24. *A New Synthesis of Oxazoles and Iminazoles including its Application to the Preparation of Oxazole.*

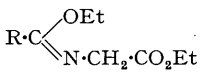
By J. W. Cornforth and (Mrs.) R. H. Cornforth.

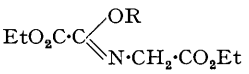
A synthesis of oxazoles and iminazoles is described. Some earlier work on oxazoles is discussed.

The preparation of 2-methylbenzoxazole by Ladenburg (*Ber.*, 1876, **9**, 1525) marks the first recognition of oxazole as a ring system, but the name is due to Hantzsch (*ibid.*, 1887, **20**, 3118). The two most general oxazole syntheses are the condensation of α-halogeno-ketones with amides and the dehydration of α-acylamino-carbonyl compounds. It is possible that attempts have been made to prepare oxazole itself by both these methods, but we can find no report of this in the literature. In any case the methods are of limited application in the preparation of monosubstituted oxazoles, though satisfactory when a 2 : 5-diaryloxazole is required (cf. Robinson, *J.*, 1909, **95**, 2167; Lister and Robinson, *ibid.*, 1912, **101**, 1302).

The present work was facilitated by the observation of Schmidt (*Ber.*, 1914, **47**, 2548) that acetimidoethyl ether and glycine ethyl ester hydrochloride afford ethyl α-ethoxyethylideneaminoacetate (I; R = Me), the structure of which followed from its ready hydrolysis to glycine ethyl ester and ethyl acetate. We have confirmed this, and shown that substances of the type (I) are thermally more stable than Schmidt indicated. It has also been found that the reaction is a very general one. Thus the imidoethers from ethyl cyanoformate and ethyl or *iso*propyl alcohol gave respectively with glycine ester hydrochloride *ethyl ethoxycarbethoxymethyleneaminoacetate* (II; R = Et) and *ethyl* iso*propoxycarbethoxymethyleneaminoacetate* (II; R = Pr^{β}). Again, acetimidoethyl ether with the hydrochloride of ethyl aminomalonate gave *ethyl α-ethoxyethylideneaminomalonate* (III). Under different conditions the last reaction gave exclusively *ethyl* 5-*keto*-2-*methyl*-4 : 5-*dihydroiminazole*-4-*carboxylate*-1-*malonate* (IV), apparently by the reaction of (III) with ethyl aminomalonate (cf. Finger, *J. pr. Chem.*, 1907, **76**, 93). The

action of moist air on (III) also gave (IV), the first stage evidently being liberation of some ethyl aminomalonate by hydrolysis. Other substances of type (I) have been made and will be reported elsewhere.


(I.)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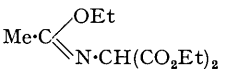
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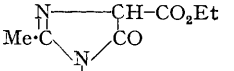
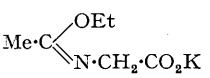

(IV.)

It was possible to saponify the ester (I; R = Me) under special conditions to *potassium α-ethoxyethylideneaminoacetate* (V). The free acid could not be isolated. The salt (V) with acetyl chloride gave a substance, $C_8H_{13}O_4N$, which gave ethyl acetate and acetylglycine on warming with water. This substance is considered to be *5-keto-2-ethoxy-3-acetyl-2-methyl-tetrahydro-oxazole* (VI) rather than the mixed anhydride (VII), for reasons given in the experimental section.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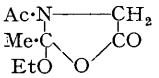
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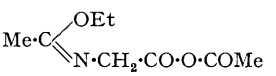
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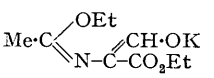
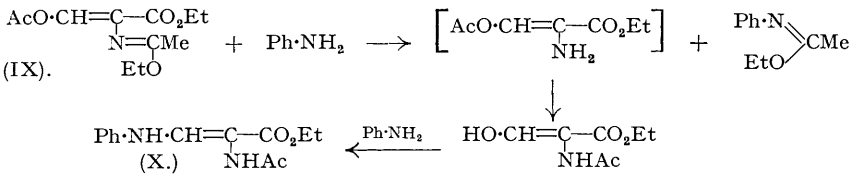
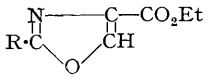

(VIII.)

Formylation of (I; R = Me) by ethyl formate and potassium ethoxide gave *potassium ethyl α-(α-ethoxyethylideneamino)-β-hydroxyacrylate* (VIII); this product still gave ethyl acetate on hydrolysis with aqueous acid and must therefore carry the hydroxymethylene group in the position shown. Acetic anhydride on the salt gave the *acetoxymethylene* compound (IX), reconverted into the salt (VIII) by cold alcoholic potash. The action of aniline on (IX) gave *ethyl β-anilino-α-acetamidoacrylate* (X), the reaction evidently proceeding by capture of the ethoxyethylidene group by aniline, followed by intramolecular acylation and reaction with another molecule of aniline :


(IX.) (X.)

The action of hydrogen chloride in ether on the salt (VIII) gave by loss of the elements of potassium ethoxide a product which can only be formulated as *ethyl 2-methyloxazole-4-carboxylate* (XI; R = Me); the properties of the substance are in accord with this view. The yield was low until it was discovered that decomposition of the potassium salt at higher temperatures was advantageous, and that good yields could be obtained by distilling a mixture of the salt with benzoic acid, or best by gradually adding the salt to boiling acetic acid.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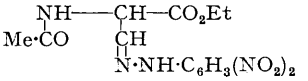
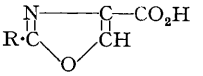

(XII.)


(XIII.)

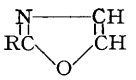
Reaction of the ester (XI; R = Me) with 2 : 4-dinitrophenylhydrazine in hydrochloric acid gave *ethyl acetamidoformylacetate dinitrophenylhydrazone* * (XII). The other oxazoles mentioned in this paper also reacted with 2 : 4-dinitrophenylhydrazine. A ring-scission of this type is apparently new in the oxazole series, but Gabriel (*Ber.*, 1910, **43**, 136) hydrolysed 2 : 5-diphenyloxazole to benzoic acid and aminoacetophenone with hydrochloric acid under pressure.

The ester (XI; R = Me) with aqueous alkali gave *2-methyloxazole-4-carboxylic acid* (XIII; R = Me). Oesterreich (*Ber.*, 1897, **30**, 2254) obtained from the oxidation of 2 : 4-dimethyloxazole an acid to which he gave this formula, on the basis of a single nitrogen estimation. It is certainly not identical with our acid and is perhaps 4-methyloxazole-2-carboxylic acid : Oesterreich's choice of the 4-methyl group as the seat of oxidation seems to be founded on a faulty analogy.

The acid (XIII; R = Me) readily lost carbon dioxide on heating in quinoline with a little copper oxide to give *2-methyloxazole* (XIV; R = Me). This was characterised as the *picrate*.

* The structure of this substance and of the anil (X) has been confirmed by a synthesis starting from ethyl formylchloroacetate. The work will be published later.

It now became of interest to attempt the synthesis of oxazole by the new method. The first difficulty was that formimido-ethers are not stable enough to be condensed with glycine ester hydrochloride in the usual way. The variation was tried of adding a mixture of the hydrochlorides of formimidoethyl ether and glycine ethyl ester to one molecular proportion of aqueous alkali under ether. There were indications that the right product was formed, but was too unstable to be isolated. Fortunately our experience with the derivatives (II) from ethyl cyanoformate had shown that the *iso*propoxy-compound (II; R = Pr^{β}) was more stable and formed in better yield than its ethoxy-analogue.* Following this indication, hydrogen cyanide was condensed with *iso*propanol to give *formimidoisopropyl ether hydrochloride*, which, treated with glycine ethyl ester hydrochloride in the manner indicated above, gave *ethyl* iso*propoxymethyleneaminoacetate* (XV). This was formylated as before, and the resulting *potassium ethyl* α-iso*propoxymethyleneamino*-β-*hydroxyacrylate* (XVI) added to boiling acetic acid, when *ethyl oxazole*-4-*carboxylate* (XI; R = H) was formed. Alkaline hydrolysis gave *oxazole*-4-*carboxylic acid* (XIII; R = H), which in quinoline was decarboxylated smoothly to *oxazole* (XIV; R = H). The yields in this synthesis were good, with the exception of the cyclisation (34%).



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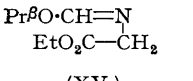
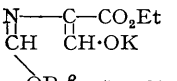


(XV.)



(XVI.)

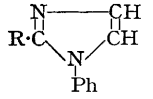
The low basicity and high volatility of oxazole tend to make its salts unstable. Thus the picrate and hydrochloride were both obtained crystalline; but the picrate became picric acid within a few minutes of being collected, and the hydrochloride vanished in a vacuum desiccator. A mercuric chloride complex (described later) is the most satisfactory derivative found so far, but cannot be kept. It may be noted that oxazole-4-carboxylic esters appear to be too weakly basic to form salts under ordinary conditions.

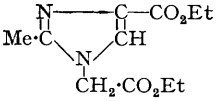
It is proposed to explore the applicability of this method as a general synthesis of oxazoles. The condensation of imidoethers with α-amino-aldehydes and -ketones or with α-amino-β-keto-esters is an obvious extension on which we hope to report.

Conversion of an oxazole into an iminazole was first achieved by Lewy (*Ber.*, 1888, **21**, 2194), who found it necessary to heat 4-phenyl-2-methyloxazole with alcoholic ammonia for sixteen hours at 220—230° in order to obtain the iminazole. We found that 2-methyloxazole-4-carboxylic acid reacted rapidly with aqueous ammonia at 150° to give 2-methyliminazole. Further, on boiling the acid with aniline 1-*phenyl*-2-*methyliminazole* (XVII; R = Me) was formed. We have not yet determined whether 2-methyloxazole will form iminazoles with equal facility. Oxazole-4-carboxylic acid with aniline gave 1-*phenyliminazole* (XVII; R = H).

The potassium salt (VIII) reacted with glycine ethyl ester hydrochloride in the cold to give *ethyl* 2-*methyliminazole*-4-*carboxylate*-1-*acetate* (XVIII). This iminazole synthesis, of which other examples will appear elsewhere, may prove useful for obtaining 1-substituted iminazoles where direct *N*-alkylation is impracticable.

(XVII.)





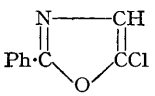
(XVIII.)

Two further matters relating to oxazole chemistry will now be discussed. In the first place, Schwanert (*Annalen*, 1859, **112**, 59) distilled hippuric acid with phosphorus pentachloride and obtained two products, C_9H_6ONCl and $C_9H_5ONCl_2$. The former (m. p. between 40° and 50°, b. p. about 220°) has the properties which would be expected of 5-chloro-2-phenyloxazole (XIX); the latter is probably the 4 : 5-dichloro-derivative. Rügheimer (*Ber.*, 1886, **19**, 1169) formulated these products as 1-chloro- and 1 : 3-dichloro-4-hydroxy*iso*quinoline, though to explain their insolubility in alkali he wrote them in the keto-form.†

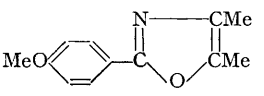
* For making substances of type (I) from unreactive cyanides, on the other hand, it is best to make the imidoether with methanol; the speed and completeness of imidoether formation outweighs a somewhat lower yield in the condensation with glycine ester hydrochloride.

† Rügheimer carried out an indecisive experiment on the reduction of the product $C_9H_5ONCl_2$ (or of a substance $C_9H_5NCl_6$ obtained by heating it with phosphorus pentachloride at 170°; the paper is ambiguous on this point) with hydriodic acid at 200°. It is surprising to find this work referred to by Hollins ("Synthesis of Nitrogen Ring Compounds", 1924) in the following terms: "Hippuric acid itself is converted by PCl_5 into a dichloroanhydro compound from which *iso*quinoline is obtained by reduction with HI". Actually there is no definite evidence in the paper cited that *iso*quinoline was formed at all.

This interpretation cannot be upheld : the boiling points are much too low for *iso*quinoline derivatives; also 1-chloro-4-hydroxy*iso*quinoline has been made (Gabriel and Colman, *Ber.*, 1900, **33**, 986), and shows no resemblance to the product C_9H_6ONCl.



(XIX.)



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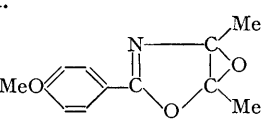
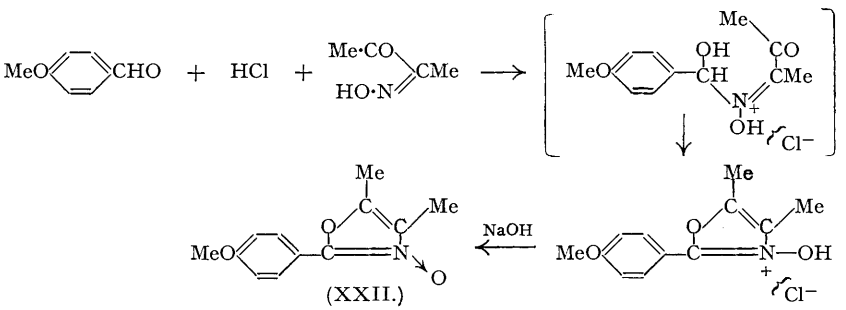


(XXI.)

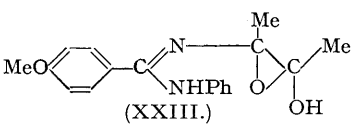
The second point refers to one of the oxazole syntheses more recently discovered, namely that of Diels and Riley (*Ber.*, 1915, **48**, 897), which was confirmed and extended by Dilthey and Friedrichsen (*J. pr. Chem.*, 1930, **127**, 292). The condensation of diacetyl monoxime with anisaldehyde in hydrochloric acid gave a basic substance, $C_{12}H_{13}O_3N$, which easily lost an oxygen atom to zinc dust and water, giving 2-(*p*-methoxyphenyl)-4 : 5-dimethyloxazole (XX). The intermediate was formulated as 2-(*p*-methoxyphenyl)-4 : 5-dimethyl-4 : 5-epoxy-4 : 5-dihydro-oxazole (XXI), a conclusion with which we do not agree.

The base $C_{12}H_{13}O_3N$ crystallised as a hydrate from water : when anhydrous it was sensitive to light. It was stable to acid and alkali, and liberated iodine on warming with potassium iodide solution. All these properties suggest an *N*-oxide (XXII), and the reaction becomes simply the *N*-alkylation of an oxime, with subsequent ring-closure :

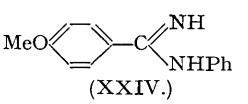


(XXII.)

No mechanism for the formation of (XXI) has been suggested, and indeed it is difficult to do so, or to explain why an ethylene oxide is produced under conditions so favourable for its destruction. Dilthey and Friedrichsen (*loc. cit.*) mention the formula (XXII) among others as a possibility, but give preference to the formula (XXI). The experimental evidence on which formula (XXI) is based needs to be reviewed. The easy reduction to an oxazole fixes the position of all atoms except the labile oxygen. Diels and Riley found that the substance on treatment with aniline at 100° gave by addition a product $C_{18}H_{20}O_3N_2$. This with aqueous oxalic acid broke down to diacetyl and an oxalate, m. p. 157°, which yielded anisamide and aniline on treatment with cold sodium bicarbonate solution. On this evidence the remarkable structure (XXIII) was given to the product $C_{18}H_{20}O_3N_2$ and the oxalate was considered to be that of *N*-phenylanisamidine (XXIV).



(XXIII.)

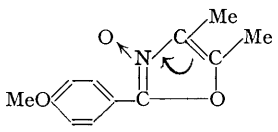


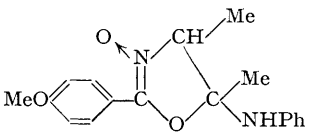
(XXIV.)

Analysis of the oxalate [Found : C, 55·2, 55·1; H, 5·1, 5·2; N, 7·0, 7·4; $(CO_2H)_2$, 25·4%] made it necessary to assume the presence of two molecules of water, neither of which was expelled by drying at 139° in a vacuum. Even so, the agreement is not good [$C_{14}H_{14}ON_2,(CO_2H)_2,2H_2O$ requires C, 54·5; H, 5·7; N, 7·9; $(CO_2H)_2$, 25·6%]. Examination of the literature shows that substances of the type (XXIV), *e.g.*, *N*-phenylbenzamidine, are certainly not so unstable as to be decomposed on liberation from their salts by weak bases. In the example cited it is necessary to heat the base with water to 120°, and the products are aniline, ammonia, benzoic acid, and benzanilide (anything but benzamide !). We suggest that the oxalate, m. p. 157°, obtained by Diels and Riley is a mixture of anisamide oxalate with a little aniline hydrogen oxalate. Anisamide with oxalic acid in methanol readily gives ***anisamide oxalate***, and we found that by crystallising a mixture of oxalic acid (2 mols.), aniline (1 mol.),

and anisamide (2 mols.) twice from methanol, a crystalline product was obtained, m. p. 152—154° : thus not far from that reported by Diels and Riley. The calculated figures for anisamide oxalate containing 8% of aniline hydrogen oxalate are C, 54·9; H, 5·1; N, 7·15; $(CO_2H)_2$, 25·1%, in excellent agreement with the values quoted, and with the observed behaviour of the product.

On the basis of formula (XXII) for the substance $C_{12}H_{13}O_3N$, it is easily seen that the N→O group would facilitate addition to the C=C double bond :





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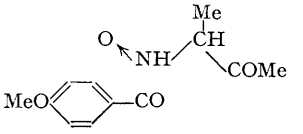
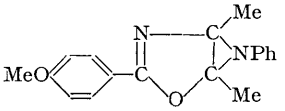


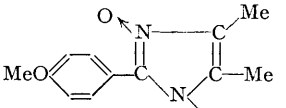
(XXVI.)

and that the aniline adduct would then be (XXV). The first stage of hydrolysis would give aniline and the intermediate (XXVI), which passes to diacetyl and anisamide by a type of intramolecular oxidation well known among *N*-oxides.

Diels and Riley also studied the action of phenyl *iso*cyanate on the substance $C_{12}H_{13}O_3N$, obtaining in poor yield a product, $C_{18}H_{18}O_2N_2$, which was formulated as (XXVII). In our view the product would probably be (XXVIII). Diels and Riley believed that the labile oxygen atom was involved in this reaction, chiefly because the product was not reduced by zinc dust and water. This is hardly a valid objection to formula (XXVIII) : *N*-oxides vary greatly in ease of reduction.



(XXVII.)



(XXVIII.)

Experimental.

Anisamide Oxalate.—Prepared from anisamide and oxalic acid in methanol, this *salt* formed colourless leaflets, m. p. 184° (decomp.) [Found : C, 55·3; H, 5·0. $2C_8H_9O_2N,(CO_2H)_2$ requires C, 55·1; H, 5·1%].

Ethyl α-Ethoxyethylideneaminoacetate (I; R = Me).—This was obtained essentially as described by Schmidt (*loc. cit.*) from acetimidoethyl ether and glycine ethyl ester hydrochloride. It was found advisable, however, to wash the ethereal solution with water before drying it. This seems to remove some substance (amidine ?) which catalyses decomposition on distillation. Thus we found, contrary to Schmidt, that the product can be distilled on the water-pump without injury; b. p. 85—86°/7·5 mm., 100—101°/19 mm. The best yield was 68% of distilled product.

Ethyl Ethoxycarbethoxymethyleneaminoacetate (II; R = Et).—Ethyl cyanoformate (9·9 g.) with ethyl alcohol (4·6 g.) in ether (15 c.c.) was treated below 0° with dry hydrogen chloride (3·7 g.). Crystallisation soon set in. The salt was washed with ether and decomposed below 0° with a strong solution of potassium carbonate (14 g.) and ether. The ethereal solution was shaken for 1 hour with glycine ethyl ester hydrochloride (14 g.) and water (8 c.c.). The ether layer was washed with water, dried (Na_2SO_4), and evaporated. The residue on distillation gave the *ester* as a colourless oil (1·6 g.), b. p. 78—80°/0·06 mm., which quickly reddened in air (Found : C, 51·8; H, 7·3. $C_{10}H_{17}O_5N$ requires C, 51·9; H, 7·4%).

Ethyl iso*Propoxycarbethoxymethyleneaminoacetate* (II; R = Pr$^\beta$).—Prepared as above, using *iso*propyl alcohol (6·0 g.) instead of ethyl alcohol, this *ester* (5·9 g.) was a colourless oil, b. p. 76—78°/0·04 mm. (Found : C, 54·1; H, 7·7. $C_{11}H_{19}O_5N$ requires C, 53·9; H, 7·8%).

Ethyl α-Ethoxyethylideaminomalonate (III).—Acetimidoethyl ether hydrochloride (9·6 g.; 50% excess) was converted into the base in the usual way with ether and potassium carbonate. The ether solution (*ca.* 100 c.c.) was shaken with ethyl aminomalonate hydrochloride (10·5 g.) and water (5 c.c.) for 2 hours. The ether layer was washed twice with very dilute hydrochloric acid (to remove ethyl aminomalonate), dried, and evaporated. The *ester* distilled at 82°/0·05 mm. as a colourless odourless mobile oil (7·5 g.; 60%) (Found : C, 53·7; H, 7·8; N, 5·8. $C_{11}H_{19}O_5N$ requires C, 53·9; H, 7·8; N, 5·7%).

Ethyl 5-*Keto*-2-*methyl*-4 : 5-*dihydroiminazole*-4-*carboxylate*-1-*malonate* (IV).—In an earlier experiment when no excess of acetimidoethyl ether was taken, and the washing with acid omitted, the product on attempted distillation reacted rapidly to give a crystalline solid. The *iminazolone* crystallised from alcohol or chloroform–light petroleum in colourless prisms, m. p. 208—209° (decomp.) after reddening at 200° (Found : C, 51·0; H, 6·3; N, 8·5. $C_{14}H_{20}O_7N_2$ requires C, 51·2; H, 6·1; N, 8·5%).

Potassium α-Ethoxyethylideneaminoacetate (V).—Potassium (0·36 g.) was dissolved in alcohol (1·1 g.) and ether (8 c.c.). The solution was diluted with ether (100 c.c.), and the ester (I, R = Me) (1·7 g.) added, followed by water (0·2 c.c.). Crystallisation was complete within a few minutes. The *salt* was collected and washed with ether (Found : N, 7·0. $C_6H_{10}O_3NK$ requires N, 7·6%). It was a white hygroscopic powder and with dilute acid was hydrolysed very rapidly to ethyl acetate and glycine.

5-*Keto*-2-*ethoxy*-3-*acetyl*-2-*methyltetrahydro-oxazole* (VI).—The salt (V) (6 g.) was shaken in ether with acetyl chloride (2·6 g.); after a few minutes the solution was filtered and distilled. The *oxazolidone*

(2·25 g.) came over at 96—98°/0·15 mm. as a colourless viscid oil, which eventually solidified to a crystalline mass, m. p. 45—46° (Found : C, 51·3; H, 7·0. $C_8H_{13}O_4N$ requires C, 51·4; H, 7·0%). The substance was readily soluble in water. On warming with water, N-hydrochloric acid, or phosphate buffer (pH 8), it gave ethyl acetate and acetylglycine, and no free glycine could be detected by the ninhydrin test. Boiling with alcohol also led to acetylglycine. This behaviour determined the choice of formula (VI), as it was concluded that the acetyl group must already be attached to nitrogen.

Potassium Ethyl α-(α-Ethoxyethylideneamino)-β-hydroxyacrylate (VIII).—Potassium * (4·5 g.) in ether (50 c.c.) was treated with alcohol (16·7 c.c.). The resulting solution was diluted with ether to 200 c.c., cooled below 0°, and treated with a mixture of the ester (I; R = Me) (20 g.) and ethyl formate (13 g.). After 1 hour, ether (300 c.c.) was added. The crystalline potassium *salt* was collected after being kept overnight at 0°, washed with ether, and freed from solvent under reduced pressure. It formed a light yellow hygroscopic powder (24 g.; 87%) (Found : N, 5·8. $C_9H_{14}O_4NK$ requires N, 5·9%). On careful addition of alcoholic ferric chloride to a dilute alcoholic solution of the salt, a deep violet colour appeared, which faded quite suddenly to a light brown as more reagent was added.

Ethyl α-(α-Ethoxyethylideneamino)-β-acetoxyacrylate (IX).—The salt (VIII) (11 g.) was stirred into acetic anhydride (15 c.c.). After ½ hour ether and sodium bicarbonate solution were added with ice cooling. The ether solution was dried and evaporated, and the residue fractionated. The *acetoxy-ester* (8·1 g.; 72%) distilled as a colourless oil, b. p. 155—159°/15 mm., 88—90°/0·1 mm. (Found : C, 54·7; H, 7·3; N, 5·8. $C_{11}H_{17}O_5N$ requires C, 54·3; H, 7·0; N, 5·8%). With cold alcoholic potash the potassium salt (VIII) was regenerated, as shown by the characteristic behaviour with alcoholic ferric chloride. On boiling with water, ethyl acetate and acetic acid were liberated; the other products appeared to contain the oxazole ester (XI; R = Me). With aqueous ferric chloride a red-purple colour slowly developed.

Ethyl β-Anilino-α-acetamidoacrylate (X).—The acetoxy-ester (IX) (2 g.) was mixed with aniline (1·5 g.) : the mixture became warm. After ½ hour reaction was completed by warming for a minute on the steam-bath. N-Hydrochloric acid (10 c.c.) was now added. The product soon crystallised and was recrystallised once from 50% alcohol and once from chloroform–light petroleum. The *anil* formed colourless, silky needles, m. p. 167—168° (Found : C, 63·1; H, 6·3; N, 11·4. $C_{13}H_{16}O_3N_2$ requires C, 62·9; H, 6·4; N, 11·3%). With 2 : 4-dinitrophenylhydrazine (1% in 2N-hydrochloric acid) it slowly gave the dinitrophenylhydrazone (XII).

Ethyl 2-Methyloxazole-4-carboxylate (XI; R = Me).—The salt (VIII) (25 g.) was added during 10 minutes to boiling acetic acid (50 c.c.). The solution was distilled at low pressure, and after acetic acid the *ester* (12·2 g.; 75%) distilled as a colourless oil, b. p. 106—110°/12 mm., which solidified in massive prisms, m. p. 24—25° (Found : C, 54·5; H, 6·0. $C_7H_9O_3N$ requires C, 54·2; H, 5·8%).

Ethyl Acetamidoformylacetate 2 : 4-*Dinitrophenylhydrazone* (XII).—The ester (XI; R = Me) was kept with a slight excess of 2 : 4-dinitrophenylhydrazine (0·5% in 2N-hydrochloric acid). After 2 days the yellow needles were collected and crystallised from alcohol, giving the *hydrazone*, m. p. 183—184° (Found : N, 19·5. $C_{13}H_{15}O_7N_5$ requires N, 19·8%).

2-*Methyloxazole-4-carboxylic Acid* (XIII; R = Me).—The ester (XI; R = Me) was hydrolysed by heating with a slight excess of aqueous potassium hydroxide for ½ hour on the steam-bath. Alcohol was removed at low pressure, and the solution was acidified (Congo-red) and extracted continuously with ether. The ether on evaporation left the acid as a hydrate, from which water was removed by drying over sulphuric acid in a vacuum. The *acid*, obtained in almost quantitative yield, crystallised from alcohol–benzene in colourless plates, m. p. 183—184° with slow decomposition (Found : C, 47·3; H, 4·2; N, 10·9. $C_5H_5O_3N$ requires C, 47·2; H, 3·9; N, 11·1%).

2-*Methyloxazole* (XIV; R = Me).—The acid (XIII; R = Me) (5 g.) was heated with quinoline (25 g.) and a little copper oxide in a bath at 180—200°. The distillate was collected over solid potassium hydroxide. The quinoline was finally boiled for a short time. The distillate was redistilled over fresh alkali, giving 2-*methyloxazole* (2·6 g.; 80%) as a colourless liquid of pyridine-like odour, b. p. 87—88°, $n_D^{16.5°}$ 1·4347 (Found : C, 58·0; H, 6·4. C_4H_5ON requires C, 57·8; H, 6·0%). The *picrate* crystallised from alcohol in fine yellow needles, m. p. 116—117° (Found : C, 38·3; H, 2·6; N, 17·9. $C_4H_5ON,C_6H_3O_7N_3$ requires C, 38·5; H, 2·6; N, 18·0%).

Formimidoisopropyl Ether Hydrochloride.—Hydrogen chloride (54 g.) was passed into a mixture, cooled below 0°, of hydrogen cyanide (39·9 g.), *iso*propyl alcohol (89 g.), and ether (350 c.c.). After four days at 0° the crystalline *salt* (158·5 g.; 87%) was collected and washed with ether. It formed colourless leaflets, m. p. 117—118° (decomp.). Analysis indicated the presence of a little ammonium chloride, as is usual in formimidoether hydrochlorides (Found : N, 12·2. $C_4H_{10}ONCl$ requires N, 11·3%).

Ethyl iso*Propoxymethyleneaminoacetate* (XV).—The above salt (15·2 g.) with glycine ethyl ester hydrochloride (17·2 g.) was added at 0° to potassium hydroxide (27 c.c. of 25%) under ether (200 c.c.). After 5—10 minutes' shaking the ether was decanted, the salt sludge washed twice with fresh ether, and the united ether extracts washed with a little water, dried (Na_2SO_4), and evaporated. Distillation gave the *ester*, b. p. 99°/19 mm. (12·2 g.; 57%), as a colourless oil (Found : C, 55·1; H, 8·7; N, 8·3. $C_8H_{15}O_3N$ requires C, 55·5; H, 8·7; N, 8·1%).

*Potassium Ethyl α-*iso*Propoxymethyleneamino-β-hydroxyacrylate* (XVI).—A solution was prepared from potassium (20·2 g.), alcohol (60 g.), and ether (250 c.c.); it was diluted to 1500 c.c. with ether, cooled to 0°, and treated with a mixture of the ester (XV) (86 g.) and ethyl formate (55 g.). Precipitation began at once. Next day the potassium *salt* (91 g.; 82%) was collected and washed with ether. It formed a light yellow hygroscopic crystalline powder (Found : N, 6·1. $C_9H_{14}O_4NK$ requires N, 5·9%) which turned sticky on being kept, even in a desiccator. It showed with alcoholic ferric chloride the same characteristic colour changes as the potassium salt (VIII).

* This metal is quickly and efficiently freed from crust by boiling with dioxan. The same method can be used to recover potassium from scrap : the globules of molten metal rise to the surface and are made to coalesce by cautious addition of a few drops of alcohol.

Ethyl Oxazole-4-carboxylate (XI; R = H).—The potassium salt (XVI) (5 g.), was added during 10 minutes to boiling acetic acid (10 c.c.). Direct distillation gave 1·0 g. (34%), b. p. 106—110°/20 mm. The product from a number of runs was redistilled, giving the *ester*, b. p. 101—102°/14 mm., as a colourless oil, which during one distillation suddenly solidified. Crystallisation from benzene–light petroleum gave colourless prisms, m. p. 47—49° (Found: C, 51·4; H, 4·6; N, 10·2. $C_6H_7O_3N$ requires C, 51·1; H, 4·9; N, 9·9%).

Oxazole-4-carboxylic Acid (XIII; R = H).—The ester (XI; R = H) (14·2 g.) was hydrolysed as described for its homologue. The acid separated during ether extraction in massive hydrated crystals. The product of ether extraction was ground and kept for 24 hours over sulphuric acid in a vacuum, leaving anhydrous *oxazolecarboxylic acid* (10·4 g.; 91%). A portion crystallised from alcohol–benzene had m. p. 142° (Found: C, 42·5; H, 3·0; N, 12·4. $C_4H_3O_3N$ requires C, 42·5; H, 2·7; N, 12·4%). The hydrated form melted at about 100° before solidifying and melting at 142°.

Oxazole (XIV; R = H).—The above acid (5 g.) was decarboxylated in the manner previously described, giving *oxazole* (2·3 g.; 75%) as a colourless mobile liquid of strong pyridine-like odour, b. p 69—70°, $n_D^{17\cdot5°}$ 1·4285 (Found: C, 52·0; H, 4·5; N, 20·5. C_3H_3ON requires C, 52·2; H, 4·4; N, 20·3%). The picrate and hydrochloride have been mentioned above. On addition of oxazole to aqueous mercuric chloride a crystalline complex separated, m. p. 148° when rapidly heated. Slow heating gave no m. p. below that of mercuric chloride. Oxazole was also lost over sulphuric acid.

The absorption spectrum of oxazole has been examined by Dr. F. B. Strauss. Absorption begins below 2400 A. and has the value $\varepsilon_{molar} = 30$ at 2300 A. There is probably a maximum below 2000 A.

2-Methyliminazole.—2-Methyloxazole-4-carboxylic acid (1 g.) was heated for 1 hour at 150° in a sealed tube with aqueous ammonia (10 c.c.; *d* 0·88). The solution was evaporated at low pressure and the residue crystallised three times from benzene, giving 2-methyliminazole (140 mg.), long colourless needles, m. p. 141—143°* (Found: C, 58·0; H, 7·3. Calc. for $C_4H_6N_2$: C, 58·5; H, 7·3%). The picrate crystallised from water in yellow needles, m. p. 215° (corr.) [Fargher and Pyman, *J.*, 1919, **115**, 231, give m. p. 213° (corr.)].

1-Phenyl-2-methyliminazole (XVII; R = Me).—2-Methyloxazole-4-carboxylic acid (1 g.) was boiled with aniline (2 c.c.) for ½ hour. After two fractionations the colourless oily *base* (0·83 g.) had b. p. 147°/20 mm. (Found: C, 76·0; H, 6·3. $C_{10}H_{10}N_2$ requires C, 76·0; H, 6·3%). The *picrate* separated from alcohol in yellow needles, m. p. 145° (Found: N, 18·3. $C_{10}H_{10}N_2,C_6H_3O_7N_3$ requires N, 18·1%).

1-Phenyliminazole (XVII; R = H).—Prepared in the same way from oxazole-4-carboxylic acid, this *base* distilled as a colourless oil at 142°/15 mm. (Found: N, 19·4. $C_9H_8N_2$ requires N, 19·4%). The *picrate* separated from alcohol in fine yellow needles, which rapidly changed to stout prisms, m. p. 155—156° (Found: N, 19·0. $C_9H_8N_2,C_6H_3O_7N_3$ requires N, 18·8%).

Ethyl 2-Methyliminazole-4-carboxylate-1-acetate (XVIII).—The potassium salt (VIII) (1·1 g.) was dissolved in a little alcohol and treated with glycine ethyl ester hydrochloride (0·75 g.). After 5 hours water and ether were added. The aqueous layer was extracted twice with fresh ether. Removal of the ether left a residue which soon crystallised. It was purified by solution in dilute acid and removal of neutral impurities with ether. Recovered in the usual way, the iminazole *ester* crystallised from water in matted, colourless hairy needles, m. p. 126—127° (Found, after drying at 60° in a vacuum: C, 54·7; H, 6·6; N, 12·0. $C_{11}H_{16}O_4N_2$ requires C, 55·0; H, 6·7; N, 11·7%).

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