LXXVIII.—*Experiments on the Walden Inversion.*
Part IV. The Influence of the Solvent on the
Sign of the Product in the Conversion of Phenyl-
chloroacetic Acid to Phenylaminoacetic Acid
 —(continued).

By GEORGE SENTER and HARRY DUGALD KEITH DREW.

RATHER more than a year ago, a new chapter in the study of the Walden inversion was opened up by the discovery announced in our previous paper (T., 1915, **107**, 638) that optically active products of opposite sign may be obtained when the same reaction is carried out in different solvents. The particular reaction studied was the displacement of chlorine in ammonium phenylchloroacetate by the NH_2 group, as represented by the equation:

$\text{C}_6\text{H}_5\cdot\text{CHCl}\cdot\text{CO}_2\text{NH}_4 + 2\text{NH}_3 \rightarrow \text{C}_6\text{H}_5\cdot\text{CH}(\text{NH}_2)\cdot\text{CO}_2\text{NH}_4 + \text{NH}_4\text{Cl}$;
 the phenylaminoacetic acid isolated from aqueous solution had the opposite sign to the chloro-acid taken, whilst the amino-acid isolated from acetonitrile had the same sign as the original acid. In both cases considerable racemisation occurred.

The present paper contains an account of further work on this subject. The action of ammonia on the active phenylchloroacetates has been examined in twelve different solvents, with the result that in six cases phenylaminoacetic acid having the same sign of rotation as the original chloro-acid was obtained, whilst in the remaining six cases the sign of the amino-acid was opposite to that of the original acid. The table on p. 1092 contains a summary of the results for reactions at the ordinary temperature. In the first and second columns the solvent used and the sign of the initial chloro-acid are given; the third column gives the specific rotation of the first crop of the amino-acid, which formed the bulk of the product, and in the fourth column the sign of the product is compared with that of the original chloro-acid.

TABLE I.

Solvent.	Sign of chloro-acid taken.	Specific rotation of amino-acid formed.	Comparison of sign of product and chloro-acid.
Liquid ammonia.....	<i>l</i> -	-20°-90°	same sign
Water	<i>l</i> -	+83°	change of sign
CH ₃ ·OH	<i>d</i> -	<i>d</i> - (very small)	same sign
C ₂ H ₅ ·OH	<i>d</i> -	+24°	"
C ₃ H ₇ ·OH (<i>n</i>)	<i>d</i> -	+8°	"
C ₃ H ₇ ·OH (<i>iso</i>)	<i>d</i> -	+4°	"
C ₄ H ₉ ·OH (<i>n</i>)	<i>l</i> -	+3° (?)	change of sign
C ₇ H ₁₅ ·OH (<i>n</i>)	<i>d</i> -	-73°	"
C ₆ H ₅ ·CH ₂ ·OH	<i>l</i> -	+2°	"
C ₆ H ₅ ·CH ₂ ·CH ₂ ·OH...	<i>d</i> -	-16°	"
CH ₃ ·CN	<i>d</i> -	+6°	same sign
C ₆ H ₅ ·CN	<i>d</i> -	-4°	change of sign

Since the pure active acids have the rotations $[\alpha]_D^{20} \pm 157.8^\circ$ (Fischer and Weichhold, *Ber.*, 1908, **41**, 1285) it is clear that the main bulk of the product from solutions in aqueous ammonia, liquid ammonia, and *n*-heptyl alcohol contains about 50 per cent. of pure *d*- or *l*-acid. The average specific rotations of the products from all the solutions are rather greater than the numbers given in the table owing to the fact that the precipitated amino-acid has to be washed with water to free it from ammonium chloride, and the optically active amino-acids are more readily soluble in water than the racemic acid (Fischer and Weichhold, *loc. cit.*). Thus, although the value of $[\alpha]_D$ for the main bulk of product from acetonitrile is only +6°, it was shown in the previous paper that the specific rotation of the much smaller second crop was +127.5°.

In the former paper it was pointed out that whereas in aqueous solution racemisation was greater the higher the temperature, no increase of racemisation was observed in acetonitrile on altering the temperature of reaction from 18° to 52°. It has now been found that when benzyl alcohol and benzonitrile are used as solvents, racemisation is greater at 52° than at 18°. In the case of liquid ammonia, however, increase of temperature does not appear to increase the racemisation; in fact, a rather more active product was obtained at 25° than at 10° (p. 1105).

As the results obtained with liquid ammonia are of particular interest on account of the fact that relatively active products of opposite sign are obtained from this solvent and from aqueous ammonia, the reaction in these two solvents was more fully investigated. It is very remarkable that the activity of the product is greatly dependent on the original concentration of the chloro-acid in liquid ammonia; thus from a solution containing 0.25 gram of *l*-phenylchloroacetic acid in 1 c.c. of liquid ammonia the amino-acid obtained was quite inactive, whilst from a solution containing 0.016 gram of the chloro-acid per c.c. the value of $[\alpha]_D$ for the

amino-acid was -89° (p. 1104). On the other hand, alteration of the concentration of the chloro-acid in aqueous ammonia had very little effect on the activity of the resulting amino-acid.

In view of these results, the effect of ammonium chloride on the extent of racemisation, both in aqueous and liquid ammonia, and the effect of other salts on the racemisation in liquid ammonia, was examined. When the displacement in liquid ammonia was carried out in the presence of ammonium chloride (2 grams in about 14 c.c.) a practically inactive product was obtained, whereas under the same conditions, but in the absence of ammonium chloride, the value of $[\alpha]_D$ exceeded 70° . On the other hand, the previous addition of ammonium chloride to the solution in aqueous ammonia had no racemising effect; in fact, a slightly more active product was obtained in the presence of the salt (p. 1103). In liquid ammonia the addition of ammonium nitrate caused a very marked increase in racemisation; sodium nitrate in this solvent had also a considerable racemising effect, although less marked than the ammonium salt.

The above results show that the marked effect of concentration on the extent of racemisation in liquid ammonia is due, in part at least, to the racemising effect of ammonium chloride, one of the products of the reaction. It may be mentioned that a product of the same optical activity is obtained from liquid ammonia whether the solution is kept for six or thirty-six days before separating the amino-acid, so that the ammonium chloride formed in the course of the reaction has no racemising effect on the active amino-acid once the latter is formed.

As mandelic acid is one of the products of the action of aqueous ammonia on phenylchloroacetic acid, the effect of the previous addition of this compound on the nature of the product from liquid ammonia (which gives a product differing in sign from that obtained from aqueous ammonia) was examined. It was found, however, that the product had the same sign, and practically the same activity, as that obtained from a solution containing no mandelic acid.

A second product, in addition to the amino-acid, was isolated from certain of the solutions, more particularly from liquid ammonia. After the phenylaminoacetic acid (consisting of a mixture of *d*- and *r*-acid) had been separated from the solution obtained by the action of liquid ammonia on *d*-phenylchloroacetic acid, the residual aqueous solution (neutral to litmus) was found to be distinctly *lævorotatory*. When the solution was made slightly acid to Congo-red and allowed to remain for a day, a small amount of substance separated in short, transparent needles. It was shown

by analysis and from the behaviour of the product that it consisted of a mixture of *r*- and *l*-iminodiphenyldiacetic acid, $\text{CO}_2\text{H}\cdot\text{CHPh}\cdot\text{NH}\cdot\text{CHPh}\cdot\text{CO}_2\text{H}$, the racemic form of which was first prepared a few months ago by Schlezinger (*J. Russ. Phys. Chem. Soc.*, 1915, **47**, 1183) by an entirely different method. The new acid is formed according to the equation:

and is no doubt present in the solution as the ammonium salt. When aqueous ammonia, *n*-butyl alcohol, and *n*-heptyl alcohol were used as solvents, small quantities of the imino-acid were obtained, and in each case the product was opposite in sign to the chloro-acid taken. As these solvents were the only ones examined for the presence of the imino-acid, it is probably always formed in small amount when ammonia acts on phenylchloroacetic acid.

It is important to add that, as shown by a separate experiment, on evaporating an ammoniacal solution of *r*-amino- and *l*-imino-acids in the approximate proportion in which they are formed in the solutions examined, the amino-acid could be separated by the usual method and showed no activity, all the active imino-acid being present in the filtrate. It might at first sight appear that the possible formation of the imino-acid renders the results uncertain when the activity of the product is slight, but the result just described shows that an objection on this ground does not arise.

The properties of the imino-acid are described in a later section of the paper (p. 1106).

The general character of the results obtained with other solvents are sufficiently indicated by the summary in table I. Details regarding the nature of the product in each case are given in the experimental portion of the paper.

Discussion of Results.

The question at once arises as to whether the results just described can be interpreted by any of the theories of the Walden inversion hitherto put forward. The best known theories of this phenomenon are those proposed almost simultaneously by Fischer (*Annalen*, 1911, **381**, 123; 1912, **394**, 350) and by Werner (*Ber.*, 1911, **44**, 881). Taking as an example the action of liquid ammonia on ammonium α -bromopropionate, Fischer assumes the intermediate formation of an additive product from these two compounds by residual affinity; when the bromine separates in the ionised form the NH_2 group can either take the place of the latter, in which case there will be no change of configuration, or one of the other three groups may take the place vacated by that group, with the

result that inversion will have occurred. Werner's theory is somewhat similar, but rather more definite. According to the nature of the groups already present, the entering group may be attracted to one of the three faces of the tetrahedron (formed by the central carbon atom and the four associated groups) contiguous to the group, X, to be displaced, in which case no inversion occurs, or the entering group may be attracted to the face remote from X, in which case inversion will occur. According to Werner, the entering group is attracted by the central carbon atom, but, according to Fischer, the entering group is not necessarily attached to the carbon atom, but may be attached to one of the four substituents (compare Frankland, T., 1913, **103**, 721).

It will be seen that these theories are of very general character, and hitherto they have not proved of much value as guides in the study of the Walden inversion. For instance, the possible influence of the solvent in such processes is ignored both by Fischer and by Werner, and the results described in the present paper therefore form a very striking illustration of the inadequacy of the theories in question. In the course of a criticism of Fischer's theory, Biilmann (*Annalen*, 1912, **388**, 330) has pointed out the importance of elucidating the exact mechanism of the changes involved, and cites in this connexion the kinetic investigations of one of us (Senter, T., 1907, **91**, 460; 1909, **95**, 1827; 1910, **97**, 346; 1911, **99**, 95) on the mechanism of the displacement of halogens by other groups (compare also Gadamer, *J. pr. Chem.*, 1913, [ii], **87**, 312). It may be added that there appears to be considerable justification for Biilmann's criticism that Fischer's theory is little more than a description of the facts.

It is becoming more and more evident that a satisfactory explanation of the Walden inversion is not likely to be reached on the lines of the general theories of Fischer and of Werner, which carry us very little further, and that the valuable experimental results of Walden, Fischer, McKenzie, and others on the general character of the phenomena require to be supplemented by a more accurate study of the mechanism of the reactions involved. The present communication is intended as a further contribution to this aspect of the subject. As only very few reactions have so far been investigated from this point of view (compare Senter, *loc. cit.*; Holmberg, *Ber.*, 1912, **45**, 997; *J. pr. Chem.*, 1913, [ii], **87**, 456) it is premature to enter on a full discussion of the bearing of the results on the general interpretation of the phenomenon.

Coming now to the discussion of the results summarised in table I, it may be stated at once that some of these results are so remarkable and unexpected that no satisfactory explanation of them has

so far been found. Apart from water and liquid ammonia, eight alcohols and two nitriles were used as solvents, the choice of solvent being limited by the condition that the ammonium phenylchloroacetate should be completely soluble in the liquid used. The observations which more particularly require explanation are: (1) that whereas there is no change of sign with the four lower alcohols, a change of sign occurs when the reaction is carried out in *n*-butyl, *n*-heptyl, or benzyl alcohol and benzylcarbinol (β -phenylethyl alcohol); (2) that products of different sign are obtained from solvents normally so similar in behaviour as water and ethyl alcohol; (3) that products of different sign are obtained from aqueous ammonia and liquid ammonia; (4) that ammonium chloride has a markedly racemising effect in liquid ammonia, but not in aqueous ammonia.

Referring first to the results obtained with aqueous and with liquid ammonia, it may be noted that Fischer has incidentally investigated the displacement of halogen by the NH_2 group in aqueous and in liquid ammonia for three different compounds (*l*- α -bromopropionic acid $\rightarrow$ *l*-alanine and ethyl *l*- α -bromopropionate $\rightarrow$ *l*-alanine, *Ber.*, 1907, **40**, 491; *d*- α -bromoisovaleric acid $\rightarrow$ *l*-valine, Fischer and Scheibler, *Ber.*, 1908, **41**, 892), and in each case amino-acids of the same sign were obtained from the two solvents. It is probable that the different results obtained by Fischer and ourselves are connected with the fact that all the compounds examined by him belong to the aliphatic series, whereas we are concerned with an aromatic compound. So far as we are aware, no other aromatic compound has hitherto been examined from this point of view, but the displacement of halogen by the NH_2 group in phenylbromoacetic acid and β -phenyl- α -bromopropionic acid is now under investigation in this laboratory, and the question will be more fully discussed when the further data are available. At present it can only be suggested that the main reactions in aqueous and in liquid ammonia are different in character, and that this difference is conditioned in some way by the phenyl group. That the reactions in the two solvents are different in character is supported by the very different effect of ammonium chloride in the two cases.

The explanation of the results described might be attempted from two different points of view: (1) that in some solvents ammonia reacts mainly with the phenylchloroacetate ion and in others with non-ionised ammonium phenylchloroacetate, which might give rise to products of opposite sign; (2) that in some solvents free ammonia, in others combined ammonia (in association with the solvent), reacts with the phenylchloroacetate. At present the data are not sufficient to enable us to test the first suggestion adequately, and the second does not appear very promising. For instance, if the differ-

ence in sign of the products from aqueous and liquid ammonia is due to the fact that in the one case combined ammonia, in the other case free ammonia reacts, it is difficult to see why amino-acids of the same sign are obtained from these two solvents when active bromopropionic acid is used.

In water and the alcohols, besides the formation of amino-acids, simultaneous reactions occur, resulting in the formation of mandelic acid and alkyloxy-acids respectively, but there is no evidence that the formation of these products has any influence on the results.

The fact that acetonitrile and benzonitrile yield products of different sign is another illustration of the rule that in solvents of high molecular weight the product is usually formed with change of sign.

It has already been mentioned that whereas from *d*-phenylchloroacetic acid the *d*-amino-acid is obtained from liquid ammonia and the *l*-amino-acid from aqueous ammonia, the imino-acid isolated from both solvents is levorotatory. At first sight it might appear that this fact throws some light on the mechanism of formation of the imino-acid. If *d*-phenylchloroacetic acid reacts equally fast with the *d*- and *l*-amino-acids, according to the equation:

then it would clearly be impossible to obtain from the two solutions imino-acids of the same sign $\left(\begin{smallmatrix} d \\ l \end{smallmatrix} \right)$ or $\left(\begin{smallmatrix} l \\ d \end{smallmatrix} \right)$, since substitution does not

take place at the asymmetric carbon atom belonging to the amino-acid (but only at the NH_2 group, which remains attached throughout to the central carbon atom), and therefore no Walden inversion can occur at this part of the molecule, and the arrangement of the groups in the imino-acids from the two solutions must necessarily be different. The fact that imino-acids of the same sign are actually obtained would then show that their formation does not take place through the intermediate formation of amino-acid, but probably by simultaneous reaction between two chloro-acid molecules and ammonia. The assumption, however, that *d*-phenylchloroacetic acid reacts equally fast with the *d*- and *l*-amino-acids is almost certainly erroneous; in fact, the method of asymmetric synthesis introduced by Marckwald and McKenzie (*Ber.*, 1899, **32**, 2130) depends on the fact that in certain cases an optically active compound reacts at different rates with the *d*- and *l*-varieties of another compound. Marckwald and Meth (*Ber.*, 1905, **38**, 801), for example, have shown that *d*-mandelic acid is more quickly converted into amide by *l*-menthylamine than is *l*-mandelic acid. As in the present case both *d*- and *l*-amino-acids are always present owing to racemisa-

tion, the formation of excess of the same imino-acid in both solvents can be readily accounted for on similar lines.

EXPERIMENTAL.

Method of Experiment.

The method employed was to dissolve a weighed amount of the active chloro-acid in a measured volume of the solvent (usually 1 gram to about 15 c.c.); the solution was then saturated with dry ammonia, and left in a sealed tube for a definite period at the desired temperature.

In the case of ten out of the twelve solvents used, the bulk of the amino-acid was precipitated, together with a variable amount of ammonium chloride, as the reaction proceeded. The precipitate was collected, washed with ether to free it from traces of the solvent, and then treated with cold water until free from ammonium chloride. This gave a first crop of amino-acid. From the residual filtrate the excess of ammonia was expelled, and the solvent was removed as completely as possible (if necessary by distilling under diminished pressure), the residue was added to the washings from the first crop, and then excess of dilute hydrochloric acid was added. The resulting solution was extracted with ether to remove any unchanged chloro-acid and any non-basic acid formed during the reaction. The aqueous acid solution then contained the hydrochloride of any amino-acid which remained in the solvent after removal of the first crop. From this solution a small second crop of amino-acid was obtained by evaporating to dryness and neutralising the product with aqueous ammonia.

In the two cases (those of aqueous and liquid ammonia) in which no amino-acid was precipitated, the solvent was evaporated, the residue dissolved in dilute hydrochloric acid, the solution extracted with ether, and the amino-acid obtained as before.

The determinations of the rotation were carried out in all cases in 0.984*N*-hydrochloric acid. As the value of $[\alpha]$ depends to some extent on the concentration of the amino-acid, the value of c , in grams per 100 c.c., is given in each case. The observations were made at the ordinary temperature.

The nature of the product was established in all cases by determining the equivalent of the amino-acid, and in certain cases the results were checked by determinations of the proportion of nitrogen in the product. A convenient method of determining the equivalent is to convert the acid into the hydrochloride and note the increase in weight, the percentage of chlorine being then determined gravimetrically as a check. A weighed amount of the dried acid is dissolved in dilute hydrochloric acid, the water and excess of hydrochloric acid driven off by heating on a water-bath, and the

drying completed by heating for about an hour in the steam-oven. The drying must not be carried out at a temperature above 100°. As the method is very accurate, and the whole of the sample is taken for the experiment, a small amount of impurity in the amino-acid can readily be detected.

As an example, 0.1033 gram of the product from *n*-propyl alcohol gave 0.1284 gram of the hydrochloride (theory, 0.1283 gram), and the latter gave 0.0982 gram of silver chloride (theory 0.0980 gram). The products from the other solvents gave exactly comparable results, and it therefore appears unnecessary to quote them in detail.

Methyl Alcohol.

Preliminary experiments with *r*-phenylchloroacetic acid in this solvent showed that after seventy hours at 52° only about 2 per cent. of the chlorine is displaced by methyl alcohol alone, and that the presence of ammonia accelerates the displacement of the chlorine to a degree only partly accounted for by the formation of amino-acid. Thus in methyl alcohol saturated with ammonia 70 per cent. of the chlorine was displaced after forty-eight hours at 52° and 88 per cent. after one hundred and forty hours, although the proportion of amino-acid formed was less than 10 per cent. The probable explanation is that in the absence of ammonia the hydrochloric acid formed according to the equation:

retards the reaction to an even greater extent than in aqueous solution (compare Senter, T., 1915, **107**, 908).

Experiments were carried out at 15° and at 52° with solutions containing 1 gram of *d*-phenylchloroacetic acid in 15 c.c. of methyl alcohol saturated with ammonia. At the lower temperature the solution was kept for forty-two days. The first crop (0.08 gram) was inactive; from the aqueous filtrate a second crop (0.0074 gram) was obtained, which for $c=0.074$ gave for $[\alpha]_D$ the value +74°. The total yield of amino-acid was 10 per cent. The ethereal solution on evaporation gave a strongly dextrorotatory, oily mixture of acids (mainly phenylmethoxyacetic acid), which contained some unchanged chloro-acid.

The amino-acid obtained from the solution at 52° was quite inactive.

Ethyl Alcohol.

One gram of *d*-phenylchloroacetic acid in 20 c.c. of ethyl alcohol saturated with ammonia was kept for one hundred and twenty days at 15°.

The first crop (0.26 gram), $c=2.240$, had $[\alpha]_D +24^\circ$; the second crop (0.0175 gram), $c=0.175$, had $[\alpha]_D +95^\circ$. The total yield of

1100 SENTER AND DREW: EXPERIMENTS ON THE

amino-acid was 32 per cent. The higher yield of amino-acid, as compared with that from methyl alcohol, is doubtless due to the fact that ethyl alcohol reacts less rapidly with the chloro-acid than does methyl alcohol.

The ethereal solution left an oil which was strongly dextrorotatory and probably contained some unchanged chloro-acid.

n-Propyl Alcohol.

One gram of *d*-phenylchloroacetic acid in 20 c.c. of *n*-propyl alcohol was kept for one hundred and twenty-three days at 15°.

The first crop (0.15 gram), $c=1.449$, had $[\alpha]_D +8^\circ$; the second crop, which was very small, was also dextrorotatory. The yield of the amino-acid was 17 per cent.

The ethereal solution on evaporation left a semi-solid residue. After conversion of the unchanged chloro-acid to *r*-mandelic acid by treatment with boiling sodium hydroxide solution (McKenzie and Clough, T., 1908, **93**, 811), acidification with hydrochloric acid, and extraction with ether, a dextrorotatory product was obtained. It appears, therefore, that phenylpropoxyacetic acid is formed from *n*-propyl alcohol and active phenylchloroacetic acid without change of sign

isoPropyl Alcohol.

One gram of *d*-phenylchloroacetic acid in 20 c.c. of *iso*propyl alcohol saturated with ammonia was kept for one hundred and twenty-nine days at 15°.

The first crop (0.34 gram), $c=1.592$, had $[\alpha]_D +4.4^\circ$; the second crop, which was very small, was also dextrorotatory. The yield of amino-acid was 39 per cent. The formation of amino-acid took place much more rapidly than in *n*-propyl alcohol, and this doubtless accounts for the smaller yield of amino-acid under similar conditions in the latter solvent.

n-Butyl Alcohol.

Two experiments were made in this solvent, 1 gram of active phenylchloroacetic acid in 15 c.c. of the alcohol saturated with ammonia being kept for fifty-two and one hundred and ninety-two days respectively at 15°. In the first experiment, with the *l*-chloro-acid, the first crop (0.09 gram), $c=0.844$, had $[\alpha]_D +3^\circ$, and the second crop, which was very small in amount, was also dextrorotatory. In the second experiment, for which the *d*-chloro-acid was used, both the first crop (0.35 gram) and the aqueous washings were quite inactive. The alcoholic filtrate from the first crop on evaporation under diminished pressure left a small residue which was acidified with hydrochloric acid and extracted several

times with ether. The aqueous portion was evaporated to dryness and the residue treated with aqueous ammonia as usual, but only a trace of amino-acid was obtained. The neutral aqueous solution was made just acid with hydrochloric acid, and on keeping a small quantity of a compound, which was later shown to be iminodiphenyl-diacetic acid, separated in colourless needles. The value of $[\alpha]_D$ for this compound, $c=0.118$, was -140° .

There is therefore a little uncertainty as regards the sign of the amino-acid obtained from *n*-butyl alcohol, as it is possible, although not probable, that the slight activity of the product in the first experiment was due to a trace of imino-acid.

n-Heptyl Alcohol.

One gram of *d*-phenylchloroacetic acid in 15 c.c. of *n*-heptyl alcohol (b. p. $174-176^\circ$) was kept for eighty-one days at 15° .

The first crop (0.10 gram), $c=0.936$, had $[\alpha]_D -73^\circ$; the second crop (0.02 gram), $c=0.200$, had $[\alpha]_D -110^\circ$. The total yield of amino-acid was 10 per cent. It is probable that the reaction was not nearly complete.

The filtrate from the second crop yielded a small quantity (0.01 gram) of imino-acid, which gave for $[\alpha]_D$ the value -136° , $c=0.110$. The acid melted at about 202° (decomp.).

Benzyl Alcohol.

One gram of *l*-phenylchloroacetic acid in 15 c.c. of benzyl alcohol was kept for eighty-one days at 15° .

The first crop (0.27 gram), $c=2.506$, had $[\alpha]_D +2^\circ$; the second crop (0.08 gram), $c=0.078$, had $[\alpha]_D +38^\circ$. The total yield of amino-acid was 32 per cent.

A similar solution was kept for sixty-five hours at 52° . The first crop (0.3 gram) proved to be quite inactive.

Benzylcarbinol.

One gram of *d*-phenylchloroacetic acid in 15 c.c. of benzylcarbinol, b. p. 212° (saturated with ammonia), was kept for seventy-nine days at 15° .

The first crop (0.23 gram), $c=1.266$, had $[\alpha]_D -16^\circ$; the filtrate gave only an extremely small quantity of amino-acid.

Acetonitrile.

The results with this solvent were described in our former paper, and are quoted in table I for the sake of completeness.

The following observations of the rotation in acetonitrile were made, because it was thought possible that phenylchloroacetic acid might form a compound with acetonitrile or with an ammoniacal

1102 SENTER AND DREW: EXPERIMENTS ON THE

solution of this solvent, and that the presence of such a compound might be indicated by some abnormal effect on the specific rotation.

The specific rotation of *l*-phenylchloroacetic acid in acetonitrile has the following values for $c = 2.258$ gram in 100 c.c.:

$$[\alpha]_{\text{Hg green}} - 199^\circ, \quad [\alpha]_{\text{yellow}} - 172.5^\circ, \quad [\alpha]_{\text{D}} - 164,$$

as compared with those in benzene for $c = 3$ grams per 100 c.c.:

$$[\alpha]_{\text{Hg green}} - 222^\circ, \quad [\alpha]_{\text{Hg yellow}} - 193^\circ, \quad [\alpha]_{\text{D}} - 185.$$

On keeping for twenty-four hours the rotation of the acetonitrile solution was practically unchanged, $\alpha_{\text{Hg green}}$ being -8.98° for $l = 2$ dm., but about three minutes after passing dry ammonia into the solution $\alpha_{\text{Hg green}}$ had fallen to -8.60° and after seventy-two hours to -3.20° . There appears, therefore, to be no abnormal effect on the rotation which might indicate the formation of a compound with the solvent.

Benzonitrile.

One gram of *d*-phenylchloroacetic acid in 20 c.c. of benzonitrile was saturated with dry ammonia at 60° (because at lower temperatures the mixture formed a jelly) and kept for sixty-five hours at 52° . The amino-acid formed (0.34 gram) was quite inactive. Yield, 34 per cent.

A similar solution, also saturated with dry ammonia at 60° , formed a jelly on cooling. This was kept for one hundred and ninety-seven days, by which time the jelly had become opaque owing to the separation of a small quantity of precipitate. The amino-acid was separated in the usual way. The first crop (0.12 gram), $c = 1.085$, had $[\alpha]_{\text{D}} - 3.7^\circ$; the second crop (0.0114 gram), $c = 0.114$, had $[\alpha]_{\text{D}} - 70^\circ$. The total yield of amino-acid was 15 per cent. The reaction appears to proceed very slowly in the jelly.

Separate experiments showed that a jelly could be obtained by passing dry ammonia into a solution of an active phenylchloroacetic acid (1) in acetonitrile when the concentration of the acid is greater than about 0.1 gram per c.c., (2) in benzonitrile when the concentration of the acid is greater than about 0.05 gram per c.c., the initial temperature of the solution being about 20° . At concentrations below these, the solutions remain clear, whilst at higher concentrations ammonium phenylchloroacetate seems to be formed as a precipitate. It appears probable that the jelly is a mechanical mixture of very finely divided ammonium phenylchloroacetate and the nitrile, for, when spread on a porous tile, the jelly seems slowly to lose the nitrile and a white, crystalline deposit of the salt remains.

Aqueous Ammonia.

It was stated in the previous paper that when the reaction was carried out in aqueous ammonia, using *l*-phenylchloroacetic acid,

the first crop of amino-acid had for $[\alpha]_D$ the value $+83^\circ$ and the second crop the value $+135^\circ$. The effect of altering the concentrations of ammonia and of phenylchloroacetic acid respectively, and the influence of ammonium chloride on the reaction, have now been investigated.

Variation in Concentration of Chloro-acid.—In each case 0.35 gram of *l*-phenylchloroacetic acid was dissolved in varying quantities of aqueous ammonia (D 0.880; $\text{NH}_3=35$ per cent.), and the solutions kept for about twenty days at the ordinary temperature. The results were as follows:

Concentration of chloro-acid (grams per 100 c.c.)	0.21	4.1	11.7
$[\alpha]_D^{20}$ of amino-acid	$+67^\circ$	$+68^\circ$	$+71.5^\circ$

Hence an alteration in the concentration of the chloro-acid in aqueous ammonia appears to be almost without influence on the amount of racemisation in the formation of the amino-acid.

Variation in Concentration of Ammonia.—In this series of experiments the amount of *l*-phenylchloroacetic acid per unit volume of the solution was kept practically constant (0.5 gram in about 13 c.c. of solvent), but the relative proportions of water and ammonia were varied. The results were as follows:

Concentration per cent. of ammonia by weight	100	93.9	55.6	35
$[\alpha]_D$ of amino-acid	-74°	-61°	± 0	$+68$

As products of different sign are obtained from aqueous ammonia and liquid ammonia, there must necessarily be a solution, containing between 35 and 100 per cent. of ammonia, which gives an inactive amino-acid. As shown in the table, the solution with this property contains 55.6 per cent. of ammonia. The proportions of nitrogen in the amino-acids from 93.9 per cent. and 55.6 per cent. ammonia were determined. The former was found to contain 9.4 per cent. and the latter 9.35 per cent. (theory requires $N=9.3$ per cent.).

Effect of Ammonium Chloride.—Half a gram of *d*-phenylchloroacetic acid and 2 grams of ammonium chloride were dissolved in 12 c.c. of aqueous ammonia (35 per cent.) and the mixture kept for nineteen days at the ordinary temperature. The first crop of amino-acid (0.16 gram), $c=1.025$, had $[\alpha]_D -114.6^\circ$, whilst an exactly corresponding experiment, but without the ammonium chloride, gave an amino-acid with $[\alpha]_D +68^\circ$ for $c=0.661$. Although the ordinary temperature was rather higher in the latter case than in the former, the difference is much too great to be accounted for in this way, and it follows that there is less racemisation in the presence of ammonium chloride. From the solution to which ammonium chloride had been added a small quantity of imino-acid was isolated; it gave for $[\alpha]_D$ the value -158° , for $c=0.184$; m. p. (decomp.) $206-208^\circ$.

In a similar experiment in which the solution was kept for sixty-

five hours at 52°, the amino-acid formed was quite inactive, as was the acid formed under corresponding conditions in the absence of ammonium chloride.

Liquid Ammonia.

The experiments with this solvent were carried out as follows. A glass tube containing a weighed amount of the chloro-acid was immersed in a mixture of solid carbon dioxide and ether, and ammonia from a cylinder, after passing up a soda-lime tower, was led into the tube, where it condensed. The tube was then sealed and the temperature allowed to rise to that of the room. At low temperatures ammonium phenylchloroacetate was only partly soluble in liquid ammonia, but as the temperature rose, complete solution occurred. It was found that the reaction was practically complete in seven days at the ordinary temperature. The amino-acid was isolated in the usual way after the ammonia had evaporated. The effect of varying the concentration of the chloro-acid, and of the addition of various salts, was examined, and the influence of other variations of the experimental conditions on the nature of the product was investigated.

Variation in Concentration of Chloro-acid.—Solutions of the following amounts of *l*-phenylchloroacetic acid in definite volumes of liquid ammonia were left for seven days at the ordinary temperature and the amino-acid examined: 0.25 gram in 15 c.c.; $[\alpha]_D$ for first crop of 0.12 gram, $c=1.086$, was -89° ; 0.5 gram in 14 c.c., $[\alpha]_D$ for first crop (0.28 gram), $c=0.976$, was -77.4° ; 1 gram in 8 c.c., $[\alpha]_D$ for first crop (0.45 gram), $c=1.088$, was -19.7° ; 0.25 gram in 1 c.c., the amino-acid (0.11 gram), $c=1.048$, was quite inactive. The results are summarised in the accompanying table:

Concentration of chloro-acid (grams per 100 c.c.)	25	12.5	3.6	1.6
Specific rotation of first crop	± 0	-20	-77°	-89°

Effect of Ammonium Chloride and other Salts.—Half a gram of *l*-phenylchloro-acid and 2 grams of ammonium chloride were dissolved in liquid ammonia (12 c.c.) and the solution kept for seven days at the ordinary temperature. The amino-acid formed (0.30 gram) was inactive, whereas in the absence of ammonium chloride the value of $[\alpha]_D$ is about -77° . It is clear from this result that the increased racemisation with increased concentration of the chloro-acid is due, in part at least, to the racemising effect of the ammonium chloride formed in the course of the reaction.

From a solution containing 1 gram of ammonium nitrate in 8 c.c. of liquid ammonia the first crop of amino-acid was inactive, but the aqueous solution had the same sign as the original chloro-acid. From a similar solution, to which 0.12 gram of ammonium nitrate

had been added, the amino-acid gave for $[\alpha]_D + 64^\circ$, $c = 1.298$, whereas in the absence of the salt the specific rotation would have been about 79° .

The addition of sodium nitrate (1 gram) reduced the specific rotation of the first crop of amino-acid from about 79° to 12.4° . This salt has therefore a specific racemising effect, although much less marked than the corresponding ammonium salt. It may be mentioned that in this case sodium chloride gradually separated as the reaction proceeded.

The addition of mandelic acid (0.1 gram) to 8 c.c. of a solution in liquid ammonia resulted in the formation of an amino-acid with $[\alpha]_D + 69^\circ$ for $c = 1.094$, whereas in the absence of the acid the specific rotation would have been about 79° . The slight racemising effect is probably due to increased concentration of ammonium salt (ammonium mandelate), and not to a specific action of the mandelic group.

A solution of 0.25 gram of *d*-phenylchloroacetic acid in 7.5 c.c. of liquid ammonia, which had been kept for thirty-six days, gave a product of specific rotation $+79^\circ$, identical with that from a solution kept for seven days, so that the active amino-acid is stable once it is formed. From a similar solution which had been kept for only one day the amino-acid (0.03 gram) gave for $[\alpha]_D$ a value of 62.5° , $c = 0.280$, which is rather less than would have been anticipated.

The effect of alteration of temperature on the activity of the product was also examined. A solution of 0.25 gram of the *l*-acid in 7 c.c. of liquid ammonia was kept at 25° for seven days, and the first crop of amino-acid (0.11 gram) gave for $[\alpha]_D$ the value -88° , as compared with about -77° when the reaction took place at 12° . The temperature range is rather small, but the results show that, contrary to what occurs in aqueous ammonia, rise of temperature does not markedly influence the extent of racemisation in liquid ammonia.

The remarkable differences thus shown to exist between the reactions in aqueous and in liquid ammonia have been discussed in a previous section (p. 1096).

The proportion of nitrogen in several of the specimens of amino-acid obtained from solutions in liquid ammonia were examined. In all cases about 9.4 per cent. was found to be present (theory requires $N = 9.3$ per cent.).

Iminodiphenyldiacetic Acid.

The method by which a mixture of *r*- and *l*-iminodiphenyldiacetic acid was obtained from a solution formed by the action of liquid

1106 EXPERIMENTS ON THE WALDEN INVERSION. PART IV.

ammonia on *d*-phenylchloroacetic acid has already been briefly described (p. 1093). In order to obtain sufficient of the *i*-acid for examination, 4 grams of *r*-phenylchloroacetic acid were dissolved in 15 c.c. of liquid ammonia and the solution kept for seven days. More than 3 grams of amino-acid were separated in the usual way, and from the neutral filtrate about 0.3 gram of the required compound was precipitated by means of dilute hydrochloric acid. The compound is acid to litmus, sparingly soluble in water, soluble in aqueous ammonia and in a large excess of hydrochloric acid, and it dissolves readily in an aqueous solution of sodium carbonate, with evolution of carbon dioxide. The aqueous solution gives an intense bluish-green solution on adding a drop or two of a very dilute solution of copper sulphate, and a solid, greenish-blue copper salt was also obtained. After crystallisation from hot water the imino-acid melted and decomposed at 196–197°.

After drying in the steam-oven at about 90° for many hours 0.4170 gram of the acid gave 17.95 c.c. N₂ (moist) at 21° and 759 mm., N=4.89, as compared with 4.91 per cent. calculated for the anhydrous imino-acid. On keeping in moist air, however, the substance appears to take up a molecule of water. It was found that 0.1904 gram of the acid which had been exposed to moist air for some days weighed 0.1787 gram after heating at 110–130°, the calculated weight for one molecule of water eliminated being 0.1784 gram. The substance showed a faint yellow tinge, and on again leaving in moist air for a day the weight became 0.1857 gram. On now heating for an hour in the steam-oven the weight became once more 0.1789 gram.

From these results there appears to be no doubt that the substance is identical with the iminodiphenyldiacetic acid recently prepared by Schlezinger (*loc. cit.*) by hydrolysis of the nitrilo-ester, CN·CHPh·NH·CHPh·CO₂Et. According to Schlezinger, the acid was obtained as the monohydrate from hydrochloric acid solution in spherical aggregates of slender needles or opaque nodules; it became anhydrous on heating at 120°, and on heating in a sealed capillary tube decomposed in the neighbourhood of 199°. In other respects also its behaviour corresponds with that shown by the imino-acid described above.

In conclusion, we desire to thank the Government Grant Committee of the Royal Society for a grant, part of which has been used to defray the expenses of this investigation.

CHEMISTRY DEPARTMENT,
BIRKBECK COLLEGE,
LONDON, E.C.

[Received, October 4th, 1916.]