218. *Mechanism and Extension of the Fischer Oxazole Synthesis.*

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A reconsideration of the Fischer oxazole synthesis has led to the preparation of 2 : 5-disubstituted oxazoles from aldehydes and α-hydroxy-amides. Unlike the Fischer synthesis (from aldehydes and α-hydroxy-cyanides) the new method is not limited to diaryloxazoles.

Emil Fischer's synthesis of 2 : 5-diaryloxazoles (*Ber.*, 1896, **29**, 205) involves the condensation, in dry ethereal hydrogen chloride, of an aldehyde with an aldehyde cyanohydrin. The oxazoles, $R{-}C_3HON{-}R'$, are regularly accompanied by substances having the composition $R{-}C_3H_3O_2N{-}R'$; these have usually been regarded as Schiff bases (I) of aldehydes with α-hydroxy-amides.

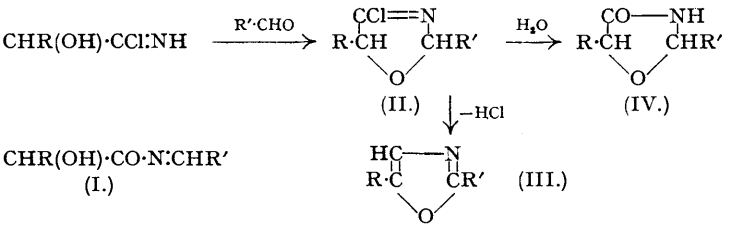
Ingham (*J.*, 1927, 692) studied the reaction of benzaldehyde with mandelonitrile and hydrogen chloride, and showed that when a small proportion of water is added there is only one product, *A* (called benzylidenemandelamide by Ingham), the formation of which can be entirely suppressed by addition of thionyl chloride. He concluded that in the Fischer synthesis compound *A* arises by hydrolysis of an intermediate substance, and suggested a mechanism in which addition of hydrogen chloride to the cyanide was the first step. The resulting iminochloride was presumed to react with benzaldehyde to give CHPh(OH)·CCl:N·CHPh·OH, which could pass to (I; R = R′ = Ph) by hydrolysis and dehydration or to 2 : 5-diphenyloxazole (III; R = R′ = Ph) *via* the intermediate (II; R = R′ = Ph).

The formulation (Michael and Jeanprêtre, *Ber.*, 1892, **25**, 1682) of compound *A* as (I; R = R′ = Ph) was criticised by Staudinger and Ruzicka (*Annalen*, 1911, **380**, 282) who preferred the oxazolidone structure (IV; R = R′ = Ph). It has been shown since that the products obtained by condensing acetone with α-hydroxy-amides are certainly oxazolidones (H. O. L. Fischer, Dangschat, and Stettiner, *Ber.*, 1932, **65**, 1032). We find that compound *A* dissolves easily in aqueous sodium hydroxide, and is recovered on acidification. Acidity in a compound of type (I) would be very surprising, but it is frequently found among cyclic imides.

Moreover, compound *A* is unaffected by boiling with acetyl chloride or with thionyl chloride in ether.

Staudinger and Ruzicka suggested that in the Fischer synthesis the oxazole (III) was produced from the oxazolidone (IV) by loss of water, and there is a paper by Schuster (*J. Pharm. Chim.*, 1936, **23**, 142) which, though ambiguous, appears to suggest that this is actually the case. Compound *A* has now been found to remain unchanged on treatment with ethereal hydrogen chloride; this idea of the mechanism is therefore incorrect.

By adopting the oxazolidone structure for compound *A* it is possible to modify and simplify Ingham's mechanism as follows:



The transformation (II) ⟶ (III) requires the mobilisation of two protons. This would occur more readily, and hence compete more successfully with the simultaneous hydrolysis of (II), if the groups R and R' are aromatic. In fact, the Fischer synthesis has been successfully applied only to aromatic-type aldehydes and their cyanohydrins; Fischer (*loc. cit.*) condensed benzaldehyde with acetaldehyde cyanohydrin and obtained only the so-called benzylidenelactamide, which is soluble in alkali and hence should be regarded as (IV; R = Me, R' = Ph).

This modified view of the synthesis suggested that an oxazolidone (IV) might be converted into an oxazole (III). In fact, compound *A* was found to afford 2 : 5-diphenyloxazole in good yield on being warmed with phosphoryl chloride; the chloro-oxazoline (II) is a likely intermediate. This new oxazole synthesis proved to be of more general application than the Fischer method. Benzaldehyde and lactamide were condensed by boiling in toluene with a little toluene-*p*-sulphonic acid. Fractionation of the acidic product gave a substance apparently identical with that obtained by Fischer and a product which had the same composition but was still not homogeneous. The oxazolidones (IV) should exist in *cis*- and *trans*-forms, and both of these were probably present. The total product on warming with phosphoryl chloride afforded 2-phenyl-5-methyloxazole.

Lactamide and *n*-heptaldehyde were also condensed. The oily acidic product, obtained in poor yield, was converted by phosphoryl chloride into 5-*methyl*-2-n-*hexyloxazole*; somewhat better results were obtained by treating the total condensation product, which was mainly neutral, with phosphoryl chloride. It is possible that, with this oxazolidone, ring-chain tautomerism occurs (I ⇌ IV); such tautomerism has been noted in certain oxazolidines (Cope and Hancock, *J. Amer. Chem. Soc.*, 1942, **64**, 1503; 1944, **66**, 1453).

Experimental.

Stability of Compound A (2 : 5-*Diphenyloxazolid*-4-*one*).—The substance (0·4 g.) was suspended in dry ether (100 c.c.) and dry hydrogen chloride passed in until the solution was saturated. The solid largely dissolved, and after some hours the ether was evaporated. The solid residue had m. p. 194—196° after crystallisation from alcohol, and was unchanged compound *A*. No indication of oxazole formation was found.

2 : 5-*Diphenyloxazole*.—Compound *A* was prepared by passing hydrogen chloride into moist ether containing equimolar amounts of benzaldehyde and mandelonitrile. The product (2 g.; m. p. 190°; not recrystallised) was warmed with phosphoryl chloride (10 c.c.) for half an hour at 85—90°. After phosphoryl chloride had been removed at low pressure the solid residue was triturated with 1% ethereal hydrogen chloride, collected (2·6 g.), and shaken with water and ether. The dried ethereal layer on evaporation left nearly pure 2 : 5-diphenyloxazole (1·5 g.), m. p. 65—67° raised to 70—71° by crystallisation from light petroleum (Found: N, 6·6. Calc. for $C_{15}H_{11}ON$: N, 6·3%). The *picrate* separated from alcohol in small yellow needles, m. p. 172—173° (Found: N, 12·6. $C_{15}H_{11}ON,C_6H_3O_7N_3$ requires N, 12·4%).

Lactamide.—Ethyl lactate (100 g.) and a saturated solution (200 c.c.) of ammonia in methanol were placed in a bottle and kept at 37° for 20 hours. After solvent had been evaporated (finally at 100°/20 mm.), the residue was recrystallised from ethyl acetate, giving lactamide (65·3 g.; 87%), m. p. 73—74°.

2-*Phenyl*-5-*methyloxazolid*-4-*one* (*so-called Benzylidenelactamide*).—Lactamide (5 g.), benzaldehyde (6 g.), and toluene-*p*-sulphonic acid (0·15 g.) in dry toluene (80 c.c.) were heated under reflux in a Soxhlet apparatus (thimble filled with anhydrous potassium carbonate) for 14 hours. Next day the long needles (4 g.) were separated from the toluene, and washed with light petroleum. This product had m. p.

122—125°, and on recrystallisation from water gave Fischer's so-called benzylidenelactamide, m. p. 129—130°, which (m. p. 129—131°) was also obtained from benzaldehyde, lactamide, and ethereal hydrogen chloride. The toluene filtrate was extracted with sodium hydroxide (25 c.c.; 2N.), and the extract treated with charcoal and acidified. The partly oily precipitate was treated again in alkaline solution with charcoal and carefully precipitated by acid. The colourless crystalline product (2·7 g.) softened at 60°; the melt was still turbid at 90° (Found: C, 67·7; H, 6·3; N, 7·6. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2; N, 7·9%). Fractional crystallisation from light petroleum failed to give a homogeneous product.

2-Phenyl-5-methyloxazole.—The above oxazolidone (2 g.; high- or low-melting material) was warmed with phosphoryl chloride (10 c.c) for 15 minutes at 80—85°. Most of the phosphoryl chloride was removed at low pressure; the residue was made strongly alkaline and distilled in steam. The volatile oil, collected by means of ether, was distilled (0·5 g.; b. p. about 245°). It was identified as 2-phenyl-5-methyloxazole by comparison of the picrate, m. p. 145—146° (Found: N, 14·3. Calc. for $C_{10}H_9ON,C_6H_3O_7N_3$: N, 14·7%), with an authentic specimen kindly supplied by Dr. D. F. Elliott.

5-Methyl-2-n-hexyloxazole.—Lactamide (20 g.), *n*-heptaldehyde (40 c.c.), toluene (150 c.c.), and glacial acetic acid (4 c.c.) were heated under reflux for 16 hours in an apparatus which automatically separated water from the condensate. The toluene solution, after being washed with water and aqueous sodium hydrogen carbonate, was concentrated at low pressure, and excess of heptaldehyde removed at 100°/20 mm. The residue (38 g.) was heated with phosphoryl chloride (100 c.c.) at 90—95° for half an hour, and then, after removal of phosphoryl chloride, was steam-distilled from its alkaline solution. The volatile oil (13·5 g.) was distilled, and gave a fraction, b. p. 220—235° (6·4 g.). The crude oxazole (1 g.) was treated with mercuric chloride (1·6 g.) in alcohol (6 c.c.), and water (3 c.c.) was added. The oily precipitate soon crystallised. A sample (1 g.) was purified by dissolution in ether (4 c.c.), slow addition of light petroleum (b. p. 40—60°; 3 c.c.), filtration, and addition of more light petroleum (1 c.c.). *5-Methyl-2-n-hexyloxazole mercurichloride* crystallised in glistening rhombic plates, m. p. 65—67° (Found: C, 27·8; H, 3·8. $C_{10}H_{17}ON,HgCl_2$ requires C, 27·4; H, 3·9%). Steam distillation of the mercurichloride gave the free base, which was collected by means of light petroleum, heated with solid potassium hydroxide, and distilled. The *5-methyl-2-n-hexyloxazole* was a colourless oil of powerful and peculiar odour; b. p. 213°/765 mm.; $n_D^{17°}$ 1·4520 (Found: C, 71·3; H, 10·3. $C_{10}H_{17}ON$ requires C, 71·8; H, 10·2%). The picrate and hydrochloride were oily. A *picrolonate* was obtained by dissolving the base (0·13 g.) and picrolonic acid (0·1 g.) in acetone, concentrating to small bulk, and adding alcohol. The long yellow needles sintered at 62° and melted at 97° (decomp.); they appeared to be solvated (Found: C, 56·5; H, 7·0; N, 14·7. $C_{10}H_{17}ON,C_{10}H_8O_5N_4,C_3H_6O$ requires C, 56·4; H, 6·4; N, 14·3%).

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