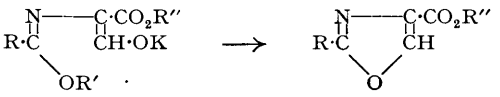
398. *Further Studies of Oxazoles and Glyoxalines.*

By J. W. Cornforth and H. T. Huang.

The condensation of imido-ethers with α-amino-ketone hydrochlorides is shown to produce both oxazoles and glyoxalines. Some observations are recorded on the synthesis of glyoxalines from oxazole-4-carboxylic acids.

In a recent memoir (Cornforth and Cornforth, *J.*, 1947, 96) a synthesis of oxazoles was described, in which the determining stage was the cyclisation by acid of a potassium enolate of type (I).

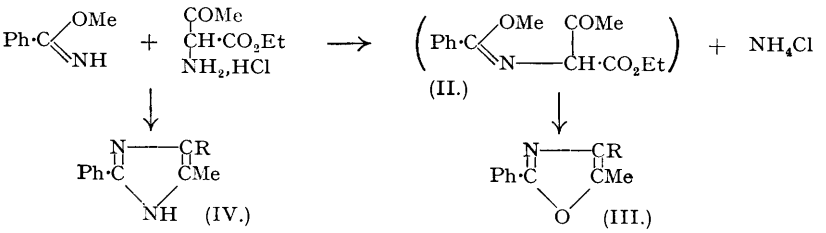


(I.)

It was suggested on the basis of these experiments that oxazoles might well result from the reaction of imido-ethers with α-amino-carbonyl compounds. This possibility has now been investigated.

Benzimidomethyl ether and ethyl α-aminoacetoacetate hydrochloride were chosen as reactants for the first trial. The imido-ether was added to a solution of the hydrochloride in acetic acid at 100°. Condensation took place readily, and the product was separated into a neutral and a basic fraction. The neutral part consisted mainly of benzamide and ethyl 2-phenyl-5-methyloxazole-4-carboxylate, which was characterised by hydrolysis to 2-phenyl-5-methyloxazole-4-carboxylic acid (III; R = CO_2H) and decarboxylation of the latter to 2-phenyl-5-methyloxazole (III; R = H).

The basic product from its composition and properties was evidently *ethyl 2-phenyl-5-methylglyoxaline-4-carboxylate* (IV; R = CO_2Et). Apparently reaction between the imido-ether and the amino-ketone hydrochloride can take place in two ways :



(II.) (IV.) (III.)

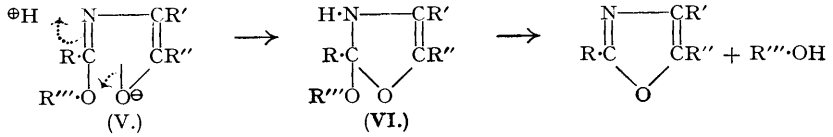
It is also possible, though less likely, that the glyoxaline (IV; R = CO_2Et) is derived from ammonium chloride and the intermediate (II). Hydrolysis of (IV; R = CO_2Et) gave the expected *2-phenyl-5-methylglyoxaline-4-carboxylic acid* (IV; R = CO_2H), which lost carbon dioxide on heating and furnished 2-phenyl-4-methylglyoxaline (IV; R = H).

The nature of the various substances which have been described in the literature as 2-phenyl-4-methylglyoxaline (VII) was discussed in an earlier paper (Cornforth and Huang, this vol., p. 731). The identity of the present specimen was checked by a synthesis from benzamidine and chloroacetone (method of Kunckell, *Ber.*, 1901, **34**, 631), which gave a product identical with our glyoxaline. The properties agreed well with those of the compound obtained by John (*Ber.*, 1935, **68**, 2290) as a by-product in the preparation of 2-styryl-4-methylglyoxaline from cinnamaldehyde and methylglyoxal; and John's formulation of this compound as (IV; R = H) is thereby confirmed. It may be mentioned that an attempt to prepare (IV; R = H) from methylglyoxal and benzaldehyde led to an intractable mixture.

Condensation of heximidomethyl ether with ethyl α-aminoacetoacetate hydrochloride proceeded smoothly; from the neutral product *5-methyl-2-amyloxazole-4-carboxylic acid* was obtained after hydrolysis, and the basic product consisted essentially of *ethyl 5-methyl-2-amylglyoxaline-4-carboxylate*. A further extension of the synthesis was found in the reaction of benzimidomethyl ether and aminoacetone hydrochloride; the process went as smoothly as before and 2-phenyl-5-methyloxazole (III; R = H) was isolated, along with 2-phenyl-4-methylglyoxaline. However, when an attempt was made to condense benzimidomethyl ether with aminoacetaldehyde hydrochloride, a tarry product resulted from which only 2 : 4 : 6-triphenyltriazine could be extricated. This last result was evidently due to the instability of

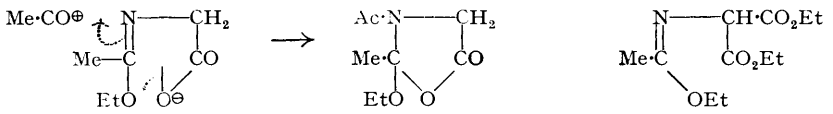
aminoacetaldehyde. No search has so far been made for conditions which would favour the production in this synthesis of oxazoles alone, or of glyoxalines alone.

Sufficient data are now available to discuss the mode of formation of the oxazole ring in this type of synthesis. Cyclisation appears only to take place under acid conditions : salts of the general formula (I) have shown no tendency to spontaneous cyclisation. The process may therefore be initiated by the acceptance of a proton (or other cation) by the nitrogen atom of the enolate ion (V), followed by a rearrangement of electrons to give the intermediate (VI), which passes to the oxazole by loss of alcohol.



(V.) (VI.)

An intermediate analogous to (VI), *viz.*, 5-keto-2-ethoxy-3-acetyl-2-methyltetrahydrooxazole (VII), appears to have been produced in this manner from potassium 1-ethoxyethylideneaminoacetate and acetyl chloride (Cornforth and Cornforth, *loc. cit.*).



(VII.) (VIII.)

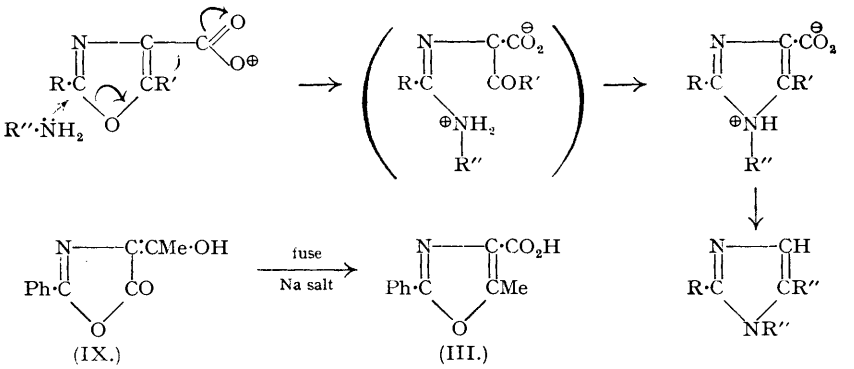
In the same paper, the preparation of ethyl 1-ethoxyethylideneaminomalonate (VIII) was described; this could be distilled unchanged and it has since been found that treatment with boiling acetic acid or anhydride had no effect on (VIII). Treatment of (VIII) with potassium ethoxide in ether and addition of the resulting potassium compound to boiling acetic acid gave ethyl acetamidomalonate as the only identifiable product. Vigorous treatment of (VIII) with sulphuric acid gave ethyl aceturate and a small quantity of an unidentified base (isolated as the *picrate*). Degeneracy of the anion of (VIII) may be the cause of this failure to cyclise : it is possible that a sufficiently high negative charge cannot be transferred to one of the carbonyl oxygen atoms to allow formation of the intermediate (VI). Alternatively, it may be that the " aromatic " stabilisation of 5-alkoxyoxazoles is not so great as that of simple oxazoles, so that loss of alcohol from the intermediate (VI) does not take place so readily.

The condensation of benzimidomethyl ether with chloroacetone was tried, in order to find out whether the resulting oxazole, if one were formed, would be 2-phenyl-4- or -5-methyloxazole. The former was the product actually obtained; a considerable amount of benzamide was also formed and it is possible that the oxazole was produced by condensation of chloroacetone with some of the benzamide. It is noteworthy that a mixture of the picrates of 2-phenyl-4- and -5-methyloxazole showed little depression in melting point. Since the individual picrates have almost the same melting point, this is a potential source of confusion.

A synthesis of glyoxalines from oxazole-4-carboxylic acids and ammonia (or aniline) has been reported (Cornforth and Cornforth, *loc. cit.*). It was of interest to determine whether the oxazoles resulting from decarboxylation of such acids would form glyoxalines with equal facility. Accordingly, 2-amyloxazole and 2-amyloxazole-4-carboxylic acid were heated with aqueous ammonia under identical conditions. At a temperature not exceeding 150° the acid was completely destroyed with formation of 2-amylglyoxaline, whereas the oxazole was recovered entirely unchanged. It is therefore certain (i) that this glyoxaline synthesis does not proceed by way of an initial decarboxylation, and (ii) that the carboxyl group facilitates the amination, presumably as on p. 1962.

A synthesis of 2-phenyl-4-methylglyoxaline in three stages from hippuric acid has been worked out, and found to be much the most satisfactory way of preparing (IV; R = H) especially in quantity. The preparation of 2-phenyl-4-(1-hydroxyethylidene)-4 : 5-dihydrooxazol-5-one (IX) from sodium hippurate and acetic anhydride has been described by Attenburrow, Elliott, and Penny (this vol., p. 310). The sodium salt of this oxazolone rearranged smoothly on melting (cf. Cornforth and Cornforth, " The Chemistry of Penicillin," Chap. XXI) to give the sodium salt of 2-phenyl-5-methyloxazole-4-carboxylic acid (III; R = CO_2H), which gave (IV; R = H) when heated with aqueous ammonia under pressure. The yields were good, and it seems that this iminazole synthesis is particularly well suited to the preparation of

2-arylglyoxalines; in this respect it is complementary to the old glyoxaline synthesis. If an iminazole unsubstituted in the 4(5)-position is required, the appropriate aroylglycine is condensed with ethyl orthoformate–acetic anhydride to give a 4-hydroxymethyleneoxazolone (cf. "The Chemistry of Penicillin"); rearrangement and amination then follow as before. This process has already been used to prepare 2-phenylglyoxaline; details will be published elsewhere.



(IX.) (III.)

Experimental.

Condensation of Benzimidomethyl Ether with Ethyl α-Aminoacetoacetate Hydrochloride.—The imido-ether (1·5 c.c.) was added during one minute to a stirred solution of the hydrochloride (2 g.) in glacial acetic acid (4 c.c.) at 100°. A strong smell of ethyl benzoate was observed, and a yellow precipitate appeared almost at once. After being kept at room temperature for 20 minutes, the mixture was cooled in ice, diluted with water, and extracted repeatedly with ether (total 30 c.c.). The ethereal extract was washed with hydrochloric acid (15 c.c. of N). The acid solution on neutralisation with sodium carbonate gave a precipitate (0·25 g.); a further quantity (50 mg.) was obtained by neutralising the aqueous acetic acid solution. The dried precipitate was recrystallised from benzene, giving *ethyl 2-phenyl-5-methylglyoxaline-4-carboxylate* (IV; R = CO_2Et) in long thin needles, m. p. 199—199·5° unchanged by further crystallisation (Found: C, 67·8; H, 6·1; N, 12·2. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H, 6·1; N, 12·0%). The compound was soluble in most organic solvents.

After the acid washing, the ethereal solution was washed with dilute sodium hydroxide solution, dried ($MgSO_4$), and evaporated. On distillation a low-boiling fraction (0·5 g.) was collected at 70—80°/15 mm.; the higher fraction distilled at 95°/0·05 mm. and partly solidified. The oil (0·3 g.) was separated by filtration from the embedded solid (identified as benzamide, m. p. 126°) (Found: C, 69·5, H, 5·8. Calc. for C_7H_7ON: C, 69·4; H, 6·1%) and redistilled thrice; it then consisted essentially of ethyl 2-phenyl-5-methyloxazole-4-carboxylate (Found: C, 67·2; H, 5·9. Calc. for $C_{13}H_{13}O_3N$: C, 67·5; H, 5·7%).

This ester (0·8 g.) was heated with potassium hydroxide (2·8 g.) in water (30 c.c.) on the steam-bath. A clear solution was obtained in 15—20 minutes; after cooling the liquor was washed with ether, warmed to expel dissolved ether, cooled in ice, and acidified to Congo-red with hydrochloric acid. The crystalline precipitate (0·69 g., m. p. 180°) had m. p. 181° after recrystallisation from benzene (Found: C, 64·7; H, 4·3; N, 6·9. Calc. for $C_{11}H_9O_3N$: C, 65·0; H, 4·4; N, 6·8%). Elliott ("The Chemistry of Penicillin," Chap. XXI), records m. p. 181° for 2-phenyl-5-methyloxazole-4-carboxylic acid (III; R = CO_2H) prepared by cyclodehydration of ethyl α-benzamidoacetoacetate followed by hydrolysis of the ester.

2-Phenyl-5-methyloxazole.—2-Phenyl-5-methyloxazole-4-carboxylic acid (0·5 g., recrystallised) was heated with a little cupric oxide. Decarboxylation began at 200° and the oxazole distilled at about 250° as a colourless oil. The chloroplatinate formed golden-yellow prisms, decomp. from 210° (Gabriel, *Ber.*, 1894, **27**, 218, records 218°). The *picrate* crystallised from ethanol in slender yellow needles, m. p. 145° (Found: C, 49·5; H, 3·2; N, 14·4. $C_{10}H_9ON,C_6H_3O_7N_3$ requires C, 49·9; H, 3·4; N, 14·7%).

2-Phenyl-5-methylglyoxaline-4-carboxylic acid (IV; R = CO_2H).—Ethyl 2-phenyl-5-methylglyoxaline-4-carboxylate (0·24 g.) was dissolved in potassium hydroxide solution (10 c.c. of 10%) by warming for ½ hour at 100°. The cooled solution was washed with ether and adjusted to pH 7. Fine needles of the *acid* (IV; R = CO_2H) (0·18 g.) separated on keeping. Recrystallisation from ethyl acetoacetate gave clusters of thin needles, m. p. 177° (decomp.) (Found: C, 64·9; H, 5·0. $C_{11}H_{10}O_2N_2$ requires C, 65·3; H, 5·0%).

The acid (0·2 g.) was heated at 15 mm. pressure in a sublimation apparatus. Effervescence began at 160° and was complete at 180°. The sublimate was recrystallised from aqueous ethanol. The shiny needles of 2-phenyl-4-methylglyoxaline had m. p. 181—182° (John, *loc. cit.*, gave m. p. 181°). The product was sparingly soluble in benzene and almost insoluble in water (Found: C, 75·8; H, 6·4; N, 17·6. Calc. for $C_{10}H_{10}N_2$: C, 75·8; H, 6·3; N, 17·7%).

Synthesis of 2-Phenyl-4-methylglyoxaline.—(a) *From benzamidine and chloroacetone.* Benzamidine hydrochloride (6 g.) was dissolved in aqueous sodium hydroxide (20 c.c. of 5%), and the free base extracted with chloroform (45 c.c.). The dried ($CaCl_2$) solution was refluxed for 4 hours with chloroacetone (3 g.). On distillation 1 g. was obtained, b. p. 350°. Sublimation (160—180°/15 mm.) and recrystallisation

from aqueous ethanol gave the glyoxaline (0·7 g.); m. p. 181° undepressed on mixing with the material described in the preceding experiment.

(b) *From hippuric acid.* 2-Phenyl-4-(1-hydroxyethylidene)-4 : 5-dihydro-oxazol-5-one was prepared by the method of Elliott and Penny (*loc. cit.*), pyridine being used. The sodium salt of the oxazolone (5 g., prepared by evaporating a neutralised solution) was thoroughly mixed with potassium acetate (5 g.; this ingredient acts as a flux) and melted by heating and stirring over a free flame. When a test portion failed to give the characteristic colour with ferric chloride (about 3 minutes), the dark melt was cooled and dissolved in water. The combined solution from four such runs was boiled with a liberal quantity of charcoal. After filtration the solution was acidified, and the precipitated 2-phenyl-5-methyloxazole-4-carboxylic acid (III; R = CO_2H) collected and dried (12 g.). A portion recrystallised from benzene formed long slender needles, m. p. and mixed m. p. 180°. The acid (2 g.) was heated in a sealed tube with aqueous ammonia (10 c.c.; *d* 0·880) for 8 hours at 190°. The crude glyoxaline was collected and dried (1·5 g.). Sublimation and recrystallisation from aqueous ethanol gave 1·3 g., m. p. 181—182°, identical with the specimens prepared by methods described above.

Condensation of Benzimidomethyl Ether with Aminoacetone Hydrochloride.—The imido-ether (1·4 c.c.) was added to a solution of the hydrochloride (1 g.) in glacial acetic acid (4 c.c.) at 100°. The product was separated into neutral and basic fractions as already described. The aqueous acetic acid solution on addition of excess alkali gave a dark precipitate which was recrystallised (charcoal) from aqueous ethanol to give 2-phenyl-4-methylglyoxaline (0·37 g.), m. p. 180°, raised to 181—182° by sublimation in a vacuum and recrystallisation. The m. p. was not depressed by admixture with an authentic sample. The ethereal solution yielded no more glyoxaline on extraction with dilute hydrochloric acid. It was evaporated, and the residue boiled with 2N-sodium hydroxide. Extraction with ether then gave crude 2-phenyl-5-methyloxazole (0·3 g.), identified as the picrate, m. p. 144° alone or mixed with authentic material.

Condensation of Benzimidomethyl Ether with Aminoacetaldehyde Hydrochloride.—Carried out under the conditions of the foregoing experiment, this reaction gave a dark and tarry product. From the ethereal extract a trace of solid was obtained, which had m. p. 228—230° after recrystallisation from ethanol and was found to be 2 : 4 : 6-triphenyltriazine (Found : C, 81·7; H, 5·0; N, 13·4. Calc. for $C_{21}H_{15}N_3$: C, 81·5; H, 4·9; N, 13·6%).

Condensation of Heximidomethyl Ether with Ethyl α-Aminoacetoacetate Hydrochloride.—The imido-ether (1·2 c.c.) was dropped into a stirred solution of the hydrochloride (2 g.) in glacial acetic acid (4 c.c.) at 100°. The reaction mixture was worked up as described before. About 60% of the basic product was found in the diluted acetic acid solution, and the remainder was obtained by acid washings of the ether extract. Recrystallisation from benzene gave *ethyl 5-methyl-2-amylglyoxaline-4-carboxylate* (0·3 g.), m. p. 98—100°. Further crystallisation from light petroleum (b. p. 60—80°) gave long slender needles, m. p. 100—101° (Found : C, 64·3; H, 8·9. $C_{12}H_{20}O_2N_2$ requires C, 64·3; H, 8·9%).

The crude neutral product from the ether extract was hydrolysed by warming with sodium hydroxide (4 c.c. of 5%) for one hour on a steam-bath. After treatment with charcoal the cooled solution was washed well with ether and acidified to Congo-red. The precipitated oil solidified after a time. Recrystallisation from benzene gave *5-methyl-2-amyloxazole-4-carboxylic acid* (0·2 g.) in shiny broad plates, m. p. 108—109° raised to 110° by two crystallisations from methanol–light petroleum (Found : C, 61·1; H, 7·7; N, 7·0. $C_{10}H_{15}O_3N$ requires C, 60·9; H, 7·7; N, 7·1%).

Experiments on the Cyclisation of Ethyl 1-Ethoxyethylideneaminomalonate.—The ester (11 g.) on treatment with 1 equiv. of potassium ethoxide in alcohol–ether, gave the potassium enolate (6·4 g.). This was added gradually to boiling acetic acid (14 c.c.). The solution was poured into excess of cold potassium carbonate solution and extracted four times with ether. On removal of the ether the residue partly crystallised. Recrystallisation (once from benzene–light petroleum, once from ether) gave colourless polyhedra, m. p. 95—96°, of ethyl acetamidomalonate (Found : C, 50·1; H, 7·0; N, 6·4. Calc. for $C_5H_{15}O_5N$: C, 49·8; H, 6·9; N, 6·5%). The filtrate from the preparation of the potassium enolate was made acid to Congo-red with alcoholic hydrogen chloride. After a few days the solution was filtered and evaporated. The residue was distilled at 15 mm. up to a bath temperature of 150°, The distillate partly crystallised on keeping in the air. Recrystallisation from benzene–light petroleum gave the hydrate of ethyl mesoxalate in large colourless plates, m. p. 58—59° (Found : C, 44·0; H, 6·2; N, nil. Calc. for $C_7H_{12}O_6$: C, 43·8; H, 6·3%).

Ethyl 1-ethoxyethylideneaminomalonate (1 g.) was warmed with concentrated sulphuric acid (1 c.c.) to 120°. When effervescence ceased (10 minutes) the light yellow solution was poured into excess of potassium carbonate solution and extracted with ether. The evaporated extract gave a crystalline picrate with aqueous picric acid. Recrystallisation from alcohol gave small, fluffy, yellow needles (40 mg.), m. p. 147—148° (Found : C, 41·9; H, 4·5; N, 17·5. $C_5H_{11}N,C_6H_3O_7N_3$ requires C, 42·0; H, 4·5; N, 17·8%). This *picrate* was obtained in three separate experiments. The m. p. was sharply depressed by piperidine picrate, m. p. 148—149°. In another experiment the evaporated ethereal extract was distilled. The main fraction, b. p. 100—110° (bath)/0·05 mm., solidified and crystallised from ether to give ethyl aceturate, m. p. 44—46° (Found : C, 49·1; H, 7·7. Calc. for $C_6H_{11}O_3N$: C, 49·7; H, 7·7%).

Reaction of Benzimidomethyl Ether with Chloroacetone.—A mixture of the imido-ether (4·5 g.) and the ketone (3·2 g.) was refluxed (oil-bath) for 4 hours. The solution was freed from separated solid (identified as benzamide) and warmed with 2N-sodium hydroxide for ½ hour on the steam-bath. The oil was recovered (ether) and distilled; the fraction, b. p. 80—90°/15 mm., on redistillation gave 2-phenyl-4-methyloxazole (0·7 g.) (Found : C, 75·4; H, 6·2. Calc. for $C_{10}H_9ON$: C, 75·5; H, 5·7%). The chloroplatinate formed light yellow prisms, decomp. at 180° (Lewy, *Ber.*, 1888, **21**, 2193, recorded 170°) The *picrate* separated from aqueous ethanol in fine, light yellow needles, m. p. 143—144°, depressed to 140° when mixed with 2-phenyl-5-methyloxazole picrate (Found : N, 14·4. $C_{10}H_9ON,C_6H_3O_7N_3$ requires N, 14·4%).

Reaction of 2-Amyloxazole-4-carboxylic Acid with Ammonia.—The acid (1·83 g.; 0·01 mole) was heated in a sealed tube with aqueous ammonia (15 c.c.; *d* 0·880) for one hour at 140° and then one hour

at 150°. After removal of most of the ammonia the liquid was extracted with chloroform. The product was distilled (mostly at 275—280°). The higher fractions smelled strongly of amyl cyanide, doubtless from pyrolysis of some by-product. The distillate was converted in good yield into the picrolonate of 2-amylglyoxaline, m. p. 189·5—190·5° from acetone (cf. Cornforth *et al.*, "The Chemistry of Penicillin," Chap. XXI). The aqueous ammoniacal liquor gave no unchanged acid on acidification.

2-Amyloxazole (1·39 g.; 0·01 mole) was heated with ammonia (15 c.c.) under precisely the same conditions as for the acid. On working up, the oxazole was recovered unchanged; there was no indication that any glyoxaline had been formed.

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