AMIDINE SALTS

AND

THE   CONSTITUTION   OF   THE   SO-CALLED

IMINOHYDRINS.

Thesis presented

for the

D.Sc. Degree (1916).

by

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The iminohydrins or isoamides are first mentioned by Eschweiler[1] who - in the attempt to prove the existence of an isomeric amide form - prepared them from the corresponding iminoether hydrochlorides by the action of moist silver oxide, or by the interaction of free iminoethers and water. The resulting compounds, from their analysis figures and apparent monomolecular condition in aqueous solution were represented as having the constitution $R.C{\stackrel{=NH}{\diagdown OH}}$, isomeric with the acid amides.

Thus the formation of glycolliminohydrin, the first of these compounds to be isolated, from glycolliminoether hydrochloride was explained according to the equation

$$CH_2OH.C{\stackrel{=NH}{\diagdown OC_2H_5}} , HCl + AgOH = CH_2OH.C{\stackrel{=NH}{\diagdown OH}} + Ag\ Cl + C_2H_5OH,$$
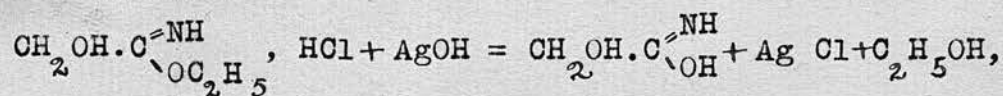
the iminohydrin together with a large proportion of glycollamide being supposed to result from the direct hydrolytic action of the water present. In addition to the above, lactiminohydrin and ᴅ-oxyisobutyro-iminohydrin were prepared and very shortly described.

The/

1. Ber. 1897, 30, 1003
   Chem. Zentr. 1898, II, 527.

The chief characteristics of these bodies as
noted by Eschweiler are their high melting-points,
fusion being generally accompanied by decomposition;
the liberation of ammonia by alkalis; and their
peculiar reaction towards certain metallic salts,
the glycollic compound for example slowly giving a
deposit of calcium glycollate on the addition of a
solution of calcium chloride.   The latter action
was said to take the course,

$$2 \ CH_2OH.C\diagup^{NH}_{\diagdown OH} + CaCl_2 + 2H_2O = (CH_2OH.COO)_2 \ Ca + 2 \ NH_4Cl.$$
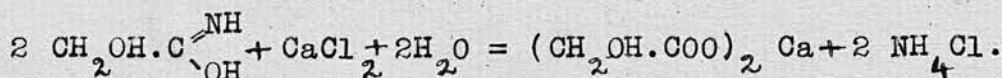
Eschweiler further states that the iminohydrins are
basic in character, and claims[1] to have isolated
definite hydrochlorides of the general type
$R.C\diagup^{NH}_{\diagdown OH}$, HCl, which are neutral in aqueous solution.
In another communication, however, the statement is
made that an aqueous solution of an iminohydrin
reacts acid to litmus if more than a half equivalent
of an acid is added.

The failure of all attempts to effect an inter-
conversion between the iminohydrins and their apparent
isomers the acid amides, led to an extended investi-
gation by Hantzsch[2], who showed that these compounds
were comparatively strong electrolytes, having in
reality a molecular weight double that assigned to
them/

1. Plinke, Inaugural Dissertation, Jena 1898.
2. Hantzsch, Ber. 1901, 34, 3142.

them by Eschweiler.   In opposition to the latter
author, Hantzsch finds the iminohydrin hydrochloride
to be strongly hydrolysed in aqueous solution, and
also comments on the fact that all the known imino-
hydrins are derivatives of α-oxy acids.[1]   Numerous
attempts were made to prepare other types, all of
which however resulted in failure.

In consideration of the discovery that the
iminohydrins were electrolytes of the general
formula $(R.CONH_2)_2$ they were represented as having
the constitution $R.C \stackrel{=NH}{\underset{O-NH_2}{\diagdown}} \quad \stackrel{HO}{\underset{}{\diagdown}} C.R$, this complex
being supposed to ionise in aqueous solution into
the ions $(R.C \stackrel{=NH}{\underset{O}{\diagdown}})'$ and $(\stackrel{HO}{\underset{NH_2}{\diagup}} C.R)^{\cdot}$. The failure
to establish any relationship with the acid amides,
despite the similarity between the structure of
these compounds and that suggested above for the
iminohydrins, was met by Hantzsch with the statement
that "amides and isoamides (iminohydrins) are not
isomers but polymers, and their relations are there-
fore different from those of genuine tautomers
which possess equal molecular weights." Nevertheless,
the 'hydrochloride of glycolliminohydrin' was
formulated as $CH_2OH.C \stackrel{=NH_2}{\underset{OH}{\diagdown}} Cl$, in which case we
should have a true isomer of glycollamide existing
in/

[1]. In a patent communication Eschweiler makes the
bare claim to have prepared acetic and benzoic
iminohydrins, but no further details are given.

in combination with hydrochloric acid.

The above formulae represent the iminohydrins as belonging to the class of amphoteric electrolytes and from this point of view the behaviour in solution of glycolliminohydrin, lactiminohydrin and their salts has been examined by Prof. James Walker.[1] From measurements of the degree of hydrolysis of glycolliminohydrin hydrochloride (glycollimino-hydrin dissolved in two molecular proportions of hydrochloric acid) by the methods of methyl acetate catalysis and of electromotive force, it appeared that in $N/8$ solution the salt was hydrolysed to the extent of about 50 per cent. The degree of hydrolysis of the sodium salt, judged from its electrical conductivity, was at the same concentration also about 50 per cent. The results with lactiminohydrin were similar. From these determinations - and working on the assumption that the iminohydrins are amphoteric electrolytes - it was possible to calculate the molecular conductivity of the parent compounds themselves. The calculated values however indicated that the iminohydrins should be very feeble conductors of electricity and bore no sort of relationship to the conductivity actually/

1. Private communication from Prof. Walker.

actually observed, which is high and roughly that of a salt. The conclusion was therefore drawn that these bodies are not amphoteric electrolytes, and that the formula usually attributed to them is erroneous.

Since the two examples investigated were of a very similar nature it was judged desirable to study other members of the class, and at the instance of Prof. Walker this work was begun first by Dr J. E. Mackenzie, who was soon compelled to relinquish it owing to other duties, and subsequently by the writer.

The method of preparation adopted by Eschweiler and later by Hantzsch, in which the iminoether hydrochloride is added in small portions at a time to an equivalent amount of silver oxide suspended in water, led to such small and variable yields that its use was abandoned. Yields of 30-35% were obtained by allowing the free iminoethers to stand with excess of water for some days at the ordinary temperature.   During this time the originally strong alkaline reaction of the iminoether gradually disappeared, and a mixture of iminohydrin and acid amide was produced from which the former could be separated by repeated crystallisation from a suitable solvent. By/

By this method considerable quantities of the glycollic, mandelic[1] and other derivatives were prepared, and submitted to careful purification.

At the outset it had been the intention to measure some of the physical constants for comparison with the figures already obtained by Hantzsch for the glycollic and by Walker for the glycollic and lactic derivatives.   After a considerable amount of work had been carried out on these lines, it was seen that the results were not in agreement with any known view of the constitution of the iminohydrins, and the problem was then attacked from the organic rather than the physical side.   The observation of Hantzsch that he was only able to prepare iminohydrins derived from α-oxy acids pointed to the possibility that the hydroxyl group was an integral part of the molecule.   Any doubt on this point, however, was eliminated by the early preparation of the methoxy-acetic compound, containing a substituted hydroxyl group, followed later by that of the acetic and phenylacetic derivatives, the isolation of the two latter being attended with considerable difficulty owing to the extreme ease with which they became hydrolysed during purification./

1. A very small amount of this compound had already been isolated by J. E. Mackenzie, using the silver oxide method.

purification.　Eventually they were only obtained
in the pure state by a prolonged extraction of the
crude dried products of reaction with dry ether in
a Soxhlet apparatus.　By this means the sparingly
soluble amide was gradually removed, leaving behind
the pure iminohydrin.　All attempts to prepare
benziminohydrin failed[1], cyaphenin and benzamide
being the only products formed.

All the above compounds, including the mandelic
derivative, were found to possess the high molecular
weight and saline properties characteristic of
glycolliminohydrin.　In aqueous solution and at
25°C the molecular conductivity of the mandelic com-
pound was found to be 56.2 at V = 2000, and for the
methoxyacetic compound μ_{25}= 71.6 at V = 1000.
Hantzsch for glycolliminohydrin gives μ_{25}= 79.5 at
V = 2048.　No quantitative measurements of conduct-
ivity were attempted in the case of the acetic and
phenylacetic derivatives owing to their comparative
instability, but qualitatively they were found to
be good electrolytes.　Determinations of the degree
of hydrolysis of mandelic and methoxyacetic imino-
hydrin hydrochlorides were also carried out in
aqueous solution, and a figure of 50 per cent ob-
tained/

1. Compare Mackenzie, Proc. Chem. Soc. 1913, 29, 175.

obtained in each case, identical with that found by Walker for the glycollic compound.
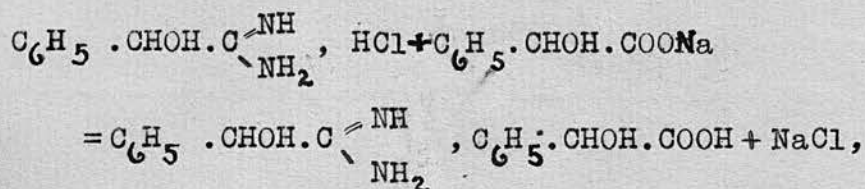
This unexpected similarity of the hydrolysis figures for salts of such widely differing imino-hydrins as the above, together with the statement that Eschweiler had isolated a hydrochloride whose reaction was neutral in aqueous solution, led to a closer chemical investigation of these substances. Glycolliminohydrin and its hydrochloride had already proved unsuitable for this purpose owing to their extremely high solubility, but a more convenient subject for examination was found in the mandelic derivative, which dissolves sparingly in water.

On evaporation of a solution of mandelimino-hydrin in excess of dilute hydrochloric acid, the iminohydrin was found to retain exactly a half equivalent of acid. The solid obtained in this way was not a pure compound, and gave an indefinite melting-point. When however mandeliminohydrin was crystallised from excess of warm dilute hydrochloric acid, well-formed crystals of a hydrochloride were deposited of melting-point 219°.

The results of these two experiments, together with the peculiar reaction of the iminohydrins to-wards metallic salt solutions, suggested that these substances/
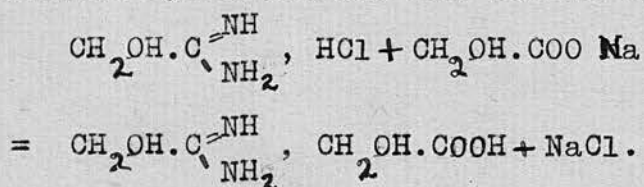
substances were derivatives of an organic base.
Fruitless attempts had already been made to remove
such a free base by extracting an alkaline imino-
hydrin solution with ether.   More success was
obtained when powdered mandeliminohydrin was rapidly
shaken up with ether and a saturated solution of
potassium hydroxide.   On evaporation of the ether
an exceedingly small amount of a white powerfully
basic substance remained behind of melting-point
(98°) - 110°, which very soon decomposed with
evolution of much ammonia.

These properties are characteristic of amidines.
Mandelamidine melts at 110°, and its hydrochloride
at 220°, from which it follows that mandelimino-
hydrin must be in reality mandelamidine mandelate and
the iminohydrins in general amidine salts of the
formula $R.C\begin{smallmatrix} \nearrow NH \\ \searrow NH_2 \end{smallmatrix}$, R.COOH.   This conclusion was
subsequently confirmed by the synthesis of the
mandelic compound from mandelamidine hydrochloride
and sodium mandelate,

$$C_6H_5.CHOH.C\begin{smallmatrix} \nearrow NH \\ \searrow NH_2 \end{smallmatrix} , HCl + C_6H_5.CHOH.COONa$$

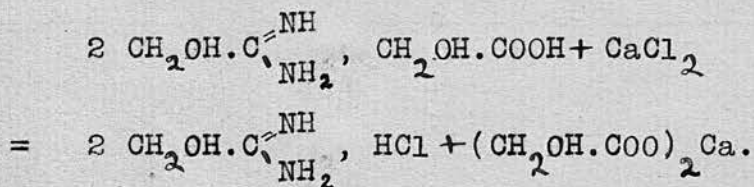$$= C_6H_5.CHOH.C\begin{smallmatrix} \nearrow NH \\ \searrow NH_2 \end{smallmatrix} , C_6H_5.CHOH.COOH + NaCl,$$

and of Eschweiler's original glycolliminohydrin
(glycollamidine glycollate) from the corresponding
amidine/

amidine hydrochloride and sodium salt,

$$CH_2OH.C{\overset{=NH}{\underset{NH_2}{\diagdown}}},\ HCl + CH_2OH.COO\ Na$$

$$=\ CH_2OH.C{\overset{=NH}{\underset{NH_2}{\diagdown}}},\ CH_2OH.COOH + NaCl.$$

In connexion with the latter synthesis, for which glycollamidine hydrochloride had first to be prepared, some of Eschweiler's work on the imino-hydrin (amidine) salts has been repeated and several inaccuracies corrected.

From the above standpoint a review of the properties of the 'iminohydrins' presents no peculiarities. Evidence of saline character is furnished by high melting-point, insolubility in ether or hydrocarbon solvents, and by high electrical conductivity in aqueous and alcoholic solutions, the latter in the case of the glycollic compound being very little short of the value for a typical salt such as sodium acetate. With a larger molecule such as that of the mandelamidine salt the conductivity is less owing to the decreased mobility of the ions. The reaction with metallic salts is seen to be an example of ordinary double decomposition, that between 'Glycoll-iminohydrin' and calcium chloride following the course:

$$2\ CH_2OH.C{\overset{=NH}{\underset{NH_2}{\diagdown}}},\ CH_2OH.COOH + CaCl_2$$

$$=\ 2\ CH_2OH.C{\overset{=NH}{\underset{NH_2}{\diagdown}}},\ HCl + (CH_2OH.COO)_2Ca.$$

The/

The soluble substance left in solution is glycoll-
amidine hydrochloride and not ammonium chloride as
stated by Eschweiler, and later by Hantzsch.
Characteristic of amidine salts is the disruption
which accompanies fusion, and the readiness with
which ammonia is evolved on treatment with alkalis;
while the decomposition suffered by the 'iminohydrins'
in general on heating with aqueous solvents is due
to hydrolysis of the amidine into amide and ammonia.
This is well illustrated in the case of the phenyl-
acetic compound where attempted crystallisation from
alcohol was found to lead to the production of
phenylacetamide and ammonium phenylacetate,

$$Ph.CH_2.C{\underset{NH_2}{\overset{NH}{}}}, \quad Ph.CH_2.COOH + H_2O$$

$$= \quad Ph.CH_2.CONH_2 + Ph.CH_2.COONH_4.$$
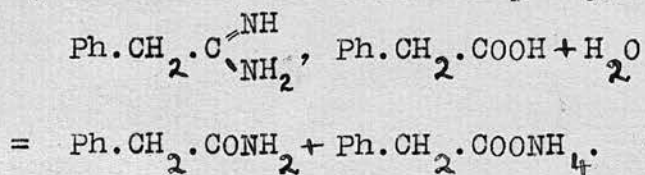
The contradictory statements of Eschweiler and
Hantzsch in connexion with the neutrality of the
'iminohydrin salts' are also made clear, since these
authors believed that the iminohydrin $(R.C{\underset{NH}{\overset{OH}{}}})_2$
was capable of uniting with two molecules of hydro-
chloric acid to yield two molecules of the salt
$R.C{\underset{NH}{\overset{OH}{}}}, HCl.$ The hydrochloride - in reality an
amidine salt - as isolated by Eschweiler proved
neutral when dissolved in water, while hydrolysis
measurements/

measurements carried out by Hantzsch with a solution
containing one molecular proportion of iminohydrin
to two of hydrochloric acid naturally led to the
conclusion that the salt was considerably hydrolysed.
The weak organic acid which is liberated in the
latter case remains practically unionised in presence
of the excess of hydrochloric acid, thus accounting
for the apparent dissociation values of 50 per cent
obtained by Walker for glycolliminohydrin and
lactiminohydrin hydrochlorides, and by the writer
for the methoxyacetic and mandelic derivatives.

MECHANISM OF THE INTERACTION OF IMINOETHERS WITH WATER.

Pinner in his monograph on the iminoethers (Die Imidoäther und ihre Derivate) states that these bodies decompose slowly on standing, generally giving rise to the alcohol and nitrile from which they are derived. In some cases the nitrile may polymerise on being liberated, while in others the decomposition may take place in a different manner and lead to the formation of an acid amide. An example of the latter type is furnished by α-oxy isobutyroiminoether[1], which on attempted distillation breaks up into the corresponding amide and alcohol; and it is probable that the interaction between benziminoether and water to form cyaphenin[2] is due to the initial formation and subsequent polymerisation of benzonitrile.

In those reactions where water is present, however, other changes may take place. Iminoethers are at once strongly alkaline and readily hydrolysable compounds, and the work of Pinner has shown that the imino- and alkoxy- groupings are extremely sensitive to attack: the actual group or groups affected varying with the reagent employed. In particular it is/

1. Pinner, die Imidoäther, p.37.

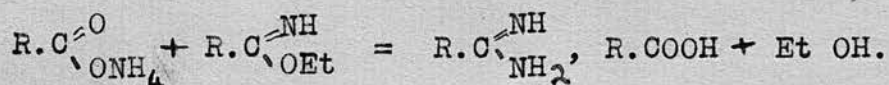2. Mackenzie, Proc. Chem. Soc. 1913, 29, 175.

is known that ammonia reacts with iminoether hydro-
chlorides with great readiness to form amidine salts.

Although in no single instance was any trace of
free ammonia observed during the above interactions
between iminoether and water, it was found by experi-
ment that the addition of an equivalent of ammonium
mandelate to an aqueous suspension of mandelimino-
ether not only doubled the yield of amidine mandelate,
but the deposition of the pure salt commenced almost
immediately after the addition had been made. In
one hour a copious crystalline precipitate of the
pure salt formed, whereas in the absence of ammonium
mandelate no crystalline deposit was observed until
after the lapse of two or three weeks at winter
temperature.

It seems probable then that in the interaction
of iminoethers with water, the first step consists
in the slow hydrolysis of a portion of the substance
in the alkaline medium to form the ammonium salt of
the corresponding acid,

$$R.C\overset{\nearrow NH}{\underset{\searrow OEt}{}} + 2\ H_2O = R.C\overset{\nearrow O}{\underset{\searrow ONH_4}{}} + Et \cdot OH.$$
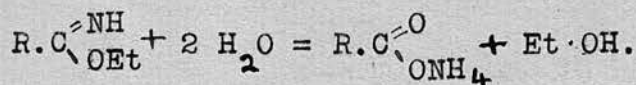
This salt then reacts with more free iminoether
to give the amidine salt or iminohydrin,

$$R.C\overset{\nearrow O}{\underset{\searrow ONH_4}{}} + R.C\overset{\nearrow NH}{\underset{\searrow OEt}{}} = R.C\overset{\nearrow NH}{\underset{\searrow NH_2}{}},\ R.COOH + Et\ OH.$$

In/

In this connection Pinner, in describing the formation of amidine hydrochloride from iminoether hydrochloride and a slight excess of alcoholic ammonia, remarks on the precipitation of ammonium chloride which then slowly redissolves with formation of the soluble amidine salt[1]. This reaction appears in every way parallel to the above and to take the course

$$R.C{\overset{=NH}{\underset{O\,Et}{\diagdown}}}, HCl + NH_3 = R.C{\overset{=NH}{\underset{O\,Et}{\diagdown}}} + NH_4Cl$$

$$R.C{\overset{=NH}{\underset{O\,Et}{\diagdown}}} + NH_4Cl = R.C{\overset{=NH}{\underset{NH_2}{\diagdown}}}, HCl + Et\,OH.$$
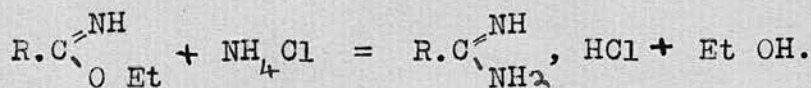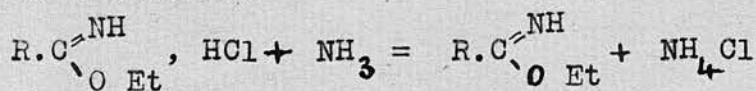
The simultaneous production of amide is due to the direct hydrolysis of iminoether and amidine in the alkaline solution, and the amount formed in any given experiment does not appear to bear any constant relation to that of the amidine salt. That the amide is an end product in the reaction is shown by the fact that the addition of this substance to a mixture of the corresponding iminoether and water produces no increase or decrease in the subsequent yield of amidine salt.

1. Since the above was first written an abstract has appeared in the Journal of the Chemical Society (1917, A.i.255) of a paper by A. Knorr, in which the author claims to have shown conclusively that free ammonia does not interact with free iminoethers, but that amidine hydrochlorides are formed from them by direct interaction with ammonium chloride.

EXPERIMENTAL.

Great difficulty was at first experienced owing to the extremely small yields obtained by the silver oxide method of preparation adopted by Eschweiler and Hantzsch. Yields of 30-35% were eventually obtained by allowing the free iminoethers to stand with excess of water in a stoppered bottle for some days at the ordinary temperature. In some cases where the iminoether was insoluble in water, action was hastened by placing the bottle in a mechanical shaker. When the change was complete - as shown by the disappearance of the originally strong alkaline reaction - the excess of water was removed in vacuo over sulphuric acid and the resultant mixture of iminohydrin and acid amide separated by repeated recrystallisation from a suitable solvent. In one or two instances the dried products of reaction were extracted continuously with ether in a Soxhlet apparatus, the insoluble iminohydrin being left behind in a comparatively pure state.

Glycolliminohydrin, glycollamidine glycollate, $CH_2OH.C{<}_{NH_2}^{NH}$, $CH_2OH.COOH$, was obtained in 30% yield by dissolving glycolliminoether in excess of water and allowing to stand ten or twelve days. On removal of/

of excess water and fractional recrystallisation of
the residual solid from alcohol, the pure iminohydrin
was obtained in the form of well-defined plates, of
m.p. 166 — 168° (decomp.)   Eschweiler (loc. cit.)
quotes 161 — 162°.

Molecular weight of Glycolliminohydrin in Methyl Alcohol.

Determined in a modified Beckmann apparatus,
provided with electrical heating and a vacuum-tube
outer vessel.   The methyl alcohol used was carefully
dried over lime and fractionated. (K_{25}= 2.04 x 10^{-6}).

Wt. of Solvent	Wt. of Substance	Elevation of b.p.	Calculated M.W.	v.
27.91 g.	0.5662 g.	0.174^O	100	9.3
27.91	1.143	0.314^O	112	4.6

The dilution v above is calculated using the
formula weight 152.   The recovered iminohydrin was
found to have been hydrolysed to a small extent
during heating, and had the melting-point 155 — 160°
(softening at 147°) as against 166 — 168° for the
pure product.

Electrical/

Electrical Conductivity in Methyl Alcohol Solution at 25°.

The following determinations were carried out in a stoppered cell having electrodes covered with a deposit of 'grey' platinum, and to reduce still further errors arising from oxidation at the electrodes, the electrolyte at each dilution was freshly made up from a weighed amount of the solid by the addition of the requisite volume of methyl alcohol, $(K_{25} = 2.04 \times 10^{-6})$. On account of the rapidity with which readings of cell-resistance could be obtained, a rotating commutator and galvanometer arrangement was used instead of the more usual coil and telephone.

$v.$	32	64	128	256	512
$\mu.$	48.35	56.6	64.3	71.5	76.9

At higher dilutions the figures obtained were unreliable owing to oxidation causing a rapid fall of the cell-resistance.

Methoxyacetiminoether. $CH_3O.CH_2.C\underset{OC_2H_5}{\overset{NH}{\diagdown}}$.
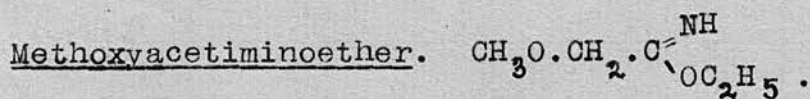
The starting point for the preparation of methoxyacetiminoether was monochlormethylether, $CH_3.O.CH_2Cl$, which was obtained according to the method of Wedekind[1].

1. Ber. 36, 1383.

Methyl alcohol was saturated with dry H Cl gas at 0°C, and the solution thoroughly shaken up with 300 gm. powdered paraformaldehyde to form a smooth cream, which changing rapidly into a yellow solution soon afterwards separated into two layers. It was allowed to stand 24 hours, with occasional shaking, and finally distilled from the water-bath. In this way the whole of the upper layer distilled over between 30° and 60°, the distillate being collected away from moisture and air in a current of dry CO_2. It was fractionated, using a column, and 115 gm. chloroether b.p. $53^{\circ} - 58^{\circ}$ obtained.

The chloride was next converted into the cyanide[1]. 250 gms. dry $Hg(CN)_2$ in a finely powdered state, were placed in a 500 c.c. flask fitted with a reflux condenser. The flask was immersed in ice-water and 80 gms. dry chlormethylether added quickly. The mixture was vigorously shaken and a violent action took place. After completing the action by five hours heating on the water-bath, the cyanide was distilled off from a sand-bath. On fractionation a product was obtained of b.p.$118^{\circ} - 119^{\circ}$.

Methoxyacetiminoether/

1. Wedekind, Ber. 36, 1383.

Methoxyacetiminoether, $CH_3O.CH_2.C\overset{NH}{\underset{OC_2H_5}{\diagup}}$,
was obtained from the nitrile in the usual manner,
29 gms. of the latter being dissolved in ether and
treated with 24 c.c. alcohol and 15 gms. dry HCl gas.
After a short time the liquid separated into two
layers, and later crystallised out.

Yield of methoxyacetiminoether hydrochloride
42.7 gms.

Some of the hydrochloride (16 gms.) was shaken
up with ether and a concentrated solution of potas-
sium carbonate. Much carbon dioxide was evolved,
and the ethereal extract, after drying over sodium
sulphate, was distilled. The boiling point of the
distillate slowly rose to 136° where it remained
constant.

Yield of methoxyacetiminoether, b.p.136°, 5.5 gm.

The iminoether is a colourless liquid with a
peculiar odour; it is alkaline to litmus and miscible
in all proportions with water. Ammonia is readily
evolved on treatment with alkalis.

Analysis:

   .1789 gm. gave .3381 gm. CO_2 and .1474 gm. H_2O

$$C = 51.52 \qquad H = 9.22$$

$C_5H_{11}O_2N$ requires $C = 51.25 \qquad H = 9.47.$

It/

It is probable that the substance was not quite pure, since all iminoethers decompose to some extent on heating. An attempt to purify a portion by distillation under 80 mm. pressure, gave a distillate coming over at 66° - 67°. This specimen on analysis gave figures similar to the above.

<u>Methoxyacetiminohydrin, methoxyacetamidine methoxyacetate,</u> $CH_3O.CH_2.C\overset{NH}{\underset{NH_2}{}}$, $CH_3O.CH_2.COOH$, was obtained by allowing the free iminoether (12 gms.), mixed with excess of water, to stand at ordinary temperature for five weeks. The water was removed in a desiccator over sulphuric acid, and the resulting mixture recrystallised repeatedly from alcohol containing about a third of its volume of benzene. The salt was obtained in the form of large well-shaped needles, m.p. 162° - 164°. Yield 2.2 gms.

.1835 gm. gave .2715 gm. CO_2 and .1332 gm. H_2O

$$C = 40.35 \quad H = 8.06$$

$C_6H_{14}O_4N_2$ requires $C = 40.42 \quad H = 7.93$

It is readily soluble in alcohol and moderately soluble in water; in ether and benzene it dissolves sparingly. On heating with aqueous sodium hydroxide ammonia is evolved.

Molecular/

Molecular Weight in Aqueous Solution. (Cryos-
copic method.)

Using 20 gms. solvent the following data were
obtained. (K for water = 1870.)

Weight of salt taken.	Depression of freezing point.	Molecular Weight.
.1225	.129°	89
.2481	.250	93
.3067	.309	93

$C_6H_{14}O_4N_2$ requires 178, hence at the above
dilutions the compound is almost completely ionised.

ELECTRICAL CONDUCTIVITY IN WATER AT 25°.

As in the case of the glycollic compound electrodes covered with a deposit of 'grey' platinum were employed. The electrolyte at each dilution was freshly made up from a stock solution by the addition of the requisite amount of water ($\mu_{25}=$ 1.6 x 10^{-6}).

An N/$_{20}$ stock solution was prepared by dissolving .8907 gm. of the salt to make 100 c.c.

v.	20	40	100	200	400	1000	2000
u_{25}	60.9	64.0	67.8	69.8	70.8	71.6	72.0

At dilution v = 2000 oxidation was noticeable, as shown by the rapid falling of the cell-resistance. The figures show 'methoxyacetiminohydrin' to be a good electrolyte, with a conductivity at high dilutions comparable with that of the glycollic derivative, for which Hantzsch finds $\mu_{25}=$ 79.5 at v = 2048.

Hydrolysis of the 'Iminohydrin Hydrochloride'. in aqueous solution at 25° C.

Determined in N/$_8$ solution (calculated on the assumption of Hantzsch that one molecule of the iminohydrin gives rise to two molecules of hydrochloride) by the methyl acetate catalysis method.

The/

The hydrochloride solution was made up from
20 c.c. $N/_8$ HCl and .2226 gm. 'Iminohydrin'.
1 c.c. of methyl acetate was added and 2 c.c. of the
mixture withdrawn for each titration.

Time in minutes	Titre	$T_\alpha - T_n$	k.
0	7.27	34.03	-------
261.5	10.70	30.60	.000405
382	12.15	29.15	.000405
1435	22.38	18.92	.000408
1711	24.30	17.00	.000405
3014	31.20	10.10	.000403
∞	41.30		-------

Mean value of k = .000405

A parallel experiment using $N/_8$ hydrochloric acid
alone gave k = .000807, from which the hydrolysis of
the hydrochloride is 50%.

<u>Acetiminohydrin, acetamidine acetate</u>,

$CH_3.C\begin{smallmatrix} \nearrow NH \\ \searrow NH_2 \end{smallmatrix}$, $CH_3.COOH$.
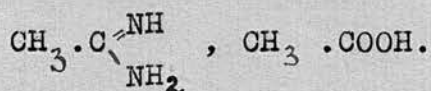
Acetonitrile (37.5 gms.) was treated with
alcohol (44 gms.) dissolved in a little absolute
ether; hydrochloric acid gas (36 gms.) was passed
in, and the solution became solid after a few hours.
The/

The iminoether hydrochloride was filtered off and converted into the free iminoether by treatment with potassium carbonate solution.

The free iminoether was mixed with excess of water in a stoppered bottle and allowed to stand for two months at the ordinary (winter) temperature. The still faintly alkaline solution was then taken down to dryness in a desiccator, and the solid residue continuously extracted with ether in a Soxhlet apparatus.   In this way a product was obtained of m.p. 66° - 148°.   A further extraction with hot benzene removed acetamide, m.p. 79° - 82°, and left an insoluble portion (3 gms.) which melted at 155° - 175°.   By solution in cold alcohol, filtering and precipitating with ligroin, a product was obtained of m.p. 185° - 187°. (decomp.)

The 'iminohydrin' was very readily soluble in water, and is easily decomposed with evolution of ammonia.   Owing to the speed with which it became hydrolysed into acetamide and ammonium acetate it was not further examined.

Phenylacetiminohydrin, (Phenylacetamidine
phenylacetate, $Ph.CH_2.C{<}^{NH}_{NH_2}$, $Ph.CH_2.COOH$.

Prepared according to the above method from benzyl cyanide (117 gms.), alcohol (48 gms.) and dry hydrochloric acid gas (40 gms.) in ethereal solution.

The hydrochloride of the iminoether so obtained
was converted into the free iminoether - by use of
sodium carbonate - and the latter allowed to stand
in contact with water.   After one month (winter
temperature) the oil had become semi-solid, and
after nine weeks it was filtered off, and the solid
dried and extracted with ether.   The solvent removed
phenylacetamide m.p. 155° - 156° and left behind in
the receiver the pure 'iminohydrin'.

$$\text{m.p.} 227^{\circ} - 230^{\circ} \text{ (decomp.)}$$

Analysis.
   .1586 gm. gave .0974 gm. H_2O and .4138 gm. CO_2

$$C = 71.08 \qquad H = 6.82$$

$C_{16}H_{18}O_2N_2$ requires $C = 71.07 \qquad H = 6.72$

The salt is a colourless crystalline compound,
soluble in hot alcohol, sparingly soluble in water
and ethyl acetate, insoluble in benzene and ether.

In all cases where crystallisation was attempted
a lower melting product was obtained, varying from
m.p. 150° - 158° with alcohol, to 226° - 229° by
dissolving in cold ethyl acetate and precipitating
with benzene.   This was found to be due to hydrolysis
of the salt into the corresponding amide and ammonium
salt.

The compound was found to be a good conductor
of electricity in a freshly made up aqueous solution,
but owing to its instability it was not further examined.

Mandeliminohydrin, (mandelamidine mandelate)

$$C_6H_5.CHOH.C\overset{NH}{\underset{NH_2}{\diagup}} \quad , \quad C_6H_5.CHOH.\ COOH.$$
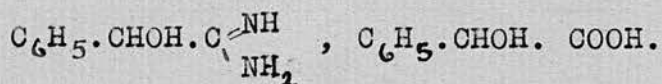
As already stated, a very small specimen of this compound had been isolated by Mackenzie[1], using the silver oxide method of preparation.

In the following preparation a yield of 35% of the theory (calculated on weight of iminoether used) was obtained without difficulty.

80 gms. potass. cyanide were placed in a flask and moistened with water. An ethereal solution of 106 gms. benzaldehyde was added and then, drop by drop, 100 c.c. of conc. hydrochloric acid, with cooling and vigorous shaking. The ethereal solution of mandelonitrile was decanted off and dried for 24 hours over sodium sulphate. It was then treated with 46 gms. alcohol and 36.5 gms. dry hydrochloric acid gas, and allowed to stand. After 12 hours the crystallised iminoether hydrochloride was filtered off at the pump.

Yield 135 gms.

The hydrochloride was converted into the free iminoether by shaking with ether and potass. carbonate solution.

Yield 87 gms.

1. Private communication to the writer.

The free iminoether was shaken up with water in a stoppered bottle at the ordinary temperature. After six days the original red oil was transformed into a yellow-red crystalline solid, which was filtered off. The mother-liquid which also contains 'iminohydrin' was evaporated to dryness.

The dried products of reaction were placed in a Soxhlet apparatus and extracted with ether until the melting point of the insoluble portion had risen to the neighbourhood of 180°.

One crystallisation from alcohol gave the pure iminohydrin, m.p. 186° - 188° (with decomp.)

Yield 28 gms.

(Mackenzie quotes m.p. 173° - 179°, but the actual figure is to some extent dependent on the rate of heating.)

The compound is a colourless substance crystallising in plates. It is moderately soluble in hot water, sparingly soluble in alcohol, and insoluble in ether, benzene, and ligroin. It is a good electrolyte, and gives off ammonia when warmed with aqueous alkalis.

Molecular Weight of Mandeliminohydrin in water. (cryoscopic method.)

The/

The following data were obtained (K = 1870)

Weight of water.	Weight of salt.	Depression of freezing point.	Calculated Molec.weight.
20.0	.1210	.073	155
20.0	.2348	.147	149

Theory for $C_{16}H_{18}O_4N_2$ = 302

From the figures it is seen that ionisation is practically complete at the above dilutions.

The following data were obtained by the boiling-point method, in anhydrous methyl alcohol solution. An electrically treated Beckmann apparatus, with a vacuum-tube jacket was employed.

Weight of alcohol.	Weight of salt.	Elevation of b.p.	Calculated Molec. Weight.
27.91	.534	.080	206
27.91	.992	.150	204
27.91	1.384	.214	200

In this case, as was to be expected, ionisation was only partial. The slow fall of molecular weight with increasing dilution is probably due to slight decomposition of the solute.

Conductivity of 'Mandeliminohydrin' in aqueous solution at 25°.

Measured in the same manner, and using the same precautions as were employed in the case of the methoxyacetic compound. Oxidation was again noticeable at the higher dilutions.

v.	20	40	100	200	400	1000	2000
$\mu._{25}$	43.0	46.0	51.0	53.0	54.4	55.2	55.4

Hydrolysis of 'Mandeliminohydrin hydrochloride' in aqueous solution.

This was determined - as for the methoxyacetic compound - by the methyl acetate catalysis method. An N/8 solution was used, at 25° C.

N/8 Hydrochloric Acid.

Time in minutes.	Titre.	$T_\alpha - T_n$	k.
0	6.35	30.15	------
109	9.39	27.11	.000973
245	11.75	24.75	.000804
374	14.18	22.32	.000803
477	16.01	20.49	.000808
603	17.99	18.51	.000808
719	19.70	16.80	.000812
1562	27.94	8.56	.000805
∞	36.80	-----	- - - - -
	Mean value for acid		.000807

N/$_8$ Hydrochloride (.3777 gm. in 20 cc. N/$_8$ HCl.)

Time.	Titre.	Tα - Tn.	k.
0	6.30	30.20	----
245.5	9.02	27.48	.000383
377.5	10.45	26.05	.000391
481.5	11.50	25.00	.000392
607.5	12.70	23.80	.000391
721.5	13.76	22.74	.000394
1560	19.97	16.53	.000386
∞	36.30	0	----

Mean value for hydrochloride .000390

Comparison of the two velocity constants shows an apparent hydrolysis of 48.3 per cent in N/$_8$ solution.

Solubility of 'Mandeliminohydrin.'

In the following determinations an excess of finely powdered iminohydrin was shaken up in a stoppered bottle with the required solvent, the bottle being immersed during the operation in a thermostat at the required temperature. The bottle was then rapidly removed and the stopper replaced by a double-bored rubber cork. One hole of the latter bore a siphon tube connected with a small weighing/

weighing bottle, the other hole carrying an upright
tube.   A second upright tube allowed for the escape
of the displaced air from the small weighing bottle.
The whole apparatus was immersed in the thermostat,
only the ends of the two upright tubes remaining
above the level of the water, and a gentle current
of dry air was forced into the first bottle, driving
the saturated solution through a small filter-pad
on the expanded end of the siphon tube and over into
the tared weighing bottle.   After drying and weigh-
ing the latter, it was placed in a desiccator and the
solvent removed over sulphuric acid, when the weight
of the residual solid could be determined.

All the following determinations were carried
out at 25° C.

Solvent.	Time of shaking.	Weight of solvent.	Weight of solute.	100 gms. solvent dissolve.
Water	3 hours	14.92	.2781	1.865
"	5 hours	15.21	.2846	1.871
Methyl Alcohol	3 hours	9.094	.4330	4.761
"	6 hours	9.250	.4426	4.785

If the time of shaking were unduly prolonged,
it was found that the solubility figure rose slightly,
owing/

owing to hydrolysis of the salt. After 27 hours
continuous shaking at 25°, a methyl alcohol solution
contained 4.85 gms. dissolved solid per 100 gms.
solvent. In this case the originally colourless
solution became yellow.

Behaviour of Mandeliminohydrin towards Acids and Alkalis.

In the course of some experiments an aqueous
solution of the iminohydrin was treated with exactly
one molecular proportion of potassium hydroxide.
At first no ammonia could be detected, but on warming
the solution the gas was freely given off. The
liquid was boiled until free from ammonia, and was
then found to react neutral to litmus. On cooling,
crystals of mandelamide were deposited, m.p. 132°,
while the mother-liquor contained ammonium mandelate.
No other product of reaction could be detected.

The addition of more alkali to the solution,
followed by the application of heat, produced a
further slow evolution of ammonia.

Mandeliminohydrin on solution in warm dilute
hydrochloric acid, gave a crystalline deposit of a
hydrochloride on cooling, of m.p. 215° - 219°.

Mandelamidine hydrochloride[1] is quoted as
melting/

1. C. Beyer, J. pr. Chem. 31, 383.

melting at 213° - 214° and a specimen prepared by the interaction of mandeliminoether hydrochloride with alcoholic ammonia, after two recrystallisations from alcohol proved identical with the above, melting at 219° - 220°.

On shaking the finely powdered iminohydrin with ether and saturated potassium hydroxide solution, the ether on evaporation in vacuo left behind a small amount of a white powerfully basic solid, of melting point ($98^{'}$) — 110°. After a short time it decomposed, turning brown and evolving much ammonia. Mandel-amidine[1] melts at 110°.

Synthesis of 'Mandeliminohydrin'.

Mandelamidine hydrochloride, prepared as above from the iminoether hydrochloride and ammonia, was treated in warm aqueous solution with one molecular proportion of sodium mandelate. On cooling, the solution deposited hard nodules, which after one crystallisation from alcohol melted at 184° - 186° (with decomp.), and had the plate formation character-istic of mandeliminohydrin.

### Synthesis of Eschweiler's 'Glycolliminohydrin.'

Glycollamidine hydrochloride[2] was treated in aqueous/

1. C. Beyer, J. pr. Chem. <u>31</u>, 383.
2. For preparation of this substance see page 39.

aqueous solution with one molecular equivalent of
sodium glycollate.   The water was removed in vacuo
over sulphuric acid, and the dry residue extracted
with alcohol.   Crystals of glycolliminohydrin were
obtained, m.p. 166° - 167° (decomp.)

p-Chlormandelamidine p-chlormandelate

$$Cl.C_6H_4.CHOH.C{\overset{=NH}{\underset{NH_2}{}}} \quad , \quad Cl.C_6H_4.CHOH.COOH.$$
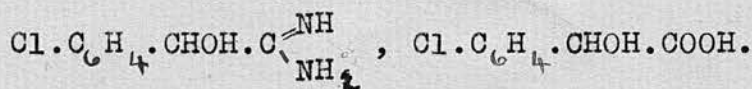
This compound was in course of preparation
before the actual constitution of the iminohydrins
as amidine salts had been established, and had been
intended for use in comparison with the mandelic
derivative.   The preparation was a lengthy process,
starting with the conversion of p-chlortoluene into
p-chlorbenzylidene chloride, $Cl.C_6H_4.CHCl_2$, by
chlorination at the boiling-point under the influence
of rays from a Uviol mercury vapour lamp.

This was then converted into p-chlorbenzaldehyde
by heating with excess water in a sealed tube at 170°
for 6 hours.   Owing to the readiness with which the
aldehyde takes up oxygen, the crystalline product
from the sealed tube - after drying - was used direct
without further purification.

p-Chlormandeliminoether, $Cl.C_6H_4.CHOH.C{\overset{=NH}{\underset{OC_2H_5}{}}}$.
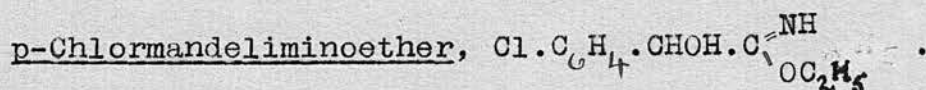
The aldehyde from 24 gms. chlorbenzylidene
chloride was converted into the iminoether hydro-
chloride/

hydrochloride by the use of KCN and hydrochloric
acid, as in the case of the mandelic derivative.
On shaking the hydrochloride out with ether and
potass. carbonate solution, the free iminoether was
obtained.   Evaporation of the ether left the imino-
ether in the form of well-defined plates of melting-
point 107° - 109°.   A portion dissolved in benzene
and precipitated with ligroin melted at 108° - 110°.

Yield 8 gms.

Analysis for Chlorine. (Carius-Volhard method).

.1172 gm. was weighed out together with
.2242 gm. $AgNO_3$, and heated in a sealed tube
with 2 c.c. fuming nitric acid for 5 hours at
240° C.

Excess of silver nitrate required 7.35 c.c.
of .1052 N thiocyanate.   Cl = 16.52

$C_{10}H_{12}O_2$ N Cl   requires   Cl = 16.60.

The iminoether is very sparingly soluble in
water, readily so in dilute acids. It is soluble in
benzene, and in alcohol. Insoluble in ligroin.

The crude product tends to oxidise in air,
turning red. The pure compound is colourless and
can be kept for some weeks without showing much
oxidation.

The/

The amidine salt (iminohydrin) was obtained
from the iminoether by allowing the latter to stand
out of contact with air in a stoppered bottle con-
taining water.   After six weeks the reaction mixture
was taken down to dryness in a desiccator over sul-
phuric acid.   The mixed yield from 20 gms. imino-
ether was extracted with ether in a Soxhlet apparatus.

p-Chlormandelamide. $Cl.C_6H_4.CHOH.CONH_2$

The ethereal extract from the mixed products of
reaction deposited white crystals m.p. $122^{\circ} - 123^{\circ}$,
which proved on analysis to be chlormandelamide.
On hydrolysis with alkali it yielded ammonia and a
salt of chlormandelic acid.

Chlorine Content. (Carius-Volhard method).

.1162 gm. heated with .2626 gm. $AgNO_3$ and
fuming nitric acid.   Excess silver nitrate required
9.10 c.c. $N/_{10}$ thiocyanate for titration.

$$Cl = 19.4$$

$$C_8H_8O_2N \; Cl \quad requires \; Cl = 19.1$$

The amide is sparingly soluble in ether and benzene,
and readily soluble in hot alcohol.

p-Chlormandelamidine p-chlormandelate was
left behind in the crude state after ether extraction
as a white powder of melting-point $170^{\circ} - 180^{\circ}$.
Recrystallisation from a mixture of alcohol and
benzene/

benzene raised the melting-point to the neighbourhood
of 195°, an exact determination of the figure being
difficult owing to rapid charring.

This substance proved unexpectedly unstable, and
very readily decomposed with evolution of ammonia on
heating with solvents.   Beyond finding that it was
qualitatively a good conductor of electricity, it was
not further examined.

Treatment with dilute hydrochloric acid and
subsequent recrystallisation from alcohol yielded the
crystalline p-chlormandelamidine hydrochloride
$Cl.C_6H_4.CHOH.C{<}^{NH}_{NH_2}$, HCl of m.p. 252° - 253° (decomp.)
Determination of ionisable chlorine:

.3360 gm. titrated with $AgNO_3$ ($N/10$) in the
presence of potassium chromate required 15.20 c.c.

$$Cl' = 16.04$$

$C_8H_{10}ON_2Cl_2$ requires $Cl' = 15.97$.

Other Amidine Salts.

Some compounds of this type have been described
by Eschweiler under the heading of 'iminohydrin salts',
but since much of the data furnished by this author
is inaccurate, and since moreover he was under a mis-
apprehension as to the structure of the compounds with
which he was dealing, it was thought desirable to re-
peat certain of the preparations.

Glycollamidine hydrochloride, $CH_2OH.C{<}^{NH}_{NH_2}$,HCl.

Eschweiler describes 'glycolliminohydrin' hydro-chloride[1], prepared by evaporation of a solution of the iminohydrin in an equivalent amount of dilute hydrochloric acid. The purified product is quoted as melting at $135°$ and having the formula $CH_2OH.C{<}^{NH}_{OH}$,HCl

Glycollamidine glycollate prepared by the inter-action of the free iminoether with water gave on evaporation with hydrochloric acid a crude product of m.p. $130° - 150°$. After repeated purification by solution in alcohol and precipitation with benzene the hydrochloride was obtained in the form of very fine needles, m.p. $150° - 151°$.

In larger quantities this salt was prepared from glycolliminoether hydrochloride and alcoholic ammonia, according to the general method recommended by Pinner[2]. After crystallisation from alcohol a product of the above melting-point was obtained.

Analysis:-

.2003 gm. was distilled with sodium hydroxide and the ammonia trapped in 25 cc. sulphuric acid (.2036 N). Titration of excess acid required 7.70 cc./

1. Chem. Zentr. 1898, II 527.
2. Pinner, Die Imidoäther.

7.70 cc. NaOH (.1934 N).

$$N = 25.17$$

$$C_2H_4ON_2Cl \text{ requires } N = 25.34.$$

.1037 gm. treated with 20 cc. $AgNO_3$ ($N/10$) required for titration 10.65 cc. thiocyanate ($N/10$)

$$Cl = 31.97$$

$$C_2H_4ON_2Cl \text{ requires } Cl = 32.08.$$

The salt is sparingly soluble in alcohol, and practically insoluble in benzene or ether. It is very soluble in water, and deliquesces in moist air.

Glycollamidine sulphate. $(CH_2OH.C{<}^{NH}_{NH_2})_2 H_2SO_4.$

The hydrochloride was treated with an equivalent of dilute sulphuric acid, and excess water evaporated on the steam-bath. Recrystallisation from aqueous alcohol gave the sulphate in the form of colourless leaflets, m.p. 205° (decomp.)

Eschweiler (loc. cit.) quotes m.p. 150° for 'glycolliminohydrin sulphate', prepared in a similar manner.
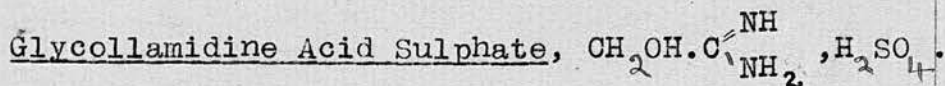
Analysis:

.2042 gm. gave .1900 gm. $BaSO_4$.

$$S = 12.78$$

$$C_4H_{14}O_6N_4S \text{ requires } S = 13.02.$$

The/

The salt is not deliquescent, is readily soluble
in water, and very sparingly soluble in absolute
alcohol.

Glycollamidine Acid Sulphate, $CH_2OH.C{<}{NH \atop NH_2}$, H_2SO_4 .

In order to ascertain if Eschweiler's sulphate
of m.p. 150° were the acid salt, some glycollamidine
hydrochloride was treated in aqueous solution with
exactly two equivalents of sulphuric acid, and taken
down to dryness in vacuo over caustic soda and sul-
phuric acid.   The product so obtained was quite free
from chloride, and, after an additional drying on
tile in vacuo, melted at 65° - 67°.

On recrystallisation from aqueous alcohol leaflets
were deposited of m.p. 150° - 175°, which proved on
analysis to contain over 90% of the normal sulphate.
Even from solvents containing a large excess of acid
the crystals deposited were mainly of the normal salt.

Glycollamidine Nitrate, $CH_2OH.C{<}{NH \atop NH_2}$, HNO_3 .
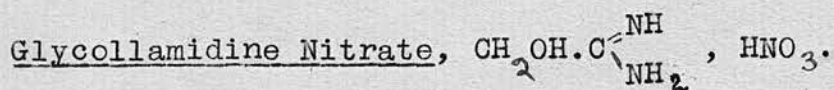
This substance was obtained by evaporating on
the steam-bath equivalent amounts of the hydrochloride
and aqueous nitric acid.   Recrystallisation from
aqueous alcohol gave the pure nitrate m.p. 110° - 111°.

Eschweiler quotes m.p. 95° for glycolliminohydrin
nitrate.

A/

A product of m.p. 110° - 111° was also obtained
from glycollamidine glycollate (iminohydrin) and
nitric acid.

Analysis:

.2330 gm. gave .1504 gm. CO_2 and .1074 gm.H_2O.

$$C = 17.58 \qquad H = 5.15$$

$C_2H_4O_4N_3$ requires $C = 17.52 \qquad H = 5.15$.

.1497 gm. gave 39.10 cc. dry N_2 at 747 mm.
and 10.5° C.

$$N = 30.88$$

$C_2H_4O_4N_3$ requires $\qquad\qquad N = 30.68$.

The salt is very soluble in water and practically
insoluble in absolute alcohol, benzene or ether.
From aqueous alcohol it is deposited in leaflets
which are stable in air.

Lactamidine sulphate $(CH_3 . CHOH . C\begin{smallmatrix}\nearrow NH \\ \searrow NH_2\end{smallmatrix})_2 H_2SO_4$
is correctly quoted by Eschweiler, under the heading
of 'lactiminohydrin sulphate', as having the melting-
point 198°. A specimen prepared from the 'imino-
hydrin' was found to melt at 200° - 202° (decomp.).
The hydrochloride and nitrate have already been
described by Pinner.

S U M M A R Y.

1. The iminohydrins or isoamides, formulated by Eschweiler as $R.C\underset{\diagdown OH}{\overset{\diagup NH}{}}$ and by Hantzsch as $R.C\underset{O - NH_2}{\overset{NH}{}} \quad \overset{HO}{\underset{}{}} C.R$, have been shown to be amidine salts of the general type $R.C\underset{NH_2}{\overset{NH}{}}$, R.COOH. This structure has been confirmed by the synthesis of the mandelic compound, and of Eschweiler's original 'glycolliminohydrin'.

2. It is suggested that the production of amidine salt by interaction between iminoether and water takes place mainly through the intermediate formation of the ammonium salt of the corresponding acid, which by subsequent reaction with free imino-ether gives rise to the amidine salt.

3. Certain inaccuracies of Eschweiler in refer-ence to iminohydrin (amidine) salts have been corrected.

In/

In conclusion I desire to express my thanks
to Professor Walker, at whose suggestion the above
piece of work was undertaken, for the interest he
has shown throughout its course.   I am also in-
debted to the Earl of Moray Research Fund for a
grant which has covered most of the expenses in
connection with this research.

                        Chemistry Department,
                            University of Edinburgh.