Studies in Pyrazine Chemistry.

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A THESIS

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DEGREE OF DOCTOR OF PHILOSOPHY

in the

FACULTY OF SCIENCE

by

WILFRED SWEENY

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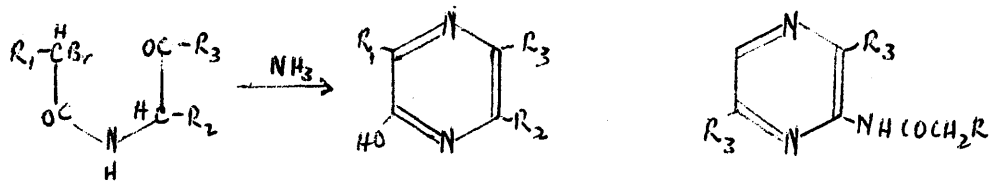
The author wishes to express his sincere gratitude to Professor F.S. Spring for his sustained interest in the work and general supervision; to Dr. G.T. Newbold for his constant help and interpretation of spectrographic data.

Thanks are also due to the Department of Scientific and Industrial Research for a maintenance grant and to the Governors of The Royal Technical College for facilities provided.

The considerable interest aroused by the antibacterial substance Aspergillic acid, which is a pyrazine cyclic hydroxamic acid, has lead to a renewed study of simple pyrazine derivatives.

Part I of the thesis is concerned with the preparation of a 2-hydroxy-3:5-disubstituted-pyrazine. Tota and Elderfield (J.Org.Chem., 7, 317, (1942).) have prepared 2-hydroxy-3:5:6-trisubstituted-pyrazines by cyclisation of α-bromoacylaminoketones with ammonia.



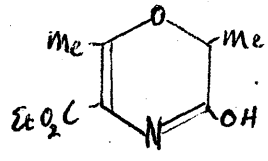
(I) (II) (III)

Treatment of an α-bromoacylaminomethylketone (I;R_2=H) with ammonia did not yield the corresponding 2-hydroxy-3:5-disubstituted-pyrazine (II;,R_2=H) but instead gave rise to a 3-acylamino-2:5-disubstituted-pyrazine (III).

The reaction appears general for aminomethylketones and affords the only general method of preparing 3-amino-2:5-disubstituted-pyrazines. A mechanism for the reaction is discussed. Under the same experimental conditions α-bromo-propionamidoacetaldehyde reacted with ammonia without giving any product which could be characterised.

An attempt to prepare 2-hydroxy-3:5-dimethylpyrazine-6-carboxyamide (II,R_2=$CONH_2$,R_1=R_3=Me) by cyclisation of

ethyl α-(α'-bromopropionamido) β-ketobutyrate (I;R_2=CO_2Et, R_1=R_3=Me) with ammonia gave ethyl 3-hydroxy-2:6-dimethyl-oxazine -6- carboxylate (IV). Ethyl α-(bromoacetamido) β-ketobutyrate likewise gave the corresponding oxazine ester. This type of compound, and those derived from it by hydrolysis of the ester grouping and decarboxylation, has not been previously mentioned in the literature.



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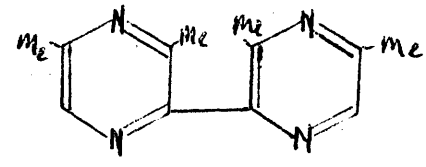
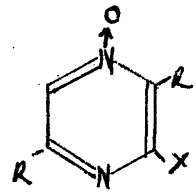


(V)

Amination of 3:5-dimethylpyrazine with sodamide, to give the aminopyrazine and hence the hydroxypyrazine, was not successful; the only product being a bipyrazyl (V).

The second part of the thesis consists of investigations into the preparation of pyrazine cyclic hydroxamic acids. Direct oxidation of substituted pyrazines, the substituent being easily converted to hydroxy, with various oxidising agents did not give a hydroxamic acid; the pyrazine ring either being split or oxidation occurring on the nitrogen atom remote from the potential hydroxyl group (VI).



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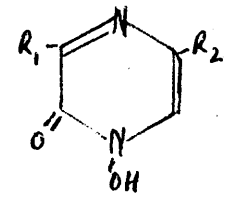
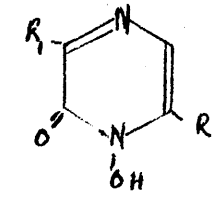


(VII)



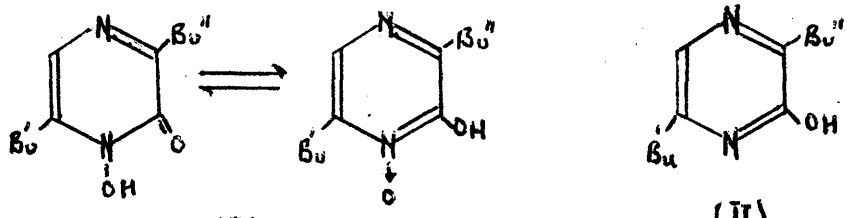
(VIII)

Condensation of an α:β-dicarbonyl compound with a straight chain hydroxamic acid under a variety of conditions has given several pyrazine cyclic hydroxamic acids though the orientation of the substituents is different from that of Aspergillic acid; the former (VII) being a 3:5-disubstituted pyrazine and the latter (VIII) a 3:6-disubstituted pyrazine. Reduction of the 3:5-disubstituted pyrazine hydroxamic acids with hydrazine has given several 2-hydroxy-3:5-disubstituted pyrazines.

C O N T E N T S .

INTRODUCTION.

The renewed interest in pyrazine chemistry may be traced largely to the great advances of chemotherapy in which a prominent part has been played by heterocyclic chemistry. The successful application of sulphapyridine, sulphathiazole and sulphadiazine led to the development of sulphapyrazine which clinically is more effective than any of the former (1). Of paticular interest is aspergillic acid (I), an antibacterial substance, isolated by White and Hill (2) from the culture filtrates of Aspergillus flavus. Aspergillic acid was examined by Dutcher and Wintersteiner (3) who have shown that it is a cyclic hydroxamic acid related to pyrazine. Mild reduction of this gave deoxyaspergillic acid (II) to which Dutcher and Wintersteiner assigned the structure of 3-hydroxy-2:5-di-sec.-butylpyrazine.

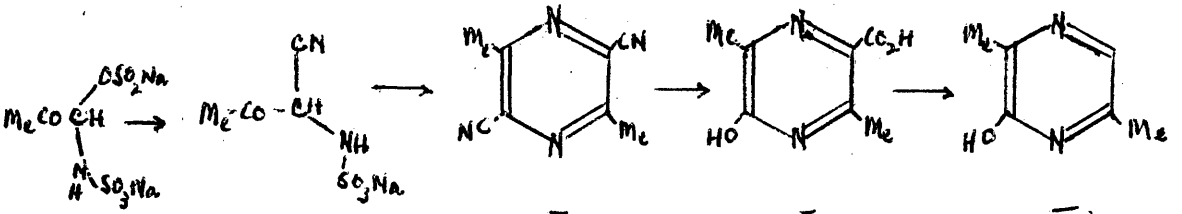


(I) (II)

More recently Dunn, Newbold and Spring (4) have shown deoxyaspergillic acid to be either 3-hydroxy-2-isobutyl-5-sec.-butylpyrazine or 3-hydroxy-2-sec.-butyl-5-isobutyl-pyrazine.

Preliminary work by the author in the synthesis of deoxyaspergillic acid consisted in the study and synthesis of hydroxypyrazines, particularly those substituted in the 3 and 5 positions by alkyl groups. When this study commenced, few general methods for the synthesis of hydroxyalkylpyrazines had been reported.

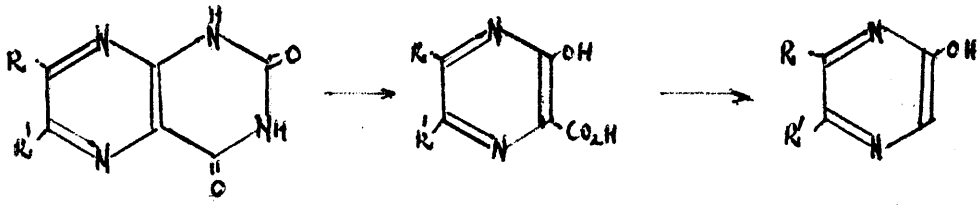
Gastaldi (5) described the synthesis of 3-hydroxy-2:5-dimethylpyrazine by treatment of iso-nitrosoacetone with sodium bisulphite, followed by reaction of the product (III) with potassium cyanide to yield 2:5-dicyano-3:6-dimethylpyrazine (IV). Hydrolysis of the latter gave directly 3-hydroxy-2:5-dimethylpyrazine-6-carboxylic acid (V) and hence by decarboxylation, 3-hydroxy-2:5-dimethylpyrazine(VI).



(III) (IV) (V) (VI)

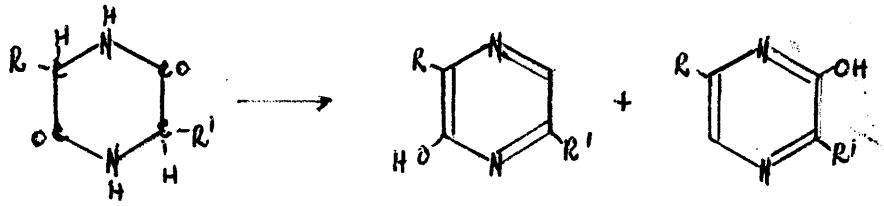
By the same method iso-nitrosoacetophenone gave 3-hydroxy-2:5-diphenylpyrazine, though at that time much confusion existed in the literature about the structure of this compound (6), but recently the author and independently Spring et al. (7) have confirmed Gastaldi's synthesis. Using the method of Gastaldi, Sharp and Spring (8) have also confirmed the author's synthesis of 3-hydroxy-2:5-diethylpyrazine as described in this thesis.

Weijlard, Tishler and Erickson (9) have shown that drastic alkaline hydrolysis of lumazines (VII) gives rise to 2-hydroxypyrazine-3-carboxylic acids (VIII) which are readily decarboxylated tothe corresponding hydroxypyrazines (IX).



(VII) (VIII) (IX)

A method for the conversion of diketopiperazines (X), by treatment with phosphoryl chloride, into hydroxypyrazines directly, or indirectly through the chloropyrazine, is described by Spring et al. (10). Using mixed diketopiperazines, however, mixtures of hydroxypyrazines are obtained and the exact position of the hydroxyl group, relative to the alkyl groups, has not been determined.

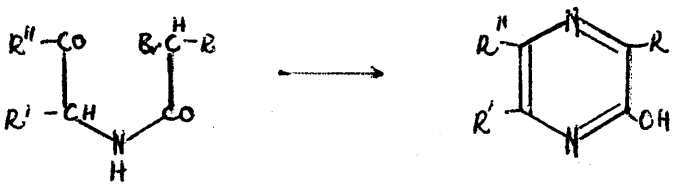


(X) (XI)

Several less general methods for the synthesis of

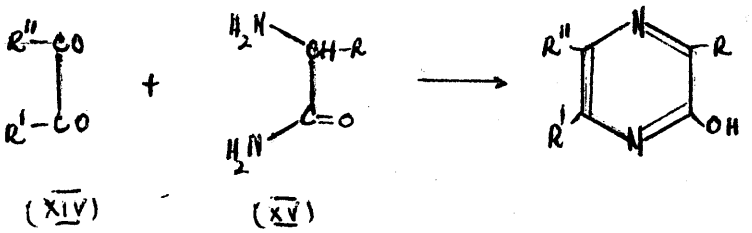
3-hydroxy-2:5-disubstituted-pyrazines are described by Baxter, Newbold and Spring (11), Newbold and Spring (12) and by Erickson and Spoerri (13).

Tota and Elderfield (14) describe one other general method for the synthesis of 5:6-disubstituted- and 3:5:6-trisubstituted- 2-hydroxypyrazines (XII) in which an α-(α'-bromoacylamino) ketone (XIII) is treated with ammonia to give the corresponding hydroxypyrazine. By this method Tota and Elderfield have prepared 3-hydroxy-5:6-dimethylpyrazine, 2-hydroxy-5-phenyl-6-methylpyrazine, 2-hydroxy-5-phenyl-6-methyl-3-ethylpyrazine, and 2-hydroxy-5-methyl-6-(2-hydroxyethyl)-pyrazine, while Newbold and Spring (15) have used it to prepare 2-hydroxy-3:5:6-trimethylpyrazine.



(XIII) (XII)

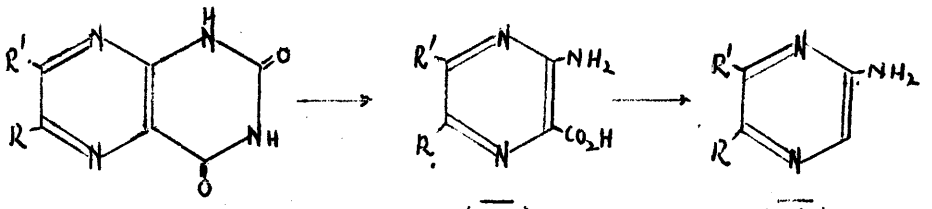
In no case however had a 2-hydroxy-3:5-disubstituted-pyrazine (XII; R'=H) been prepared; though quite recently Jones (16) has given a general method for their preparation by thecondensation of α:β-dicarbonyl compounds (XIV) with α-aminoacid amides (XV).



(XIV) (XV)

To compare deoxyaspergillic acid with 3:5-disubstituted-pyrazines, it was decided to adapt the method of Tota and Elderfield to their synthesis by cyclisation of an α-bromoacylaminomethyl ketone (XIII; R'=H) with ammonia. Such a reaction however, as is shown in Part I of the theoretical, yielded 3-acylamino-2:5-disubstituted-pyrazines. These may be converted to the corresponding amino- and hence hydroxypyrazines, thus affording the only general method for the preparation of 3-amino-2:5-disubstituted-pyrazines and an alternative route to 3-hydroxy-2:5-disubstituted-pyrazines.

The only other general method for the synthesis of amino-pyrazines is that of Weijlard, Tishler and Erickson (9), whereby lumazines are hydrolysed by alkali to the corresponding 2-amino-5:6-disubstituted-, 2-amino-6-substituted- and 2-amino-5-substituted-pyrazine-3-carboxylic acids (XVI) and hence by decarboxylation to the aminopyrazines (XVII).

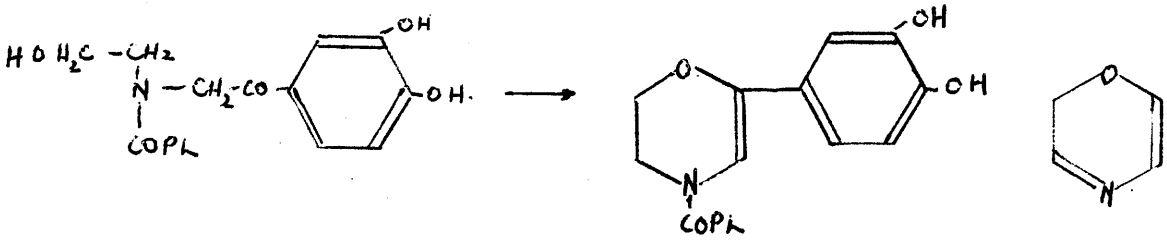


(XVI) (XVII)

Direct amination of pyrazine bases to aminopyrazines, by use of sodamide, gives varied yields of products and the conditions of reaction are specific in each case. Tschitschababin and Schukina (17) and Joiner and Spoerri (18) claim yields of 10% and 35% respectively of 3-amino-2:5-dimethylpyrazine by amination of the base with sodamide, while Newbold and Spring (15) obtained 3-amino-2:5-di-sec.-butylpyrazine in 60-65% yield from 2:5-di-sec.-butylpyrazine and sodamide using dimethylaniline as solvent. Pyrazine itself has been aminated under a variety of conditions but mostly in poor yield (19). All other aminopyrazines which appear in the literature have been prepared through the Hofmann degradation of the acid amides (20, 9) or by ammonolysis of chloropyrazines (13).

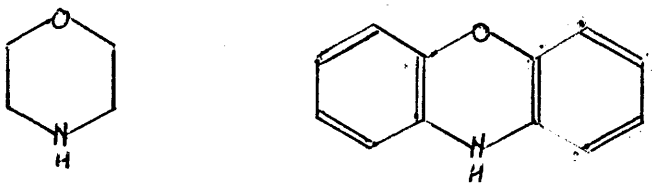
Several cyclisations of α-bromoacylamino-ketones in Part I have led to the formation of 1:4-oxazines (XVIII) and a search of the literature reveals that this type of compound is practically unknown. Hill and Powell (21) in a preparation of amines of the eprocaine type related

to adrenaline obtained, by the cyclisation of N-(3:4-dihydroxyphenylacyl)-N-(2-hydroxyethyl)-benzamide(XIX), a compound which they suggested was 2-(3:4-dihydroxyphenyl)-4-benzoyl-5:6-dihydroparoxazine (XX) but no further communication on oxazines has been recorded by these authors.



(XIX) (XX) (XVIII)

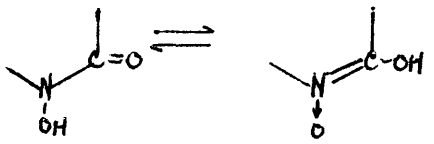
Tetrahydro-1:4-oxazine (XXI), morpholine (22), is well described in the literature but all other 1:4-oxazines that have been synthesised are present in fused-ring systems such as phenoxazine (XXII).



(XXI) (XXII)

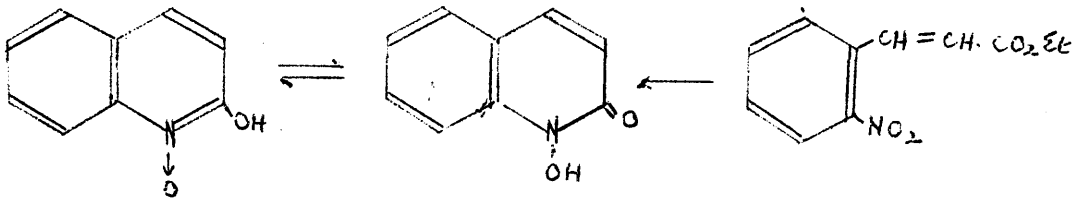
PartII of the thesis concerns reactions leading to the formation of cyclic hydroxamic acids. Interest in these compounds has been aroused by the high inhibitory in vitro activity of aspergillic acid against some Gram-negative and Gram-positive organisms (2,23) and against M. tuberculosis (24). Reduction of the hydroxamic acid

gives deoxyaspergillic acid which is relatively ineffective as an antibacterial agent (25). It would seem then that the activity of aspergillic acid is due solely to the hydroxamic acid grouping (XXIII).



(XXIII)

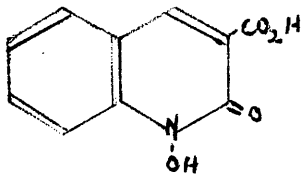
Few cyclic hydroxamic acids have been described in the literature. 2-Hydroxyquinoline-1-oxide (oxycarbostyril) (XXIV) or more correctly N-hydroxy-2-quinolone (26; XXV) was obtained by Friedlander and Ostermaier (27) in small yield by the reduction of ethyl o-nitrocinnamate (XXVI).



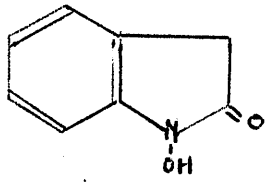
(XXIV) (XXV) (XXVI)

The related oxycarbostyril carboxylic acid (XXVII) was obtained by Heller and Wunderlich (28) by reduction of o-nitrobenzylidene malonic acid with zinc and acetic acid and Reissert (29) obtained 1:2-dioxindole (XXVIII) by a similar type of reduction of o-nitrophenylacetic acid. Di Carlo (30) also describes 1:2-dioxindole as a biproduct

in the preparation of oxindole.

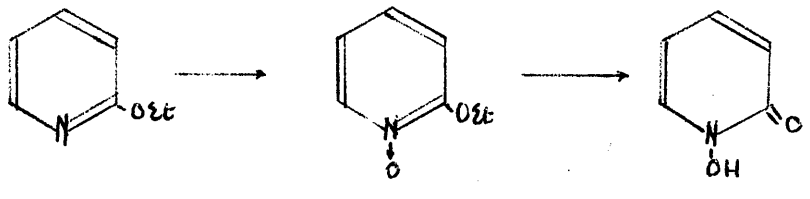


(XXVII)

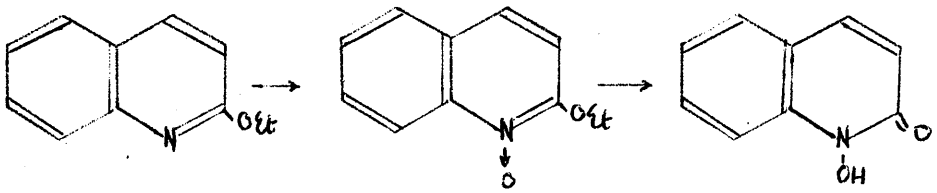


(XXVIII)

Recently Newbold and Spring et al. (31) have prepared the hydroxamic acids of pyridine (XXIX) and of several quinolines (XXX) by N-oxidation of the α-ethoxy-bases (XXXI) with hydrogen peroxide, followed by acid hydrolysis of the ethoxy-oxide.

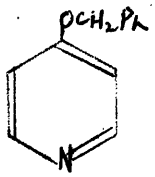


(XXXI) (XXIX)

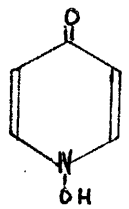


(XXXI) (XXX)

Shaw (26) has confirmed these results in the pyridine series using the 2-benzyloxy- and 4-benzyloxy-pyridines (XXXII) oxidation of which with perbenzoic acid gave the corresponding N-oxides, which on catalytic hydrogenation gave the hydroxamic acids (XXIX; XXXIII).

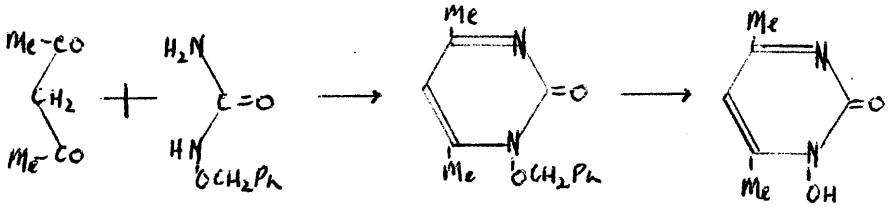


(XXXII)



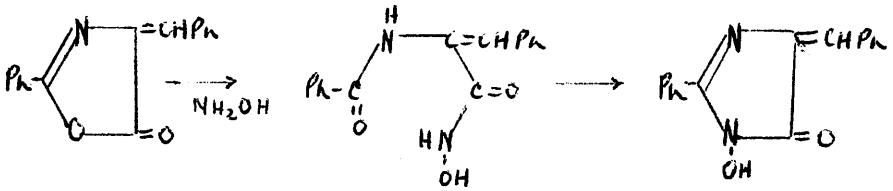
(XXXIII)

N-Hydroxy-4:6-dimethyl-2-pyrimidone (XXXIV) has been synthesised by Lott and Shaw (32) by condensation of acetylacetone with benzyloxyurea (XXXV) and the resulting N-benzyloxypyrimidone cleaved by catalytic hydrogenation to give the pyrimidine hydroxamic acid.



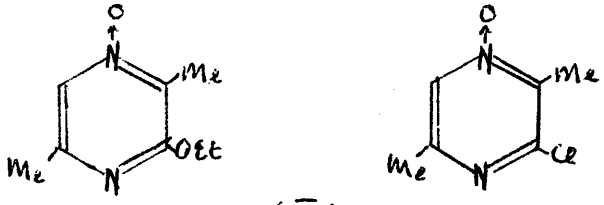
(XXXV) (XXXVI) (XXXIV)

Shaw and McDowell (33) have reacted hydroxylamine with the azlactone, 2-phenyl-4-benzylidene-5-oxazolone (XXXVII), obtaining α-benzamidocinnamohydroxamic acid (XXXVIII) which on treatment with hot aqueous hydrochloric acid undergoes ring closure to the cyclic hydroxamic acid, 1-hydroxy-2-phenyl-4-benzylidene-5-imidazolone (XXXIX).



(XXXVII) (XXXVIII) (XXXIX)

In the pyrazine series, Baxter, Newbold and Spring (34) oxidised 3-ethoxy-2:5-dimethylpyrazine and 3-chloro-2:5-dimethylpyrazine with hydrogen peroxide giving only the 4-oxides (XXXX) which did not yield hydroxamic acids on acid hydrolysis of the ether grouping



(XL)

Before this work no pyrazine cyclic hydroxamic acid had been prepared synthetically.

Acylamidopyrazines.

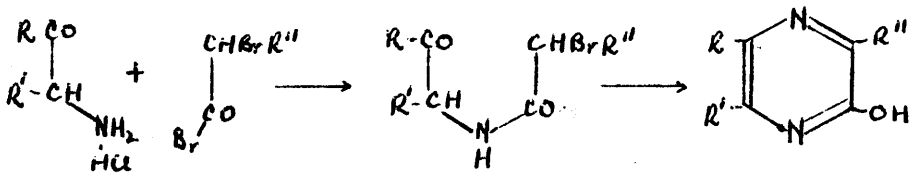
THEORETICAL.

PART I.

Cyclisations of α-Bromoacylaminoketones.

Acylamidopyrazines.

When this work was initiated no 3:5-disubstituted-2-hydroxypyrazines had been synthesised. For comparison with deoxyaspergillic acid it was decided to prepare a compound of this type, using the method of Tota and Elderfield (14) who had synthesised 3:5:6-trisubstituted-2-hydroxypyrazines by cyclisation of α-bromoacylamino-ketones with ammonia.

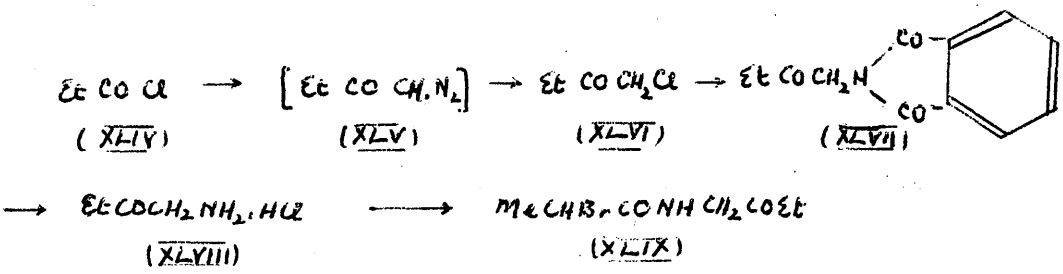


(XLI) (XLII) (XLIII)

The preparation of a 2-hydroxy-3:5-disubstituted-pyrazine by this method involves the condensation of an aminomethyl-ketone (XLI; R=H) with an α-bromoacyl bromide followed by cyclisation of theproduct with ammonia.

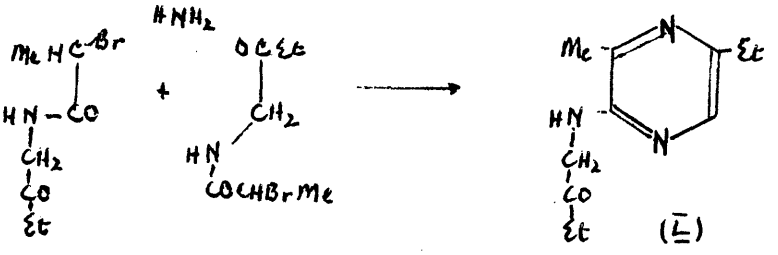
Propionyl chloride, prepared by the recent benzoyl chloride technique of Brown (35), was reacted with excess diazo-methane to give the diazoketone (XLV), which on treatment with hydrogen chloride yielded chloromethylethyl ketone (XLVI). This method is general for the preparation of α-halogen-methyl ketones such as chloromethylethyl ketone (36) where direct halogenation gives the isomeric chloro-ethylmethyl ketone. Conversion of the chloromethylethyl ketone into phthalimidomethylethyl ketone (XLVII) was

effected by heating with potassium phthalimide in boiling xylene giving the product in 67% yield. Hydrolysis with a large excess of constant boiling hydrochloric acid gave aminomethylethyl ketone hydrochloride (XLVIII) in 63% of the theoretical yield.



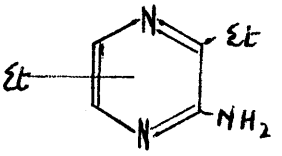
Using the modified procedure of Newbold and Spring (15) whereby a strong tertiary base, N-methylmorpholine, is used in place of calcium carbonate as a halogen acid acceptor, as in the method of Tota and Elderfield, aminomethylethyl ketone hydrochloride was condensed in anhydrous chloroform solution with α-bromopropionyl bromide to give α-bromopropionamidomethylethyl ketone (XLIX) in 63% theoretical yield. The use of α-bromoacyl chlorides was found to give an even better yield of the α-bromoacylamino ketones. When treated with a large excess of liquid ammonia in the presence of ammonium iodide as catalyst, the α-bromoacylamino ketone dissolved giving a deep-red solution. After retaining in an autoclave at room temperature for 16 hours, removal of the ammonia left a red gummy residue, which on extraction with benzene gave a colourless crystalline product m.p. 98°.

Analysis of the compound and molecular weight determination indicated a molecular formula $C_{11}H_{17}ON_3$. This was obviously not the expected 2-hydroxy-3:5-diethylpyrazine, $C_8H_{12}ON_2$, a fact which was confirmed by a comparison of the physical and chemical properties of the compound $C_{11}H_{17}ON_3$ with those of known hydroxy-alkylpyrazines. An ethanolic solution of the compound showed two absorption bands with maxima at 2260 Å (ϵ max. 6,100) and 2790 Å (ϵ max. 6,600). Though the former compares well with the first maximum of the spectra of hydroxypyrazines, the latter band is clearly not in the characteristic region of the second hydroxypyrazine band which has a maximum at about 3200 Å. Chemically, the compound $C_{11}H_{17}ON_3$ appeared basic and could be extracted readily from caustic soda solution with ether, whereas hydroxypyrazines are retained in the aqueous phase under such conditions. A tentative suggestion was that two molecules of the α-bromopropionamidomethylethyl ketone had reacted together forming a compound structurally represented by (L).



Such an isolated ketone group should be readily identified, but the usual ketone reagents did not reveal its presence

and the compound gave no iodoform on treatment with iodine and alkali indicating that the compound was probably not a simple methyl-ketone. Alkaline hydrolysis, followed by ether extraction yielded a colourless compound m.p. 42° which appeared slightly hygroscopic. Though sublimed for analysis, the results were unsatisfactory and indicated a molecular formula of $C_8H_{13}N_3.\frac{1}{2}H_2O$; attempts to remove the water completely being unsuccessful. Analysis of the picrate m.p. 157° gave a molecular formula of $C_8H_{13}N_3$ for the base. Examined spectroscopically the compound showed maxima at 2360 Å (εmax.12,200) and 3190 Å (εmax.8,000) which suggested a relationship of the compound to 3-amino-2:5-dimethylpyrazine which shows maxima at 2340 Å (εmax. 2,000) and 3190 Å (εmax.7,500). It appeared then that the compound $C_8H_{13}N_3$ was an aminodiethylpyrazine (LI), and must be either 3-amino-2:5-diethylpyrazine or 2-amino-3:5-diethylpyrazine.

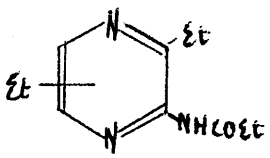


(LI)

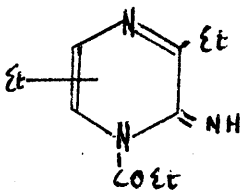
Treatment of the base, $C_8H_{13}N_3$, with nitrous acid gave the expected hydroxydiethylpyrazine, $C_8H_{12}ON_2$, m.p. 135°, which was characterised by its ultra-violet absorption spectrum, having maxima at 2270 Å (εmax.6,800) and 3220 Å (εmax.8,100) which is similar to that of 3-hydroxy-2:5-dimethylpyrazine

which has maxima at 2270 Å (ϵmax.7,600) and 3230 Å (ϵmax. 3,600).

The ease of hydrolysis of the compound, $C_{11}H_{17}ON_3$, to the base $C_8H_{13}N_3$, indicated that the former must be an acylated aminodiethylpyrazine, namely, propionamidodiethylpyrazine. On warming the base, $C_8H_{13}N_3$, with propionic anhydride a compound m.p. 98° was obtained, identical in all respects with the compound $C_{11}H_{17}ON_3$ obtained by the action of ammonia on α-bromopropionamidomethylethyl ketone. Compound $C_{11}H_{17}ON_3$ is therefore propionamidodiethylpyrazine (LII), and although (LIII) is not rigidly excluded it is considered less likely.



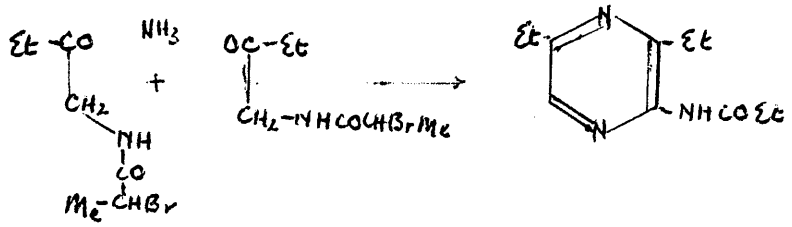
(LII)



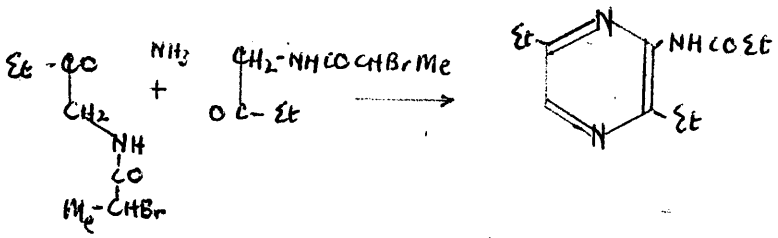
(LIII)

The reaction may then be formulated by either of the two expressions (LIV) or (LV):-

(LIV)



(LV)



Essentially the difference betweenthe α-bromoacylamino ketone used in this reaction and those used by Tota and Elderfield and Newbold and Spring (15) to give hydroxypyrazines is that the former is an α-bromoacylaminomethyl ketone, that is, it contains the grouping (-CO-NH-CH_2-) as against the grouping (-CO-NH-CHR-) in the latter cases. It would seem then that acylated aminomethyl ketones in general might give acylaminopyrazines instead of hydroxypyrazines. To confirm this, the reaction between ammonia and other α-bromoacylaminomethyl ketones was examined. Aminoacetone hydrochloride prepared by the method of Gabriel and Pinkus (37), by reduction of isonitrosoacetone, was obtained as a gummy material which would not condense with α-bromopropionyl bromide in anhydrous solution. As an alternative route aminoacetone hydrochloride was prepared through phthalimidoacetone (38) giving a 67% yield of crystalline product, which was readily acylated, with α-bromopropionyl chloride in the presence of N-methylmorpholine, to give α-bromopropionamidoacetone as colourless needles m.p. 80° in high yield. On treatment with liquid ammonia a red gum was obtained, which on extraction with boiling benzene, followed by chromatography, yielded a colourless crystalline product m.p. 106-108°. The compound on analysis and molecular weight determination had the molecular formula $C_9H_{13}ON_3$. Examined spectroscopically its relationship to the previously described compound $C_{11}H_{17}ON_3$ was well established and it exhibited

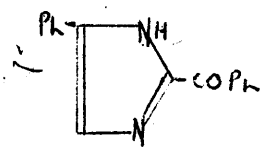
maxima at 2260 Å (ε max. 6,400) and 2805 Å (ε max. 6,800); the compound $C_{11}H_{17}ON_3$ having maxima at 2260 Å and 2790 Å. Alkaline hydrolysis of the compound $C_8H_{13}ON_3$ gave a slightly hygroscopic base which analysed $C_6H_9N_3.\frac{1}{2}H_2O$ and which melted at 111°. A mixed melting point with 3-amino-2:5-dimethylpyrazine prepared by the action of sodamide on 2:5-dimethylpyrazine (18) showed no depression. Similarly the picrate obtained by treatment of the base m.p. 111° with ethanolic picric acid melted at 205° undepressed in melting point with the picrate of authentic 3-amino-2:5-dimethylpyrazine. Treatment of the base m.p. 111° with nitrous acid gave 3-hydroxy-2:5-dimethylpyrazine identical in all respects with an authentic specimen (11). The base $C_8H_{13}ON_3$ m.p. 111° must then be 3-amino-2:5-dimethylpyrazine. On warming the base with propionic anhydride 3-propionamido-2:5-dimethylpyrazine m.p. 106-108° was obtained identical with that obtained by the action of ammonia on α-bromopropionamidoacetone.

By analogy, the compound $C_{11}H_{17}ON_3$ obtained by the action of ammonia on α-bromopropionamidomethylethyl ketone must be formulated as 3-propionamido-2:5-diethylpyrazine; the base $C_8H_{13}N_3$ as 3-amino-2:5-diethylpyrazine and the hydroxypyrazine as 3-hydroxy-2:5-diethylpyrazine.

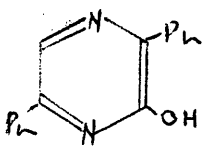
Dr. W. Sharp in these laboratories has recently confirmed the structure of the latter compound by its synthesis using the method of Gastaldi (5) whereby the bisulphite

compound of oximinomethylethyl ketone was treated with potassium cyanide and the reaction product heated with hydrochloric acid to give 2:5-dicyano-3:6-diethylpyrazine. Hydrolysis of the dinitrile with alkali gave 2-hydroxy-3:6-diethylpyrazine-5-carboxylic acid and hence, by decarboxylation, 3-hydroxy-2:5-diethylpyrazine.
It would seem then that expression (LV) is true and that the reaction between ammonia and ∝-bromoacylaminomethyl ketones yields 3-acylamino-2:5-disubstituted pyrazines.

Much confusion exists in the literature concerning the preparation of 3-hydroxy-2:5-diphenylpyrazine (LVI). Pinner (6) by the action of ammonia on phenylglyoxal isolated two compounds, one melting at about 200° and the other at 280°. The lower melting compound was, according to Pinner, 1:4-diphenyl-3-hydroxypyrazine (LVI) and the other, 2-benzoyl-5-phenylglyoxaline (LVII).



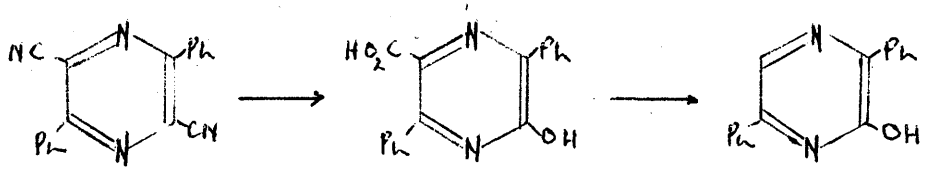
(LVII)



(LVI)

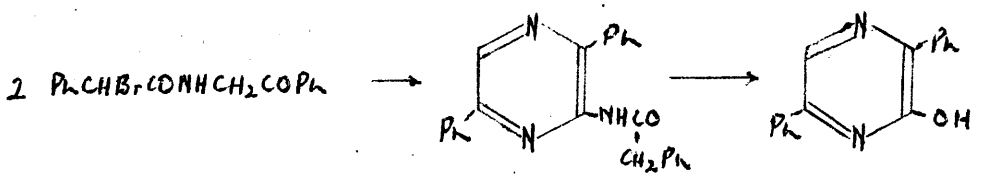
The compound m.p. ca. 200° was also obtained by treatment of ω-dibromoacetophenone (39) or the bisulphite compound of iso-nitrosoacetophenone (6) with ammonia, benzil with hydrogen cyanide (6), mandelonitrile with hydrogen chloride (6) or by heating ethanolic phenylpyruvylhydrazide.

Gastaldi (5), however, considered this compound to be the glyoxaline (LVII), and based on his experiences with 3-hydroxy-2:5-dimethylpyrazine declared the compound m.p. 280° which he had obtained by way of the dinitrile (LVIII) and hydroxy acid (LIX), to be 3-hydroxy-2:5-diphenyl-pyrazine.



(LVIII LIX)

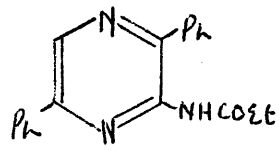
Using the reaction previously described 3-hydroxy-2:5-diphenylpyrazine could be prepared unambiguously by way of a 3-acylamino-2:5-diphenylpyrazine (LXI) obtained by cyclisation of an ω-(α'-bromoacylamino) acetophenone (LX) with ammonia.



(LX LXI)

ω-Aminoacetophenone hydrochloride was most conveniently prepared according to Rupe (40) whereby iso-nitrosoaceto-phenone is reduced with stannous chloride in hydrochloric acid and the precipitated chlorostannate hydrolysed. The detinning of the solution was found to be much simpler using a method of Tiffeneau (41) in which the salt was

hydrolysed by warming with a large excess of water. The ω-aminoacetophenone hydrochloride, so obtained, was condensed with α-bromopropionyl bromide in the presence of N-methylmorpholine to give ω-(α-bromo propionamido) acetophenone in 66% yield. Treatment with ammonia gave a purple solution which was left overnight at room temperature. Removal of the ammonia left a resin which was extracted with benzene and chloroform. Both extracts gave colourless compound m.p. 212.5°, analysis of which indicated a molecular formula $C_{19}H_{17}ON_3$, and by analogy, the compound must be 3-propionamido-2:5-diphenylpyrazine (LXII).

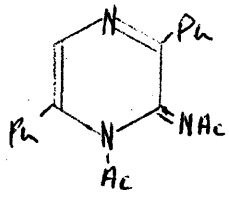


(LXII)

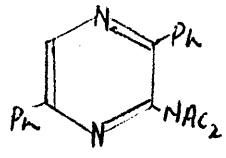
Examined spectrographically it showed maxima at 2780 Å (ε max.13,200) and 3293 Å (ε max.16,800) indicating a shift of absorption maxima for acylaminopyrazines to the higher wavelength region of the ultra-violet spectrum. This is in accordance with the absorption spectrum of 3-hydroxy-2:5-diphenylpyrazine, prepared by Dr. J.C. Woods according to the method of Pinner (6), which shows maxima in ethanolic solution at 2650 Å (ε max.9,350) and 3570 Å (ε max.15,400) and also indicates a shift of wavelength, as compared with alkyl hydroxypyrazines, to the higher

regions of the spectrum.

The colourless compound m.p. 212.5° was insoluble in water but a suspension in aqueous alkali, to which a little ethanol had been added, was hydrolysed by refluxing for several hours. On cooling, the suspension gave 3-amino-2:5-diphenylpyrazine as yellow plates m.p. 186°. A solution in ethanol when examined spectrographically again showed a shift to the higher regions having maxima at 2640 Å (ε max. 12,500) and 3560 Å (ε max. 24,000). The compound was soluble in most organic solvents and showed a strong violet flueorescence in solution. As might be expected, it was only weakly basic, forming an orange hydrochloride decomposed by water to regenerate the parent base, and under normal conditions no picrate could be obtained. The base, however, gave a positive carbylamine reaction, and was characterised by a diacetyl derivative (LXIII) or (LXIV).



(LXIII)

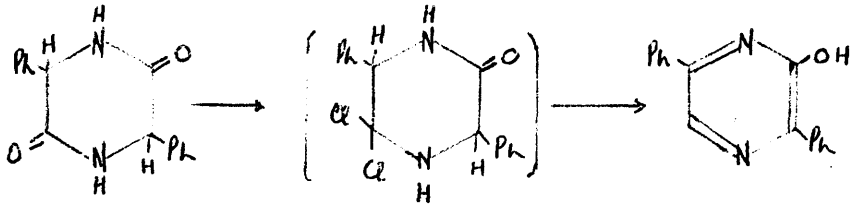


(LXIV)

Attempts to prepare the same compound by the action of sodamide on 2:5-diphenylpyrazine were unsuccessful.

The 3-amino-2:5-diphenylpyrazine was smoothly converted to 3-hydroxy-2:5-diphenylpyrazine in 60% yield by treatment of the base with nitrosylsulphuric acid.

Recrystallisation of the product from glacial acetic acid gave yellow-green prisms m.p. 286° undepressed in melting point with a specimen of 3-hydroxy-2:5-diphenylpyrazine prepared by the method of Gastaldi.
Further proof of the identity of the compound was obtained by Mr. J.J. Gallagher (7) in this Department, who obtained the same compound by treatment of DL-phenylglycine anhydride with phosphoryl chloride.



(LXV) (LXVI) (LXVII)

Treatment of 3-amino-2:5-diphenylpyrazine with propionic anhydride gave 3-propionamido-2:5-diphenylpyrazine, m.p. 212.5°, identical with that obtained by the action of ammonia on ω-(α'-bromopropionamido) acetophenone.

Condensation of ω-aminoacetophenone hydrochloride with phenylbromoacetyl bromide under the usual conditions gave ω-(phenylbromoacetamido) acetophenone as colourless needles m.p. 119° in very high yield. Treatment with ammonia gave a brown oily residue from which a compound $C_{24}H_{18}ON_3$, m.p. 194°, was isolated by extraction with acetone. The yield in this case was only 25% and a large amount of unidentifiable gum remained. The compound was characterised as 3-phenylacetamido-2:5-diphenyl-

pyrazine by hydrolysis with alkali to 3-amino-2:5-diphenylpyrazine and phenylacetic acid.

On heating 3-amino-2:5-diphenylpyrazine under reflux with phenylacetyl chloride 3-phenylacetamido-2:5-diphenylpyrazine was obtained identical with the specimen obtained by the action of ammonia on ω-(phenylbromoacetamido) acetophenone.

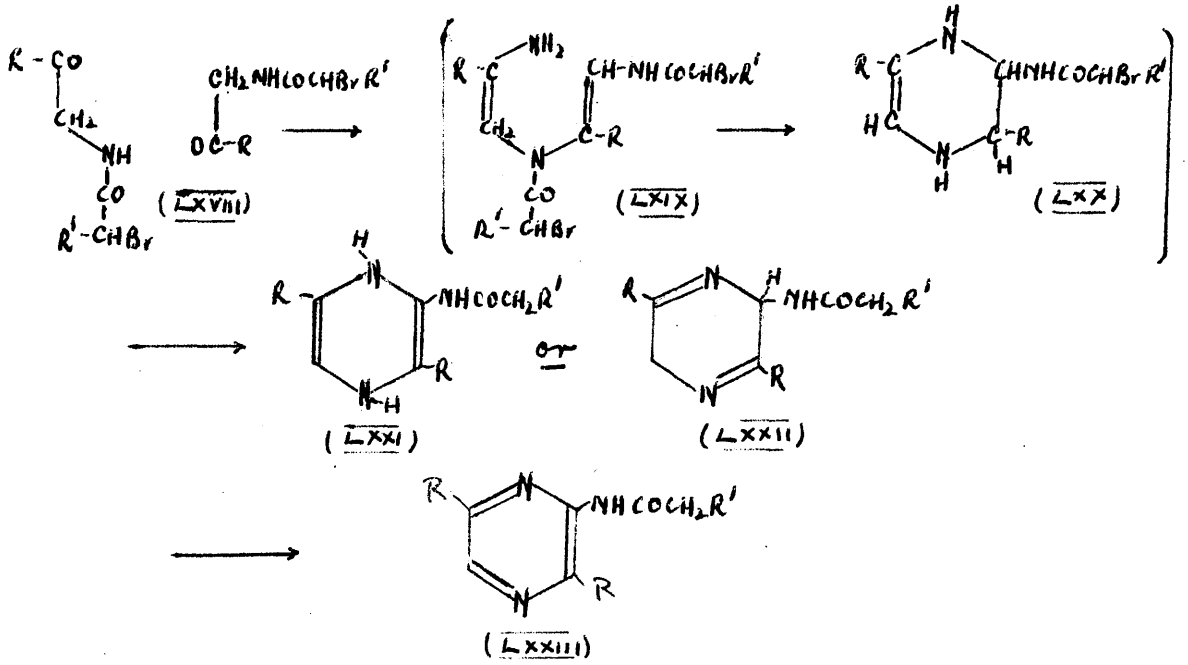
Phenylbromoacetamidoacetone, obtained by acylation of aminoacetone with phenylacetyl bromide, was dissolved in liquid ammonia and retained in a glass-lined autoclave at room temperature for 16 hours. Removal of the ammonia left an oily residue, extraction of which with benzene gave a colourless compound m.p. 154°, which had the properties of the expected 3-phenylacetamido-2:5-dimethylpyrazine, but which showed no selective absorption in the ultra-violet. Analysis indicated a compound richer in hydrogen than calculated for the pyrazine and the molecular formula corresponded to $C_{14}H_{17}ON_3$.

The compound appeared unstable on prolonged standing in air and after three weeks the melting point had fallen to less than 130°. Hydrolysis of the product with dilute alkali gave 3-amino-2:5-dimethylpyrazine and one molecular equivalent of phenylacetic acid.

On repeating the cyclisation with ammonia in an iron autoclave, without the glass liner, a compound $C_{14}H_{15}ON_3$, m.p. 130°, was isolated and which showed no depression of melting point with the compound m.p. 154°. Alkaline

hydrolysis likewise gave 3-amino-2:5-dimethylpyrazine and one molecular proportion of phenylacetic acid.
Examined spectroscopically it showed maxima at 2200 Å (εmax.8,700) and 2795 Å (εmax.8,300) and hence must be 3-phenylacetamido-2:5-dimethylpyrazine.
Acylation of 3-amino-2:5-dimethylpyrazine with phenylacetyl chloride in dry benzene gave the compound m.p. 130°.
Treatment of the compound m.p. 154° with hydrogen peroxide in the cold, or on prolonged standing in air, gave a quantitative yield of 3-phenylacetamido-2:5-dimethylpyrazine m.p. 130°. The compound m.p. 154° must then be 3-phenylacetamido-2:5-dimethyldihydropyrazine.

At this point it may be well to consider a mechanism for the reaction. As has been shown the acyl residue of the intermediate acylaminomethyl ketone is not directly attached to the pyrazine nucleus of the product, i.e. both the 2 and 5 substituents of the resulting 3-acylamino-2:5-disubstituted pyrazine are the same and have their origin in the ketone part of the intermediate bromoacylamino ketone.



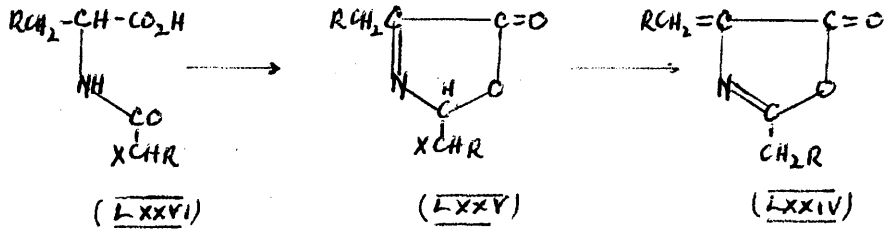
(LXVIII) (LXIX) (LXX) (LXXI) (LXXII) (LXXIII)

Steps (LXVIII → LXX) in the postulated mechanism for the general reaction assume the condensation of 2 molecules of bromoacylamino ketone with one molecule of ammonia giving rise to the tetrahydropyrazine (LXX). The conversion of this intermediate to the aromatic pyrazine (LXXIII) most probably takes place in two stages, giving first of all the dihydropyrazine (LXXI or LXXII), which on air oxidation loses one molecule of hydrogen giving the final product (LXXIII). In one case only, was the dihydropyrazine isolated, though this is not surprising due to their general instability in air, making isolation difficult or impossible.

Most pyrazine synthesis involve the formation of dihydropyrazine derivatives as readily oxidisable intermediates.

It is believed that the tetrahydropyrazine (LXX) is oxidised to the dihydropyrazine by a simultaneous reductive dehalogenation of the bromoacyl group. The latter view received support in that the bromine atom appears necessary for the reaction; propionamidoacetone being recovered unchanged after treatment with ammonia, and under the same conditions acetyllactamidoacetone gave no evidence of pyrazine formation.

A similar type of reductive dehalogenation has been observed by Bergmann and Stern (42) and Bergmann Kann and Mieckley (43) who prepared azlactones such as (LXXIV) from α'-halogen-acyl-derivatives of α-amino-acids (LXXVI).



(LXXVI) (LXXV) (LXXIV)

Using such a method, N-chloroacetyl-dl-β-phenylalamine is converted, by acetic anhydride and pyridine, at room temperature, into α-acetaminocinnamic azlactone (44) and N-chloroacetyl-l-tyrosine into 2-methyl-4-p-acetoxy-benzal-5-oxazolone (45).

The position of the double bond in the dihydropyrazine (LXXI) or (LXXII) must be an arbitrary choice and in the preparation of 3-phenylacetamido-2:5-dimethylpyrazine the

isolated dihydropyrazine shows no absorption in the ultra-violet region of the spectrum and hence it does not appear to contain a conjugated system of double bonds.

Ultra-violet absorption spectra.

		Maxima, Å		max.	
1.	3-Propionamido-2:5-dimethylpyrazine.	(a)	2260; 2805	6,400;	6,800
		(b)	2250; 2810	6,000;	6,500
2.	3-Propionamido-2:5-diethylpyrazine.	(a)	2260; 2790	6,100;	6,600
		(b)	2250; 2800	5,800;	6,000
3.	3-Propionamido-2:5-diphenylpyrazine.	(a)	2780; 3295	13,200;	16,800
		(b)	2770; 3290	12,600;	16,000
4.	3-Phenylacetamido-2:5-dimethylpyrazine.	(a)	2200; 2795	8,700;	8,300
5.	3-Phenylacetamido-2:5-diphenylpyrazine.	(a)	2760; 3300	13,000;	14,700
6.	3-Amino-2:5-dimethylpyrazine.	(c)	2340; 3190	12,000;	7,500
		(d)	2350; 3195	11,500;	7,300
7.	3-Amino-2:5-diethylpyrazine.	(d)	2360; 3190	12,200;	8,000
8.	3-Amino-2:5-diphenylpyrazine.	(d)	2640; 3560	12,500;	24,000
9.	3-Hydroxy-2:5-dimethylpyrazine.	(c)	2270; 3230	7,600;	3,600
		(e)	2270; 3230	7,600;	3,600
10.	3-Hydroxy-2:5-diethylpyrazine.	(e)	2270; 3220	6,800;	8,100
11.	3-Hydroxy-2:5-diphenylpyrazine.	(e)	2650; 3570	9,350;	15,400

(a) Specimen obtained by the action of ammonia on a bromoacylamino-ketone.

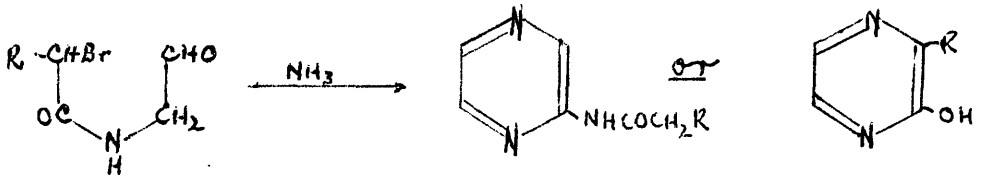
(b) Specimen obtained by propionylation of the corresponding aminopyrazine.

(c) Specimen by Baxter, Newbold and Spring. (11).

(d) Specimen obtained by hydrolysis of corresponding propionyl derivative (a).

(e) Specimen obtained by the action of nitrous acid on the aminopyrazine (d).

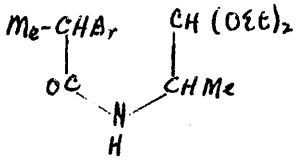
Having established the generality of acylaminopyrazine formation from α-bromoacylaminomethyl ketones it was decided to treat an α-bromoacylaminomethyl aldehyde (LXXVII) with ammonia to give the unsubstituted acylaminopyrazine (LXXVIII), or less likely, the corresponding hydroxypyrazine (LXXIX).



(LXXVII) (LXXVIII) (LXXIX)

α-Bromopropionamidoacetaldehyde (LXXVII; R = Me) was chosen as the intermediate (LXXVII) for the reaction. Baxter, Newbold and Spring (11) in the synthesis of 3-hydroxy-2:5-dimethylpyrazine describe unsuccessful attempts to crystallise the resinous α-aminopropionaldehyde hydrochloride (46) and as this salt did not condense with α-bromopropionyl bromide; an experience similar to that of the author who could not acylate non-crystalline aminoacetone hydrochloride under the conditions described. Using a modified method, in which the aldehyde grouping was protected by acetal formation, the above authors successfully acylated α-aminopropionaldehyde diethylacetal (47) with α-bromopropionyl bromide to give α-(α'-bromo-propionamido) propionaldehyde diethylacetal (LXXX) in good yield. However, attempts to hydrolyse the acetal

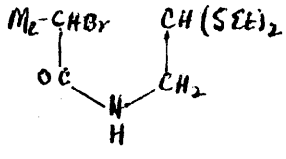
to the aldehyde resulted in cleavage of the amide linkage and likewise attempts to convert the acetal directly to 3-hydroxy-2:5-dimethylpyrazine were unsuccessful.



(LXXX)

As an alternative means of protecting the aldehyde group, mercaptal formation was examined; mercaptals being readily converted to the aldehyde by double decomposition with mercuric chloride in the presence of an insoluble carbonate. (48).

Treatment of α-(α'-bromopropionamido) propionaldehyde diethylmercaptal with mercuric chloride in the presence of cadmium carbonate, followed by treatment of the filtrate with ammonia, gave 3-hydroxy-2:5-dimethylpyrazine (11). The intermediate aldehyde was not isolated. In view of the experience of these authors it was decided to prepare α-(α'-bromopropionamido) acetaldehyde through the mercaptal (LXXXI).



(LXXXI)

Chloroacetaldehyde diethylacetal was aminated by heating

in an autoclave with a large excess of ethanolic ammonia and the resultant mixture of amines fractionated to give aminoacetaldehyde diethylacetal as a colourless oil in 21% yield; which is an improvement upon the yield of Buck and Wrenn (49) who claim 11.1% yield. The acetal was readily decomposed at 0° with concentrated hydrochloric acid and the resulting aldehyde treated with ethythiol; the latter being prepared by a modification of the method of Arndt (50), from thiourea and ethylbromide, followed by hydrolysis of the product with alkali. On making alkaline, the mercaptal separated as a light-yellow oil which was isolated by means of chloroform. Fractionation of the extract gave aminoacetaldehyde diethylmercaptal as a colourless, practically odourless liquid, b.p. 94-95°/3mm. in high yield.

The product was characterised as its picrate which was obtained using benzene picric acid, the former being dissociated in ethanol.

Acylation of the amine was carried out in a slightly different manner from previous cases, in so far as the α-bromopropionyl chloride was added dropwise to a solution of the amine and N-methylmorpholine in chloroform. Removal of the solvent gave α-bromopropionamido acetaldehyde diethylmercaptal, as a light-yellow oil, which crystallised from light petroleum as colourless, low melting (47°), prisms which could be retained indefinitely at 0°, but which decomposed on long standing

at room temperature liberating an unpleasant mercaptan-like odour. The high yield of product, 95% of theory, was probably due to the complete insolubility of the mercaptal in the aqueous washing solutions.

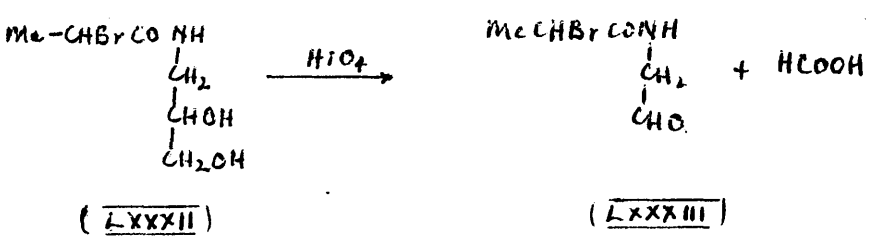
The initial conditions for the decomposition of the mercaptal and treatment of the aldehyde with ammonia were similar to those used by Baxter, Newbold and Spring (11), in which the intermediate aldehyde was not isolated after treatment of the mercaptal with mercuric chloride. Under these conditions - α-bromopropionamido acetaldehyde diethylmercaptal, after removal of the ammonia and solvents, gave a yellow-brown gum smelling strongly of mercaptan. Extraction of this with benzene and chloroform gave in each case yellow resins which did not yield crystalline products by chromatography, or by crystallisation from various petroleum ethers and other solvents. The use of various reagents such as picric acid, Brady's reagent, did not reveal any characteristic groups and likewise hydrolysis with acid or alkali gave no material which could be characterised.

Throughout, the mercaptan-like odour had persisted, being especially noticeable during the hydrolysis, and indicating that perhaps incomplete decomposition of the mercaptal had taken place during the treatment with mercuric chloride, and that the free aldehyde had not been liberated for further reaction with ammonia. Accordingly, it was

necessary to isolate the free aldehyde.

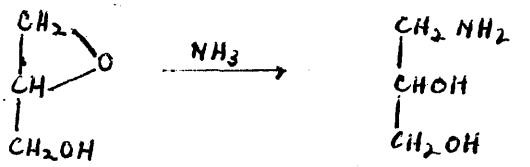
α-Bromopropionamidoacetaldehyde diethylmercaptal was treated with mercuric chloride for twenty hours at room temperature. Removal of the solvent after treatment with cadmium carbonate, followed by extraction of the residue with chloroform, gave α-bromopropionamidoacetaldehyde as a yellow gum, in theoretical yield, characterised as its 2:4-dinitrophenylhydrazone. Treatment of the aldehyde, as before, with liquid ammonia gave a yellow resin which could neither be crystallised nor characterised.
It is assumed that some type of polymer had formed from the aldehyde.

Concurrent with the preparation of α-bromopropionamido-acetaldehyde (LXXXIII) by way of the mercaptal, was an attempt to prepare the same compound by treatment of γ-(α-bromopropionamido) propan-$\alpha:\beta$-diol (LXXXII) with periodic acid.
Treatment with periodic acid in aqueous solution constitutes a general method of cleaving glycols to carbonyl containing products; thus glycerol yields two molecules of formaldehyde and one of formic acid (51).



(LXXXII) (LXXXIII)

γ-Aminopropan-α:β-diol (LXXXIV) (52) was prepared in 80% yield by the action of aqueous ammonia on glycidol (LXXXV).

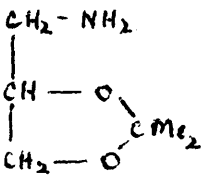


(LXXXV) (LXXXIV)

The product was a thick colourless oil which solidified on standing to colourless hygroscopic needles, insoluble in all solvents but water and alcohol; this property precluding anhydrous acylation.

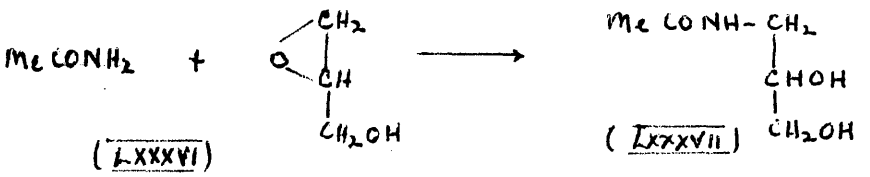
Attempts to acylate the amine by a modified Schotten-Baumann proceedure gave a non-characterisable gum.

No isopropylidene derivative (LXXXV) of the γ-amino-propan-α:β-diol could be prepared for acylation due to the great insolubility of the amine in acetone, even on addition of 20% of ethanol.



(LXXXV)

In a model experiment, as illustrated below, the direct condensation of acetamide with glycidol was unsuccessful.

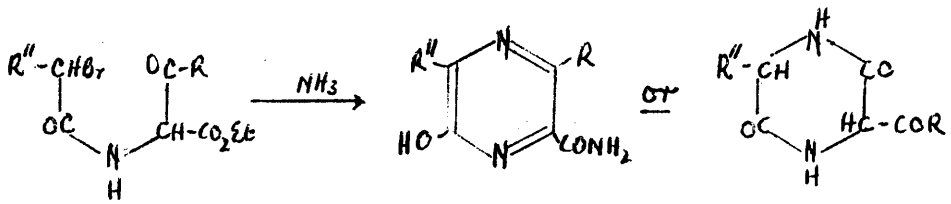


On account of these difficulties and since the aldehyde obtained from the mercaptal route did not cyclise with ammonia the projected periodate oxidation synthesis was abandoned.

Oxazines.

The Formation of Oxazines.

Since Tota and Elderfield (14) and Newbold and Spring (15) had obtained hydroxy-trisubstituted pyrazines by the cyclisation of α-bromoacylamino ketones of the type $R''.CHBr.CONH.CHR'.COR$ (LXXXVIII) with ammonia, it was inferred, that when $R' = CO_2Et$, the product on cyclisation would be 2-hydroxy-3-R''-5-R-pyrazine-6-carboxyamide (LXXXIX) or less likely the diketopiperazine (LXXXX).



(LXXXVIII) (LXXXIX) (XC)

Hydrolysis of the amide (LXXXIX), followed by decarboxylation of the resulting acid, would give the then unknown 2-hydroxy-3:5-disubstituted pyrazine.

The preparation of (LXXXVIII) when $R'' = R = Me$ involves the condensation of α-bromopropionyl halide with ethyl α-amino-β-ketobutyrate.

Ethyl oximinoacetate (53), prepared by the improved method of Adkins and Reeve (54), was reduced with stannous chloride in concentrated hydrochloric acid to give ethyl α-amino-β-ketobutyrate hydrochloride as hygroscopic needles in a better yield than that claimed by Gabriel and Posner

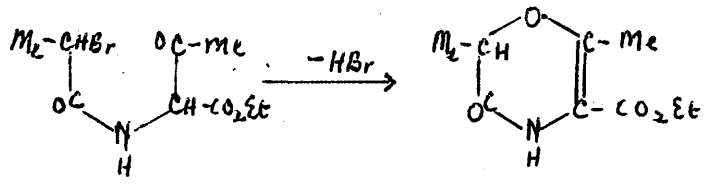
(55); this method being preferred to the catalytic reduction preparation of Duschinsky and Dolan (56).
The acylation proceedure was as before; the N-methylmorpholine being added dropwise to a mixture of α-bromopropionyl chloride and ethyl α-amino-β-ketobutyrate, giving ethyl α-(α'-bromopropionamido)β-ketobutyrate in 84% yield.

The ester was dissolved in liquid ammonia in the presence of ammonium iodide and kept in an autoclave at room temperature for 16hours. Removal of the ammonia left a brownish crystalline residue, extraction of which gave a colourless crystalline product m.p. 96°.
The analysis of the compound indicated a molecular formula $C_9H_{13}O_4N$ which suggested that the product was neither the expected pyrazine amide (LXXXIX) nor the diketopiperazine (XC).
An ethanolic solution of the compound showed maxima at 2300 Å (ε max.6300) and 2810 Å (ε max.5,100) as compared with 3-hydroxy-2:5-dimethylpyrazine which has maxima at 2270 Å (ε max.7,600) and 3230 Å (ε max.3,600). The result is close to that obtained for 3-propionamido-2:5-dimethylpyrazine, 2260 Å (ε max.6,400) and 2805 Å (ε max.6,800), but the analytical results obtained, and the failure to formulate this type of compound for the reaction product suggested that the similarity in spectrum maxima was coincidental.

Alkaline hydrolysis of the compound, $C_9H_{13}O_4N$, liberated ammonia, and on acidification, the solution yielded a crystalline compound m.p. 328° (decomp.).
The latter product was soluble only in water, and an accurate analysis of it could not be obtained owing to the presence of adsorbed inorganic material which repeated crystallisation failed to remove.

The relationship of the product, $C_9H_{13}O_4N$, to ethyl α-(α'-bromopropionamido) β-ketobutyrate, $C_9H_{14}O_4NBr$, was surprisingly obvious, hydrogen bromide having been eliminated from the bromo-intermediate.

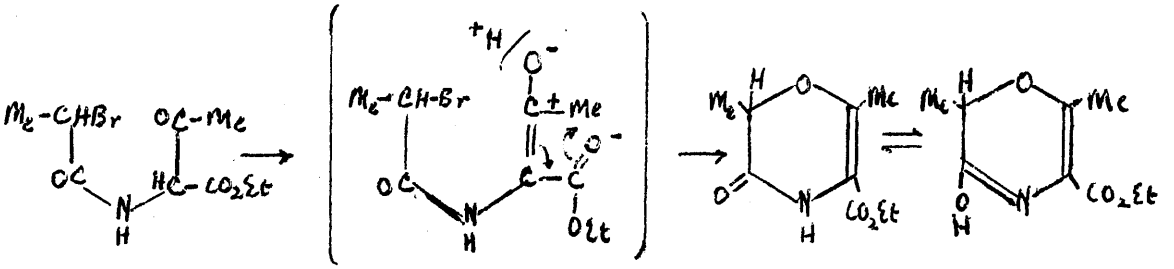
Graphically, the reaction could be represented thus:-



(XCI) (XCII)

Ethyl α-(α'-bromopropionamido) β-ketobutyrate is, in effect, a substituted acetoacetic ester in which the keto group exists in a high state of enolisation due to the electron attractive effect of the carbethoxy group.
In a basic solvent the substituted acetoacetic ester must exist then in an ionised state, allowing ready elimination of halogen acid, so that the ammonia acts merely as a base, allowing facile removal of hydrogen

bromide from the ethyl α-(α-bromopropionamido)β-keto-butyrate.



(XCIII) (XCIV) (XCV) (XCVI)

The product (XCVI) is then ethyl 3-hydroxy-2:6-dimethyl-oxazine-5-carboxylate; the latter structure being preferred to (XCV) on the ultra-violet absorption data which seems to indicate a system of conjugated double bonds.

That the compound, $C_9H_{13}O_4N$, was indeed the oxazine, was shown by the fact that treatment of the bromo-intermediate with sodium ethoxide gave the same product m.p. 96°.

It is surprising that the ester grouping remains unaffected by liquid ammonia and an attempt to replace the ether oxygen by heating under pressure with ethanolic ammonia was unsuccessful.

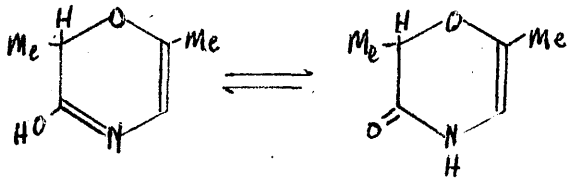
The properties of the alkaline hydrolysis product, m.p. 328° (decomp.), were not those of a simple oxazine acid; no effervescence was observed with aqueous sodium hydrogen carbonate; the melting point was much too high for such a compound; and the ultra-violet absorption spectrum indicated only one maximum at 2730 Å (ε max.2,330).

Whereas, a spectrum similar to the ester, with two maxima, was more likely. Elimination of ammonia on hydrolysis indicated a certain degree of ring fission having occurred and more mild conditions were indicated.

A suspension of the oxazine ester (XCVI) in the equivalent of decinormal caustic soda was left for a day at room temperature when almost complete solution occurred. On acidification, 3-hydroxy-2:6-dimethyl-oxazine-5-carboxylic acid, $C_7H_9O_4N$, was obtained as colourless prisms m.p. 214°, with liberation of carbon dioxide at the melting point. An aqueous solution of the compound showed absorption maxima at 2240 Å (ϵmax.7,300) and 2780 Å (ϵmax.5,000) which agrees well with that of the ester. Further alkaline hydrolysis of the acid gave the product m.p. 328° (decomp.), though no structure could be elucidated for this.

The acid, m.p. 214°, was not decarboxylated by refluxing in nitrobenzene alone, or in the presence of copper powder. Decarboxylation, however, readily occurred, with charring, by heating the acid to above its melting point and on subjecting the residue to vacuum sublimation, 3-hydroxy-2:6-dimethyl-oxazine was obtained as colourless hygroscopic plates, m.p. 73°. A solution of the latter compound in ethanol, examined spectrographically, showed a maximum at 2680 Å (ϵmax.3,262) from which the absence of a system of conjugated

double bonds was inferred, so that the hydroxy-oxazine exists in the tautomeric amide form (XCVIII).



(XCVII) (XCVIII)

The generality of the reaction was examined.

Bromoacetyl chloride was condensed with ethyl α-amino-β-ketobutyrate to give ethyl-α-bromoacetamido-β-ketobutyrate in high yield and treatment of the latter with liquid ammonia, as before, gave ethyl 3-hydroxy-6-methyloxazine-5-carboxylate $C_8H_{12}O_4N$, in only 14% theoretical yield; the low yield was due to the presence of a large amount of non-characterisable resin.

The same compound was obtained in 60% yield by treatment of the bromo-intermediate with sodium ethoxide.

Examination of the absorption spectrum showed maxima at 2260 Å (εmax.5,210) and 2800 Å (εmax.5,210) which is in very good agreement with the previous oxazine ester.

Mild alkaline hydrolysis of the ester with decinormal caustic soda gave 3-hydroxy-6-methyloxazine-5-carboxylic acid, $C_6H_8O_4N$, as colourless prisms m.p. 226° with elimination of carbon dioxide.

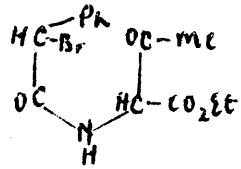
Decarboxylation of the acid at 240°, followed by isolation of the product by sublimation, gave 3-hydroxy-6-methyl-

oxazine, $C_5H_7O_2N$, as colourless hygroscopic plates m.p. 54°.

Neither of the hydroxyoxazines showed any well defined basic properties and no picrate could be obtained.

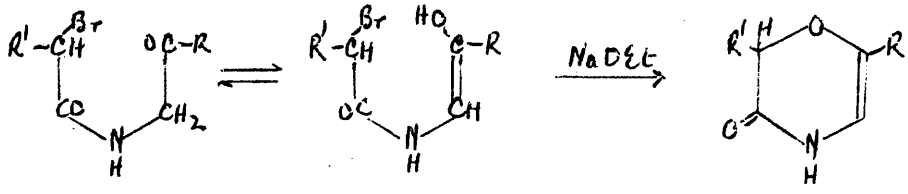
An attempt to prepare ethyl 3-hydroxy-2-phenyl-6-methyl-oxazine-5-carboxylate was not successful.

Ethyl α-phenylbromoacetamido-β-ketobutyrate was obtained in high yield as a low melting solid by acylation of ethyl α-amino-β-ketobutyrate with phenylbromoacetyl chloride. Treatment of which with ammonia gave a reddish-green gum from which phenylacetamide only could be isolated. Alkaline hydrolysis of the gum, after removal of the phenyl-acetamide, eliminated ammonia but acidification of the mother liquor gave only an oil which could not be characterised. Similarly, treatment of the bromo-acyl-intermediate with sodium ethoxide gave a gum which could not be characterised. This anomalous case is due, probably, to steric factors and the phenyl group must prevent easy elimination of the halogen acid.



(IC)

In order to obtain hydroxy-oxazines directly from the acylated aminoacetoacetic ester intermediate, entails the removal of the carbethoxy group and cyclisation of the resulting bromoacylamino ketone. Treatment of the latter with ammonia had given 3-acyl-amino-2:5-disubstituted-pyrazines, but the use of sodium ethoxide, by elimination of hydrogen bromide, should theoretically lead directly to the corresponding 3-hydroxy-2:6-disubstituted oxazine.



(C) (CI)

α-Bromopropionamidoacetone was treated with an ethanolic solution of sodium ethoxide giving a bright-orange solution and immediate elimination of sodium bromide. After standing, the solvent was removed and the orange resin which remained, extracted with light petroleum giving a colourless, slightly hygroscopic solid, m.p. 65°.

A mixed melting point taken with the 3-hydroxy-2:6-dimethyl-oxazine, previously obtained, showed a large depression.

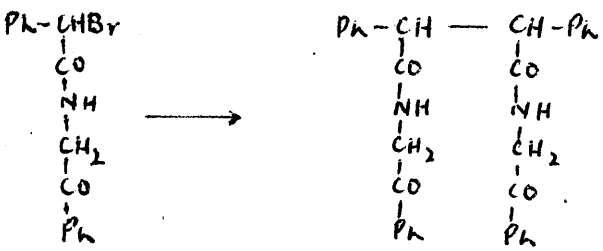
On analysis the compound, m.p. 65°, had the molecular formula $C_8H_{15}O_3N$ which indicated that the bromine atom of the intermediate had been replaced by ethoxy (CII).

(CII)

The generality of this replacement was shown by the fact, that α-(α'-bromopropionamido) ethylmethyl ketone and ω-(α'-bromopropionamido) acetophenone on treatment with sodium ethoxide gave respectively α-(α'-ethoxypropionamido) ethylmethyl ketone and ω-(α'-ethoxypropionamido) acetophenone.

A further attempt to prepare hydroxy-oxazines from α-bromoacylamino ketones, by use of powdered sodium in either boiling benzene or xylene, gave only a quantitative recovery of starting material.

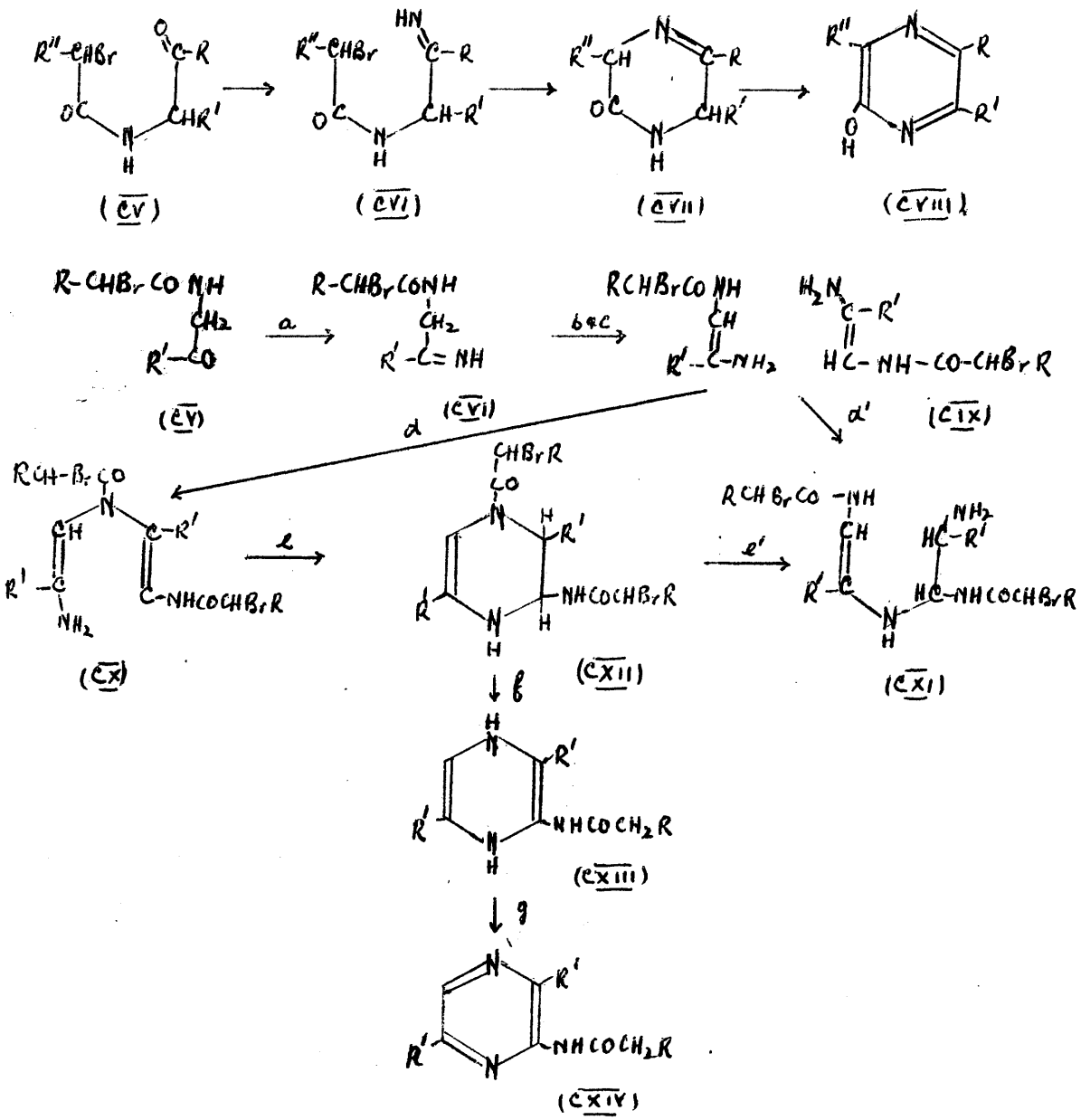
One anomalous case was noted in that ω-(phenylbromoacetamido) acetophenone on treatment with sodium in boiling benzene gave a halogen free compound $C_{16}H_{14}O_4N$ whose structure may be indicated by (CIV).

(CIII)  (CIV)

Since no hydroxy-oxazines were obtained from α-bromoacylamino-ketones, it must be concluded that these compounds do not exist in the enol form but totally in the keto form, and such a conclusion must favour some modification of the mechanism put forward for the formation of acylaminopyrazines by the action of ammonia on the former type of compound.

The initial stage in this reaction and also in that of

Tota and Elderfield is most probably imine formation and the following mechanism is proposed for both reactions:-



Stages (CVI→CVII), the elimination of hydrogen bromide, occur at a very slow reaction rate and the reaction leading to acylamino-pyrazines, where possible, is favoured, as is shown by the much higher yields of these products. Thus whenever possible the latter reaction must occur due to the slow rate of elimination of hydrogen bromide, and this is only precluded in the reaction of Tota and Elderfield, when the ketone used is not an aminomethyl ketone, because the necessary aromatisation (f) cannot then take place.

Much of the resin in this reaction may be product of type (CXII).

In no case examined does direct replacement of the bromine atom by amino take place; or in the cases of oxazine formation pyrazines would instead be obtained, extraction of halogen acid rather occurs.

Ultra-violet absorption spectra.

	Maxima, Å		ε max.	
Ethyl 3-hydroxy-2:6-dimethyloxazine-5-carboxylate.	2,300;	2,810	6,300;	5,100
Ethyl 3-hydroxy-6-methyloxazine-5-carboxylate.	2,260;	2,800	5,200;	5,200
3-Hydroxy-2:6-dimethyloxazine-5-carboxylic acid.	2,240;	2,780	7,300;	5,000
3-Hydroxy-6-methyloxazine-5-carboxylic acid.	2,270;	2,810	4,900;	6,000
3-Hydroxy-2:6-dimethyloxazine.		2,680		3,300
3-Hydroxy-6-methyloxazine.		2,680		4,300

Amination of 3:5-Dimethylpyrazine.

Amination of 3:5-Dimethylpyrazine.

A further attempt was made to prepare 2-hydroxy-3:5-dimethylpyrazine by direct amination of the base with sodamide.

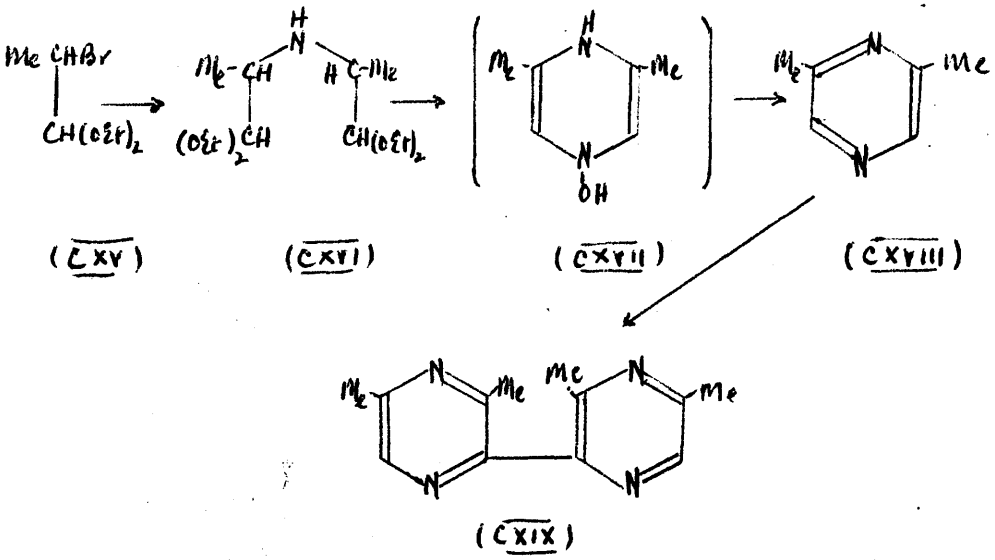
The best method of preparing 3:5-dimethylpyrazine consisted in an adaptation of the pyrazine synthesis of Wolff and Marburg (57).

α-Bromopropaldehyde diethylacetal (CXV) was prepared using a variation of Kuhn and Grundmann's method (58) for the preparation of α-bromo-n-valeraldehyde diethylacetal and consisted in adding bromine dropwise at -15° to an irradiated solution of propaldehyde in chloroform, followed by treatment of the product with a large excess of dry ethanol.

Amination of the product with ethanolic ammonia gave a mixture of α-aminopropaldehyde diethylacetal (22% yield) and an 18% yield of dipropionacetalylamine (CXVI). Treatment of the latter with hydrochloric acid, followed by hydroxylamine, gave 3:5-dimethylpyrazine (CXVIII) as a colourless oil in a 75% theoretical yield, characterised by its picrate. On treatment of the 3:5-dimethylpyrazine with freshly prepared sodamide (59) in dimethylaniline a thick tarry material was obtained, chromatography of which yielded a very small amount of crude solid. Sublimation gave colourless needles m.p. 90° in insufficient

quantity for analysis, but which yielded a yellow-green picrate containing 22.3% nitrogen.

The picrate of the bipyrazyl (CXIX) requires 22.1% nitrogen and Tschitschababin (17) refers to the formation of this type of compound during the amination of 2:5-dimethylpyrazine.



(CXV) (CXVI) (CXVII) (CXVIII)

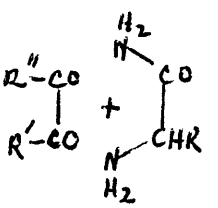
(CXIX)

No other compound was isolated.

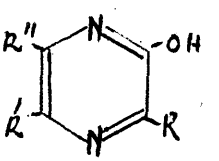
Summary.

The Tota and Elderfield reaction whereby α-bromoacylamino ketones with ammonia yield hydroxy-pyrazines has been extended to the preparation of acylamino-pyrazines and oxazines. A mechanism for the reaction is proposed. Amination of 3:5-dimethylpyrazine with sodamide has given only a bipyrazyl.

Since this work Jones (16) has prepared 2-hydroxy-3:5-di-substituted-pyrazines by the condensation of α:β-dicarbonyl compounds with α-aminoacid amides in the presence of alkali at low temperatures.



(CXX)



(CXXI)

This reaction had previously been attempted in this Department using entirely different reaction conditions with lack of success.

Pyrazine cyclic hydroxamic acids, substituted in the 3 and 5 positions have been prepared by the author, in conjunction with Dr. G.T. Newbold and Mr. G. Dunn, reduction of which has given 2-hydroxy-3:5-disubstituted-

pyrazines similar to those obtained by Jones, who quotes melting points, in some cases, 10-12° lower than found by the author and his colleagues.

PART II.

Pyrazine Cyclic Hydroxamic Acids.

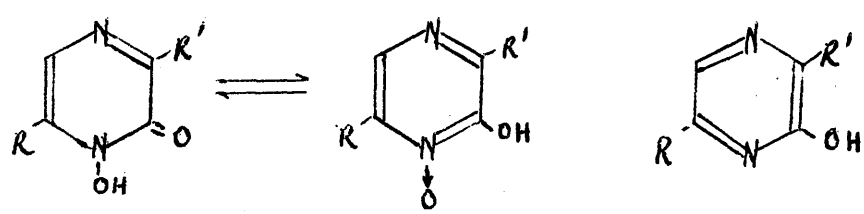
N-oxidation.

N-Oxidation.

Aspergillic acid has been shown to have a high inhibitory in vitro activity against some Gram-negative and Gram-positive organisms (2, 23) and against M. tuberculosis (24).

The toxicity of aspergillic acid is such that it is unlikely to find useful applications in the treatment of systemic infections.

Aspergillic acid is a hydroxamic acid related to pyrazine and although there is some dubiety concerning the nature of the side chains R and R' it is correctly represented by the structures (CXXII, CXXIII), the former structure being preferred on spectrographic evidence (26).



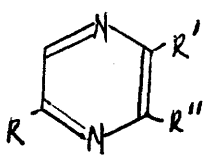
(CXXII) (CXXIII) (CXXIV)

On reduction with hydrazine, or other such mild reducing agents, aspergillic acid is converted into the neutral hydroxypyrazine (CXXIV), deoxyaspergillic acid (15,25,4), which is ineffective as an antibacterial agent.

The hydroxamic acid grouping, therefore, would seem to be an essential feature of the molecule for biological activity and antibacterial effect and such a conclusion is supported by the observation that certain simple hydroxamic acids, unrelated to pyrazine, also inhibit bacterial growth. (25).

The object of this section of the thesis was to develop synthetic methods whereby the hydroxamic acid grouping, as in aspergillic acid, might be introduced into a pyrazine ring.

Firstly, direct oxidation of substituted pyrazines of the type (CXXV) where R'' was hydroxyl or some grouping easily converted to hydroxyl was attempted and secondly, was the use of a pre-formed straight chain hydroxamic acid involving simultaneous ring closure and formation of the heterocyclic hydroxamic acid. The latter method was found the only means of preparing a pyrazine hydroxamic acid.

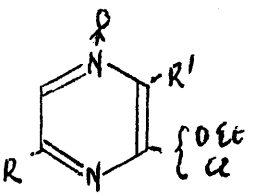


$R'' = OH, OEt, Cl.$

(CXXV)

Although Newbold and Spring et.al., (31) and Lott and Shaw (26) had prepared various hydroxamic acids of quinoline and pyridine, the former authors were unsuccessful

in their attempts to oxidise ethoxy- and chloro-2:5-dimethylpyrazines, with hydrogen peroxide, on the nitrogen atom adjacent to the potential hydroxyl grouping, instead, they obtained the corresponding 4-N oxide (CXXVI).

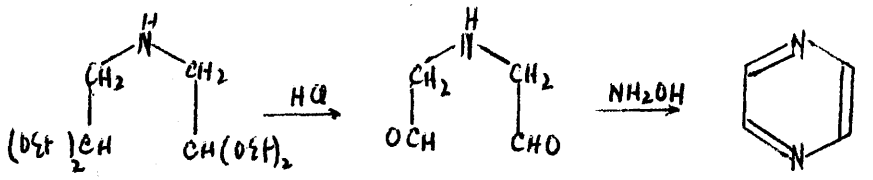


(CXXVI)

In spite of the lack of success of the above authors in preparing pyrazine cyclic hydroxamic acids by direct oxidation a further such attempt was made using various oxidising agents under different experimental conditions.

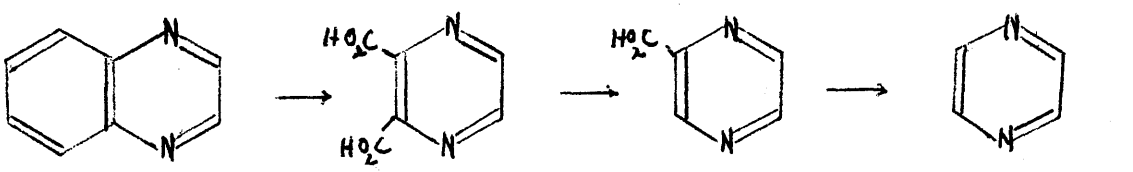
No attempt had yet been made to oxidise derivatives of the parent pyrazine, few derivatives of which are known, and it was decided to carry out the initial experiments on chloropyrazine, ethoxypyrazine and hydroxypyrazine.

Pyrazine was most readily obtained by two routes; the first according to the method of Wolff and Marburg (57) who obtained the parent base by treating diacetalylamine successively with hydrochloric acid and hydroxylamine,



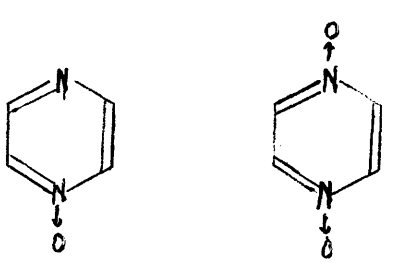
(CXXVII) (CXXVIII) (CXXIX)

and the second, by the oxidation of quinoxaline to pyrazine-2:3-dicarboxylic acid followed by stepwise decarboxylation. (20,60).



(CXXX) (CXXXI) (CXXXII) (CXXXIII)

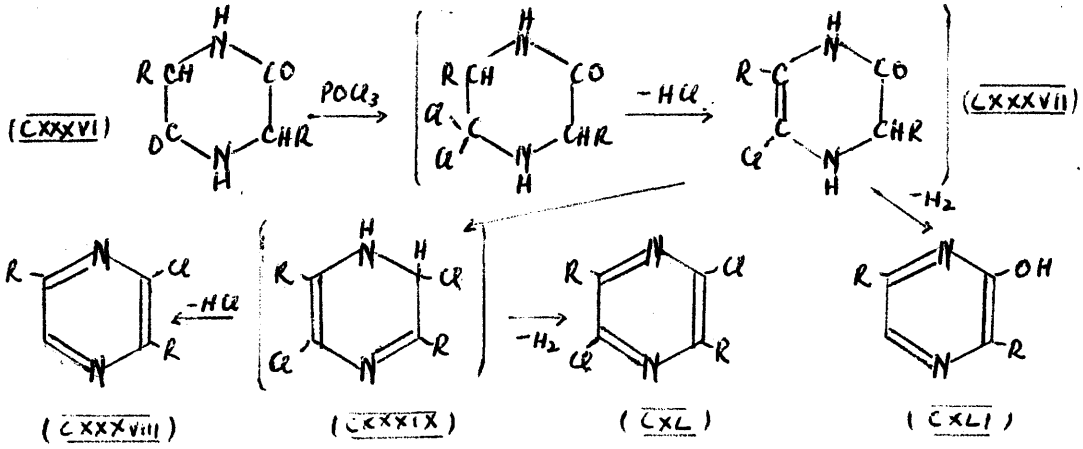
Oxidation with hydrogen peroxide in acetic acid gave a mixture of the monoxide (CXXXIV) and dioxide (CXXXV) readily separable by their different solubilities in chloroform.



CXXXIV CXXXV

In the homologous case, treatment of 2:5-dimethylpyrazine monoxide with phosphoryl chloride gave a good yield of 3-chloro-2:5-dimethylpyrazine (12) but an attempt to apply the reaction to pyrazine monoxide gave, under a variety of experimental conditions, only a very poor yield of chloropyrazine. Most of the starting material was converted to a charred mass, whilst use of thionyl chloride as chlorinating agent gave a complete recovery of the monoxide.

In view of this failure to obtain the appropriate intermediates a further attempt was made to prepare the pyrazine derivatives by treatment of glycine anhydride (61) with phosphoryl chloride; a reaction which should lead to a mixture of chloro-, dichloro-, and hydroxy-chloropyrazines. (cf. Baxter and Spring (10)).

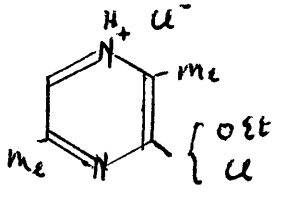


No pyrazine derivatives were obtained and the starting material was practically quantatively degraded to carbon.

The difficulty encountered in preparing derivatives of the parent pyrazine led to the use of substituted 2:5-dimethylpyrazines for the oxidation experiments.
Alanine anhydride (61), prepared by refluxing alanine in ethylene glycol, was smoothly converted to a mixture of 2-chloro-, 2:5-dichloro and 2-hydroxy-5-chloro-3:6-dimethylpyrazine by treatment of the diketopiperazine with phosphoryl chloride and the products, were in part, converted to ethoxy- and diethoxy-dimethylpyrazine by the action of sodium ethoxide on the chloro-derivatives.

. . Under conditions similar to those of Baxter, Newbold and Spring (34) 2:5-diethoxy-, 2-ethoxy-5-chloro- and 2-amino-5-chloro-3:6-dimethylpyrazine failed to react with peracetic acid and attempts to enforce oxidation using more vigorous reaction conditions resulted in cleavage of the pyrazine ring

By use of hydrochloric acid, with the peracetic acid, to form a quaternary ammonium salt with the nitrogen remote from the potential hydroxyl group, only poor yields of the 4-oxides of 3-ethoxy-2:5-dimethylpyrazine and 3-chloro-2:5-dimethylpyrazine were obtained.



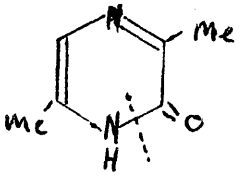
(CXLII)

Similar results were obtained using an anhydrous solution of hydrogen peroxide in tertiary-butyl alcohol.

A series of reactions was then carried out using perbenzoic acid, persulphuric acid and lead tetraacetate as oxidising agents.

Perbenzoic acid gave better yields of the 4-oxides of hydroxy- and ethoxypyrazine than obtained with peracetic acid while lead tetraacetate did not react with the former. Lead tetraacetate, however, converted dimethylpyrazine monoxide into the dioxide in good yield.

With persulphuric acid 3-ethoxy-2:5-dimethylpyrazine gave a small amount of the 4-oxide and a large recovery of starting material, whilst the pyrazine ring, on oxidising 3-hydroxy-2:5-dimethylpyrazine, was largely cleaved giving ammonium sulphate. The destruction of the ring in the latter case is possibly due to the fact that hydroxy-pyrazines exist in the tautomeric amide form (CXLIII) which is not truly aromatic; cleavage occurring at the amide linkage.



(CXLIII)

Cyclic Hydroxamic Acids.

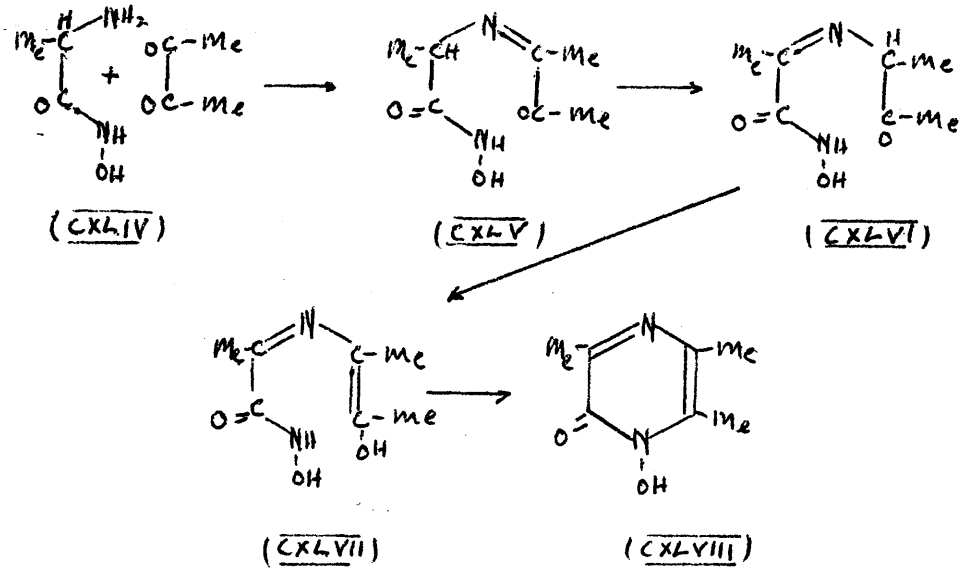
Pyrazine Cyclic Hydroxamic Acids.

In view of the failure to obtain a pyrazine cyclic hydroxamic acid by direct oxidation, the possibility of obtaining such a compound using a preformed hydroxamic acid grouping was examined.

Condensation of N-alanine hydroxamic acid (CXLIV), prepared by the action of hydroxylamine on Di-alanine ester, with diacetyl, using conditions similar to those of Jones (16) for the preparation of hydroxypyrazines, gave a gummy residue which on sublimation yielded a colourless solid exhibiting all the properties of a cyclic hydroxamic acid.

The product dissolved with effervescence in sodium hydrogen carbonate; a property which distinguishes cyclic hydroxamic acids from straight chain hydroxamic acids, and gave a claret colouration with ferric chloride. Examination of its ultra-violet absorption in ethanol with that of aspergillic acid showed a striking similarity with maxima at 2330 Å (εmax.11,600) and 3340 Å (εmax.7,000) as against 2360 Å (εmax.10,700) and 3300 Å (εmax.8,000) for the latter.

The compound analysed for the molecular formula $C_7H_{10}O_2N_2$ and was ascribed the structure of 1-hydroxy-2-keto-3:5:6-trimethyl-1:2-dihydropyrazine (CXLVIII).



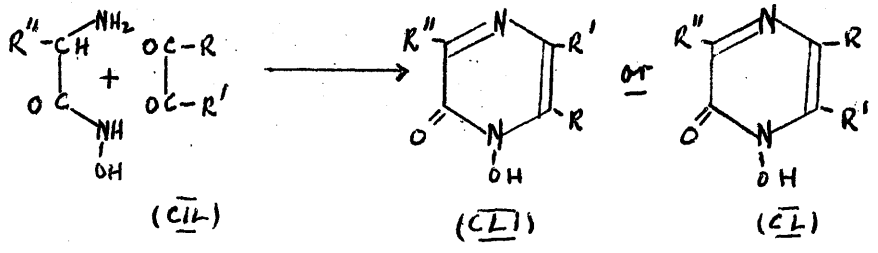
(CXLIV) (CXLV) (CXLVI)

(CXLVII) (CXLVIII)

Reduction of the hydroxamic acid with hydrazine gave 2-hydroxy-3:5:6-trimethylpyrazine identical with that prepared by Newbold and Spring (15).

The initial stage in the mechanism of the reaction would appear to be the formation of the Schiff base (CXLV), followed by a rearrangement of the double bonds leading to conjugation (CXLVI). The tendency of the molecule to form an aromatic system causes ready cyclisation leading to the pyrazine hydroxamic acid.

Theoretically when the dicarbonyl compound used is not symmetrical, both carbonyl groups being assumed equivalent, a mixture of two hydroxamic acids is possible.



(CIL) (CLI) or (CL)

As this work was mainly concerned with investigating synthetic routes to aspergillic acid, which is a 3:6-di-substituted-pyrazine hydroxamic acid, for a model synthesis R' = H(CLI) and the dicarbonyl compound used must be a keto-aldehyde.

DL-Alanine hydroxamic acid was condensed with methyl-glyoxal (CIL, R' = Me; R = H) giving a cyclic dimethyl-pyrazine hydroxamic acid, $C_6H_8O_2N_2$, which on reduction with hydrazine gave a dimethylpyrazine m.p. 147° different from 3-hydroxy-2:5-dimethylpyrazine m.p. 211° and whose properties corresponded to that of 2-hydroxy-3:5-dimethyl-pyrazine (Jones. loc.cit.).

The hydroxypyrazine was then 2-hydroxy-3:5-dimethylpyrazine and hence by analogy the hydroxamic acid must be 1-hydroxy-2-keto-3:5-dimethyl-1:2-dihydropyrazine.

A rigorous examination of the products of reaction,

revealed no other cyclic hydroxamic acid.

Similarly, condensation of DL-alanine hydroxamic acid with phenylglyoxal led to 1-hydroxy-2-keto-3-methyl-5-phenyl-1:2-dihydropyrazine, reduction of which with hydrazine gave 2-hydroxy-3-methyl-5-phenylpyrazine, identical with the hydroxypyrazine obtained by condensation of DL-alanine amide and phenylglyoxal to which Jones ascribes the structure of 2-hydroxy-3-methyl-5-phenylpyrazine.
It is of interest to note that Jones gives a melting point of 212-213° for the product, whereas samples prepared by both methods by the author were found to melt at 222-223°.

Dr. G.T. Newbold similarly prepared 1-hydroxy-2-keto-3:5-diphenyl-1:2-dihydropyrazine, from DL-phenylglycine hydroxamic acid and phenylglyoxal, reduction of which gave 2-hydroxy-3:5-diphenylpyrazine dissimilar to the known 3-hydroxy-2:5-diphenylpyrazine and identical with the Jones product from DL-phenylglycine amide and phenylglyoxal and Mr. G. Dunn in poor yield obtained 1-hydroxy-2-keto-5-phenyl-1:2-dihydropyrazine from glycine hydroxamic acid and phenylglyoxal.

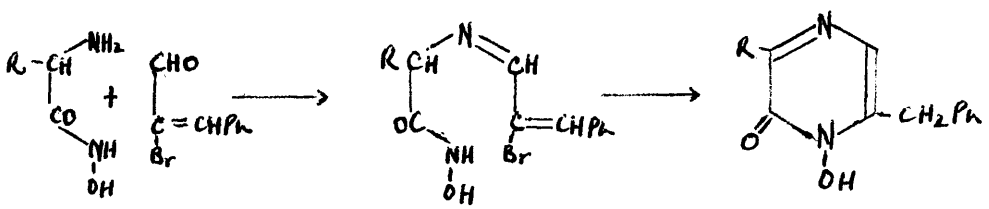
Attempts to modify the reaction, and so obtain a 3:6-disubstituted hydroxamic acid, by varying the pH of the aqueous reaction mixture merely varied the yield of the product previously obtained; the best yield being obtained

in very alkaline conditions.

Latterly using either glacial acetic acid or pyridine as solvents 1-hydroxy-2-keto-5-phenyl-1:2-dihydropyrazine and 1-hydroxy-2-keto-3:5-diphenyl-1:2-dihydro-pyrazine have been obtained in high yield.

The above synthesis thus, is not suitable for the preparation of pyrazine cyclic hydroxamic acids of the aspergillic acid type.

Such a synthesis has been developed in this Department by Dr. J.A. Elvidge and Mr. D. Ramsay, who condensed glycine hydroxamic acid with α-bromocinnamaldehyde to give the Schiff base (CLIII), which on treatment with potassium t-butoxide gave 1-hydroxy-2-keto-6-benzyl-1:2-dihydro-pyrazine (CLIV).



(CLII) (CLIII) (CLIV)

Treatment of the Schiff base from α-bromocinnamaldehyde and α-amino-n-butyrohydroxamic acid gave 1-hydroxy-2-keto-3-ethyl-6-benzyl-1:2-dihydropyrazine (CLIV; R = Et).

This method or a simple variant offers a route to the

synthesis of aspergillic acid by the introduction of different substituents in the 3 and 6 positions.

Ultra-violet absorption spectra.

	Maxima, Å		εmax.	
Aspergillic acid.	2360,	3300;	10,700,	9,250
Deoxyaspergillic acid.	2295,	3250;	6,700,	8,000
1-Hydroxy-2-keto-3:5:6-trimethyl-1:2-dihydropyrazine.	2330,	3340;	11,600,	7,000
2-Hydroxy-3:5:6-trimethylpyrazine.	2295,	3360;	7,900,	7,400
1-Hydroxy-2-keto-3:5-dimethyl-1:2-dihydropyrazine.	2340,	3300;	8,100,	5,400
2-Hydroxy-3:5-dimethylpyrazine.	2280,	3270;	5,000,	4,200
1-Hydroxy-2-keto-3-methyl-5-phenyl-1:2-dihydropyrazine.	2810,	3450;	17,500,	8,800
2-Hydroxy-3-methyl-5-phenylpyrazine.	2760,	3400;	17,100,	6,500
1-Hydroxy-2-keto-3:5-diphenylpyrazine.	2770,	3890;	17,300,	7,700
2-Hydroxy-3:5-diphenylpyrazine.	2780,	3720;	19,300,	9,200
1-Hydroxy-2-keto-5-phenyl-1:2-dihydropyrazine.	2720,	3540	18,900	5,300

Summary.

Direct oxidation of substituted pyrazines, the substituent being readily converted to hydroxy, under a variety of conditions with several oxidising agents has failed to give a pyrazine cyclic hydroxamic acid.

Pyrazine cyclic hydroxamic acids have been obtained by cyclisation of simple straight chain hydroxamic acids with α-β-dicarbonyl compounds.

Reference is made to a route for the possible synthesis of aspergillic acid.

Experimental Part I.

Acylamidopyrazines.

All melting points are uncorrected.

Microanalyses by Mr. W. McCorkindale and Miss N. Henderson, The Royal Technical College.

Diazomethane.

(Org. Syn.) Coll.Vol. 11, p. 165).

Potassium hydroxide solution (225 c.c., 40%) and ether (700 c.c.) were cooled in ice and nitrosomethylurea (79g. from acetamide. Org.Syn., Coll. Vol. 11, p. 462) added in small portions with shaking. The yellow-green ethereal solution was separated and dried by contact with solid potassium hydroxide pellets for 2 hours.

Propionyl Chloride.

(Brown. J. Amer. Chem. Soc., 60, 1325, (1938)).

Propionic acid (1 mole.) was mixed with benzoyl chloride (2 moles.) and rapidly distilled up a short column until the stillhead thermometer read 120°. The crude acid chloride was fractionated through a 7 in. Fenske column, using a high reflux ratio initially, to remove dissolved hydrogen chloride, giving propionyl chloride b.p. 77-78° in 85% theoretical yield.

Chloromethylethyl Ketone.

Propionyl chloride (39g.) in dry ether (100 c.c.) was run slowly into the decanted diazomethane solution above with hand agitation and ice-cooling.

Vigorous evolution of gas took place. After standing overnight protected by a soda-lime tube the light-yellow solution was cooled in ice and a steady stream of dry hydrogen chloride passed in for 2-3 hours. Evolution of gas took place and the solution became almost colourless. The reaction mixture was allowed to stand overnight, protected by a calcium chloride tube, and as much hydrogen chloride removed as possible by application of reduced pressure. The solution was then cautiously washed with saturated sodium carbonate solution until the ethereal phase was no longer acid. After washing with water and drying (Na_2SO_4) the ether was removed leaving a colourless lachrimatory oil which on distillation at 59-60°/30mm. gave chloromethylethyl ketone. Yield 15g. 27% of theory.

Phthalimidomethylethyl Ketone.

(cf. Gabriel and Colman. Ber., 35, 3805, (1902)).

A mixture of the chloroketone (30g.), dry xylene (70 c.c.) and potassium phthalimide (52g. Org. Syn., Coll. Vol. I, p. 119) was heated at 140-150° (bath temp.) with mechanical stirring for 4 hours. After filtering and extracting the residue with boiling benzene (3 x 100 c.c.) the combined filtrates were evaporated to small bulk, about 100 c.c., under reduced pressure and treated with light petroleum (b.p. 40-60°).

The crystalline material which separated on cooling (41g.) had m.p. 100-105°. Crystallisation from light petroleum (b.p. 60-80°) gave long fine colourless needles m.p. 105-107° not raised by further crystallisation. The yield was 67% of theory.

Aminomethylethyl ketone hydrochloride.

The phthalimido-ketone (41g.) was heated under reflux with constant boiling hydrochloric acid (300 c.c.) for 6 hours, charcoal (1g.) added and the solution boiled for a further 30 minutes. The reaction mixture was then chilled to 0° and the phthalic acid which separated filtered off along with the charcoal and the residue washed with a little ice-water. The light-brown filtrate was evaporated to dryness under reduced pressure, ice-water (50 c.c.) added, the mixture filtered free of a little phthalic acid and the solution evaporated to dryness. A gummy residue remained and this was dissolved in dry ethanol (200 c.c.) and the solution evaporated under reduced pressure to small bulk until crystallisation had largely taken place. After leaving overnight at 0° the hydrochloride was filtered off, washed with a little dry ether and dried in a vacuum desiccator over phosphorous pentoxide. Aminomethylethyl ketone hydrochloride was so obtained as light-brown hygroscopic plates.

Yield 13g., 63.5% of theory.

α-Bromopropionyl bromide.

(Weinig. Annalen, 280, 247, (1894). Anwers and Bernhardi. Ber., 24, 2219, (1891)).

A mixture of propionic acid (136g.) and red phosphorus (10g.) was treated with bromine (600g.) added dropwise over 4 hours at 90°. The mixture was then distilled under reduced pressure giving two main fractions (a) b.p. 40-60°/5-10mm. and (b) 90-100°/10mm. Fraction (a) was distilled through a 7 in. Fenske column using a high reflux ratio giving α-bromopropionyl bromide b.p. 54-55°/7-8mm. as a colourless fuming liquid. 250g. (62% of theory).

α-Bromopropionyl Chloride.

The higher boiling fraction above was distilled under reduced pressure giving α-bromopropionic acid as a colourless oil, b.p. 113°/25mm., 65g. (23% of theory). The acid so obtained was refluxed on the steambath with a 10% excess of thionyl chloride. Fractional distillation of the products gave α-bromopropionyl chloride as a light-yellow liquid b.p. 132°/760mm. in 85% yield.

N-Methylmorpholine.

(Atherton, Openshaw and Todd. J., 660, (1945)).

Paraform (105g.) was added to morpholine (261g.) and

the mixture well shaken to wet the former. After maintaining under a wide reflux condenser for a short time, a vigorous reaction set in and most of the paraform dissolved. Formic acid (170g. of 98%) was then added dropwise over 2 hours, carbon dioxide being steadily evolved, after which the mixture was heated on the steambath for 3 hours. At the end of this time gas evolution was virtually negligible and the reaction mixture had formed two layers. Caustic soda (about 200g.) was added with cooling, the upper organic layer separated and further treated with caustic soda until no more separation of the aqueous phase took place. The base was then diluted with benzene (200 c.c.), dried overnight with potassium hydroxide pellets, and distilled (Fenské) giving N-methylmorpholine as a colourless oil b.p. 114°. The product was stored over sodium wire. Yield 225g., 74% of theory.

α-Bromopropionamidomethylethyl ketone.

A suspension of aminomethylethyl ketone hydrochloride (5g.) in dry chloroform (30 c.c.) was mixed with a solution of α-bromopropionyl bromide (9g.) in dry chloroform (30c.c.); the mixture with stirring cooled to 0° and a solution of N-methylmorpholine (9g.) in dry chloroform (25c.c.) added dropwise over 15 minutes. Complete solution was almost effected and then a solid began to separate.

The mixture was stirred at 0° for a further 15 minutes and during the next hour allowed to attain room temperature. After washing successively with water, dilute hydrochloric acid, saturated aqueous sodium carbonate and water, the chloroform solution was dried over sodium sulphate. Removal of the solvent under reduced pressure gave a crystalline residue filtered with addition of light petroleum (b.p. 40-60°) to give 5.7g. of crude product (63% of theory) m.p. 73-75°. Recrystallisation from benzene-light petroleum (b.p. 40-60°) gave α-bromopropionamidomethylethyl ketone as colourless needles m.p. 77°. The crude product was contaminated with a powerful lachrimator.

Found: C, 37.9 ; H, 5.3 ; N, 6.3%.

$C_7H_{12}O_2NBr$ required : C, 37.8 ; H, 5.4 ; N, 6.3%.

Treatment of the Above Compound with Ammonia.

3-Propionamido-2:5-diethylpyrazine.

A mixture of α-bromopropionamidomethylethyl ketone (4g.) and ammonium iodide (0.5g.) was dissolved in liquid ammonia (50c.c.) giving a reddish solution which was kept in a glass-lined autoclave for 16 hours at 15°. The ammonia was then removed on the waterbath leaving a red gummy residue which was extracted with boiling benzene (6 x 25c.c.). Removal of the benzene under reduced pressure from the dried extract (Na_2SO_4) left a solid crystalline residue (1.18g.), crystallisation

of which from benzene-light petroleum (b.p. 40-60°) gave 3-propionamido-2:5-diethylpyrazine as colourless needles m.p. 98°. Yield 62% of theory. The product was soluble in water and most organic solvents and sublimed readily at 70°/0.5mm. In elucidating the structure attempts to prepare a picrate and a 2:4-dinitrophenyl-hydrazone were unsuccessful.

Found: C,63.9,64.1;H,8.0,8.0;N,18.6%.Mol.wt.201. $C_{11}H_{17}ON_3$ required: C,63.8 ;H,8.2 ;N,18.9%.Mol.Wt.207. Light absorption in ethanol: Maxima at 2260Å (εmax. 6,100) and 2790 Å (εmax. 3,930).

3-Amino-2:5-diethylpyrazine.

A solution of 3-propionamido-2:5-diethylpyrazine (0.2g.) in sodium hydroxide solution (10c.c.; N.) was heated under reflux. After about 1 hour it was noticed that a colourless oil had separated and after 3 hours refluxing the mixture was allowed to cool when the oil solidified as as needles. The product was filtered off and the alkaline filtrate extracted with ether (3 x 5c.c.). After drying (Na_2SO_4) the ether was removed, the residue combined with the solid obtained by filtration and the product sublimed at 55°/10^{-4} mm. giving 3-amino-2:5-diethylpyrazine (0.12g.) as colourless needles m.p. 42°. The compound was extremely soluble in water and the common organic solvents and along with its hygroscopicity this precluded efficient crystallisation.

For analysis it was sublimed at 35°/10^{-4}mm. and the sublimate dried at room temperature in vacuo over phosphorus pentoxide.

Found: C, 60.2,60.5 ; H,8.2,8.8; N,25.9,26.0%.

$C_8H_{12}N_3.\frac{1}{2}H_2O$ required: C. 60.0 ; H,8.7 ; N,26.2 %.

Light absorption in ethanol: Maxima at 2360 Å(εmax.12,200) and 3190 Å (εmax. 8,000).

On treatment with ethanolic picric acid a solution of the above aminopyrazine readily yielded a picrate which separated from ethanol as yellow needles m.p. 157°.

Found: C,44.7; H,4.2; N,22.2%.

$C_{14}H_{16}O_7N_6$ required: C,44.4; H,4.2; N,22.1%.

Propionylation of 3-amino-2:5-diethylpyrazine.

A mixture of 3-amino-2:5-diethylpyrazine (0.2g.) and propionic anhydride (5c.c.) - from propionyl chloride and sodium propionate - was kept at 90° for 15 minutes, solution then being complete. After allowing to cool the solution was treated with water (10c.c.). It was found necessary to warm the solution on the steambath to decompose the excess anhydride. The solution was then neutralised by the addition of aqueous sodium hydrogen carbonate, evaporated to dryness under reduced pressure and the residual solid extracted with boiling benzene (3x20cc). The filtered extract was dried(Na_2SO_4) and evaporated to dryness under reduced pressure leaving a crystalline

residue which crystallised from benzene-light petroleum b.p. 40-60) to give 3-propionamido-2:5-diethylpyrazine (0.2g.) as colourless needles m.p. 107° alone and when admixed with the specimen obtained by the action of ammonia on α-bromopropionamidomethylethyl ketone.

Found: N, 20.3%

$C_{11}H_{17}O N_3$ required: N, 20.3%

Light absorption in ethanol showed maxima at 2250 Å (εmax. 5,800) and 2800 Å (εmax. 6,000).

3-Hydroxy-2:5-diethylpyrazine.

A solution of 3-amino-2:5-diethylpyrazine (0.2g.) in hydrochloric acid (10c.c.; N.) was treated at 0° with solid sodium nitrite (0.2g.) added in small quantities over 10 minutes with good stirring. After keeping at 0° for 15 minutes, the solution was allowed slowly to attain room temperature and kept at this temperature for 3 hours. It was then neutralised with saturated aqueous sodium hydrogen carbonate and the solution extracted with chloroform (5 x 60c.c.). The dried (Na_2SO_4) extract was evaporated and the crystalline residue recrystallised from light petroleum (b.p. 100-120°) from which 3-hydroxy-2:5-diethylpyrazine (0.1g.) separated as colourless needles m.p. 135°.

Found: C, 63.7; H, 8.0; N, 18.2%.

$C_8H_{12}ON_2$ requires: C, 63.2; H, 7.9; N, 18.4%.

Light absorption in ethanol: Maxima at 2270 Å (εmax. 6,800) and 3220 Å (εmax. 8,100).

The compound is not basic and no picrate could be obtained from ethanolic picric acid. Later Sharp and Spring (J., 1948, 1862) prepared the above hydroxypyrazine by an independent route and their compound m.p. 135° showed no depression of melting point on admixture with the above.

Chloroacetone.

(Fritsch. Ber., 26, 597; Annalen, 279, 313; Kling. Bull. Soc. chim., [3]., 33, 322; Ann. Chim., [8], 5, 477.)

A mixture of acetone (1000c.c.), calcium carbonate (200g.) and water (500c.c.) - contained in a 5l. flask, fitted with an inlet-tube, thermometer and wide condenser - was warmed to 60° when a rapid stream of chlorine was passed through the mixture. The initial reaction was vigorous and the flask was water-cooled. When almost all the calcium carbonate had reacted (about 4 hours) the passage of chlorine was stopped, calcium carbonate (50g.) added and the mixture left overnight at room temperature. The upper organic layer was separated, dried over calcium chloride and distilled through a 2ft. Fenske column giving chloroacetone b.p. 117-118° as a colourless lachrimatory liquid which darkens on standing. Yield 356g., 96% of theory.

Phthalimidoacetone.

(Gabriel and Colman, Ber., 35, 3805, (1902)).

Chloroacetone (18g.) potassium phthalimide (32g.) and dry xylene (100 c.c.) were refluxed at 140-150° for 4 hours with good mechanical stirring. The mixture was filtered when hot, the residue extracted with boiling benzene (4 x 50c.c.) and the combined extracts evaporated to small bulk (50c.c.) under reduced pressure. Light petroleum (b.p. 40-60°) was added and the crystalline residue filtered and air dried (35g.). Crystallisation from benzene-light petroleum (b.p. 40-60°) gave phthalimidoacetone m.p. 121° as long colourless needles. Yield 88% of theory.

Aminoacetone hydrochloride.

(Gabriel and Pinkus, Ber., 26, 2197, (1893); Gabriel and Colman, ibid, 35, 3805, (1902); Gabriel, ibid, 41, 1127(1908)).

(a) Phthalimidoacetone (42g.) was refluxed with constant boiling hydrochloric acid (300c.c.) for 4 hours when complete solution took place, charcoal (1g.) was added, the solution refluxed for a further 1 hour. After cooling to 0° the brown filtrate was evaporated to dryness under reduced pressure, the residue dissolved in ice-water (50c.c.), filtered free of a little phthalic acid and the solution re-evaporated to dryness. Successive solution of the residue in absolute ethanol, followed by evaporation to small bulk, finally gave crystalline aminoacetone

hydrochloride as practically colourless hygroscopic plates which were retained over phosphorus pentoxide. Yield 14g; 67% of theory.

iso-Nitrosoacetone.

(Freon, Ann. Chim., 11, [11], 460, (1939)).

Ethyl acetoacetate (200g.) was added to a solution of caustic soda (71.5g.) in water (3000c.c.) and the solution left for 24 hours at 15°. Sodium nitrite (104g.) in water (400c.c.) was added, the solution cooled to 0° and sulphuric acid (860g. of 20%) added slowly with cooling and stirring. After standing at 0° for 1 hour the solution was extracted with ether (6 x 300c.c.) and the dried (Na_2SO_4) extract removed giving iso-nitrosoacetone (100g.) as colourless needles m.p. 63-65°.

Aminoacetone hydrochloride.

(b) Reduction of iso-nitrosoacetone (87g.) by stannous chloride in hydrochloric acid, followed by removal of the tin by hydrogen sulphide and crystallisation of the syrup, obtained by evaporation of the filtrate, from ethanol-ether with strong cooling, gave aminoacetone hydrochloride 77g. 70% of theory.

Note. More trouble was encountered with this method owing to the difficulty in effecting complete removal of the tin salts from solution. Crystallisation of the syrup under these circumstances being difficult and for most of the condensations with bromoacyl halides method (a) was used

for preparing aminoacetone hydrochloride.

α-Bromopropionamido-acetone.

The acylation was carried out as for the preparation of α-bromopropionamidomethylethyl ketone. The chloroform extract from the action of α-bromopropionyl bromide (27g.) on aminoacetone hydrochloride (11g.) in the presence of N-methylmorpholine (23g.) gave α-bromopropionamidoacetone m.p. 74-77°. Yield 14.1g., 67% of theory. It separated from benzene-light petroleum (b.p. 40-60°) as colourless needles m.p. 80°.

Found: C, 34.7; H, 4.7; N, 6.5%.

$C_6H_{10}O_2NBr$ requires: C, 34.6; H, 4.8; N, 6.7%.

Treatment of the Above Compound with Ammonia.

3-Propionamido-2:5-dimethylpyrazine.

A solution of α-bromopropionamidoacetone (2.6g.) and ammonium iodide (0.5g.) in liquid ammonia (50c.c.) was kept at room temperature in a glass-lined autoclave for 16 hours. Removal of the ammonia left a reddish resin, which was extracted with boiling benzene (4 x 25c.c.) and the extract was filtered through a column of alumina (75 x 16 mm.). After eluting with benzene (250c.c.), the combined filtrates were evaporated to dryness yielding a colourless crystalline residue, crystallisation of which from benzene-light petroleum (b.p. 40-60°) gave 3-propionamido-2:5-dimethylpyrazine (0.9g., 80% of theory) as colourless blades m.p. 106-108°. The product was very soluble in

water and the common organic solvents, save light petroleum, and could be extracted from aqueous alkaline solution with ether. It sublimes readily at 100°/10^{-3} mm.

Found: C,60.6,60.6;H,7.4,7.2;N,23.3,23.2%. Mol.Wt. 181.

$C_9H_{13}ON_3$ requires: C,60.3 ;H,7.2 ;N,23.5 %. Mol.Wt. 179.

Light absorption in ethanol: Maxima at 2260 Å (εmax. 6,400) and 2805 Å (εmax. 6,800).

3-Amino-2:5-dimethylpyrazine.

3-Propionamido-2:5-dimethylpyrazine (0.2g.) was heated under reflux for 4 hours with aqueous potassium hydroxide (4c.c. of 10%). The solution was neutralised with 10% hydrochloric acid and after evaporating to dryness the residue was extracted with boiling benzene (3 x 10c.c.). The filtered extract was dried (Na_2SO_4) and the solvent removed under reduced pressure leaving a crystalline residue. Recrystallisationfrom benzene gave 3-amino-2:5-dimethyl-pyrazine as colourless needles (0.12g.) m.p. 111°. For analysis a specimen was sublimed at 70°/1mm.

Found: C,55.0; H, 7.6; N, 31.6%.

$C_6H_9N_3.\frac{1}{2}H_2O$ requires: C,54.6; H, 7.6; N, 31.8%.

A solution of the amine in ethanol gave a picrate m.p.205°. A mixed melting point of the above aminopyrazine with 3-amino-2:5-dimethylpyrazine prepared by the method of Joiner and Spoerri (J.Amer.Chem.Soc., 63, 1929, (1941)) showed no depression. The picrate m.p. 205° likewise was

undepressed in melting point when admixed with an authentic specimen of the picrate of 3-amino-2:5-dimethylpyrazine. Tschitschababin and Schukina (J. Russ. Phys. Chem. Soc., 62, 1189, (1930),) gave m.p. 205° for the picrate. Light absorption of the amine in ethanol: Maxima at 2350 Å (εmax. 11,500) and 3195 Å (εmax. 17,300).

3-Propionamido-2:5-dimethylpyrazine.

3-Amino-2:5-dimethylpyrazine (0.22g.) was heated to 90° with propionic anhydride (5c.c.) for 15 minutes. The reaction mixture was poured into water and the excess anhydride decomposed by warming the mixture. After neutralisation with saturated aqueous sodium hydrogen carbonate, the solution was evaporated to dryness under reduced pressure and the residue extracted with boiling benzene (3 x 10c.c.). The filtered extract was evaporated to dryness and the residue recrystallised from benzene-light petroleum (b.p. 40-60°) from which 3-propionamido-2:5-dimethylpyrazine separated as needles m.p. 107° above or when admixed with the specimen obtained by the action of ammonia on α-bromopropionamidoacetone.

Found: N, 23.3%.

$C_9H_{13}ON_3$ required: N, 23.5%.

A mixture of the above compound with 3-amino-2:5-dimethyl pyrazine melted at 98-100°.

3-Hydroxy-2:5-dimethylpyrazine.

A solution of 3-amino-2:5-dimethylpyrazine (0.5g.) in

hydrochloric acid (15c.c. ; N.) was treated at 0° with sodium nitrite (0.6g.) added in small portions over 15 minutes. The solution was kept at room temperature for 2 hours, heated to 60° for 5 minutes, neutralised with sodium hydrogen carbonate and evaporated to dryness under reduced pressure. The residue was extracted with boiling benzene (3 x 40c.c.), evaporation of which gave 3-hydroxy-2:5-dimethylpyrazine m.p. 211° either alone or when admixed with a specimen prepared by Baxter, Newbold and Spring (J., 372, (1947)). Yield 60%.

iso-Nitrosoacetophenone.

(cf. Claisen and Manasse. Ber., 20, 656, 2194, (1887)). To a cooled solution of sodium ethoxide, made from sodium (46g.) and absolute ethanol (2,300c.c.), was slowly added amyl nitrite (234g.) with stirring and then acetophenone (240g.) in 20g. portions. The flask was tightly stoppered (to prevent the escape of ethyl nitrite) and allowed to stand at room temperature for several days, during which the red-brown sodium salt of iso-nitrosoacetophenone crystallised out. It was filtered off with suction, washed with ether (2 x 200c.c.) and air dried. Yield 200g. ; 58% of theory. The dried salt was dissolved in ice-water (800c.c.) and the theoretical quantity (70.2g.) of glacial acetic acid slowly added with cooling and stirring, when the product began almost immediately to crystallise out. After standing overnight at 0° the

yellow prisms of iso-nitrosoacetophenone were filtered off, washed with a little cold water and air dried. A sample recrystallised from chloroform as pale yellow prisms. m.p. 127-128°. Yield 150g. ; 86% of theory.

ω -Aminoacetophenone hydrochloride.

(Rupe. Ber., 28, 254, (1895).)

A concentrated solution of iso-nitrosoacetophenone (35g.) in ethanol was slowly added over 30 minutes, with vigorous stirring, to an ice-cooled solution of stannous chloride (114g.) in hydrochloric acid (172c.c. of 30%) containing metallic tin (2g.). The tin double salt of the base separated immediately. When the addition was complete the reaction mixture was allowed to stand overnight at 0°, the tin double salt filtered off and heated with 100 x weight of water for 20 hours at 90°. After filtering off the tin dioxide with aid of Hyflo filter-aid, the filtrate was evaporated to dryness under reduced pressure and the residue recrystallised from ethanol giving ω-aminoacetophenone hydrochloride as colourless needles m.p. 186-187° (decomp.) Yield 30g. ; 75% of theory.

The aminoketone is not very hygroscopic and keeps well in a stoppered bottle.

ω -(α-Bromopropionamido) acetophenone.

To a suspension of ω-aminoacetophenone hydrochloride (14.2g.) in dry chloroform (100c.c.) was added a solution of α-bromopropionyl bromide (22g.) in dry chloroform (50c.c.),

the mixture stirred and cooled to 0°. A solution of N-methylmorpholine (19g.) in dry chloroform (25c.c.) was then added dropwise, with vigorous stirring, over 15 minutes. The mixture almost at once assumed a reddish colour and a solid separated. After the final addition of the base the mixture was stirred for a further 30 minutes at 0° and then allowed to attain room temperature over 1 hour. The solution was washed successively with water, dilute hydrochloric acid solution, saturated aqueous sodium carbonate, water and dried over sodium sulphate. Removal of the chloroform left a pinkish crystalline mass (14.5g.; 66% of theory) crystallisation of which from light petroleum (b.p. 60-80°) gave ω-(α'-bromopropionamido) acetophenone as colourless needles m.p. 90°.

Found: C, 48.6; H, 4.75; N, 5.5; Br, 30.2%.

$C_{11}H_{12}O_2NBr$ required: C, 48.9; H, 4.4 ; N, 5.2; Br, 29.6%.

3-Propionamido-2:5-diphenylpyrazine.

ω -(α' -Bromopropionamido) acetophenone (15g.) and ammonium iodide (1g.) were dissolved in liquid ammonia (200c.c.) to give a purple-red solution which was sealed in an autoclave at 15° for 16 hours. Removal of the ammonia left a brown resin interdispersed with a crystalline solid. This was extracted with boiling benzene (4 x 25c.c.) and boiling chloroform (4 x 25c.c.). The benzene extract was filtered through a column (7 x ½in.) of alumina, the column eluted with benzene (250c.c.) and the combined filtrates

evaporated to dryness giving yellow needles (2g.) m.p. 207-208°. Removal of the solvent from the chloroform extract gave a further quantity (3.22g.) of the same compound m.p. 207-208°. Both fractions were combined and crystallised from ethanol from which 3-propionamido-2:5-diphenylpyrazine separated as long felted needles m.p. 212.5°. Yield 60%.

The product sublimed readily at 120°/10^{-3} mm. as colourless needles and was insoluble in water and aqueous sodium hydroxide solution.

Found: C, 75.0; H, 5.7; N, 14.0, 14.1%.

$C_{19}H_{17}ON_3$ required: C, 75.2; H, 5.6; N, 13.9 %.

Light absorption in ethanol: Maxima at 2780 Å (εmax. 13,200) and 3295 Å (εmax. 16,800).

3-Amino-2:5-diphenylpyrazine.

A suspension of 3-propionamido-2:5-diphenylpyrazine (3.0g.) in aqueous sodium hydroxide (25c.c.; N.) and ethanol (0.5c.c.), to increase the partial solubility of the pyrazine in the aqueous phase, was refluxed for 5 hours. During this period the suspension gradually changed to a bright yellow colour. The mixture was then cooled, the yellow solid filtered off, washed free of alkali with a little water and air dried. Yield 2.2g. (90% of theory). The product dissolved in boiling ethanol, giving a solution with a strong violet fluorescence, from which 3-amino-2:5-diphenylpyrazine

separated as brilliant yellow plates m.p. 186°. It was slightly soluble in benzene, cold alcohols, acetone, giving solutions having a distinct violet fluorescence. The aminopyrazine was only weakly basic and with hydrochloric acid (d, 1.19) gave an orange-coloured hydrochloride which was decomposed with water giving back the parent base. With ethanolic picric acid, or picric acid in benzene, no picrate could be obtained, but 3-amino-2:5-diphenylpyrazine gave a positive carbylamine reaction.

Found: C, 78.0; H, 5.2; N, 16.8%.

$C_{16}H_{13}N_3$ requires: C, 77.7; H, 5.3; N, 17.0%.

Light absorption in ethanol: Maxima at 2640 Å (εmax.12,500) and 3560 Å (εmax.24,000).

The diacetyl derivative of 3-amino-2:5-diphenylpyrazine was obtained by heating the base (0.2g.) under reflux with acetic anhydride (10c.c.) for 15 minutes. The mixture was then poured onto ice, the crystalline precipitate collected and crystallised from methanol from which the diacetyl derivative of 3-amino-2:5-diphenylpyrazine separated as long colourless needles, m.p. 117°.

Found: C, 72.3; H, 5.3%.

$C_{20}H_{17}O_2N_3$ requires: C, 72.3; H, 5.4%.

3-Propionamido-2:5-diphenylpyrazine.

A mixture of 3-amino-2:5-diphenylpyrazine (0.2g.), propionic anhydride (10c.c.) and ethanol was warmed at 90° for 15 minutes.

Complete solution was effected and after 15 minutes an orange-red colour developed. The solution was poured onto ice (25g.) and warmed on the waterbath till the excess propionic anhydride had reacted, when the solution was filtered giving a colourless crystalline residue (2g.). Recrystallisation from ethanol gave 3-propionamido-2:5-diphenylpyrazine as colourless needles m.p. 212.5° alone or when mixed with the specimen previously obtained.

Found: C, 75.6; H, 5.6; N, 13.9%.

$C_{19}H_{17}ON_3$ requires: C, 75.2; H, 5.6; N, 13.9%.

3-Hydroxy-2:5-diphenylpyrazine.

Sodium nitrite (0.1g.) was added in small portions, with stirring, to concentrated sulphuric acid (1.5c.c.) at 0°. The mixture was gradually heated up to 60° when a clear solution resulted, then cooled to 0° and treated with a solution of 3-amino-2:5-diphenylpyrazine (0.25g.) in concentrated sulphuric acid (3c.c.) added dropwise with stirring while keeping the temperature at or slightly below 0°. When the addition was complete, sodium nitrite (0.05g.) was added, the solution kept at 0° for 1 hour and then poured onto ice (25c.c.) and stirred till the evolution of nitrogen ceased. The greenish precipitated solid was collected and crystallised from glacial acetic acid from which 3-hydroxy-2:5-diphenylpyrazine (0.15g.) separated as yellow-green prisms, m.p. 286° alone and

when mixed with that obtained by Gastaldi (Gazzetta, 51,233, (1921)) by decarboxylation of the acid obtained from the hydrolysis of 3:6-dicyano-2:5-diphenylpyrazine.

Found: C, 77.2; H, 5.1; N, 11.1%.

$C_{16}H_{12}ON_2$ requires: C, 77.4; H, 4.8; N, 11.3%.

Phenylbromoacetyl bromide.

(Fourneau and Nicolitsch. Bull. Soc. chim., 43, 1239, (1928)).

Phenylacetyl chloride was obtained from phenylacetic acid and thionyl chloride in 83% yield as a light-yellow oil b.p. 112°/26mm.

A mixture of the acid chloride (100g.) and bromine (130g.) was heated on an oil-bath at 140-145° for 2 hours and the product distilled under reduced pressure to give phenylbromoacetyl bromide as a light-yellow oil, b.p. 151°/32mm. in 94% theoretical yield.

ω-(Phenylbromoacetamido) acetophenone.

Using the previous technique aminoacetophenone hydrochloride (10g.) was acylated with phenylbromoacetyl bromide (18g.) in the presence of N-methylmorpholine (13.5g.) to give ω-(phenylbromoacetamido) acetophenone 18g. (90% of theory.). The product was crystallised from light petroleum (b.p. 100-120°) as colourless needles, m.p. 119°.

Found: C, 57.8; H, 4.3; N, 4.4%.

$C_{16}H_{14}O_2NBr$ requires: C, 57.8; H, 4.2; N, 4.2%.

3-Phenylacetamido-2:5-diphenylpyrazine.

ω-(Phenylbromoacetamido) acetophenone (6g.) in the presence of ammonium iodide (1g.) was treated with ammonia (200c.c.) at 15° for 16 hours. Removal of the solvent left an oily brown residue which on extraction with boiling acetone yielded 3-phenylacetamido-2:5-diphenylpyrazine as long colourless needles, which after recrystallisation from the same solvent had m.p. 194°. Yield 25% of theory.

Found: C, 79.2; H, 5.2; N, 11.4%.

$C_{24}H_{18}ON_3$ requires: C, 79.8; H, 5.2; N, 11.5%.

Light absorption in ethanol: Maxima at 2760 Å (εmax. 13,000) and 3300 Å (εmax. 14,700).

3-Amino-2:5-diphenylpyrazine.

A suspension of 3-phenylacetamido-2:5-diphenylpyrazine in caustic soda (30c.c. of 0.1N.) was refluxed for 3 days, the mixture cooled and the yellow solid which had formed filtered, washed free of alkali with water and air dried. Recrystallisation from ethanol gave 3-amino-2:5-diphenylpyrazine as yellow plates, m.p. 186°, alone or when mixed with an authentic specimen. Yield quantitative. The alkaline filtrate from the reaction mixture was neutralised with decinormal hydrochloric acid, evaporated to dryness under reduced pressure and the solid residue extracted with ether (2 x 25c.c.). Evaporation of the dried (Na_2SO_4) extract gave phenylacetic acid (0.11g.) m.p. 74° alone or

when mixed with an authentic specimen. The acid was characterised by its conversion to its amide by successive treatment with thionyl chloride and aqueous (0.88s.g.) ammonia. Phenylacetamide was obtained as colourless plates from water m.p. 157° alone or admixed with an authentic specimen.

3-Phenylacetamido-2:5-diphenylpyrazine.

Treatment of 3-amino-2:5-diphenylpyrazine (0.2g.) with phenylacetyl chloride (0.15g.) by heating under refluxed for 3 hours, followed by pouring the product into water and crystallisation of the residue, from filtration, from acetone gave 3-phenylacetamido-2:5-diphenylpyrazine m.p. 194° alone or when mixed with the specimen obtained by the action of ammonia on ω-(phenylbromoacetamido) acetophenone.

Phenylbromoacetamidoacetone.

Aminoacetone hydrochloride was acylated with phenylbromoacetamidoacetone in the presence of N-methylmorpholine to give a light-brown solid, crystallisation of which from light petroleum (b.p. 100-120°) gave phenylbromoacetamidoacetone as colourless plates, m.p. 108°. Yield 85% of theory.

Found: C, 49.0; H, 4.3; N, 5.3%.

$C_{11}H_{12}O_2NBr$ requires: C, 48.9; H, 4.4; N, 5.2%.

3-Phenylacetamido-2:5-dimethyldihydropyrazine.

Phenylbromoacetamidoacetone (6g.) and ammonium iodide (1g.)

were dissolved in liquid ammonia (100c.c.) and sealed for 16 hours at 15° in a glass-lined autoclave. Removal of the ammonia left an oily crystalline residue which was extracted with boiling benzene (5 x 25c.c.) Evaporation of the extract gave a crystalline residue (1.5g.) recrystallisation of which from benzene gave 3-phenylacetamido-2:5-dimethyldihydropyrazine as colourless plates, m.p. 154°. Yield 60% of theory. For analysis it was crystallised from light petroleum (b.p. 100-120°).

Found: C, 69.9; H, 7.3; N, 17.1%.

$C_{14}H_{17}ON_3$ requires: C, 69.1; H, 7.0; N, 17.3%.

The dihydropyrazine was unstable in air; the melting point gradually falling. After 3 weeks the melting point was less than 130° and after 6 months it was 116-124°. Examined by ultra-violet spectroscopy the above compound showed no selective absorption, demonstrating the absence of a system of conjugated double bonds.

3-Phenylacetamido-2:5-dimethylpyrazine.

(a) A solution of 3-phenylacetamido-2:5-dimethyldihydropyrazine (0.14g.) in methanol (2c.c.) was shaken overnight at room temperature with a solution of hydrogen peroxide (1c.c.; 100 vol.). Evaporation of the solution under reduced pressure gave 3-phenylacetamido-2:5-dimethylpyrazine (0.12g.) which separated from light petroleum (b.p.100-120°) as colourless plates m.p. 130°.

Found: C, 69.7; H, 6.2; N, 17.3%.

$C_{14}H_{15}ON_3$ requires: C, 69.7; H, 6.2; N, 17.4%.

A mixed melting point with the dihydropyrazine melted at 135-140° showed no depression.

(b) When phenylbromoacetamidoacetone was treated with ammonia in an iron autoclave without the glass-liner, the product was 3-phenylacetamido-2:5-dimethylpyrazine, m.p. 130°. (Yield 60% of theory.) Admixture with a specimen prepared according to (a) showed no depression.

3-Amino-2:5-dimethylpyrazine.

3-Phenylacetamido-2:5-dimethylpyrazine (0.5g.) in aqueous sodium hydroxide (30c.c.; 0.1N.) was refluxed for 13 hours, the solution cooled and extracted with ether (3 x 25c.c.). After drying (Na_2SO_4) the ether was removed yielding 3-amino-2:5-dimethylpyrazine (0.25g.). A specimen crystallised from benzene- light petroleum (b.p. 40-60°) as needles m.p. 112°, undepressed when mixed with an authentic specimen. The aqueous alkaline phase from the extraction was acidified with dilute hydrochloric acid to pH 3.0, evaporated to dryness under reduced pressure and the residue extracted with ether (4 x 10c.c.) evaporation of which gave phenylacetic acid (0.2g.), m.p. 69°. It was characterised by its amide which separated from water as plates, m.p. 157° alone and when mixed with an authentic specimen.

3-Phenylacetamido-2:5-dimethylpyrazine.

A solution of 3-amino-2:5-dimethylpyrazine (0.05g.) in dry benzene (5c.c.) was refluxed for 3 hours with phenylacetic acid (0.2c.c.). The solid which separated on cooling was collected, suspended in caustic soda (10c.c.; 3N.) and the mixture extracted with ether (100c.c.). Removal of the ether after drying over sodium sulphate gave 3-phenylacetamido-2:5-dimethylpyrazine which had m.p. 130° alone and when mixed with the specimen previously described.

Propionamidoacetone.

Aminoacetone hydrochloride (3g.) in dry chloroform (25c.c.) was condensed with propionyl chloride (3g.) in dry chloroform (25c.c.) in the presence of N-methylmorpholine (5.5g.). Without washing the reaction mixture, the chloroform was removed under reduced pressure leaving a colourless solid residue which was extracted (Soxhlet) with dry benzene. The extract was filtered through a column of alumina (6 x ½in.), eluted with benzene (250c.c.) and the combined filtrates evaporated leaving a light-yellow liquid. On distillation, propionamidoacetone (4.2g.) was obtained as a colourless liquid, b.p. 112°/3mm., which solidified on cooling. A specimen crystallised from light petroleum (b.p. 40-60°) as colourless hygroscopic plates, m.p. 38-40°. The product was very soluble in water and most organic solvents and the former property precluded aqueous washing as in previous acylations.

Action of Ammonia on Propionamidoacetone.

A solution of propionamidoacetone (2g.) and ammonium iodide (0.5g.) in liquid ammonia (50c.c.) was sealed in a glass-lined autoclave at 15° for 16 hours. Removal of the ammonia from the colourless solution left a residue which was extracted with boiling benzene (4 x 25c.c.). After drying (Na_2SO_4) the benzene was evaporated under reduced pressure giving a colourless oil (1.7g.) which solidified on cooling. A sample crystallised from light petroleum, (b.p. 40-60°) melted at 40°, undepressed on admixture with starting material.

Lactamidoacetone.

A solution of N-methylmorpholine (8.8g.) in dry chloroform (40c.c.) was added dropwise over 15 minutes, with stirring and cooling at 0°, to a suspension of aminoacetone hydrochloride (4.7g.) and acetyllactyl chloride (6.5g.) (Anschutz and Bertram. Ber., 36, 467, (1903)) in dry chloroform (60c.c.). the solution was stirred for a further 45 minutes at 0°, the suspended solid filtered, washed with a little chloroform, and the combined filtrates evaporated to dryness under reduced pressure. The oily residue which remained was extracted with boiling benzene (2 x 25c.c.). After concentrating the extract, light petroleum, (b.p. 40-60°) was added and by scratching the sides of the containing vessel the solution yielded minute needles, recrystallisation of which from benzene gave

acetyllactamidoacetone (3.12g.) as colourless needles, m.p. 70°.

Found: C, 51.3; H, 6.9; N, 7.4%.

$C_8H_{13}O_4N$ requires: C, 51.3; H, 6.9; N, 7.5%.

Action of Ammonia on Acetyllactamidoacetone.

Acetyllactamidoacetone (3.0g.) and ammonium iodide (0.5g.) were dissolved in liquid ammonia (150c.c.), the solution sealed in a glass-lined autoclave and left at 15° for 16 hours. Removal of the ammonia left a brownish oil (2.3g.) which was extracted with (a) boiling benzene (4 x 10c.c.) and (b) boiling chloroform (2 x 10c.c.). Most of the oil remained and was dissolved in ethanol (50c.c.) treated with charcoal and the ethanol removed. The brown gum which remained could not be characterised and did not give a picrate, methiodide or 2:4-dinitrophenylhydrazone. A red colour was obtained with ferric chloride solution; probably being due to the presence of ammonium acetate in the gum. An attempt to acylate the gum with acetyl chloride in pyridine was unsuccessful. The benzene extract (a) gave a yellow gum which on sublimation at 70°/10^{-3} mm. yielded acetamide m.p. 80°. Extract (b) gave a negligible amount of a brown gum which could not be characterised.

Action of Ammonia on α-Bromopropionamidoacetaldehyde Diethylmercaptal.

Aminoacetaldehyde diethylacetal.

(Buck and Wrenn. J.Amer.Chem.Soc., 51, 3612, (1929)).

A solution of chloroacetaldehyde diethylacetal (110g.) and liquid ammonia (250c.c.) in absolute ethanol (100c.c.) was heated in an autoclave at 120° for 16 hours. On cooling, the solution was filtered free of ammonium chloride and the ethanol removed by heating to 110°, leaving a brown oil. Water (250c.c.) was added, the mixture vigorously shaken and the aqueous layer separated. Potassium carbonate was added till the aqueous phase was saturated and the solution extracted with ether (6 x 50c.c.) Removal of the ether from the dried (Na_2SO_4) extract left a brown oil which distilled giving two fractions; aminoacetaldehyde diethylacetal as a colourless oil, b.p. 163-165°/760mm. 28g., (28% of theory); and diacetalylamine (20g.) as a colourless fluorescent oil b.p. 140°/25mm.

Ethylthiol. (Ethyl mercaptan).

(cf. Arndt, Ber., 54, 2236, (1921)).

A mixture of thiourea (76g.), water (50c.c.) and ethyl bromide (105g.) was refluxed for 8 hours at 100-120°. On cooling the mixture separated into two layers, the upper of which was removed and boiled under reflux with aqueous caustic soda (100c.c.; 5N.). From a lead at the top of the condenser ethylthiol was continuously collected into a vessel cooled in an acetone-solid carbon dioxide bath. The distillate was redistilled through a 7in. Fenske column giving ethylthiol as a colourless liquid, b.p. 37°, with a characteristic garlic-like odour. Yield 40g.; 64.5% of theory.

Aminoacetaldehyde diethylmercaptal.

To a solution of aminoacetaldehyde diethylacetal (12g.) in water (10c.c.) at 0°, with vigorous stirring, was added concentrated hydrochloric acid (50c.c.) over 15 minutes. Ethylthiol was then added dropwise over a further 15 minutes at 0° and the mixture stirred for 20 hours at 15° to give a colourless solution which was poured into aqueous caustic soda (125c.c. of 40%) and ice (250g.). A colourless oil at once separated and the mixture was extracted with chloroform (4 x 50c.c.). Removal of the solvent from the dried extract (Na_2SO_4) gave amino-acetaldehyde diethylmercaptal, b.p. 94-95°/3mm. as a colourless, practically odourless, liquid. Yield 10.15g.; 70% of theory.

Found: C, 44.1; H, 9.1%.

$C_6H_{15}NS_2$ requires: C, 43.6; H, 9.1%.

On standing in air the amine formed a solid carbonate. No picrate could be obtained using ethanolic picric acid but a picrate was obtained using picric acid in benzene. Recrystallisation from benzene gave the picrate as yellow needles m.p. 128°.

Found: C, 37.2; H, 4.8; N, 14.0%.

$C_{12}H_{18}O_7N_4S$ requires: C, 36.6; H, 4.6; N, 14.2%.

α-Bromopropionamidoacetaldehyde diethylmercaptal.

To a solution of aminoacetaldehyde diethylmercaptal (8.2g.) and N-methylmorpholine (5.7g.) in dry chloroform (50c.c.) at 0° was added α-bromopropionyl chloride (7.3g.) in dry chloroform (25c.c.) dropwise, with stirring, over 15 minutes. After stirring for a further hour at 0° the solution was washed successively with water, dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate, water, and the solution dried over sodium sulphate. Removal of the solvent under reduced pressure left a colourless, odourless, oil which solidified on cooling. Yield 14.2g.; 95% of theory. The solid was crystallised from light petroleum (b.p. 40-60°) from which α-bromopropionamidoacetaldehyde diethylmercaptal separated as prisms, m.p. 47°. The product kept well at 0°, but at room temperature it decomposed on prolonged standing liberating a mercaptan-like odour.

Found: C,36.4; 36.2; H,6.4; 6.8; N,4.67;S,21.3%.

$C_9H_{18}ONS_2Br$ requires:C,36.0 ; H,6.0 ; N,4.51;S,21.3%.

Decomposition of the Mercaptal and Treatment of the Product with Ammonia.

(a) Cadmium carbonate (42g.) was suspended in a solution of α-bromopropionamidoacetaldehyde diethylmercaptal (12.6g.) in ethanol (750c.c.) and water (40c.c.) and with stirring, treated with a solution of mercuric chloride (24g.) in ethanol (200c.c.).

The mixture was vigorously stirred at 15° for a further 24 hours, the solution filtered, liquid ammonia (200c.c.) added and the solution left at 0° for 48 hours. After filtering off the inorganic material which had separated, the filtrate was evaporated to dryness under reduced pressure leaving a brown gum interdispersed with inorganic material and smelling strongly of mercaptan. The gum was extracted (a) with benzene (4 x 25c.c.) and (b) chloroform (4 x 25c.c.), the extracts dried over sodium sulphate, and on removal of the solvents each extract yielded a gum, neither of which would distil under reduced pressure. Both residues were chromatographed after dissolving in benzene, and also treated with charcoal but the residues on removal of the solvents remained in their original gummy state. Extraction with various solvents failed to produce crystalline or identifiable material. The gum obtained from the benzene extract (a) when subjected to sublimation at 10^{-2} mm. gave propionamide (0.1g.), m.p. 73-74° undepressed on admixture with an authentic specimen. Yield of gum from (a) and (b) was 2.2g.

The gum from the chloroform extract (b) was refluxed with aqueous caustic soda (25c.c.; N.) for 6 hours. The odour of mercaptan was evident but the major portion of the gum did not dissolve. On decantation, the aqueous phase was extracted with (c) ether (4 x 20c.c.) and (d) chloroform (2 x 20c.c.) and the residue (e) dissolved in chloroform (50c.c.). Removal of the solvents, after drying (Na_2SO_4),

from c, d, and e, gave in each case a gum, extraction of which with light petroleum (b.p. 60-80°) gave light-yellow oils, none of which would distil under reduced pressure and which did not solidify even on prolonged standing at 0°. No functional groups could be identified.

(b) α-Bromopropionamidoacetaldehyde.

A solution of α-bromopropionamidoacetaldehyde diethylmercaptal (7.0g.) in ethanol (100c.c.) and water (20c.c.) was treated at 60°, with stirring, with a solution of mercuric chloride (12.7g.) in ethanol (75c.c.) added over 5 minutes. Stirring was continued for a further 20 hours at 20°, the solution warmed at 60° for 30 minutes in an atmosphere of nitrogen and then saturated with hydrogen sulphide. The mercury sulphide was removed by filtration and the filtrate freed from excess hydrogen sulphide by passing nitrogen through the solution for 2 hours. Cadmium carbonate (12g.) was added, the mixture left for 16 hours in nitrogen and the filtrate evaporated to dryness under reduced pressure. The residue was extracted with chloroform (3 x 50c.c.) removal of which gave α-bromopropionamidoacetaldehyde (4.5g.) as a yellow gum. With Brady's reagent the 2:4-dinitrophenylhydrazone was obtained, crystallising from ethanol as golden yellow needles m.p. 200°

Found: C, 35.6; H, 3.3; N, 18.5%.

$C_{11}H_{12}O_5N_3Br$ requires: C, 35.30; H, 3.2; N, 18.7%.

The aldehyde (4.5g.) and ammonium iodide (0.5g.) were

dissolved in liquid ammonia (100c.c.) and sealed in an autoclave for 16 hours at 15°. Removal of the ammonia left a brown gum which was extracted with boiling benzene (4 x 25c.c.) and boiling chloroform (4 x 25c.c.). On evaporation of the solvents a brown gum was obtained in both cases (total yield 1.3g.) from which no crystalline or identifiable material could be obtained, even after chromatography.

Attempt to Prepare β-(α'-Bromopropionamido) propan-α:β-diol.

Glycerol-α-monochlorohydrin.

(Conant and Quayle. Org.Syn., Coll.Vol.I, 244).

Hydrogen chloride was passed into a solution of glycerol (500g. of 90%) and glacial acetic acid (10g.) at 105-110° until 190g. of the halogen acid had been absorbed. The product was fractionally distilled giving glycerol-α-monochlorohydrin (350g.) as a colourless oil b.p. 114-120°/14mm. Yield 64% of theory.

Glycidol.

(Rider and Hill. J.Amer.Chem.Soc., 52, 1526, (1930)).

To a well stirred solution of glycerol-α-monochlorohydrin (110.5g.) in dry ether (1000c.c.), maintained throughout the reaction at 14-15°, was added sodium wire (17.5g.) in such a way that the wire wrapped round the stirrer and was swept through the solution thus keeping a clean surface. After stirring for 16 hours the sodium chloride

formed in the reaction was filtered off and the ether removed leaving a colourless oil, distillation of which gave glycidol b.p. 58°/9mm. in almost theoretical yield. 22g. of chlorohydrin was recovered unchanged from the reaction mixture.

γ-Aminopropan-α:β-diol.

(Knorr and Knorr, Ber., 32, 752, (1899)).

Glycidol (10g.) was added with good shaking to a solution of ammonia (500c.c. of s.g. 0.88) in water (1500c.c.) and left for 2 days at room temperature. Removal of the solvent under reduced pressure and distillation of the residue gave γ-aminopropan-α:β-diol as a thick colourless oil b.p. 128°/1.5mm. Yield 9.6g. (80% of theory.) On standing the oil solidified as colourless needles, soluble only in water and the common alcohols. The product was very hygroscopic.

Attempt to Acylate the γ-Aminopropan-α:β-diol using a Modified Schotten Baumann Procedure.

Calcium carbonate (7g.) was suspended in a solution of γ-aminopropan-α:β-diol (8.6g.) in water (25c.c.) and α-bromopropionyl chloride added dropwise at 0°, with vigorous stirring, over 20 minutes. The solution was left at 0° for 16 hours, filtered, and the solvent removed under reduced pressure leaving a white gum interdispersed with solid inorganic material ($CaCl_2$). The residue was extracted with dry ethanol (4 x 25c.c.) which left a

white hygroscopic gum on removal of the solvent. The product could not be crystallised, even on prolonged standing at 0° and attempts at distillation by heating up to 300° at 10^{-2} mm. were unsuccessful.

An isopropylidene derivative of γ-aminopropan-α:β-diol could not be prepared due to the insolubility of the amine in acetone even on addition of 20% ethanol and attempts at anhydrous acylation were abandoned.

In a model condensation to give γ-acetamidopropan-α:β-diol, glycidol would not condense with acetamide by heating in benzene at 100° for 2 days; the acetamide being recovered unchanged and the glycidol converted to a polymer.

Oxazines.

Substituted Oxazines.

Ethyl oximinoacetate.

(Adkins and Reeve. J.Amer.Chem.Soc., 60, 1328, (1938)).

Ethyl acetoacetate (750g.) was dissolved in glacial acetic acid (840c.c.) and a solution of sodium nitrite (450g.) in water (1000c.c.) added dropwise with stirring over 1 hour at 0°. Stirring was continued for a further 30 minutes, the solution diluted with water (3,000c.c.) and stirred for 2 hours at 25-35°. The solution was extracted with ether (3 x 350c.c.), the extract washed successively with saturated aqueous sodium hydrogen carbonate and dried over sodium sulphate. The ether was removed and the residual oil crystallised by dissolving in half its volume of toluene and cooling to -35° when ethyl oximinoacetate separated as colourless prisms, m.p. 58°. Yield 683g.

Ethyl α-amino-β- ketobutyrate hydrochloride.

(cf. Gabriel and Posner. Ber., 27, 1141, (1894)).

Ethyl oximinoacetate (9g.) was added in small portions over 15 minutes to a solution of stannous chloride (27g.) in concentrated hydrochloric acid (45c.c.) at 0°. Tin (9g.) was then added, the mixture heated to 90° for 10 minutes, diluted to 1000c.c. with water and saturated with hydrogen sulphide till the solution was free of tin salts. After filtering, the solution was evaporated to dryness under reduced pressure ($\lesssim$ 50°), the residue extracted with

dry ethanol (50c.c.) and filtered. On removing the solvent from the filtrate the residue was crystallised from dry ethanol giving ethyl α-amino-β-ketobutyrate as practically colourless prisms m.p. 95°. Yield 7g.; 68% of theory. The product was hygroscopic and was stored over phosphorus pentoxide.

Ethyl α-(α'-bromopropionamido) β-ketobutyrate.

A solution of α-bromopropionyl chloride (11g.) in dry chloroform (50c.c.) was added to a suspension of ethyl α-amino-β-ketobutyrate (10g.) in dry chloroform (150c.c.), the mixture cooled to 0° with stirring and treated with a solution of N-methylmorpholine (13g.) in dry chloroform (25c.c.) added dropwise over 30 minutes. The mixture was stirred for a further hour at 0°, washed successively with water, dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate, water and dried over sodium sulphate. Removal of the solvent under reduced pressure left a colourless oil which solidified on cooling. Recrystallisation from light petroleum (b.p. 40-60°) gave ethyl α-(α'-bromopropionamido) β-ketobutyrate m.p. 70°. Yield 13g.; 84% of theory.

Found: C, 38.5; H, 5.0; N, 5.0%.

$C_9H_{14}O_4NBr$ requires: C, 38.5; H, 5.0; N, 5.0%.

Ethyl 3-hydroxy-2:6-dimethyloxazine-5-carboxylate.

(a) Ethyl α-(α'-Bromoapropionamido) β-ketobutyrate (10g)

was dissolved in liquid ammonia (100c.c.) containing ammonium iodide (0.5g.) and the solution sealed in an autoclave at 15° for 16 hours. After removal of the ammonia the residue was extracted with light petroleum (b.p. 60-80°) in a Soxhlet apparatus. Concentration of the extract gave ethyl 3-hydroxy-2:6-dimethyloxazine-5-carboxylate as colourless needles m.p. 96°. Yield 4.3g.; 61% of theory.

Found: C, 54.1,54.3; H, 6.5,6.8; N, 7.3,6.8%.
$C_9H_{13}O_4N$ requires: C, 54.2 ; H, 6.5 ; N, 7.0 %.
Light absorption in ethanol: Maxima at 2300 Å (εmax. 6,300) and 2810 Å (εmax. 5,100).

(b) Ethyl α-(α-bromopropionamido)β-ketobutyrate (0.8g.) was dissolved in dry ethanol and added to a solution of sodium ethoxide from sodium (0.07g.) and ethanol (2c.c.). There was an almost immediate separation of sodium bromide, the solution became orange coloured and after standing overnight at 15° the solvent was removed under reduced pressure. The residue was extracted with boiling light petroleum (b.p. 60-80°; 3 x 10c.c.). On cooling ethyl 3-hydroxy-2:6-dimethyl-oxazine-5-carboxylate separated as needles m.p. 96° alone and when mixed with the specimen described as in (a). Yield 0.40g.

3-Hydroxy-2:6-dimethyloxazine-5-carboxylic acid.

Ethyl 3-hydroxy-2:6-dimethyloxazine-5-carboxylate (3.0g.) was suspended in aqueous sodium hydroxide (150c.c.; 0.1N.)

and shaken for 16 hours at 15°. Most of the ester had dissolved and the filtered solution acidified to pH 4.0 with dilute hydrochloric acid when a crystalline solid separated. The mixture was evaporated to half bulk under reduced pressure and after cooling to about 5° the crystalline solid was filtered off, washed with ethanol and air dried. Yield 2.15g.; 83% of theory. 3-Hydroxy-2:6-dimethyloxazine-5-carboxylic acid separated from methanol as colourless prisms m.p. 214° (decomp.)

Found: C, 49.6; H, 5.6; N, 8.5%. Equivalent 172. $C_7H_9O_4N$ requires: C, 49.2; H, 5.3; N, 8.2%. Equivalent 171. Light absorption in water: Maxima 2240 Å (εmax. 7,300) and 2780 Å (εmax. 5,000).

The compound gave no colouration with ferric chloride.

On leaving the mother liquors from the above acid at 0° overnight (0.2g.) of a compound m.p. 328° (decomp.) separated. The same compound could be obtained directly by hydrolysis of the ester with 3N. alkali when ammonia was liberated and on acidification to pH3·0the compound m.p. 328° separated. The product did not effervesce with sodium hydrogen carbonate and could not be titrated with baryta. Analyses were complicated due to adsorbed sodium chloride from which the compound, which was soluble only in water, could not be separated. The compound contained nitrogen and seemed like some type of amino-acid.

Found: C, 45.8; H, 4.9; N, 7.9%. + residue.

after correcting for the residue present, assuming it to be sodium chloride, analysis was C,52.3; H, 5.6; N, 9.0%. which corresponds to no suitable empirical formula.

3-Hydroxy-2:6-dimethyloxazine.

3-Hydroxy-2:6-dimethyloxazine-5-carboxylic acid (0.2g.) was heated to 235° at atmospheric pressure in a sublimation apparatus till effervescence ceased, about 15 minutes. A large amount of charring took place and a colourless oil separated. Sublimation of the oil and residue at 120°/1mm. gave 3-hydroxy-2:6-dimethyloxazine as plates m.p. 73°. Yield 40mg. The product was very hygroscopic and was kept over calcium chloride.

Found: C, 55.1; H, 6.9; N, 10.9%.

$C_6H_9O_2N$ requires: C, 55.6; H, 7.1; N, 11.0%.

Light absorption in ethanol: Maximum at 2680 Å (εmax. 3,300).

The compound was very soluble in all cold common organic solvents save light petroleum and gave no colouration with ferric ions and no picrate.

The above oxazine acid did not decarboxylate in boiling nitrobenzene, even in the presence of copper powder.

Ethyl α-bromoacetamido-β-ketobutyrate.

Using the previously described method of acylation ethyl α-amino-β-ketobutyrate hydrochloride (13.5g.) was acylated with bromoacetyl chloride (15.0g.) in the presence of N-methylmorpholine (20.0g.) to gave ethyl α-bromoacetamido-β-ketobutyrate (16.5g.; 84% of theory.) as colourless needles

m.p. 99° from light petroleum (b.p. 80-100°).

Found: C, 36.2; H, 4.5; N, 5.1%.

$C_8H_{12}O_4NBr$ requires: C, 36.1; H, 4.5; N, 5.3%.

Ethyl 3-hydroxy-6-methyloxazine-5-carboxylate.

(a) Ethyl α-bromoacetamido-β-ketobutyrate (5.1g.) was dissolved in liquid ammonia (50c.c.), ammonium iodide added (0.3g.) and the solution kept of 15° for 16 hours in an autoclave. Removal of the ammonia gave a gummy residue which was extracted with light petroleum (b.p. 80-100°; 6 x 25c.c.). Concentration of the extract under reduced pressure gave ethyl 3-hydroxy-6-methyl-oxazine-5-carboxylate as colourless needles m.p. 112°. Yield 0.5g.; 14% of theory.

Found: C, 51.6; H, 5.9; N, 7.85%.

$C_8H_{10}O_4N$ requires: C, 51.8; H, 5.9; N, 7.6 %.

(b) Ethyl α-bromoacetamido-β-ketobutyrate (4.1g.) in dry ethanol (25c.c.) was treated at 15° with a solution of sodium ethoxide, from sodium (0.4g.) and ethanol (5c.c.), and the solution left for 16 hours. Evaporation of the solvent under reduced pressure and extraction of the residue (Soxhlet) with light petroleum (b.p. 60-80°) gave on concentration of the extract, ethyl 3-hydroxy-6-methyloxazine-5-carboxylate (1.55g.; 52.5% of theory.) as colourless needles m.p. 112° alone or admixed with the specimen prepared by (a).

Light absorption in ethanol: Maxima at 2260 Å (εmax.5,210) and 2800 Å (εmax. 5,210).

3-Hydroxy-6-methyloxazine-5-carboxylic acid.

Ethyl 3-hydroxy-6-methyloxazine-5-carboxylate (1.0g.) was suspended in aqueous caustic soda (60c.c.; 0.1N.) and the mixture left for 24 hours at room temperature. Complete solution had almost taken place and the filtered solution was made acid to pH 4.0 and evaporated to half bulk under reduced pressure. After cooling to 0° the product (0.55g.) was filtered off, washed with a little water and ethanol and air dried. Yield 65% of theory. 3-Hydroxy-6-methyloxazine-5-carboxylic acid separated from methanol as colourless prisms m.p. 226° (decomp.)

Found: C, 46.1; H, 4.3; N, 9.4%. Equivalent 161.
$C_6H_7O_4N$ requires: C, 45.8; H, 4.5; N, 8.9%. Equivalent 157.
Light absorption in water. Maxima at 2270 Å (εmax.4,900) and 2810 Å (εmax.6,000).

3-Hydroxy-6-methyloxazine.

3-Hydroxy-6-methyloxazine-5-carboxylic acid (100mg.) was decarboxylated by heating at ordinary pressure to 250° for 15 minutes followed by sublimation of the resultant oil and residue at 120°/3mm. 3-Hydroxy-6-methyloxazine was so obtained as a colourless oil, resublimation of which at 80°/0.5mm. gave colourless hygroscopic prisms (20mg.) m.p. 54-55°.

Found: C, 52.95; H, 6.4; N, 12.3%.

$C_5H_7O_2N$ requires: C, 53.0 ; H, 6.2; N, 12.4%.

Light absorption in ethanol: Maximum at 2680 Å (εmax. 4,300).

α-Ethoxypropionamidoacetone.

α-Bromopropionamidoacetone (0.8g.) in dry ethanol (10c.c.) was added to a solution of sodium ethoxide from sodium (0.11g.) and ethanol (5c.c.) and the solution left overnight at 15°. The orange reaction mixture, filtered from sodium bromide, was evaporated under reduced pressure to give a gum from which α-ethoxypropionamidoacetone sublimed at 60°/0.5mm. as colourless hygroscopic needles m.p. 65°. Yield 0.2g.

Found: C,55.4; H, 8.7; N, 8.3%.

$C_8H_{15}O_3N$ requires: C,55.5; H, 8.7; N, 8.1%.

α-(α'-Ethoxypropionamido) ethylmethyl ketone.

α-(α'-Bromopropionamido) ethylmethyl ketone (1.5g.) was dissolved in dry ethanol (15c.c.) and added to a cold solution of sodium ethoxide, from sodium (0.2g.) and ethanol (5c.c.), and left for 36 hours at 15°. The solution immediately turned orange-red and sodium bromide separated. The resulting solution was evaporated to dryness under reduced pressure and the residue extracted with boiling light petroleum (b.p. 80-100°; 3 x 5c.c.). Removal of the solvent under reduced pressure gave an oil which solidified on cooling. Sublimation at 70°/0.1mm. followed by crystallisation of the sublimate from light

petroleum (b.p. 60-80°) gave α-(α'-ethoxypropionamido) ethylmethyl ketone as colourless prisms m.p. 45°. Yield 0.66g.

Found: C, 57.3; H, 9.0; N, 7.4%.

$C_9H_{17}O_3N$ requires: C, 57.6; H, 9.1; N, 7.5%.

ω-(α'-Ethoxypropionamido) acetophenone.

ω-(α'-Bromopropionamido) acetophenone (2.5g.) on treatment with sodium ethoxide at 15° for 16 hours gave ω-(α'-ethoxypropionamido) acetophenone as colourless needles m.p. 89° from light petroleum (b.p. 100-120°). Yield 0.27g.

Found: C, 66.5; H, 7.4; N, 6.3%.

$C_{13}H_{17}O_3N$ requires: C, 66.4; H, 7.2; N, 6.0%.

Ethyl α-(phenylbromoacetamido)β-ketobutyrate.

Using the general method previously described ethyl α-amino-β-ketobutyrate hydrochloride (7.0g.) was acylated with phenylbromoacetyl bromide (10.6g) in the presence of N-methylmorpholine (7.7g.) to give ethyl α-(phenylbromoacetamido)β-ketobutyrate (12.0g.; 92% of theory) as colourless prisms m.p. 68-70° from light petroleum (b.p. 100-120°).

Found: C, 49.2; H, 4.7; N, 4.1%.

$C_{14}H_{16}O_4NBr$ requires: C, 49.1; H, 4.7; N, 4.1%.

Action of Ammonia on Ethyl α-(Phenylbromoacetamido) β-ketobutyrate.

Ethyl α-(phenylbromoacetamido)β-ketobutyrate (8.0g.) was

dissolved in liquid ammonia (150c.c.) and left in an autoclave at 15° for 16 hours. The ammonia was removed leaving a reddish-green gum which was extracted successively with hot benzene (4 x 15c.c.; extract A) and hot methanol (100c.c.; extract B). Removal of the benzene from extract A gave phenylacetamide (1.1g.) m.p. 154° alone on admixed with authentic specimen. Extract B was boiled with charcoal, filtered and evaporated to give a gum containing solid. The latter was filtered with aid of methanol and proved to be ammonium bromide. The gum obtained by evaporation of the methanol filtrate was extracted with hot water (4 x 25c.c.) to remove any remaining ammonium bromide, the residue dissolved in ethanol and again treated with charcoal. Removal of the solvent, from filtration of the charcoal, left a red-brown gum (2.0g.). Attempts to crystallise this from ethanol, acetone, chloroform and dioxane were unsuccessful. The gum was insoluble in benzene and water but soluble in both acid and alkali. On boiling with alkali ammonia was liberated but no solid separated on acidification of the cooled solution.

Action of Sodium Ethoxide on Ethyl α-(phenylbromoacetamido) β-ketobutyrate.

Ethyl α-(phenylbromoacetamido) β-ketobutyrate (5g.) in dry ethanol (10c.c.) was added to a solution of sodium ethoxide from sodium (0.4g.) and ethanol (50c.c.) and left for 24 hours at 15°. The ethanol was removed under reduced pressure

and the residue extracted with boiling benzene (10 x 10c.c.) Removal of the benzene left a yellow gum (2.3g.) which did not solidify on keeping at 0° for 2 days; attempts to crystallise the gum from the usual solvents were unsuccessful. The gum was dissolved in ethanol (15c.c.), treated in the cold with sodium hydroxide solution (25c.c.; N.) and left at room temperature for 5 days. The alkaline solution was extracted with chloroform (2 x 10c.c.), made acid to pH 2.0-3.0 and again extracted with chloroform (2 x 10c.c.) Both extracts were washed with water, dried over sodium sulphate. Removal of the chloroform from the acid extract gave a red-brown resin (1.3g.) which could not be characterised. The alkaline solution extract gave a yellow gum (0.4g.) which again could not be characterised.

Amination of 3:5-Dimethylpyrazine.

Amination of 3:5-Dimethylpyrazine.

α-Bromopropionaldehyde diethylacetal.

(Baxter, Newbold and Spring. J., 371, (1947); Kuhn and Grundmann. Ber., 70, 1894, (1937)).

To a solution of propaldehyde (58g.) in dry chloroform (65g.) with rapid stirring at -20° was added bromine (47c.c.), dropwise over 4 hours. The solution was irradiated throughout with ultra-violet light. After stirring for a further 3 hours the solution was added to precooled (-10°) dry ethanol (1,200c.c.) and left at 20° for 38 hours. The solution was then poured, with hand stirring, into a mixture of caustic soda (670g. ; 3N.) and ice (400g.) and the chloroform layer separated. The aqueous phase was extracted with chloroform (2 x 100c.c.), the combined extracts dried (Na_2SO_4) and the chloroform removed. Distillation of the residual oil gave α-bromopropionacetal as a slightly pink liquid b.p. 63-64°/14mm. Yield 60% of theory.

Dipropionacetalylamine.

(cf. Wolff and Marburg. Annalen, 363, 169, (1908)).

α-Bromopropionacetal (200g.) was heated in an autoclave at 115-120° for 20 hours with a solution of ethanolic ammonia (200g.) saturated at 0°. After heating for a further 20 hours at 125-130° the solution was cooled, filtered free of ammonium bromide and the ethanol removed. The residual oil was diluted with twice its volume of water, the solution saturated with potassium carbonate and extracted with ether

(6 x 100c.c.). Removal of the ether from the dried (Na_2SO_4) extract and fractionation of the residual oil gave dipropionacetalylamine (19g.) b.p. 102°/1mm. as a slightly green oil.

3:5-Dimethylpyrazine.

(cf. Wolff and Marburg. loc. cit.).

Dipropropionacetalylamine (15g.) was treated at 0° with concentrated hydrochloric acid (45c.c.) over 2 hours, the resulting solution evaporated to half bulk under reduced pressure, hydroxylamine hydrochloride (4.2g.) in water (25c.c.) added and the solution left for 48 hours at 15°. After warming to 60-80° for 15 minutes the solution was cooled, made strongly alkaline with potassium hydroxide solution (10N.) and extracted with ether (3 x 10c.c.). Removal of the ether from the dried (Na_2SO_4) extract left a colourless oil, distillation of which gave 3:5-dimethylpyrazine b.p. 150°/760mm. Yield 4g.; 75% of theory.

Found: C, 65.6; H, 7.7%.

$C_6H_8N_2$ requires: C, 66.6; H, 7.4%.

On coolingthe base solidified as hexagonal plates m.p. 25°.

The picrate was obtained from ethanol as yellow needles m.p. 176°.

Found: C, 42.4;H,3.4; N, 20.9%.

$C_{12}H_{11}O_7N_5$ requires:C, 42.7; H,3.3; N, 20.8%.

Attempted Amination of 3:5-Dimethylpyrazine.

(cf. Joiner and Spoerri. J. Amer. Chem. Soc., 63, 1929,(1941)).
A solution of 3:5-dimethylpyrazine (3.0g.) in freshly distilled dimethylaniline (8c.c.) was heated to 165° with rapid stirring with freshly prepared sodamide (Org. Syn. 20, 86) for 2 hours. The thick dark oily liquid was poured onto ice (50g.), the mixture made alkaline with potassium carbonate and extracted with ether (6 x 10c.c.). After drying (Na_2SO_4) the ether was removed leaving a thick red oil which partially solidified on cooling. The crude oil was dissolved in dry benzene (50c.c.) and passed through a column of alumina (10 x ½ in.). After eluting with benzene (250c.c.) the combined filtrates were evaporated to give 20mg. of crude material which on sublimation at 70°/2 x 10^{-3} mm. gave practically colourless needles m.p. 90°. With ethanolic picric acid a greenish-yellow picrate m.p. 215-220° (decomp.) was obtained and crystallised as needles from the same solvent.

Found: N, 22.3%.

$C_{18}H_{17}O_7N_7$ requires: N, 22.1%.

P A R T II.

N-oxidation.

Diacetalylamine.

(Wolff and Marburg. Annalen, 363, 169, (1908)).
Chloroacetal (150g.) was heated in an autoclave with saturated ethanolic ammonia (200g.) for 20 hours at 115-120° and a further 20 hours at 125-130°. The ethanol was removed at 110°, the residual oil shaken with three times its volume of water and the aqueous phase extracted with ether (10 x 200c.c.). After drying (K_2CO_3), the ether was removed and the residue fractionally distilled giving diacetalylamine b.p. 125-128°/7.9mm. as a colourless oil possessing a violet fluorescence. Yield 39g.; 31.5% of theory.

Pyrazine.

(Wolff and Marburg. loc.cit.).
(a) Diacetalylamine (25g.) was added to concentrated hydrochloric acid (75c.c.) at 0°, dropwise over 2 hours. The solution was evaporated to 50c.c., hydroxylamine hydrochloride (7.2g.) in water (50c.c.) added and the brown solution left for 2 days at 15°. After warming to 60-80° for 15 minutes the cooled solution was made strongly alkaline with solid potassium hydroxide and the solution steam distilled till a drop of the distillate showed no cloudiness with mercuric chloride solution. Potassium hydroxide pellets were added till the distillate was strongly alkaline and the aqueous phase extracted with ether (5 x 25c.c.). The dried (KOH) extract on evaporation

gave pyrazine hydrate as colourless prisms, m.p. 54°. Yield 6g. (73% of theory).

Quinoxaline.

(Hinsberg. Ber., 17, 318, (1884); Annalen, 237, 334 (1887)). o-Phenylene diamine (12g.) was condensed with glyoxal bisulphite (38g.) giving quinoxaline b.p. 112°/25mm. Yield 14.3g.; 98% of theory.

Pyrazine-2:3-dicarboxylic acid.

(Gabriel and Sonn. Ber., 40, 4851, (1907)).
Oxidation of quinoxaline (14.2g.) with alkaline permanganate and working up by way of the barium salt (30g.; 90% of theory), decomposed by sulphuric acid, gave the dihydrate m.p. 182° (decomp.). Yield 14.2g. 68% of theory .

Pyrazine monocarboxylic acid.

(Hall and Spoerri. J.Amer.Chem.Soc., 62, 664, (1940)). Anhydrous pyrazine-2:3-dicarboxylic acid (11g.) (made by warming the dihydrate to 80°/0.1mm. in the presence of phosphorus pentoxide), was heated rapidly in 1g. portions to 210° in a sublimation apparatus at 5-10mm., when simultaneous decarboxylation and sublimation took place, giving pyrazine carboxylic acid m.p. 225° as colourless prisms. Yield 6.7g.; 82% of theory.

Pyrazine.

(Ramsay. C.A., 40, 5074).

(b) Pyrazine carboxylic acid was suspended in dibutylphthalate, the temperature raised to 190° for 1 hour, and the pyrazine distilled as a colourless oil b.p. 115° which solidified on cooling. Yield 42% of theory.

Pyrazine dioxide.

A solution of pyrazine dihydrate (4g.) in glacial acetic acid (16c.c.) and hydrogen peroxide (32c.c.; 100 vol.) was warmed at 56° for 16 hours. The solution was evaporated to small bulk under reduced pressure, the residue cooled in ice, made alkaline with 3N. caustic soda and extracted with chloroform (10 x 25c.c.). The dried extract (Na_2SO_4) was evaporated under reduced pressure to about 25c.c. when a white solid separated and was collected by filtration (a). Recrystallisation from water gave pyrazine dioxide as colourless needles which did not melt below 300°. Yield 0.3g.

Found: C, 43.0; H, 3.8%.

$C_4H_4O_2N_2$ requires: C, 43.0; H, 3.6%.

Pyrazine oxide.

The filtrate (a) was evaporated to dryness under reduced pressure leaving a colourless residue, recrystallisation of which from ethanol gave pyrazine oxide (2.8g.) as needles m.p. 117°. For analysis it was sublimed at 80°/5mm.

Found: C, 50.1; H, 4.2%.

$C_4H_4ON_2$ requires: C, 50.0; H, 4.4%.

Chloropyrazine.

Pyrazine monoxide (1.8g.) was added in small portions to phosphoryl chloride (15c.c.) at 0°. No reaction took place and the oxide did not go into solution. The mixture was refluxed for 30 minutes when considerable charring was evident and a little hydrogen chloride was evolved. Excess phosphoryl chloride was removed under reduced pressure, the residue triturated with ice (50g.) made alkaline with aqueous sodium hydrogen carbonate and extracted with ether (6 x 50c.c.). The dried (Na_2SO_4) extract was evaporated and the residual oil distilled giving chloropyrazine (cf. Erickson and Spoerri. J.Amer.Chem.Soc., 68, 400, (1946)), b.p. 154° as a colourless oil. Yield 0.3g.
No improvement of yield was obtained by allowing the reaction to take place at room temperature for 24 hours or by using phosphoryl chloride-phosphorus pentachloride chlorinating mixtures.

Glycine anhydride.

(Sannié. Bull.Soc.chim., 9, 487, (1942)).
Glycine anhydride was obtained in 50% yield by refluxing glycine in ethylene glycol for 1 hour. On cooling the anhydride separated as colourless prisms m.p. 310° (decomp.)

Action of Phosphoryl Chloride on Glycine Anhydride.

Glycine anhydride (5g.) was heated to 120° for 45 minutes with phosphoryl chloride, the excess chloride removed under reduced pressure and the residue poured onto ice (100g.).

The mixture was filtered and the solid air-dried. This proved to be carbon (2.2g.). The filtrate was made alkaline to pH 8.0 with caustic soda and finally sodium bicarbonate and the solution extracted with ether (6 x 30c.c.). On evaporation of the ether nothing remained.

Alanine anhydride.

(Sannie. loc.cit.).

Alanine was refluxed in ethylene glycol for 1 hour. On cooling, alanine anhydride was obtained as colourless prisms m.p. 271-273° in 80% yield.

2:5-Dichloro-3:6-dimethylpyrazine.

(Baxter and Spring. J., 1179, (1947)).

Alanine anhydride (32g.) was refluxed with phosphoryl chloride (300c.c.) for 1 hour, the excess chloride removed under reduced pressure and the residue triturated with ice-water (100g.). The solid residue was filtered, air dried and sublimed at 50°/0.1mm. to give 2:5-dichloro-3:6-dimethylpyrazine (2.4g.) as colourless prisms m.p. 70°.

3-Chloro-2:5-dimethylpyrazine.

(Baxter and Spring. loc.cit..).

The filtrate from above was exactly neutralised with 3N. caustic soda, extracted with ether (10 x 25c.c.) and the dried (Na_2SO_4) extract evaporated leaving a brownish oil. Distillation under reduced pressure gave 3-chloro-2:5-dimethylpyrazine (9.5g.) as a colourless oil b.p.

106°/25mm. The residue from the distillation of the chloropyrazine was sublimed at 120°/10^{-5} mm. to give 2-hydroxy-5-chloro-3:6-dimethylpyrazine as colourless prisms m.p. 224°. Yield 0.2g.

2:5-Diethoxy-3:6-dimethylpyrazine.

(Baxter and Spring. loc.cit.).

2:5-Dichloro-3:6-dimethylpyrazine (2.74g.)in ethanol (20c.c.) was heated with sodium ethoxide, from sodium (0.92g.) and ethanol (20c.c.), at 180° for 16 hours. After removal of the solvent under reduced pressure the residue was sublimed at 60°/0.1mm. to give 2:5-diethoxy-3:6-dimethylpyrazine (2.1g.) as colourless plates m.p. 80°.

2-Ethoxy-5-chloro-3:6-dimethylpyrazine.

(Baxter and Spring. loc.cit.).

2:5-Dichloro-s:6-dimethylpyrazine (1.7g.) in ethanol (40c.c.) was treated with sodium ethoxide from sodium (0.25g.) at 130° for 16 hours. Removal of the solvent and sublimation of the residue at 30°/0.1mm. gave 2-ethoxy-5-chloro-3:6-dimethylpyrazine (1.17g.) as colourless prisms m.p. 30°.

3-Ethoxy-2:5-dimethylpyrazine.

(Baxter and Spring. loc.cit.).

3-Ethoxy-2:5-dimethylpyrazine was obtained in 80% yield

from chloropyrazine and sodium ethoxide as a colourless oil b.p. 81°/15mm. by refluxing in ethanol for 4 hours.

3-Hydroxy-2:5-dimethylpyrazine.

(Baxter and Spring. loc.cit.).

3-Chloro-2:5-dimethylpyrazine (5g.) was refluxed for 16 hours with aqueous potassium hydroxide (50c.c.; 20%). After neutralisation and evaporation of the solution under reduced pressure the residue was extracted (Soxhlet) with benzene to give 3-hydroxy-2:5-dimethylpyrazine m.p. 211° as colourless needles. Yield 3.6g.

Hydrogen Peroxide Oxidations.

In acetic acid.

2:5-Diethoxy-3:6-dimethylpyrazine (2g.) was dissolved in glacial acetic acid (15c.c.), hydrogen peroxide (15c.c. of 30%) added and the solution warmed at 56° for 16 hours. The solvent was removed under reduced pressure, at as low a temperature as possible to prevent the sublimation of any product, the residue neutralised with aqueous sodium hydrogen carbonate and the solution extracted with ether (5 x 20c.c.). Removal of the ether gave a recovery (1.2g.) of starting material m.p. 80°. The low recovery of starting material was due to the material partially subliming on removal of the solvent.

2-Ethoxy-5-chloro-3:6-dimethylpyrazine and 2-amino-5-chloro-3:6-dimethylpyrazine treated similarly were recovered

unchanged.

Attempts to enforce oxidation by heating in a sealed tube led to rupture of the pyrazine ring giving in each case a small amount of material m.p. > 300° which could not be characterised.

With hydrochloric acid.

(a) 3-Chloro-2:5-dimethylpyrazine (0.5g.) was treated with hydrochloric acid (1c.c.; d, 1.19.), hydrogen peroxide (2c.c. of 30%) added and the solution warmed at 56° for 16 hours. Some chloropyrazine (0.3g.) had separated and the supernatant liquor was removed, neutralised with caustic soda and extracted with chloroform (4 x 5c.c.). Removal of the solvent from the dried ($NaSO_4$) extract gave 3-chloro-2:5-dimethyl-pyrazine-4-oxide (0.1g.) as needles from benzene-light petroleum (b.p. 40-60°) m.p. 112-114° alone or when mixed with an authentic specimen. (Baxter, Newbold and Spring. J., 1859, (1948)).

(b) Hydrochloric acid (1c.c.; d, 1.19) was added to 3-ethoxy-2:5-dimethylpyrazine (0.5g.) and the product treated with hydrogen peroxide (2c.c. of 30%) at 56° for 16 hours. The aqueous phase was separated from a little ethoxypyrazine, neutralised with 3N. caustic soda and extracted with chloroform. After drying (Na_2SO_4) the chloroform was removed leaving a colourless residue (0.2g.),

sublimation of which at 90°/0.5mm. gave 3-ethoxy-2:5-dimethylpyrazine-4-oxide as colourless needles m.p. 92° alone or admixed with a specimen described by Baxter, Newbold and Spring (loc.cit.).

Hydrogen peroxide in t.-butanol.

(a) 2-Ethoxy-5-chloro-3:6-dimethylpyrazine (0.15g.) was dissolved in a solution of anhydrous hydrogen peroxide in t.-butanol (4c.c.; 20%) and warmed at 56° for 16 hours. Removal of the solvent under reduced pressure gave a small amount (10mg.) of colourless solid which did not melt below 300° and which was not characterised.

(b) 3-Hydroxy-2:5-dimethylpyrazine similarly treated gave 50mg. of colourless solid which crystallised from methanol as colourless needles m.p. 208°. A mixed melting point with starting material (m.p. 210°) melted at 183-193°. No colouration with ferric chloride was obtained.
For analysis the product sublimed at 140°/1mm.

Found: C,31.8; H,5.7;N,26.8%.

Calc.for; Hydroxy-dimethylpyrazine $C_6H_8ON_2$: C,58.9; H,6.4;N,21.6%.

Hydroxy-dimethylpyrazine -oxide $C_6H_8O_2N_2$: C,51.4; H,5.7; N,20.0%

Alanine $C_3H_7O_2N$: C,40.5; H,8.0;N,15.7%.

Perbenzoic Acid Oxidations.

(a) 3-Ethoxy-2:5-dimethylpyrazine (1g.) was treated with a solution of perbenzoic acid (1.8g.) in dry chloroform (24c.c.) at 0° for 4 days. There was distinct heating of solution on admixture of the reagents. The chloroform solution which gave no colouration with ethanolic ferric chloride solution was washed with saturated aqueous sodium hydrogen carbonate, dried over sodium sulphate and the chloroform removed under reduced pressure leaving a light-yellow oil (0.95g.) which partially solidified on cooling. The solid material was filtered giving 3-ethoxy-2:5-dimethylpyrazine-4 oxide (0.2g.) m.p. 92° alone or when mixed with an authentic specimen. Treatment of a portion of the filtrate with ethanolic picric acid gave the picrate of 3-ethoxy-2:5-dimethylpyrazine m.p. 108°. Hydrolysis of the bulk of the filtrate with dilute hydrochloric acid gave 3-hydroxy-2:5-dimethylpyrazine (0.6g.) m.p. 210° alone or when mixed with an authentic specimen. Acidification of the bicarbonate washing gave only benzoic acid.

(b) Treatment of 3-hydroxy-2:5-dimethylpyrazine (1g.) with perbenzoic acid (2.2g.) in chloroform (29c.c.) at 0° for 4 days gave only 3-hydroxy-2:5-dimethylpyrazine-4-oxide (0.3g.) as colourless needles, from ethanol, m.p. 250° (decomp.) alone or admixed with an authentic specimen.

The bicarbonate washing gave only benzoic acid.

Persulphuric Acid Oxidations.

(a) With cooling at 0°, 3-ethoxy-2:5-dimethylpyrazine (1g.) was added dropwise to a solution of persulphuric acid (1.9g.) in sulphuric acid (25c.c.; 15%.) and warmed for 10 hours at 40-50°. On neutralisation with 3N. caustic soda an oil separated and was extracted with ether giving a recovery (0.9g.) of starting material (picrate m.p. 108°). The aqueous phase was evaporated to dryness under reduced pressure, the residue extracted with boiling chloroform (4 x 10c.c.) removal of which gave a small amount of red gum. Sublimation of the gum at 140°/10^{-3} mm. gave colourless needles m.p. 140-170°. Yield 10mg. After hydrolysis with dilute acid the product which remained gave no colouration with ferric chloride and was not identified. Compound m.p. 140-170° was probably crude 3-hydroxy-2:5-dimethylpyrazine.

(b) 3-Hydroxy-2:5-dimethylpyrazine (1g.) was likewise treated with persulphuric acid (2.3g.) in sulphuric acid (29c.c.; 20 % .). The residue after neutralisation and evaporation was extracted with benzene (Soxhlet) and removal of the solvent left a yellow gum (0.1g.) which gave no colouration with aqueous ferric chloride. Extraction of the gum with boiling ethanol gave 3-hydroxy-2:5-dimethylpyrazine-4-oxide as colourless needles m.p. 250°

(decomp.) alone and when mixed with an authentic specimen. The inorganic residue from the benzene extract readily liberated ammonia on boiling with alkali, showing ring cleavage to have occurred.

(c) 2:5-Dimethylpyrazine oxide (1g.) was treated with a solution of persulphuric acid (2.3g.) in sulphuric acid (29c.c.; 20%) at 40-50° for 10 hours. After neutralisation with 3N. caustic soda the solution was evaporated to dryness under reduced pressure and the residue extracted with benzene (Soxhlet). Removal of the benzene under reduced pressure left a white residue (0.5g.) sublimation of which at 140°/10^{-3} mm. gave 2:5-dimethylpyrazine dioxide as colourless needles m.p. 288° (decomp.).

Found: C,51.3; H, 5.9; N, 20.1%.

Calc.for $C_6H_8O_2N_2$: C, 51.3;H, 5.7; N, 20.0%.

Lead Tetraacetate Oxidations.

2:5-Dimethylpyrazine oxide (1.0g.) was dissolved in glacial acetic acid (25c.c.), lead tetraacetate (1.78g.) added and the mixture shaken at room temperature for 16 hours, for a further 10 hours at 40-45° and 2 hours at 80°. Excess lead tetraacetate was decomposed by the addition of a little glycerol, the solution evaporated to dryness under reduced pressure and the residue dissolved in water (10c.c.). The solution was saturated with hydrogen sulphide and the lead-free filtrate

evaporated under reduced pressure leaving a red gum (1.0g.) interdispersed with solid. This was filtered with aid of a little cold methanol and the residue (0.1g.) sublimed at 140°/10^{-3} mm. to give 2:5-dimethylpyrazine dioxide as colourless needles m.p. 288° (decomp.).

Found: C, 51.6; H, 5.6; N, 19.7%.

Calc.for $C_6H_8O_2N_2$ C, 51.3; H, 5.7; N, 20.0%.

The filtrate was treated with ethanolic picric acid giving the picrate of 2:5-dimethylpyrazine oxide as yellow needles m.p. 156-157° alone or when mixed with an authentic specimen. Yield 0.8g.

(b) Under the same experimental conditions 3-hydroxy-2:5-dimethylpyrazine and 3-hydroxy-2:5-di-isobutylpyrazine were recovered unchanged on treatment with lead tetraacetate.

Cyclic Hydroxamic Acids.

Pyrazine Cyclic Hydroxamic Acids.

dl-Alanine methyl ester.

(Fischer. Ber., 34, 433, (1901)).

dl-Alanine (150g.) was refluxed with dry methanol (300c.c.) for 5 hours while dry hydrogen chloride was passed through the mixture. The solvent was removed under reduced pressure, the residue dissolved in water (150c.c.), ether (150c.c.) added and the aqueous phase made strongly alkaline with 25% caustic soda while cooling at 0°. Sodium carbonate was added until a thick slurry was formed, the ether decanted and the slurry further extracted with ether (5 x 75c.c.). After drying (Na_2SO_4) the ether was removed and the residual oil distilled giving alanine methyl ester b.p. 34-36°/6mm. as a colourless liquid. Yield 92g.

dl-Alanine amide.

(Yang and Rising. J.Amer.Chem.Soc., 53, 3183, (1931)).

dl-Alanine methyl ester (30g.) was added with shaking at 0° to a solution of ammonia (175g.) in dry methanol (500c.c.) and the solution left at 0° for 4 days. Removal of the solvent under reduced pressure left a colourless oil which solidified on cooling. This was dissolved in dry chloroform (120c.c.) and precipitated by addition of dry ether (300c.c.) giving alanine amide as a hygroscopic solid m.p. 63-67°. Yield 18g.

dl-Alanine hydroxamic acid.

(Newbold, Spring, et al., Private Communication).

dl-Alanine methyl ester (50g.) was treated at -10° with a methanolic solution of hydroxylamine (Org.Syn., Vol.26, p.74.) from hydroxylamine hydrochloride (200g.) and the clear solution left for 2 days at 0° during which time a colourless solid separated. The solid was filtered off and crystallised from water-methanol to give alanine hydroxamic acid (30g.) as colourless prisms m.p. 163°.

1-Hydroxy-2-keto-3:5:6-trimethyl-1:2-dihydropyrazine.

A suspension of dl-alanine hydroxamic acid (3.0g.) in water (100c.c.) and methanol (75c.c.) was cooled to -60° and treated with a precooled (-30°) solution of diacetyl (2.9g.) in methanol (15c.c.). Aqueous sodium hydroxide (8c.c.; 5N.) was then added dropwise with stirring over 5 minutes, the temperature being maintained below -30°. The reaction mixture was gradually heated to -10° over 1 hour, solution thenbeing complete. After standing overnight at 0° the filtered solution was acidified to pH 3.0 with hydrochloric acid (d, 1.19) and evaporated under reduced pressure. The residue was extracted with boiling chloroform (3 x 25c.c.) and the dried (Na_2SO_4) extract evaporated. Sublimation of the residue at 130-140°/2mm. gave a colourless crystalline sublimate (1.2g.) m.p. 159°, crystallisation of which from acetone-methanol

gave 1-hydroxy-2-keto-3:5:6- trimethyl-1:2-dihydropyrazine as colourless prisms m.p. 176-177°.

Found: C, 54.3; H, 6.5; N, 18.5%.

$C_7H_{10}O_2N_2$ requires: C, 54.5; H, 6.5; N, 18.2%.

Light absorption in ethanol: Maxima at 2330 Å (εmax.11,600) and 3340 Å (εmax.7,000).

The hydroxamic acid gives a claret colour with aqueous ferric chloride and liberates carbon dioxide from aqueous sodium hydrogen carbonate. It is very soluble in water, ethanol, pyridine, slightly so in benzene acetone, chloroform, dioxane and insoluble in light-petroleum.

2-Hydroxy-3:5:6-trimethylpyrazine.

A solution of 1-hydroxy-2-keto-3:5:6-trimethyl-1:2-dihydropyrazine (0.4g.) in methanol (25 c.c.) was treated with hydrazine (1g.; 90%) and heated at 180° for 4 hours. Removal of the methanol under reduced pressure followed by sublimation of the residue (0.35g.) at 100°/0.1mm. gave 2-hydroxy-3:5:6-trimethylpyrazine as needles m.p. 197° either alone or admixed with the specimen described by Newbold and Spring. (J., 373, 1947.).

1-Hydroxy-2-keto-3:5-dimethyl-1:2-dihydropyrazine.

Using the method previously described a solution of methylglyoxal (1.5g.) in methanol (25c.c.) was reacted with DL-alanine hydroxamic acid (1.8g.) in water (75c.c.) and methanol (75c.c.) in the presence of sodium hydroxide solution (6c.c.; 5N.). After acidification to pH 3.0 the

light-yellow solution was evaporated to dryness under reduced pressure and the residue extracted with boiling chloroform (5 x 20c.c.) and then with boiling methanol (2 x 25c.c.). Evaporation of both extracts gave yellow prisms m.p. 118-120° sublimation of which at 90°/10^{-5} mm. followed by crystallisation of the sublimate from acetone gave 1-hydroxy-2-keto-3:5-dimethyl-1:2-dihydropyrazine as colourless needles m.p. 135°. Yield 1.2g.

Found: C, 51.4; H, 5.9; N, 20.3%.

$C_6H_8O_2N_2$ requires: C, 51.4; H, 5.7; N, 20.0%.

Light absorption in ethanol: Maxima at 2340 Å (εmax.8,100) and 3300 Å (εmax.5,400).

The hydroxamic acid gives a claret colour with ferric chloride solution and liberates carbon dioxide from aqueous sodium hydrogen carbonate.

2-Hydroxy-3:5-dimethylpyrazine.

Treatment of 1-hydroxy-2-keto-3:5-dimethyl-1:2-dihydropyrazine (0.3g.) with hydrazine at 180° for 4 hours gave a colourless solid sublimation of which at 140°/2mm. and crystallisation from light petroleum (b.p. 60-80°) yielded 2-hydroxy-3:5-dimethylpyrazine as colourless prisms m.p. 146-147°. Yield 0.13g.

Found: C, 58.2; H, 6.6; N, 22.4%.

Calc.for $C_6H_8ON_2$: C, 58.1; H, 6.45;N, 22.6%.

Light absorption in ethanol: Maxima at 2280 Å

(εmax.5,000) and 3270 Å (εmax.4,200).

Jones (J.Amer.Chem.Soc., 71, 78, (1949)) gives m.p. 145-146° for 2-hydroxy-3:5-dimethylpyrazine obtained by condensation of methylglyoxal and alanine amide.

1-Hydroxy-2-keto-3-methyl-5-phenyl-1:2-dihydropyrazine.

A solution of DL-alanine hydroxamic acid (3.0g.) in water (75c.c.) and methanol (50c.c.) was condensed with phenylglyoxal hydrate (5.1g) in methanol (35c.c.) in the presence of aqueous sodium hydroxide (8c.c.; 5N.) as previously described. Acidification of the reaction mixture to pH 3.0 with hydrochloric acid (d, 1.19) gave a solid (3.6g.) m.p. 183° which was collected after cooling to 0° for 1 hour. After sublimation at 140°/10^{-4} mm. followed by crystallisation from aqueous methanol, 1-hydroxy-2-keto-3-methyl-5-phenyl-1:2-dihydropyrazine separated as colourless needles m.p. 185°.

Found: C, 65.5; H, 5.2; N, 14.2%.

$C_{11}H_{10}O_2N_2$ requires : C, 65.4; H, 4.95; N, 13.9%.

Light absorption in ethanol: Maxima at 2810 Å (εmax.17,500) and 3450 Å (εmax. 8,800).

The hydroxamic acid is soluble in aqueous sodium hydrogen carbonate with effervescence and gives a claret colour with ethanolic ferric chloride.

The reaction was carried out in very alkaline (5 moles. caustic soda added), neutral and aqueous phosphoric acid solution giving the above hydroxamic acid only, in yields

of 75%, 39% and 34% respectively.

2-Hydroxy-3-methyl-5-phenylpyrazine.

Treatment of 1-hydroxy-2-keto-3-methyl-5-phenyl-1:2-dihydropyrazine (0.5g.) with methanolic hydrazine at 180° for 4 hours gave 2-hydroxy-3-methyl-5-phenylpyrazine (0.42g.) which after sublimation at 140°/10^{-4} mm. and crystallisation from methanol formed needles m.p. 222-223°.

Found: C, 71.25; H, 5.7; N, 15.05%.

Calc.for $C_{11}H_{10}ON_2$: C, 71.0 ; H, 5.4; N, 15.05%.

Light absorption in ethanol: Maxima at 2760 Å (εmax.17,100) and 3400 Å (εmax.6,500).

A specimen of 2-hydroxy-3-methyl-5-phenylpyrazine prepared as described by Jones (loc.cit.) by condensation of phenylglyoxal and alanine amide was obtained as needles from methanol m.p. 222-223° alone or admixed with the above specimen. Jones gives m.p. 212-213° for this compound.

Ethyl α-β-diketobutyrate.

(Bouveault and Wahl, Comptes rendus., 138, 1222; Bull.Soc. chim., 33, 478).

Nitrous fumes, from fuming nitric acid and arsenious oxide, were passed into ethyl acetoacetate (44g.) at -10° until 50g. of vapour had been absorbed, the green solution left at 0° for 2 days and then at 15-20° for 2 more days. Excess nitrous fumes were removed at 40°/100mm. and the

brown oil which remained was distilled giving ethyl α:β-diketobutyrate (25g.) as a golden yellow liquid b.p. 70°/10mm.

Attempted Condensation of Alanine Hydroxamic Acid with Ethyl α:β-diketobutyrate.

Alanine hydroxamic acid (3.6g.) was suspended in water (30c.c.) and methanol (50c.c.) and with stirring cooled to -60° when a precooled (-30°) solution of ethyl α:β-diketobutyrate (5g.) in methanol (50c.c.) was added. Aqueous caustic soda (8c.c.; 5N.) was added, dropwise over 10 minutes and the light-yellow mixture warmed to 0° over 1½ hours when almost complete solution took place. After leaving overnight at 0° the solution was filtered, made acid to pH 3.0 with hydrochloric acid (d, 1.19) and evaporated to dryness under reduced pressure. The residue was extracted with (a) boiling chloroform (3 x 25c.c.), little solution taking place and with (b) cold dry methanol 2 x 25c.c.). Both extracts gave a very slight claret colouration with ferric ions. Evaporation of extract (a) left a negligible portion of yellow gum which gave a very slight colour with ferric chloride and which could not be characterised. Extract (b) gave a yellow-brown gum which partially sublimed at 100°/10^{-4} mm. giving a light-yellow gum, which yielded a pea-green copper salt with copper acetate. The salt was insoluble in dioxane and water.

Found: C, 16.5; H, 2.1; Cu; 15.8%.

which corresponds to no expected calculated formula.

The gum from extract (b) was refluxed with caustic soda (12c.c.; 5N.) for 12 hours. Acidification of the reaction mixture to pH 3.0 with hydrochloric acid (d, 1.19) gave no solid material. Extraction with chloroform gave a gum which gave no colouration with ferric chloride and which could not be characterised.

1-hydroxy-2-keto-5-phenyl-1:2-dihydropyrazine.

(a) A solution of phenylglyoxal hydrate (2g.) in glacial acetic acid (10c.c.) was added to a suspension of glycine hydroxamic acid (1g.) in glacial acetic acid (15c.c.) and the mixture left at room temperature for 4 hours. Initially the mixture was light-orange and as reaction took place the hydroxamic acid went into solution and the colour went from orange to dark-red. The solution was then evaporated to dryness under reduced pressure, the dark-brown residue dissolved in cold chloroform (15c.c.) and extracted with aqueous caustic soda (2 x 20c.c.; 2N.). On acidification of the aqueous extract to pH 3.0 with hydrochloric acid (d, 1.19) the solution deposited light-brown needles (1.3g.), readily soluble in ethanol and giving a deep-red colouration with ferric chloride. The product sublimed at 120°/5 x 10^{-3} mm. and crystallised from methanol as colourless plates, m.p. 191° alone or mixed with the specimen prepared by G.Dunn (private

communication) using the same aqueous methanolic conditions previously described for the preparation of 1-hydroxy-2-keto-3:5-dimethyl-1:2-dihydropyrazine.
Light absorption in ethanol: Maxima at 2720 Å (εmax.18,900) and 3540 Å (εmax.5,300).

(b) A solution of phenylglyoxal hydrate (2g.) in pyridine (10c.c.) was added to a suspension of glycine hydroxamic acid (1g.) in pyridine (15c.c.) and the mixture left at 15° for 48 hours. The deep-red solution was filtered free of unreacted acid and evaporated to dryness under reduced pressure leaving a dark-red resin. The resin was dissolved in chloroform (25c.c.), the solution extracted with aqueous caustic soda (2 x 10c.c.; 2N.) and the aqueous extract acidified to pH 3.0 with hydrochloric acid (d, 1.19) when an oily brown solid separated. After filtering and air drying the solid was dissolved in boiling ethanol, treated with charcoal and filtered. On cooling a light-brown solid separated as plates m.p. 188-189°, recrystallisation of which from methanol gave 1-hydroxy-2-keto-5-phenyl-1:2-dihydropyrazine as colourless plates m.p. 191° alone or mixed with the specimen described in (a). A further crop was obtained by treatment of the ethanolic mother liquor with water. Total yield 0.5g.

<u>1-Hydroxy-2-keto-3:5-diphenyl-1:2-dihydropyrazine.</u>
The hydroxamic acid was obtained in 90% theoretical yield

by method (a) using glacial acetic acid as solvent for the reaction. The melting point of the product was undepressed on admixture with a specimen prepared by Dr.G.T.Newbold using aqueous alkaline conditions as previously described. Melting point and mixed melting point 165°.

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