In a second experiment, the sodium salt of diethoxy-acetate, dissolved in methyl alcohol, was heated with dimethyl sulfate. The yield of ester, however, was less than that obtained by the former procedure, since it amounted to only 20% of the calculated value. The low yield here is accounted for by the fact that dimethyl sulfate was partially destroyed by the action of methyl alcohol with formation of dimethyl ether and methyl sulfuric acid. Baulin and Simon[1] showed that this is the case.

$$SO_2(OCH_3)_2 + CH_3OH \longrightarrow SO_2(OH)(OCH_3) + CH_3.O.CH_3.$$

It was shown that unaltered sodium salt of diethoxy-acetic acid was present in the aqueous solution in both of the above experiments. After extraction of methyl diethoxy-acetate with ether, barium hydroxide was added to remove sulfates. After the excess of barium had been removed as carbonate by saturating the solution with carbon dioxide, silver nitrate was added to precipitate the silver salt of diethoxy-acetate. This salt dried and subjected to the action of ethyl iodide in ether solution gave ethyl diethoxy-acetate.[2] From the aqueous solution which remained in Expt. 1 we recovered 15 g. of this ester and in Expt. 2, 25 g. These results show conclusively that only a part of the sodium salt of diethoxy-acetic acid interacted with dimethyl sulfate during esterification. Dimethyl sulfate does not interact with the copper salt of diethoxy-acetate.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS.]

A STUDY OF THE POSSIBLE ASYMMETRY OF THE ALIPHATIC DIAZO COMPOUNDS.[3]

BY C. S. MARVEL WITH W. A. NOYES.

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During the last 20 years a large number of papers on the electron theory of valence have appeared in the literature. Most of the papers are of a speculative nature and the applications of the theory have been developed farther than the experimental evidence seems to justify. For some time one of us has been attempting to isolate some of the isomers which, according to this theory, should logically exist and, in that way, to obtain evidence to substantiate the theory.

A study of the aliphatic diazo compounds has been undertaken, since in these compounds, according to the structure usually accepted, 2 nitrogen atoms are combined with one carbon atom. The method of preparation of this class of compounds is such that one of the nitrogen atoms comes

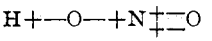
[1] Baulin and Simon, *Compt. rend.*, 170, 392 (1920).

[2] Johnson and Cretcher, *J. Biol. Chem.*, 26, 99 (1916).

[3] An abstract of a thesis submitted by C. S. Marvel in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the University of Illinois.

from ammonia, while the other comes from nitrous acid. These compounds have the following electronic formulas

Ammonia.



Nitrous Acid.

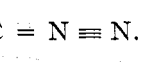
The electronic formula for an aliphatic diazo compound could then be written R — C — R′. It is readily seen that such a molecule would be

asymmetric and optical isomers would be expected to exist.

The aliphatic diazo compounds were discovered by Curtius.[1] Diazoacetic ethyl ester, $N_2CHCOOC_2H_5$, the first of the series to be prepared, was obtained by the action of nitrous acid on glycocoll ester hydrochloride. The reaction has been extended to cover other α-amino esters and also similar compounds, as α-amino cyanides, α-amino ketones, and α-amino imides.

Curtius[2] assigned to the diazo compounds the structure R — C — R′,

after a thorough study of their reactions. This structure was accepted for about 20 years until Angeli[3] suggested that the structure might be



. After Staudinger[4] showed that the diazo compounds could be obtained by the oxidation of hydrazones, Thiele[5] again brought forward the open-chain structure as more logical for these compounds. Hantzsch[6] from a study of the absorption spectra of diazomethane supported the Curtius structure. Darapsky and Prabhakar[7] studied the reduction of diazoacetic ethyl ester and from their results concluded that the Thiele-Angeli structure was correct. Forster and Cardwell[8] studied the action of the Grignard reagent on diazo compounds and stated that their results could best be explained on the Thiele-Angeli structure. Staudinger[9] with his co-workers carried out a very thorough investigation of the reactions of the aliphatic diazo compounds. He attempted without success to isolate isomeric diazo compounds one of which he expected to

[1] Curtius, *Ber.*, **16**, 2230 (1883).
[2] Curtius, *J. prakt. Chem.*, [2] **38**, 394 (1888).
[3] Angeli, *Atti accad. Lincei*, **16**, II, 790 (1907); **20**, I, 626 foot note (1911).
[4] Staudinger, *Ber.*, **44**, 2198 (1911).
[5] Thiele, *ibid.*, **44**, 2522 (1911).
[6] Hantzsch, *ibid.*, **45**, 3022 (1912).
[7] Darapsky and Prabhakar, *ibid.*, **45**, 1657 (1912).
[8] Forster and Cardwell, *J. Chem. Soc.*, **103**, 867 (1913).
[9] Staudinger, *Ber.*, **49**, 1884–1974 (1916).

have the Curtius formula and the other the Thiele-Angeli formula. Recently Langmuir[1] has assigned to diazomethane an open chain structure based on Lewis' octet theory.

From the above it would seem that the true structure of the aliphatic diazo compounds is not definitely determined. The reactions which they undergo can be explained equally well by means of either the Curtius or the Thiele-Angeli formula. The formula originally proposed by Curtius is perhaps more generally accepted.

Levene[2] has suggested the possibility of electromers in aliphatic diazo compounds. He has presented as evidence for their existence, the conversion of certain hexosaminic acids into the corresponding anhydrosugar acids without racemization of the carbon atom bearing the amino group. In a previous paper[3] it had been shown that the benzal derivative of the ethyl ester of one of the hexosaminic acids gave a diazo compound on treatment with nitrous acid. This fact has apparently been considered as evidence that in replacement of an aliphatic amino group by an hydroxyl group the diazo compound is an intermediate product. Walden,[4] Fischer,[5] and others had shown previously that almost any optically active amino acid gave an active hydroxy acid on treatment with nitrous acid. However, no one has ever been able to obtain a diazo compound from an α-amino acid although such compounds can be obtained in a more or less pure condition from almost any of the α-amino esters. These facts make it appear doubtful that the diazo compound is an intermediate in the replacement of an amino group by a hydroxyl group when the free amino acid is treated with nitrous acid.

Another objection may be made against Levene's evidence for the existence of electromers in the aliphatic diazo series. The hexosaminic acids contain 4 asymmetric carbon atoms. Even if one of these carbon atoms does pass through a symmetrical structure in the replacement of the amino group, the final product would probably consist mainly of one of the 2 possible isomeric hydroxy acids, on account of the influence of the 3 other asymmetric carbon atoms present in the molecule.[6]

There are 3 general methods available for the preparation of aliphatic diazo compounds: (1) the method of Curtius,[7] by the action of nitrous acid on α-amino esters; (2) the method of v. Pechmann[8] by the decom-

[1] Langmuir, THIS JOURNAL, **41**, 1546 (1919).
[2] Levene, *J. Biol. Chem.*, **36**, 89 (1918).
[3] *Ibid.*, **21**, 348 (1915).
[4] Walden, *ibid.*, **28**, 2772 (1895).
[5] Fischer, *ibid.*, **41**, 2897 (1908); **45**, 2448 (1912).
[6] Fischer, *Ann.*, **270**, 64 (1892).
[7] Curtius, *Ber.*, **16**, 2230 (1883).
[8] von Pechmann, *ibid.*, **27**, 1889 (1894); **28**, 855 (1895).

position of nitroso-imides with alkali; and (3) the method of Staudinger[1] by the oxidation of hydrazones with mercuric oxide.

The method of Staudinger is not applicable to the production of an optically active diazo compound since the hydrazones are symmetrical in structure. The method of v. Pechmann could not be used on account of the difficulties met in attempting to prepare the necessary nitroso-imides.

The diazo compounds studied were prepared by Curtius' method. The purification of the impure diazo compounds offered considerable difficulty. Curtius recommends steam distillation of small quantities as the best method of purification, although this method destroys a large part of the diazo compound. In working with ethyl α-diazo-caproate, $CH_3CH_2CH_2CH_2CN_2COOC_2H_5$, it was found that no purification was obtained by steam distillation and that approximately $^2/_3$ of the diazo compound was destroyed. This ester was found to be easily purified by vacuum distillation of the impure ester and yields as high as 30% of the calculated amount were obtained. Diazo esters were prepared from phenylamino-acetic acid, and α-amino-caprylic acid. These could not be obtained pure by vacuum distillation since on distillation they decomposed into the corresponding hydroxy esters. This result agrees with Curtius' earlier work with the diazo ester from phenylalanine.[2]

After having established the best method for obtaining the pure diazo ester from optically inactive amino-caproic acid, samples of ester were prepared from the *d*- and *l*-isomers. These samples were found to be inactive when examined in the polariscope. Since the difference between a positive and a negative nitrogen atom might not cause rotation the diazo esters were hydrolyzed with dil. sulfuric acid. If the diazo esters were asymmetric, on hydrolysis the positive nitrogen should have been replaced by a hydrogen atom and the negative nitrogen by an hydroxyl group. However, the products obtained on hydrolysis of the samples of ester from the active amino acid were found to be inactive.

In order to show that the hydrolysis with dilute acids actually produced an hydroxy ester from ethyl α-diazo-caproate, a larger sample was treated for some time with dil. acetic acid. The products obtained consisted of approximately equal parts of ethyl α-hydroxy-caproate, $CH_3CH_2CH_2CH_2CHOHCOOC_2H_5$, and ethyl Δ^1-hexenoate, $CH_3CH_2CH_2$-$CH : CHCOOC_2H_5$. The result was unexpected, since text-books usually state that dilute acids decompose diazo esters quantitatively to the corresponding hydroxy esters. The acetic acid used was so dilute (10%) that it hardly seems probable that it could dehydrate the hydroxy ester after it had been formed. Curtius[3] has obtained fumaric ester from diazo-

[1] Staudinger, *Ber.*, **44**, 2198 (1911).

[2] Curtius, *ibid.*, **37**, 1270 (1904).

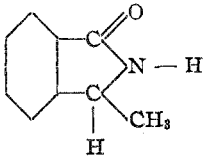
[3] Curtius, *J. prakt. Chem.*, [2] **38**, 477 (1888).

succinic ester by boiling it with water. This would be expected, as it is fairly easy to dehydrate malic ester, which may be regarded as a β-hydroxy ester.

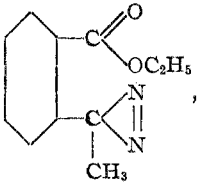
The fact that inactive diazo compounds were obtained by the treatment of active amino esters with nitrous acid may be explained in 3 ways: (1) the 2 nitrogen atoms may be alike; (2) the nitrogen atoms may be different but the compounds racemize during the reactions; or (3) the Curtius formula may not be the correct expression for the structure of the diazo compounds. There is, however, a possibility of asymmetry even in the Thiele-Angeli formula, as the structure may be $\begin{matrix} R \\ R' \end{matrix}\!\!>\!C\overset{+}{-}\overset{-}{N}\equiv N$. It is impossible to say which of these explanations is correct.

Curtius[1] prepared crystalline diazo compounds from the ester hydrochlorides of glycylglycine, diglycylglycine, and triglycylglycine by treatment with nitrous acid in the presence of sodium acetate. These diazo compounds were high-melting substances and quite stable. The reaction does not seem general for dipeptide esters, since it was found in this investigation that the ester hydrochloride of α-amino-*n*-caproylglycine on treatment with nitrous acid did not give a stable diazo compound but the hydroxy ester was isolated.

On account of the difficulty of obtaining pure diazo compounds by the Curtius method of preparation, it was decided to try out v. Pechmann's method or a modification of it as applied by Oppe[2] to the preparation of *o*-carboxyethyl-phenyl-diazomethane. Methyl phthalimidine



was prepared according to Gabriel's method.[3] The nitroso derivative was easily formed by treatment with nitrous acid in water solution. The diazo compound,



was obtained as a red, oily product but was never obtained pure. No

[1] Curtius, *Ber.*, **37**, 1295 (1904); **39**, 1373, 1379 (1906).
[2] Oppe, *ibid.*, **46**, 1095 (1913).
[3] Gabriel, *ibid.*, **26**, 706 (1893).

further work was carried out on this compound since it was not possible to obtain crystalline salts of methyl phthalimidine to be used for its resolution into *d*- and *l*-forms.

An unsuccessful attempt was made to prepare nitroso *secondary*-butylurethane to use for the preparation of methylethyl-diazomethane by v. Pechmann's method.

The only evidence, which may be considered as pointing to the existence of asymmetric diazo compounds, was obtained by treatment of the optically active amino ester hydrochlorides with nitrous acid under special conditions which favored the production of hydroxy esters. The hydroxy esters obtained had a small rotation showing that the racemization was not complete. In carrying out these reactions the yellow color of the diazo compound was noticed indicating that it was formed as an intermediate product. The evidence, however, is not at all conclusive, since there is no evidence that the reaction must go entirely through the diazo stage.

In the attempt to obtain certain of the diazo compounds several new compounds were prepared and the methods of preparation of some known compounds were improved. These methods have been included in this paper.

EXPERIMENTAL.

1. Derivatives of Phenylamino-acetic Acid.

Phenylamino-acetic Acid.—The method used was similar to that described by Zelinsky and Stadinoff[1] but was slightly changed to make it applicable to the production of larger amounts of material.

One hundred g. of sodium cyanide was dissolved in 400 cc. of water and to this solution 106 g. of ammonium chloride was added. When all had dissolved there was added a solution of 212 g. of benzaldehyde in 400 cc. of methyl alcohol. The mixture was shaken thoroughly and then allowed to stand for 1 to $1^1/_2$ hours. The reaction began very quickly and the flask became quite warm. After the reaction was completed, a liter of water was added to throw the oily amino cyanide out of solution. This was collected in a liter of benzene, and the benzene solution was separated and washed thoroughly with water. The benzene also extracted some unchanged benzaldehyde and some condensation products.

The amino cyanide was extracted from the benzene solution by shaking it twice with 600 cc. of hydrochloric acid (1 volume of hydrochloric acid, sp. gr. 1.19, to one volume of water). To hydrolyze the amino cyanide, the hydrochloric acid solution was refluxed for 2 hours. The solution was cooled and filtered from some tarry material and the free amino acid precipitated with ammonium hydroxide. The amino acid was filtered off with suction, washed with water and alcohol to remove the color and

[1] Zelinsky and Stadinoff, *Ber.*, **39**, 1725 (1906).

dried. The yield varied from 105 to 110 g. (34–36% of the calculated amount).

A purer product was obtained by recrystallizing from hot water. This was rather tedious on account of the limited solubility of the amino acid in hot water. Larger runs were made with practically the same percentage yields. Longer standing of the first solution did not increase the yield. The yield was not improved by longer hydrolysis.

dl-**Ethyl Phenylamino-acetate.**—This ester has previously been prepared by Kossel.[1]

Two hundred g. of phenylamino-acetic acid was suspended in one liter of absolute alcohol and 70 to 80 g. of hydrogen chloride was passed in. The acid dissolved completely. The solution was refluxed on the water-bath for 3 hours and then the alcohol was distilled under reduced pressure. The residue was dissolved in a little water, the solution covered with benzene and the free ester liberated with ammonium hydroxide. The benzene layer was separated, dried over anhydrous sodium sulfate and distilled. After the benzene was removed, the amino ester was distilled under reduced pressure. The yield varied from 142 to 153 g. (60 to 65% of the calculated amount) in different runs. The product boiled at 114–115° at 5 mm.; n_D at 25° is 1.500.

To obtain pure ester hydrochloride, the free ester was dissolved in 5 volumes of dry benzene and dry hydrogen chloride was passed into the solution. The product was filtered with suction and dried in a vacuum desiccator over solid sodium hydroxide. The yield was practically theoretical. M. p. 200°.

Acetyl *dl*-**Ethyl Phenylamino-acetate.**—Ten cc. of acetic anhydride was added to 11.5 g. of the free ester in a small flask. The solution was allowed to stand for about 2 hours and was then heated for one hour on the water-bath. The excess of acetic anhydride was destroyed with alcohol and the reaction mixture warmed to drive off the ethyl acetate and acetic acid. An oily product was left which crystallized when treated with ligroin and stirred. The crystals were filtered off and dried on a clay plate. The yield was 11 g., m. p. 65–66°.

Subs., 0.3961: 21.9 cc. N at 23° and 748.5 mm.
Calc. for $C_{12}H_{15}O_2N$: N, 6.33. Found: 6.30.

Carbethoxy *dl*-**Ethyl Phenylamino-acetate.**—Eighteen g. (2 mols.) of the free amino ester was dissolved in 50 cc. of dry ether, and 5.5 g. (one mol) of ethyl chlorocarbonate was slowly added. After one hour the ester hydrochloride was filtered off with suction (11 g. was obtained) and the benzene evaporated. The residue was crystallized from ligroin. The yield was 7 g. M. p. 57°.

[1] Kossel, *Ber.*, **24**, 4145 (1891).

Subs., 0.4233: 21.9 cc. N at 25° and 740 mm.
Calc. for $C_{13}H_{17}O_4N$: N, 5.58. Found: 5.80.

Acetyl ethyl phenylamino-acetate and carbethoxy ethyl phenylamino-acetate did not yield nitroso compounds when treated with nitrous oxides in dry ether, with sodium nitrite in glacial acetic acid solution, or with sodium nitrite in hydrochloric acid solution.

Attempts to Prepare Ethyl Phenyl-diazoacetate.—Curtius[1] and Kossel[2] have tried without success to prepare this diazo compound. By using essentially the same method that Curtius employed we have obtained 0.1 g. of diazo ester (12.3% N; calculated 14.7%) from 46 g. of ethyl phenylamino-acetate hydrochloride. By the use of Kossel's method a crude diazo ester was obtained by the action of silver nitrite on ethyl phenylamino-acetate in dry ether. The product could not be purified. Neither of these methods is of any practical use for preparing this compound. By the action of sodium nitrite and acetic acid on ethyl phenylamino-acetate hydrochloride in sodium acetate solution, the impure diazo ester may be prepared in fairly good yields. The details of this preparation are identical with those given later for the preparation of ethyl diazocaproate. However, on attempting to distil the impure ethyl diazophenylacetate it decomposed giving ethyl mandelate which was identified by its boiling-point and its melting-point.

Resolution of Phenylamino-acetic Acid.—This amino acid has been resolved by Betti and Mayer[3] by means of *d*-camphor-sulfonic acid. This method is easy to carry out and a pure *l*-acid is easy to obtain. The *d*-acid is obtained in purity of about 90–95%.

One hundred and fifty-one g. of phenylamino-acetic acid and 232 g. of *d*-camphor-sulfonic acid (Reychler) were dissolved in 750 cc. of boiling water. The solution was allowed to cool overnight. The first crop of crystals was filtered with suction. The yield of *l*-salt was 153–167 g. and the specific rotation was —37° to —40°. The pure *l*-salt has a rotation of —44°. By concentrating the mother liquors to $^1/_2$ volume, a second crop of crystals weighing 10–20 g. was obtained. The specific rotation was —25° to —26°. The mother liquors were saved for the preparation of the *d*-amino acid.

The first crop of crystals was recrystallized from 500 cc. of boiling water. The yield of pure *l*-salt was 107–114 g. (54–58%) with specific rotation of —43.5° to —44°. The yield may be increased somewhat by working up the mother liquors.

From the original mother liquor after filtering off the second crop of *l*-salt the *d*-amino acid was obtained by adding a slight excess of ammonium

[1] Curtius, *Ber.*, **37**, 1266 (1904).
[2] Kossel, *ibid.*, **24**, 4155 (1891).
[3] Betti and Mayer, *ibid.*, **41**, 2071 (1908).

hydroxide. Sixty-five to 70 g. of the *d*-acid (with rotation of +127° to +146° was obtained from 151 g. of inactive acid.

The *l*-acid was prepared by dissolving the *l*-salt in hot water and adding the theoretical quantity of sodium hydroxide. From 206 g. of *l*-salt, 80 g. of pure *l*-acid were obtained.

l-**Ethyl Phenylamino-acetate Hydrochloride.**—The *l*-ester hydrochloride was prepared according to the directions used in preparing the inactive ester. The free ester was not distilled, as distillation of one run caused racemization. The pure ester hydrochloride is obtained by drying the benzene solution of the free ester thoroughly and then passing in dry hydrogen chloride. From 81 g. of *l*-acid there was obtained 83 g. *l*-ester hydrochloride with specific rotation of —84.6°. Fischer and Weichbold[1] give the rotation as —88.95°. It seems probable that their ester hydrochloride was less pure and contained some of the amino acid hydrochloride, since they took no precautions to remove this impurity.

Acetyl *l*-**Ethyl Phenylamino-acetate.**—4.3 g. of *l*-ester hydrochloride was dissolved in 10 cc. of water. The free ester was liberated with ammonium hydroxide and taken up in benzene. The benzene solution was dried and treated with 2.5 g. of acetic anhydride. The reaction mixture was refluxed for 1 to 2 hours, the benzene and excess acetic anhydride distilled off and the residue crystallized from ligroin. Only about one g. of product was obtained. M. p. 69–70°.

Subs., 0.3965 in 19.3006 g. abs. alcohol gave rotation of —4.37° in a 2-dcm. tube for sodium light. $[\alpha]_D = -138.7°$.

Attempts to Prepare an Optically Active Diazo Compound from the *l*-**ester Hydrochloride.**—*A. Curtius Method.*—21.5 g. of the *l*-ester hydrochloride was diazotized as described under the inactive compound. The crude ether solution after concentration to 20 cc. gave a rotation of —1° in a 2-dcm. tube. After steam distillation twice the oil was taken up in ether and the rotation observed was —0.1°. There was only 0.0087 g. material obtained on evaporating the ether and this was too small an amount to analyze. Other runs were made with less favorable results.

B. Kossel Method.—Ten g. of the *l*-ester hydrochloride was treated in dry ether with 8 g. of silver nitrite. After 10 days the solution was filtered from the silver chloride. On concentrating the ether about 2 g. of the nitrite of the ester was obtained. After filtering off the solid ester nitrite the ether solution was washed thoroughly with cold water to remove any of the ester nitrite which had remained in solution. The ether solution was then dried and made up to 25 cc. The solution had a deep yellow color. In a 2-dcm. tube the rotation was —4.21°.

Five cc. of this ether solution was titrated with iodine solution. 3.5

[1] Fischer and Weichbold, *Ber.*, 41, 1292 (1908).

cc. of 0.1 *N* iodine solution was used up, showing that the 5 cc. of solution contained 0.033 g. of diazo ester.

Fifteen cc. of the ether solution was shaken up with 20% sulfuric acid until the yellow color was destroyed, the ether dried over sodium sulfate, and the solution again made up to 15 cc. In a 2-dcm. tube the rotation was —0.96°.

This experiment may indicate the existence of an optically active diazo ester which on hydrolysis gives an active hydroxy ester. It has been found, however, that 20% sulfuric acid will cause racemization of active ethyl mandelate. This is shown by the following experiment.

l-Ethyl mandelate was prepared as described in the following experiment. The rotation of a sample was taken in a one-dcm. tube and found to be —2.02°. The ester was then shaken with 20% sulfuric acid for 15 minutes, taken up in ether, dried, and after the ether had been removed, again examined in the polariscope. The rotation in a one-dcm. tube was only —1.6°.

This evidence makes it seem probable that the rotation observed in the diazo ester solution was due to the presence of *l*-ethyl mandelate and that the treatment with sulfuric acid caused racemization of this ester.

Attempts to Prepare *l*-Ethyl Mandelate.—Fischer and Weichbold[1] have found that treatment of *d*-ethyl phenylamino-acetate in dil. sulfuric acid solutions with sodium nitrite gave ethyl mandelate with slightly negative rotation.

21.5 g. of the *l*-ester hydrochloride was dissolved in 130 cc. of *N* sulfuric acid and the solution cooled to 0°. A solution of 6.4 g. of sodium nitrite in 10 cc. of water was added slowly and with stirring. A yellow oil soon began to separate from the solution. After all of the nitrite was added, the solution was kept at 0° for one hour and then gradually allowed to warm up to room temperature. After about 2 hours the evolution of gas had stopped and the oily layer was collected in ether, the ether solution dried and distilled under reduced pressure. 7.5 g. of mandelic ester boiling at 130–135° at 13 mm. was obtained. The rotation was taken in a one-dcm. tube and was found to be —5.25°. The ester was then crystallized from petroleum ether, and was found to melt at about 30°.

The result confirms the previous work in that most of the ester was racemized. In this experiment, however, the mandelic ester obtained rotates in the same direction as the amino ester from which it was prepared.

Action of Acetic Anhydride on the Nitrite of *l*-Ethyl Phenylamino-acetate.—1.6 g. of the *l*-ester nitrite obtained by the action of silver nitrite on an *l*-ester hydrochloride in dry ether[2] was dissolved in 20 cc. of dry ether and treated with 2 g. of acetic anhydride. The solution warmed

[1] Fischer and Weichbold, *Ber.*, 41, 1294 (1908).

[2] Kossel, *ibid.*, 24, 4155 (1891).

up slightly. After 2 days the solution was concentrated under reduced pressure over solid sodium hydroxide. After several days crystals separated. These were dried on a clay plate. They melted at 68–70°. A mixed melting-point with the acetyl derivative of *l*-ethyl phenylaminoacetate showed that the 2 compounds were identical.

2. Derivatives of Methyl Phthalimidine.

Methyl Phthalimidine.—The compound was prepared according to Gabriel's directions through phthalyl-acetic acid. Phthalyl-acetic acid[1] was obtained in 48% yield when the directions in the literature were followed. When this compound is treated with alkali and then with acid and hydrazine sulfate methyl phthalazone was obtained in 67% yields.[2] Gabriel's directions for the reduction of methyl phthalazone[3] are not very definite and the directions used for this step are given here.

Eighty g. of methyl phthalazone was dissolved in 400 cc. of hydrochloric acid (sp. gr. 1.19). To this solution 150 g. of granulated zinc was added in portions. After about 2 hours the zinc had dissolved and the solution was treated with an excess of sodium hydroxide solution. The methyl phthalimidine was obtained by extracting this solution 15 to 20 times with 100-cc. portions of ether. The methyl phthalimidine is not very soluble in ether and therefore the extraction is slow.

After evaporating the ether 30 g. of crude methyl phthalimidine was obtained. The product was purified by vacuum distillation. The yield was 25 g. The substance boiled at 180° at 10 mm. and melted at 100°. The material crystallizes very slowly. It oxidizes in the air to give a reddish colored substance.

Nitroso Methyl Phthalimidine.—Twenty g. of methyl phthalimidine was dissolved in 200 cc. of hydrochloric acid (one volume of acid of sp. gr. 1.19 to one volume of water) and the solution cooled to 0°. While the solution was cooled 10 g. of sodium nitrite in 20 cc. of water was added slowly. The nitroso compound first separated as an oil but soon solidified. After one hour the crystals were filtered off and recrystallized from 50% alcohol, with a yield of 20 g. (83% of the calculated amount).

For analysis the product was again recrystallized from 50% alcohol. The purified product melts at 86.5–87°.

Subs., 0.1104: 16 cc. N at 744 mm. and 26°.
Calc. for $C_9H_8O_2N$: N, 15.9. Found: 16.2.

Attempt to Prepare *o*-Carboxethyl Phenyl Methyl Diazomethane.—3.5 g. of nitroso methyl phthalimidine was dissolved in 300 cc. of dry ether. The solution was cooled to —10° and a solution of one g. of sodium in 10 cc. of absolute alcohol was added in portions. After about

[1] Gabriel, *Ber.*, **26**, 952 (1893).
[2] *Ibid.*, **26**, 706 (1893).
[3] *Loc. cit.*

1/2 hour carbon dioxide was passed into the solution to react with the sodium ethylate. The ether solution became deep red in color. The sodium carbonate was filtered off and washed with dry ether, and the ether was removed under reduced pressure. A reddish oil remained. On standing for sometime this oil gradually changed to a yellow solid which melted at 195–200°. This was recrystallized from alcohol and melted at 220°. The amount obtained was too small for satisfactory analysis.

Attempts to Resolve Methyl Phthalimidine.—The resolution was attempted with *d*-camphor-sulfonic acid and *d*-bromocamphor-sulfonic acid. Neither of these acids gave a crystalline salt with the base. The methyl phthalimidine was then boiled with a solution of sodium hydroxide the excess of sodium hydroxide was neutralized with nitric acid and the *o*-α-aminoethyl-benzoic acid precipitated as the silver salt. The silver salt was boiled with ethyl iodide in dry ether, the silver iodide removed and the ether evaporated. An oily substance was obtained. Its properties corresponded to those of an amino ester. It did not give crystalline salts with *d*-camphor-sulfonic acid or *d*-bromocamphor-sulfonic acid.

Since it was not possible to resolve the methyl phthalimidine, the work on this series was abandoned.

3. Derivatives of α-Amino-*n*-caproic Acid.

The amino acid was prepared from the bromo acid according to the method described in the literature.[1] The amino acid was resolved through the formyl derivative.[2] α-Amino-*n*-caproic ethyl ester was prepared according to the method of Fischer.[3] Thirty g. of amino acid gave 29 g. of ester, boiling at 82–83° at 9 mm. The ester hydrochloride was prepared from this by dissolving the ester in dry ether and passing hydrogen chloride into the solution. The yield was 33 g.

Ethyl α-Diazo-*n*-caproate.—Fifty g. of the ester hydrochloride (free from excess of hydrochloric acid) was dissolved in 150 cc. of water, and the solution was cooled to —10°. To this solution 60 g. sodium acetate and 60 g. sodium nitrite were added. Then, during one hour, 75 cc. of glacial acetic acid was added. Very little evolution of nitrogen occurred. The solution was kept at —5° to —10° for 3 1/2 hours. The ether became deeply colored, due to the formation of the diazo ester.

After the reaction was practically complete, the ether layer was separated, washed 2 or 3 times with water, 2 or 3 times with sodium hydrogen carbonate solution and then allowed to stand over solid barium hydroxide to remove all of the acetic and nitrous acids. This was found to be very necessary as any trace of acid caused decomposition later on in the preparation. The ether solution was then thoroughly dried over calcium

[1] *Z. physiol. Chem.*, 86, 454 (1913); THIS JOURNAL, 42, 320 (1920).

[2] *Ann.*, 362, 333 (1908).

[3] Fischer, *Ber.*, 34, 433 (1901).

chloride. The ether was removed in a vacuum desiccator over solid sodium hydroxide and the residue distilled under reduced pressure. About 2 g. of low-boiling material came over and then the diazo ester boiled between 75 and 78° at 10 mm. The yield was 15 g. The ester was redistilled and 13 g. (30% of the calculated amount) was obtained; the variation in boiling-point was less than 1°.

Steam distillation did not purify this diazo ester, as was shown by the following experiment. 1.4 g. of diazo ester (N = 11.7%) was distilled with 25 cc. of water and 5 g. of barium hydroxide. From the distillate 0.5 g. diazo ester (N = 11.6%) was recovered. Approximately $^2/_3$ of the ester was destroyed and no purification was obtained.

The ester was analyzed by the sulfuric acid method.[1]

Subs., 0.1414, 0.1730, 0.1614: 19.0 cc. N at 25° and 749 mm., 23.0 cc. N at 26° and 745 mm., 23.2 cc. N at 25° and 745 mm.

Calc. for $C_8H_{14}O_2N_2$: N, 16.47. Found:. 15.2, 15., 16.2.

The ester is lemon-yellow in color; crystallizes when cooled in mixtures of carbon dioxide-snow and ether; it is lighter than water; n_D at 26° = 1.453.

Decomposition of Ethyl α-Diazo-*n*-caproate with Dilute Acetic Acid.—Ten g. of the diazo ester was refluxed for one hour with 50 cc. of 10% acetic acid. The ester loses its yellow color. The reaction mixture was cooled and the ester taken up in ether. The ether solution was dried and distilled under reduced pressure. The following fractions were obtained: I, 2.5 g. boiling at 67–72° at 10 mm.; II, 1.5 g. boiling at 72–85° at 10 mm.; III, 3 g. boiling at 85–90° at 10 mm. Fraction I decolorized a solution of bromine in carbon tetrachloride and reacted with dil. potassium permanganate solution. On saponification with potassium hydroxide solution and acidification, an acid was obtained which was volatile with steam. The acid was distilled with steam to separate it from any non-volatile hydroxy acid. The volatile acid was taken up in ether and dried and the ether evaporated. One g. of the acid in 5 cc. of carbon disulfide was treated with 1.6 g. of bromine and the solution allowed to stand overnight. Most of the bromine color disappeared. On spontaneous evaporation an oily dibromo acid was obtained but it could not be obtained in crystalline condition.

Subs., (dibromo acid) 0.7165: 25.7 cc. of 0.101 *N* NaOH.

Neutral equivalent calc. for $C_6H_{10}O_2Br_2$: 274. Found: 276.

Fittig[2] has prepared Δ^1-hexenoic acid and gives its melting-point as 30–32°. He also describes the α-β-dibromo-hexoic acid and gives its melting-point at 71°. Although in this work these acids were not obtained in crystalline condition, there is little doubt that both were prepared.

[1] Curtius, *J. prakt. Chem.*, [2] **38**, 418 (1888).

[2] *Ann.*, **283**, 118 (1894).

Fraction III was saponified with potassium hydroxide solution. The solution was made acid and distilled with steam to remove the small amount of unsaturated acid. The solution was then extracted with ether to obtain the hydroxy acid. The hydroxy acid from the ether layer was obtained as an oil. By crystallizing from petroleum ether it was obtained in white crystals melting at 58°. Abderhalden[1] gives the melting-point of α-hydroxy-caproic acid at 60°. The copper salt was prepared as described by Abderhalden. The analysis and decomposition temperature of the copper salt confirmed the conclusion that the acid was α-hydroxy-caproic acid.

Copper salt decomposed at 270°.

Subs. (Cu salt), 0.1727: CuO, 0.0416.
Calc. for $(C_4H_9CHOHCO_2)_2Cu$: Cu, 19.54. Found: 19.50.

l-Ethyl α-Amino-n-caproate.—Thirteen g. of *l*-amino acid [$(\alpha)_D$ —22°] was esterified in the usual manner. The yield of free ester was 11.5 g. (72% of that calculated) boiling at 86–87° at 12 mm. The rotation in a one-dcm. tube was —11.65°. The hydrochloride was prepared as described before. The yield was 14 g.

1.7582 g. of the hydrochloride in 13.4371 g. of water gave a rotation of —1.7° in a 2-dcm. tube in sodium light; $(\alpha)_D$ = —7.25°.

d-Ethyl α-Amino-n-caproate.—Thirteen g. of *d*-amino acid [$(\alpha)_D$ = +17°] gave 11 g. ester boiling at 85° at 10 mm. The rotation in a one-dcm. tube was +6.15°. The ester gave 13 g. of the hydrochloride. The rotation of the salt was not taken.

Attempts to Prepare Optically Active Diazo Compounds from the *d*- and *l*-ester Hydrochlorides.—Fourteen g. of *l*-ester hydrochloride was dissolved in 50 cc. of water and diazotized as described under the preparation of ethyl diazo-caproate. 20 g. of sodium acetate, 20 g. of sodium nitrite and 25 cc. of glacial acetic acid were used. The yield of diazo ester was 1.5 g., boiling at 70–71° at 7 mm.

Subs., 0.2817: 35.8 cc. N at 23° and 743 mm.
Calc. for $C_8H_{14}O_2N_2$: N, 16.47. Found: 14.45.

The ether solution first separated from the diazotization reaction mixture, was examined in the polariscope and seemed to show a possible rotation of about —0.03°. After distillation the ester was inactive.

0.626 g. of diazo ester in 10.24 g. dry ether was examined in a 2-dcm. tube. There was no rotation. The ether solution was shaken with dil. sulfuric acid until it became colorless, dried and the solution again examined in the polariscope. It was inactive.

Twelve g. of *d*-ester hydrochloride was diazotized and 2 g. of diazo ester boiling at 72–73° at 8 mm. was obtained. The nitrogen content was

[1] Abderhalden, *Z. physiol. Chem.*, 84, 39 (1913).

14.6%. Neither the crude ether solution nor the purified ester dissolved in dry ether showed any signs of optical activity.

Attempt to Prepare *l*-Ethyl α-Hydroxy-*n*-caproate.—Thirteen g. of *d*-ethyl α-amino-caproate hydrochloride (from free ester with rotation of only +2.15°) was dissolved in 130 cc. of *N* sulfuric acid. The solution was cooled to 0° and diazotized with a solution of 7 g. of sodium nitrite in 10 cc. of water. A yellow oil soon began to separate. After standing for about one hour at 0° the solution was removed from the ice-bath and gradually warmed to about 40°. The oily product was collected in ether, dried and distilled under reduced pressure. The total distillate weighed 4 g. It boiled partly at 65–70° and partly at 87–90° at 10 mm. 2 g. of dry ether was added and the rotation taken in a one-dcm. tube. The rotation was +0.7°. The free ester decolorized bromine and reacted with permanganate solution, showing the presence of Δ^1-hexenoic ester. The product was not investigated further to show the relative proportions of unsaturated ester and hydroxy-ester. As nearly as could be determined by the boiling-point they were present in almost equal amounts.

α-Bromo-*n*-caproyl Chloride.—Fifty g. of α-bromo-caproic acid was heated with 28 g. of thionyl chloride under a reflux condenser until no more sulfur dioxide was evolved. The residue was distilled under diminished pressure. A very little low-boiling material was obtained and then the acid chloride came over. There was considerable residue of high-boiling material, doubtless unchanged acid. The yield was 37 g. (67% of the amount calculated) boiling at 102–105° at 30 mm.

Subs., 0.2144: 19.42 cc. of 0.1 *N* $AgNO_3$ (method of Stepanow).
Calc.: 20.08 cc.

α-Bromo-*n*-caproyl-glycine.—This compound was prepared according to the directions which Fischer[1] gives for α-bromo-*iso*-caproyl-glycine.

22.5 g. of glycocoll was dissolved in 300 cc. of *N* sodium hydroxide solution. The solution was cooled to 0° and in alternate portions 65 g. of α-bromo-caproyl chloride and 350 cc. of *N* sodium hydroxide solution were added. The temperature was kept below 10°. The mixture was shaken vigorously during the reaction. When the odor of the acid chloride had disappeared, 75 cc. of 5 *N* hydrochloric acid was added. The bromo-caproyl-glycine separated as an oil and was taken up immediately in ether. The ether solution was separated and the bromo-caproyl-glycine precipitated by means of an equal volume of petroleum ether. The product separated in white crystals. Yield 58 g. (76% of the amount calculated); m. p. 114–115°.

Subs., 0.4993, 0.4994: 20.2 cc., 20.2 cc.; 0.101 *N* NaOH.
Neutral equivalent calc. for $C_8H_{14}O_3NBr$: 252. Found: 244.8; 244.7.

α-Amino-*n*-caproyl-glycine.—Thirty g. of α-bromo-*n*-caproyl-glycine

[1] Fischer, *Ann.*, **340**, 142 (1905).

was dissolved in 150 cc. of ammonium hydroxide (sp. gr. 0.9). The solution was allowed to stand for 4 days at room temperature and then was evaporated to dryness on the water-bath. The ammonium bromide was removed by 3 extractions with 75 to 100 cc. of boiling alcohol. The yield was 19 g. (85% of the calculated amount).

To obtain a pure sample for analysis, 3 g. was dissolved in 60 cc. of hot water, and to the solution 120 cc. of alcohol was added. The dipeptide was filtered with suction. Yield 2.8 g.; m. p. 226°. The compound melted sharply and then decomposition occurred. The dipeptide burns with difficulty when the Dumas method is employed for determination of nitrogen.

Dumas Method.

Subs., 0.1858: 23.0 cc. N at 24° and 738 mm.
Calc. for $C_8H_{16}O_3N_2$: N, 14.89. Found: 14.85.

Kjeldahl Method.

Subs., 0.2000, 0.2000: 21.36 cc., 21.31 cc. 0.1 *N* H_2SO_4.
Calc. for $C_8H_{16}O_3N_2$: N, 14.89. Found: 14.95, 14.91.

Ethyl Ester Hydrochloride of α-Amino-*n*-caproyl-glycine.—Ten g. of dipeptide was suspended in 100 cc. of absolute alcohol. The solution was saturated with dry hydrogen chloride which caused all of the dipeptide to dissolve. The solution was then refluxed for 15 minutes on the water-bath and cooled. Many of the dipeptide ester hydrochlorides will crystallize from the alcohol. In this case the compound did not crystallize when the solution was cooled in an ice-bath for several hours. Ether would not cause the ester to separate from solution. When the solution was concentrated *in vacuo*, a gum-like mass remained. Finally after standing for over a week *in vacuo* over sodium hydroxide a little free hydrochloric acid could be detected but the compound did not crystallize. The yield of crude product was 14.5 g.

Subs., 0.411: 17.27 cc. 0.01022 *N* $AgNO_3$.
Calc. for $C_{10}H_{20}O_3NCl$: Cl, 14.05. Found: 15.12.

That the compound really was the ester hydrochloride was shown by the fact that it gave the corresponding hydroxy ester on treatment with nitrous acid.

Ethyl Ester of α-hydroxy-*n*-caproyl-glycine.—Fourteen g. of the crude ester hydrochloride prepared in the above experiment was dissolved in 50 cc. of water, 10 g. of sodium acetate was added and the solution was cooled to 0°. Then 5 g. of sodium nitrite was added, and after it had dissolved 6 cc. of glacial acetic acid was gradually added. Nitrogen gas was evolved and an oily substance separated. This soon changed to a white solid. After sometime the solid was filtered off. A little yellow oil came through with the water. This oil is not diazo ester, as it does not decolorize iodine solution and does not give gas when treated with sulfuric acid. The solid hydroxy ester was purified by dissolving it in a little

ether and adding petroleum ether to the solution. Yield 3–4 g. M. p. 90–91°.

Subs., 0.2308: (Kjeldahl), 10.75 cc. 0.1 *N* H_2SO_4.
Calc. for $C_{10}H_{19}O_4N$: N, 6.45. Found: 6.52.

4. Derivatives of α-Amino-caprylic Acid.

α-Amino-caprylic Acid.—This compound has been prepared in 35% yields by treating the ammonium addition compound of heptaldehyde with aqueous hydrocyanic acid followed by hydrolysis.[1] Fifty-five g. of sodium cyanide was dissolved in 100 cc. of water and to the solution 57 g. of ammonium chloride was added. To this solution was then added a solution of 114 g. of heptaldehyde in 100 cc. of methyl alcohol. The solution became warm and after about a half hour a layer of the amino cyanide began to separate. The reaction mixture was allowed to stand overnight. The amino cyanide was taken up in ether and the ether distilled off. To accomplish the hydrolysis, 500 cc. of hydrochloric acid (350 cc. of acid sp. gr. 1.19, and 150 cc. of water) was added and the solution was refluxed for $2^1/_2$ hours. It was cooled and filtered to remove most of the oily impurity which had separated. The amino acid was precipitated from the filtrate by adding ammonium hydroxide. The product obtained was quite dark in color. For purification it was dissolved in dilute solution of sodium hydroxide and boiled with bone black. The solution was filtered and the amino acid precipitated by means of a saturated solution of ammonium chloride. The product was filtered with suction and washed with water and dried on filter paper. The yield was 70–75 g. (43–47% of the calculated amount). The amino acid may be crystallized from water, but it is not very soluble even in boiling water.

Ethyl α-Amino-caprylate Hydrochloride.—Fifty g. of the amino acid was esterified as described under the corresponding caproic acid derivatives. The yield of ester was 40 g. It boiled at 110° under 10 mm. pressure; n_D at 21° is 1.436.

The amino ester was converted to the hydrochloride in the usual way. The yield was nearly quantitative, m. p. 76–77°.

Subs., 0.4980, 0.4971: 21.55 cc., 21.49 cc. 0.1022 *N* $AgNO_3$ (Volhard).
Calc. for $C_{10}H_{22}O_2NCl$: Cl, 15.88. Found: 15.66, 15.67.

Attempt to Prepare Ethyl α-Diazo-caprylate.—The ester hydrochloride was diazotized according to the directions followed in the preparation of the ethyl α-diazo-caproate. Twenty-three g. of the ester hydrochloride gave 2 g. of yellow oil boiling at 102–107° at 11 mm. Analysis by the sulfuric acid method showed only 5% of nitrogen. A second run decomposed during distillation after the product was distilling at 90° at 6 mm., and 2.5 g. of ethyl α-hydroxy-caprylate boiling at 80–85° at 7 mm. was obtained. This was identified only by the saponification number.

[1] Erlenmeyer and Sigel, *Ann.*, **176**, 344 (1875).

Subs., 1.452: 8.16 cc. 0.9782 *N* NaOH.
Saponification number: Calc. from $C_6H_{13}CHOHCO_2C_2H_5$: 188. Found: 182.

Another experiment was carried out in which the free ester was diazotized in acetic acid solution. The results were not much better.

18.7 g. of ethyl amino-caprylate was dissolved in 50 cc. of water and 6 cc. of glacial acetic acid. The solution was cooled below 0° and 20 g. of sodium acetate and 15 g. of sodium nitrite were added. The solution was covered with ether and 20 cc. of glacial acetic acid slowly added. After standing at 0° for 4 hours the ether layer was separated and worked up according to the usual method. Nine g. of product boiling at 105–110° at 10 mm. was obtained. This product contained only 8.15% of nitrogen. The product was then refractionated at 6 mm. and divided into 3 portions.

Fraction 1. 4 g. boiling below 90°: N = 4.6%.
Fraction 2. 3 g. boiling below 90–95°: N = 9.2%.
Residue. 2 g. not analyzed.

The percentage of nitrogen should be 14.14%. Therefore, the diazo compound was about 65% pure.

5. Derivatives of Secondary Butylamine.

Ethylmethyl-ketoxime.[1]—250 g. of hydroxylamine sulfate (90% pure) was dissolved in 1500 cc. of water. To the solution were added 216 g. of ethylmethyl-ketone and 160 g. of sodium carbonate. The solution was allowed to stand for 24 hours. The oxime was taken up in ether, dried over calcium chloride and distilled. The yield was 203 g. (85% of that calculated); b. p. 150–155°.

Secondary **Butylamine.**—Ninety g. of methylethyl-ketoxime was dissolved in one liter of absolute alcohol. To the solution 150 g. sodium was added in portions, within one hour. The solution was boiled and more absolute alcohol was added from time to time until all the sodium had reacted. About 300 cc. of absolute alcohol was added. When all the sodium was in solution, the amine and alcohol were distilled with steam. To the distillate a slight excess of hydrochloric acid (sp. gr. 1.19) was added and the solution evaporated to dryness on the water-bath. The amine hydrochloride was placed in a flask attached to a condenser and the free amine liberated with a very concentrated solution of sodium hydroxide. The free amine was separated and dried over solid sodium hydroxide and distilled. Yield 40 g. (53% of the amount calculated), boiling at 66–70°.

Secondary **Butyl Urethane,** $\begin{matrix} CH_3 \\ C_2H_5 \end{matrix}\!\!>\!CHNHCOOC_2H_5$.[2]—Forty g. of *secondary* butylamine was dissolved in 100 cc. of dry ether and to the

[1] Janny, *Ber.*, **15**, 2779 (1882).
[2] *Rec. trav. chim.*, **14**, 19 (1895).

cold solution was added a solution of 30 g. of ethyl chlorocarbonate in an equal volume of dry ether. The reaction was very vigorous. After the reaction was complete the amine hydrochloride was filtered off and 28.5 g. was obtained. The ether was evaporated and the urethane distilled under reduced pressure. Yield 30 g. (75% of the calculated amount); b. p. 87–88° at 14 mm.

Attempts to Prepare the Nitroso Derivative of *Secondary* Butyl Urethane.—The urethane was dissolved in glacial acetic acid and treated with sodium nitrite but was recovered unchanged. The solution in 30% acetic acid did not give better results. The urethane was treated in dry ether with amyl nitrite and dry hydrogen chloride but was recovered unchanged from the reaction mixture.

Summary.

1. Ethyl α-diazo-*n*-caproate was prepared in 30% yields from the corresponding amino ester hydrochloride by a slight modification of Curtius' method of preparing diazo esters.

2. Samples of this diazo ester prepared from the *d*- and *l*-forms of the amino ester hydrochloride were found to be optically inactive. They were decomposed by dil. sulfuric acid and the resulting compounds were also optically inactive.

3. Ethyl α-diazo-*n*-caproate was decomposed by dil. acids and the products formed were ethyl α-hydroxy-*n*-caproate and ethyl Δ^1 hexenoate.

4. Impure diazo esters were prepared from phenylamino-acetic acid and α-amino-caprylic acid. These esters decomposed on attempting to purify them by vacuum distillation and the corresponding hydroxy esters were obtained.

5. The treatment of optically active amino ester hydrochlorides with nitrous acid under certain conditions gave optically active hydroxy esters. If the diazo ester is an intermediate product this is evidence for the existence of an asymmetric diazo compound.

6. Improved methods for the preparation of *dl*-phenylamino-acetic acid, *dl*-ethyl phenylamino-acetate, *l*-phenylamino-acetic acid, *l*-ethyl phenylamino-acetate hydrochloride, methyl phthalimidine, α-amino-caprylic acid, *secondary* butyl amine and *secondary* butyl urethane were devised.

7. The following new compounds were prepared:

dl-Acetyl-ethyl phenylamino-acetate, $C_{12}H_{15}O_3N$, m. p. 65–66°.

dl-Carboethoxy ethyl phenylamino-acetate, $C_{13}H_{17}O_4N$, m. p. 57°.

l-Acetyl ethyl phenylamino-acetate, $C_{12}H_{15}O_3N$, m. p. 69–70°, $[\alpha]_D = -138.7°$.

Nitroso methyl phthalimidine, $C_9H_8O_2N_2$, m. p. 86.5–87°.

Ethyl α-diazo-*n*-caproate, $C_8H_{14}O_2N_2$, b. p. 75–76° at 10 mm.

l-Ethyl α-amino-*n*-caproate, $C_8H_{17}O_2N$, b. p. 86–87° at 12 mm., $[\alpha]_D$ = —11.65° in a one-dcm. tube

l-Ethyl α-amino-*n*-caproate hydrochloride, $C_8H_{18}O_2NCl$, $[\alpha]_D$ = —7.25°.

α-Bromo-*n*-caproyl chloride $C_6H_{10}OClBr$, b. p. 102–105° at 30 mm.

α-Bromo-*n*-caproyl-glycine, $C_8H_{14}O_3NBr$, m. p. 114–115°.

α-Amino-*n*-caproyl-glycine, $C_8H_{16}O_3N_2$, m. p. 226°.

Ethyl ester of α-oxy-*n*-caproyl-glycine, $C_{10}H_{19}O_4N$, m. p. 90–91°.

Ethyl α-amino-caprylate, $C_{10}H_{21}O_2N$, b. p. 110° at 10 mm.

Ethyl α-amino-caprylate hydrochloride, $C_{10}H_{22}O_2NCl$, m. p. 76–77°.

URBANA, ILL.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH.]

SYNTHESES IN THE CINCHONA SERIES. VI. AMINOAZO AND HYDROXYAZO DYES DERIVED FROM CERTAIN 5-AMINO CINCHONA ALKALOIDS AND THEIR QUINOLINE ANALOGS.

BY WALTER A. JACOBS AND MICHAEL HEIDELBERGER.

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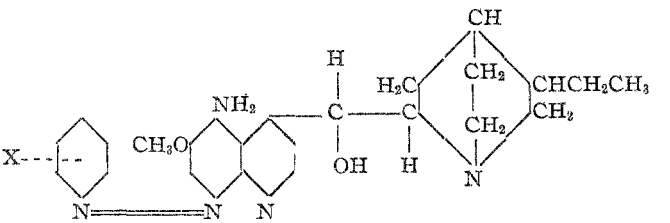
In our study of 5-amino-dihydroquinine[1] it was found to couple smoothly in dil. acetic acid solution with diazo compounds to form aminoazo dyes in which we assume the azo group to enter Position 8 in the quinoline portion of the molecule



This assumption seems justified since, on the one hand, Position 8 is the only one which satisfies the usual laws of substitution for a 5-amino-6-methoxyquinoline (analogous to α-amino-β-methoxynaphthalene), and finally, since 5-aminoquinoline was also found to yield aminoazo dyes which could be reduced to 5,8-diamino-quinoline.

Of the dyes from 5-amino-dihydroquinine the phenylazo-, *p*-sulfo-phenylazo-, and the *p*-methoxy- and *p*-ethoxy-phenylazo-compounds were prepared and studied. 5-Amino-dihydroquinidine and 5-amino-ethyldihydrocupreine also readily yielded phenylazo compounds. These substances are usually red, well defined, crystalline compounds, forming orange-red solutions in neutral solvents and deep purple solutions in

[1] THIS JOURNAL, 42, 1485 (1920).