di-(1-phenyl) isopropylamine[34]

(a) A soln of No. 2 (1·1 g) in EtOH was hydrogenated at room temp in presence of PtO_2 (0·15 g): after the absorption of 2 moles of H_2 the reaction stopped. The solvent was eliminated *in vacuo* and the residue was treated with 2N HCl: the semi-solid insoluble residue was treated first with ether and then crystallized from EtOH–Et_2O to give di-(1-phenyl) isopropylamine hydrochloride (0·15 g) m.p. 201–203°. (Found: C, 74·5; H, 8·4; N, 4·8; Cl, 12·1. $C_{18}H_{24}NCl$ requires: C, 74·6; H, 8·35; N, 4·8; Cl, 12·2%.)

(b) Methyl benzyl ketone (2 g) in EtOH containing NH_3 (12 ml) and Pd on C (0·5 g) was hydrogenated at room temp. H_2 absorption ceased after 15 hr, the soln was evaporated and the residue was treated with 2N HCl: the insoluble white solid was crystallized from EtOH–Et_2O to give di-(1-phenyl) isopropylamine hydrochloride identical to the compound prepared according to (a).

3-Phenyl-4-(1-piperidylmethyl) isoxazolin-5-one (No. 3)

To 3-phenylisoxazolin-5-one[35] (1·6 g) and piperidine (1·1 ml) dissolved in EtOH (8 ml) was slowly added at 0° a standard formaldehyde soln (4 ml). A solid started soon to crystallize out: the soln was kept at room temp overnight, then filtered to give No. 3 (2·1 g) which was next crystallized from MeOH. (Found: C, 69·8; H, 7·2. $C_{15}H_{18}N_2O_2$ requires: C, 69·7; H, 7·0%.)

Reduction of 3-phenyl-4-(1-piperidylmethyl) isoxazolin-5-one

An EtOH soln of No. 3 (2 g) containing HCl (1·32 ml) and PtO_2 (0·02 g) was hydrogenated at room temp for 7 hr, then further PtO_2 (0·02 g) was added and hydrogenation was continued until one mole of H_2 was absorbed. The solvent was eliminated *in vacuo*, the residue was taken up in 0·1N NaOH and extracted with ether. The extract was evaporated *in vacuo* and the residue was kept under high vacuum for several hr to eliminate some accompanying piperidine, then HCl–Et_2O was added. The precipitated salt was crystallized from EtOH and found to be identical to a sample of β-N-piperidinopropiophenone. HCl.[16]

3-Methyl-4-(1-piperidylmethyl)isoxazolin-5-one (No. 4)

To 3-methylisoxazolin-5-one[36] (3 g) and piperidine (3·4 ml) in EtOH (20 ml) was slowly added at 0°

[31] Prepared according to the procedure described[32] for the synthesis of methylolmorpholine.

[32] M. Zief and J. P. Mason, *J. Org. Chem.* **8**, 1 (1943).

[33] W. Logenann, L. Almirante e L. Caprio, *Chem. Ber.* **87**, 1178 (1954).

[34] Unknown stereochemistry. The product could be isolated and identified owing to the low solubility of its hydrochloride.

[35] F. B. Dains and E. L. Griffin, *J. Am. Chem. Soc.* **35**, 959 (1913).

[36] A. R. Katritzky and S. Øksne, *Tetrahedron* **18**, 789 (1962).

a standard formaldehyde soln (14 ml). The soln was left overnight at room temp. the solvent was eliminated *in vacuo* and the residue was extracted 3 times with CH_2Cl_2. The insoluble material was crystallized from EtOH–Et_2O to give No 4 (4·3 g). (Found: C, 61·1; H, 8·1; N, 13·8. $C_{10}H_{16}N_2O_2$ requires: C, 61·2; H, 8·2; N, 14·3%.)

2-(1-*Piperidylmethyl*) 3-*amino*-4-*phenylisoxazolin*-5-*one* (No. 5)

To 3-amino-4-phenylisoxazolin-5-one[37] (1 g) and piperidine (0·5 g) in EtOH (3 ml) was slowly added at 0° a standard formaldehyde solution (3·5 ml). Compd No. 5 soon separated as crystalline ppt and it was collected after 15 min (1·2 g). (Found: C, 65·8; H, 7·1. $C_{15}H_{19}N_3O_2$ requires: C, 65·9; H, 7·0%.)

2-(*Piperidylmethyl*) 4-*ethyl*-5-*aminoisoxazolin*-3-*one* (No. 6)

To 4-ethyl-5-aminoisoxazolin-3-one (2·6 g) and piperidine (1·1 equivs) in EtOH (13 ml) was slowly added at 0° a standard formaldehyde soln (1·1 equivs). The soln was kept overnight at 0° and No. 6 was collected by filtration (88% yield). (Found: C, 58·3; H, 8·4; N, 18·6. $C_{11}H_{19}N_3O_2$ requires: C, 58·6; H, 8·5; N, 18·65%.)

2-(1-*Piperidylmethyl*) 4-*phenyl*-5-*isoxazolin*-3-*one* (No. 7)

The same procedure reported for No. 6 was adopted. The soln was kept overnight at room temp. the solvent was eliminated *in vacuo* and No. 7 was obtained in 70% yield by crystallizing the residue from MeOH–Et_2O. (Found: C, 65·9; H, 7·0. $C_{15}H_{19}N_3O_2$ requires: C, 65·9; H, 7·0%.)

3-*Amino*-4-(2-*dimethylaminoethyl*)*isoxazolin*-5-*one* (No. 8)

2-Dimethylaminoethylcyanoacetate (7·1 g) in EtOH (50 ml) was treated with NH_2OH (1·1 equivs) at reflux temp for 6 hr. The solvent was eliminated *in vacuo* and the residue was treated first with Et_2O then with AcOEt (Et_2O) and AcOEt extracts were discarded) and finally was crystallized from EtOH to give No. 8 (2 g). (Found: C, 54·1; H, 8·6; N, 21·1. $C_9H_{17}N_3O_2$ requires: C, 54·25; H, 8·6; N, 21·1%.)

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[37] L. Bauer, C. N. V. Nambury and C. L. Bell, *Tetrahedron* **20**, 165 (1964).