Three- and Four-membered Heterocyclic Rings.

THE TILDEN LECTURE, DELIVERED AT THE ROYAL INSTITUTION, LONDON, ON JANUARY 20TH, 1949, AND IN NEWCASTLE ON JANUARY 28TH, 1949.

By F. E. KING, M.A., D.Phil., D.Sc.

THE 3- and 4-membered rings, with their unique stereochemical problems and exceptional reactivity, have remained since the days of their discovery in the 1880's one of the most attractive themes in Chemistry. Under the stimulus afforded by the researches of the younger W. H. Perkin, the early history of this subject is chiefly concerned with the carbocyclic compounds, and, although the smaller heterocyclic systems were also well known at the beginning of the century, their derivatives were not so closely or consistently studied.

For several reasons this group of heterocyclic compounds has in more recent times begun to attract wider attention, and in view of its growing importance it seemed of interest to summarise progress in this division of chemistry. It was soon evident, however, on undertaking a survey of the literature, that the 3- and 4-membered heterocyclic compounds were already far too numerous to be covered in a single lecture, and it has been necessary to limit the types to be discussed. The group which has been selected for review consists of the smaller rings containing a single atom of nitrogen as the hetero-element, *i.e.*, the ethylene- and trimethyleneimines, and the corresponding lactams and imides.

Cyclic Imines.

From the ease of formation of pyrrolidine and piperidine rings on the one hand, and of the analogous *cyclo*paraffins on the other, it may be assumed that, on substituting the heteroatom for one of the carbons of the 3- and 4-membered homocyclic structures, no new stereochemical factor will be introduced. According to the general principles of ring-formation as stated by Ruzicka,[1] the preponderating effect of the more favourable " distance factor " should cause ethyleneimine (aziridine) to be somewhat more readily synthesised than trimethyleneimine (azetidine), though neither would be expected to be formed with the ease of their higher homologues, pyrrolidine and piperidine.

This conclusion cannot be verified, as can sometimes be done in the carbocyclic series, by comparing the relative yields of the various cyclic imines, since the necessary data do not exist. The 38% of ethyleneimine obtained by distilling a mixture of 2-bromoethylamine hydrobromide and strong aqueous potassium hydroxide—the original method of preparation [2]—is of the undried base, b. p. 54—67°; the yield of trimethyleneimine from the 3-bromopropylamine hydrobromide [3] has not been recorded. Ladenburg's synthesis, viz., pyrolysis of the alkylenediamine hydrochlorides, gives an unknown but evidently limited yield of trimethyleneimine,[4] and does not succeed with ethylenediamine (which affords piperazine).[5] The remaining preparation of trimethyleneimine is from toluene-*p*-sulphonyltrimethyleneimide, formed with its 8-ring dimer from trimethylene bromide, toluene-*p*-sulphonamide, and alkali; the imine is then obtained by sodium–amyl alcohol reduction.[6] The original paper does not state the amounts obtained, and the sole recorded figures (39% and 14%), which are from recent work,[7, 8] refer only to the second stage of the synthesis.

The corresponding ethylenesulphonimide has not been prepared, except as a derivative of the already formed imine, although the syntheses of some substituted 3-ring sulphonimides from open-chain compounds have been described.[9] Whether reductive fission of the sulphonyl group is possible is not known, but there is evidence in the hydrogenolysis of toluene-*p*-sulphonyl-2-phenylethyleneimide to phenylethylamine or its sulphonamide [10] and of 2 : 2-dimethylethyleneimine to *tert.*-butylamine,[11] that it would lead to destruction of the imine ring.

Fortunately, the bromo-amines readily undergo intramolecular condensation in dilute solutions at ordinary temperatures, so that accurate measurements of the velocity of the reaction can be made. The velocity constants at 25°, determined by Freundlich and Salomon,[12] are shown in Table I, and they give convincing proof to Ruzicka's theory of ring formation in its application to the cyclic imines.

The rate of cyclisation to ethyleneimines is generally increased, sometimes very markedly, by the presence of substituents. This is strikingly shown by the following data collected by Salomon,[13] on the ring-closure of some 2-chloroethylamines.

TABLE I.

Ring-closure constants ($t = 25°$) : effect of chain length.

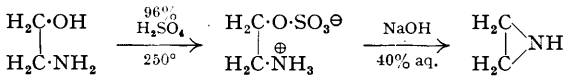
		k.
$Br·[CH_2]_2·NH_2$	Ethyleneimine	0·036
$Br·[CH_2]_3·NH_2$	Trimethyleneimine	0·0005
$Br·[CH_2]_4·NH_2$	Pyrrolidine	*ca.* 30
$Br·[CH_2]_5·NH_2$	Piperidine	0·5

TABLE II.

Ring-closure constants ($t = 25°$) : effect of substituents.

	k.		k.
$Cl·CH_2·CH_2·NH_2$	0·0005	$Cl·CHMe·CH_2·NH_2$	0·002
$Cl·CHPh·CH_2·NH_2$	0·4	$Cl·CH_2·CHMe·NH_2$	0·015
$Cl·CH_2·CHPh·NH_2$	*ca.* 0·0003		

The study of the ethyleneimines was greatly assisted when ethanolamine and some of its homologues became available as technical products. From these the chloroethylamines are then readily obtained by the action of thionyl chloride, and improved methods of treating the chloro-compounds with alkalis have led to high yields of the cyclic bases, 60—70% over-all in the case of ethyleneimine.[14] A useful contribution was made in 1935 by Wenker,[15] who found that ethyleneimine is very conveniently prepared from ethanolamine through the sulphuric ester-salt :



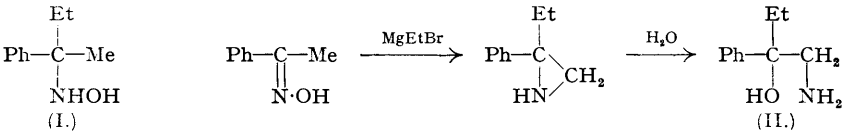
This synthesis is particularly successful for some of the *C*-alkylethyleneimines, as shown by the following data due to G. D. Jones : [8]

Ethanolamine.	Imine.	Yield.	B. p.
$HO·CH_2·CH_2·NH_2$	Ethyleneimine	32%	55—56°
$HO·CHMe·CH_2·NH_2$	2-Methylethyleneimine	65%	63—64°
$HO·CH_2·CHEt·NH_2$	2-Ethylethyleneimine	46%	88—89°
$HO·CHMe·CHMe·NH_2$	2 : 3-Dimethylethyleneimine	47%	65—77° (mixed isomers)
$HO·CH_2·CMe_2·NH_2$ *	2 : 2-Dimethylethyleneimine	68%	69—70°
$HO·CHMe·CMe_2·NH_2$	2 : 2 : 3-Trimethylethyleneimine	19%	83—85°
$HO·CHPr·CMe_2·NH_2$	2 : 2-Dimethyl-3-*n*-propylethyleneimine	57%	128—129°

* $HO·CMe_2·CH_2·NH_2$ does not give 2 : 2-dimethylethyleneimine.[16]

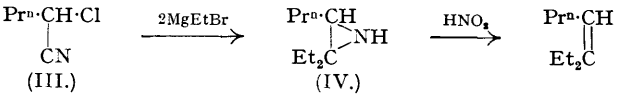
The aryl-substituted ethanolamines cannot be cyclised in this way, as they are too readily dehydrated, giving vinylamines which then resinify. The preparation of trimethyleneimines by the Wenker method has apparently not been investigated.

A remarkable synthesis of the aziridine ring occurs when alkyl- or aryl-magnesium halides react with the aryl alkyl ketoximes.[17] The reaction appeared to be of use for the preparation of substituted hydroxylamines, *e.g.*, (I), but the supposed hydroxylamines proved to be ethanolamines (II) arising from the primary products, the ethyleneimines, which were then isolated in good yield by modifying the experimental procedure :

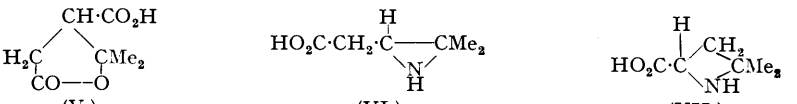


As is well known, the valency distortion consequent on the formation of the smaller imine rings gives them abnormal reactivity; this is especially marked with ethyleneimines owing to the small dimensions of the 3-membered ring. Freundlich and Neumann [18] have shown that the reaction, $Br·CH_2·CH_2·NH_2 = (CH_2)_2NH,HBr$, is quantitatively reversed in hydrobromic acid solution, and have measured the velocity of the change. Trimethyleneimine has long been known to undergo a similar change, in warm dilute hydrochloric acid, to 3-chloropropylamine hydrochloride,[6] but there are no data from which a quantitative comparison with

ethyleneimine can be made. The greater acid-stability of the 4-ring base is evident, however, in its reaction with nitrous acid to form *N*-nitrosotrimethyleneimine, whereas the fragility of the ethyleneimine ring precludes the formation of nitroso-compounds. Reaction with nitrous acid may therefore sometimes serve as a means of identifying ethyleneimines, for example, the imine (IV) synthesised from the α-chloro-nitrile (III) and ethylmagnesium bromide : [19]



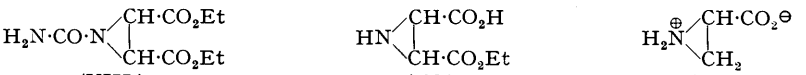
(III.) (IV.)



(V.) (VI.) (VII.)

Of the two structures suggested by Corselli [20] for the product obtained on heating terebic acid (V) with alcoholic ammonia, the ethyleneimine (VI) can at once be rejected since the compound gives a crystalline nitroso-derivative. On the other hand, from the stability of the substance to acids, the alternative constitution (VII) is also very improbable.

The existence of ethyleneimine-carboxylic acids has never definitely been established; compounds obtained from ethyl dibromosuccinate and ammonia, and described in the early literature as cyclic imines, are most probably derivatives of aminofumaric (iminosuccinic) acid. A more recent example, to which Curtius and Dörr [21] have assigned the constitution (VIII), is the principal compound obtained from the action of carbamic azide on ethyl fumarate.



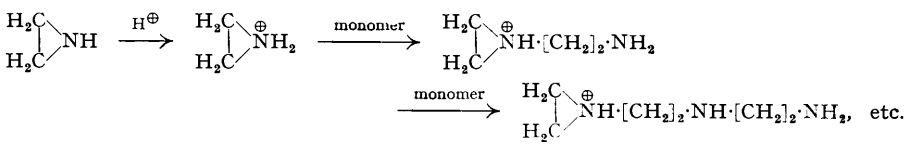
(VIII.) (IX.) (X.)

Its hydrolysis product, regarded as (IX), has m. p. 73° and is thus not identical with the corresponding half ester (m. p. 98°, 100°) originating from ethyl dibromosuccinate, but the cyclic nature of these substances has since been disputed.[22] Compounds of this series would almost certainly be internal salts, as in (X); in view of the instability of the ethyleneimmonium ion, it is unlikely that the ethyleneimino-acids could be isolated.

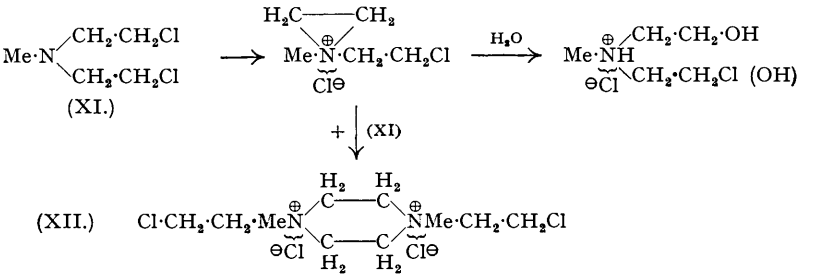
The most important feature of the ethyleneimines, and to a limited extent of trimethyleneimine, is their ability to undergo additive polymerisation when catalysed by acids (including CO_2). In this, ethyleneimine behaves as if it were the unknown vinylamine, $H_2C{:}CH{\cdot}NH_2$, the constitution attributed to the base by its discoverer Gabriel, until the sulphonamides were found by Marckwald [23] to be alkali-insoluble.

In the last 10—12 years a considerable patent literature has accumulated covering not only polymerisation, but also crossed polymerisations of ethyleneimine with halogenated paraffins, saturated and unsaturated organic acids, *iso*cyanates, *iso*thiocyanates, carbon disulphide, sulphur chloride, mercaptans, etc., to give numerous products of potential value in rubber, paint, leather, and petroleum technology, and in the various ramifications of the plastics industry. Obviously, these phases of the subject are far too vast for description here.

G. D. Jones *et al.*[24] have investigated the mechanism of ethyleneimine polymerisation by observing the behaviour of the imine with hydrochloric acid in ether and in aqueous solution. On adding the solid freshly precipitated from ethereal hydrogen chloride to alkali, there were obtained ethyleneimine, and a base, $C_4H_{10}N_2$, also readily polymerised, which was identified by synthesis as 2-aminoethylethyleneimine. 2-Chloroethylamine hydrochloride is not formed in ethereal hydrogen chloride except after being kept for some time, and the free chloroamine is only comparatively slowly polymerised at room temperature. From these observations it is concluded that polymerisation is a bimolecular reaction of monomer with ethyleneimmonium (and then substituted immonium) ions, which can be represented as follows :



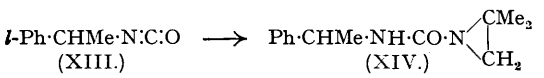
The formation of cyclic ethyleneimmonium salts was the subject of detailed investigation during the late war as it is closely bound up with the chemistry of the "nitrogen mustard gases." * Methylbis-2-chloroethylamine (XI), for example, undergoes dimerisation—which can be very rapid in alcohol—to the dipiperazinium salt (XII), and it is also slowly hydrolysed in contact with water. These reactions have been found to depend on an initial cyclisation to the 2-chloroethylimmonium salt : [26]



3-Bromopropylamines, $Br{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NR_2$ (R = Et, Pr^n, Bu^n), also undergo condensation when allowed to stand without a solvent or in concentrated solution, forming quaternary salts with 4-ring structures, but the dimethylamino-base gives a linear polymer. A monomeric quaternary salt can be obtained if the dimethylaminopropyl bromide is left in dilute (0·01M.) ethanol solution, but it is unstable and readily polymerises.[27]

Many of the substituted ethyleneimines will exist in stereoisomeric forms. There are two such modifications of 2 : 3-diphenylethyleneimine, *meso* (*cis*) and racemic (*trans*), but optically-active ethyleneimines can only be prepared by ring-closure of the active 2-chloroethylamines,[28] and have never been obtained by resolution at the imine stage. On the other hand, several independent attempts were made about 10 years ago to prepare and resolve 2 : 2-disubstituted ethyleneimines in the hope of obtaining products in which optical activity would be due to asymmetry of the tervalent nitrogen atom; the subject was well reviewed at the time by Maitland.[29] The expectation that ethyleneimines would be resolved is based on the view that the 3-membered cyclic imines afford the nearest approach among saturated nitrogen compounds to the strained $>C{=}N^-$ group of the oximes, etc., which owe their geometrical isomerism to its non-planar structure. At the time these attempts were made, the stability of the separate pyramidal forms of the nitrogen in the ethyleneimine ring was merely a plausible supposition. However, later calculation from spectroscopic data [30] shows that the activation energies of racemisation for the stereoisomeric forms of a given ethyleneimine are considerably above the minimum value necessary for stability, so that the project now has secure theoretical foundation.

In the attempted resolution, salt formation with the imino-group must, of course, be avoided, or the nitrogen atom will lose its asymmetry through the formation of an immonium ion, $>\overset{\oplus}{N}HR$. Of the methods employed, the condensation of an optically active *iso*cyanate (XIII) with 2 : 2-dimethylethyleneimine is a later example,[31] but fractional crystallisation of the product (XIV) gave no evidence of separation into isomers.



It has been suggested by Pauling [32] that aryl or acyl groups attached to the nitrogen may inhibit the resolution owing to resonance between the unshared electrons and the adjacent unsaturated groups, thereby producing a planar molecule.

Unsaturated Cyclic Imines.

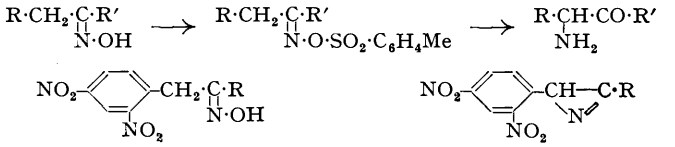
The inclusion of a double bond in the 3- and 4-membered rings will obviously add considerably to their instability. The strain factor will be especially high in the 3-ring (azirine); not only may the unsaturated link be expected to increase the tendency to self-condensation, but, if the unsaturation is situated between nitrogen and carbon—implying Schiff's base

* Ethyleneimine is itself an active vesicant.[25]

properties—the molecule may be even more labile. These characteristics, on the whole, would be less pronounced in the 4-membered azetine ring, and it is conceivable that this might have a certain measure of stability. These conclusions are supported by analogies in the carbocyclic series, where the existence of the 3-membered *cyclo*propene ring is generally considered to be improbable. *cyclo*Butene, on the other hand, is a fully authenticated hydrocarbon prepared by Willstätter in the experiments on *cyclo*butadiene.[33]

Compounds supposedly containing the unsaturated 3-membered azirine nucleus have been mentioned from time to time in the early literature,[34] but they have invariably been shown to possess other structures, *e.g.*, dihydropyrazine, or their polymeric nature can be inferred on general grounds.

A recent example of an alleged azirine structure which cannot so easily be dismissed is provided by the interesting synthesis of α-amino-ketones by Neber.[35] Oximes of aliphatic or mixed aliphatic–aromatic ketones are treated with toluene-*p*-sulphonyl chloride in pyridine solution. In general, the expected toluene-*p*-sulphonates are formed, from which, by dissolution in alcoholic potassium ethoxide, α-amino-ketones are obtained, but the action of toluene-*p*-

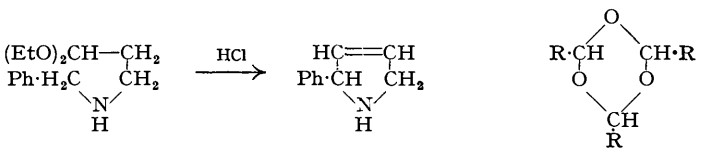


(XV.) (XVI.)

R = Me, m. p. 79°; Ph, m. p. 100°.

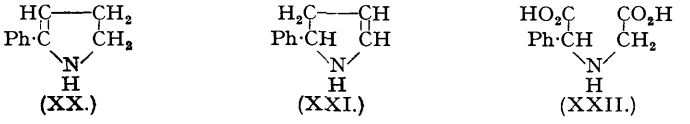
sulphonyl chloride and pyridine on the oximes (XV; R = Me) and (XV; R = Ph) gives salts of amines to which cyclic imine structures (XVI) have been ascribed. Analyses, and in one instance (XVI; R = Me) molecular-weight estimations, attest the molecular formulæ of the compounds, from both of which under suitable acid conditions the expected α-amino-ketones were then obtained.

No authentic examples of the unsaturated 4-membered azetine nucleus can be traced, though it might be supposed that a ring system of this kind would result from the intramolecular condensation of β-amino-aldehydes or -ketones. The self-condensation of β-amino-aldehydes leads generally to polymers,[36] but there existed an apparent exception in the cyclisation of β-benzylaminopropaldehyde diethyl acetal (XVII) in cold hydrochloric acid to the hydrochloride of the Δ^3-phenylpyrroline (XVIII).[37]



(XVII.) (XVIII.) (XIX.)

Re-examination showed that the product did not possess the properties of a pyrroline; a 4-ring structure therefore seemed possible, but was disproved when the base was found to be a trimer (XIX; R = $CH_2{\cdot}CH_2{\cdot}NH{\cdot}CH_2Ph$) [74] similar in constitution to the trimer of α-aminoacetaldehyde (XIX; R = $CH_2{\cdot}NH_2$).[38] Consequently, doubt arises as to the constitution of the phenylpyrroline obtained by Gitsels and Wibaut [39] in 1941 from the reduction of 2-phenylpyrrole. The product is readily methylated, and cannot therefore be a Δ^1-(or Δ^5-)pyrroline. 2-Phenyl-Δ^2-pyrroline (XX) had already been unambigously synthesised,[40] and the apparent exclusion of the Δ^3-isomer (XVIII) had therefore left only (XXI) for the structure of the new pyrroline.

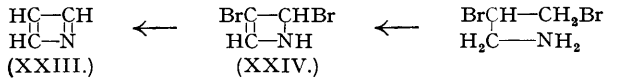


(XX.) (XXI.) (XXII.)

The supposed Δ^4-pyrroline has now been oxidised with ozone and hydrogen peroxide, but, instead of the expected product (β-amino-β-phenylpropionic acid), the known *N*-α-carboxy-

benzylglycine (XXII) was isolated.[74] The reduction of 2-phenylpyrrole is therefore analogous to that of pyrrole itself in giving the Δ^3-compound, and the Δ^4-phenylpyrroline is for the present unknown.

The non-existence of azirine and of azetine would seem to exclude all possibility of still more highly unsaturated structures such as (XXIII), although, as W. Baker [33] has suggested with reference to the yet unknown *cyclo*butadiene, the increased angular strain of aza-*cyclo*butadiene might in some degree be compensated by resonance.

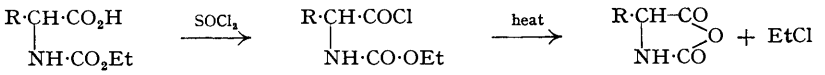


(XXIII.) (XXIV.)

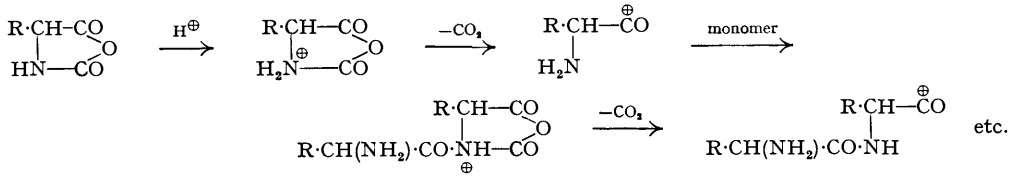
The structure (XXIII) was in fact assigned by Abderhalden and Paquin [41] to a volatile base (" pyriculine ") prepared by the action of sodium on the ethereal solution of a dibromo-amine believed to be (XXIV). The hydrobromide of this dibromo-base was said to be precipitated, with evolution of hydrogen, on leaving a solution of 2 : 3-dibromopropylamine in ether to stand for several days. The work has lately been repeated,[42] and the precipitated salt shown to be the hydrobromide of 2 : 3-dibromopropylamine; the bromine-free compound obtained from the intermediate dibromo-amine with sodium is, of course, allylamine, formerly obtained in this way by Paal.[43] The 2-methylpyriculine of Oesterreich,[44] prepared from 2 : 4-dimethyl oxazole and acetaldehyde, may in all probability also be discounted.

Lactams.

The recent accelerated growth in the hitherto limited field of the lower cyclic amides is a result of the interest in the chemistry of the penicillins, as in this group of substances there is recorded for the first time the natural occurrence of a β-lactam structure. The simplest possible cyclic amides, the α-lactams, do not exist; as a result of the over-riding tendency to form either diketopiperazines or chain condensates,[45] cyclic intramolecular anhydrides of the α-amino-acids have never been observed. Yet, their synthesis deserves attention, since, by a process similar to that which leads to polymethyleneimines, products of a polypeptide structure should become available. Synthetic substances of this type are already known, having been obtained from the anhydrides of *N*-carboxyamino-acids first synthesised by Leuchs.[46]

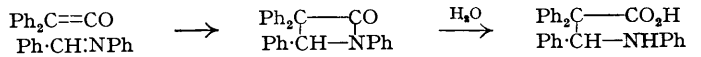


These anhydrides may be recrystallised, but, if left in moist air or solvents, or in contact with any substance able to liberate protons, loss of carbon dioxide occurs, accompanied by chain polymerisation :

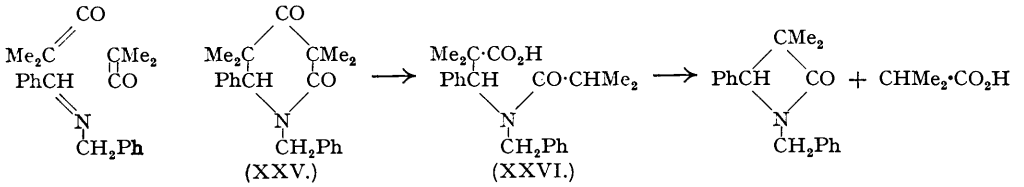


With the development of polymer chemistry, this reaction has acquired a new significance, and, in addition to the earlier experiments, the copolymerisation of carboxyanhydrides has now been investigated.[47] The Leuchs synthesis of peptides might be expected to give some monomeric compounds, but there is no evidence that they are present in the reaction products. It is possible that they may be obtainable under other experimental conditions, if the 3-ring structure is not rendered too unstable by resonance in the amide group.

Although there is at least one earlier reference to β-lactams,[48] these compounds were virtually unknown until Staudinger's synthesis of the lactam of β-anilino-αα-triphenyl-propionic acid from diphenylketen and benzylideneaniline.[49]



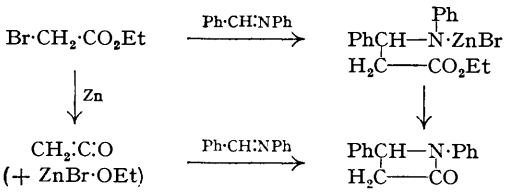
The constitution of this and similar products was confirmed by hydrolysis to the amino-acids. Some of the β-amino-acids have been recyclised to lactams by acid chlorides,[50] but it is a method of limited application. Not infrequently, *e.g.*, with dimethylketen, piperidine-diones (XXV) are obtained, formed from two molecules of the keten and one of Schiff's base. However, they are readily hydrolysed to acylamido-compounds (XXVI), and, when these are heated, the β-lactam ring is sometimes closed by loss of aliphatic acid.



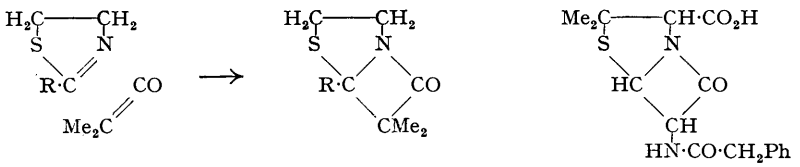
(XXV.) (XXVI.)

A further means of cyclising β-amino-acids was described by Breckpot in 1923,[51] depending on the action of the organomagnesium halides on their esters. From the ethyl esters of β-ethylamino- and β-methylamino-*n*-butyric acid and ethylmagnesium bromide, the corresponding β-lactams were isolated in low yields as distillable oils, of which the latter was hydrolysed to the amino-acid with concentrated hydrochloric acid. The application of this reaction to α-amino-esters, as a means of obtaining α-lactams, is being investigated.

1 : 4-Diphenylazetidinone, obtained by Staudinger from keten and benzylideneaniline,[52] was also synthesised by Gilman and Speeter [53] from the Schiff's base, ethyl bromoacetate, and zinc in boiling toluene. This condensation has been represented as a further example of the Reformatsky reaction, but it may be no more than a convenient modification of the Staudinger synthesis with the keten formed *in situ*. With the bromoacetic ester the method gives 56% of lactam, and with ethyl α-bromopropionate 85%.



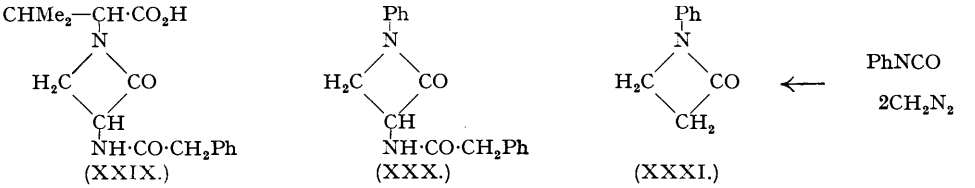
Adaptations of all these methods have been applied to the synthetical problems of penicillin chemistry, and they are extensively discussed elsewhere.[54] The results were disappointing; crystalline compounds containing the fused thiazolidine-β-lactam structure (XXVII) were obtained by condensing dimethyl- or diphenyl-keten with the >C=N– link of 2-methyl- or 2-phenyl-thiazoline, but it was not found possible to build up structures with the characteristic exocyclic acylamido-group of the penicillins, *e.g.*, (XXVIII).



(XXVII.) (XXVIII.)

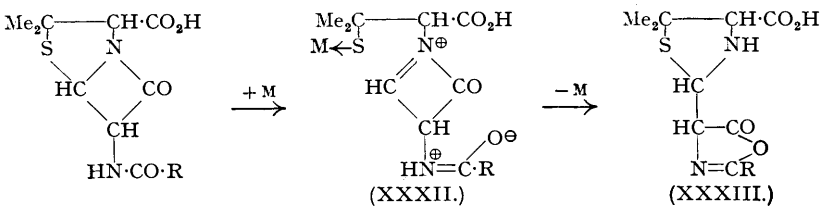
The outstanding characteristic of the chemistry of the penicillins—in which they contrast sharply, not only with the purely synthetic β-lactams, but also with dethiobenzylpenicillin (XXIX)—is the instability of the β-lactam ring. The tetraphenylazetidinone of Staudinger is extraordinarily difficult to hydrolyse; resistance to alkali is much less marked when features of the penicillin structure are present, as in the fused thiazolidine-β-lactams just mentioned, and in the acylamido-β-lactam (XXX) which requires approximately 1½ hours at 100° for complete hydrolysis with N-alkali. Still more readily attacked, though it has little in common with the penicillins, is the *N*-phenyl-β-lactam (XXXI), which is quantitatively converted into β-anilinopropionic acid by N-alkali at 70—80° in 10—12 minutes. The anilinopropionic-β-

lactam, a readily-soluble crystalline solid, m. p. 78—79°, is a recent addition to the series;[55] its preparation from phenyl *iso*cyanate and diazomethane is reminiscent of the synthesis



of *cyclo*butanone from diazomethane and keten. It is probably one of the simplest β-lactams yet known; the product obtained by Delépine[56] from the permanganate oxidation of one of the tricrotonylidenetetra-amines is too insoluble and inert to be the monomeric lactam of β-aminobutyric acid, though it forms this compound on vigorous hydrolysis.

Chain[57] has shown that the biological inactivation of the penicillins, *e.g.*, by methanol, is catalysed by traces of metals (copper, zinc, tin), and suggests that under the influence of adventitious traces of these elements it is the thiazolidine ring and not the lactam which is first broken. This leads to a strained, and hence highly reactive structure (XXXII), which by well-known electronic displacements re-arranges into an oxazolone (XXXIII). The metal atom is simultaneously transferred to another molecule, and re-formation of the thiazolidine ring follows. The various reactions by which the penicillins are so readily inactivated can then be expressed in terms of the well-established lability of the saturated oxazolone ring:



Before leaving the subject of the β-lactams, it is interesting to recall that one of the first references to this 4-membered heterocyclic system is to be found in some early experiments by Kipping and Perkin.[58] The compound they formulated as (XXXIV) was obtained from the diketo-ester (XXXV) by the action of cold alcoholic ammonia; although an 8-ring structure is a possible alternative, the constitution (XXXIV) has never been challenged. (A similar unsaturated structure is postulated for a compound prepared by Ruhemann and Allhusen.[59])

Cyclic Imides.

Of the 3- and 4-membered imides there are few if any authentic oxalimides. It does not seem possible to prepare the unsubstituted imide from oxamic acid, and the ethyl ester has given tetraketopiperazine.[60] Sabanéef's so-called phenyldicarbylamine, $PhNC_2$ (!), in its vigorous oxidation on exposure to air, is supposed to have given phenyloxalimide (oxanil), but there is little to prove its structure except that with water[61] the compound yields oxanilic acid. In this respect it differs considerably from the oxanil which Warren and Briggs[62] prepared from oxanilic acid by heating with thionyl chloride. The substance obtained by them is attacked only by concentrated sulphuric acid and alkaline reagents; it does not melt and has the low solubility of a polymer, despite the apparently normal molecular weight as determined in boiling nitrobenzene. The alcohol-soluble compound, m. p. 146°, described by A. G. Perkin[63] as 2 : 4 : 6-trinitro-oxanil, corresponds in properties much more closely with a simple cyclic imide.

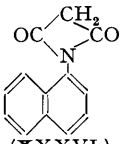
The action of boiling thionyl chloride on malonanilic acid is likewise said to give *N*-phenylmalonimide[62] (malonanil), another inert, high-melting solid, but the preparation of this

substance is proving difficult to repeat. It was hoped that malonimide might be prepared by hydrogenolysis of " malonylphenylhydrazine," a compound of m. p. 128° due to E. Fischer and Passmore.[64] It was said to be formed on heating at 200° the phenylhydrazine salt of the semiphenylhydrazide of malonic acid obtained on warming an aqueous acetic acid solution of phenylhydrazine and malonic acid.

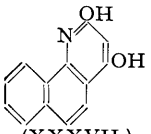
$$HO_2C{\cdot}CH_2{\cdot}CO_2H + 2NHPh{\cdot}NH_2 + AcOH\ aq.$$
$$\downarrow 100°$$
$$NHPh{\cdot}NH{\cdot}CO{\cdot}CH_2{\cdot}CO_2H, NHPh{\cdot}NH_2,\ m.\ p.\ 154°$$
$$\overset{200°}{\downarrow}\ 15\ min.$$
$$H_2C(CO)_2N{\cdot}NHPh,\ m.\ p.\ 128°$$

The reputed imide was again mentioned in 1940 by Biquard and Grammaticakis,[65] but they failed to obtain the salt of m. p. 154°, the compound of m. p. 128° separating in its stead. This has since been confirmed, though the supposed imide has been identified as acetylphenylhydrazide, MeCO·NH·NHPh.[74] The salt, m. p. 154°, is obtained only if the acetic acid is omitted from the preparation, but no product other than acetylphenylhydrazide can be isolated from its pyrolysis.

By refluxing ethyl malonate with α-naphthylamine R. Meyer [66] obtained a crystalline solid to which he ascribed a malonimide structure (XXXVI). It was noticed that the conditions of its formation were not unlike those of 2 : 4-dihydroxy-7 : 8-benzquinoline (XXXVII) [67] and a comparison of the two products has now established their identity.[75]

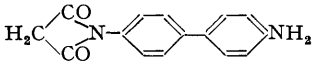


(XXXVI.)

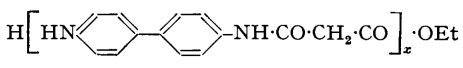


(XXXVII.)

This observation suggested a possible new structure for malonylbenzidine, first obtained by Remfry.[68] For the original multimembered ring, based on the Kaufler diphenyl structure, Le Fèvre [69] has substituted a malonimide formula (XXXVIII), characterised by an amorphous



(XXXVIII.)



(XXXIX.)

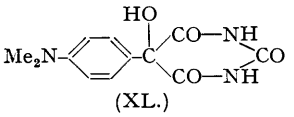
sulphate and a crystalline salicylidene derivative, m. p. 298—300°. Reinvestigation [74] of the sulphate discloses that the sulphur content varies with different preparations and is only a fraction of that required by the formula, $C_{15}H_{12}O_2N_2,H_2SO_4$. The derivative, m. p. *ca.* 300°, obtained from malonylbenzidine and salicylaldehyde by heating for a short time in phenol is heterogeneous, and contains disalicylidenebenzidine, m. p. 260°, which can be extracted with boiling benzene. After heating for 1¾ hours in phenol, almost the entire product is converted into disalicylidenebenzidine, m. p. and mixed m. p. 260°. The highly insoluble malonylbenzidine has all the characteristics of a polymeric substance (XXXIX), and there is no evidence to support the 4-ring-imide structure.

If on re-examination the small-ring imides seem to be a diminishing series, there remains one group, formed with remarkable ease, for which there is at least much circumstantial evidence.

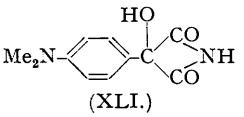
The first of these compounds was discovered long ago by Pellizzari [70] while investigating the condensation of alloxan with aromatic amines. When dissolved in dilute alkali, the resulting dialuric acids were decomposed with evolution of ammonia; typical of the products then precipitated on acidification is that from 5-*p*-dimethylaminophenyldialuric acid (XL), for which, among other possibilities, the structure (XLI) was proposed.

Dialuric acids of a similar nature, including many derived from phenols, are mentioned in several patents by Boehringer; [71] they are of interest as a source of aryltartronic acids, *e.g.*, (XLII), to which they are hydrolysed by boiling alkali. The supposed 4-ring imides

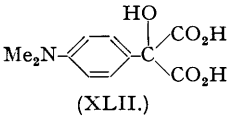
have not yet been degraded to tartronic acids, so that the isomeric 5-ring-imide (XLIII) formula can not be entirely excluded.



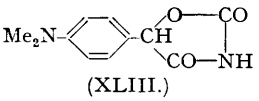
(XL.)



(XLI.)

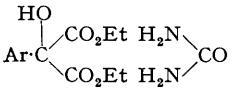


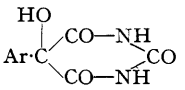
(XLII.)



(XLIII.)

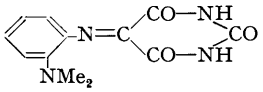
On the other hand, imides of apparently the same type have since been synthesised from various tartronic acids.[72] Ethyl esters of the tartronic acids were heated in alcoholic sodium ethoxide with urea, as in the standard pyrimidine synthesis, in the expectation that dialuric acids would be formed, but analyses indicated that the products were tartronic imides. This



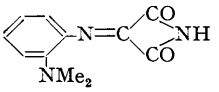


view was strengthened when the identical compounds were again obtained—though less successfully—on substituting ammonia for urea as the source of the imide nitrogen. The alternative 5-ring thus seems to be disproved, for it is difficult to imagine by what mechanism such a structure could be elaborated from a tartronic ester. Unfortunately, a direct comparison of the products obtained by the synthetic method with those from the alkaline hydrolysis of dialuric acids is not yet possible, as in no case have materials with the same aromatic substituents been used.

There is an apparent resemblance between the compounds just described and the imide which results from the hydrolysis of *o*-dimethylaminoaniline-alloxan anil (XLIV) with hot



(XLIV.)



(XLV.)

30% alkali.[73] The derivative is extraordinarily stable to hot concentrated alkalis and to hydrochloric acid, but its constitution as (XLV) is supported by analyses, determinations of molecular weight, and by a colour reaction with hydrogen peroxide and hydrochloric acid said to be specific for an *o*-dimethylamino-anil.

It is clear that there is still much to be learnt of the characteristics of the smaller ring systems. The further elucidation of their properties, and their examination by physico-chemical methods, may well lead to interesting progress in the chemistry of the heterocyclic compounds.

Added on March 24th, 1949.—Experiments completed (by Mr. J. W. C. Lewis) after the above account had been written show that the alkali-soluble hydrolysis product of 5-(2′ : 4′-dimethoxyphenyl)dialuric acid forms a monoacetate, and a monomethyl derivative insoluble in alkali and resistant to acetylation. This degradation product therefore appears to be 5-(2′ : 4′-dimethoxyphenyl)oxazolidine-2 : 4-dione, and despite indications to the contrary, *e.g.*, the synthetical work of Riebsohmer,[72] the existence of tartronic imides is thereby rendered improbable. It is significant that the so-called phenyltartronic imide [72] has m. p. 107·5—108°, a figure almost identical with that recorded for 5-phenyloxazolidine-2 : 4-dione (Traube and Ascher, *Ber.*, 1913, **47**, 2082). A further search instituted as a result of these observations has revealed that the alkali degradation products of some 5-substituted dialuric acids have in fact been identified synthetically as oxazolidinediones (Aspelund, *Acta Acad. Abœnsis Math. et Phys.*, 1939, **11**, No. 7, 4; 1939, **11**, No. 14, 3).

References.

[1] Ruzicka *et al.*, *Helv. Chim. Acta*, 1926, **9**, 499.
[2] Gabriel and Stelzner, *Ber.*, 1895, **28**, 2929.
[3] Gabriel and Weiner, *Ber.*, 1888, **21**, 2676.
[4] Ladenburg and Sieber, *Ber.*, 1890, **23**, 2727.
[5] Ladenburg and Abel, *Ber.*, 1888, **21**, 758.
[6] Howard and Marckwald, *Ber.*, 1899, **32**, 2031.
[7] Yanbikov and Dem'yanov, *Chem. Abs.*, 1939, **33**, 4583.
[8] Jones, *J. Org. Chem.*, 1944, **9**, 484.
[9] Likhosherstov, Arkhangel'skaya, and Shalaeva, *Chem. Abs.*, 1940, **34**, 3673.
[10] Kharasch and Priestley, *J. Amer. Chem. Soc.*, 1939, **61**, 3425.
[11] Karabinos and Serijan, *ibid.*, 1945, **67**, 1856; Campbell, Sommers, and Campbell, *ibid.*, 1946, **68**, 140.
[12] Freundlich and Salomon, *Ber.*, 1933, **66**, 355.
[13] Salomon, *Helv. Chim. Acta*, 1933, **16**, 1361.
[14] Private communication from Dr. Goodings, I.C.I. Ltd., Blackley; cf. Berchet, U.S.P. 2,212,146.
[15] Wenker, *J. Amer. Chem. Soc.*, 1935, **57**, 2328.
[16] Adams and Cairns, *ibid.*, 1939, **61**, 2464.
[17] Hoch, *Compt. rend.*, 1934, **198**, 1865; Campbell, *J. Org. Chem.*, 1939, **4**, 198; 1943, **8**, 99, 103; 1944, **9**, 185.
[18] Freundlich and Neumann, *Z. physikal. Chem.*, 1914, **87**, 69.
[19] Theunis, *Bull. Acad. roy. Belg.*, 1926, **12**, 785; de Booseré, *Bull. Soc. chim. Belg.*, 1923, **32**, 26.
[20] Corselli, *Gazzetta*, 1891, **21**, 271.
[21] Curtius and Dörr, *J. pr. Chem.*, 1930, **125**, 425.
[22] " Beilstein," 4th Ed., **22**, 117.
[23] Howard and Marckwald, *Ber.*, 1899, **32**, 2036.
[24] G. D. Jones *et al.*, *J. Org. Chem.*, 1944, **9**, 125.
[25] *Idem, ibid.*, p. 133; cf. Danehy and Pflaum, *Ind. Eng. Chem.*, 1938, **30**, 778.
[26] Hanby and Rydon, *J.*, 1947, 513 *et seq.*; Golumbic, Fruton, and Bergmann, *J. Org. Chem.*, 1946, **11**, 518 *et seq.*
[27] Gibbs and Marvel, *J. Amer. Chem. Soc.*, 1935, **57**, 1137; Mannich and Baumgarten, *Ber.*, 1937, **70**, 210.
[28] Weissberger and Bach, *Ber.*, 1931, **64**, 1095; 1932, **65**, 631.
[29] Maitland, *Ann. Reports*, 1939, **36**, 239.
[30] Kincaid and Henriques, *J. Amer. Chem. Soc.*, 1940, **62**, 1474.
[32] Cairns, *loc. cit.*, 1941, **63**, 871.
[32] Pauling, Gilman's " Organic Chemistry," 1938, Vol. 1, p. 334; cf. Tarbell and Fukushima, *J. Amer. Chem. Soc.*, 1946, **68**, 2499.
[33] W. Baker, *J.*, 1945, 258.
[34] Hollins, " Synthesis of Nitrogen Ring Compounds," 1924; Patterson and Capell, " The Ring Index," 1940, p. 32.
[35] Neber and Burgard, *Annalen*, 1932, **493**, 281; Neber and Huh, *ibid.*, 1935, **515**, 283.
[36] Wohl, *Ber.*, 1905, **38**, 4154; Voet, *Bull. Soc. chim.*, 1929, **45**, 61.
[37] Wohl, *Ber.*, 1901, **34**, 1914.
Richmond and Wright, *Canadian J. Res.*, 1945, **23**, 158.
[39] Gitsels and Wibaut, *Rec. Trav. chim.*, 1941, **60**, 50.
[40] Gabriel and Colman, *Ber.*, 1908, **41**, 513.
[41] Abderhalden and Paquin, *Ber.*, 1920, **53**, 1125.
[42] Gensler, *J. Amer. Chem. Soc.*, 1947, **69** 1966.
[43] Paal, *Ber.*, 1888, **21**, 3190; 1889, **22**, 3076.
[44] Oesterreich, *Ber.*, 1897, **30**, 2254.
[45] A. Bowman, D.Phil. Thesis, Oxford, 1940; Frankel and Katschalski, *J. Amer. Chem. Soc.*, 1942, **64**, 2264, 2268.
[46] Leuchs, *Ber.*, 1906, **39**, 857; see also Katchalski, Grossfield, and Frankel, *J. Amer. Chem. Soc.*, 1948, **70**, 2094, for other references.
[47] L. G. Goldsworthy, F. E. King, and (Sir) R. Robinson, unpublished experiments, 1936—1939; Woodward and Schramm, *J. Amer. Chem. Soc.*, 1947, **69**, 1551; Astbury, Dalgliesh, Darman, and Sutherland, *Nature*, 1948, **162**, 596.
[48] Einhorn, *Ber.*, 1883, **16**, 2649.
[49] Staudinger, *Ber.*, 1907, **40**, 1145.
[50] Staudinger *et al.*, *Annalen*, 1910, **374**, 1; Merck, CPS, 483.
[51] Breckpot, *Bull. Soc. chim. Belg.*, 1923, **32**, 412; see also Pfizer, CPS, 156, 456; Merck, CPS, 421.
[52] Staudinger, *Ber.*, 1917, **50**, 1035.
[53] Gilman and Speeter, *J. Amer. Chem. Soc.*, 1943, **65**, 2255.
[54] A. H. Cook, *Quarterly Reviews*, 1948, **2**, 203; H. T. Clarke, J. R. Johnson, and (Sir) R. Robinson, " The Chemistry of Penicillin."
[55] Sheehan and Izzo, *J. Amer. Chem. Soc.*, 1948, **70**, 1985.
[56] Delépine, *Compt. rend.*, 1943, **216**, 785.
[57] Chain, *Endeavour*, 1948, **7**, 152; Chain, Philpot, and Callow, *Arch. Biochem.*, 1948, **18**, 171.
[58] Kipping and Perkin, *J.*, 1889, **55**, 339.
[59] Ruhemann and Allhusen, *J.*, 1894, **65**, 9.
[60] de Mouilpied and Rule, *J.*, 1907, **91**, 176.
[61] Sabaneéff and Prosin, *Bull. Soc. chim.*, 1901, **25**, 823; *A*, 1902, i, 604.
[62] Warren and Briggs, *Ber.*, 1931, **64**, 28.
[63] A. G. Perkin, *J.*, 1893, **63**, 1066.
[64] E. Fischer and Passmore, *Ber.*, 1889, **22**, 2735.
[65] Biquard and Grammaticakis, *Bull. Soc. chim.*, 1940, **7**, 766.
[66] R. Meyer, *Annalen*, 1906, **347**, 23.
[67] Baumgarten and Kärgel, *Ber.*, 1927, **60**, 832.
[68] Remfry, *J.*, 1911, **99**, 610.
[69] Le Fèvre, *J.*, 1929, 733.
[70] Pellizzari, *Gazzetta*, 1887, **17**, 412; 1888, **18**, 340; 1889, **19**, 397; 1911, **41**, 21; see also Széki, *Ber.*, 1923, **56**, 2464.
[71] Boehringer, " Friedländer," **5**, 117, 863; **6**, 158 *et seq.*
[72] Riebsohmer *et al.*, *J. Amer. Chem. Soc.*, 1939, **61**, 3491.
[73] Rudy and Cramer, *Ber.*, 1938, **71**, 1234; *Oesterr. Chem.-Ztg.*, 1939, **42**, 329.
[74] F. E. King and J. R. Marshall, C. R. P. Morgan (Oxford), and J. W. C. Lewis, P. Smith (Nottingham), forthcoming publications.