72. *Some 4-Substituted Oxazoles.*

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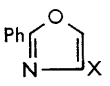
A variety of chemical transformations has been carried out on 2-phenyloxazoles bearing carboxy-, formyl-, and cyano-substituents in the 4-position. Parallel studies with 5-amino-2-phenyloxazoles bearing similar 4-substituents were less rewarding as the ring system was too readily disrupted.

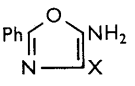
The useful properties of certain five-membered heterocyclic compounds as analgæsic, anti-inflammatory, and anti-convulsant drugs turned our attention to oxazoles, a class which has hitherto escaped detailed pharmacological examination. It was fortunate that studies related to penicillin [1] had rendered accessible several convenient starting materials.

Our primary interest has been the preparation of compounds bearing a nitrogenous side chain. The ready availability of 2-phenyloxazole-4-carboxylic acid (I; X = CO_2H) from the sodium salt of 4-hydroxymethylene-2-phenyloxazolone [2] made the preparation of a series of amides (I; X = CO·NRR′) and their reduction with lithium aluminium hydride appear a simple route to amines (I; X = CH_2·NRR′). It is stated [3] that oxazoles are not stable to this reagent and that an ethoxycarbonyl group, for example, cannot be reduced to an alcohol without disruption of the ring system. We found, however, that the ester (I; X = CO_2Et) was smoothly reduced to the alcohol by the stoicheiometric quantity of lithium aluminium hydride at room temperature. With amides our success varied: amines were obtained from the diethylamide, dimethylamide, and piperidide in 24—35% yield and the reaction failed with the cyclohexylamide and di(hydroxyethyl)amide.

Another route to 4-aminomethyloxazoles proved in general to be superior. The alcohol (I; X = CH_2·OH), most conveniently prepared by reduction of the acid chloride (I; X = COCl) with sodium borohydride, was converted into its chloride by thionyl chloride and into its bromide by phosphorus pentabromide. The latter yielded the piperidide (I; X = CO·N < C_5H_{10}) in 87% yield. The reaction was also successful with morpholine and diethanolamine but failed with diethylamine. Quaternary ammonium compounds were obtained on treatment of the bromide with 1-ethylpiperidine or triethylamine.



(I)



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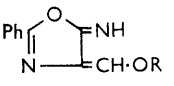
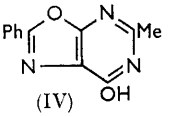


(III)



(IV)

A few unsuccessful attempts were made to prepare 4-2′-aminoethyloxazoles (I; X = CH_2·CH_2·NRR′). The acid chloride (I; X = COCl) with diazomethane gave the crystalline diazoketone (I; X = CO·CHN_2), but efforts to effect a Wolff rearrangement were unavailing.

4-Formyl-2-phenyloxazole condensed with nitroethane under the conditions described by Shepard and his co-workers [4] to give the nitroalkene (I; X = CH:CMe·NO_2) in 47% yield, but a similar reaction with nitromethane resulted in resins. By the use of ammonium acetate instead of butylamine as the condensing agent,[5] the condensation with nitromethane occurred in 30% and that with nitroethane in 80% yield, but the products could not be reduced to the saturated amines with lithium aluminium hydride. Some intermediates for other routes to an ethylamine side chain were also prepared, *viz.*, the nitrile (I; X = CH_2·CN) (from the bromide) and the propionic acid (I; X = CH_2·CH_2·CO_2H)

[1] "The Chemistry of Penicillin," Princeton Univ. Press, 1949, Chapter 21.
[2] Cornforth and Cookson, *J.*, 1952, 1085.
[3] See Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publ. Inc., New York, 1956, p. 797 for references.
[4] Shepard, Noth, Porter, and Simmons, *J. Amer. Chem. Soc.*, 1952, **74**, 4611.
[5] Cf. Young, *J.*, 1958, 3493.

(by hydrogenation of the acrylic acid obtained by condensing the 4-aldehyde with malonic acid), but transformation of these products was not pursued.

Curtius degradation of the acid azide [2] (I; X = $CO{\cdot}N_3$) offered a route to other nitrogenous derivatives. The resulting isocyanate (I; X = ·NCO) (which was obtained crystalline, as was also its bisulphite derivative) was treated with cyclohexanol and with benzyl and 2-chloroethyl alcohol, to yield the urethanes (I; X = $NH{\cdot}CO_2C_6H_{11}$, etc.) and with allylamine, cyclohexylamine, piperidine, 3-dimethylaminopropylamine, and glycine to yield the *N*-substituted ureas (I; X = $NH{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH{:}CH_2$, etc.).

We have also examined the potentiality of 5-amino-4-ethoxycarbonyl-, -4-cyano-, and -4-formyl-2-phenyloxazole (II; X = CO_2Et, CN, and CHO) which are now readily available. In general, however, the 5-amino-group greatly reduced the stability of the ring system and few of the reactions described above could be brought about with derivatives possessing this substituent.

Efforts to cause the ester (II; X = CO_2Et) to react with amines were unpromising, as mixtures resulted which could not readily be separated. With hydrazine, however, a crystalline hydrazide (II; X = $CO{\cdot}NH{\cdot}NH_2$) was obtained, which with nitrous acid gave the crystalline azide (II; X = $CO{\cdot}N_3$). Interaction of this with amines, unfortunately, gave only intractable products as did also attempts to bring about a Curtius rearrangement.

Attempts to hydrolyse the ester (II; X = CO_2Et) and its *NN*-diacetyl derivative to the amino-carboxylic acid failed, apparently as the result of disruption of the ring system. Treatment of the nitrile (II; X = CN) (prepared by the action of phosphorus oxychloride on benzamidomalondiamide) with concentrated sulphuric acid gave the crystalline amide (II; X = $CO{\cdot}NH_2$) but efforts to prepare the acid from this by hydrolysis and by treatment with nitrous acid were also unavailing.

5-Amino-4-formyl-2-phenyloxazole,[6] some of the reactions of which, for example, its red coloration with ferric chloride, suggest that it exists in the tautomeric form (III; R = H), reacted readily with benzylamine, morpholine, and piperidine, to form non-basic products which must have the open-chain structures $Ph{\cdot}CO{\cdot}NH{\cdot}C(CN){:}CHX$, where X = $NH{\cdot}CH_2Ph$, $N<[CH_2{\cdot}CH_2]_2>O$, and $N<C_5H_{10}$, as their infrared spectra had a strong band at 4·5 μ, characteristic of the $-CN$ group and absent from the spectrum of the aldehyde. Basic analogues were also prepared from dimethyl- and diethyl-aminoethylamine and 3-dimethylaminopropylamine. An attempt to re-form the ring system by treatment of the products with acetic anhydride led only to 4-acetoxymethylene-5-imino-2-phenyloxazoline (III; R = Ac), identified by its infrared spectrum and failure to give a colour with ferric chloride.

The oxazolopyrimidine (IV) was obtained by treating 5-acetamido-4-cyano-2-phenyloxazole with alkali and hydrogen peroxide,[7] the structural assignment being based on the analysis, solubility in alkali, and ultraviolet and infrared spectra.

Experimental

Ultraviolet spectra were measured for EtOH solutions unless otherwise stated.

2-*Phenyloxazole-4-carboxyamides*: *General Method.*—2-Phenyloxazole-4-carbonyl chloride (0·80 g., 0·0038 mole) in dry benzene (15 ml.) was added dropwise to a chilled solution of the amine (0·015 mole) in benzene (15 ml.). The mixture, sometimes containing precipitated amine hydrochloride, was washed successively with water, dilute hydrochloric acid, and water. After evaporation under diminished pressure the residue was crystallised from an appropriate solvent (see Table).

4-*Hydroxymethyl-2-phenyloxazole*.—(*a*) An ethereal M-solution (0·5 ml.) of lithium aluminium hydride was added to 4-ethoxycarbonyl-2-phenyloxazole (0·2 g.) in dry ether (10 ml.) After 10 min. at room temperature the mixture was treated with water, followed by hydrochloric

[6] Ref. 1, p. 728.
[7] Cf. Bogart and Hand, *J. Amer. Chem. Soc.*, 1902, **24**, 1031; Robins, *J. Org. Chem.*, 1958, **23**, 191.

acid. Evaporation of the water-washed ethereal layer left the oily *alcohol* which crystallised from light petroleum in needles (0·1 g.), m. p. 82—83°, $\lambda_{max.}$ 268 (ε 11,600) and 218 mμ (ε 2880) (Found: C, 68·5; H, 5·2; N, 8·1. $C_{10}H_9NO_2$ requires C, 68·55; H, 5·2; N, 8·0%).

(*b*) Sodium borohydride (0·66 g., 0·0175 mole) was added to a solution of 2-phenyloxazole-4-carbonyl chloride (0·52 g., 0·0025 mole) in dry dioxan (10 ml.) and the ensuing exothermic reaction was completed by heating the heterogeneous mixture on a steam-bath for 2 hr. The

2-Phenyloxazole-4-carboxyamides.

		Yield	Found (%)				Required (%)		
Amine	M. p.	(%)	C	H	N	Formula	C	H	N
Allylamine	92—93°	81 [1]	68·4	5·3	12·15	$C_{13}H_{12}N_2O_2$	68·4	5·3	12·3
Benzylamine	146·5—148·5	94 [2]	73·45	5·3	9·75	$C_{17}H_{14}N_2O_2$	73·4	5·1	10·1
Cyclohexylamine	130—131	90 [2]	—	—	9·85	$C_{16}H_{18}N_2O_2$	—	—	10·3
Diethanolamine	97—99	26 [3] *	61·3	5·8	10·0	$C_{14}H_{16}N_2O_4$	60·85	5·8	10·1
Diethylamine	42—43	61 [8]	69·1	6·6	11·35	$C_{14}H_{16}N_2O_2$	68·8	6·6	11·15
3-Dimethylamino-propylamine hydrochloride	46—48 (b. p. 80—84/0·5 mm.) 141—142	59 [4]	58·2	6·5	12·9	$C_{15}H_{19}N_3O_2$,HCl	58·15	6·5	13·6
2-Hydroxyethyl-amine	133·5—134	88 [3]	61·9	5·3	11·55	$C_{12}H_{12}N_2O_3$	62·1	5·2	12·1
D-Glucosamine	201—202	31 [5] *	—	—	8·4	$C_{16}H_{18}N_2O_7$	—	—	8·0
Glycine	219—221	65 [1] *	59·0	4·0	12·4	$C_{12}H_{10}N_2O_4$	58·5	4·0	11·9
Guanidine	226·5—228	72 [6] *	—	—	24·0	$C_{11}H_{10}N_4O_2$	—	—	24·3
Morpholine	70·5—71·5	76 [1]	65·1	5·7	10·3	$C_{14}H_{14}N_2O_3$	65·1	5·5	10·85
Piperidine	64—66	90 [7]	70·2	6·2	10·8	$C_{15}H_{16}N_2O_2$	70·3	6·3	10·9

Solvent for crystallisation: 1, aq. EtOH; 2, aq. MeOH; 3, C_6H_6; 4, EtOH–Et_2O–HCl; 5, EtOAc; 6, $CHCl_3$; 7, EtOH; 8, Et_2O.

* A solution of the acid chloride in dioxan was added to the base in aqueous alkali in the Schotten–Baumann manner.

solvent was removed *in vacuo* and the residue dissolved in water (25 ml.). After decomposition of the unchanged sodium borohydride the mixture was extracted with ether (5 × 20 ml.). The extracts were washed, dried, and evaporated, leaving crystals (0·3 g., 68%), m. p. 80—82°. Recrystallisation from light petroleum raised the m. p. to 82—83°, not depressed on admixture with the product from (*a*).

The *acetyl derivative*, prepared with acetyl chloride in pyridine had m. p. 39·5—40° (Found: C, 66·1; H, 5·2; N, 6·15. $C_{12}H_{11}NO_3$ requires C, 66·35; H, 5·1; N, 6·45%).

4-Diethylaminomethyl-2-phenyloxazole.—A solution of 4-diethylaminocarbonyl-2-phenyloxazole (1·88 g.) in dry ether (20 ml.) was added slowly to stirred ethereal 0·9M-lithium aluminium hydride (4·8 ml.) diluted with dry ether (20 ml.). The resulting yellow liquid was stirred for 1 hr. at room temperature, then the excess of the reducing agent was decomposed with water (5 ml.), and the ethereal solution was extracted with 2N-hydrochloric acid. The combined acidic extracts were rendered strongly alkaline with 10% sodium hydroxide solution and extracted with ether. After the removal of the solvent the base was left as a yellow oil (0·75 g., 41%). The hygroscopic *hydrochloride* (0·57 g., 28%), precipitated from benzene solution by ethereal hydrochloric acid, had m. p. 138·5—140°, $\lambda_{max.}$ 262 mμ (ε 16,500) (Found: C, 62·0; H, 7·2; Cl, 13·2. $C_{14}H_{19}ClN_2O$ requires C, 63·0; H, 7·2; Cl, 13·3%). The *picrate* separated from an ethanol solution of the base and recrystallised from 90% ethanol as yellow needles, m. p. 116—116·5° (Found: C, 52·5; H, 4·7; N, 14·9. $C_{20}H_{21}N_5O_8$ requires C, 52·3; H, 4·6; N, 15·25%). The two following compounds were prepared similarly.

4-Dimethylaminomethyl-2-phenyloxazole.—The free amine was obtained as a pale yellow oil (29%). The very hygroscopic hydrochloride softens from 121°, m. p. at 154—156°, $\lambda_{max.}$ 263 mμ (ε 17,200). The *picrate* crystallised from 60% ethanol as needles, m. p. 156—158° (Found: C, 49·8; H, 4·1; N, 15·8. $C_{18}H_{17}N_5O_8$ requires C, 50·1; H, 4·0; N, 16·2%).

4-Piperidinomethyl-2-phenyloxazole.—(*a*) The free base, a pale yellow oil (35%), was converted into the *hydrochloride* (33%), m. p. 210—211°, $\lambda_{max.}$ 263 mμ (ε 17,900) (Found: C, 64·8; H, 6·9; N, 9·7. $C_{15}H_{19}ClN_2O$ requires C, 64·6; H, 6·9; N, 10·05%). The *picrate* crystallised from ethanol as needles, m. p. 186—187° (Found: C, 52·7; H, 4·6; N, 14·7. $C_{21}H_{21}N_5O_8$ requires C, 53·5; H, 4·5; N, 14·9%).

(*b*) 4-Bromomethyl-2-phenyloxazole (see below) (0·90 g., 0·0038 mole) and piperidine (0·65 g., 0·0076 mole) were refluxed in ethanol (10 ml.) for 2 hr. After the removal of the solvent, the residual oil was taken up in water and extracted with ether. The ethereal solution was shaken with 5% hydrochloric acid, and the acidic extract was treated with sodium nitrite (0·2 g.) at 60° and extracted with ether. The aqueous solution was basified and the product collected in ether. Evaporation of the solvent from the dried (Na_2SO_4) solution left the base (0·81 g., 87%) as a colourless oil. It was converted into the hydrochloride in dry benzene with ethereal hydrochloric acid, to give needles (0·82 g., 78%), m. p. and mixed m. p. 209—210·5°.

4-*Chloromethyl-2-phenyloxazole*.—4-Hydroxymethyl-2-phenyloxazole (0·88 g., 0·005 mole) was treated with thionyl chloride (5 ml.), first in the cold and then under reflux for 1 hr. The excess of reagent was removed *in vacuo* and the residue, after treatment in ethanol with charcoal, was distilled. The main fraction, b. p. 158—160°/13 mm., solidified (0·68 g., 71%). Recrystallisation of this *chloride* from a very small quantity of cold (−50°) light petroleum (b. p. 80—100°) afforded needles, m. p. 55·5—56°, $\lambda_{max.}$ 266 and 216·5 mμ (ε 13,300 and 2100 respectively), (Found: C, 62·1; H, 4·05; N, 7·4. $C_{10}H_8ClNO$ requires C, 62·0; H, 4·2; N, 7·2%).

4-*Bromomethyl-2-phenyloxazole*.—To a solution of 4-hydroxymethyl-2-phenyloxazole (0·94 g.) in dry benzene (20 ml.) was added, with stirring, a solution of phosphorus pentabromide (2·52 g.) in dry benzene (50 ml.). The solvent was removed, leaving a yellow solid. Crushed ice was added and the crude *bromide* (1·05 g., 82%) collected. It crystallised from aqueous methanol as colourless needles, m. p. 69·5—71·5°, $\lambda_{max.}$ 268 and 210 mμ (ε 15,900 and 13,150 respectively) (Found: N, 6·1; Br, 33·8. $C_{10}H_8BrNO$ requires N, 5·9; Br, 33·8%).

4-*Morpholinomethyl-2-phenyloxazole*.—4-Bromomethyl-2-phenyloxazole (1·20 g., 0·005 mole) reacted with morpholine (0·88 g., 0·01 mole) at room temperature with evolution of heat. The resulting yellow syrup was extracted with benzene and the extracts were shaken with 5% hydrochloric acid. To remove any morpholine present, the acidic solution was treated with sodium nitrite (0·30 g.) at 60° and extracted with ether. The amine was precipitated by an excess of 10% sodium hydroxide solution and extracted with ether. Evaporation of the solvent left the base as a pale yellow oil (0·83 g., 68%). The *hydrochloride*, prepared in dry benzene, gave plates, m. p. 218—219·5°, $\lambda_{max.}$ 262 mμ (ε 15,700) (Found: C, 59·6; H, 6·0; Cl, 12·85; N, 10·15. $C_{14}H_{17}ClN_2O_2$ requires C, 59·9; H, 6·1; Cl, 12·6; N, 10·0%). The *picrate* crystallised from ethanol as yellow needles, m. p. 199—201° (Found: N, 14·3. $C_{20}H_{19}N_5O_9$ requires N, 14·8%).

4-*Di-*(2-*hydroxyethyl*)*aminomethyl-2-phenyloxazole*.—The bromide (1·20 g., 0·005 mole) and diethanolamine (0·50 g., 0·0047 mole) were refluxed in 95% ethanol (15 ml.) for 2 hr. After evaporation of the solvent, the residue was taken up in water (15 ml.) and extracted with ether. The aqueous phase was basified with 10% sodium hydroxide solution and extracted with ether. The amine was obtained as a colourless oil (0·20 g., 15%) after the removal of the solvent. The *picrate*, recrystallised twice from ethyl acetate, was obtained in yellow columns, m. p. 122·5—123·5° (Found: C, 49·0; H, 4·55; N, 14·75. $C_{20}H_{21}N_5O_{10}$ requires C, 48·9; H, 4·3; N, 14·25%).

1-*Ethyl*-1-(2-*phenyloxazol*-4-*ylmethyl*)*piperidinium Bromide*.—The bromide (1·20 g.) was heated on a steam-bath with 1-ethylpiperidine (1·13 g.) for 10 min. The resulting glass was taken up in water (15 ml.), some undissolved white solid removed, and the filtrate evaporated to dryness *in vacuo*. The residue crystallised in a desiccator over phosphorus pentoxide to give a pale yellow solid *bromide* (0·65 g., 37%), m. p. indefinite (70—100°) (Found: C, 58·5; H, 6·45; N, 7·9. $C_{17}H_{23}BrN_2O$ requires C, 58·1; H, 6·6; N, 8·0%).

NNN-*Triethyl*-N-(2-*phenyloxazol*-4-*ylmethyl*)*ammonium Bromide*.—This *compound*, prepared (78%) in an analogous manner, had an indefinite m. p. (162—173°), $\lambda_{max.}$ 261 mμ (ε 15,750) (Found: C, 55·9; H, 6·5; N, 7·8. $C_{16}H_{23}BrN_2O$ requires C, 56·6; H, 6·8; N, 8·3%).

Diazomethyl 2-*Phenyloxazol*-4-*yl Ketone*.—2-Phenyloxazole-4-carbonyl chloride (1·25 g.) in dry ether (75 ml.) was added dropwise to a stirred solution of diazomethane (0·81 g.) in ether (60 ml.). After a further 30 minutes' stirring, the solvent was removed *in vacuo*, leaving a yellow solid (1·25 g.). This *diazo-ketone* was purified by precipitation with light petroleum (b. p. 60—80°) from ether, to give yellow plates, m. p. 148—149° (decomp.), $\lambda_{max.}$ 292, 268, and 212 mμ (ε 19,200, 20,500, and 11,700 respectively) (Found: C, 61·2; H, 3·4; N, 20·1. $C_{11}H_7N_3O_2$ requires C, 61·0; H, 3·3; N, 19·7%).

4-(2-*Nitroprop*-1-*enyl*)-2-*phenyloxazole*.—(*a*) A mixture of 4-formyl-2-phenyloxazole [8] (0·81 g., 0·005 mole), nitroethane (0·38 g., 0·005 mole), and butylamine (0·05 ml.) was left at room temperature for 10 days. A crystalline *product* was formed which, recrystallised from ethanol in yellow prisms (0·50 g., 47%), had m. p. 173—174°, $\lambda_{max.}$ 322, 272, and 209 mμ (ε 12,590, 12,720, and 13,900 respectively) (Found: C, 62·4; H, 4·3; N, 12·1. $C_{12}H_{10}N_2O_3$ requires C, 62·6; H, 4·4; N, 12·2%).

(*b*) The aldehyde (1·5 g., 0·0086 mole) and ammonium acetate (0·3 g.) were refluxed in nitroethane (10 ml.) for 35 min. On cooling, yellow columns separated (1·57 g., 79·5%) that had m. p. and mixed m. p. 172—173°.

4-2′-*Nitrovinyl*-2-*phenyloxazole*.—The aldehyde (1·5 g.) and ammonium acetate (0·3 g.) were refluxed in nitromethane (10 ml.) for 30 min. Brown crystals (0·56 g., 30%) of the *nitroalkene* separated on cooling. Recrystallisation first from aqueous ethanol, then from nitromethane, afforded yellow needles, m. p. 156—158°, $\lambda_{max.}$ 317 and 258 mμ (ε 16,200 and 14,200 respectively) (Found: C, 61·3; H, 3·9; N, 13·3. $C_{11}H_8N_2O_3$ requires C, 61·1; H, 3·7; N, 13·0%).

4-*Cyanomethyl*-2-*phenyloxazole*.—4-Bromomethyl-2-phenyloxazole, (1·2 g.) and potassium cyanide (0·50 g.) were refluxed in dry methanol (10 ml.). After 6 hr., the precipitated potassium bromide (0·65 g.) was filtered off. The dark brown filtrate was treated with charcoal and evaporated to *ca.* 5 ml. Water (3 ml.) was added and the precipitated needles (0·47 g.), m. p. 72—84°, were collected, and chromatographed in benzene (3 ml.) on deactivated alumina (200 g.). Elution with 1 : 20 chloroform–benzene afforded pale yellow crystals (0·39 g., 42%). Recrystallisation from aqueous methanol gave the *nitrile* as needles, m. p. 87·5—88·5°, $\lambda_{max.}$ 264·5 mμ (ε 14,000), (in Nujol) 4·42 μ (CN) (Found: C, 71·9; H, 4·45; N, 14·95. $C_{11}H_8N_2O$ requires C, 71·7; H, 4·4; N, 15·2%).

β-2-*Phenyloxazol*-4-*ylacrylic Acid*.—4-Formyl-2-phenyloxazole (0·5 g.), malonic acid (0·3 g.), and dry pyridine (5 ml.) were heated under anhydrous conditions on a steam-bath for 2½ hr. After cooling, the mixture was poured into dilute hydrochloric acid and the white *acrylic acid* collected. Recrystallisation from aqueous ethanol gave needles (0·37 g., 60%), m. p. 191—193·5°, $\lambda_{max.}$ 286 and 216 mμ (ε 22,600 and 20,000 respectively) (Found: N, 6·6. $C_{12}H_9NO_3$ requires N, 6·5%).

β-2-*Phenyloxazol*-4-*ylpropionic Acid*.—The acrylic acid (2·25 g.) was hydrogenated in ethanol (70 ml.) with 10% palladium–charcoal at room temperature and pressure until gas absorption ceased. After removal of the catalyst the filtrate was evaporated; the residual *propionic acid* recrystallised from ethanol as flakes (1·3 g., 58%), m. p. 86—87°, $\lambda_{max.}$ 270 mμ (ε 16,120) (Found: N, 6·4. $C_{12}H_{11}NO_3$ requires N, 6·5%).

2-*Phenyloxazol*-4-*yl Isocyanate*.—2-Phenyloxazole-4-carbonyl azide (4·1 g., 0·019 mole) was boiled in dry xylene (40 ml.) for 15 min. The solvent was removed *in vacuo* and the residue distilled to give a colourless *isocyanate* (1·9 g.), b. p. 116°/0·8 mm., m. p. sinters at 186°, m. p. 194°, $\lambda_{max.}$ 277 mμ (ε 8500) (Found: C, 64·4; H, 3·4; N, 14·8. $C_{10}H_6N_2O_2$ requires C, 64·5; H, 3·25; N, 15·05%). The product became brown in air.

The *bisulphite adduct* was prepared by shaking the isocyanate (0·83 g.) in xylene (12 ml.) with a saturated solution of sodium hydrogen sulphite (20 ml.) for 3 hr. After 20 hr. in the cold the yellow precipitate was collected and dried (0·85 g.). Washing with dioxan (20 ml.) removed some oil, leaving a white solid (0·63 g.), m. p. 173·5—174° (decomp.) $\lambda_{max.}$ 298 and 228 mμ (ε 12,660 and 17,800 respectively) (Found: C, 41·65; H, 2·85; N, 9·9. $C_{10}H_7N_2NaO_5S$ requires C, 41·25; H, 2·4; N, 9·65%).

Cyclohexyl 2-*Phenyloxazol*-4-*ylcarbamate*.—The azide (1·07 g.) was heated in dry xylene (15 ml.) in the presence of cyclohexanol (1 ml.) until gas evolution ceased, and then for a further 3 hr. The solvent was removed at reduced pressure; the residual *carbamate* crystallised from methanol as pale yellow prisms (0·74 g., 52%), m. p. 87—88°, $\lambda_{max.}$ 290 and 221 mμ (ε 7100 and 11,000 respectively) (Found: C, 66·7; H, 6·0; N, 9·15. $C_{16}H_{18}N_2O_3$ requires C, 67·1; H, 6·3; N, 9·8%).

Benzyl 2-*Phenyloxazol*-4-*ylcarbamate*.—This *compound* was prepared in an analogous manner. Fawn crystals (65%) obtained from methanol had m. p. 130·5—131·5°, $\lambda_{max.}$ 290 and 220 mμ (ε 8210 and 13,600 respectively) (Found: C, 69·0; H, 4·4; N, 9·8. $C_{17}H_{14}N_2O_3$ requires C, 69·4; H, 4·8; N, 9·5%).

2-*Chloroethyl* 2-*Phenyloxazol*-4-*ylcarbamate* —To a solution of the isocyanate (0·83 g.) in

[8] Cornforth, Fawaz, Goldsworthy, and Robinson, *J.*, 1949, 1552.

xylene (12 ml.) was added 2-chloroethanol (2 ml.). The *product* separated overnight (0·85 g., 63%). It crystallised from ethanol as prisms, m. p. 154·5—155·5°, $\lambda_{max.}$ 298·5 and 215·5 mμ (ε 12,100 and 16,050 respectively) (Found: C, 54·3; H, 4·2; N, 9·8. $C_{12}H_{11}ClN_2O_3$ requires C, 54·0; H, 4·1; N, 10·05%).

N-*Allyl*-N′-2-*phenyloxazol*-4-*ylurea*.—The azide (1·07 g., 0·005 mole) was rearranged to the isocyanate by heating it in dry xylene (15 ml.), and the cooled solution was added to allylamine (1·5 ml.) in xylene (10 ml.). Heat was evolved and the *urea* (0·75 g.), m. p. 140—142°, separated on cooling. Recrystallisation from aqueous ethanol gave prisms (0·71 g., 58%), m. p. 143—143·5°, $\lambda_{max.}$ 289 and 220·3 mμ (ε 14,600 and 25,650 respectively) (Found: C, 64·6; H, 5·3. $C_{13}H_{13}N_3O_2$ requires C, 64·2; H, 5·4%).

The following *NN′*-disubstituted ureas were prepared in a similar manner:

N-*Cyclohexyl*-N′-2-*phenyloxazol*-4-*ylurea* crystallised from the reaction mixture on cooling. Recrystallisation from aqueous ethanol afforded prisms (62%), m. p. 175—175·5°, $\lambda_{max.}$ 299 and 221 mμ (ε 9860 and 17,050 respectively) (Found: C, 66·9; H, 6·2; N, 14·7. $C_{16}H_{19}N_3O_2$ requires C, 67·3; H, 6·7; N, 14·7%).

1-(N-2-*Phenyloxazol*-4-*ylcarbamoyl*)*piperidine* recrystallised from aqueous methanol as prisms (57%), m. p. 119·5—122°, $\lambda_{max.}$ 294 and 222 mμ (ε 11,400 and 18,000 respectively) (Found: N, 15·3. $C_{15}H_{17}N_3O_2$ requires N, 15·5%).

N-3-*Dimethylaminopropyl*-N′-(2-*phenyloxazol*-4-*yl*)*urea* (47%) crystallised from benzene–cyclohexane (1 : 3) as colourless prisms, m. p. 132·5—134°, $\lambda_{max.}$ 298 and 218·5 mμ (ε 9530 and 18,250 respectively) (Found: C, 62·8; H, 6·9; N, 19·35. $C_{15}H_{20}N_4O_2$ requires C, 62·5; H, 7·0; N, 19·4%).

N-(2-*Phenyloxazol*-4-*ylcarbamoyl*)*glycine*.—A solution of 2-phenyloxazol-4-yl isocyanate (0·80 g., 0·0043 mole) in dry dioxan (15 ml.) was added with stirring to a solution of the sodium salt (0·41 g.) of glycine in dioxan (15 ml.) and water (8 ml.). A white solid was precipitated. A further quantity (30 ml.) of dioxan was added and the *sodium salt* (1·02 g., 79%) of the product was collected. Recrystallisation from water gave plates, sintering at 110°, m. p. 220—221° (decomp.), $\lambda_{max.}$ 299 and 221 mμ (ε 10,800 and 19,350 respectively) (Found: loss on drying, 6·1; N, 13·05. $C_{12}H_{10}N_3NaO_4,H_2O$ requires H_2O, 6·0; N, 12·95%). The free *acid* crystallised from aqueous ethanol as needles, m. p. 194·5—196° (decomp.), $\lambda_{max.}$ 296 and 219 mμ (ε 10,700 and 17,750 respectively) (Found: N, 14·85. $C_{12}H_{11}N_3O_4,H_2O$ requires N, 15·05%).

5-*Amino*-4-*hydrazinocarbonyl*-2-*phenyloxazole*.—A mixture of 5-amino-4-ethoxycarbonyl-2-phenyloxazole [9] (0·23 g.), hydrazine hydrate (1 ml.), and ethanol (1 ml.) was heated on a steam-bath for ¾ hr., then evaporated to dryness on the bath under reduced pressure. Water was added to the residue and the whole was again evaporated to dryness *in vacuo*. This process was repeated several times to remove all the excess of hydrazine. Finally more water was added and the insoluble material (0·15 g.), decomp. *ca.* 220°, was collected. For analysis, the *hydrazide* was recrystallised from boiling water and a little alcohol, affording prisms, decomp. 230—240°, $\lambda_{max.}$ 229·5 mμ (ε 21,480) (Found: N, 25·5. $C_{10}H_{10}N_4O_2$ requires N, 25·65%).

5-*Amino*-2-*phenyloxazole*-4-*carbonyl Azide*.—The 4-ethoxycarbonyloxazole (0·5 g.), hydrazine hydrate (2·25 ml.), and ethanol (5 ml.) were refluxed for ¾ hr. and then evaporated to dryness *in vacuo*. Water was added and the evaporation was repeated as in the preceding experiment. The residue was dissolved in an excess of 2N-hydrochloric acid (10 ml. more than was required for neutrality), and sodium nitrite (1·2 g.) in water (12 ml.) was added with ice-cooling until an excess was detected. The orange *azide* (0·35 g.) was collected, washed with water, and dried in a vacuum-desiccator. It was washed with a little methanol and then recrystallised from methanol, giving orange prisms (30 mg.), decomp. *ca.* 95° (Kofler), $\lambda_{max.}$ 277 mμ (ε 1095), $\lambda_{max.}$ (in $CHBr_3$) 4·67 (N_3) and 5·89 μ (CO) (Found: C, 52·3; H, 3·0. $C_{10}H_7N_5O_2$ requires C, 52·4; H, 3·1%).

5-*Amino*-4-*carbamoyl*-2-*phenyloxazole*.—5-Amino-4-cyano-2-phenyloxazole (3 g.) was added portionwise to concentrated sulphuric acid (8·1 ml.) with cooling at 0°. The mixture was heated for ¾ hr. on a steam-bath, and the red liquid poured into ice and water. The brown solid *amide* was collected, shaken with 2N-sodium carbonate, and recrystallised from methanol, yielding pale brown crystals (2·2 g., 66%), m. p. 172—174°, $\lambda_{max.}$ 312, 271, and 224 mμ (ε 15,400, 10,680, and 6660 respectively) (Found: C, 59·45; H, 4·6; N, 20·65. $C_{14}H_{15}N_3O_3$ requires C, 59·1; H, 4·5; N, 20·7%).

[9] Ref. 1, p. 726.

Morpholinomethylenehippuronitrile.—5-Amino-4-formyl-2-phenyloxazole (7 g.), morpholine (3·5 g.), and ethyl acetate (150 ml.) were heated on a steam-bath for 30 min. and the solution was concentrated to about 50 ml.; brown crystals of the *nitrile* separated. Recrystallisation from ethyl acetate yielded colourless needles (4·2 g., 44%), m. p. 205°, $\lambda_{max.}$ 263·5 and 227 mμ (ε 17,400 and 12,600 respectively) (Found: C, 65·2; H, 5·7; N, 16·55. $C_{14}H_{15}O_2N_3$ requires C, 65·35; H, 5·9; N, 16·3%).

Piperidinomethylenehippuronitrile.—The aldehyde (0·1 g.), piperidine (0·05 g.), and ethanol (10 ml.) were heated on a steam-bath for 30 min. and the solution was evaporated to dryness under reduced pressure. The solid *product* was recrystallised twice from ethyl acetate, yielding needles (0·01 g.), m. p. 183—184°, $\lambda_{max.}$ (in Nujol) 2·98 (NH) and 4·54 μ (CN) (Found: C, 71·1; H, 6·9. $C_{15}H_{17}N_3O$ requires C, 70·85; H, 6·4%).

2-*Dimethylaminoethylaminomethylenehippuronitrile.*—The aldehyde (1·29 g.), *NN*-dimethylethylenediamine (0·76 g.) and ethanol (50 ml.) gave, as above, a *nitrile* that crystallised from ethyl acetate as pale yellow prisms (1·4 g., 79%), m. p. 136—137°, $\lambda_{max.}$ 259·5 and 225·5 mμ (ε 12,850 and 9890 respectively) (Found: C, 64·35; H, 6·8; N, 21·3. $C_{14}H_{18}N_4O$ requires C, 65·0; H, 7·0; N, 21·7%).

2-*Diethylaminoethylaminomethylenehippuronitrile.*—The aldehyde (3 g.), *NN*-diethylethylenediamine (2 g.), and ethanol (50 ml.) yielded, as above, a gummy nitrile that was converted into the *dihydrochloride* with alcoholic hydrochloric acid. This recrystallised from ethanol–ethyl acetate as pink prisms (1·3 g., 49%), m. p. 182—183° (Found: N, 15·5; Cl, 21·1. $C_{16}H_{24}Cl_2N_4O$ requires N, 15·7; Cl, 20·7%).

3-*Dimethylaminopropylaminomethylenehippuronitrile.*—The aldehyde (4 g.), *NN*-dimethylpropylenediamine (2·8 ml.), and absolute alcohol (100 ml.) gave, as above, the *nitrile* as pale brown prisms (4·5 g., 78%), m. p. 125° (from benzene), $\lambda_{max.}$ 260 and 225 mμ (ε 18,100 and 13,000 respectively) (Found: C, 66·2; H, 7·4; N, 20·3. $C_{15}H_{20}N_4O$ requires C, 66·15; H, 7·4; N, 20·6%).

4-*Acetoxymethylene*-5-*imino*-2-*phenyloxazoline.*—Morpholinomethylenehippuronitrile (0·3 g.), acetic anhydride (5 ml.), and four drops of concentrated sulphuric acid were heated for 30 sec. on a steam-bath. The red solution was poured into water (150 ml.) and after 1 hr. the crystalline *imine* was collected and recrystallised from 95% ethanol, giving pink needles (0·13 g.), m. p. 152—153°, $\lambda_{max.}$ 285 mμ (ε 27,800), $\lambda_{max.}$ (in Nujol) 3·12, 3·27 (NH), 5·75 (Ac), and 6·16, 6·3 μ (C=N) (Found: C, 62·6; H, 4·4; N, 12·05. $C_{12}H_{10}N_2O_3$ requires C, 62·6; H, 4·4; N, 12·2%).

A similar procedure carried out with 3-dimethylaminopropylaminohippuronitrile yielded the same oxazoline.

7-*Hydroxy*-5-*methyl*-2-*phenyloxazolo*[5,4-d]*pyrimidine.*—5-Acetamido-4-cyano-2-phenyloxazole [10] (0·84 g.) was heated on a steam-bath for 2 hr. in a mixture of 10% potassium hydroxide solution (5·2 ml.) and 6% hydrogen peroxide (6 ml.), and the hot solution was treated with charcoal (0·2 g.). On cooling, crystals separated, recrystallisation of which from chloroform yielded colourless prisms (0·10 g., 12%), m. p. 314—316°, $\lambda_{max.}$ 305, 296, 223·5, and 217·5 mμ (ε 20,200, 20,200, 10,700, and 11,450 respectively), $\lambda_{max.}$ (in Nujol) 3·22, 3·29 (OH or NH), 5·8 (CO), 6·36 μ (C=N). The *compound* was soluble in aqueous alkali and precipitated unchanged on acidification (Found: C, 63·65; H, 3·9; N, 18·6. $C_{12}H_9N_3O_2$ requires C, 63·4; H, 4·0; N, 18·5%).

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[10] Ref. 1, p. 729.