LV.—*The Condensation of Phenylglycinoacetic Esters in Presence of Sodium Alkylloxides.*

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THE reaction taking place between ethyl phenylglycine and sodium alkylloxides has been investigated by Vorländer and the author (*Ber.*, 1901, **33**, 2467). Condensation resulted, but the products varied with the solvent employed. In alcoholic solution, the anhydride α -diphenyl-diacylpiperazine was formed, whilst in benzene solution an isomeride was obtained having very different properties. This was found to be anilino-*N*-phenylhydroxypyrroline, analogous to the compounds obtained by Rügheimer with the esters of hippuric acid. This condensation to ring compounds by the loss of two molecules of alcohol led me, at the suggestion of Professor Vorländer, to examine the reaction taking place between sodium alkylloxides and a number of substituted alkyl phenylglycinoacetates, both when alone and in presence of a third substance such as benzaldehyde or ethyl oxalate.

This investigation seemed to be of interest, because the use of sodium ethoxide in the synthesis of ring compounds by a reaction analogous to the formation of ethyl acetoacetate has been comparatively limited. The condensations undergone by succinic and malonic esters are well known and ring formations of this type have also been studied by W. Wislicenus (*Annalen*, 1888, **246**, 252) and by Auwers (*Ber.*, 1893, **26**, 364). We owe to W. Dieckmann, who has applied it with great success to the higher members of the group of the fatty dibasic acids, the most important recent development of the method (*Ber.*, 1904, **27**, 965; *Annalen*, 1901, **27**, 317). He found that the formation of penta- and hexa-methylene derivatives took place easily, that the formation of seven-membered rings was far more difficult and that it was impossible to obtain rings containing less than five or more than seven members, results which are in accord with von Baeyer's "strain theory." The method is extended in this work to the esters of dibasic acids containing a nitrogen atom linked to a phenyl group in the place of a methylene group.

The objects in view were :

1. To study the influence of the nitrogen atom.
2. To see whether the unsaturated condition of the nitrogen had a further effect.

Ethyl phenylglycinoacetate may thus be compared with ethyl glutarate, $\text{C}_6\text{H}_5\cdot\overset{\text{N}}{\underset{|}{\text{N}}}(\text{CH}_2\cdot\text{CO}_2\cdot\text{C}_2\text{H}_5)_2$ with $\text{CH}_2(\text{CH}_2\cdot\text{CO}_2\cdot\text{C}_2\text{H}_5)_2$, and the nitrogen in the former may be regarded as unsaturated. In this

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particular case, experiments showed that condensation could not be induced and that saponification alone takes place.

On the other hand, ethyl phenylglycinopropionate, which is described later, condensed in presence of sodium ethoxide to a phenylhydroxypyrroline derivative, behaving in the same manner as ethyl adipate. Up to this point, therefore, the nitrogen has no special influence beyond the fact that the yields are somewhat inferior to those obtained by Dieckmann.

The reaction next investigated was that found to take place between ethyl phenylglycinoacetate and benzaldehyde in benzene solution and in the presence of the theoretical amount of sodium ethoxide. The product which has the formula $C_{19}H_{19}O_4N$ and the following constitution, $CO \begin{smallmatrix} \diagup O-CHPh \\ \diagdown CH_2 \cdot NPh \end{smallmatrix} > CH \cdot CO_2 \cdot C_2H_5$, is a lactone, yielding the corresponding acid on saponification. Ethyl *o*-tolylglycinoacetate behaved similarly.

The most interesting results were obtained in consequence of the condensations brought about by sodium alkylloxides between various esters of phenylglycinoacetic acid and oxalic acid.

Ethyl phenylglycinoacetate (1 mol.), ethyl oxalate (1 mol.), and sodium ethoxide (2 mols.), when heated, interact energetically and completely, and, on acidifying the sodium salt obtained, a well-defined crystalline product separated which melted at 137° .

It was thought at first that this compound was a pentamethylene derivative obtained in the following manner:

Analysis led to the formula $C_{10}H_{17}O_6N$, which accords with this supposition, but the properties of this substance were found to differ greatly from those of the compound obtained by Dieckmann on condensing ethyl glutarate and oxalate in presence of sodium ethoxide. It was expected that on saponification with dilute acids a ketonic hydrolysis would take place, yielding a new type of ortho-diketonic five-membered ring with the group $N \cdot C_6H_5$ replacing one of the methylenes of the pentamethylene nucleus. But saponification could not be brought about, either by acids or alkalis, whether on heating or after prolonged digestion at the ordinary temperature. This seemed to preclude the presence of carboxyl groups in the manner suggested and also the foregoing formation.

No action took place between the compound and hydroxylamine or phenylhydrazine; in fact, it crystallised unchanged from the latter. Further, it is insoluble in aqueous sodium carbonate in the cold, but dissolves in sodium hydroxide with the formation of a yellow salt.

The alcoholic solution gives a reddish-blue coloration with ferric chloride, and the compound is precipitated from an ethereal solution by means of dry ammonia. Finally, it reacts with phenylcarbimide. These properties indicate the enolic character of the substance, and the existence of a yellow sodium salt suggested the possibility of a quinonoid structure arising in the following way :

This formula explains several of the properties of this new substance, but does not account for the fact that it does not undergo saponification. A substance of this type described by Guthzeit and Dressel (*Ber.*, 1893, **26**, 2795) was readily saponified.

Ethyl phenylglycinoacetate still possesses some basic properties and dissolves in hydrochloric acid, but this compound is insoluble.

The manner in which the molecules of alcohol are split off was next investigated. If both the -OR groups come from the ethyl oxalate, as they do in the Dieckmann condensations, then it is immaterial whether methyl or ethyl oxalate be used; the product would be the same in both cases :

But on condensing ethyl phenylglycinoacetate with methyl oxalate in presence of sodium ethoxide, a substance was obtained melting at 146—147°.

The third factor was then altered, and it was found that the final result depended on whether sodium methoxide or ethoxide were used. Methyl phenylglycinoacetate was then prepared, and all the possible condensations were carried out with the following results :

Phenylglycinoacetic esters.	Oxalic esters.	Sodium alkylloxides.	Melting point of product.
Ethyl	Ethyl	Ethoxide	137°
Ethyl	Methyl	Ethoxide	146—147
Ethyl	Ethyl	Methoxide	175
Ethyl	Methyl	Methoxide	188
Methyl	Ethyl	Methoxide	188
Methyl	Ethyl	Ethoxide	147
Methyl	Methyl	Ethoxide	159
Methyl	Methyl	Methoxide	195

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The influence of the introduction of methyl groups on the melting point is clearly shown, and it is of interest to note that the first condensation takes place far more readily than the last. The methyl group exerts its maximum effect when introduced as methoxide. Some of these products are identical; using the same alkoxide, it is immaterial whether methyl phenylglycinoacetate and methyl oxalate or ethyl phenylglycinoacetate and methyl oxalate are employed; the esters are interchangeable.

In the other cases, we are probably dealing with structural isomerides, and it is hoped that further work will establish their constitution.

The compound having the formula $C_{16}H_{17}O_6N$ and melting at 137° has been more specially investigated. A completely satisfactory constitutional formula has not been established, but the results obtained show that these condensations give rise to compounds differing very much from those obtained by Dieckmann, and that this difference must be due to the fact that, in the compounds used by the author, a nitrogen atom linked to a phenyl group takes the place of a methylene group.

EXPERIMENTAL.

Preparation of Phenylglycine.

Several methods of preparation have been described, but the yields are not very satisfactory. Michelson and Lippmann (*Compt. rend.*, 1865, **61**, 739), Schultzen and Nencki (*Ber.*, 1869, **2**, 570), and Schwebel (*Ber.*, 1876, **10**, 2045) caused aniline and chloro- or bromoacetic acid to interact in ethereal solution. Hausdörfer (*Ber.*, 1890, **23**, 1987), who allowed them to react in presence of crystallised sodium acetate and a little water, obtained a yield of 26–30 per cent.

The following method was adopted. A mixture of 95 grams (1 mol.) of chloroacetic acid, 186 grams of aniline (2 mols.), and 500 c.c. of water was heated on the water-bath for $1\frac{1}{2}$ hours, shaking frequently, the hot liquid was poured into a dish, and the crystalline product collected and washed with cold water until free from hydrochloric acid. The yield varied between 105 and 120 grams, that is, between 70 and 80 per cent. When prepared in this way, the product contains a small proportion of phenylglycinoacetic acid, which is no disadvantage in view of the next step.

Preparation of Phenylglycinoacetic Acid.

This substance was prepared by the method given by Vorländer and Mumme for *o*-tolylglycinoacetic acid (*Ber.*, 1903, **36**, 1470): 74.5 grams of chloroacetic acid (2 mols.) and 197 grams ($1\frac{3}{4}$ mols.) of soda crystals

are dissolved in 200 c.c. of water ; 61 grams (1 mol.) of phenylglycine are then gradually added and the mixture warmed until all has dissolved. The whole is then heated for 2 hours in a boiling water-bath. On adding strong hydrochloric acid to the liquid, a milkiness appears, which disappears on adding an excess. After some time, the phenylglycinoacetic acid crystallises out, and it should be filtered off at once and washed at the pump with cold water until free from hydrochloric acid. The yield is 60—70 per cent.

The proportions were varied at different times, as also the period of heating, and in one case anhydrous sodium carbonate was used, but the foregoing quantities gave the best results.

The acid crystallises from ether in four- or six-sided plates, and from hot water in small pyramids melting at 155—156°.

Preparation of Ethyl Phenylglycinoacetate.

Fifty grams of the acid were heated on the water-bath for 6 hours with quantities of absolute alcohol varying from 100 to 500 grams in presence of 25 grams of concentrated sulphuric acid. The influence of the amount of alcohol used was small provided that at least four times the theoretical amount was used ; the yield of ester from 50 grams of acid varied from 30 to 39 grams.

The product was poured into water, the oily ester separated off and dissolved in ether, the ethereal solution washed with dilute aqueous sodium carbonate and dried over anhydrous sodium sulphate. After evaporating off the ether, the ester was distilled under diminished pressure and came over at 195—200° under 17 mm. pressure, the main fraction boiling at 197—198°. The ester is a heavy, colourless oil, the alcoholic solution of which gives no coloration with ferric chloride.

0.2879 gave 0.6640 CO₂ and 0.1880 H₂O. C = 63.04 ; H = 7.25.

C₁₄H₁₉O₄N requires C = 63.39 ; H = 7.17 per cent.

In this distillation, a fraction boiling some 30—40° higher than the normal ester was always obtained. This less volatile substance dissolved in sodium carbonate with effervescence and was titrated against standard baryta solution. 0.8528 gram dissolved in absolute alcohol required 5.0 c.c. baryta [1 c.c. = 0.00605 Ba(OH)₂]; giving a molecular weight of 241, the molecular weight of the acid ester being 237. This non-volatile fraction thus consists of the acid ester of phenylglycinoacetic acid, CO₂H·CH₂·NPh·CH₂·CO₂Et (see p. 441).

Methyl phenylglycinoacetate was prepared in a similar manner ; it is an almost colourless oil which distils over at 210—211° under 18 mm. pressure ; 50 grams of the acid gave 50 grams of the ester, the yield being 52 per cent.

Preparation of o-Tolylglycinoacetic Acid.

Tolylglycine was first prepared in the manner described for phenylglycine, from *o*-toluidine and chloroacetic acid. The *o*-tolylglycinoacetic acid was prepared in the same way as the phenyl compound. When recrystallised, it melts at 154–156° with slight decomposition.

Ethyl *o*-tolylglycinoacetate, $C_7H_7N(CH_2 \cdot CO_2C_2H_5)_2$, was prepared in the manner described for the phenyl ester; it distils at 205–207° under 16 mm. pressure as a viscid, colourless oil, which readily crystallises in beautiful needles melting at 59–60°. The alcoholic solution gives no coloration with ferric chloride.

0.4021 gave 18.0 c.c. nitrogen at 15.5° and 762 mm. $N = 5.21$.

$C_{15}H_{21}O_4N$ requires $N = 5.02$ per cent.

Action of sodium ethoxide on ethyl phenylglycinoacetate. (a) In benzene solution: 1.2 gram of sodium (1 atom) in the form of wire was placed in dry benzene and rather more than the theoretical amount of alcohol for conversion with ethoxide added. When the sodium had disappeared, 13.25 grams (1 mol.) of ethyl phenylglycinoacetate were added, and after standing 12 hours the whole was heated for 1½ hours. Water was then added, the benzene layer separated off, and the aqueous part was acidified with hydrochloric acid; nothing was precipitated, nor could anything be extracted with ether. Condensation does not take place, and this ester behaves like ethyl glutarate. The benzene portion yielded on evaporation a very small amount of a white substance, which, sparingly soluble in water and alkalis, dissolved readily in alcohol, acetone, or ether. Its alcoholic solution gave a violet coloration with ferric chloride. The compound crystallised from alcohol in needles melting at 170°. On warming the substance with water, the latter acquired an alkaline reaction, and with hydrochloric acid a gummy product was obtained. On attempting to analyse the substance, it was found to leave an ash on combustion, and the percentage of sodium was determined.

0.2522 gave 0.0344 Na_2SO_4 . $Na = 4.42$ per cent.

This sodium salt of high molecular weight has the exceptional property of being soluble in benzene, but dissolving only with difficulty in water.

(b) In alcoholic solution, the ester is partially saponified. After heating for half an hour on the water-bath, a sodium salt was precipitated, which was collected, decomposed with hydrochloric acid, and extracted with ether. The product, which crystallised from hot water and melted at 121–122°, is the acid ester,

already described in the liquid form (see p. 439). [View Article Online](#) This is proved by the fact that on further saponification with 50 per cent. caustic potash it yielded phenylglycinoacetic acid (m. p. 155—156°). Similarly no condensation products were obtained in the case of ethyl *o*-tolylglycinoacetate.

β-Phenylglycinopropionic Acid and its Esters.

Preparation of the Ethyl Ester, $C_6H_5 \cdot N(CH_2 \cdot CO_2Et) \cdot CH_2 \cdot CH_2 \cdot CO_2H$.

A mixture of 10 grams of β -iodopropionic acid (1 mol.) and 18 grams of ethyl phenylglycine (2 mols.) was heated at 90° in the water-bath for 2½ hours; the viscid oily product obtained was treated several times with aqueous sodium carbonate to neutralise the acid ester formed, and the excess of ethyl phenylglycine was extracted with ether. A slight excess of hydrochloric acid was added, and the liquid repeatedly extracted with ether, owing to the solubility of the ester in the acid. After drying and evaporating off the ether, a viscid, faintly yellow oil was obtained, which did not solidify *in vacuo*; the yield was 10—12 grams.

0.2318 gave 10.6 c.c. nitrogen at 16° and 766 mm. $N = 5.38$.

$C_{13}H_{17}O_4N$ requires 5.58 per cent.

0.5628 required for neutralisation 15.0 c.c. baryta solution.

[1 c.c. = 0.0125 Ba(OH)₂]. Equivalent found, 250.6.

$C_{13}H_{17}O_4N$ requires 251.

Preparation of the Isomeric Ester, $C_6H_5 \cdot N(CH_2 \cdot CO_2H) \cdot CH_2 \cdot CH_2 \cdot CO_2Et$.

Ethyl β -iodopropionate was first prepared by heating together for 4 hours, 50 grams of the acid with 200 grams of absolute alcohol containing 1 per cent. of dry hydrogen chloride (Harris, *Ber.*, 1896, 29, 513).

To prepare ethyl β -anilinopropionate, $C_6H_5 \cdot NH \cdot CH_2 \cdot CH_2 \cdot CO_2Et$, 46 grams of ethyl β -iodopropionate (1 mol.) were heated for 20 minutes at 80° with 38 grams (2 mols.) of aniline. Condensation took place with the separation of aniline hydriodide. The mixture was shaken up with water, and the heavy oily product extracted with ether and dried over potassium carbonate. This oil distilled at 175° under 18 mm. pressure, the yield being 30 grams.

Condensation of this Ester with Chloroacetic Acid.—It was found advantageous to work with small quantities. Eight grams (2 mols.) of ethyl β -anilinopropionate were heated in the water-bath with 2 grams (1 mol.) of chloroacetic acid for 3 hours. When cold the solid mass was shaken up with aqueous sodium carbonate, and any unchanged ester extracted with ether. After acidifying with hydrochloric acid, the liquid was repeatedly extracted with ether. The

ethereal solution yielded on evaporation an oil which solidified under diminished pressure. The ester crystallises from aqueous methyl alcohol in rhombic prisms melting at 60—61°. Its alcoholic solution gives no coloration with ferric chloride.

0.2096 gave 10.1 c.c. nitrogen at 16.5° and 766 mm. $N = 5.65$.

$C_{13}H_{17}O_4N$ requires 5.58 per cent.

0.1517 required for neutralisation 17.4 baryta solution of factor 0.0374. Equivalent found, 238. $C_{13}H_{17}O_4N$ requires 254.

β-Phenylglycinopropionic Acid, $C_6H_5 \cdot N(CH_2 \cdot CO_2H) \cdot CH_2 \cdot CH_2 \cdot CO_2H$.—This acid was obtained by the saponification of both the acid esters just described, a reaction which is best brought about by weak alkali at 80°. The potassium salt was obtained in needles which were decomposed by dilute hydrochloric acid, and the solution was extracted with ether. The solid obtained on evaporation was recrystallised from benzene and a little light petroleum, and separated out in white needles melting at 137°. This acid decomposes on heating, and its alcoholic solution gives a reddish-brown coloration with ferric chloride.

0.1560 gave 0.3360 CO_2 and 0.0888 H_2O . $C = 58.94$; $H = 6.32$.

$C_{11}H_{13}O_4N$ requires $C = 59.19$. $H = 5.82$ per cent.

0.0959 required for neutralisation 23.2 c.c. baryta solution.

[1 c.c. = 0.0032 $Ba(OH)_2$]. Equivalent found, 110.5.

$C_{11}H_{13}O_4N$ requires 111.5.

Ethyl β-Phenylglycinopropionate.—The normal ester was prepared from both the acid esters, but it is best obtained from the liquid ester, for in the preparation of the solid ester one-half of the ethyl *β*-anilino-propionate used is lost. Twenty-five grams of the liquid acid ester were boiled for 6 hours with 250 grams of absolute alcohol and 25 grams of concentrated sulphuric acid. The product was worked up in the usual way and 21 grams of the diethyl ester obtained. This boils at 210—211° under 16 mm. pressure as a colourless, viscid oil.

0.3192 gave 0.7539 CO_2 and 0.2153 H_2O . $C = 64.44$; $H = 7.50$.

0.3190 „ 14.0 c.c. nitrogen at 15.5° and 765 mm. $N = 5.16$.

$C_{15}H_{21}O_4N$ requires $C = 64.51$; $H = 7.53$; $N = 5.02$ per cent.

Action of Sodium Ethoxide on Ethyl β-Phenylglycinopropionate.—1.2 grams of sodium wire (1 atom) were placed in 40 c.c. of dry benzene and heated up with rather more than the theoretical amount of absolute alcohol until the metal had disappeared. To this were then added 14 grams (1 mol.) of the ester, and the mixture was boiled for $\frac{1}{2}$ to $\frac{3}{4}$ of an hour in a reflux apparatus. As a rule, the sodium salt which separated was shaken up with water and the benzene

separated from the aqueous layer. The addition of a small amount of ether destroys the emulsion which tends to form. The aqueous part is purified by shaking up with ether, and the last traces of the latter are removed by aspiration. On passing carbon dioxide through the solution, a white substance is precipitated. If acetic acid is used, the precipitate is crystalline. The acidified solution may also be extracted with ether, from which the substance crystallises in needles.

The following method was, however, found to be more satisfactory. The sodium salt is collected and washed with a little alcohol and ether; it is dissolved in water, the filtered solution being then acidified with acetic acid, when the white substance separates in a fairly pure condition. This compound crystallises from aqueous alcohol in small, hexagonal plates and from alcohol in needles; it melts at 69—70°.

0.2012 gave 0.4904 CO₂ and 0.1218 H₂O. C = 66.51; H = 6.70.

0.2338 „ 11.1 c.c. of nitrogen at 16.3° and 768 mm. N = 6.15.

C₁₃H₁₅O₃N requires C = 66.95; H = 6.43; N = 6.01 per cent.

0.1256 in 16.1699 naphthalene gave Δ*t* = 0.223°; M. W. = 242.

C₁₃H₁₅O₃N requires M. W. = 233.

The alcoholic solution gives a dark violet coloration with ferric chloride. The substance dissolves in warm aqueous sodium carbonate, but the sodium salt separates on cooling; it is soluble in hydrochloric acid, but not so readily in caustic alkali. A coloured product is not obtained either by treatment with fuming sulphuric acid or after fusion with caustic potash. With phenylhydrazine, a light yellow product is obtained, melting, after recrystallisation from alcohol, at 160—161°.

Dieckmann found that ethyl adipate condensed in presence of sodium ethoxide to ethyl β-ketopentamethylenecarboxylate by the loss of one molecule of alcohol. This reaction, if on corresponding lines, would yield a substance having the empirical formula C₁₃H₁₅O₃N, and both the analysis and the molecular weight found agree with this. The colour reaction with ferric chloride points to an enolic form, as does the existence of salts. This compound has thus in all probability the following constitution:

and is ethyl phenylhydroxypyrrolinecarboxylate.

The saponification of this ester is not easily effected by alkalis. The ester was dissolved in alcohol, an excess of 50 per cent. caustic potash added, and the whole heated on the water-bath. The potassium derivative separates out first, as was shown by the fact that on acidifying it yields the original ester melting at 68°. After heating for two hours, the solid disappeared; the filtered solution was acidified

with dilute sulphuric acid and extracted 12 times with ether. The acid was obtained on evaporation; it crystallised from water and melted at 143—144°.

0.1116 gave 6.1 c.c. of nitrogen at 16.1° and 765 mm. $N = 6.42$.

$C_{11}H_{11}O_3N$ requires $N = 6.83$ per cent.

The acid is soluble in cold aqueous sodium carbonate and in acids. The alcoholic solution gives no coloration with ferric chloride. When the acid was heated at 170—180° for 15 minutes, carbon dioxide was eliminated. The oily product was dissolved in alcohol and warmed with a little ferric chloride, when a greenish-blue precipitate was formed. This was collected, washed, and dried, and treated with pure concentrated sulphuric acid; on warming, a violet colour was produced. The amount of substance obtained was so small that further investigation was not possible. This colour reaction is, however, interesting, because it may be compared with the behaviour of phenyl-methylpyrazolone (Knorr, *Annalen*, 1887, **238**, 172). On warming an alcoholic solution of ethyl β -phenylglycinopropionate with sodium ethoxide, the ester is partially saponified, and the solid ester, $C_6H_5 \cdot N(CH_2 \cdot CO_2H) \cdot CH_2 \cdot CH_2 \cdot CO_2Et$ (m. p. 60—61°), is obtained.

Condensation of Ethyl Phenylglycinoacetate with Benzaldehyde.—Claisen (*Ber.*, 1890, **23**, 976) obtained ethyl cinnamate by the action of sodium on a mixture of ethyl acetate and benzaldehyde. Stobbe (*Ber.*, 1894, **27**, 2405), using ethyl succinate, obtained ethyl phenylitaconate. R. Fittig (*Annalen*, 1894, **282**, 334) prepared benzylideneglutaric acid by acting on a mixture of equal molecules of glutaric acid and benzaldehyde. In the author's experiments, 26.5 grams (1 mol.) of ethyl phenylglycinoacetate were dissolved in 100 grams of anhydrous benzene; then 2.3 grams of sodium (1 atom) as wire were introduced in the cold, and to this were added 10.6 grams (1 mol.) of freshly distilled benzaldehyde. After some 20 minutes, the mixture became brown, much heat was developed, and an energetic reaction took place, which was moderated by cooling. After a few hours, all the sodium had disappeared and the mixture became very dark. Water was now added and the benzene separated from the aqueous layer. The benzene portion was shaken with water until the aqueous extract no longer gave a precipitate with hydrochloric acid. The aqueous part is then cleared by shaking with a little ether, and finally purified by aspiration. On passing a stream of carbon dioxide through the solution, a light yellow substance was precipitated, and of this 12 grams were obtained. A second precipitate was produced on adding hydrochloric acid to the filtrate, which proved to be identical with the first. The total crude product, which weighed 29 grams, tended to decompose, and after two or three days it became

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pasty and a gas was evolved. The substance is soluble in alcohol, benzene, and chloroform, but does not crystallise very readily from any of these solvents; the alcoholic solutions yield prismatic plates, and aqueous alcohol gives needles melting at 137—138°.

This substance, when pure, is light yellow; it dissolves with difficulty in cold aqueous sodium carbonate, but readily on warming, and it is reprecipitated unchanged on the addition of acid. After heating with water, the solution acquires an acid reaction, indicating the possibility of the substance being a lactone. The alcoholic solution gives a brownish-red coloration with ferric chloride. No coloured product was obtained by fusion with caustic potash and subsequent treatment with water, hydrochloric acid, and ferric chloride. When heated up to 160°, the substance loses carbon dioxide, and a dark brown, viscous liquid remains behind.

0.2584 gave 0.6633 CO₂ and 0.1404 H₂O. C = 70.02; H = 6.03.

0.2213 „ 0.5720 CO₂ „ 0.1167 H₂O. C = 70.47; H = 5.86.

0.1780 „ 6.8 c.c. nitrogen at 12° and 757 mm. N = 4.51.

C₁₉H₁₉O₄N requires C = 70.15; H = 5.85; N = 4.31 per cent.

The properties of this substance are those of a lactone and its constitution is probably that shown on p. 436. The silver salt was obtained as a bulky, yellow precipitate which was collected and successively washed with water, alcohol, and ether, and dried in an exhausted desiccator. This salt was prepared several times, but it always contained too much silver, owing possibly to some reduction having taken place.

0.1697 gave 0.0459 Ag. Ag = 27.10.

0.1968 „ 0.0530 Ag. Ag = 26.96.

C₁₉H₂₀O₅NaAg and C₁₉H₁₈O₄NaAg require Ag = 24 and Ag = 25 per cent. respectively.

The calcium salt, obtained by heating an ammoniacal solution of the substance with a 20 per cent. solution of calcium chloride, has a yellow colour.

0.1912 gave 0.0162 CaO. Ca = 8.4.

(C₁₉H₁₈O₄N)₂Ca requires Ca = 8.14 per cent.

A weighed amount of the pure substance was dissolved in chloroform and a solution containing 2.91 grams of bromine in 100 grams of this solvent added until the colour, which disappeared rapidly at first, became permanent. The amount added corresponded with 3 molecules of bromine, and hydrogen bromide was evolved. A white substance crystallised in needles (m. p. 175°). The filtrate left a very slight residue on evaporation.

0.1110 gave 0.1152 AgBr. Br = 44.15.

$C_{19}H_{14}O_3NBr_3$ requires Br = 44.11 per cent.

No insoluble product was obtained by shaking up an alkaline solution of the substance with benzoyl chloride. The compound was saponified by dissolving in alcohol and adding from 2 to $2\frac{1}{2}$ times the theoretical amount of 50 per cent. caustic potash. After the solution had been left for a week, the potassium salt, which had separated in yellow needles, was collected and dissolved in water. Carbon dioxide was passed through the solution and acetic acid then added, but in neither case was a precipitate obtained, although the original substance is easily thrown down by both these reagents. However, on adding hydrochloric acid, a straw-coloured substance was deposited.

This acid is soluble in hot water, separating again on cooling; it is not easily recrystallised, but separates best from aqueous methyl alcohol. Boiling should be avoided as decomposition sets in; the acid melts and decomposes at 91—93°.

0.1239 gave 0.3102 CO_2 and 0.0584 H_2O . C = 68.26; H = 5.23.

0.1225 „ 0.3073 CO_2 „ 0.0584 H_2O . C = 68.44; H = 5.34.

$C_{17}H_{15}O_4N$ requires C = 68.68; H = 5.05 per cent.

0.1226 required 11.0 c.c. baryta solution [1 c.c. = 0.0032 $Ba(OH)_2$].

Found M. W. = 298. $C_{17}H_{15}O_4N$ requires M. W. = 297.

The acid is therefore monobasic and has the constitution

Ethyl *o*-tolylglycinoacetate behaves similarly and yields an acid which crystallises from alcohol and melts at 165°.

Action of Ammonia on Ethyl Phenylglycinoacetate.—On adding an excess of concentrated ammonia solution (0.88) to an alcoholic solution of this ester, there separated after some time a white substance which melted at 238° and was insoluble in cold water, but readily soluble in acids. Ammonia is evolved on heating with caustic soda.

0.1852 gave 32.3 c.c. nitrogen at 14° and 744.5 mm. N = 20.10.

The diamide, $C_6H_5N(CH_2 \cdot CO \cdot NH_2)_2$, requires N = 20.28 per cent.

Ethyl *o*-tolylglycinoacetate treated in the same way is at first deposited unchanged (m. p. 60°). When left for several days in contact with its mother liquor, the ester disappears, and on evaporation a white substance crystallises out in needles (m. p. 160—161°). This was found to have the same properties as the phenyl derivative.

0.1840 gave 29.0 c.c. nitrogen at 14° and 764.5 mm. N = 18.66.

The diamide, $C_7H_7 \cdot N(CH_2 \cdot CO \cdot NH_2)_2$, requires N = 19.0 per cent.

Condensation of Phenylglycinoacetic Esters with Oxalic Esters in Presence of Alkylloxides.

One molecular proportion of sodium in the form of wire was heated in a reflux apparatus with slightly more than the theoretical amount of absolute alcohol required to convert it into the ethoxide. A mixture of one molecule of each ester was gradually poured down the condenser, the liquid being gently heated. After an interval of from 5—20 minutes, depending on the ester used, an energetic reaction took place and the pasty mass became solid and was then heated on the water-bath for an hour. When cold, the solid mass was dissolved in water, a considerable amount of solvent being required owing to its insolubility. Any unchanged ester was extracted by shaking up with a little ether. On gradually adding dilute hydrochloric acid, the sodium salt was decomposed and the condensation product precipitated in the crude state. All the following substances are conveniently recrystallised from alcohol.

The Condensation of Ethyl Phenylglycinoacetate, Ethyl Oxalate, and Sodium Ethoxide.—This condensation was carried out many times with varying proportions and the product obtained was always the same, but only with the following proportions was the reaction complete: 2·3 grams of sodium (1 mol.) were heated with rather more than 4·6 grams (1 mol.) of absolute alcohol. To this was added a mixture of 13·25 grams (1 mol.) of ethyl phenylglycinoacetate and 7·3 grams (1 mol.) of ethyl oxalate. On treating the product in the manner described, 13—15 grams of substance were obtained, corresponding with an 80 per cent. yield. This substance recrystallises from alcohol in long, silky needles which are quite white after two crystallisations; it is very soluble in chloroform, but less readily so in glacial acetic acid, from which solvent it crystallises very well. The solubility in ether is slight, and from this solution are obtained small, brilliant crystals (m. p. 137°). The compound is insoluble in water or in sodium carbonate solution; cold aqueous caustic soda dissolves it, forming a yellow solution; it is insoluble in concentrated hydrochloric acid, but dissolves readily in concentrated sulphuric acid. An alcoholic solution of ferric chloride develops a dark greenish-blue coloration; silver nitrate is reduced at once in the cold. The barium salt is yellow, the copper salt greenish-blue, and the lead salt white.

An alcoholic solution was heated with phenylhydrazine dissolved in glacial acetic acid; in another experiment, the two compounds were heated directly together for varying times. In no case did condensation take place, the substance crystallising out unchanged. Negative results were also obtained with hydroxylamine and with the Schotten-

Baumann reaction. The substance was distilled under the ordinary pressure; it melted and almost at once emitted fumes which solidified in the receiver and in the side tube of the flask. This solid, when crystallised from alcohol, melted at 137° , and therefore consisted of the unaltered substance.

0.2585 gave 0.5734 CO_2 and 0.1240 H_2O . $\text{C} = 60.49$; $\text{H} = 5.33$.

0.2195 „ 0.4823 CO_2 „ 0.1078 H_2O . $\text{C} = 59.97$; $\text{H} = 5.45$.

0.1269 „ 5.0 c.c. nitrogen at 14.5° and 753 mm.; $\text{N} = 4.58$.

$\text{C}_{16}\text{H}_{17}\text{O}_6\text{N}$ requires $\text{C} = 60.19$; $\text{H} = 5.33$; and $\text{N} = 4.38$ per cent.

This empirical formula gives a molecular weight 319. The substance must contain at least one atom of nitrogen, and the percentage of nitrogen found leads to a molecular weight of 306.

The substance was dissolved in 100 c.c. of alcohol and titrated against baryta [1 c.c. = 0.0065 $\text{Ba}(\text{OH})_2$].

0.2030 gram of the substance required 17.0 c.c. for neutralisation, deducting 1 c.c. required by the alcohol. Equivalent weight = 157.5.

This result shows the acid to contain two hydroxyl groups and to have $\text{M. W.} = 315$. $\text{C}_{16}\text{H}_{17}\text{O}_6\text{N}$ requires $\text{M. W.} = 319$; 0.1158 dissolved in 18.83 benzene gave $\Delta t = 0.098^{\circ}$. $\text{M. W.} = 307.4$.

The number of alkoxy groups present in the molecule was determined by Zeisel's method. The substance used was that which was obtained from ethyl phenylglycinoacetate, methyl oxalate, and sodium methoxide, melting at 188° .

0.1909 gave 0.301 AgI . $\text{OMe} = 20.8$.

$\text{C}_{14}\text{H}_{13}\text{O}_6\text{N}$ requires $\text{OMe} = 21.3$ for two methoxy groups.

No reaction takes place with phenylcarbimide in the cold but, on warming gently, a solution was obtained which remained clear for some time and slowly deposited white crystals on cooling. The precipitate was collected and recrystallised from aqueous alcohol (m. p. 169°). This substance possesses very different properties from the original. Ferric chloride no longer gives a coloration, and no yellow coloration is obtained with caustic soda in the cold; this only appears on boiling, when decomposition takes place and the odour of carbimide is observed. Silver nitrate is no longer reduced in the cold.

0.213 gave 12.1 c.c. nitrogen at 16° and 754 mm. $\text{N} = 6.57$.

$\text{C}_{23}\text{H}_{22}\text{O}_7\text{N}_2$ requires $\text{N} = 6.39$ per cent.

This result corresponds with the addition of 1 molecule of phenylcarbimide, and establishes the presence of at least one hydroxyl group.

The presence of hydroxyl groups is further shown by the fact that

if a solution of the substance is treated with a current of dry ammonia it is thrown out unchanged. [View Article Online](#)

Some of the substance, dissolved in chloroform, was treated with a solution of bromine in the same solvent. The colour of the bromine disappeared rapidly at first, fumes of hydrogen bromide being abundantly evolved. The white, crystalline powder, which separated out slowly, was recrystallised from aqueous alcohol, and thus obtained in transparent needles melting at 119—120°. This substance, which was insoluble in caustic soda and gave no coloration with ferric chloride, was identified on analysis as tribromoaniline (m. p. 119°).

It was thought at the outset that the saponification of this substance would be readily brought about, but it was never accomplished.

The substance was left for several days in contact with aqueous and alcoholic caustic potash. At other times, the mixture was heated for 3 hours. In every case, the potassium salt obtained yielded the original substance on acidifying. Acids were then tried, 0.65 gram of the compound being heated for 3 hours with 15 c.c. of concentrated hydrochloric acid. After cooling, the solid matter was collected and found to consist of the unaltered substance. The filtrate, on extraction with ether, yielded only a little tarry matter.

The analogous substances enumerated on p. 437 were prepared in the same manner and showed no difference in properties. Analyses of some of these are now given, and it will be seen that they are derived from the substance $C_{16}H_{17}O_6N$ by the replacement of one or more ethyl groups by methyl. Ethyl phenylglycinoacetate (13.25 grams), when condensed with 1 molecule of methyl oxalate in presence of sodium methoxide, yielded a substance which, after recrystallisation, melted at 188°.

0.2006 gave 0.4225 CO_2 and 0.0866 H_2O . $C = 57.44$; $H = 4.79$.

0.2249 „ 0.4768 CO_2 „ 0.0919 H_2O . $C = 57.81$; $H = 4.54$.

0.1944 „ 8.4 c.c. nitrogen at 14° and 740 mm. $N = 4.94$.

$C_{14}H_{13}O_6N$ requires $C = 57.73$; $H = 4.47$; $N = 4.81$ per cent.

This result corresponds with the replacement of two ethyl by two methyl groups.

By condensation of methyl phenylglycinoacetate with ethyl oxalate in presence of sodium methoxide, a substance melting at 188° is obtained, identical with that just described.

0.2133 gave 0.4539 CO_2 and 0.0931 H_2O . $C = 58.03$; $H = 4.84$.

0.275 gave 12.0 c.c. nitrogen at 14° and 769 mm. $N = 4.81$ per cent.

The third type of compound is illustrated by the condensation product melting at 175°, and obtained from ethyl phenylglycinoacetate and ethyl oxalate in the presence of sodium methoxide.

0.2276 gave 0.4888 CO₂ and 0.1033 H₂O. C = 58.57; H = 5.04. [View Article Online](#)

0.2402 „ 0.5202 CO₂ „ 0.1020 H₂O. C = 59.06; H = 4.72.

0.4970 „ 18.2 c.c. nitrogen at 16° and 770 mm. N = 4.33.

C₁₅H₁₅O₆N requires C = 59.04; H = 4.91; N = 4.58 per cent.

The substance is derived from the original C₁₆H₁₇O₆N by the substitution of one methyl for one ethyl group.

Of the other products, two are identical, melt at 147—148°, and have the formula C₁₅H₁₅O₆N. The remaining two have the formula C₁₄H₁₃O₆N, one melting at 195° and the other at 159°.

For the sake of comparison, 14 grams of ethyl *o*-tolylglycinoacetate were condensed with 6.5 grams of ethyl oxalate in presence of sodium ethoxide. The recrystallised product melted at 146°.

0.3477 gave 12.7 c.c. nitrogen at 15° and 765 mm. N = 4.30.

C₁₇H₁₉O₆N requires N = 4.20 per cent.

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