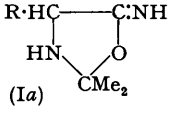
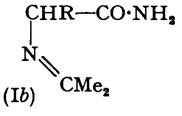
768. *The Interaction of α-Amino-nitriles and Aldehydes and Ketones.*

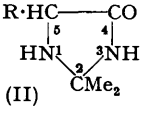
By A. C. Davis and A. L. Levy.

α-Amino-nitriles react with aldehydes to give Schiff's bases, which may isomerise to glyoxalines, and with ketones in the presence of sodium alkoxides to give 5-imino-oxazolidines or Schiff's bases of the corresponding α-amino-amides (I). The latter rearrange, when heated, to the little known tetrahydro-4-ketoglyoxalines (II), whose acylation, alkylation, and coupling with diazo-compounds are studied. The compounds (I) and (II) react with aromatic aldehydes to give α-arylideneamino-amides, except in the case of benzaldehyde and (II) which give derivatives of β-phenylserine. The reactions of *N*-methylaminoaceto-nitrile and -amide with aldehydes and ketones are also studied. Preliminary attempts are made to synthesise benzyldethiopenillonic acid, and some general observations on the reactions between carbonyl compounds and α-amino-acid derivatives are recorded.

Cook, Heilbron, and Levy (*J.*, 1948, 201) described the reaction of acetone with aminoacetonitrile in the presence of a catalytic quantity of sodium ethoxide. The highly crystalline product, which was formulated as 5-imino-2 : 2-dimethyloxazolidine (I*a*; R = H), was shown to be readily hydrolysed by cold water to aminoacetamide and acetone. In the present paper, the generality of this reaction of α-amino-nitriles, and other aspects of the chemistry of the products derived from it, are examined.


(I*a*)


(I*b*)

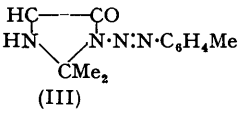

(II)

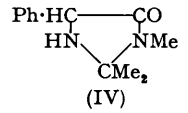
It has been shown (Cook, Heilbron, and Mahadevan, *J.*, 1949, 1061) that α-amino-α-phenylacetonitrile similarly condenses with dry acetone in the presence of sodium methoxide, the crystalline product (I*a*; R = Ph) being hydrolysed by water in an analogous fashion to α-amino-α-phenylacetamide and acetone. A corresponding compound (I*a*; R = Me) was obtained from α-aminopropionitrile and acetone (Cook and Levy, *J.*, 1950, 642), though aminocyanoacetic ester has not been induced to react. The products of these reactions were labile, and all attempts to prepare hydrochlorides or picrates led to the salts of the corresponding α-amino-amides. The fission of the oxazolidine (I*a*; R = H) by water, leading to aminoacetamide and acetone, has been found to be an equilibrium reaction which can be driven in one or the other direction by removing the acetone or the water. When treated with hydrogen sulphide, (I*a*; R = H) gave aminoacetamide and thioacetone. Further, aceturamide and α-acetamido-α-phenylacetamide were the only isolatable products from attempts to acetylate the imino-oxazolidines (I*a*; R = H or Ph). These results seem to indicate the Schiff's base (I*b*) as a better formulation, though in this case the cyclic structure (I*a*) would doubtless be its precursor. Chemical evidence is at present insufficient to allow a final decision between (I*a*) and (I*b*) (the tautomeric 5-amino-2 : 2-dimethyloxazoline structure seems far less likely), which must await accumulation of further physical data. A similar problem was encountered by Cope and Hancock (*J. Amer. Chem. Soc.*, 1942, **64**, 1503; 1944, **66**, 1453, 1738, 1747) during a study of the readily hydrolysed condensation products of aldehydes and ketones with α-amino-ethanols. From consideration of molecular refractivities they concluded that either oxazolidines or Schiff's bases could be formed, depending on the nature of the substituents. From infra-red spectroscopic work by Daasch and Hanninen (*ibid.*, 1950, **72**, 3673) it appears that the corresponding condensation products from aromatic aldehydes have the Schiff's base structure.

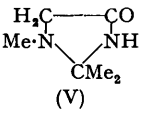
When *cyclo*hexanone was condensed with aminoacetonitrile at 90—100° with a sodium methoxide catalyst, the product was differed from the corresponding acetone compound (I; R = H), in so far as it formed a stable acetyl derivative and a picrate and was not hydrolysed by water. It was then found that when both the compounds (I; R = H or Ph) were heated, suitably in pyridine, they rapidly rearranged to more stable compounds which formed crystalline hydrochlorides and picrates and were readily monoacetylated; the rearranged bases can thus

be formulated with some certainty as tetrahydro-4-ketoglyoxalines (II; R = H or Ph). This isomerisation is reversible, in the case of (II; R = H), which appears to undergo partial reconversion into (I; R = H) on fusion or in hot pyridine. The *cyclo*hexanone product, also, is regarded as a tetrahydroketoglyoxaline (II; R = H; $[CH_2]_5>C$ in place of Me_2C), its production doubtless resulting from the high temperature of the reaction. Rearrangement in the case of (I*a*) is paralleled by the stages which are thought to occur during the Bucherer reaction (see, *e.g.*, Cook, Heilbron, and Levy, *J.*, 1947, 1589), or in the case of (I*b*) involves addition of the amide group to the Schiff's base linkage.

Unlike the primary products (I), the glyoxaline derivatives (II; R = H and Ph) were not hydrolysed by cold water, and only slowly by boiling water. For complete hydrolysis of (II; R = H) cold concentrated alkali was effective, but the phenyl analogue (II; R = Ph) required refluxing with this reagent. Both were hydrolysed rapidly by hot dilute acid. α-Aminoamides were formed in the hydrolyses, but not quantitatively owing to their instability under such conditions. The primary products (I) and the glyoxalines (II) were conveniently differentiated by their behaviour towards 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid: the former gave an immediate yellow precipitate of acetone 2 : 4-dinitrophenylhydrazone whereas the latter were stable. Tetrahydro-4-keto-2 : 2-dimethylglyoxaline (II; R = H)


(III)


(IV)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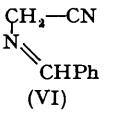
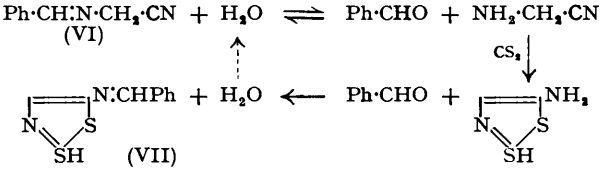

(VI)

coupled with toluene-*p*-diazonium chloride to give a colourless crystalline derivative containing an incipient diazonium group, for, when treated with a phenol, acidified and then made alkaline, it gave a precipitate of azo-dye. The compound was stable towards cold alkali, but with warm dilute hydrochloric acid lost nitrogen and yielded *p*-cresol; it is formulated as the 3-*p*-tolueneazo-compound (III), since the 1 : 2 : 2-trimethylglyoxaline derivative also coupled with diazonium salts. Tetrahydro-4-keto-2 : 2-dimethyl-5-phenylglyoxaline (II; R = Ph) was unaffected by diazomethane, but with methyl sulphate and sodium hydroxide gave a monomethyl derivative. As this afforded α-amino-α-phenylacetic acid on hydrolysis, it is the 2 : 2 : 3-trimethyl compound (IV). However, attempts to cause the compounds (II; R = H or Ph) to react similarly with α-bromo-acids or -esters, and thereby to establish a new route to dipeptides, were unsuccessful. The phenyl compound (II; R = Ph) was also unaffected by diazoacetic ester at 110°.

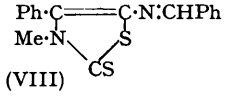
Methylaminoacetonitrile has been shown to condense with acetone in the presence of sodium methoxide, to give a 1 : 1 addition product (Cook and Cox, *J.*, 1949, 2337). This was not hydrolysed by cold hydrochloric acid, formed a stable picrate, and could not be rearranged by boiling bases or by fusion. We therefore prefer to regard it as tetrahydro-4-keto-1 : 2 : 2-trimethylglyoxaline (V) (contrast Cook and Cox, *loc. cit.*).

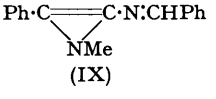
We shall consider next the reaction of aldehydes with α-amino-nitriles. Equimolecular quantities of benzaldehyde and aminoacetonitrile reacted exothermally in chloroform, one molecular proportion of water being eliminated. Distillation gave a colourless oil, which was readily hydrolysed to benzaldehyde by warm water and, from its analysis and light absorption

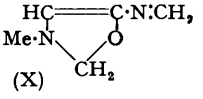

(VII)

at 2580 Å is certainly to be formulated as *N*-benzylideneaminoacetonitrile (VI). On being kept for 6 weeks in a sealed tube, this partly changed to 2-phenylglyoxaline, obtained previously only from dinitrotartaric acid, benzaldehyde, and ammonia (Maquenne, *Ann. Chim. Phys.*, 1891, **24**, 543; Fargher and Pyman, *J.*, 1919, **115**, 232). Similarly, ethyl benzylideneaminocyanoacetate (not isolated) yielded on storage ethyl 2-phenylglyoxaline-4-carboxylate. This change is to be compared with the corresponding isomerisation of (XI) which may be presumed (see below) to occur in the Minovici preparation of 2 : 4-diphenylglyoxaline, though it was not accelerated by acid. When benzylidenaminoacetonitrile and carbon disulphide were kept together in technical ether, 5-benzylideneamino-2-mercaptothiazole (VII) soon separated, whereas in thoroughly dried ether no such reaction took place; the small quantity of water

present in technical ether presumably sets up an equilibrium between the Schiff's base and its components, whereupon the aminoacetonitrile reacts irreversibly with carbon disulphide giving 5-amino-2-mercaptothiazole; this will at once combine with the benzaldehyde to form (VII), liberating an equivalent quantity of water which repeats the cycle. In this connection, it has been observed that certain α-amino-nitriles decompose during distillation to compounds of the composition $R{\cdot}CH(NH_2){\cdot}CN + R{\cdot}CHO - H_2O$, which on treatment with carbon disulphide give rise to Schiff's bases of the corresponding aldehyde and 5-amino-2-mercaptothiazole (R = Me, Cook, Heilbron, and Levy, *J.*, 1947, 1598; R = C_9H_{13}, Cook, Heilbron, and Stern, *J.*, 1948, 2031). It appears, therefore, from the present work, that these distilled amino-


(VIII)

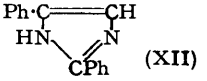

(IX)


(X)

nitriles are probably the Schiff's bases $R{\cdot}CH(N{:}CHR){\cdot}CN$ (cf. Delépine, *Bull. Soc. chim.*, 1909, **29**, 1184). This cannot apply, however, to an interesting compound obtained by distillation of α-methylamino-α-phenylacetonitrile, analysis of which indicates reaction of the nitrile with benzaldehyde with loss of water; this product affords the Schiff's base (VIII) with carbon disulphide; the structure (IX) has been proposed (Mahadevan, Thesis, London, 1948). Mention should also be made of a by-product isolated by Cook and Cox (*J.*, 1949, 2334) from the preparation of α-methylaminoacetonitrile, which gave methylaminoacetonitrile sulphate with sulphuric acid and from its analysis resulted by reaction with two additional molecules of formaldehyde with elimination of one of water. A possible structure for this compound is (X) (Cox, Thesis, London, 1949). It appears that this compound was first prepared and described by Dalgliesh and Mann (*J.*, 1947, 658), following an early preparative method for methylaminoacetonitrile, and was believed by them to be the nitrile itself. In spite of their further preparation from this material of salts of the true nitrile, the physical properties recorded (b. p. 95—105°/0·2 mm.) show that it was in fact Cook and Cox's formaldehyde condensation product (b. p. 90°/0·1 mm.), since methylaminoacetonitrile boils at 65°/19 mm.

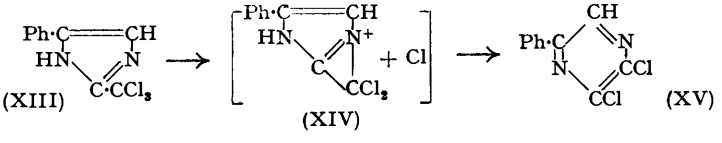
Benzaldehyde and α-amino-α-phenylacetonitrile are already known (Plochl, *Ber.*, 1881, **14**, 1143) to yield α-benzylideneamino-α-phenylacetonitrile (XI). The compound has alternatively been called " benzoylazotide " and " hydrocyanbenzide," and has been made also by the action


(XI)


(XII)

of ammonium cyanide on benzaldehyde (Snape and Brooke, *J.*, 1897, **71**, 529). However, when hydrogen chloride is passed into an ethereal solution of α-amino-α-phenylacetonitrile and benzaldehyde, 2 : 5-diphenylglyoxaline hydrochloride (XII) (cf. Haines and Wagner, *J. Amer. Chem. Soc.*, 1949, **71**, 2793) is produced (Minovici, *Ber.*, 1896, **29**, 2097). We have found that attempted distillation of the Schiff's base (XI) gave the glyoxaline (XII), which was also produced in impure form by distillation of α-amino-α-phenylacetonitrile at 0·05 mm., although in a high vacuum the nitrile sublimed unchanged.

Chloral reacted vigorously with aminoacetonitrile (charring occurred in the absence of a diluent), to give a crystalline product, m. p. 81°, analysis of which indicated a formula $Cl_3C{\cdot}CHO + NH_2{\cdot}CH_2{\cdot}CN$. It was not hydrolysed by water, and formed a stable picrate;


(XIII) (XIV) (XV)

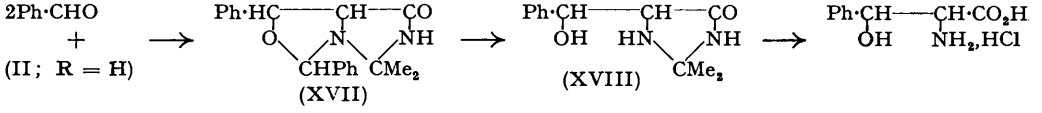
its structure is not known. It is of interest that Minovici and Bente (*Bul. Chim.*, 1915, **17**, 161) claimed that condensation of chloral with α-amino-α-phenylacetonitrile gave 5-phenyl-2-trichloromethylglyoxaline (XIII), which then rearranged, with loss of hydrogen chloride, to 2 : 3-dichloro-5-phenylpyrazine (XV). The mechanism of this change may well involve the bicyclic immonium salt (XIV), as in the interesting ring expansion of 2-chloromethyl-1-ethylpyrrolidine to 3-chloro-1-ethylpiperidine noted by Fuson and Zirkle (*J. Amer. Chem. Soc.*, 1948, **70**, 2760).

In order to ascertain whether the compounds (I), (II; R = H), and (V) possessed active methylene groups, allowing their use in amino-acid syntheses as with 2-phenyloxazolone, hydantoin, rhodanine, 2-mercaptothiazolone, etc., their reactions with aromatic aldehydes were investigated. When (I; R = H) was warmed with benzaldehyde, acetone was evolved and a crystalline product readily obtained, whose analysis indicated replacement of acetone by benzaldehyde. It was a labile substance, being readily hydrolysed by warm water to benzaldehyde and aminoacetamide, though resynthesised when these substances were combined in ethanol. It showed light absorption maxima at 2510 and 2560 Å, characteristic of the grouping Ph·CH:N, and is, therefore formulated as the Schiff's base *N*-benzylideneaminoacetamide (XVI; R = H). The reaction was catalysed by water, and may be represented as :

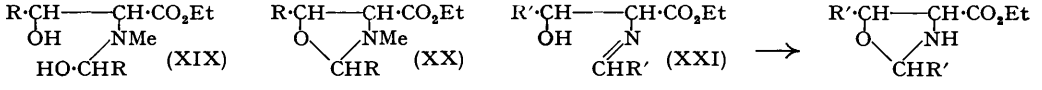
$$CMe_2{:}N{\cdot}CHR{\cdot}CO{\cdot}NH_2 + H_2O \rightleftharpoons COMe_2 + NH_2{\cdot}CHR{\cdot}CO{\cdot}NH_2 \overset{Ph{\cdot}CHO}{\rightleftharpoons} CHPh{:}N{\cdot}CHR{\cdot}CO{\cdot}NH_2 + H_2O$$
(XVI)

The phenyl compound (I; R = Ph) reacted similarly, the product (XVI; R = Ph) being in this case already known (Clarke and Francis, *J.*, 1911, **99**, 320). Attempts to cyclise the products (XVI; R = H or Ph) failed.

The glyoxaline derivative (II; R = H) and benzaldehyde, when warmed together, gave a crystalline product (XVII) in good yield; analysis indicated addition of two molecules of benzaldehyde to one of the glyoxaline with elimination of water. With cold hydrochloric acid, it readily lost one molecule of benzaldehyde, giving the hydrochloride of a base (XVIII), which was converted by 12 hours' refluxing with ethanolic hydrogen chloride into β-phenylserine ethyl ester hydrochloride. This series of reactions is, therefore, formulated as follows :



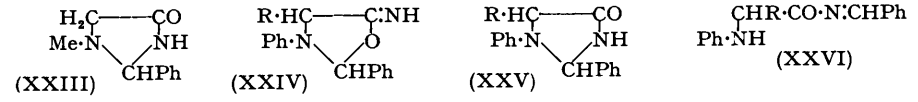
These reactions are closely comparable with the condensation of 3 : 4-di(ethyl carbonato)-benzaldehyde with sarcosine ester in the presence of sodium (Dalgliesh and Mann, *J.*, 1947, 658), in which two molecules of the aldehyde were consumed to give an intermediate product, readily hydrolysed by acid to a substituted phenylserine ester. This intermediate was formulated as (XIX) by Dalgliesh and Mann (*loc. cit.*); but a better expression would appear to be (XX), comparable with the oxazolidine (XVII) above, particularly as Dalgliesh (*J.*, 1949, 90) has made the interesting observation that the Schiff's base (XXI) isomerises in ethanol to the oxazolidine (XXII). Compounds analogous to (XXI) have also been made by the action of aromatic aldehydes on glycine in alkaline solution (Erlenmeyer and Bade, *Annalen*, 1904, **337**, 222; Gulland and Mead, *J.*, 1935, 210) and on glycine ester in the presence of sodium (Rosenmund and Dornsaft, *Ber.*, 1919, **52**, 1734).



The compound (II; R = Ph) also condensed readily with benzaldehyde, to give a pale yellow, highly crystalline product, which was considerably more stable than (XVII), for 36 hours' refluxing with 20% hydrochloric acid merely afforded its hydrochloride. Analysis showed, indeed, that the reaction was not analogous to that taking place in the glycine series, since the product had a composition corresponding to (II; R = Ph) + 2Ph·CHO − H_2O − Me_2CO. Its structure is not known.

The reaction of tetrahydro-4-keto-1 : 2 : 2-trimethylglyoxaline (V) with benzaldehyde followed the same course as that of (I), acetone being expelled and a compound obtained, which is probably to be formulated as (XXIII). Thus it was more stable than the Schiff's bases (XVI) and could be recrystallised from hot water. It gave benzaldehyde 2 : 4-dinitrophenylhydrazone with Brady's reagent only after boiling, and was unchanged after one hour's refluxing in pyridine. An imino-structure cannot be entirely dismissed, however; but a benzylideneamide expression such as (XXVI) (see below) is excluded, as the compound did not show the required characteristic ultra-violet absorption. The same substance was produced by condensation of benzaldehyde with sarcosine amide, and a higher homologue similarly from

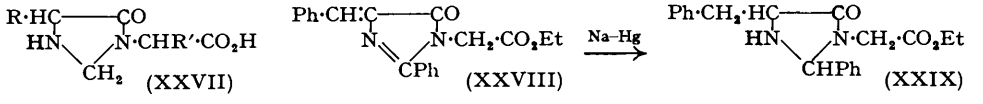
benzaldehyde and *N*-methylvaline amide. It is relevant in this connection that Miller and Plochl (*Ber.*, 1898, **31**, 2699) reported a general reaction between α-arylamino-nitriles and aromatic aldehydes in the presence of ethanolic potassium cyanide or hydroxide, leading to two isomeric compounds formulated by them as (XXVI). These could be reversibly interconverted by heating them in solvents, and in view of the present work are probably to be



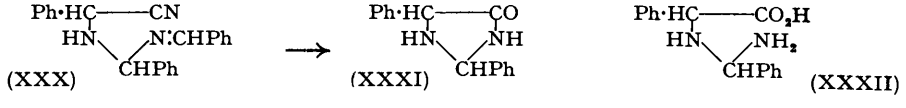
regarded as the 5-imino-oxazolidine (XXIV) and tetrahydro-4-ketoglyoxaline (XXV), although the possibility of *cis–trans*-isomerism of one cyclic structure also arises. Formally, structures such as (XXVI) are alternatives to (I) and (XVI), but the literature shows that such amide "Schiff's bases" are only produced in exceptional circumstances, compounds such as R'·CO·NH·CHR·OH and R'·CO·NH·CHR·NH·COR" being the normal products of interaction of an aldehyde and an amide (Agarwal, Pandya, and Tripathi, *J. Indian Chem. Soc.*, 1944, **21**, 283, and earlier papers in this series; cf. also Moscheles, *Ber.*, 1891, **24**, 1805). In some other cases where such alkylideneamides have been proposed, the compounds are better regarded as cyclic structures such as (XXV) (cf. Cornforth and Cornforth, *J.*, 1949, 1028).

It was noted by Erlenmeyer and Bade and by Dalgliesh and Mann (*locc. cit.*) that the formation of phenylserines by reaction of benzaldehydes with glycine or glycine ester was dependent on the substitution in the benzene ring, and it was therefore of interest to study the behaviour of anisaldehyde, piperonaldehyde, and salicylaldehyde towards our compounds (I), (II), and (V). In all cases, except that of (V) where it is not stoicheiometrically possible, the products were Schiff's bases of aminoacetamide or α-amino-α-phenylacetamide. Thus the behaviour of (II), in condensing with two molecules of benzaldehyde and giving rise to a derivative of phenylserine, is exceptional. With (V), compounds analogous to (XXIII) were produced.

The tetrahydro-4-ketoglyoxaline ring system does not appear to be well known, and we have so far found only four examples. The structure (XXVII) has been suggested by French and Edsall (*Adv. Protein Chem.*, 1945, **2**, 277) for the rather ill-defined compounds obtained by the action of formaldehyde on certain dipeptides (Franzen and Fellmer, *J. prakt. Chem.*, 1917, **95**, 299; Wadsworth and Pangborn, *J. Biol. Chem.*, 1936, **116**, 423).



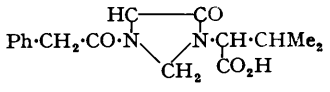
An interesting peptide synthesis involving a tetrahydroketoglyoxaline intermediate was effected by Granacher and Mahler (*Helv. Chim. Acta*, 1927, **10**, 248). The heterocyclic ring of 4-benzylidene-2-phenyloxazolone was opened with glycine ester, and then closed with alkali or phosphorus oxychloride to give the dihydroglyoxaline derivative (XXVIII). Reduction with sodium amalgam gave the tetrahydro-compound (XXIX), which was hydrolysed with loss of benzaldehyde to give phenylalanylglycine.



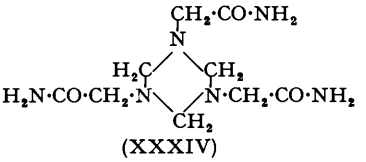
The third example (XXXI) arose from the action of hydrochloric acid on (XXX), obtained by the addition of one molecule of hydrogen cyanide to hydrobenzamide (Plochl, *Ber.*, 1880, **13**, 2118; 1881, **14**, 1139, 1316). An alternative α-lactam structure proposed by Plochl for (XXXI) now appears very unlikely. The compound formed a hydrochloride, and was said to be opened by aqueous ammonia to give the acid (XXXII), which was recyclised by heating to 100°; however, from its properties, (XXXII) may well be a hydrate of (XXXI).

The most important monocyclic tetrahydro-4-ketoglyoxaline, however, is benzyldethiopenillonic acid (XXXIII), which is obtained by the desulphurisation of the thermal rearrangement product of benzylpenicillin (methyl ester) ("The Chemistry of Penillicin," Oxford Univ. Press, 1949, p. 160), and some preliminary experiments towards its synthesis have been undertaken. Reaction of aminoacetamide with formaldehyde, in the hope of obtaining the parent

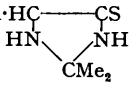
substance tetrahydro-4-ketoglyoxaline, gave a product, m. p. 162°, which appeared to be the trimer (XXXIV) because of its insoluble character, lack of NH_2-reactions, and ease of hydrolysis to formaldehyde (cf. the behaviour of aminoacetonitrile). Under other conditions the reaction leads to polymers (Marvel, Elliott, Boettner, and Yuska, *J. Amer. Chem. Soc.*, 1946, **68**, 1681). Treating *N*-hydroxymethyl-α-iodoacetamide with aqueous ammonia and ammonium carbonate for several days at room temperature gave aminoacetamide hydriodide, but with methanolic ammonia gave a crystalline hydriodide, m. p. 161—166°, which with phenylacetyl chloride and alkali gave an unidentified compound, $C_{12}H_{24}O_4N_3I$.



(XXXIII)



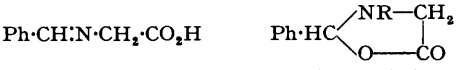
(XXXIV)



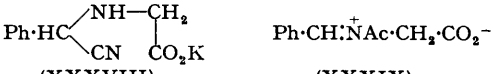
(XXXV)

The corresponding 4-thiones (XXXV) have been investigated by Cook and Mahadevan (*loc. cit.*), and arise from the spontaneous condensation of acetone with α-amino-thioamides, or with α-amino-nitriles and hydrogen sulphide in the presence of pyridine.

The interaction of carbonyl compounds and amino-acid derivatives, generally, is a subject of great interest to the biochemist, and we conclude with a brief discussion of three aspects of this broader field, of which the present study forms a part. They are (*a*) the possible occurrence of cyclic forms of compounds hitherto thought to have open chains, (*b*) the transposition of the double bond in Schiff's bases, resulting in loss of the α-amino-nitrogen atom, and (*c*) secondary interactions with the amino-acid side chains.

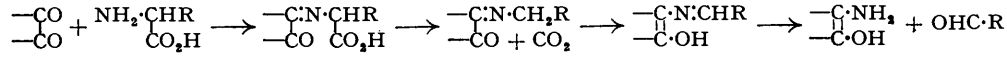


(XXXVI) (XXXVII)



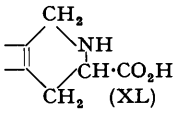
(XXXVIII) (XXXIX)

The compound benzylideneglycine arose as a by-product from the condensation of benzaldehyde with glycine in the presence of acetic anhydride, acetic acid, and sodium acetate (Dakin, *J. Biol. Chem.*, 1929, **82**, 439), and was formulated as either (XXXVI) or (XXXVII; R = H). The structure (XXXVII; R = H) was independently proposed by Scheibler and Baumgarten (*Ber.*, 1922, **55**, 1358) for a compound which was obtained from the substituted amino-nitrile (XXXVIII), by elimination of potassium cyanide. On treatment with alkali this gave the sodium salt of (XXXVI), and with acetic anhydride the latter afforded a monoacetyl derivative, hydrolysed by water to benzaldehyde and aceturic acid. Scheibler and Baumgarten (*loc. cit.*) formulated the acetyl derivative as (XXXIX), but the expression (XXXVII; R = Ac) is clearly more satisfactory. This evidence, coupled with the fact that no other free acid such as (XXXVI) has yet been isolated (benzylidene-arginine and -lysine are stabilised by internal-salt formation), makes the cyclic structure (XXXVII; R = H) highly probable, though it is not certain whether this applies to Dakin's compound also.



When the aldehyde or ketone function is adjacent to, or in conjunction with another carbonyl group, the double bond in the Schiff's base formed with an amino-acid migrates, so that on hydrolysis the amino-group is transferred from the amino-acid moiety to that of the diketone or keto-acid. This process is frequently accompanied by decarboxylation at the α-unsaturated acid stage, and the formation of an aldehyde thus, from the corresponding amino-acid, has been termed by Schönberg, Moubasher, and Said (*J.*, 1948, 176) the Strecker degradation. This change may be brought about by a wide variety of carbonyl compounds, including many of natural origin such as sugars, vitamin K, alloxan, and dehydroascorbic acid, but the two most important examples are to be found in the ninhydrin (Ruhemann, *J.*, 1911, **99**, 1492) and the trans-amination reactions (Braunstein, *Adv. Protein Chem.*, 1946, **3**, 4). In the latter case, pyruvic, oxaloacetic, and ketoglutaric acids are chiefly implicated, and it appears to be the primary mechanism whereby amino-acids are degraded and synthesised *in vivo*. Similar deaminations may also be brought about in special circumstances with such simple compounds as benzaldehyde (Erlenmeyer, *Ber.*, 1871, **4**, 2896) and formaldehyde (Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571).

α-Amino-group–side chain interactions chiefly concern the highly reactive formaldehyde molecule (French and Edsall, *loc. cit.*), though many of the examples are paralleled in the case of less versatile aldehydes and ketones. Thus serine and threonine yield oxazolidines, and cysteine a thiazolidine. Asparagine gives a hexahydropyrimidine, and phenylalanine, tyrosine, tryptophan, and histidine all receive a tetrahydropyridine ring fused to the aromatic nucleus, as shown in the partial formula (XL). The cross linking of free amino- with amide and guanidino-groups by formaldehyde is a prime cause of its tanning and hardening action on proteins (Fraenkel-Conrat and Olcott, *J. Amer. Chem. Soc.*, 1948, **70**, 2673).



(XL)

Experimental

5-Imino-2 : 2-dimethyloxazolidine.—Aminoacetamide (2·5 g.) in 50 c.c. of a mixture of acetone (320 c.c.) and benzene (80 c.c.) was heated under reflux for 30 minutes. The solution was then distilled slowly, with addition of the remainder of the solvent mixture to maintain a constant volume, and finally concentrated to 20 c.c. The colourless crystals (2·5 g.) which separated overnight had m. p. 85—90°. One recrystallisation from acetone gave 1·7 g. (50%) of nearly pure 5-imino-2 : 2-dimethyloxazolidine, m. p. 98°, undepressed by admixture with an authentic sample, which had m. p. 100—101°. The oxazolidine with picric acid in hot absolute ethanol gave *aminoacetamide picrate* in hair-like orange-yellow needles; on recrystallisation from ethanol the salt melted at 200° (Found : C, 32·0; H, 3·2. $C_8H_9O_8N_5$ requires C, 31·7; H, 3·0%). The oxazolidine (0·8 g.) in chloroform (10 c.c.) (dried over $CaCl_2$) was treated with acetic anhydride (1 c.c.) at room temp. to give, in 4 hours, crude aceturamide (0·4 g.), m. p. 132°, undepressed by admixture with a pure sample.

5-Imino-2 : 2-dimethyl-4-phenyloxazolidine.—The following procedure was found more satisfactory than that earlier described (Cook, Heilbron, and Mahadevan, *loc. cit.*). α-Amino-α-phenylacetonitrile (10 g.) was dissolved in acetone (30 c.c.) (dried over K_2CO_3). 1 C.c. of a solution of sodium (0·5 g.) in methanol (5 c.c.) was added and the mixture was kept for 15 minutes at 40—50°, this temperature being originally attained owing to the heat of reaction. After being kept for 1 hour at 0°, the colourless crystalline product (11 g., 80%) was collected, washed with acetone, and dried *in vacuo*; it had m. p. 144°. The oxazolidine was treated with picric acid in hot ethanol to give α-amino-α-phenylacetamide picrate, m. p. 195—200° (on recrystallisation from ethanol, 203—205°, undepressed by admixture with a sample prepared from α-amino-α-phenylacetamide). The imino-oxazolidine reacted vigorously with acetic anhydride containing 0·1% of sulphuric acid; cooling and dilution with benzene gave crystals of α-acetamido-α-phenylacetamide, m. p. 224°, undepressed by admixture with an authentic sample.

Tetrahydro-4-ketoglyoxaline-2-spirocyclohexane.—To a mixture of aminoacetonitrile (40 g.) and *cyclo*hexanone (80 g.) (dried over K_2CO_3) was added dropwise a solution of sodium methoxide (as above) until a spontaneous rise in temperature was produced. The solution was kept for 15 minutes on the steam-bath, after which it solidified on cooling. Filtration, washing with a mixture of acetone (20 c.c.) and light petroleum (10 c.c.), and drying *in vacuo* gave the product (50 g., 45%) in fine crystals, m. p. 116°. On recrystallisation from chloroform–light petroleum, the *spiran* formed colourless needles, m. p. 121° (Found : C, 62·0; H, 9·0; N, 18·3. $C_8H_{14}ON_2$ requires C, 62·3; H, 9·15; N, 18·2%). Acetylation with acetic anhydride gave the *monoacetyl* derivative, which formed needles (from ethanol), m. p. 209—210° (Found : C, 61·2; H, 8·2. $C_{10}H_{16}O_2N_2$ requires C, 61·2; H, 8·2%). The picrate formed needles, m. p. 142°.

Tetrahydro-4-keto-2 : 2-dimethylglyoxaline.—5-Imino-2 : 2-dimethyloxazolidine (16 g.) and pyridine (8 c.c.) (dried over KOH) were heated together under reflux for 30 minutes; the solution was allowed to cool to 100° and poured into benzene (25 c.c.). After 2—3 hours at 0°, the product was broken up, filtered, and washed with benzene. The pale yellow crystals (11·8 g.; m. p. 120°), which contained some unchanged oxazolidine, were recrystallised from acetone, to give *tetrahydro-4-keto-2 : 2-dimethylglyoxaline* (9·3 g., 58%) in short colourless rods, m. p. 126° (Found : C, 52·7; H, 9·0; N, 24·8. $C_5H_{10}ON_2$ requires C, 52·6; H, 8·8; N, 24·5%). The rearrangement also occurred on refluxing in ethanol, but 3 hours' refluxing in acetone proved insufficient to effect it. The *hydrochloride*, precipitated by ether from a solution of the base in ethanolic hydrogen chloride, formed needles, m. p. 153°, on recrystallisation from ethanol–ether (Found : C, 39·6; H, 7·1; N, 18·1. $C_5H_{11}ON_2Cl$ requires C, 39·9; H, 7·4; N, 18·6%). The picrate, formed in aqueous, ethanolic, or acetone solution, had m. p. 123°. The acetyl derivative, formed readily with acetic anhydride, was first isolated as the *hemihydrate*, m. p. 90° (with resolidification, and remelting at 160°) (Found : C, 50·3; H, 8·0; N, 17·4. $C_7H_{12}O_2N_2,\frac{1}{2}H_2O$ requires C, 50·9; H, 7·9; N, 17·0%). Recrystallisation from benzene gave the anhydrous *monoacetyl* derivative, m. p. 160° (Found : C, 53·5; H, 8·0; N, 18·35. $C_7H_{12}O_2N_2$ requires C, 53·8; H, 7·8; N, 17·95%). Partial reverse rearrangement of the glyoxaline derivative was effected (*a*) by heating the fused base for a short time at 130—140° and (*b*) by heating, for 30 minutes under reflux, a solution of the derivative (0·5 g.) in pyridine (5 c.c.), followed by evaporation *in vacuo* which assured the absence of any acetone formed by hydrolysis. Either product, when dissolved in cold water and treated with 2 : 4-dinitrophenylhydrazine in dilute hydrochloric acid, gave a heavy precipitate of the acetone derivative, and gave a small yield of aminoacetamide picrate with ethanolic picric acid.

Tetrahydro-4-keto-2 : 2-dimethyl-5-phenylglyoxaline.—5-Imino-2 : 2-dimethyl-4-phenyloxazolidine (15 g.) and pyridine (30 c.c.) (dried over KOH) were heated under reflux for 15 minutes. After evaporation of the solvent, a single recrystallisation from ethyl acetate (75 c.c.) gave fine colourless needles (12·2 g., 81%) of *tetrahydro-4-keto-2 : 2-dimethyl-5-phenylglyoxaline*, m. p. 154° (Found : C, 69·4; H, 7·6; N, 15·1. $C_{11}H_{14}ON_2$ requires C, 69·5; H, 7·4; N, 14·7%). The compound was soluble in cold dilute hydrochloric acid, and reprecipitated by addition of aqueous sodium hydroxide, but the hydrochloride

could not be isolated in a crystalline state. Acetylation with acetic anhydride containing 0·1% of sulphuric acid gave readily the *acetyl* derivative, which formed clusters of short needles (from benzene), m. p. 182° (Found: C, 67·5; H, 7·0; N, 11·8. $C_{13}H_{16}O_2N_2$ requires C, 67·2; H, 6·9; N, 12·1%).

Hydrolysis of the Tetrahydroketoglyoxalines.—When tetrahydro-4-keto-2 : 2-dimethylglyoxaline was boiled with water for 10—30 minutes, copious evolution of ammonia and acetone occurred, but no crystalline product was isolated from the hydrolysate, which probably contained aminoacetamide and glycine. Therefore the glyoxaline (1 g.) and water (10 c.c.) were heated under reflux for 1 minute, cooled, and freed from acetone and water by evaporation *in vacuo*. The aminoacetamide was separated from unchanged starting material by precipitation with carbon disulphide from alcohol as the dithiocarbamate (0·5 g.) (Cook, Heilbron, and Levy, *J.*, 1948, 201), the yield of which indicated about 25% hydrolysis to aminoacetamide. In the course of attempts to condense (II; R = H) with α-bromo-acids, it was found that the compound was decomposed by cold caustic alkalis. Although decomposed at once by hot dilute hydrochloric acid to glycine, ammonia, and acetone, it was stable to cold acid. Tetrahydro-4-keto-2 : 2-dimethyl-5-phenylglyoxaline (II; R = Ph) was stable in the cold towards both acid and alkali. It was decomposed by 20% aqueous sodium hydroxide at 100° in 3 hours, yielding α-amino-α-phenylacetic acid, acetone, and ammonia. After hydrolysis in 2N-hydrochloric acid for 10 minutes under reflux, acetone was liberated; both α-amino-α-phenylacetamide hydrochloride (decomp. 210°, m. p. 270°) and α-amino-α-phenylacetic acid were isolated in low yield.

*Coupling of the Tetrahydroketoglyoxalines with Toluene-*p*-diazonium Chloride.*—*p*-Toluidine (2·1 g.) was diazotised in the normal manner with concentrated hydrochloric acid (5 c.c.) and sodium nitrite (1·37 g.) in water (5 c.c.). The solution was added slowly to a stirred suspension of potassium hydrogen carbonate (15 g.) in a solution of tetrahydro-4-keto-2 : 2-dimethylglyoxaline (2·24 g.) in water (50 c.c.) at 0°. After 1 hour, the pale pink crude product (2·75 g., 60%), m. p. 158—159°, was collected and washed with water. On crystallisation from *iso*propyl ether, *tetrahydro-4-keto-2 : 2-dimethyl-*p*-tolyl-azoglyoxaline* formed colourless needles, m. p. 163—164° (Found: C, 62·2; H, 7·1; N, 24·3. $C_{12}H_{16}ON_4$ requires C, 62·0; H, 6·9; N, 24·1%). The compound was soluble in cold 2N-sodium hydroxide, and was recovered on acidification; it was insoluble in cold mineral acid. Tetrahydro-4-keto-2 : 2 : 3-trimethylglyoxaline gave in the same way a poor yield of crude coupling product, m. p. 128—130°; it formed colourless needles, m. p. 131—132°, on recrystallisation from *iso*propyl ether. Both the azo-compounds were decomposed by warm dilute mineral acid to give *p*-cresol and nitrogen. When added to a solution of β-naphthol in aqueous sodium hydroxide, they produced only a faint tinge, but after acidification with concentrated hydrochloric acid, followed immediately by addition of excess of sodium hydroxide, a brilliant light red azo-compound was produced.

Methylation of Tetrahydro-4-keto-2 : 2-dimethyl-5-phenylglyoxaline.—This compound (1 g.), suspended in 10% aqueous sodium hydroxide (5 c.c.), was shaken with methyl sulphate (0·8 g.). It rapidly dissolved, and was replaced by a colourless oil which soon crystallised. The crude product (0·7 g., 64%) was washed with water and dried *in vacuo*; on recrystallisation from light petroleum (b. p. 80—100°), *tetrahydro-4-keto-2 : 2 : 3-trimethyl-5-phenylglyoxaline* formed thick colourless needles, m. p. 158—159° [Found: C, 70·7; H, 8·3; N, 13·6; *M* (Rast), 213. $C_{12}H_{16}ON_2$ requires C, 70·55; H, 7·9; N, 13·7%; *M*, 204]. This compound (1 g.) was hydrolysed by heating it for 2 hours under reflux with 20% hydrochloric acid (2·5 c.c.), α-amino-α-phenylacetic acid hydrochloride, m. p. 218—220°, separating on cooling. The free acid (subliming at 225°) also was obtained by neutralisation of the filtrate with sodium hydrogen carbonate.

No other *N*-alkyl derivatives of the tetrahydroketoglyoxalines or of their 3-acyl derivatives could be obtained by any method tried.

N-*Benzylideneaminoacetonitrile.*—Redistilled benzaldehyde (21·2 g.) was added to a solution of aminoacetonitrile (11·2 g.) in chloroform (20 c.c.), and the solution was set aside until the turbid liquid had separated into two layers (1 hour). The water (3·6 c.c.) was removed, and the chloroform layer was dried (Na_2SO_4), concentrated, and distilled *in vacuo*. The product (21·2 g., 74%), b. p. 92—93°/0·1 mm., was twice redistilled *in vacuo*. N-*Benzylideneaminoacetonitrile* formed a colourless, slightly viscous liquid, odourless when pure, n_D^{20} 1·5651 (Found: C, 74·9; H, 5·5; N, 19·6. $C_9H_8N_2$ requires C, 75·0; H, 5·6; N, 19·4%). Light absorption: $\lambda_{max.}$ 2580 Å; ε = 19,260. The compound decomposed slowly in moist air, producing benzaldehyde. It was miscible with organic solvents, and sparingly soluble in water; acidification of the solution gave an emulsion of benzaldehyde. Treatment with alcoholic hydrochloric or picric acid gave the corresponding salt of aminoacetonitrile. Ethereal hydrogen chloride produced a bulky colourless precipitate of the hydrochloride, which formed a deliquescent powder, m. p. 140° (decomp.), decomposed instantly by water to benzaldehyde.

Parallel reactions were carried out at room temperature between the Schiff's base (0·2 g.) and carbon disulphide (0·3 g.) in (*a*) commercial ether (*d* 0·720) and (*b*) ether (5 c.c.) thoroughly dried over sodium. Solution (*a*) developed a yellow colour in 5 minutes, and in 2 hours had deposited a quantity of thick yellow needles, m. p. 194—197° (decomp.); in 2 days solution (*b*) yielded none of this product, but had acquired a pale yellow colour. The product from (*a*) was recrystallised from methanol, to give bright yellow needles, m. p. 194—197°, of *5-benzylideneamino-2-mercaptothiazole* (Found: C, 54·9; H, 3·7; N, 12·5. $C_{10}H_8N_2S_2$ requires C, 54·5; H, 3·6; N, 12·7%). The thiazole was also prepared by warming 5-amino-2-mercaptothiazole (Cook, Heilbron, and Levy, *J.*, 1948, 201) with benzaldehyde in ethanol.

Benzylideneaminoacetonitrile did not appear to undergo any change when heated, a pure sample giving little distillation residue. A sample stored at 0° for 6 weeks, however, was found to have deposited a small quantity of hard, colourless prisms, m. p. 148—149°; after 10 months' storage, conversion appeared complete, giving a yellowish crystalline mass. Recrystallisation from ethanol gave colourless needles, m. p. 148—149°, of 2-phenylglyoxaline (Found: N, 19·9. Calc. for $C_9H_8N_2$: N, 19·4%). The Pauly test with diazotised sulphanilic acid was unsuccessful when applied to an aqueous

solution or suspension of the compound, but in aqueous-ethanolic sodium hydroxide the characteristic cherry-red colour developed slowly, and was changed to orange-yellow on acidification.

Similarly, benzaldehyde (3·2 g.) and ethyl aminocyanoacetate (4 g.), when set aside overnight in chloroform (20 c.c.), condensed with elimination of water; the oily Schiff's base (not isolated), when kept for 4 weeks in benzene, deposited colourless crystals (0·2 g.), m. p. 210°. The product, which formed colourless needles (from toluene), m. p. 225°, was almost certainly to be formulated, on the basis of analysis and a positive Pauly reaction, as *ethyl 2-phenylglyoxaline-4-carboxylate* (Found: C, 66·8; H, 5·8; N, 13·0. $C_{12}H_{12}O_2N_2$ requires C, 66·65; H, 5·6; N, 13·0%).

Condensation of Benzaldehyde with α-Amino-α-phenylacetonitrile.—α-Amino-α-phenylacetonitrile (10 g.) and benzaldehyde (9 g.) were kept overnight in chloroform (20 c.c.). The separated water (0·8 c.c., *ca.* 50%) was removed, and after drying and concentration the reaction mixture was distilled at 0·05 mm. After a low-boiling fraction (benzaldehyde), a reddish-yellow oil (4 g.) distilled at 160—170°. The distillation residue was an extremely viscous oil, which set to a mass of crystals, m. p. 265°, apparently crude lophine (2 : 4 : 5-triphenylglyoxaline, m. p. 275°, the highest-melting of the several thermal decomposition products of α-benzylideneamino-α-phenylacetonitrile; Beilstein's "Handbuch," Vol. XXIII, p. 318 and Vol. XIV, p. 469). The distillate crystallised slowly when kept in ether, giving prisms, m. p. 160—164°. On crystallisation from ethanol, the 2 : 4-diphenylglyoxaline formed needles, m. p. 164—166°, although on recrystallisation further from chloroform–methanol, the m. p. fell to 156—164° (Found: C, 81·55; H, 5·6; N, 12·15. Calc. for $C_{15}H_{12}N_2$: C, 81·8; H, 5·5; N, 12·7%). The isolation of this compound in three different forms, interconvertible by treatment with different solvents, was described by Haines and Wagner (*loc. cit.*). α-Amino-α-phenylacetonitrile when distilled at 0·05 mm. evolved water and ammonia, and gave a small yield of a light yellow oil, purified with ether–light petroleum to colourless prisms, m. p. 148—156°, undepressed on admixture with the sample of 2 : 4-diphenylglyoxaline of m. p. 164—166°. The bulk of the nitrile was converted into a resin. When heated at 50—60°/0·00001 mm., the nitrile (4 g.) sublimed to yield 1·5 g. of unchanged material, but the remainder again formed a hard resin.

Reaction of Aminoacetonitrile with Chloral.—Chloral (9 g.) was added slowly to aminoacetonitrile (3 g.) in chloroform (15 c.c.) with ice cooling. Dilution with benzene (5 c.c.) gave a mass of colourless leaflets (5 g.), m. p. 77—78°, which were collected and washed with ice-cold chloroform (5 c.c.). The addition *product* crystallised from benzene in colourless leaflets, m. p. 81° (Found: C, 24·2; H, 2·7; N, 13·55. $C_4H_5ON_2Cl_3$ requires C, 23·6; H, 2·5; N, 13·8%). On storage the compound decomposed completely in 3 months. The compound was treated with picric acid in aqueous ethanol to give the picrate in golden yellow platelets, m. p. 125°, strongly depressed on admixture with aminoacetamide picrate.

Reaction of 5-Imino-2 : 2-dimethyloxazolidine with Aromatic Aldehydes.—The oxazolidine (10 g.), benzaldehyde (redistilled) (13 g.), and water (1 drop) were heated together until an exothermic reaction commenced, and kept for 2 minutes at such a temperature that acetone slowly distilled from the mixture. After the residue had cooled to 100°, benzene (10 c.c.) was added. Cooling to 0° and further addition of benzene (*ca.* 10 c.c.) to the point of precipitation gave the Schiff's base (10·4 g., 73%) in colourless crystals, m. p. 125—126°. On recrystallisation from benzene, the *N-benzylideneaminoacetamide* formed short needles, m. p. 126° (Found: C, 66·7; H, 6·4; N, 17·0. $C_9H_{10}ON_2$ requires C, 66·7; H, 6·2; N, 17·3%). Light absorption in ethanol: $\lambda_{max.}$ 2510 Å, ε = 17,010; $\lambda_{infl.}$ 2560 Å, ε = 15,390. In the preparation of the Schiff's base, a small quantity of a by-product was usually obtained, forming colourless leaflets (from ethanol), m. p. 178—179°, which was found to be the water-soluble salt *carbamylmethylammonium benzoate* (Found: C, 55·3; H, 6·3; N, 14·1. $C_9H_{12}O_3N_2$ requires C, 55·1; H, 6·2; N, 14·3%). The reaction of 5-imino-2 : 2-dimethyloxazolidine with piperonaldehyde, *p*-anisaldehyde, or salicylaldehyde was effected by the same technique, using in each case 1 g. of the oxazolidine and 2·5 g. of the aldehyde. Thus, were obtained (3 : 4-*methylenedioxybenzylideneamino*)*acetamide* (58%), needles (from ethyl acetate), m. p. 185—186° (Found: C, 58·0; H, 4·9; N, 13·3. $C_{10}H_{10}O_3N_2$ requires C, 58·2; H, 4·9; N, 13·6%), α-p-*methoxybenzylideneaminoacetamide* (47%), felted needles, m. p. 153° (from ethanol) (Found: C, 62·2; H, 6·4. $C_{10}H_{12}O_2N_2$ requires C, 62·5; H, 6·3%), and α-N-o-*hydroxybenzylideneaminoacetamide* (44%), short, very pale yellow needles (from ethyl acetate), m. p. 134°, which imparted a bright yellow colour to solvents (Found: C, 60·5; H, 6·0. $C_9H_{10}ON_2$ requires C, 60·7; H, 5·7%). Samples of the last and of the benzylidene compound were readily prepared, in low yield, by warming aminoacetamide with an equivalent quantity of the aldehyde, alone or in ethanol. All the Schiff's bases were broken down in 1—2 minutes by boiling water, to the aldehyde and aminoacetamide (isolatable as the picrate). In cold ethanol they formed crystalline picrates of indefinite m. p., passing into aminoacetamide picrate on recrystallisation. The benzylidene compound was unchanged by refluxing it with pyridine or acetic anhydride, although coloration and resinification occurred on treatment with acetic anhydride containing 0·1% of sulphuric acid.

Reaction of 5-Imino-2 : 2-dimethyl-4-phenyloxazolidine with Aromatic Aldehydes.—The oxazolidine (3 g.), salicylaldehyde (4·5 g.), and water (1 drop) were heated together until reaction commenced, and kept at the distillation temperature for 2 minutes. The solution was cooled, diluted with ethyl acetate (7·5 c.c.), and left at 0° until the crude α-*o*-hydroxybenzylideneamino-α-phenylacetamide (3·6 g., 90%) separated. The m. p. rose, on recrystallisation from methanol, from 148—150° to 151—152°, and was undepressed by admixture with a sample prepared as described by Clarke and Francis (*loc. cit.*). The benzylidene compound was also prepared from 5-imino-2 : 2-dimethyl-4-phenyloxazolidine, and proved to have m. p. 125—126° (corr.) and not 120—121° as found by the above authors (Light absorption: $\lambda_{max.}$ 2510, 2560 Å; ε = 23,320, 22,380).

Condensation of Tetrahydro-4-keto-2 : 2-dimethylglyoxaline with Benzaldehyde.—The glyoxaline (5 g.) and benzaldehyde (10 g.) were heated together under reflux for 5 minutes, cooled to 100°, diluted with benzene (10 c.c.), and left at 0° until separation of the crystalline product (5·05 g., 37%), m. p. 176—

179°, was complete. Recrystallisation from ethyl acetate gave the 2 : 3 : 4 : 5-*tetrahydro*-4-*keto*-2 : 2-*dimethyl*-2′ : 5′-*diphenyloxazolidino*(3′ : 4′-1 : 5)*glyoxaline* (XVII) in colourless needles, m. p. 187° (Found : C, 74·0; H, 6·8; N, 9·0. $C_{19}H_{20}O_2N_2$ requires C, 74·0; H, 6·5; N, 9·1%). The compound was stable to hot water, and decomposed very slowly in boiling aqueous sodium hydroxide, although instantly decomposed by mineral acid. The compound (XVII) (6·5 g.), and concentrated hydrochloric acid (15 c.c.) were heated for 1 minute on the steam-bath. On cooling, benzaldehyde was removed by extraction with carbon tetrachloride, and the aqueous layer was treated with potassium hydroxide (5 g.) in water (10 c.c.). After 10 minutes at 0°, the separated base, m. p. 178° (4·2 g., 91%), was collected and washed with water. On crystallisation from methanol, the *tetrahydro*-5-α-*hydroxybenzyl*-4-*keto*-2 : 2-*dimethylglyoxaline* (XVIII) formed colourless prisms, m. p. 178° (Found : C, 65·8; H, 7·3; N, 13·2. $C_{12}H_{16}O_2N_2$ requires C, 65·4; H, 7·3; N, 12·7%). The base formed a stable picrate, m. p. 159°, but the hydrochloride (formed in ethanol), m. p. 146—147°, decomposed in a desiccator. It was resistant to acetylation, and was recovered unchanged after 5 minutes' refluxing in concentrated hydrochloric acid.

β-Phenylserine Ethyl Ester.—The glyoxaline derivative (XVIII) (1·1 g.) and 20% ethanolic hydrogen chloride (10 c.c.) were heated together under reflux for 16 hours, cooled, and freed from ammonium chloride (0·24 g.) which had separated. The filtrate was evaporated to a syrup, taken up in absolute ethanol (3 c.c.), and filtered once more from ammonium chloride. On dilution with dry ether, the solution deposited a crystalline salt (1·1 g., 81%), m. p. 128—130°. On recrystallisation from ethanol–ether, the β-phenylserine ethyl ester hydrochloride formed cubical masses of colourless prisms, m. p. 134—135° (Found : C, 53·5; H, 6·7; N, 5·8. Calc. for $C_{11}H_{16}O_3NCl$: C, 53·8; H, 6·6; N, 5·7%). (Since the completion of this work, Hayes and Gever, *J. Org. Chem.*, 1951, **16**, 269, have described the preparation, from β-phenylserine, of the ethyl ester hydrochloride, m. p. 136—137°.) An ethanolic solution of the hydrochloride was treated with picric acid to yield the *picrate* of the ester in bright yellow needles, m. p. 156—157° (Found : C, 46·7; H, 4·5; N, 12·9. $C_{17}H_{18}O_{10}N_4$ requires C, 46·6; H, 4·1; N, 12·8%).

Condensation of Tetrahydro-4-*keto*-2 : 2-*dimethyl*-5-*phenylglyoxaline with Benzaldehyde.*—The glyoxaline (5 g.) and benzaldehyde (10 g.) were heated for 2 minutes under reflux. After cooling to 70—80°, the solution was diluted with methanol (15 c.c.) and kept at 0° until crystallisation was complete. The large yellow needles (4·7 g., 55%) were washed with methanol and dried in air. After crystallisation from ethanol the *substance* produced formed short pale yellow needles, m. p. 215° (Found : C, 81·0; H, 5·4; N, 8·6. $C_{22}H_{18}ON_2$ requires C, 80·8; H, 5·6; N, 8·6%). Crystallisation from ethyl acetate gave colourless felted needles, m. p. 225°, which had an identical analysis. The light yellow colour and lower m. p. were again observed on recrystallisation of this material from ethanol or aqueous ethanol. Prolonged refluxing with concentrated aqueous or ethanolic hydrogen chloride gave only the *hydrochloride*, m. p. 214° (Found : C, 73·2; H, 5·3; N, 7·8. $C_{22}H_{19}ON_2Cl$ requires C, 72·6; H, 5·5; N, 7·7%), from which the base was easily regenerated with pyridine in methanol. The picrate formed yellow needles, m. p. 170—171°.

Condensation of the Tetrahydroketoglyoxalines (II; R = H and Ph) *with Other Aldehydes.*—The compounds (II) were treated with salicylaldehyde, *p*-anisaldehyde, and piperonaldehyde, either by the technique employed for the 5-imino-oxazolidines, or in boiling pyridine, to give in moderate yields the appropriate Schiff's bases of (respectively) aminoacetamide and α-amino-α-phenylacetamide. The spiran described above also underwent this reaction, benzaldehyde in this case reacting as did other aromatic aldehydes to give the α-arylideneaminoacetamide. The compound (II; R = H) did not react with *cyclo*hexanone or phenylacetaldehyde under comparable conditions.

Reactions of Tetrahydro-4-*keto*-1 : 2 : 2-*trimethylglyoxaline and of α-Alkylamino-amides with Aldehydes.*—The glyoxaline (1 g.) and benzaldehyde (2·5 g.) were heated for 3 minutes under reflux with 1 drop of water, cooled, and treated with benzene (7 c.c.) and ice-cold light petroleum to the point of precipitation; after 1 day the colourless crystalline product (0·6 g., 39%) was collected, and washed with ether, and dried *in vacuo*; it then had m. p. 108—109°, unchanged on recrystallisation from light petroleum, which gave the 5-*imino*-3-*methyl*-2-*phenyloxazolidine* in plates (Found : C, 68·6; H, 6·8. $C_{10}H_{12}ON_2$ requires C, 68·2; H, 6·8%). The oxazolidine was hydrolysed very slowly by boiling water, or by cold 2N-hydrochloric acid, but immediately by hot mineral acid. Use of *p*-anisaldehyde (2 g.) similarly yielded 5-*imino*-3-*methyl*-2-p-*methoxyphenyloxazolidine* (1·4 g., 45%), m. p. 117—119°, which formed hexagonal plates, m. p. 117°, on recrystallisation from benzene (Found : C, 64·1; H, 6·7; N, 13·6. $C_{11}H_{14}ON_2$ requires C, 64·1; H, 6·8; N, 13·6%).

Sarcosine amide (1·8 g.), benzaldehyde (2·2 g.), ethanol (7 c.c.), and sodium ethoxide (trace) were heated under reflux for 3 hours. On concentration to 8—9 c.c., the solution commenced to deposit crystals; after 30 minutes in ice, the crystals were collected, and a second crop was obtained by evaporation (total : 3·1 g., 86%). Recrystallisation from light petroleum gave 5-imino-3-methyl-2-phenyloxazolidine, m. p. 108—109°, undepressed by the material prepared at above.

N-Methylvaline amide (2·6 g.), benzaldehyde (2·1 g.), ethanol (10 c.c.), and sodium ethoxide (trace) were heated under reflux for 3 hours and kept at 0° overnight. The product was obtained in two crops (total : 3 g., 70%) of large plates, m. p. 160—163°. On recrystallisation from ethanol, 5-*imino*-3-*methyl*-2-*phenyl*-4-iso*propyloxazolidine* formed platelets, m. p. 165—166° (Found : C, 71·7; H, 8·2; N, 13·1. $C_{13}H_{18}ON_2$ requires C, 71·5; H, 8·3; N, 12·8%).

Anilinoacetamide (Bischoff, *Ber.*, 1899, **22**, 1809) (1 g.), benzaldehyde (0·7 g.), methanol (15 c.c.), and sodium ethoxide (trace) were heated for 21 hours at 140°. On evaporation to 7 c.c. and storage for a short time in ice, the solution deposited the condensation product (0·55 g., 35%) in pale yellow needles, m. p. 218—220°; on recrystallisation from methanol the latter were obtained as short colourless rods, m. p. 222° (Found : C, 75·7; H, 5·95; N, 11·8. Calc. for $C_{15}H_{14}ON_2$: C, 75·6; H, 5·9; N, 11·8%). Light absorption in ethanol, $\lambda_{max.}$ 2420 Å; $\varepsilon = 16{,}600$. The compound did not depress the m. p. of a sample, m. p. 220°, prepared in poor yield from " anhydroformaldehydeaniline," benzaldehyde,

and potassium cyanide [Miller and Plochl, *loc. cit.*, recorded m. p. 219° and assigned the structure (XXVI; R = H)].

Condensation of Aminoacetamide and Formaldehyde.—Aminoacetamide (6·5 g.) in methanol (25 c.c.) containing sodium ethoxide (trace) was treated with gaseous formaldehyde, swept into the apparatus by a slow stream of nitrogen from a vessel in which paraformaldehyde (4 g.) was depolymerised by heat. The solution was cooled in ice during the reaction, after which the product crystallised when kept for 1 hour at 0°. The crude material (6·2 g., 82%) had m. p. 155—157°; recrystallisation from methanol gave the 1 : 3 : 5-*tri*(*carbamylmethyl*)*hexahydro*-1 : 3 : 5-*triazine* (XXXIV) as colourless needles, m. p. 162° (Found: C, 42·5; H, 7·15; N, 32·55. $C_9H_{18}O_3N_6$ requires C, 41·85; H, 7·0; N, 32·55%). Determination of molecular weight by Rast's method was impossible owing to decomposition. No crystalline salts or acyl derivatives were formed; treatment with phenylacetyl chloride and aqueous sodium hydrogen carbonate gave phenaceturamide and formaldehyde.

α-Chloro-*N*-hydroxymethylacetamide (Einhorn, *Annalen*, 1906, **343**, 207) was treated with hot ethanolic ammonia, to yield ammonium chloride (nearly quantitatively) and an oily substance which could not be characterised. *N*-Hydroxymethyl-α-iodoacetamide (Einhorn, *loc. cit.*) (8 g.) was shaken with saturated aqueous ammonium carbonate (600 c.c.) and aqueous ammonia (*d* 0·880; 200 c.c.) until dissolved, and set aside for 10 days. The resulting solution was evaporated *in vacuo* at 50—55°; the residual syrup was treated with ethanol (25 c.c.) to give, in two crops (total, 5 g.), colourless cubical crystals of aminoacetamide hydriodide, m. p. 195°, raised to 200—203° on recrystallisation from acetic acid. The salt was soluble in water but sparingly soluble in ethanol or methanol, and oxidised on storage.

A solution of *N*-hydroxymethyl-α-iodoacetamide (4 g.) in saturated methanolic ammonia (50 c.c.) was kept for 2 days at room temperature. On evaporation, a semisolid mass remained, which yielded colourless cubical crystals (3·7 g.) of a hydriodide, m. p. 161—166°, on methanol–acetone recrystallisation. The m. p. remained indefinite on further crystallisation. The salt (1 g.) was treated with 10% sodium hydroxide (5 c.c.) and phenylacetyl chloride (0·4 g.) at 0° with shaking; in 10 minutes colourless plates (0·65 g.) separated, which had m. p. 167—170°. On recrystallisation from methanol, the *product* formed colourless octahedra, m. p. 173—174° [Found: C, 35·5; H, 6·35; N, 10·35; I (volumetric, as iodide), 31, 34. $C_{12}H_{24}O_4N_3I$ requires C, 35·8; H, 6·2; N, 10·4; I, 31·6%).

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