192. *Some Reactions of Oxazole-4-carboxylic Acids.*

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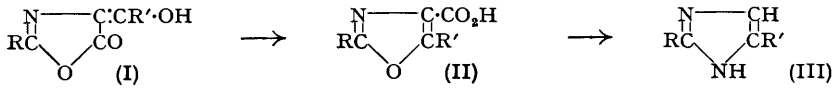
The preparation of 2-substituted oxazole-4-carboxylic acids by rearrangement of the corresponding 4-hydroxyalkylideneoxazol-5-ones is described. Several of these acids were converted into glyoxalines. Novel reactions of 2-phenyloxazole-4-carboxylic acid include (*a*) nuclear methylation of the methyl ester by lead tetra-acetate, and (*b*) a Curtius degradation leading to ring-fission. The preparation of 2-benzamido-3-ketobutaldehyde (VI) extends the scope of a method previously reported.

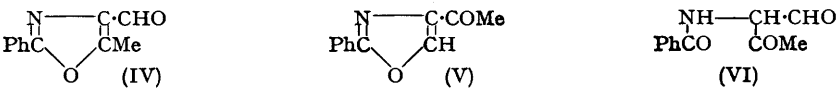
OXAZOLE-4-CARBOXYLIC ACIDS substituted in the 2-position are conveniently prepared by rearrangement of 4-hydroxyalkylideneoxazol-5-ones, a general reaction illustrated in the change (I) ⟶ (II). The oxazolones (I) most readily available have an aryl or substituted vinyl group in the 2-position (Cornforth, " The Chemistry of Penicillin," Princeton Univ. Press, 1949, Ch. XXI).



The oxazolones (I) are preferably rearranged in the form of a sodium or potassium salt; ferric chloride is used to test for complete reaction, for (I) give a colour reaction and (II) do not. The temperature of reaction is high, and the heating should be as brief as possible; it is helpful to mix the oxazolone salt with sodium or potassium acetate to lower the fusion temperature, or alternatively to suspend the salt in liquid paraffin. Of the four oxazole-4-carboxylic acids (II; R = Ph or styryl, R′ = Me or H), one has already been made in this way (Cornforth and Huang, *J.*, 1948, 1960). The other three acids have now been prepared and converted into the corresponding glyoxalines (III) by heating them with aqueous ammonia (Cornforth and Cornforth, *J.*, 1947, 96; Cornforth and Huang, *loc. cit.*).

A reaction between lead tetra-acetate and methyl 2-phenyloxazole-4-carboxylate proceeded rapidly in acetic acid at 100° with evolution of gas, and the main product after hydrolysis was 5-methyl-2-phenyloxazole-4-carboxylic acid (II; R = Ph, R′ = Me). This nuclear methylation by lead tetra-acetate has been observed with naphthaquinones and various benzene derivatives (Fieser *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 2043, 2052) but not to our knowledge with any heterocyclic system. It is the second substitution reaction so far observed in oxazoles, the other being a bromination (Brodrick *et al.*, *op. cit.*, p. 698).

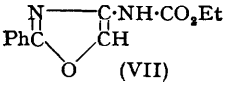
5-Methyl-2-phenyloxazole-4-carboxylic acid (II; R = Ph, R′ = Me) was converted by Rosenmund reduction of the acid chloride into the corresponding aldehyde (IV). It was necessary to distinguish this from the ketone (V) which might arise from it by re-



arrangement. The compound both reduced ammoniacal silver nitrate and gave a strongly positive iodoform reaction, but the aldehyde (IV) was indicated by the ready formation of a dimedone derivative. This aldehyde when shaken with cold dilute sodium hydroxide was slowly hydrolysed to 2-benzamido-3-ketobutaldehyde (VI); more drastic conditions destroyed the product. The reaction is analogous to a synthesis of acylaminomalondialdehydes already reported (Cornforth *et al.*, *J.*, 1949, 1549), but here the yield was poor.

As 4-amino-oxazole derivatives were unknown, the Curtius degradation of 2-phenyloxazole-4-carboxylic acid was studied. The acid chloride, azide, and *iso*cyanate were prepared by standard methods. The *iso*cyanate with alcohol yielded a normal urethane, 4-carbethoxyamino-2-phenyloxazole (VII). Attempts to prepare 4-amino-2-phenyl-

oxazole (VIII) from this compound or directly from the *iso*cyanate have been unsuccessful. Hydrolysis of the *iso*cyanate with cold fuming hydrochloric acid afforded a basic substance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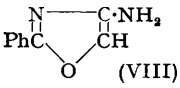
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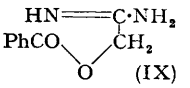
(IX)

which was conveniently isolated as the picrate. The product was shown to be *O*-benzoylglycollamidine (IX) by its synthesis from benzoyloxyacetonitrile *via* the imido-ether. This fission of an oxazole ring between atoms 2 and 3 is unique, though it is normal with Δ^2-oxazolines.

Experimental

4-Ethoxymethylene-2-styryloxazol-5-one.—Cinnamoylglycine (4 g.) was added gradually to a boiling (bath temp. 160°) mixture of ethyl orthoformate (5·5 c.c.), acetic anhydride (10 c.c.), and xylene (10 c.c.). The volatile products were distilled through a short fractionating column, the temperature at the top being controlled at about 110°. After addition was complete the mixture was heated for a few minutes (total time 25 min.) and then evaporated at 100°/20 mm. The dark residue was repeatedly extracted with boiling light petroleum (b. p. 80—100°). From the cooled extracts the light yellow crystalline oxazolone (2·2 g.), m. p. 102—103°, separated. The yield by this procedure is higher than that from the original preparation (*op. cit.*, p. 804).

The oxazolone (2·2 g.) in ether was shaken with sodium hydroxide (25 c.c.; 0·8N) until precipitation was complete. The product was collected, washed with ether, then a little water, and finally acetone, and dried (2·1 g.). This was the sodium salt of 4-hydroxymethylene-2-styryloxazol-5-one.

4-1′-Hydroxyethylidene-2-styryloxazol-5-one.—The sodium salt (19 g.) of cinnamoylglycine (prepared by precipitation of a neutral aqueous solution with acetone, and dried at 140° for 10 hours) was stirred vigorously for 5 hours with acetic anhydride (25 c.c.) and dry pyridine (26 c.c.), moisture being excluded. Ethanol (17 c.c.) was added dropwise, the temperature being kept at 30—35° by cooling. Stirring was continued for another hour; water (200 c.c.) was then added and the mixture was acidified to Congo-red (external cooling). The crude yellow solid was dissolved in one equivalent of sodium hydroxide (2N) and the filtered solution after being boiled (charcoal) was treated with hydrochloric acid. Recrystallization of the precipitated solid from ethyl acetate gave yellowish plates (10 g.), m. p. 218—219° undepressed by a sample prepared by the method (18% yield) previously reported (*op. cit.*, p. 830).

2-Phenyloxazole-4-carboxylic Acid.—A saturated ethereal solution of 4-ethoxymethylene-2-phenyloxazol-5-one (20 g.) was shaken with sodium hydroxide (50 c.c., 2N) for 2 hours or until precipitation appeared to be complete. The *sodium* salt of 4-hydroxymethylene-2-phenyloxazol-5-one (12 g.) was obtained in colourless plates by recrystallizing the ether-washed, dried precipitate from ethanol; it had m. p. 254—255° (decomp.) (Found : N, 6·1. $C_{10}H_6O_3NNa,H_2O$ requires N, 6·1%).

A powdered mixture of the sodium salt (2 g.) and sodium acetate (1 g.) in a thin-walled test-tube was introduced into a metal-bath maintained at 290—300°. The contents were stirred with a glass rod until the melt gave with aqueous ferric chloride no green colour extractable with ethyl acetate (about 5 minutes). The cooled melt was boiled in water (10 c.c.) with charcoal for 2 minutes and then filtered through charcoal. 2-Phenyloxazole-4-carboxylic acid (1·4 g.) was obtained by addition of acid to the filtrate and recrystallization of the precipitate from benzene; fine colourless needles, m. p. 210° undepressed by authentic material, were obtained.

2-Styryloxazole-4-carboxylic Acid.—The sodium salt of 4-hydroxymethylene-2-styryloxazol-5-one (2·15 g.) was suspended in liquid paraffin (5 c.c.) and stirred at 280° until the ferric chloride test was negative (about 10 minutes). The cooled mixture was treated with dilute hydrochloric acid and with ether–chloroform, and filtered to break an emulsion. The organic layer was extracted with very dilute aqueous ammonia. The acid precipitated from the ammonia extracts was dried and recrystallised from ethyl acetate. The *acid* separated in colourless leaflets (1·10 g., and 0·155 g. second crop), m. p. 199·5—200·5° (Found : C, 67·1; H, 3·9. $C_{12}H_9O_3N$ requires C, 67·0; H, 4·2%).

5-Methyl-2-styryloxazole-4-carboxylic Acid.—4-1′-Hydroxyethylidene-2-styryloxazol-5-one (1·075 g.) was stirred for a few minutes with alcoholic potassium hydroxide (10 c.c.; 0·5N). The solid remaining after evaporation of the alcohol was mixed with potassium acetate (0·5 g.)

and transferred to a test-tube which was then placed in a metal-bath at 290°. After being stirred for 5 minutes the melt gave a negative test with ferric chloride. A charcoal-treated, filtered aqueous solution of the melt was treated at the boiling-point with dilute hydrochloric acid. The crystalline precipitate was recrystallized from benzene; the *acid* (0·45 g.) separated in needles, m. p. 183—185° (Found: C, 67·8; H, 4·8. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8%).

Glyoxalines from Oxazole-4-carboxylic Acids.—The acid was dissolved in aqueous ammonia (about 10 c.c./g.; *d* 0·88), and the solution heated in a sealed tube. The basic product was isolated in the normal manner, the following glyoxalines being obtained.

2-Phenylglyoxaline, from 2-phenyloxazole-4-carboxylic acid in ammonia at 200° for 8 hours, formed colourless plates (45% yield), m. p. 149—150°, from aqueous ethanol (Found: C, 74·8; H, 5·3. Calc. for $C_9H_8N_2$: C, 75·0; H, 5·6%). 2-*Styrylglyoxaline*, from 2-styryloxazole-4-carboxylic acid in ammonia at 190° for 24 hours, formed colourless needles (yield 20%), m. p. 178—179°, after sublimation at 180°/0·05 mm. and recrystallization from benzene (Found: C, 77·2; H, 6·0. $C_{11}H_{10}N_2$ requires C, 77·6; H, 5·9%). The ethereal solution had a blue fluorescence.

4-Methyl-2-styrylglyoxaline was obtained from 5-methyl-2-styryloxazole-4-carboxylic acid in ammonia at 240° for 9 hours. It formed colourless needles (25% yield), m. p. 232—233°, from ethyl acetate (Found: C, 78·0; H, 6·8; N, 15·0. Calc. for $C_{12}H_{12}N_2$: C, 78·2; H, 6·5; N, 15·2%); John (*Ber.*, 1935, **68**, 2289) records m. p. 235°. The preparation of 4-methyl-2-phenylglyoxaline from 5-methyl-2-phenyloxazole-4-carboxylic acid has already been described (Cornforth and Huang, *loc. cit.*).

Nuclear Methylation of Methyl 2-Phenyloxazole-4-carboxylate.—2-Phenyloxazole-4-carboxylic acid (3·25 g.) in dry methanol (20 c.c.) was treated with acetyl chloride (2 c.c.). After one hour's refluxing, water was added and the mixture made alkaline. The crystalline *methyl* ester (3·25 g.; m. p. ~80°) was collected; a sample recrystallized from light petroleum (40—60°) formed colourless silky needles, m. p. 85·5—87° (Found: N, 6·8. $C_{11}H_9O_3N$ requires N, 6·9%). Lead tetra-acetate (6·9 g.) was added to the ester (3·15 g.) in acetic acid (25 c.c.; purified). On heating to 105° there was a brisk evolution of gas and after 15 minutes the tetra-acetate had all been consumed. A further 3·45 g. of tetra-acetate was also reduced quite rapidly. The mixture was diluted with water and extracted twice with ether; the ether was washed with aqueous sodium carbonate and evaporated. The partly crystalline residue was heated for 15 minutes (steam-bath) with aqueous sodium hydroxide (15 c.c.; 2N) and a little alcohol, and the solution was diluted with water and acidified. One crystallization from alcohol and two from benzene gave 5-methyl-2-phenyloxazole-4-carboxylic acid, m. p. 179—180·5°. A mixture with an authentic specimen, m. p. 181—182°, had m. p. 180·5—182° (Found: N, 6·6. Calc. for $C_{11}H_9O_3N$: N, 6·9%). The crude acid was apparently contaminated with some unmethylated material.

5-*Methyl-2-phenyloxazole-4-aldehyde.*—5-Methyl-2-phenyloxazole-4-carboxylic acid (2 g.) was refluxed with thionyl chloride (1·2 c.c.) until the solid had dissolved. Recrystallization of the product from thiophen-free benzene gave prisms, m. p. 133—135°, of the acid chloride. This product (1 g.) with xylene (6 c.c.) and palladium–barium sulphate (0·5 g.) were refluxed in a current of hydrogen. Within 2 hours 92% of the theoretical quantity of hydrogen chloride had been evolved. Evaporation of the filtered xylene solution left a crystalline residue which was recrystallized from a little alcohol and washed with chilled (−25°) alcohol. The *aldehyde* formed colourless needles, m. p. 90·5—91·5° (Found: C, 70·2; H, 5·3; N, 7·8. $C_{11}H_9O_2N$ requires C, 70·6; H, 4·9; N, 7·5%). A *dimedone* derivative was prepared in the usual way; it crystallized from alcohol in colourless aggregated prisms, m. p. 263—264°, and appeared to be in the unusual anhydro-form (Found: C, 74·7; H, 7·0. $C_{27}H_{29}O_4N$ requires C, 75·1; H, 6·8%).

2-*Benzamido-3-ketobutaldehyde.*—The above aldehyde (132 mg.) was shaken overnight with sodium hydroxide (3 c.c.; 0·5N). The solution was filtered and the alkali-insoluble residue again shaken overnight with fresh alkali. From the united alkaline filtrates by acidification and ether extraction the *keto-aldehyde* was obtained; when recrystallized from light petroleum (b. p. 60—80°) and then from a little ether, there were obtained prismatic needles (10 mg.), m. p. 86° (Found: C, 64·8; H, 5·5. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4%). The aldehyde dissolved easily in alkali hydroxides and the neutral solution gave a blood-red colour with ferric chloride. The main reaction product was yellowish, alkali-insoluble, and apparently polymeric.

Curtius Degradation of 2-Phenyloxazole-4-carboxylic Acid.—Sodium azide (0·7 g.) in water (3 c.c.) was cooled to 0° and added gradually with good stirring to a similarly cooled solution

of 2-phenyloxazole-4-carboxychloride (2·07 g.) in acetone (25 c.c.); 20 minutes after the addition was completed, water (75 c.c.) was added, and the crude azide (2 g.), m. p. 120—121° (decomp.), collected and dried. It was refluxed in dry xylene (10 c.c.) until effervescence ceased (about 5 mins.). The cooled solution was shaken with aqueous hydrochloric acid (7 c.c.; saturated at 0°) at about 25°, again until effervescence ceased (10 minutes). The separated lower layer was diluted with water (40 c.c.), cooled, filtered, overlaid with ether, chilled in ice–salt and treated (swirling) with a concentrated aqueous solution of potassium carbonate (25 g.). A precipitate of carbamate separated in the ether; it was collected, and the ethereal layer separated and evaporated. The carbamate was treated with aqueous picric acid; the residue from the ether evaporation was dissolved in a little alcoholic picric acid and aqueous picric acid added as long as crystalline material separated. The two picrates were united (803 mg.) and recrystallized from methanol, giving 643 mg. of material, m. p. 207—209°. Another crystallization from methanol and one from *iso*propanol gave yellow needles, m. p. 215—216° (decomp.) of the *picrate* (Found: C, 44·2, 44·4; H, 3·8, 3·7; N, 16·6. $C_{10}H_{10}O_2N_2,C_6H_3O_7N_3$ requires C, 44·2; H, 3·2; N, 16·7%). In another experiment the solid carbamate was decomposed with sodium hydroxide in the presence of ether. Recrystallization from anhydrous ether gave the *base* in boat-shaped prisms, m. p. 88° (Found: C, 61·0; H, 6·1; N, 15·3. $C_{10}H_{10}O_2N_2$ requires C, 60·7; H, 5·7; N, 14·7%). The base decomposed with evolution of ammonia when warmed with dilute sodium hydroxide solution.

Benzoyloxyacetonitrile (2 g.) in dry ethanol (0·58 g.) was cooled slightly during the passage of dry hydrogen chloride. The mixture solidified when two-thirds of the theoretical amount had been absorbed. Next day the solid was collected (dry ether) and dried (NaOH). This imido-ether hydrochloride (1·65 g.) was suspended in a little ethanol and treated with one equivalent of ethanolic ammonia. Next day water was added, followed by aqueous picric acid until precipitation was complete. Recrystallization from methanol gave O-*benzoylglycollamidine picrate* as yellow needles (1·8 g.), m. p. 215—216° unchanged by recrystallization from *iso*-propanol (Found: C, 44·0; H, 4·2; N, 16·6%). The m. p. was not depressed on admixture with the picrate from the Curtius degradation (above). A specimen was converted into the base; O-*benzoylglycollamidine* had m. p. 88°, undepressed by the Curtius degradation product. The base appeared to be dimorphic, for needles m. p. above 100° were first deposited, then giving place to the characteristic boat-shaped prisms.

4-*Carbethoxyamino*-2-*phenyloxazole*.—When the crude azide (1 g.) was decomposed in xylene as above and the product was boiled with ethanol for 3 hours, the *urethane* separated from the concentrated solution and was recrystallized from *cyclo*hexane; it formed colourless prisms (0·58 g.), m. p. 105° (Found: C, 62·1; H, 5·3. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·2%).

One of us (J. W. C.) thanks Mrs. P. Perkins for assistance with the preparations.

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