554. *Some Consequences of the Additive Property of the Activated Azomethine Group.*

By W. Davies, T. H. Ramsay, and E. R. Stove.

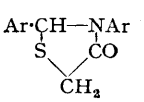
The additive property of *N*-acylated diphenylketimines accounts for the formation of 3-hydroxy-3-phenylphthalimidine (IX; R = Ph) by the permanganate oxidation of 1-phenyl-*iso*quinoline. The oxidative degradation of *iso*quinoline to form phthalimide is explained similarly. The additive property of the activated azomethine group renders Fischer's formula $CHPh{:}N{\cdot}CO{\cdot}CHR_1{\cdot}OH$, for "benzylidenelactamide" and "benzylidenemandelamide" improbable, and it has now been proved that these compounds are substituted oxazolidines. Similarly the condensation of benzaldehyde with the thioglycollamide gives 2-*phenylthiazolid*-4-*one* (XXI), and not $CHPh{:}N{\cdot}CO{\cdot}CH_2{\cdot}SH$. The oxazolidine and the thiazolidine structure of other, related compounds are discussed.

It has been shown by Banfield, Brown, Davey, Davies, and Ramsay (*Austral. J. Sci. Res.*, 1948, **1**, *A*, 330) that formation of crystalline addition products with alcohols, amines, and thiols is a characteristic property of *N*-acylketimines (I) when R_1 and R_2 are aromatic. For example, (I) forms (II) with ethanol. It has also been found that the electrophilic group on the nitrogen atom need not be acyl, since carbalkoxy-groups are effective. The addition

$CR_1R_2{:}N{\cdot}CO{\cdot}R_3$	$EtO{\cdot}CR_1R_2{\cdot}NH{\cdot}CO{\cdot}R_3$	$CPhEt{:}N{\cdot}CO{\cdot}CH_3$	$CH_3{\cdot}CH{:}CPh{\cdot}NH{\cdot}CO{\cdot}CH_3$
(I.)	(II.)	(III.)	(IV.)

is much diminished or prevented by steric hindrance, *e.g.*, it does not occur when R_1 is α-naphthyl though it does when R_1 is β-naphthyl. Another limiting factor is seen when one of the groups in (I) is aliphatic, as in *N*-acetylphenyl ethyl ketimine (III) which does not form a crystalline adduct and behaves in all respects as though it were (IV), in which the azomethine group is absent.

A consideration of the properties of the azomethine group in (I) and in the related Schiff's base (V) indicates that *N*-acylaldimines will combine with alcohols, amines, and thiols. Thiols seem not to have been recorded as forming addition products with Schiff's bases, but addition products are apparently formed when they can be stabilised by ring formation through subsequent condensation. Thus, Erlenmeyer and Oberlin (*Helv. Chim. Acta*, 1947, **30**, 1329) and Surrey (*J. Amer. Chem. Soc.*, 1947, **69**, 2911) found that (V) will slowly combine with hot thioglycollic acid to form a thiazolid-4-one (VII), to which the intermediate product (VI) is the only reasonable precursor. As the nitrogen atom in a Schiff's base is not attached

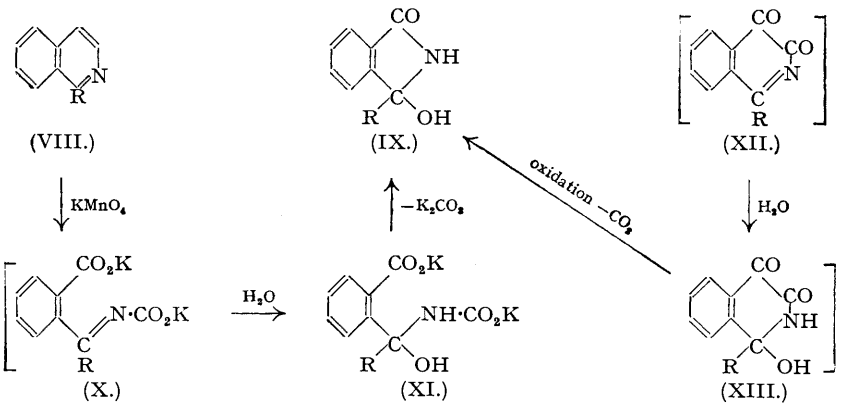
$CHAr{:}N{\cdot}Ar$	$CO_2H{\cdot}CH_2{\cdot}S{\cdot}CHAr{\cdot}NHAr$	
(V.)	(VI.)	(VII.)

to a strong electrophile as it is in *N*-acylaldimines it is to be expected that the additive power of the latter class will be greater than that of Schiff's bases. Also a comparison of the properties

of aldimines and ketimines shows that the *N*-acylaldimines should be at least as reactive as *N*-acylketimines.

This tendency of the C:N linkage to combine additively explains the formation of 3-hydroxy-3-phenylphthalimidine (IX; R = Ph) in the permanganate oxidation of 1-phenyl*iso*quinoline. Though ammonium *o*-benzoylbenzoate is converted (Beilstein, vol. X, p. 749) at 160—170° into (IX; R = Ph), this is not formed by prolonged heating of *o*-benzoylbenzoic acid with dilute ammonia and is thus unlikely to be produced below 100° from these probable by-products in the above oxidation. Accordingly, the following explanation of the formation of (IX; R = Ph) is advanced. The oxidation product (X; R = Ph) of 1-phenyl*iso*quinoline is an aryl phenyl ketimine with the electrophilic CO_2K group attached to the nitrogen atom. The addition of water would produce (XI; R = Ph) which by loss of carbon dioxide, followed by ring closure, would give (IX; R = Ph). The oxidising medium is slightly alkaline, and it has been found that bases catalyse the addition of alcohols and presumably water to *N*-acyl diphenyl ketimines. An alternative route to (IX; R = Ph) is *via* (XII; R = Ph), and (XIII; R = Ph), further oxidation and loss of carbon dioxide being followed by cyclisation. There are other possible routes to (IX; R = Ph), but the greater probability of one mechanism compared to another is, with the knowledge at present available, a matter of conjecture. The mechanism now put forward is that oxidation results in the formation of an electrophilic group on the nitrogen atom, thus causing the addition of water to the azomethine group, and that the carbon atom on the nitrogen atom is lost as carbon dioxide.

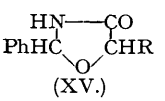
The same mechanism explains the formation of phthalimide in the oxidation of *iso*quinoline itself in the presence of magnesium sulphate (Goldschmiedt, *Monatsh.*, 1888, **9**, 676), but not with acid oxidising agents. Oxidation of *iso*quinoline could give (X; R = H) or (XII; R = H); addition of water to the activated azomethine group would result in (XI; R = H) and (XIII; R = H) in the ways already suggested. The product (IX; R = H) from *iso*quinoline is a secondary alcohol which is oxidised to the corresponding ketone, phthalimide.

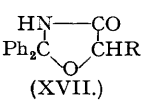


Several reported examples of hydroxy-*N*-acylaldimines are shown in this paper to be cyclic compounds. In an attempt to prepare a phenylmethyloxazole from benzaldehyde and acetaldehyde cyanohydrin in ethereal hydrogen chloride, Fischer (*Ber.*, 1896, **29**, 213) obtained " benzylidenelactamide " (XIV), m. p. 133—134°. In view of the present work it is likely that the compound is actually 2-*phenyl*-5-*methyloxazolid*-4-*one* (XV; R = Me). The recorded properties, such as solubility in alkali and hydrolysis with mineral acids to form benzaldehyde, do not distinguish between (XIV) and (XV). However, it is now found that there is no chemical evidence for the presence of the hydroxyl group in the compound, which is inert to phenyl *iso*cyanate and thionyl chloride, though lacto-*p*-toluidide (XVI), which has some resemblance to (XIV), reacts with them as expected. Absence of an activated azomethine group is indicated

CHPh:N·CO·CHMe·OH
(XIV.)

p-C_6H_4Me·NH·CO·CHMe·OH
(XVI.)

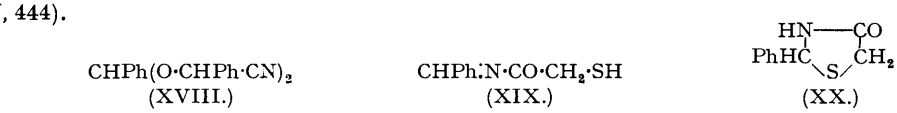

(XV.)


(XVII.)

by inability of the compound to add piperidine, or alcohols in the presence of a basic catalyst, and also by its inertness to magnesium in boiling methyl alcohol. This reagent readily reduces

azomethine groups in Schiff's bases (Zechmeister and Truka, *Ber.*, 1930, **63**, 2883) and that in *N*-propionyldiphenylketimine, which is converted into *propionobenzhydrylamide*. The probability of the cyclic structure was further shown by the condensation of lactamide and diphenyl ketimine (which has many analogies with benzaldehyde) to form ammonia and 2 : 2-*diphenyl*-5-*methyloxazolid*-4-*one* (XVII; R = Me), the structure of which was shown by the absence of a hydroxyl group. " Benzylidenelactamide " was similarly made by heating lactamide and benzaldehyde, and this total of chemical evidence for the formula (XV) is confirmed by infra-red spectral analysis.

" Benzylidenemandelamide," colourless needles, was prepared by Michael and Jeanprêtre (*Ber.*, 1892, **25**, 1682) from mandelonitrile and fuming hydrochloric acid, and by heating mandelamide with benzaldehyde into which it is reconverted by hydrolysis (Fischer, *loc. cit.*, p. 207). Michael and Jeanprêtre preferred the structure benzylidenemandelamide (as XIV) to 2 : 5-*diphenyloxazolid*-4-*one* (XV; R = Ph) because the compound gave a monoacetyl derivative but not a nitroso-compound. " Benzylidenemandelamide " (which, when pure, has m. p. 203—204°) was obtained (m. p. 195°) as a by-product in the synthesis of 2 : 5-diphenyloxazole (Fischer, *loc. cit.*; cf. Ingham, *J.*, 1926, 692). The elucidation of its structure has been hindered by its confusion (unnoticed in Wiley's survey of oxazoles, *Chem. Reviews*, 1945, **37**, 401) with the acetal (XVIII), for which similar m. p.s (196·5° to 202°) are recorded. Thus Schuster (*J. Pharm. Chim.*, 1936, [viii], **23**, 142) obtained yellow crystals, m. p. 196°, considered to be " benzylidenemandelamide " by the reaction of potassium cyanide with the bisulphite compound of benzaldehyde. Savelsberg (*J. pr. Chem.*, 1916, [ii], **93**, 271; 1917, **96**, 186) had previously used this reaction for the preparation of the acetal (XIX), greenish crystals, m. p. 202°, the constitution of which had been established by Stollé (*Ber.*, 1902, **35**, 1590). Schuster's conversion of his " benzylidenemandelamide " into 2 : 5-diphenyloxazole by hydrogen chloride is now understandable, because any water present would regenerate the original components of the acetal which could then react according to the Fischer oxazole synthesis. The evidence that Schuster's compound was the acetal is supported indirectly by his condensation of potassium cyanide with the bisulphite compound of anisaldehyde, which gave yellow needles, m. p. 154° ($C_{25}H_{20}O_5N_2$), of unknown constitution. His analysis shows the compound to be *anisaldehyde bis*-α-*cyano*-p-*methoxybenzyl acetal*, *p*-MeO·C_6H_4·CH[O·CH(CN)·C_6H_4·OMe-*p*]$_2$ (Found : C, 70·0; H, 6·0; N, 6·5%; *M*, 433. $C_{26}H_{24}O_5N_2$ requires C, 70·3; H, 5·4; N, 6·3%; *M*, 444).



The present work has shown that the actual structure of " benzylidenemandelamide " is 2 : 5-diphenyloxazolid-4-one (XV; R = Ph), which is supported by the kind of chemical and physical evidence which has proved the structure of (XV). The acetyl derivative, m. p. 123° (Michael *et al.*, *loc. cit.*), is possibly 4-*acetoxy*-2 : 5-*diphenyloxazoline*. Though the present authors have not experimented with " anisylidenemandelamide," m. p. 182° (Minovici, *Ber.*, 1896, **29**, 2099), its method of preparation shows it to be analogous to (XV), *i.e.*, 5-*phenyl*-2-p-*methoxyphenyloxazolid*-4-*one*. " Benzylidene-*p*-methoxymandelamide," m. p. 183° (Minovici, *loc. cit.*, p. 2100), is likewise considered to be 2-*phenyl*-5-p-*methoxyphenyloxazolid*-4-*one*.

It is to be expected that, if *N*-benzylidenethioglycollamide (XIX) could be prepared, simple chemical tests for the thiol group would decide whether it existed as such or as the cyclic isomeride 2-*phenylthiazolid*-4-*one* (XX). Benzaldehyde readily condenses with thioglycollamide to form (XX). The lack of reaction with sodium nitroprusside and cold sodium plumbite supports this formula, with which the infra-red spectrum is not inconsistent. The only evidence in favour of formula (XIX) is that the compound in alcohol gives a positive test with iodine–sodium azide; however, some thiazolidines (*Quart. Reviews*, 1948, **2**, 203) are hydrolysed, to give thiol reactions with the sensitive iodine–sodium azide reagent. (XX) is rapidly hydrolysed to benzaldehyde by boiling water, whereas the oxazolidine analogue (XV) requires the use of hot mineral acid. 2 : 2-*Diphenylthiazolid*-4-*one*, from diphenyl ketimine and thioglycollamide, has properties similar to those of (XX). Both are rapidly hydrolysed by cold acid or boiling sodium hydroxide solution, but only slowly by cold dilute aqueous ammonia.

Experimental.

Conversion of 1-*Phenyl*iso*quinoline into* 3-*Hydroxy*-3-*phenylphthalimidine*.—Potassium permanganate (2 g.) in water (70 ml.) was gradually added during 2 hours to a continuously stirred refluxing suspension of 1-phenyl*iso*quinoline (1 g.) in water (100 ml.) on a boiling water-bath. The precipitated manganese

dioxide was well washed with boiling water, and the washings and filtrate were concentrated to 50 ml. and cooled overnight; 0·7 g. of the phthalimidine (IX; R = Ph) m. p. 165°, separated in felted needles (Found: C, 74·5; H, 4·9; N, 6·4. Calc. for $C_{14}H_{11}O_2N$: C, 74·7; H, 4·9; N, 6·2%). It was readily soluble in hot, sparingly in cold, water, soluble in mineral acid and sodium hydroxide solution, insoluble in aqueous ammonia. It was identical (mixed m. p.) with a specimen made from phenylmagnesium bromide and phthalimide (Béis, *Compt. rend.*, 1904, **139**, 62).

Propionobenzhydrylamide.—Diphenyl *N*-propionyl ketimine (2 g.) (Banfield *et al.*, *loc. cit.*), magnesium turnings (1 g.), and methanol (15 ml.) were warmed until reaction began; cooling was then required. After final heating on the water-bath (total time of reaction, 1 hour), the methanol was distilled off at ordinary pressure, acetic acid (20 ml.; 40%) added to the residue, and the undissolved portion recrystallised from light petroleum (b. p. 100—120°) in plates, m. p. 144·5° (Found: C, 80·25; H, 7·2. $C_{16}H_{17}ON$ requires C, 80·4; H, 7·11%). *Propionobenzhydrylamide* was hydrolysed by heating it with dilute hydrochloric acid for 4 hours; the solution with alkali yielded to ether a base, the benzoyl derivative of which was identical with benzobenzhydrylamide (m. p. and mixed m. p. 172—174°).

Reactions of Lacto-p-toluidide.—Lacto-*p*-toluidide (XVI) (Leipen, *Monatsh.*, 1888, **9**, 49) reacted instantly with thionyl chloride to form sulphur dioxide and hydrogen chloride. The *urethane*, m. p. 150—151° (from alcohol), is formed by heating equimolecular quantities of the toluidide and phenyl *iso*cyanate in a sealed tube for an hour at 100° (Found: N, 9·2. $C_{17}H_{18}O_3N_2$ requires N, 9·4%).

2-*Phenyl*-5-*methyloxazolid*-4-*one* (XV; R = H).—This was obtained essentially after Fischer (*loc. cit.*), the ethereal solution of acetaldehyde cyanohydrin and benzaldehyde being kept for a month at room temperature, the ether then allowed to evaporate, and the residue crystallised from water or light petroleum, to give needles, m. p. 133—134°. It was also formed in much better yield by heating lactamide with a slight excess of benzaldehyde at 120—150° for 4 hours. Unchanged reactants were removed by washing with a little ether, and the residue crystallised from water. Only a little unchanged (XV) was obtained when it was treated with excess of magnesium and methanol for 12 hours. (XV) also did not react with thionyl chloride or phenyl *iso*cyanate on the water-bath, either undiluted (1·5 hours) or with xylene (6 hours).

2 : 2-*Diphenyl*-5-*methyloxazolid*-4-*one* (XVII; R = Me).—This *compound* was formed in good yield when lactamide was heated with twice its weight of diphenyl ketimine at 140° for 10 hours, ammonia being gradually evolved. The cooled mass was extracted with a little ether and the residue crystallised from alcohol in needles, m. p. 183—184° (Found: N, 5·7. $C_{15}H_{15}O_2N$ requires N, 5·8%). It was inert to thionyl chloride.

2 : 5-*Diphenyloxazolid*-4-*one* (XV; R = Ph).—This *oxazolidone* was prepared essentially after Ingham (*loc. cit.*, expt. 2, p. 696). From mandelonitrile (5·5 g.) and benzaldehyde (4·8 g.) in 200 ml. of ether, 5·8 g. of unrecrystallised " benzylidenemandelamide " were obtained in 4 days, either at room temperature or at −2°. The trace of alkali suggested by Ingham was added, and the flask loosely stoppered so that moisture was not completely excluded. The product was washed with ether, and crystallised from alcohol and then light petroleum (b. p. 120—150°) in needles, m. p. 203—204° (Found: N, 6·1. $C_{15}H_{13}O_2N$ requires N, 5·9%). There was a large depression in m. p. when mixed with the acetal (XVIII) made from benzaldehyde *via* its bisulphite compound and potassium cyanide after Savelsberg (*loc. cit.*).

Dr. J. B. Willis reports as follows on the infra-red spectra of (XV) and (XV; R = Ph): " Each compound shows a strong carbonyl frequency, the band lying at 1704 cm.$^{-1}$ in ' benzylidenelactamide ' and at 1712 cm.$^{-1}$ in the ' mandelamide.' In neither compound is there any absorption between 1500 and 1700 cm.$^{-1}$. The C=N frequency usually lies at about 1640 cm.$^{-1}$. Benzylideneaniline shows C=N absorption at 1634 cm.$^{-1}$, and benzylidene-ethylamine shows bands at 1644 cm.$^{-1}$ (C=N) and 1710 cm.$^{-1}$ (due to benzaldehyde present as an impurity). The infra-red spectroscopic evidence, therefore, is that there is no support for the ' benzylidenelactamide ' and ' mandelamide ' formulæ, but that the formulæ (XV) and (XV; R = Ph) are quite possible."

2-*Phenylthiazolid*-4-*one* (XX).—Thioglycollamide was made *via* ethyl thioglycollate (b. p. 58—62°/20 mm.) after Klason and Carson (*Ber.*, 1906, **39**, 736), and is deliquescent. Benzaldehyde (0·6 ml.) was added to thioglycollamide (0·5 g.) at its m. p. (52°); the mixture, when shaken, at once became hot and rapidly solidified on cooling. The *product* crystallised from benzene in plates, m. p. 87—88° (Found: N, 7·8; S, 17·4. C_9H_9ONS requires N, 7·8; S, 17·9%). It was almost insoluble in cold, and moderately soluble in hot, water, from which it was recovered by rapid crystallisation. However, benzaldehyde was driven off when the solution was boiled, and concentration nearly to dryness gave only dithiodiglycollamide, m. p. 161·5—162·5° (Found: S, 35·5. Calc. for $C_4H_8O_2N_2S_2$: S, 35·55%), of which the recorded m. p.s vary from 149° to 160°. In aqueous alcohol (XX) gave a negative test with sodium nitroprusside made alkaline with ammonia, though the addition of alkali gave a transient reddish-brown colour. The characteristic, though momentary, violet colour developed in the nitroprusside test was obtained when (XX) was hydrolysed for a minute with hot dilute sulphuric acid and the product made alkaline. The aqueous alcoholic solution of (XX) at once gave a black precipitate with boiling sodium plumbite, but the cold reagent very slowly led to a light-brown colour. No precipitate was formed with cold copper acetate solution. However (XX) instantly gave a positive iodine–sodium azide test, which was also given, though much more slowly, with an analytically pure specimen of dithiodiglycollamide which gave a negative nitroprusside test.

2 : 2-*Diphenylthiazolid*-4-*one.*—This was produced when a slight excess of diphenyl ketimine was heated at about 180° for 5 minutes with thioglycollamide in the presence of a trace of dimethylamine hydrochloride. The onset of the reaction was marked by a transient green colour. The *product*, which solidified on cooling, was extracted with boiling xylene and recrystallised from benzene, in which it was sparingly soluble, in needles, m. p. 227—228° (Found: N, 5·5. $C_{15}H_{13}ONS$ requires N, 5·5%). It resembled (XX) in its behaviour towards nitroprusside, cold copper acetate, and sodium plumbite solution, though the alcoholic solution with cold sodium plumbite became brown more rapidly at ordinary temperatures. A positive test was given with the iodine–sodium azide reagent, and acid hydrolysis liberated a thiol group (nitroprusside test).

Dr. J. B. Willis reports on the infra-red spectra of " benzylidenethioglycollamide " (XIX or XX) as follows : " ' Benzylidenethioglycollamide ' (XX) was studied (*a*) as solid film, formed by melting the compound between two rock-salt plates and allowing it to solidify, and (*b*) as a suspension of the original powder in heavy paraffin (' Nujol '). A smell of benzaldehyde and mercaptan is noticeable on melting. A small band appears at 2550 $cm.^{-1}$ in (*a*) but not (*b*), and seems to be due to free thiol groups formed by decomposition. If allowance is made for the lack of data on the infra-red spectra of thiols (the only ones studied being the simple thiols with a small band at 2580 $cm.^{-1}$ due to SH), it seems probable that in the undecomposed compound there is no SH group. Both specimens show a band at 3370 $cm.^{-1}$ which is most probably due to NH, though possibly to the hydrogen bonded OH (produced by the tautomerism : $\cdot NH\cdot CO\cdot \longleftrightarrow \cdot N{:}C(OH)\cdot$, followed by hydrogen-bonding between the OH of a molecule of the enolic form and the CO of a molecule of the keto-form). The question of tautomerism could be settled only by identifying a band definitely due to C=N, but unfortunately this region of the spectrum (1600—1700 $cm.^{-1}$) contains two overlapping bands, due to CO and aromatic C–C vibrations, and it is not possible to say whether a weak C=N band is present or not. The formula (XX) is therefore the most probable from the infra-red evidence."

Mr. N. L. Lottkowitz made the micro-analyses. We thank Dr. J. B. Willis for determining the infra-red spectra.

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