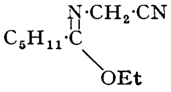
400. *Synthesis of a 4-Cyano-oxazole.*

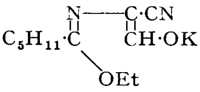
By J. W. CORNFORTH and H. T. HUANG.

The preparation of 4-*cyano*-2-n-*amyloxazole* is described, together with some curious reactions of an intermediate (II).

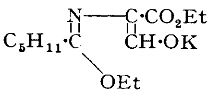
THE extension of a method previously described (*J.*, 1947, 96) to the preparation of 4-cyano-oxazoles has been achieved without complications. Heximidoethyl ether with the hydrochloride or hydrogen sulphate of aminoacetonitrile afforded 1-*ethoxyhexylideneaminoacetonitrile* (I) which with potassium ethoxide and ethyl formate in ether was converted into the *potassium*


$C_5H_{11}\cdot C(OEt){:}N\cdot CH_2\cdot CN$

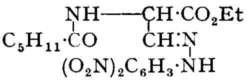
(I.)


$C_5H_{11}\cdot C(OEt){:}N\cdot C(CN){:}CH\cdot OK$

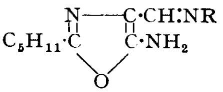
(II.)


$C_5H_{11}\cdot C(OEt){:}N\cdot C(CO_2Et){:}CH\cdot OK$

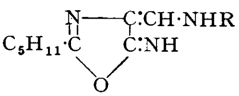
(III.)


$C_5H_{11}\cdot CO\cdot NH\cdot CH(CO_2Et)\cdot CH{:}N\cdot NH\cdot C_6H_3(NO_2)_2$

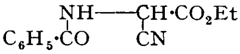
(IV.)



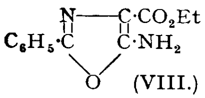
(V.)



(VI.)


$C_6H_5\cdot CO\cdot NH\cdot CH(CN)\cdot CO_2Et$

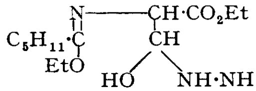
(VII.)

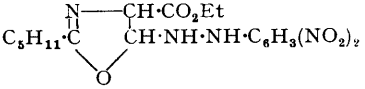


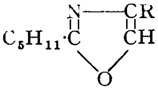
(VIII.)

derivative of α-(1-ethoxyhexylideneamino)-β-hydroxyacrylonitrile (II). Schotten–Baumann benzoylation of (II) yielded the O-*benzoyl* derivative. The action of 2 : 4-dinitrophenylhydrazine in hydrochloric acid on (II) and on its carbethoxy-analogue (III) was examined in passing. The latter afforded the yellow 2 : 4-dinitrophenylhydrazone (IV) of ethyl *n*-amylpenaldate : the product from (II), though having the analogous composition of an amylpenaldonitrile 2 : 4-dinitrophenylhydrazone, was dark red and is regarded as 5-*amino*-2-n-*amyloxazole*-4-*aldehyde* 2 : 4-*dinitrophenylhydrazone* [V; R = $NH{\cdot}C_6H_3(NO_2)_2$], or a tautomeric 5-imino-oxazoline form [VI; R = $NH{\cdot}C_6H_3(NO_2)_2$]. Ethyl benzamidocyanoacetate (VII) has been shown to isomerise readily to ethyl 5-amino-2-phenyloxazole-4-carboxylate (VIII) (I.C.I. Ltd., " The Chemistry of Penicillin ", Chap. XXI) and it seems probable that [V; R = $NH{\cdot}C_6H_3(NO_2)_2$] was similarly formed from the open-chain penaldonitrile derivative.

The action of benzylamine on (II) produced a substance which is formulated as 5-*amino*-4-*benzyliminomethyl*-2-n-*amyloxazole* (V; R = CH_2Ph) or the tautomeric 5-*imino*-2-n-*amyl*-4-*benzylaminomethylene*-4 : 5-*dihydro-oxazole* (VI; R = CH_2Ph); the close resemblance of the ultra-violet absorption spectrum to that of an analogous oxazolone renders the latter formula preferable. The same substance has been obtained from benzylamine and the formylation product of hexamidoacetonitrile (Cornforth and Fawaz, " The Chemistry of Penicillin," Chap. XXI).


(IX.)


(X.)


(XI.)

The hydrolysis of imido-ethers by acids normally does not produce amides, but causes fission to an amine and an ester. It seems unlikely, therefore, that hydrolysis at the imido-ether linkage is responsible for the formation of (IV) from (III) and of the analogous nitriles (later rearranged to amino-oxazoles) from (II). It appears more probable that the action, *e.g.*, of 2 : 4-dinitrophenylhydrazine on (III) proceeds through an adduct (IX) to the oxazoline (X) (displacement of ethoxyl in the imido-ether) which then undergoes scission or hydrolysis at C5 to produce (IV). It may be noted that, although (IV) is produced at room temperature from ethyl 2-*n*-amyloxazole-4-carboxylate (XI; R = CO_2Et) and 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid (Cornforth and Cornforth, " The Chemistry of Penicillin," Chap. XXI), yet the same ester is unaffected by the acid alone; and it would seem that the intermediate (X) is involved here too.

The action of hydrogen chloride in ether, or better of boiling acetic acid, on (II) gave the expected 4-*cyano*-2-n-*amyloxazole* (XI; R = CN), the structure of which was confirmed by hydrolysis to the known 2-*n*-amyloxazole-4-carboxylic acid amide and subsequently to the free acid.

EXPERIMENTAL.

1-*Ethoxyhexylideneaminoacetonitrile* (I).—A mixture of *n*-amyl cyanide, dry ethanol, and dry hydrogen chloride in equimolar amount was kept at 0° for 7—10 days. The liquid was decomposed in the usual manner with potassium carbonate and ether, and distilled, b. p. 68—77°/11 mm. (55—60 g. from 60 g. of amyl cyanide); it consisted largely of heximidoethyl ether but contained some unreacted nitrile. This product (25 g.) in ether (25 c.c.) was shaken vigorously with a solution of aminoacetonitrile hydrochloride (16 g.; or an equivalent amount of the hydrogen sulphate) in water (16 c.c.) for 15 minutes; the ethereal layer was washed well with water and dried (Na_2SO_4). On distillation 1-*ethoxyhexylideneamino-acetonitrile* (16 g.) was collected, b. p. 70—71°/0·15 mm. (Found : C, 66·2, 66·2; H, 10·1, 9·8. $C_{10}H_{18}ON_2$ requires C, 65·9; H, 9·9%).

Potassium Salt of α-(1-*Ethoxyhexylideneamino*)-β-*hydroxyacrylonitrile* (II).—Potassium ethoxide was made under anhydrous conditions from the metal (3·6 g.), ethanol (10 c.c.), and ether (35 c.c.); the solution after dilution with ether to 350 c.c. was cooled to −10° and treated with a cooled mixture of the above nitrile (16 g.) and ethyl formate (7 g.). After two hours at −15° the mixture was left at 0° overnight, and the pale yellow *potassium* salt (15 g.) collected, washed quickly with ether, and dried in a vacuum (Found : N, 10·8. $C_{11}H_{17}O_2N_2K$ requires N, 11·3%). With dilute alcoholic ferric chloride the characteristic reaction was observed (*J.*, 1947, 96).

α-(1-*Ethoxyhexylideneamino*)-β-*benzoyloxyacrylonitrile.*—Benzoyl chloride (1 c.c.) was added dropwise with stirring to an ice-cooled solution of the potassium salt (II; 1·5 g.) in sodium hydroxide (0·5 c.c. of 2N). After one day, ether extraction and distillation of the dried extract at 14 mm. pressure gave the O-*benzoyl* derivative as an oil (Found: C, 68·6; H, 7·3; N, 8·7. $C_{18}H_{22}O_3N_2$ requires C, 68·8; H, 7·0; N, 8·9%). In alcohol the substance gave no colour with ferric chloride; after gentle warming with N-sodium hydroxide, however, the characteristic test was again positive on neutralisation.

Reaction of Potassium Salts (II) *and* (III) *with* 2 : 4-*Dinitrophenylhydrazine.*—Addition of the potassium salt (II) to excess of the hydrazine in 2N-hydrochloric acid precipitated a colourless oil which changed to a red solid on shaking. Recrystallisation from ethanol gave the 2 : 4-*dinitrophenylhydrazone*

[V or VI; R = $NH{\cdot}C_6H_3(NO_2)_2$], dull red prisms, m. p. 175° (Found: C, 49·7; H, 5·0. $C_{15}H_{18}O_5N_6$ requires C, 49·6; H, 5·2%). In the same manner the potassium salt (III) afforded bright yellow silky needles of ethyl *n*-amylpenaldate 2 : 4-dinitrophenylhydrazone (IV), m. p. 166° (Found: C, 50·1; H, 5·5. Calc. for $C_{17}H_{23}O_7N_5$: C, 49·8; H, 5·6%).

5-*Imino*-2-n-*amyl*-4-*benzylaminomethylene*-4 : 5-*dihydro-oxazole* (VI; R = CH_2Ph).—Benzylamine (0·5 c.c.) was dropped into a rapidly stirred solution of the potassium salt (II) (1·2 g.) in water (5 c.c.). The mixture was brought slowly to pH 7 by dropwise addition of 2N-hydrochloric acid. The yellow gummy precipitate was collected, dried, and triturated with ether. Recrystallisation from benzene–light petroleum (b. p. 40—60°) gave the *imino-oxazoline* in minute, faintly yellow prisms, m. p. 126—127° (Found: C, 70·9; H, 7·8; N, 15·4. $C_{16}H_{21}ON_3$ requires C, 70·8; H, 7·8; N, 15·5%). The m. p. was unchanged by admixture with the product obtained by Cornforth and Fawaz (*loc. cit.*). The absorption spectrum showed maxima at 3090 A. (ε, 10,550) and 2310 A. (ϵ, 8400). 2-Benzyl-4-benzylaminomethylene-4 : 5-dihydro-oxazol-5-one shows maxima at 3200 A. and 2400 A. (Merck & Co., "Penicillin Monograph", M-12c, 30).

4-*Cyano*-2-n-*amyloxazole* (XI; R = CN).—The potassium salt (II) (1 g.) was added during two minutes to boiling acetic acid (5 c.c.). The cooled solution was diluted with water, made alkaline with sodium hydroxide, and extracted with ether. The dried ethereal extract was distilled; the *cyano*-compound (0·5 g.), a colourless oil, had b. p. 130°/12 mm. The analytical sample was twice redistilled (Found: C, 66·2, 65·9; H, 7·7, 7·3; N, 16·6. $C_9H_{12}ON_2$ requires C, 65·8; H, 7·3; N, 17·1%). The nitrile (0·4 g.) was warmed with sodium hydroxide (4 c.c. of 2N) on a steam-bath until dissolved (24 hours). On cooling, 2-*n*-amyloxazole-4-carboxylic acid amide (0·2 g.) separated, m. p. and mixed m. p. 151°. Further hydrolysis (2N-alkali; refluxing for 2 hours) gave 2-*n*-amyloxazole-4-carboxylic acid, m. p. and mixed m. p. 94° (Cornforth and Cornforth, *op. cit.*).

We thank the British Council for enabling one of us (H. T. H.) to take part in this work.

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