THE CHEMISTRY OF 5-OXAZOLONES

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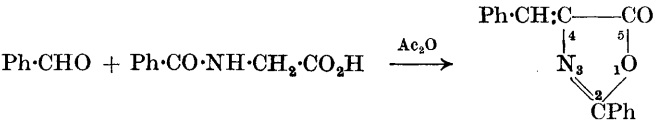
THE condensation of aromatic aldehydes with hippuric acid was discovered in 1883 by Plöchl.[1] This reaction (1) proved to be one of the most satisfactory of general synthetic methods, and its products, the "azlactones", are quite valuable intermediates.

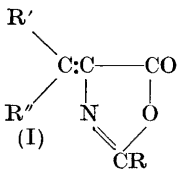


(1)

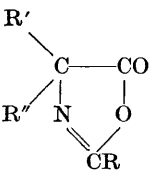
Interest in these derivatives (which can be described as 5-oxazolones), as well as in the related oxazoles and oxazolines, arises from their close relation to the *N*-acylamino-acids, and their importance as intermediates in various syntheses.

During the last war the chemistry of oxazolones made a considerable advance because it was linked to the chemistry of penicillin, for which a structure having an oxazolone moiety was proposed. New methods for the preparation of these compounds have been devised, and their properties thoroughly investigated.

Azlactones are conveniently classified as unsaturated (I) or saturated (II). According to these formulæ, now generally adopted, it is possible to regard



(I)

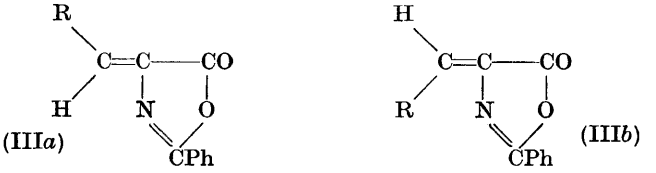


(II)

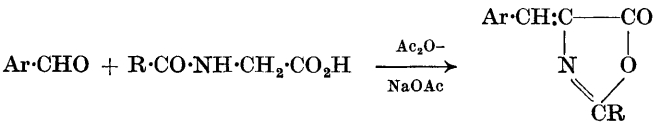
them as the inner anhydrides of the α-acylamino-acids. Different suggestions have been made concerning the structure of these compounds.[2] However, it was Erlenmeyer, with various co-workers, who determined the structure of the unsaturated azlactones,[3] extended the reaction to numerous aldehydes, both aromatic and aliphatic,[4] and established the usefulness of the derivatives as intermediates in the synthesis of α-keto- [5] and α-amino-acids.[4, 6] For this reason, the reaction Plöchl discovered is usually referred to as Erlenmeyer's reaction.

[1] Plöchl, *Ber.*, 1883, **16**, 2815; cf. Carter in "Organic Reactions", J. Wiley & Sons, New York, 1947, Vol. III, p. 198.
[2] Rebuffat, *Ber.*, 1889, **22**, 551c.
[3] Erlenmeyer *et al.*, *Annalen*, 1893, **275**, 1.
[4] *Idem*, *ibid.*, 1899, **307**, 138; 1904, **337**, 271, 283, 294.
[5] *Idem*, *ibid.*, 1892, **271**, 137; 1895, **284**, 36.
[6] *Idem*, *ibid.*, 1893, **275**, 13.

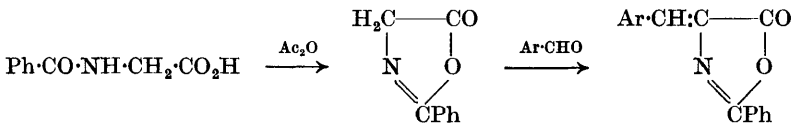
According to the formula (I) geometric isomerism is possible, and the *cis*- and the *trans*-isomers of two substances, benzamido-cinnamic and -crotonic (III*a* and III*b* ; R = Ph or Me) azlactones, have been isolated.[7]



Preparation of Unsaturated Azlactones (I).—The commonest route to unsaturated azlactones is the reaction of an aldehyde with an acylglycine in the presence of acetic anhydride and, usually, fused sodium acetate :



This reaction can be regarded as a special case of the Perkin condensation.[8] Erlenmeyer thought it proceeded in two steps,[5, 9] the intermediate involved being Ar·CH(OH)·CH(NH·COR)·CO$_2$H. However, convincing evidence now indicates that hippuric acid is first converted into its azlactone, which contains an active methylene group, and that the condensation involves the aldehyde and this intermediate :



This view is supported by the following facts : First, the Erlenmeyer reaction occurs under much milder conditions than those required for the Perkin condensation. Secondly, the condensation reaction in azlactone synthesis does not seem to be the limiting step because the yields do not vary as they do in the Perkin reaction. Finally, benzoyl-*N*-methylglycine, which cannot form an azlactone, condenses with aldehydes much less readily than does hippuric acid. Similarly, benzenesulphonylglycine fails to condense with piperonaldehyde. The saturated azlactone from hippuric acid contains a highly reactive methylene group and, most probably, is the intermediate in the formation of the unsaturated azlactones. Indeed, benzaldehyde condenses smoothly with hippuric azlactone.[10]

Aromatic, heterocyclic aldehydes of the most varied types, and unsaturated aldehydes, can be used for this reaction. The yields, especially

[7] Carter and Stevens, *J. Biol. Chem.*, 1940, **133**, 117 ; Carter and Risser, *ibid.*, 1941, **139**, 255 ; cf. Lur'e and Vlodina, *Zhur. fiz. Khim.*, 1952, **22**, 1883.

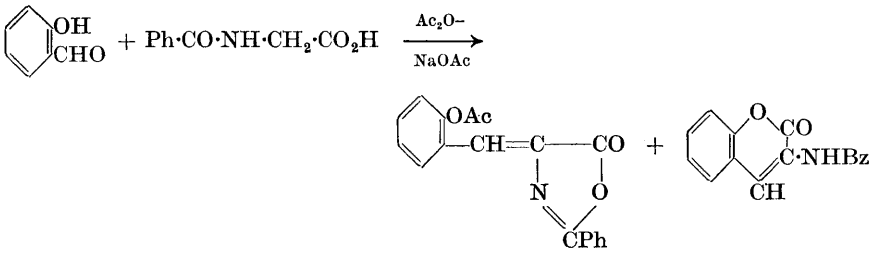
[8] Johnson, " Organic Reactions ", J. Wiley & Sons, New York, 1942, Vol. I, p. 231.

[9] Erlenmeyer, *Annalen*, 1899, **307**, 70.

[10] " Chemistry of Penicillin ", Princeton Univ. Press, N.J., 1949, pp. 732, 783.

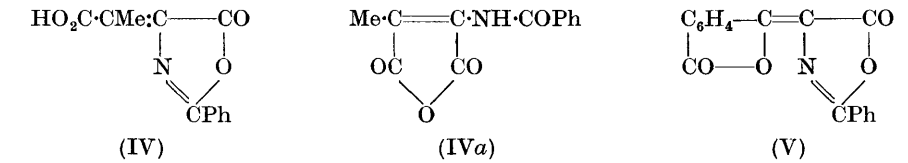
in the aromatic series, are good. However, from the literature, no general conclusions can be drawn regarding the effect of the structure of the aldehyde on the yield of azlactone.

Certain hydroxyaldehydes, such as salicylaldehyde [2, 4] and 2 : 4- [11] and 2 : 5-dihydroxybenzaldehyde,[12] afford, along with the acetoxyazlactone, benzamidocoumarin derivatives :



However, only the azlactone is obtained by reaction of salicylaldehyde with acetylglycine.[13]

Pyruvic acid [14] and phthalic anhydride [3] give, on condensation with hippuric acid, products to which have been assigned respectively the structures (IV) and (V). The structure (IV) has, however, been disproved by new evidence : an anhydride formulation (IV*a*) is more likely to be correct.[15]



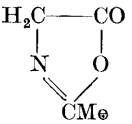
(IV) (IV*a*) (V)

When an acetal is more readily available than the corresponding aldehyde, owing to the instability of the latter, it could possibly be used for formation of the azlactone, as was done in the case of 2-diethoxymethylthiophen.[16] Azlactones can be obtained in good yields from $\alpha\beta$-unsaturated aldehydes which cannot undergo an aldol condensation.[17] Saturated aliphatic aldehydes generally give low yields. It is, however, possible to get fair results with some of them by the use of lead acetate at room temperature.[18] Acetone reacts to give an azlactone.[19] Other ketones were tried without much success, except in the case of *cyclo*hexanone.[20]

[11] Deulofeu, *Ber.*, 1936, **69**, 2456.
[12] Neubauer and Flatow, *Z. physiol. Chem.*, 1907, **52**, 375.
[13] Dakin, *J. Biol. Chem.*, 1929, **82**, 439.
[14] Erlenmeyer and Arbenz, *Annalen*, 1904, **337**, 302.
[15] Ref. 10, p. 772.
[16] Yuan and Li, *J. Chinese Chem. Soc.*, 1937, **5**, 214.
[17] Rodionov and Korolev, *Z. angew. Chem.*, 1929, **42**, 1091.
[18] Finar and Libmann, *J.*, 1949, 2726.
[19] Ramage and Simonsen, *J.*, 1935, 532 ; ref. 10, pp. 462, 783.
[20] Boekelheide and Schramm, *J. Org. Chem.*, 1949, **14**, 298 ; Cook, Harris, and Shaw, *J.*, 1949, 1437.

A very marked improvement, which notably increases the accessibility of a number of azlactones from aliphatic or arylaliphatic aldehydes and ketones, has been attained by carrying out the azlactonisation in boiling tetrahydrofuran and in the presence of lead acetate ; various 4-alkylideneoxazolones have been prepared in good yields by this method.[21]

Different acylglycines have been used for the preparation of azlactones, including those containing the acetyl, benzoyl, phenylacetyl, and galloyl group. Of these, hippuric acid generally gives the best yields and the most stable products. When the azlactone is used as intermediate in the synthesis of an α-keto-acid, acetylglycine is to be preferred to hippuric acid ; the resulting compound can be hydrolysed under milder conditions than one made from hippuric acid, and the acetic acid produced can be separated from the α-keto-acid more readily than can benzoic acid. Various acetates, besides sodium acetate, have been used as catalysts for this reaction, *e.g.*, cupric acetate in the case of thioaldehydes[22] and lead acetate in the case of aliphatic aldehydes.[18, 21] Galat[23] reports better yields by using potassium hydrogen carbonate, or potassium carbonate, and stirring without external heating. Since unsaturated azlactones slowly decompose when heated, and hippuric acid azlactone is not extremely stable, a short reaction time seems often to be desirable. Some variations in the mode of addition of the reactants have been suggested, but they are of doubtful value.



(VI)

The Dakin method[13] is most convenient for the preparation of 2-methyl-5-oxazolones. Glycine in acetic acid is treated with one mol. of acetic anhydride, then the aldehyde, sodium acetate, and more acetic anhydride are added. The acylglycine first formed is not isolated, which is an appreciable advantage. 2-Methyl-5-oxazolones can also be obtained by heating the free amino-acid with the other reactants, but the yields obtained in that way are lower, owing probably to condensation of the aldehyde with the amino-group of glycine. The reported reaction times are longer with acetylglycine than with hippuric acid, and the temperatures higher. Probably 2-methyl-5-oxazolone (VI) either condenses less rapidly with aldehydes than does 2-phenyl-5-oxazolone, or is formed more slowly.

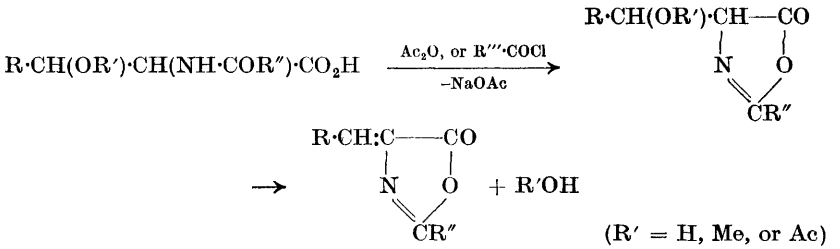
Unsaturated azlactones can also be prepared by another method, which consists in the reaction of an acid chloride, or an acid anhydride, with an α-acylamino-β-hydroxy-acid.[5, 7, 24] The saturated azlactone, which is first formed, has an extremely active α-hydrogen atom, and this splits out with the β-substituent under very mild conditions. Thus, α-benzamido-β-methoxybutyric acid, on short heating with acetic anhydride, yields a mixture of isomeric benzamidocrotonic azlactones.[7]

[21] Baltazzi and Robinson, *Chem. and Ind.*, 1954, 191.

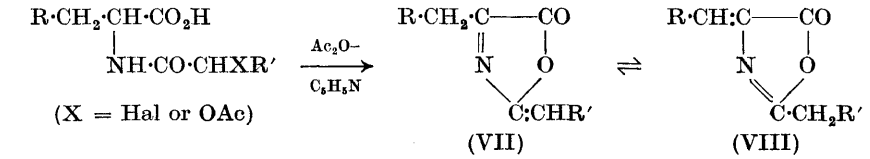
[22] Fischer and Hofmann, *Z. physiol. Chem.*, 1936—7, **245**, 139.

[23] Galat, *J. Amer. Chem. Soc.*, 1950, **72**, 4436.

[24] *Inter al.*, Erlenmeyer and Bade, *Annalen*, 1904, **337**, 222 ; Bettzieche and Mentzer, *Z. physiol. Chem.*, 1927, **172**, 56 ; Carter, Handler, and Melville, *J. Biol. Chem.*, 1939, **129**, 359.



A reaction, which has been used for the synthesis of an α-keto-acid from the corresponding amino-acid, is the conversion of an α-(α′-halogenoacyl)- or α-(α′-acyloxyacyl)-amino-acid into an unsaturated azlactone by means of acetic anhydride and pyridine, either at 0° or at room temperature. Bergmann and Stern [25] suggested the following mechanism :



When alanine, or a β-substituted alanine, is treated with chloro-α-phenylacetyl chloride, it yields a *N*-(chlorophenylacetyl)alanine, or a β-substituted product which, heated with acetic anhydride, affords (VIII) (where R′ = Ph, and R = H, Br, Cl, OMe, OEt, OAc, SMe, SEt, or S·CH_2Ph).[26] These compounds are useful for the preparation of certain derivatives, some of which possess antibiotic properties.

The fact that the same "*pseudo*oxazolone" (best called the 2*H*-form) (VII ; R = H, R′ = Ph) has been obtained either from α-chlorophenylacetylalanine, or from α-phenylacetamidoacrylic acid, suggests that 2*H*-oxazolones are not only intermediates in the Bergmann–Stern synthesis, but also that a dynamic equilibrium between the forms (VII) and (VIII) probably exists. This equilibrium would be influenced by the nature of the substituents of the oxazolone ring : for instance, when R′ is aromatic, the structure (VII) is stabilised because of its greater degree of conjugation. Thus, *N*-(α-bromophenylacetyl)alanine affords 2-benzylidene-4-methyl-2*H*-oxazolone.[27]

When 2*H*-oxazolones are heated with alcoholic hydroxylamine acetate they give solutions showing the colour reactions, with copper acetate and ferric chloride, characteristic of the α-hydroxyimino-hydroxamic acids. True oxazolones do not respond to this test.

The azides of αβ-unsaturated α-benzamido-acids yield unsaturated azlactones on treatment with pyridine or hot alcohol.[28] This method is not applicable to saturated azlactones.

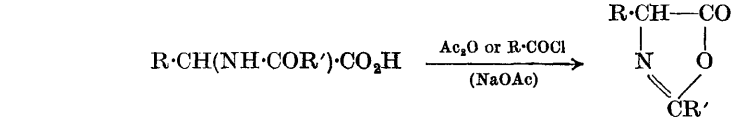
[25] Bergmann and Stern, *Annalen*, 1926, **448**, 20 ; see also Cahill and Rudolf, *J. Biol. Chem.*, 1942, **145**, 201 ; Sheehan and Duggins, *J. Amer. Chem. Soc.*, 1950, **72**, 2475.

[26] Cook, Hook, and Kushner, U.S.P. 2,569,801/1951 ; *Chem. Abs.*, 1952, **46**, 5089.

[27] King and Waley ; Abraham, Baker, and Robinson, ref. 10, p. 793 ; King and McMillan, *J. Amer. Chem. Soc.*, 1950, **72**, 835.

[28] Ref. 10, p. 780.

Preparation of Saturated Azlactones (II).—These compounds are usually obtained from the corresponding α-amino-acids. Mohr and his co-workers were the first to synthesise saturated azlactones by the action of acetic



anhydride on α-acylamino-acids.[29] Bergmann, with various collaborators, used this reaction as an intermediate step in the synthesis of peptides.[30]

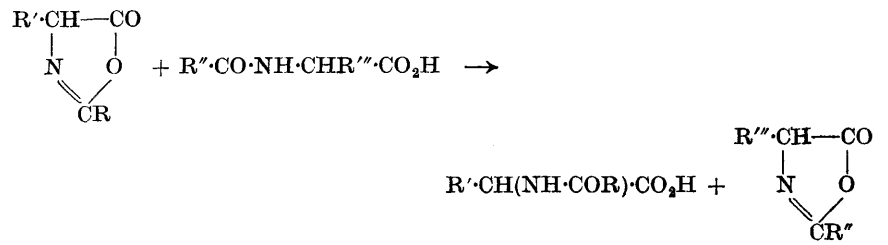
The commonest ways of forming azlactones from α-amino-acids are : (i) The action of an acyl chloride [24] on the sodium salt of a free or acylated amino-acid in aqueous solution and in the presence of a suitable basic catalyst. (ii) The action of an acid anhydride on a free or acylated α-amino-acid.[7, 29, 30] (iii) The action of an acid anhydride or chloride on a pyridine solution of an α-amino-acid.[24, 31]

None of these methods is adequate for the preparation of unsaturated azlactones, because the unsaturated α-acylamino-acids are not readily available, except through the corresponding azlactones themselves. Provided the α-acylaminoacrylic acid is available, the first method gives good yields of unsaturated azlactones. But it is inadequate for the preparation of saturated ones because they undergo hydrolysis under the experimental conditions.

The second method is the most convenient and most generally used for saturated azlactones. Sometimes it is possible to get the azlactone from the corresponding α-amino-acid in one step by heating it with a large excess of acetic anhydride.[7]

The action of silver oxide on thiohippuric acid yields crystalline 2-phenyl-5-oxazolone ; silver benzenesulphonate has been used instead of silver oxide, and 2-benzyl-5-oxazolone has thus been obtained from phenylthioacetylglycine.[32]

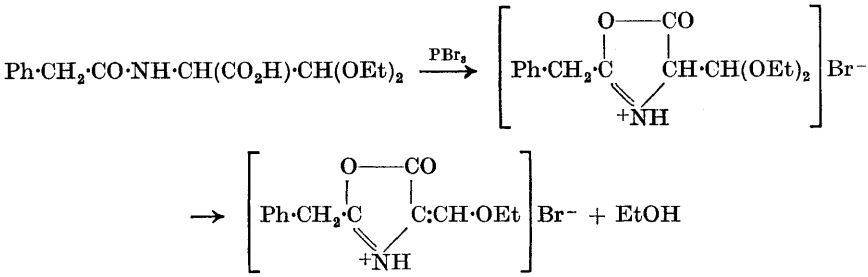
When an α-amino-acid is in the presence of an oxazolone, an equilibrium is attained as follows :



[29] Mohr *et al.*, *Ber.*, 1908, **41**, 798 ; *J. pr. Chem.*, 1910, **81**, 49, 473.
[30] Bergmann *et al.*, *Annalen*, 1926, **449**, 277.
[31] Carter, Handler, and Stevens, *J. Biol. Chem.*, 1941, **138**, 169.
[32] Ref. 10, p. 779.

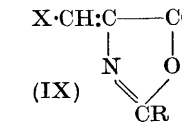
The establishment of an equilibrium of this kind can be used for the preparation of oxazolones. For instance, when *N*-benzoylphenylalanine was warmed with one equivalent of 2-benzyl-4-methyl-5-oxazolone, a good yield of 4-benzyl-2-phenyl-5-oxazolone resulted.[28]

During World War II, the Merck and the May & Baker group made an interesting discovery, that the so-called halides of the acyl-α-amino-acids are in fact oxazolone salts.[33] Karrer and Widmer [34] had already prepared 2-phenyl-5-oxazolone by the action of diazomethane on " hippuryl chloride ". Later, the correct structure of this halide was recognised.[35] It was, for instance, thought that the product of phosphorus tribromide on ββ-diethoxy-α-phenylacetamidopropionic acid was β-ethoxy-α-phenylacetamidoacryloyl bromide. But the same product was obtained from 2-benzyl-4-ethoxymethylene-5-oxazolone with hydrogen bromide. Therefore, it was an oxazolone salt. The following scheme gives the suggested explanation :



Elimination of one molecule of ethanol is characteristic of these compounds.[33]

These facts suggested that any reagent capable of transforming an α-acylamino-acid into its " halide " might be expected to convert it into the corresponding oxazolone. Phosphorus tribromide, phosphoryl chloride, thionyl chloride, acetyl chloride, chloroacetyl chloride, and benzyl chloroformate have been used for this reaction. Most of these reagents give good results in the presence of pyridine or potassium carbonate. Azlactone salts with halogen acids can also be obtained by the reaction of the dry hydrogen halide on the azlactone. They lose the acid either on storage *in vacuo*, or when washed with ether or benzene.



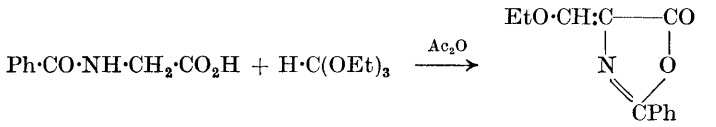
(IX)

The oxazolones obtained in this reaction are represented by formula (IX), where X is attached through an oxygen, nitrogen, or sulphur atom or is halogen, and have played an important part in the penicillin chemistry.[36]

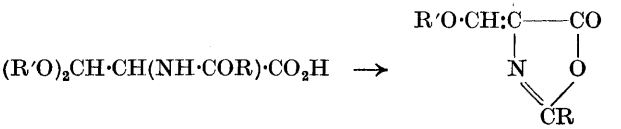
The first method of preparing these compounds, the " orthoformate " method, is an extension of the condensation of orthoformates with active methylene groups, first studied by Claisen.[37] Either hippuric acid and acetic anhydride, or 2-phenyl-5-oxazolone, can be used for the condensation

[33] Ref. 10, p. 911.
[34] Karrer and Widmer, *Helv. Chim. Acta*, 1925, **8**, 203.
[35] Karrer and Bussmann, *ibid.*, 1941, **24**, 645.
[36] Cf. ref. 10, p. 743.
[37] Claisen, *Annalen*, 1897, **297**, 1.

with ethyl orthoformate. Although the overall yields are good, the range of the method is rather limited.



The second, the "penaldate", method is of wider application. It depends in its final stage on removal by dehydrating agents, such as acetic anhydride or phosphorus halides, of the elements of alcohol and water from a penaldic acid:



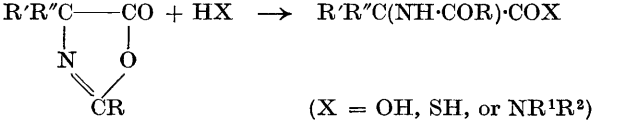
Penaldic acids are prepared by *C*-formylation of an *N*-acylglycine ester followed by conversion into the acetal and hydrolysis, by acylation of *ββ*-diethoxyalanine, or by acylation of an *ββ*-diethoxyalanine ester followed by hydrolysis.

The third method, due to Cook, Hook, and Kushner, has been outlined on p. 154.

Attempts to prepare true 4-formyl oxazolones, with a blocking group (*e.g.*, Br) at the 4-position to prevent enolisation, met with little success.

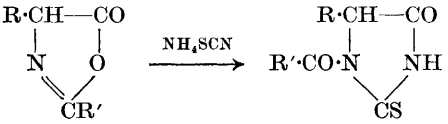
Properties and Chemical Behaviour of Unsaturated and Saturated Azlactones.—As already indicated, azlactones in themselves are of little interest. It is their properties and chemical behaviour which make them most valuable as intermediates.

Unsaturated azlactones are for the most part high-melting solids, light yellow to dark red. Saturated azlactones are colourless liquids or low-melting solids. In many respects both types behave like acid anhydrides and react with compounds containing active hydrogen. They undergo aminolysis, alcoholysis, and hydrolysis, the first being the fastest reaction and the last the slowest. The general pattern of these ring-opening reactions can be formulated:



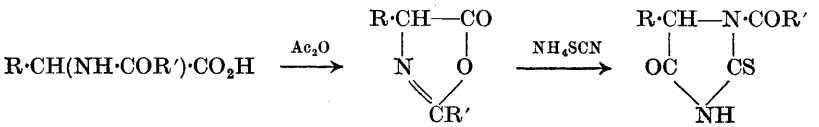
Saturated azlactones, being much more reactive than the unsaturated compounds, are readily alcoholysed and hydrolysed; this is probably the reason why Erlenmeyer failed to isolate them. Unsaturated azlactones on the other hand, with few exceptions, can be recrystallised from ethanol and remain unaffected by long contact with water.

Saturated and unsaturated azlactones behave differently towards ammonium thiocyanate. The first are converted into thiohydantoins, whereas the second remain unaffected.[38]



Saturated azlactones often undergo self-condensation at room temperature, some liquid members being converted into translucent semi-solid waxes, whereas unsaturated azlactones are relatively stable. The nature of substituents in the 4-position has a very marked effect on the self-condensation of unsaturated azlactones. The 2-phenyl-5-oxazolones having two alkyl groups at the 4-position are more stable than those with only one alkyl group in this position, and the least stable is the one that has no such substituent (hippuric azlactone). This suggests that the self-condensation is probably of the aldol type, a view supported by the fact that the hydrogen atoms in the 4-position, being flanked by two unsaturated groups :CO and ·N:C<, are highly reactive.

The lability of these hydrogen atoms accounts also for the fact that optically active substances of this type quickly racemise. Indeed, an optically active azlactone has only recently been isolated. Since an optically active thiohydantoin could be obtained from an optically active α-amino-acid, Csonka and Nicolet [38] thought that, if the reaction had taken the postulated course, an optically active oxazolone must have been present at some time in the solution. Several attempts were made to isolate it. Many failed; only recently, during the penicillin investigations, were some



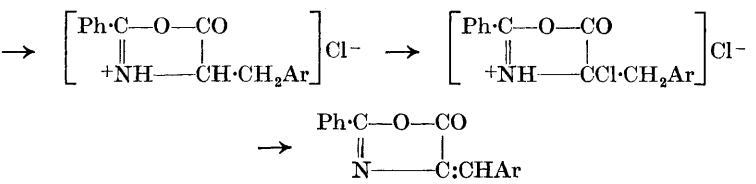
optically active oxazolone isolated.[39] Two experiments were carried out under similar conditions, at room temperature. In one, the azlactonisation of benzoyl-L-leucine with acetic anhydride was followed by measurements of the intensity of absorption at the 2430 Å maximum; in the other, the same reaction in dioxan was followed polarimetrically. It was found that the initial dextrorotation passed rapidly to strong lævorotation; the latter was at a maximum when the ultraviolet absorption showed oxazolone formation to be complete. The rotation then fell steadily, and was finally constant at a small dextrorotation, due probably to some impurity. Dioxan was found to retard racemisation. By the use of this solvent, its subsequent removal, and the washing of the reaction mixture with sodium hydrogen

[38] Johnson and Scott, *J. Amer. Chem. Soc.*, 1913, **35**, 1136; Nicolet, *ibid.*, 1930, **52**, 1192; Csonka and Nicolet, *J. Biol. Chem.*, 1932, **99**, 213.

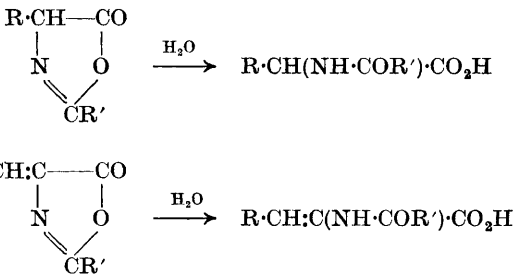
[39] Ref. 10, p. 742.

carbonate, optically active (though partly racemised) 4-*iso*butyl-2-phenyl-5-oxazolone was isolated. This method has been notably improved and optically active oxazolones have thus been prepared nearly pure. It was found that treatment with methanol, benzylamine, or even crystallisation led to rapid racemisation, which explains the previous failures.

Two methods for the racemisation of amino-acids are based on these observations.[40] In the first, the amino-acid is heated in glacial acetic acid with two mols. of acetic anhydride. In the other, the aqueous solution of the sodium salt of the amino-acid is treated with a large excess of this reagent. Both methods yield the racemic acetyl derivative of the amino-acid. Botvinnik and Severin [41] observed recently that *N*-benzoyl-*β*-*m*-methoxyphenyl-L-alanyl chloride (or bromide) exists only momentarily and rearranges rapidly to the corresponding salt of the azlactone, which racemises quickly. On the contrary, the benzyloxycarbonyl and toluene-*p*-sulphonyl derivatives give the normal acid halides with retention of optical configuration.



It is possible to hydrolyse azlactones in presence of acids. However, alkalis are more affective :



The nature of the oxazolone ring has a marked effect on the rate of this reaction, an aryl group in the 2-position having, usually, a stabilising effect on the molecule. Sodium hydroxide in aqueous methanol is very convenient for this hydrolysis ; [7, 42] it converts the azlactone first into the

[40] Bergmann and Koster, *Z. physiol. Chem.*, 1926, **159**, 179 ; Bergmann and Zervas, *Biochem. Z.*, 1928, **203**, 280 ; du Vigneaud and Meyer, *J. Biol. Chem.*, 1932—3, **99**, 143.

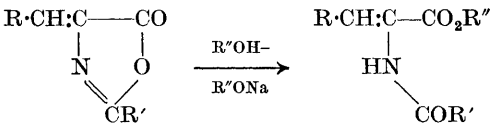
[41] Botvinnik and Severin, *Zhur. fiz. Khim.*, 1950, **20**, 1062.

[42] Schmamfusz and Peschke, *Ber.*, 1929, **62**, 2591 ; Lamb and Robson, *Biochem. J.*, 1931, **25**, 1231 ; Slotta and Soremba, *Ber.*, 1936, **69**, 566.

α-acylamino-ester, which is subsequently hydrolysed. It is less drastic than aqueous alkali, prolonged action of which may hydrolyse the α-acylamino-acrylic acid to the corresponding α-keto-acid. 2-Phenyl-5-oxazolone was found to react so violently with hydroxyl ion that it could be titrated as an acid ; it dissolves rapidly in sodium hydrogen carbonate solution.[43] The 2*H*-oxazolone (VII ; R = H, R′ = Ph) gives phenylacetamide on acid hydrolysis, and α-phenylacetamidoacrylic acid $Ph{\cdot}CH_2{\cdot}CO{\cdot}NH{\cdot}C(:CH_2){\cdot}CO_2H$ on alkaline hydrolysis.[44]

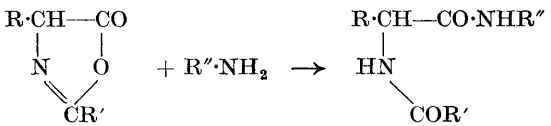
Unsaturated azlactones, with few exceptions, are stable to alcohol. The presence of an acid or a base is needed to effect ring opening. With sodium hydroxide or alkoxide the reaction is complete in few minutes at room temperature.[4, 7, 22, 45]

The product of alcoholysis is the ester of the corresponding α-acylamino-acid. Higher alcohols, in the presence of sodium alkoxide, very rapidly split the azlactone ring, yielding the corresponding ester. Sodium carbonate [46] or neutral sodium acetate [47] also promotes alcoholysis ; with



both a short period of boiling is necessary. Yields range from excellent to quantitative. An interesting exception is 4-ethylidene-2-phenyl-5-oxazolone which fails to undergo alcoholysis, under various conditions, into α-benzamidocrotonate : alcohol probably adds to the double bond at the 4-position. Methanolysis of saturated azlactones gives, besides the normal ester, dipeptides.[43]

When a saturated azlactone is treated at room temperature with ammonia or an amine, either in the pure state or in aqueous or ethanolic solution, a vigorous reaction occurs and the oxazolone ring is opened.[7, 29, 30, 48] The presence of a trace of an amine hydrochloride markedly increases the

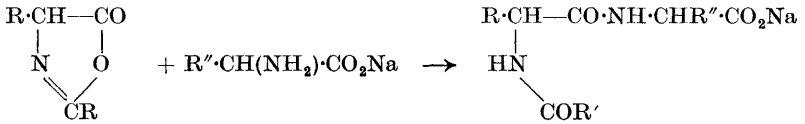


rate of reaction between a saturated azlactone and aniline.[31] Piperidine is reported to open the ring of 4-benzyl-2-phenyl-5-oxazolone rapidly at 100°. Weakly basic amines do not give this reaction.[49] The aminolysis of unsaturated azlactones occurs less rapidly and reactions of this kind are

[43] Ref. 10, p. 734.
[44] Ref. 10, p. 739.
[45] Posner and Sichert, *Ber.*, 1930, **63**, 3078.
[46] Kropp and Decker, *Ber.*, 1909, **42**, 1184 ; King and Stiller, *J.*, 1937, 466.
[47] McDonald, *J.*, 1948, 376.
[48] Lettre and Fernholz, *Z. physiol. Chem.*, 1940, **266**, 37.
[49] Barnes, Campaigne, and Shriner, *J. Amer. Chem. Soc.*, 1948, **70**, 1769.

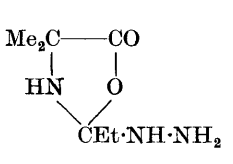
often carried out at 50—100°. Nearly all types of oxazolones react with benzylamine to give benzylamides; and this reaction is used for their determination in mixtures. The course of reaction of (+)-1-phenylethylamine with oxazolones has also been followed polarimetrically.[50]

Aminolysis of azlactones finds an interesting application in the synthesis of polypeptides.[30, 51] For this purpose the azlactone is added to a solution of an amino-acid in aqueous acetone containing an equivalent amount of sodium hydroxide. The method affords excellent results with unsaturated azlactones and in many cases with saturated ones:

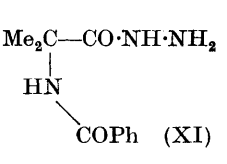


Certain saturated azlactones give better results when heated with the amino-acid in acetic acid solution,[52] and by using the ester of the amino-acid instead of the acid itself, the reaction can be carried out in ether, ethanol or ethyl acetate.[51, 53]

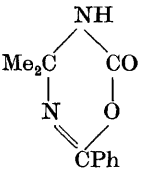
The action of hydrazine on oxazolones has received some attention. Heller and Lauth [54] suggested that the usual product is an oxazolidone (X) and the higher-melting product which they isolated is the usual hydrazide (XI). Wilson, Abraham, Baker, Chain, and Robinson isolated only



(X)



(XI)



(XII)

the lower-melting product which had the properties of a hydrazide.[50] They suggested that the higher-melting product was the diacylhydrazine. Apparently the former workers could not reconcile the normal hydrazide structure with the solubility of the product in alkali. For that there is now ample evidence. Moreover, the hydrazide (XI) gave an azide which, in hot xylene, was converted into a dihydro-2-oxo-1 : 3 : 5-oxadiazine (XII). This, on hydrolysis with aqueous alkali, gave ammonia and sodium carbonate. To quote: "The formation of carbon dioxide consequent on a typical Curtius rearrangement is diagnostic of the site of the hydrazine residue." Vanghelovici, Moise, and Stefanescu [55] stated that certain oxazolones on mild treatment with hydrazine yield addition compounds, whereas

[50] Ref. 10, p. 735.

[51] Bergmann and his co-workers, *Annalen*, 1927, **458**, 40; *J. Biol. Chem.*, 1938, **124**, 321; 1939, **129**, 587.

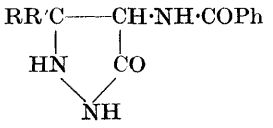
[52] Steiger, *Helv. Chim. Acta*, 1934, **17**, 563.

[53] Granächer and Mahler, *ibid.*, 1927, **10**, 246.

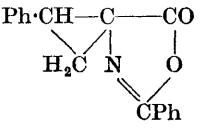
[54] Heller and Lauth, *Ber.*, 1919, **52**, 2302.

[55] Vanghelovici, Moise, and Stefanescu, *Chem. Zentr.*, 1943, II, 1275.

on more vigorous treatment they give the isomeric hydrazide. It has been proved that under mild conditions these oxazolones yield the normal hydrazide which can be converted into the corresponding azide. At a higher temperature they yield a pyrazolidone (XIII), which is also obtained

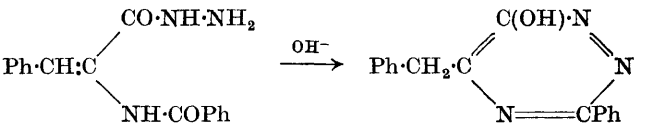


(XIII)



(XIV)

when the hydrazide is heated with alcoholic hydrazine hydrate. The properties of these hydrazides are interesting, particularly the conversion into 1 : 2 : 4-triazines by warm alkali :

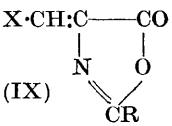


The action of diazomethane on 4-benzylidene-2-phenyl-5-oxazolone yielded a compound which did not add bromine and differed by CH_2 from the starting material. It was considered likely to be the spiran (XIV).[56]

Attempts to make oxazolones react with Grignard reagents have met with little success. 4-Methyl-2-phenyl-5-oxazolone and phenylmagnesium bromide gave a small yield of 2-benzamido-1 : 1-diphenylpropanol ; no ketone was obtained.[57] Potassium cyanate with 4-benzyl-2-phenyl-5-oxazolone in acetic anhydride was found to yield 1-benzamido-1-benzylacetone but no hydantoin.[58] Saturated oxazolones give complexes with silver perchlorate.[59] The reduction of unsaturated to saturated azlactones has been achieved over palladised charcoal.[10]

Reactions of 5-Oxazolones of Type (IX).[60]—This section deals with oxazolones of type (IX) where X is hydroxyl, alkoxyl, or amino. The reactions of these derivatives involve the substituted methylene group or the heterocyclic ring, or both.

(i) *Reactions of the substituted methylene group.* The behaviour of this group resembles that of the α-ethoxymethylene derivatives of ethyl acetoacetate, cyanoacetate, and malonate studied by Claisen.[37] When 4-alkoxymethylene-5-oxazolones are treated with cold dilute alkali, they afford 4-hydroxymethyleneoxazolones which must be regarded not as aldehydes, but as hydroxy-compounds. Indeed, they are strongly acidic, the hydroxyl group behaving like that of a carboxylic acid. Accordingly, 4-alkoxymethyleneoxazolones are considered to be analogues to esters. 4-Hydroxymethyleneoxazolones do not reduce Fehling's solution or ammoniacal silver ; with ferric chloride they give a bluish-green colour extractable by organic solvents.

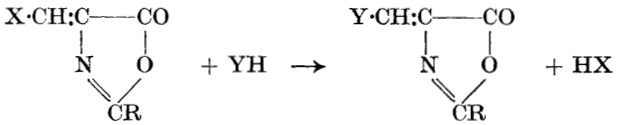


(IX)

[56] Ref. 10, p. 737. [57] Ref. 10, pp. 171, 452. [58] Ref. 10, p. 736.
[59] Ref. 10, p. 792. [60] Cf. ref. 10, p. 747.

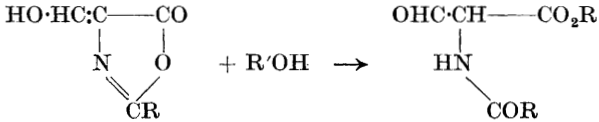
Reaction of 4-alkoxymethyleneoxazolones with ammonia, primary or secondary amines, or amino-acids gives (substituted) 4-aminomethyleneoxazolones which are feebly acidic in accordance with their amide-like character. 4-Aminomethyleneoxazolones can also be prepared from 4-hydroxymethyleneoxazolones although this is, generally speaking, a less easy route. Reconversion of 4-aminomethyleneoxazolones, unsubstituted at the amino-group, into the corresponding hydroxymethylene derivatives has been effected by cold dilute alkali. It is also possible to replace the alkoxy-group of 4-alkoxymethyleneoxazolones by other alkoxy- or alkylthio-groups.

The replacement reactions of the heteromethyleneoxazolones can, with few exceptions, be summarised as follows :



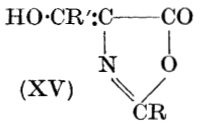
In some cases when a bifunctional reagent is used, *e.g.*, hydrogen sulphide or *p*-phenylenediamine, bifunctional replacement takes place.

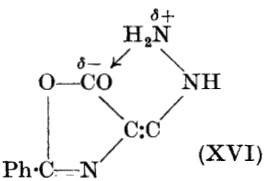
(ii) *Reactions involving the oxazolone ring.* They are similar to the general ring-opening reactions of the 5-oxazolones described above. Thus, 4-hydroxymethylene-5-oxazolones with alcohols form esters of penaldic acids :



However, the behaviour of these oxazolones is more complicated because the substituted methylene and the carbonyl group compete for nucleophilic reagents. According to the nature of the oxazolones, the reagent, and the conditions, the methylene group, the oxazolone ring, or both, react. The oxazolone ring is sometimes stabilised by the substituent in the 4-position which is often attacked preferentially.

4-Hydroxyalkylidene-5-oxazolones (XV) have been prepared and their general behaviour is found, with some discrepancies, similar to that of the 4-hydroxymethyleneoxazolones.



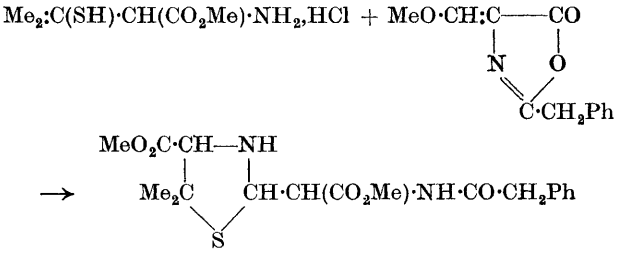


An interesting phenomenon of chromoisomerism has been observed with 4-aminomethyleneoxazolones containing hydrazino-, acetamidino-, and guanidino-groups. The deeper-coloured varieties of these compounds are

considered to be *cis* chelated forms, *e.g.*, (XVI), in which the electronic surplus is to be regarded as shared by the oxazolone ring as a whole. The *trans*-varieties are the more stable.[61]

(iii) *Reactions with penicillamine and similar substances.* The possibility of a penicillin synthesis involving condensation of penicillamine with one of these oxazolones has been investigated. However, most of the experiments in that line led to no definite results, because the hydroxymethylene oxazolones do not give thiazolidines smoothly in the manner of normal aldehydes.

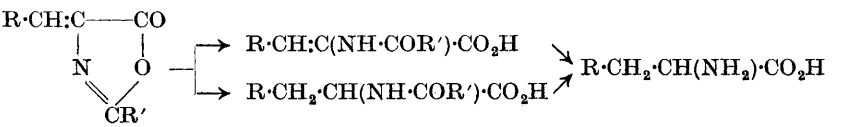
An interesting reaction is the preparation of penicillinates from β-mercapto-α-amino-acids and 4-alkoxy- or 4-hydroxy-methyleneoxazolones under such conditions that concomitant opening of the oxazolone ring occurs. For instance, the reaction of penicillamine methyl ester hydrochloride with 2-benzyl-4-methoxymethylene-5-oxazolone in pyridine afforded 4-methoxycarbonyl-2-(α-methoxycarbonyl-α-phenylacetamidomethyl)-5 : 5-dimethylthiazolidine (XVII).[62]



(XVII)

Importance of 5-Oxazolones as Intermediates.—A variety of compounds can be prepared from 5-oxazolones.

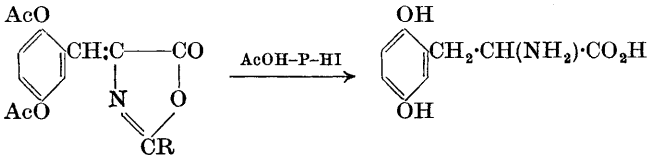
Reduction of unsaturated azlactones or of α-acylaminoacrylic acids affords α-amino-acids :



Erlenmeyer [6] first succeeded in reducing the α-benzamidoacrylic acid with 3% sodium amalgam, and his method has been improved by Fischer [6] and by Deulofeu.[64] Sodium and ethanol has also been used but hydrolyses a considerable part of the product to the free α-amino-acid.[65] Hydriodic acid (*d* 1·7) and red phosphorus, in the presence of acetic acid, or anhydride give excellent results in such cases where an alkaline medium cannot be

[61] Ref. 10, p. 758.
[62] Ref. 10, p. 922.
[63] Fischer, *Ber.*, 1899, **32**, 3638.
[64] Deulofeu, *Anales Soc. españ. Fís. Quím.*, 1934, **32**, 152.
[65] Ellinger and Flamand, *Ber.*, 1907, **40**, 3029.

used (*e.g.*, in the synthesis of thyroxine [66]). The method yields the free amino-acid directly, and the alkyl phenyl ether or phenyl ester linkages are cleaved at the same time:

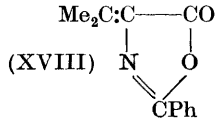


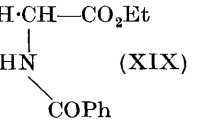
The corresponding acrylic acid or ester usually gives better results than the oxazolone itself. Catalytic reduction, except when other reducible or catalyst-poisoning groups are present, seems to be a satisfactory procedure. The four methods outlined above provide, therefore, a route to an α-amino-acid from an aldehyde with two carbon atoms less.

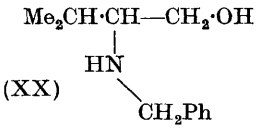
When reduced by lithium aluminium hydride in tetrahydrofuran at − 65° to − 30°, 4-arylidene-2-phenyloxazolones undergo fission, yielding substituted benzamidocinnamyl alcohols Ar·CH:C(NHBz)·CH_2·OH, a molecular type which was hitherto unknown and for which it would be difficult to devise an alternative synthesis.

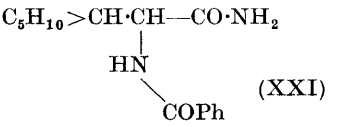
Acid hydrolysis of these alcohols would be expected to afford keto-alcohols, Ar·CH_2·CO·CH_2·OH, and in certain cases the corresponding 2 : 4-dinitrophenylosazones have been isolated. Catalytic hydrogenation saturates the double bond in the benzamidocinnamyl alcohols, but treatment with 20% hydrochloric acid at 60—70° effected hydrolysis and rearrangement to Ar·CH_2·CO·CH_2·OBz, probably by way of an oxazolidine intermediate.[67]

The 4-*iso*propylidene derivative (XVIII) is reduced at the double bond by lithium aluminium hydride under the experimental conditions used in the previous cases. The excess of reagent is decomposed by the addition of ethyl acetate, and the ethanol that is produced reacts with the saturated azlactone to form the ester (XIX) in excellent yield. On further reduction with the same reagent, the base (XX) was obtained in 90% yield.[68]









The corresponding 4-*cyclo*hexylidene derivative, when reduced under the same experimental conditions, gives the amide (XXI). Here, aminolysis

[66] Harington *et al.*, *Biochem. J.*, 1927, **21**, 168, 852; *J.*, 1949, 1374; cf. Baltazzi and Davis, *Compt. rend.*, 1955, **240**, 208.

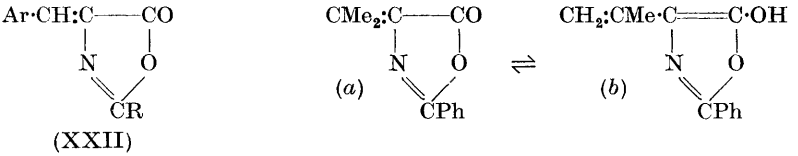
[67] Baltazzi and Robinson, *Chem. and Ind.*, 1953, 540.

[68] *Idem, ibid.*, p. 868.

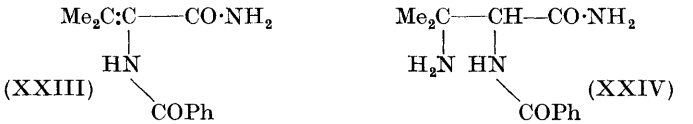
of the saturated azlactone first produced is carried out by the saturated aqueous solution of ammonium chloride used for hydrolysing the lithium aluminium complex. 4-Propylidene-, 4-*iso*butylidene-, and 4-ethoxymethylene-oxazolones give condensation products under the same experimental conditions,[69] as does 2-benzylidene-4-methyl-2*H*-oxazolone.[70]

The conversion of the oxazolone (XVIII) into the ester (XIX) has also been effected by potassium borohydride in aqueous alcohol.[68]

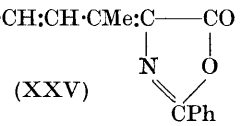
This contrast in behaviour between 4-arylidene- and 4-alkylidene-2-phenyloxazolones is perhaps due to the fact that in the former type the double bond is a middle member of a conjugated system (XXII) (cf. the stability of the diarylpolyenes). A further difference in structure is the potential



tautomerism ($a \rightleftharpoons b$). Indeed, 2-phenyl-4-*iso*propylidene-5-oxazolone has some remarkable properties associated with the double bond.[71] With liquid ammonia it gives the amide (XXIII) and a basic substance, possibly (XXIV).



It condenses with benzaldehyde to yield (XXV). Bromosuccinimide substitutes a methyl group. All this behaviour illustrates the activation of a methylene by a carbonyl group through a double bond (crotonoid system),



often associated with the existence of a pseudoacidic character. 2-Phenyl-4-*iso*propylidene-5-oxazolone exhibits a weak fluorescence in triethanolamine solution; on addition of sodium methoxide to its alcoholic solution an intense blue fluorescence is observed in ultraviolet light, which disappears when the oxazolone is converted into the corresponding ester. This behaviour is attributed to the propenyloxazole form.

The alcohol (XXVI) has been obtained from the oxazolone (XVIII) in two steps, *viz.*, alcoholysis to the acrylate, and then reduction, the acrylate double bond being less reactive than that of the oxazolone. When, after treatment of the same oxazolone with lithium aluminium hydride, decom-

[69] Baltazzi and Robinson, unpublished results.
[70] Baltazzi and Waley, unpublished results.
[71] Ref. 10, p. 738.

position of the excess of reducing agent is carried out with an aqueous solution of glycine ethyl ester hydrochloride, the peptide (XXVII) was

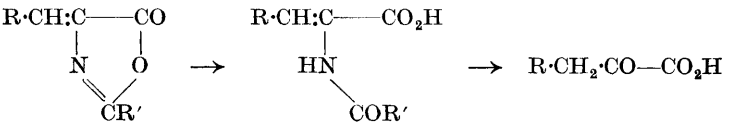
$Me_2C{:}C(NHBz)\cdot CH_2\cdot OH$ (XXVI)

$Me_2CH\cdot CH(NHBz)\cdot CO\cdot NH\cdot CH_2\cdot CO_2Et$ (XXVII)

$Me_2CH\cdot CO\cdot CH_2\cdot OBz$ (XXVIII)

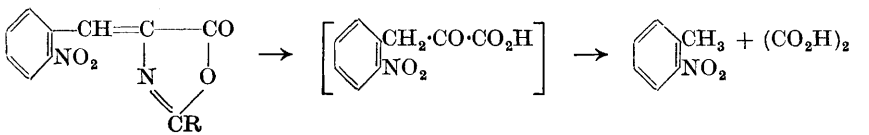
obtained. *N–O*-Transbenzoylation is not confined to the aromatic series ; the unsaturated alcohol (XXVI) afforded the ester (XXVIII) on short treatment with boiling 20% hydrochloric acid.[69] 2-Phenyl-4-*iso*propylidene-5-oxazolone reacts with alcoholic sodium hydrogen sulphide to yield, probably, 2-phenyl-4-*iso*propylidene-5-thiazolone.

Unsaturated azlactones and α-acylamino-acrylic acids are converted by strong acids or alkalis into α-keto-acids. Concentrated hydrochloric acid, or sodium, potassium, or barium hydroxide in aqueous or alcoholic solution, are usual agents for this conversion :



γ-Methylthio-α-oxobutyric acid has thus been prepared from α-bromopropionyl-DL-methionine.[25] There is evidence that fission of the α-benzamidoacrylic acid occurs between the acrylic acid residue and the nitrogen atom, resulting in the formation of the α-keto-acid and benzamide. The latter has, in fact, been isolated.[5] However, hydrolytic cleavage between the benzoyl group and the nitrogen atom cannot be completely excluded. Both reactions probably occur and their relative rates may be influenced by the various substituents in the azlactone molecule. The 2-methyl derivatives are converted more readily into the corresponding α-keto-acids, and by the use of these compounds the separation of benzoic acid from the reaction mixture, often a troublesome procedure, is avoided. An excellent method of obtaining α-keto-acids from 2-methyl-5-oxazolones proceeds in two steps : first, alkaline hydrolysis to the α-acetamidoacrylic esters, then acid hydrolysis with dilute hydrochloric acid.[72]

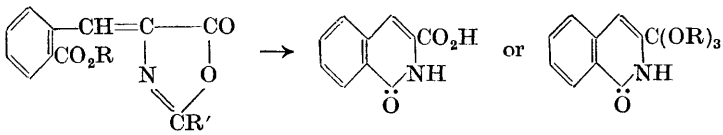
Certain *ortho*-substituted, namely, 2-nitro- and 2-alkoxycarbonyl-benzylideneoxazolones, behave abnormally on alkaline hydrolysis. The unsubstituted 2-nitrobenzylideneoxazolone yields *o*-nitrotoluene. The reaction probably proceeds through the following steps, accounted by vinylogous activation of the methylene group by the *o*-nitro-substituent :



[72] Niederl and Ziering, *J. Amer. Chem. Soc.*, 1942, **64**, 885.

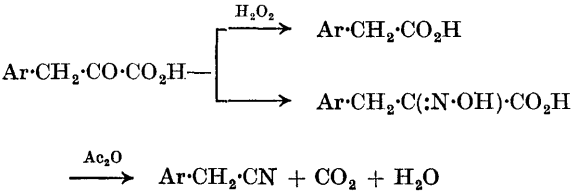
When the *o*-nitrobenzylideneoxazolones have a methoxy-substituent *ortho* to the nitro-group, the final products are isatin derivatives.[73] These two types of decomposition can be avoided by the use of ethanolic hydrochloric acid.[74]

When refluxed with 10% aqueous potassium hydroxide, *o*-alkoxycarbonylbenzylideneoxazolones are converted into derivatives of *iso*carbostyril-3-carboxylic acid.[46, 75] The corresponding orthoester is obtained when the reaction is carried out in methanol or ethanol.[76]



Various other abnormal hydrolyses of less interest have also been reported: *e.g.*, decomposition of certain substituted azlactones, other than those with *o*-nitrobenzylidene substituents, into toluene derivatives;[77] and formation of naphthalene and 1-naphthoic acid from cinnamylideneoxazolone on treatment with hydrochloric acid.[4]

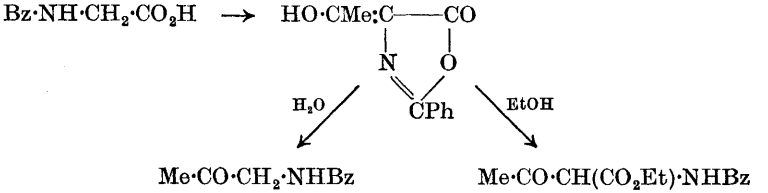
The α-keto-acid, resulting from the hydrolysis of an azlactone, can be oxidised with hydrogen peroxide directly in the reaction mixture, to yield the corresponding arylacetic acid.[78] Dehydration and decarboxylation of the oximes of α-keto-acids with acetic anhydride result in the formation of the corresponding arylacetonitriles.[74, 79]



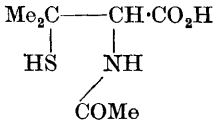
Esters of α-acylamino-β-keto-carboxylic acids and α-acylamino-ketones can also be obtained *via* azlactones. Thus, when sodium hippurate is treated with acetic anhydride in the presence of β-picoline, it gives 4-1′-hydroxyethylidene-2-phenyl-5-oxazolone. Benzamidoacetone and ethyl α-benzamidoacetoacetate are obtained from this compound in nearly quanti-

[73] Burton and Stoves, *J.*, 1937, 402.
[74] Avenarius and Pschorr, *Ber.*, 1929, **62**, 321.
[75] Bain, Perkin, and Robinson, *J.*, 1914, **105**, 2392.
[76] Stiller, *J.*, 1937, 473.
[77] Mauthner, *J. pr. Chem.*, 1917, **95**, 55; Forster, Robertson, and Healey, *J.*, 1939, 1594; Henze, Whitney, and Eppright, *J. Amer. Chem. Soc.*, 1940, **62**, 565.
[78] Snyder, Buck, and Ide, "Organic Syntheses", 1943, Coll. Vol. II, p. 333.
[79] Baker and Robinson, *J.*, 1929, 152, *et al.*

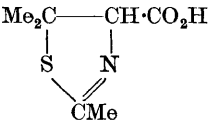
tative yield, the first by boiling water, and the second by boiling absolute ethanol.[80]



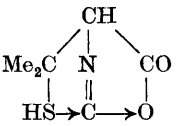
Hydrogen sulphide adds to 2-methyl-4-*iso*propylidene-5-oxazolone in methanol to give *N*-acetyl-DL-penicillamine (XXIX), and another compound which could be converted into *N*-acetyl-DL-penicillamine by heating its aqueous solution. The second of these primary compounds is considered to be 2 : 5 : 5-trimethylthiazoline-4-carboxylic acid (XXX); addition of hydrogen sulphide to the double bond is probably followed by a displacement, as shown in (XXX*a*).[81] When *N*-chloroacetyl-DL-*iso*leucine is heated with



(XXIX)

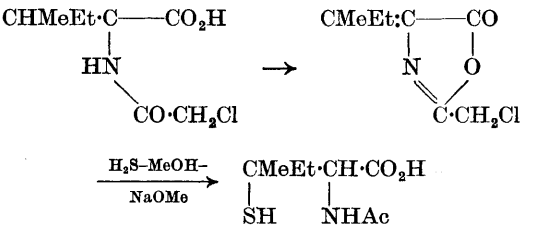


(XXX)



(XXX*a*)

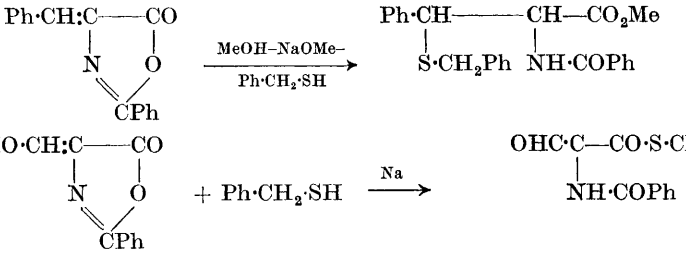
acetic anhydride at 55—60°, 2-methyl-3-1′-methylpropylidene-5-oxazolone is formed, which with sodium methoxide in methanol saturated with hydrogen sulphide affords *N*-acetyl-*β*-ethyl-*β*-methyl-DL-cysteine in excellent yield.[82]



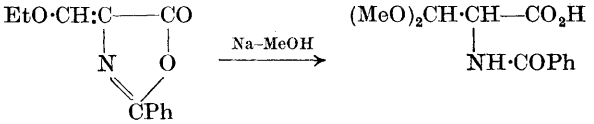
Similarly, when the corresponding unsaturated azlactone is treated with toluene-*ω*-thiol it gives a nearly quantitative yield of *N*-benzoyl-*S*-benzyl-*β*-phenylcysteine methyl ester.[83] Treatment of 4-hydroxymethylene-2-phenyl-5-oxazolone with toluene-*ω*-thiol affords benzyl phenylthiopenaldate in quantitative yield.[84]

α-Acylamino-*ββ*-dialkoxy-carboxylic acids can be obtained in almost

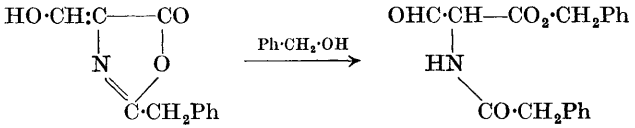
[80] Attenburrow, Elliott, and Penny, *J.*, 1948, 310.
[81] Crooks, Jun., *op. cit.*, pp. 455, 737.
[82] du Vigneaud, Stacy, and Todd, *J. Biol. Chem.*, 1948, **176**, 907.
[83] Cook, Harris, and Heilbron, *J.*, 1948, 1060.
[84] Brown, *op. cit.*, p. 516.



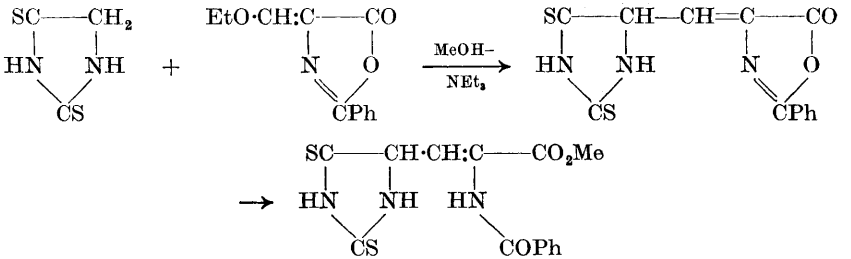
quantitative yield from the corresponding 4-alkoxymethyleneoxazolones by means of sodium in absolute methanol.[85] 2-Benzyl-4-hydroxymethylene-



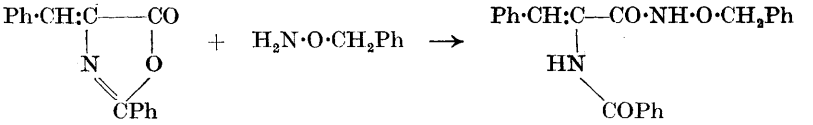
oxazolone affords benzyl benzylpenaldate on treatment with benzyl alcohol in boiling benzene.[86]



An interesting methine condensation was carried out with thiohydantoin and 4-ethoxymethylene-2-phenyloxazolone in the presence of triethylamine in methanol,[87] *viz.*:

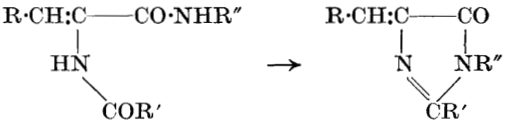


Esters of hydroxamic acids have also been prepared from azlactones. 4-Benzylidene-2-oxazolone, treated with *O*-benzylhydroxylamine in boiling ether–chloroform, yielded benzyl α-benzamidocinnamohydroxamate.[88]



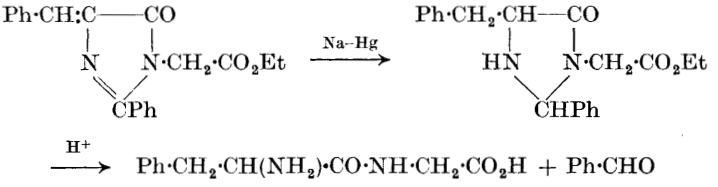
[85] Schulz, *Ber.*, 1952, **85**, 249.
[86] Brown, *op. cit.*, p. 508.
[87] Davis and Levy, *J.*, 1949, 2179.
[88] Shaw and McDowell, *J. Amer. Chem. Soc.*, 1949, **71**, 1691.

4 : 5-Dihydro-5-oxoglyoxaline derivatives are prepared from the amides of the α-acylaminoacrylic acids under a variety of conditions.[4, 53] The ring closure is attained by the action of sodium hydroxide or phosphorus oxychloride, or by heating the acid above its melting point, depending on the



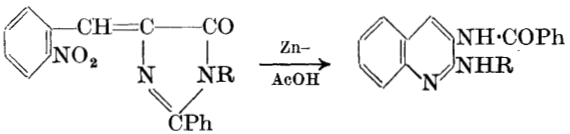
nature of the substituents. Direct conversion of an oxazolone into a dihydro-oxoglyoxaline has also been achieved with aqueous-alcoholic ammonia and potassium [89] or sodium carbonate.[23]

Certain glyoxaline derivatives have been converted into dipeptides, according to the following scheme : [53]

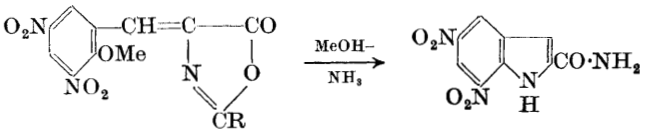


N-(α-Benzamido-ββ-dimethylacryloyl)-β-alanine has been obtained from 2-phenyl-4-*iso*propylideneoxazolone and β-alanine in aqueous acetone in the presence of sodium hydroxide.[90] Saturated azlactones react with cysteine (as the sodium salt) in aqueous acetone, to yield *N*-acyldipeptides, *i.e.*, in the same manner as simple α-amino-acids.[91]

Dihydro-oxoglyoxalines from 4-*o*-nitrobenzylidene-5-oxazolones give substituted diaminoquinolines on reduction with zinc and acetic acid : [92]



Hill and Robinson obtained an indole derivative from a substituted azlactone : [93]

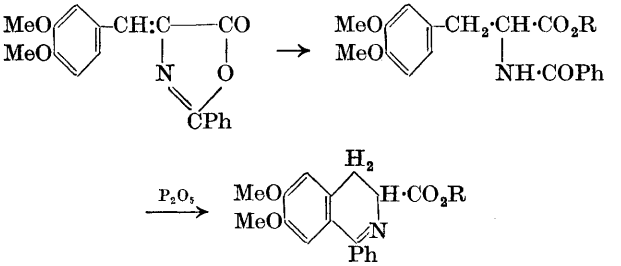


[89] Williams and Ronzio, *ibid.*, 1946, **68**, 647.
[90] Lipton and Strong, *ibid.*, 1949, **71**, 2364.
[91] Ref. 10, p. 214.
[92] Narang and Ray, *J.*, 1931, 976.
[93] Hill and Robinson, *J.*, 1933, 486.

When α-benzamidocinnamic acids are heated with copper chromite in quinoline at 120—180°, decarboxylation occurs and a styrylamide is obtained. This reaction has been used as an intermediate step in the synthesis of substituted *iso*quinolines : [94]

$$Ar{\cdot}CH{:}C(NHBz){\cdot}CO_2H \longrightarrow Ar{\cdot}CH{:}CH{\cdot}NHBz$$

Another route to *iso*quinolines from azlactones is outlined in the following scheme : [95]

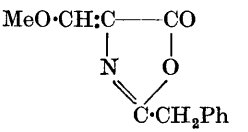


Reduction of 2-benzylidene-4-methyl-2*H*-oxazolone in ethyl acetate over Raney nickel afforded 2-benzyl-4-methyl-5-oxazolone, whereas methyl phenylacetamidopropionate was obtained when the reaction was carried out in methanol.[44]

Minute amounts of synthetic benzylpenicillin in the form of its triethylammonium salt have been obtained by the reaction of D-penicillamine hydrochloride (XXXI) with 2-benzyl-4-methoxymethylene-5-oxazolone (XXXII).[96]

$Me_2{:}C(SH){\cdot}CH(NH_2,HCl){\cdot}CO_2H$

(XXXI)



(XXXII)

Physiological Effects of Oxazolones.—Various oxazolones were found to provoke allergic phenomena such as skin eruptions and general malaise. 2*H*-Oxazolones are strong irritants and must be handled with care.

Infrared and Ultraviolet Absorption of Oxazolones.[97]—The infrared and ultraviolet absorption of a great number of these compounds have been studied.

Infrared spectra have been measured with special reference to the frequencies due to the C=N and C=O groups of the oxazolone ring. Two intense bands corresponding to these groups appear between 1600 and

[94] Sugasawa, *J. Pharm. Soc. Japan*, 1935, **55**, 224 ; Sugasawa and Kakemi, *ibid.*, p. 1283.

[95] Hardwood and Johnson, *J. Amer. Chem. Soc.*, 1934, **56**, 468 ; Redel and Bouteville, *Bull. Soc. chim. France*, 1949, 443.

[96] Du Vigneaud, Carpenter, Holler, Livermore, and Rachele, *Science*, 1946, **104**, 431.

[97] Ref. 10, pp. 387, 758 ; cf. Bennett and Hoerger, *J. Amer. Chem. Soc.*, 1952, **74**, 5975.

1830 cm.$^{-1}$. When no conjugated substituents are attached to the oxazolone ring the C=N and C=O frequencies are found respectively at 1670 and 1820 cm.$^{-1}$. These values, especially the latter, are influenced by the attachment of functional groups, particularly of an exocyclic double bond at the 4-position. When such is the case, a large fall in the frequency of the carbonyl group occurs. However, other electronic or charge transfers might influence the position of these bands.

Saturated azlactones (II), unless the 2-substituent is an aryl or a similar group, show only end absorption in the ultraviolet. Unsaturated azlactones (I) exhibit characteristic absorption bands of high intensity in the region 2600—3600 Å. The longest wavelengths are found when R is aryl and when R′ is attached through an oxygen or, particularly, a nitrogen or sulphur atom.