659. iso*Oxazolones. Part III.** *Some Reactions of Arylaminomethylene*iso*oxazolidones with Bases.*

By G. Shaw.

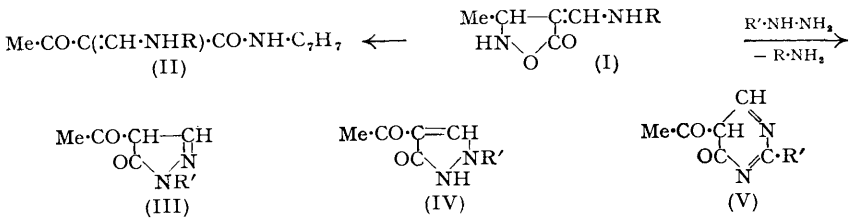
The reaction of arylaminomethylene*iso*oxazolidones (I) with a number of basic substances has been examined. Reaction with *p*-toluidine gave the *p*-toluidide (II); with hydrazines the pyrazolone ketones (III) or (IV); and with aromatic amidines the pyrimidone ketones (V). However, with aliphatic amidines, or more generally with strong bases, a novel rearrangement occurred with formation of the *iso*oxazolidone ketones (VI), and the mechanism of this reaction is discussed. Reaction of either (I; R = *p*-tolyl) or (VI; R = *p*-tolyl) with hydroxylamine was more complex; in each case the same products, namely, *p*-toluidine, the *iso*oxazolone (XI; R″ = *p*-tolyl), and a base $C_{11}H_{14}ON_2$, postulated as a dihydro-1 : 2 : 6-oxadiazine (XII; R = Me, R′ = H, R″ = *p*-tolyl), were isolated.

The preparation and properties of arylaminomethylene*iso*oxazolidones (I) were described in Parts I and II (*J.*, 1950, 720; 1951, 1017). The present paper is concerned with further reactions of these substances with bases.

* Part II, *J.*, 1951, 1017.

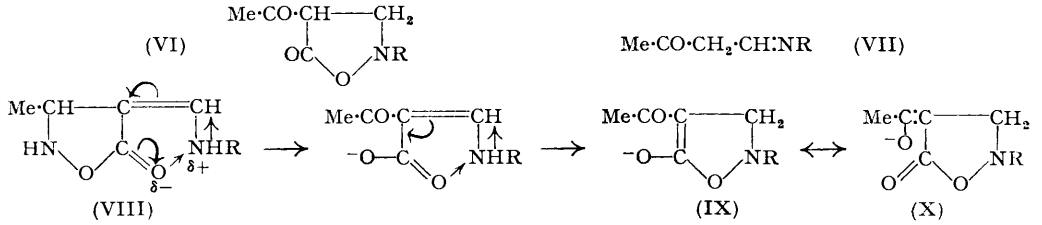
The *iso*oxazolidone (I; R = *p*-tolyl) and *p*-toluidine in hot alcohol gave smoothly the *p*-toluidide (II). This suggested that the *iso*oxazolidones might be used for the synthesis of a variety of heterocyclic systems. Accordingly (I; R = Ph) was treated in boiling ethanol for a short time with hydrazine; ammonia was evolved and an excellent yield of a substance was obtained which may be designated as either of the tautomeric forms (III; R = H) or (IV; R = H) of a pyrazolonyl ketone. The compound, also isolated after reaction of (I; R = *p*-tolyl) and hydrazine, was readily soluble in sodium hydroxide solution and insoluble in sodium hydrogen carbonate solution, and an alcoholic solution gave a reddish-purple colour with ferric chloride. Similarly, reaction of (I; R = Ph or *p*-tolyl) with phenylhydrazine gave a compound of similar solubility behaviour and giving a red colour with alcoholic ferric chloride; this may be formulated as (III or IV; R = Ph). An attempt to oxidise it with sodium hypoiodite solution to either of the known phenylpyrazolones failed.

Analogous reactions occurred rapidly when (I; R = Ph or *p*-tolyl) was heated in boiling ethanol for a short time with benzamidine or *p*-methanesulphonylbenzamidine, giving good yields of the alkali-soluble 2-arylpyrimidones (V; R′ = Ph and *p*-Me·SO_2Ph), the latter being isolated initially as the amidinium salt.



When, however, (I; R = Ph) was heated under reflux in ethanol with aliphatic amidines, including acetamidine, guanidine, and *S*-methyl*iso*thiourea, a smooth reaction occurred with liberation of ammonia but, instead of the expected pyrimidone, a crystalline solid $C_{11}H_{11}O_3N$ was obtained. An analogous substance $C_{12}H_{13}O_3N$ was formed from (I; R = *p*-tolyl) and the amidines. The same compounds were more conveniently prepared by treatment of the *iso*oxazolidones (I; R = Ph and *p*-tolyl) with aqueous or alcoholic sodium hydroxide at room temperature for a few minutes. No reaction occurred, however, with a weak base, *e.g.*, ammonia. The molecular formulæ of these compounds suggested that the arylaminomethylene group had been unaffected during the reaction and this was confirmed by careful alkaline hydrolysis of the substance $C_{12}H_{13}O_3N$ to the ketoanil (VII; R = *p*-tolyl), which on more vigorous hydrolysis gave *p*-toluidine and acetone (cf. Part II, *loc. cit.*). In addition, the compounds were readily soluble in aqueous sodium hydroxide but insoluble in sodium hydrogen carbonate solution, and alcoholic solutions gave red-purple colours with ferric chloride. Thus the compounds may be acetyl*iso*oxazolidones (VI; R = Ph and *p*-tolyl). The mechanism of this novel base-catalysed rearrangement may be as shown below and requires an explanation of the greater reactivity of the *iso*oxazolidones than of analogous *iso*oxazolones (cf. Part II, *loc. cit.*). The activity of the 5-carbonyl group in the *iso*oxazolone ring will be reduced considerably by migrations of the type $-C\overset{\curvearrowright}{=}N\cdot O\cdot C\overset{\curvearrowright}{=}O$ in contrast to the greater activity of analogous oxazolones in which migrations $C\overset{\curvearrowright}{=}N$ increase the positive charge on $C_{(5)}$, *i.e.*, $N\overset{\curvearrowleft}{=}C\cdot O\cdot C\overset{\curvearrowright}{=}O$. In the *iso*oxazolidone system the inhibiting effect of $C\overset{\curvearrowright}{=}N$ is lost, and indeed a small activating effect may be present $CH\cdot\overset{\longleftarrow}{NH}\cdot O\cdot C\overset{\curvearrowright}{=}O$; this results in basicity of the cyclic NH as shown by ready formation of stable hydrochlorides and picrates (cf. Parts I and II, *locc. cit.*). The *iso*oxazolidone system will, however, be stabilised by an exocyclic double bond $NH\cdot O\cdot(C\overset{\curvearrowright}{=}O)\cdot C\overset{\curvearrowleft}{=}C$. In the arylaminomethylene*iso*oxazolidones the movements will be as depicted (VIII), with a slightly positive exocyclic nitrogen atom. Rupture of the ring

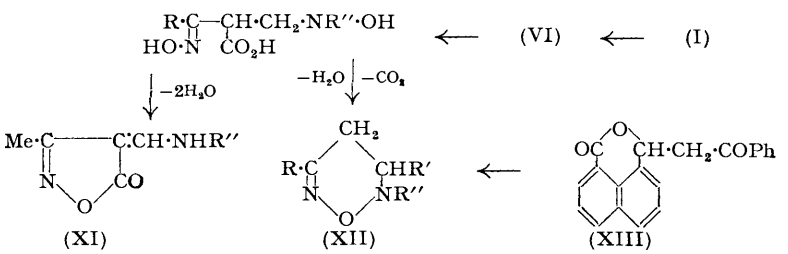
in the presence of a strong base is followed by a prototropic change and formation of the anionic forms (IX and X) of the *iso*oxazolidone ketones, which will be stabilised by movements such as $Me{\cdot}C(O^-){=}C$ and $R{\cdot}N{\cdot}O{\cdot}C{=}O$.



An attempt was made to follow the course of the reaction by titration of the ammonia (or titratable base) formed, the reaction being stopped by addition of excess of acid (a preliminary experiment revealed that the arylaminomethylene*iso*oxazolidone was not sufficiently strong a base to interfere in the titration if methyl-red was used as an indicator). The reaction proceeded too rapidly, however, for an accurate estimation, being substantially complete in aqueous sodium hydroxide at 25° in about 5 minutes.

In an attempt to obtain a thio-analogue of (VI), the reaction of (I; R = *p*-tolyl) with sodium hydrogen sulphide was examined. In alcoholic solution at room temperature, no reaction occurred during several hours, but, when the solution was heated, a vigorous reaction commenced with formation of much dark tar from which only the keto-anil (VII; R = *p*-tolyl) could be isolated.

When the *iso*oxazolidone (I; R = *p*-tolyl) was warmed with 1 equivalent of hydroxylamine in alcohol, ammonia was freely liberated, and from the reaction mixture were isolated *p*-toluidine, 3-methyl-4-*p*-toluidinomethylene*iso*oxazol-5-one (XI; R″ = *p*-tolyl), and a base $C_{11}H_{14}ON_2$. The first product of the reaction appears to be (VI; R = *p*-tolyl) since this gave the same mixture when warmed with hydroxylamine solution. The above-mentioned base, which was colourless, gave a yellow salt with hydrogen chloride: its molecular formula suggests that it may be the dihydro-1 : 2 : 6-oxadiazine (XII; R = Me, R′ = H, R″ = *p*-tolyl) and the mode of formation of such a substance and of (XI) may be as indicated. The only analogous substance recorded is the compound (XII; R = Ph, R′ = 8-carboxy-1-naphthyl, R″ = H) prepared by the reaction of (XIII) and hydroxylamine (Zink, *Monatsh.*, 1901, **22**, 822), a reaction not unlike that between (VI; R = *p*-tolyl) and hydroxylamine. Zink (*loc. cit.*) states that his product gave a yellow colour with hydrochloric acid. The formation of *p*-toluidine is not indicated in the scheme but would occur by the reaction $>C{:}CH{\cdot}NHR + NH_2{\cdot}OH \longrightarrow >C{:}CH{\cdot}NH{\cdot}OH + RNH_2$.



Experimental

α-p-*Toluidinomethyleneacetoaceto*-p-*toluidide* (II; R = *p*-tolyl).—A solution of 3-methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one (0·5 g.) and *p*-toluidine (0·25 g.) in ethanol (10 ml.) was refluxed for 1 hour, then evaporated to small bulk and acidified with dilute acetic acid; α-p-*toluidinomethyleneacetoaceto*-p-*toluidide* (0·45 g.) separated as a yellow solid and crystallised from ethanol–water as pale lemon-yellow needles, m. p. 156° (Found: C, 73·8; H, 6·4; N, 9·05. $C_{19}H_{20}O_2N_2$ requires C, 74·1; H, 6·55; N, 9·1%).

4-*Acetylpyrazol*-3-*one* (III; R′ = H).—3-Methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one

(1 g.) in ethanol (10 ml.) was refluxed with hydrazine (0·32 ml. of a 50% aqueous solution) for 1 hour; ammonia was freely evolved and the clear solution when evaporated *in vacuo* gave 4-*acetylpyrazol*-3-*one* (0·5 g.), which separated from water as colourless needles, m. p. 225° (decomp.) (Found: C, 47·8; H, 4·85; N, 22·3. $C_5H_6O_2N_2$ requires C, 47·7; H, 4·8; N, 22·25%). The same compound was obtained from 4-anilinomethylene-3-methyl*iso*oxazolid-5-one and hydrazine.

4-*Acetyl*-1(or 2)-*phenylpyrazol*-3-*one* (III *or* IV; R′ = Ph).—3-Methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one (1 g.) when similarly treated with phenylhydrazine (0·6 g.) gave 4-*acetyl*-1(or 2)-*phenylpyrazol*-3-*one* (0·7 g.), which separated from water as needles, m. p. 191—192° (decomp.) (Found: C, 65·0; H, 5·2; N, 13·85. $C_{11}H_{10}O_2N_2$ requires C, 65·3; H, 5·0; N, 13·85%).

5-*Acetyl*-2-*phenylpyrimid*-4-*one* (V; R′ = Ph).—Benzamidine hydrochloride hydrate (1 g.) was added to a solution of sodium (0·12 g.) in ethanol (5 ml.), followed by 3-methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one (1·1 g.). The solution was refluxed for 1 hour; ammonia was liberated and the solution became yellow. An equal volume of water was added to the cooled solution, and a small precipitate filtered off. Acidification of the filtrate with acetic acid gave a granular, pale yellow solid; 5-*acetyl*-2-*phenylpyrimid*-4-*one* (0·5 g.) separated from ethanol as white laths, m. p. 237—241° (decomp.) [Found: C, 67·2; H, 4·75; N, 13·1%; *M* (Rast), 210. $C_{12}H_{10}O_2N_2$ requires C, 67·25; H, 4·7; N, 13·05%; *M*, 214].

5-*Acetyl*-2-p-*methanesulphonylphenylpyrimid*-4-*one* (V; R′ = *p*-Me·SO_2Ph).—3-Methyl-4-*m*-toluidinomethylene*iso*oxazolid-5-one (1·1 g.) and *p*-methanesulphonylbenzamidine (1·2 g.) were refluxed together in ethanol (5 ml.), ammonia being evolved. When cooled, the solution deposited the pyrimidone as the p-*methanesulphonylbenzamidinium* salt (0·7 g.), which separated from ethanol as plates, m. p. 259—260° (decomp.) (Found: C, 51·5; H, 4·7; N, 11·25. $C_{13}H_{12}O_4N_2S$,$C_8H_{10}O_2N_2S$ requires C, 51·4; H, 4·5; N, 11·4%). The salt (0·5 g.) readily dissolved in N-sodium hydroxide (5 ml.), and when the solution was acidified with hydrochloric acid a thick crystalline precipitate appeared; 5-*acetyl*-2-p-*methanesulphonylphenylpyrimid*-4-*one* (0·25 g.) separated as laths (from ethanol), m. p. 275—276° (Found: C, 53·5; H, 4·4; N, 9·45. $C_{13}H_{12}O_4N_2S$ requires C, 53·4; H, 4·15; N, 9·6%).

4-*Acetyl*-2-p-*tolyl*iso*oxazolid*-5-*one* (VI; R = *p*-tolyl).—3-Methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one (3·8 g.) in ethanol (80 ml.) was treated with N/20-sodium hydroxide (350 ml.), and the solution kept at room temperature (20°) for 30 minutes; during this time a small amount of crystalline precipitate appeared but soon redissolved. The filtered solution when acidified with 2N-hydrochloric acid gave a mass of white needles; 4-*acetyl*-2-p-*tolyl*iso*oxazolid*-5-*one* (1·5 g.) separated from ethanol as needles, m. p. 151—152° (decomp.) [Found: C, 65·8; H, 5·85; N, 6·35%; *M* (Rast), 229. $C_{12}H_{13}O_3N$ requires C, 65·7; H, 5·9; N, 6·4%; *M*, 233], having the solubility and colour reaction described on p. 3429. The same compound was obtained by reaction of 3-methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one with acetamidine, guanidine, and sodium alkoxides in alcohols, and also in a number of attempted condensations involving the use of sodium alkoxides. When the acetyl*iso*oxazolidone (0·5 g.) was warmed with N-sodium hydroxide (5 ml.) for a short time on the steam-bath, a milky solution was obtained which, when cooled, deposited 4-p-*tolyliminobutan*-2-*one* (VII; R = *p*-tolyl) (0·3 g.); this separated from ethanol–water as laths, m. p. 110—111° (Found: C, 75·2; H, 7·4; N, 7·8. $C_{11}H_{13}ON$ requires C, 75·4; H, 7·5; N, 8·0%). Arylaminomethylene*iso*oxazolones showed no tendency to rearrange in the presence of strong bases; *e.g.*, 3-methyl-4-*p*-toluidinomethylene*iso*oxazol-5-one (1·1 g.) was dissolved in ethanol (10 ml.) containing sodium (0·12 g.), and the solution warmed on the steam-bath for 1 hour then kept overnight. A thick precipitate appeared and was dissolved by addition of an equal volume of water. Acidification of the solution gave the unchanged *iso*oxazolone (0·85 g.) as pale yellow prisms (from ethanol), m. p. 200° (decomp.) unaltered on admixture with an authentic specimen.

4-*Acetyl*-2-*phenyl*iso*oxazolid*-5-*one* (VI; R = Ph).—A solution of 4-anilinomethylene-3-methyl*iso*oxazolid-5-one monohydrate (2·2 g.) in ethanol (10 ml.) containing sodium (0·23 g.) was warmed to 50° for 10 minutes. A yellow turbidity rapidly appeared; the cooled solution was treated with water and a gelatinous precipitate appeared (sodium salt ?); this was dissolved by further addition of water (*ca.* 20 ml. in all). The clear brown solution when acidified with acetic acid deposited a mass of crystals; 4-*acetyl*-2-*phenyl*iso*oxazolid*-5-*one* (1 g.) separated from ethanol as laths, m. p. 123—125° (decomp.) [Found: C, 64·15; H, 5·4; N, 7·1%; *M* (Rast), 202. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4; N, 6·85%; *M*, 205]. The *iso*-oxazolidone in alcoholic solution gave a red colour with ferric chloride.

Reaction of 3-*Methyl*-4-p-*toluidinomethylene*iso*oxazolid*-5-*one with Sodium Hydrogen Sulphide.*

—(*a*) The *iso*oxazolidone (1 g.) was dissolved in a solution of sodium (0·12 g.) in ethanol (15 ml.) which had been saturated with hydrogen sulphide. After 4 hours at room temperature (25°) dilute acid was added to precipitate the unchanged material (0·9 g.), m. p. 184° (decomp.). (*b*) The experiment (*a*) was repeated but the solution was heated on the steam-bath for 1 hour, during which it rapidly became turbid and dark reddish-brown. To the cooled solution was added dilute acetic acid to precipitate a dark tar which was filtered off; the dark brown filtrate, after 2 hours, deposited a crystalline solid (0·4 g.) which separated from ethanol–water as laths, m. p. 110° alone and when mixed with 4-*p*-tolyliminobutan-2-one, m. p. 110—111°. Attempts to isolate crystalline material from the tar were unsuccessful.

Reaction of 3-*Methyl*-4-p-*toluidinomethylene*iso*oxazolid*-5-*one with Hydroxylamine.*—The *iso*-oxazolidone (2·1 g.) was added to a solution of hydroxylamine hydrochloride (0·7 g.) and sodium (0·23 g.) in ethanol (30 ml.); it readily dissolved and an odour of ammonia soon became noticeable. The mixture was gently warmed on the steam-bath, and ammonia was more freely liberated. After 30 minutes, the solution was filtered from sodium chloride, and the filtrate evaporated to dryness *in vacuo*, to give a pale brown oil which had an odour of *p*-toluidine. The oil was stirred with light petroleum (3 × 20 ml.) and when set aside it soon crystallised. The crystalline mass was lixiviated with water (5 ml.) and filtered, to give a pale yellow solid. The latter was treated with dilute sodium hydroxide (5 ml.) and it partly dissolved. The insoluble residue separated from ethanol–water as plates (0·3 g.), m. p. 149—150°, and may be *dihydro*-3-*methyl*-6-p-*tolyl*-1 : 2 : 6-*oxadiazine* (XII; R = Me, R′ = H, R″ = *p*-tolyl) (Found: C, 69·0; H, 7·25; N, 14·9. $C_{11}H_{14}ON_2$ requires C, 69·45; H, 7·4; N, 14·75%). The oxadiazine (0·1 g.) was dissolved in ether (5 ml.), and concentrated hydrochloric acid (1 drop) added, precipitating a yellow solid; this *hydrochloride* (0·08 g.) separated from ethanol–ether as pale yellow plates, m. p. 212° (decomp.) (Found: C, 58·0; H, 6·5; N, 12·0. $C_{11}H_{14}ON_2$,HCl requires C, 58·25; H, 6·65; N, 12·35%). Acidification of the above alkaline solution precipitated 3-methyl-4-*p*-toluidinomethylene*iso*oxazol-5-one (0·25 g.), which separated from ethanol–water as very pale yellow laths, m. p. 198—199° (decomp.) (Found: N, 13·15. Calc. for $C_{12}H_{12}O_2N_2$: N, 12·95%), not depressed on admixture with an authentic specimen, m. p. 200° (decomp.). The light petroleum extract when evaporated to dryness gave an oil which soon crystallised and was largely *p*-toluidine (0·4 g.). The same compounds were isolated similarly from the reaction of 4-acetyl-2-*p*-tolyl*iso*oxazolid-5-one (VI; R = *p*-tolyl) with hydroxylamine.

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