*p*H of the solution to 7 and heating at 100° for 3 hours.[14] Methylcysteine superimposed γ-aminobutyric acid on these chromatograms, but the latter was effectively removed by using an excess of ion-exchange resin IRC-50.

Aliquots containing 50 μg. of nitrogen were then chromatographed and the amino acids determined quantitatively.[10,11] Standard curves were obtained by treating the pure compounds in the same way as the samples.

Cysteine determinations were made by microbiological assay with *L. mesenteroides*.[12]

(14) P. B. Hamilton, *J. Biol. Chem.*, **158**, 375 (1945).

ITHACA, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

The Formation of N-(N-Acetyl-N-arylglycyl)-N-arylglycines in the Acetylation of N-Arylglycines

BY PHILIP L. SOUTHWICK, HAROLD L. DIMOND[1] AND ROGER E. STANSFIELD[2]

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Treatment of certain N-arylglycines with an excess of acetyl chloride at the reflux temperature resulted in the formation of N-(N-acetyl-N-arylglycyl)-N-arylglycines (II) in yields as high as 72%. N-Arylglycines which yielded products of this type included N-phenylglycine, N-*p*-chlorophenylglycine, N-*m*-chlorophenylglycine, N-*p*-tolylglycine and N-*p*-nitrophenylglycine. Experiments with N-phenylglycine and N-*p*-chlorophenylglycine showed that under certain conditions products of the same type are obtained when acetic anhydride is used. An explanation for the formation of these products has been formulated, based upon the observation that N-(N-acetyl-N-arylglycyl)-N-arylglycines (II) also can be obtained following treatment of a mixture of an N-acetyl-N-arylglycine (III) and an N-arylglycine ester (VI) with an excess of acetyl chloride.

The present investigation was prompted by the observation that treatment of N-*p*-chlorophenylglycine with a large excess of acetyl chloride at the reflux temperature led to an acidic product melting at 216–217°, and not to the expected N-acetyl-N-*p*-chlorophenylglycine, m.p. 175–176°. Similar experiments with N-phenylglycine and with N-*p*-tolylglycine subsequently revealed that under the same conditions other N-arylglycines (I) also yielded products other than those which would result from simple acetylation. It therefore became of interest to investigate the structures of the compounds obtained in this manner and to seek an explanation for the unexpected type of reaction which had occurred.

The composition and neutralization equivalents of the compounds indicated that they were N-(N-acetyl-N-arylglycyl)-N-arylglycines (II),[3] formed by the over-all reaction

$$2\underset{\text{I}}{\text{ArNHCH}_2\text{CO}_2\text{H}} + 2\text{CH}_3\text{COCl} \longrightarrow \underset{\text{II}}{\text{CH}_3\text{CONCH}_2\text{CONCH}_2\text{CO}_2\text{H}} + \text{CH}_3\text{CO}_2\text{H} + 2\text{HCl}$$

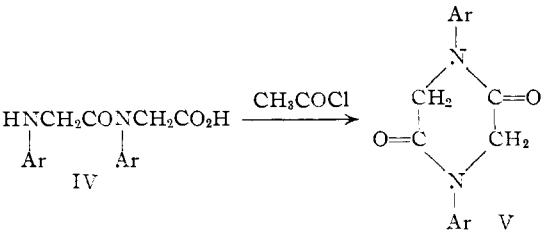
(Ar on the first N and on the second N)

The infrared absorption spectrum which was determined for the product from N-*p*-chlorophenylglycine seemed in accord with this interpretation, for the bands which were observed in the 5–7 μ region occurred at 6.22 and 6.70 μ (assigned to the substituted phenyl groups) and at 5.76 and 5.95 μ (assigned to carboxylic acid and amide carbonyl groups, respectively). In order to confirm the structure, however, and at the same time to gain some insight into the manner in which the compounds, II, were formed, a number of attempts were made to achieve the synthesis of a compound of this type from intermediates which might conceivably be involved in the reaction process.

The compounds, II, evidently did not arise as a result of an acyl replacement brought about in any manner by a reaction involving two molecules of an intermediate N-acetyl-N-arylglycine (III); N-acetyl-N-*p*-chlorophenylglycine (III, Ar = *p*-ClC_6H_4) was recovered unchanged after being heated with excess acetyl chloride

$$\underset{\text{III (Ar)}}{2\text{CH}_3\text{CONCH}_2\text{CO}_2\text{H}} \xrightarrow{\text{CH}_3\text{COCl}} \text{II} + \text{CH}_3\text{CO}_2\text{H}$$

Moreover, these compounds did not result from acetylation of an intermediate N-(N-arylglycyl)-N-arylglycine (IV), for treatment of N-(N-phenylglycyl)-N-phenylglycine (IV, Ar = C_6H_5) with acetyl chloride produced 1,4-diphenyl-2,5-diketopiperazine (V, Ar = C_6H_5), and the diketopiperazine was recovered unchanged after heating at the reflux temperature with acetyl chloride



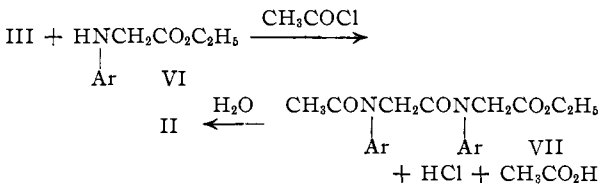
It seems reasonable to conclude, therefore, that the acetylated dipeptides II were formed during the acetylation process by the reaction of an acylating agent derived from an intermediate N-acetyl-N-arylglycine (III) with a portion of the original N-arylglycine (I) which had not yet been acetylated on nitrogen.

(1) Institute Fellow in Organic Chemistry, 1951–1953.

(2) Research Corporation Fellow, 1953–1954. This paper is based mainly on a portion of a thesis submitted by Roger E. Stansfield in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Carnegie Institute of Technology, July, 1954.

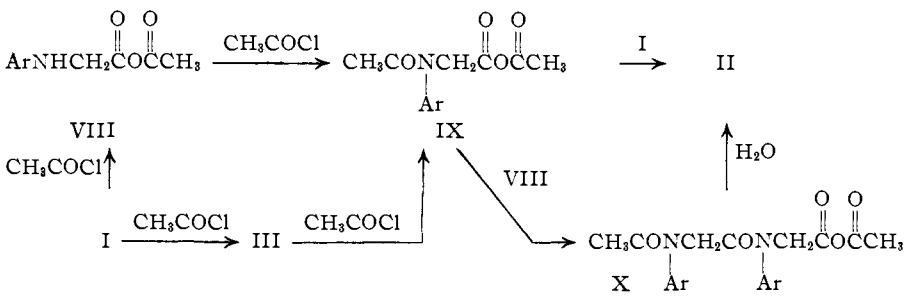
(3) This result is reminiscent of the observation of T. Curtius, *J. prakt. Chem.*, [2] **24**, 239 (1881); [2] **26**, 145 (1882), that hippurylglycine is one of the products of the reaction of benzoyl chloride with the silver salt of glycine. It should be noted, however, that the acylation of α-amino acids with acid chlorides to give the expected simple N-acyl derivatives has been carried out successfully in a number of instances; see E. Ronwin, *J. Org. Chem.*, **18**, 127 (1953).

This hypothesis was supported by the results of two experiments. In the first an equimolecular mixture of N-acetyl-N-*p*-chlorophenylglycine (III, Ar = *p*-ClC_6H_4) and N-*p*-chlorophenylglycine ethyl ester (VI, Ar = *p*-ClC_6H_4) was heated with excess acetyl chloride. Following saponification of the crude reaction product N-(N-acetyl-N-*p*-chlorophenylglycyl)-N-*p*-chlorophenylglycine (II, Ar = *p*-ClC_6H_4) was obtained in almost precisely the same yield (72%) as that produced by treatment of N-*p*-chlorophenylglycine (I, Ar = *p*-ClC_6H_4) directly with acetyl chloride. In the second experiment an equimolecular mixture of N-acetyl-N-phenylglycine (III, Ar = C_6H_5) and N-*p*-chlorophenylglycine ethyl ester (VI, Ar = *p*-ClC_6H_4), after similar treatment, yielded a product which was evidently the expected N-(N-acetyl-N-phenylglycyl)-N-*p*-chlorophenylglycine, a compound of type II in which the two aryl groups were different. Although the yield in the second experiment was low (16%), the results of the two experiments taken together seemed to demonstrate conclusively that reactions could be achieved of the form[4]

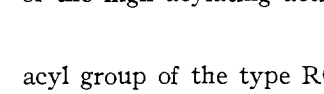


An analogous process, in which the role of the N-arylglycine ester VI is taken by the N-arylglycine (I) as such (or possibly by the N-arylglycine in the form of a mixed anhydride (VIII)) could thus easily account for the formation of the acetylated dipeptides II when the N-arylglycines alone are treated with acetyl chloride.

On the basis of this conclusion and the assumption that the form of the N-acetyl-N-arylglycines (III) in which they function as active acylating agents is probably that of the mixed anhydrides IX, it is possible to explain our observations by means of the reactions



The formation of the acetylated dipeptides II as the chief reaction products demands that the simple N-acetylations I → III or VIII → IX be slower than the acylations I + IX → II or VIII + IX → X, even in the presence of a very large excess of acetyl chloride. These results therefore provide what would appear to be a striking demonstration of the high acylating activity of an α-substituted



acyl group of the type RCONCHCO– when combined in a mixed anhydride structure. Wieland has remarked upon this high activity in a recent discussion[5] of new methods of peptide synthesis and has cited an experiment of Boissonnas and Schumann (see footnote 4) as an illustration. Wieland has also cited evidence that the formation of mixed anhydrides from acid chlorides is often very rapid, as, indeed, it would need to be if it plays the assumed role in producing the results recorded here.

What effect, if any, is exerted upon the course of these reactions by the hydrogen chloride formed is not clear. Since the strongest basic function present is the nitrogen of the N-arylglycines (I) (or of their mixed anhydrides VIII), it would be expected that hydrochlorides of the compounds I and/or VIII would be formed as the reactions progressed. The yields in excess of 50% make it evident, however, that the occurrence of hydrochloride formation is considerably less than completely effective in preventing N-acylation of I or VIII. In an experiment in which N-phenylglycine hydrochloride was heated with excess acetyl chloride no reaction occurred, but the failure to react may well have been due to the fact that the preformed hydrochloride was not appreciably dissolved by the pure acetyl chloride.

A few acetylation experiments also have been performed in which acetic anhydride has been substituted for acetyl chloride. In the past, the treatment of N-phenylglycine and N-*p*-tolylglycine with relatively small excess quantities of acetic anhydride at room temperature has been employed for the preparation of the simple acetylation products III.[6] However, we have observed that the heating of N-phenylglycine with a larger excess of acetic anhydride produced a mixture of acetylation products containing a considerable amount of the acetylated dipeptide II, and similar treatment of N-*p*-chlorophenylglycine gave this type of product in 70% yield. The factors which determine which reaction course will predominate have not as yet been defined. It was evident from evolution of heat and the changes in the appearance of the undissolved solids that both acetyl chloride and acetic anhydride react quite rapidly with N-phenylglycine at room temperature, but whereas, when acetic anhydride was used, N-acetyl-N-phenylglycine (III, Ar = C_6H_5) was obtained in yields exceeding

(4) Recently R. A. Boissonnas and I. Schumann, *Helv. Chim. Acta*, **35**, 2229 (1952), carried out an analogous reaction under quite different conditions. Approximately one equivalent of ethyl chloroformate was added to a mixture containing an equivalent each of phthalylglycine and glycine ethyl ester, and an excess of tri-*n*-butylamine, with the result that phthalylglycylglycine ethyl ester was produced in 58% yield.

(5) T. Wieland, *Angew. Chem.*, **66**, 507 (1954). Wieland reviews new methods of peptide synthesis with particular attention to those based upon the use of mixed anhydrides which have been introduced by himself, by J. R. Vaughan and by R. A. Boissonnas.

(6) C. A. Bischoff and A. Hausdorfer, *Ber.*, **25**, 2270, 2280 (1892).

50% after a reaction period of a few minutes starting at room temperature, the acetyl chloride mixtures yielded only traces of acid-insoluble material with properties suggesting that it was a mixture of products of the types II and III. With acetyl chloride the initial rapid reaction which was evident may have merely produced mixed anhydrides of type VIII, or their hydrochlorides.

In order to discover whether acetylation with acetyl chloride leads to similar results with N-arylglycines in general, experiments were performed with a total of nine such compounds. Of this number there were five which yielded N-(N-acetyl-N-arylglycyl)-N-arylglycines (II). These were N-phenylglycine (65% yield), N-*p*-tolylglycine (28% yield), N-*p*-chlorophenylglycine (72% yield), N-*m*-chlorophenylglycine (14.6% yield) and N-*p*-nitrophenylglycine (33% yield). On the other hand, in the case of three of the compounds, *p*-methoxyphenylglycine, N-*o*-tolylglycine and N-*o*-chlorophenylglycine, the only product isolated was the simple N-acetyl-N-arylglycine (III). The yield of this type of product was reasonably good in the case of N-*o*-chlorophenylglycine (68%), but low with *p*-methoxyphenylglycine (17.7%) and N-*o*-tolylglycine (5%). *m*-Nitrophenylglycine gave an oily mixture from which no pure product was isolated. Thus there is an indication that *o*-substituents favor simple acetylation and that perhaps base-strengthening groups such as the *p*-methoxy group may have the same effect. However, it must be mentioned that the initial crystallization of many of the acetylated dipeptides II was difficult to start and slow to reach completion. The yield obtained and even the nature of the product isolated may in some cases have been determined to a considerable extent by this difficulty in the first crystallization. There were indications that crystallization of either type of product (II or III) from a hydrolyzed reaction mixture was particularly slow and incomplete when both types happened to be formed in somewhat comparable amounts. It seems doubtful that in any of these experiments either II or III was formed to absolute exclusion of the other.

In addition to the N-(N-acetyl-N-arylglycyl)-N-arylglycines (II), a number of previously unreported derivatives of several of the N-arylglycines were prepared and are described in the Experimental section. A number of N-acetyl-N-arylglycines (III) were prepared by dissolving the corresponding N-arylglycines (I) in an aqueous sodium carbonate solution and treating the solution with acetic anhydride as in the procedure described by Lumiere, Lumiere and Barbier.[7] Apparently only the expected simple acetylation takes place under these conditions.

Experimental[8,9]

Preparation of N-(N-Acetyl-N-arylglycyl)-N-arylglycines (II). A. By Treatment of N-Arylglycines with Acetyl Chloride.—The N-arylglycines were mixed with an excess of acetyl chloride, which served as the solvent for the reaction. The mixture was then heated under reflux for periods ranging from 30 minutes to 3.5 hours, during which time the N-arylglycine dissolved. The reaction mixtures were then added cautiously to an excess of ice or cold water (about 50 g. in the case of runs on the usual scale) to destroy the unused acetyl chloride and precipitate the product. The acetylated dipeptides (II) often separated rather slowly, and sometimes in the form of oils. It was therefore frequently advisable to allow the mixtures to stand for 12 hours after the addition of water to allow for complete precipitation and, if possible, crystallization of the crude product if the precipitate was oily at first. The crude products were recrystallized from 95% ethanol to yield white crystals or micro-crystalline powders. The periods of heating used and yields of recrystallized product obtained in the preparation of individual N-(N-acetyl-N-arylglycyl)-N-arylglycines are given below along with the characterizing data:

N-(N-Acetyl-N-phenylglycyl)-N-phenylglycine: heating period 1 hour, yield 5.3 g. (65%) from 7.5 g. (0.05 mole) of N-phenylglycine and 20 ml. of acetyl chloride; m.p. 203–204°.

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.58; neut. equiv., 326. Found: C, 66.25; H, 5.62; N, 8.54; neut. equiv., 329.

N-(N-Acetyl-N-*p*-chlorophenylglycyl)-N-*p*-chlorophenylglycine: heating period 3 hours, yield 7.1 g. (72%) from 9.35 g. (0.05 mole) of N-*p*-chlorophenylglycine[10] and 50 ml. of acetyl chloride; m.p. 216–217°

Anal. Calcd. for $C_{18}H_{16}O_4N_2Cl_2$: C, 54.75; H, 4.08; N, 7.09; neut. equiv., 395. Found: C, 54.99; H, 4.03; N, 6.70; neut. equiv., 394.

N-(N-Acetyl-N-*m*-chlorophenylglycyl)-N-*m*-chlorophenylglycine: heating period 30 minutes, yield 0.93 g. (14.6%) from 6.0 g. (0.032 mole) of N-*m*-chlorophenylglycine[11] and 25 ml. of acetyl chloride; m.p. 188–189°.

Anal. Calcd. for $C_{18}H_{16}O_4N_2Cl_2$: C, 54.75; H, 4.08; N, 7.09; neut. equiv., 395. Found: C, 54.40; H, 4.06; N, 7.00; neut. equiv., 380.

N-(N-Acetyl-N-*p*-nitrophenylglycyl)-N-*p*-nitrophenylglycine: heating period 3.5 hours, yield 3.5 g. (33%) from 10 g. (0.051 mole) of N-*p*-nitrophenylglycine[12] and 25 ml. of acetyl chloride; m.p. 204–205°.

Anal. Calcd. for $C_{18}H_{16}O_8N_4$: C, 51.92; H, 3.87; N, 13.46; neut. equiv., 416. Found: C, 52.10; H, 3.85; N, 13.5; neut. equiv., 420.

N-(N-Acetyl-N-*p*-tolylglycyl)-N-*p*-tolylglycine: heating period 30 minutes, yield 1.5 g. (28%) from 5 g. (0.03 mole) of N-*p*-tolylglycine[6] and 25 ml. of acetyl chloride; m.p. 219–220°.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.91; neut. equiv., 354. Found: C, 67.64; H, 6.21; N, 7.90; neut. equiv., 349.

B. By Treatment of an N-Arylglycine with Acetic Anhydride. Preparation of N-(N-Acetyl-N-*p*-chlorophenylglycyl)-N-*p*-chlorophenylglycine.—A mixture of 2.0 g. (0.0108 mole) of N-*p*-chlorophenylglycine and 20 ml. of acetic anhydride was heated under reflux for 90 minutes. The excess acetic anhydride was then removed by evaporation in a stream of air. After crystallization from ethanol the residual oil yielded 1.5 g. (a 70% yield) of N-(N-acetyl-N-*p*-chlorophenylglycyl)-N-*p*-chlorophenylglycine identical with the product obtained with acetyl chloride.

C. By Treatment of a Mixture of an N-Acetyl-N-arylglycine and the Ethyl Ester of an N-Arylglycine with Acetyl Chloride.—This procedure was employed to prepare two of the N-(N-acetyl-N-arylglycyl)-N-arylglycines (II), one of which had previously been prepared by methods A and B. The details of the procedure were somewhat different in the two cases.

N-(N-Acetyl-N-*p*-chlorophenylglycyl)-N-*p*-chlorophenylglycine.—A mixture of 5 g. (0.022 mole) of N-acetyl-N-*p*-chlorophenylglycine[13] and 4.7 g. (0.022 mole) of N-*p*-chloro-

(7) A. Lumiere, L. Lumiere and H. Barbier, *Bull. soc. chim.*, [3] **33**, 786 (1905).

(8) Melting points are corrected.

(9) Microanalyses by Drs. G. Weller and F. B. Strauss, Oxford, England, and by Micro Tech Laboratories, Skokie, Ill.

(10) W. Baker, W. D. Ollis and V. D. Poole, *J. Chem. Soc.*, 313 (1949).

(11) C. G. Schwalbe, W. Schulz and H. Jochheim, *Ber.*, **41**, 3792 (1908).

(12) W. Borsche and J. Camper-Titsingh, *ibid.*, **40**, 5008 (1907). The material used in this experiment was prepared by the acid hydrolysis of N-*p*-nitrophenylglycine ethyl ester, preparation of which is described below.

(13) P. L. Southwick and H. L. Dimond, THIS JOURNAL, **76**, 5667 (1954).

phenylglycine ethyl ester[10] was heated with 50 ml. of acetyl chloride for 20 minutes under reflux. An oil separated when the reaction mixture was added to approximately 50 g. of ice. The oil, which did not solidify after standing for some time, was dissolved in excess 5% aqueous sodium hydroxide by heating for 15 minutes at the boiling point. Acidification of the resulting solution precipitated 6.2 g. (a 72% yield) of N-(N-acetyl-N-*p*-chlorophenylglycyl)-N-*p*-chlorophenylglycine, m.p. 214–216°. There was no melting point depression when this product was mixed with the products obtained from N-*p*-chlorophenylglycine by methods A or B.

N-(N-Acetyl-N-phenylglycyl)-N-*p*-chlorophenylglycine.—A mixture of 9.5 g. (0.05 mole) of N-acetyl-N-phenylglycine[6,7] and 10.5 g. (0.05 mole) of N-*p*-chlorophenylglycine ethyl ester[10] was heated under reflux with 50 ml. of acetyl chloride for 30 minutes. The mixture was then poured over ice. An oil which separated gradually dissolved as the mixture was allowed to stand. Concentration of the resulting solution by evaporation under an air stream caused the separation of 3 g. (a 16% yield) of white crystals, which were recrystallized from 95% ethanol. The product melted at 153–156°.

Anal. Calcd. for $C_{18}H_{17}O_4N_2Cl$: C, 59.92; H, 4.75; N, 7.77. Found: C, 59.70; H, 4.66; N, 7.95.

D. Other Attempted Methods.—N-(N-Phenylglycyl)-N-phenylglycine[14,15] (9 g.), prepared in the crude form by the saponification of 1,4-diphenyl-2,5-diketopiperazine, was refluxed with excess acetyl chloride. Addition of the mixture to ice caused the separation of 8.0 g. (60% yield) of 1,4-diphenyl-2,5-diketopiperazine.

The refluxing of 1,4-diphenyl-2,5-diketopiperazine[14] with excess acetyl chloride for one hour and hydrolysis of the excess acetyl chloride by pouring the mixture onto ice resulted in a 94% recovery of the diketopiperazine. Similarly, refluxing of a mixture of N-acetyl-N-*p*-chlorophenylglycine with excess acetyl chloride for 30 minutes resulted in a 90% recovery of the starting material.

N-Acetyl-N-arylglycines.—A number of these compounds were prepared for comparison with the acetylated dipeptides. They were made by treating solutions of the N-arylglycines in aqueous sodium carbonate with acetic anhydride according to the procedure of Lumiere, Lumiere and Barbier.[7] The following were new compounds:

N-Acetyl-N-*m*-tolylglycine: yield 92%, m.p. 146–147° when crystallized from hot water.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.90; H, 6.60; N, 7.21.

N-Acetyl-N-*m*-chlorophenylglycine: yield 33%, m.p. 167–168° after crystallization from 95% aqueous ethanol.

Anal. Calcd. for $C_{10}H_{10}O_3NCl$: C, 52.76; H, 4.43; N, 6.16. Found: C, 52.75; H, 4.47; N, 6.10.

(14) P. W. Abenius, *J. prakt. Chem.*, [2] **40**, 425 (1889).

(15) A. Hausdorfer, *Ber.*, **21**, 1665 (1889). Hausdorfer reports that this compound undergoes ring closure when warmed with dilute hydrochloric acid, or even upon standing.

N-Acetyl-N-*o*-chlorophenylglycine.—This compound had been reported previously,[11] but with a melting point of 210°; our yield was 88%, m.p. 219–220° after crystallization from 95% ethanol.

Anal. Calcd. for $C_{10}H_{10}O_3NCl$: C, 52.76; H, 4.43; N, 6.15. Found: C, 52.81; H, 4.68; N, 6.02.

This compound was also obtained by treating N-*o*-chlorophenylglycine with refluxing acetyl chloride; heating period 90 minutes, yield 4.5 g. (68%) from 5.4 g. (0.29 mole) of N-*o*-chlorophenylglycine and 25 ml. of acetyl chloride.

N-*p*-Nitrophenylglycine Ethyl Ester.—A mixture of 16.7 g. (0.1 mole) of ethyl bromoacetate, 14 g. (0.1 mole) of *p*-nitroaniline and 13.6 g. (0.1 mole) of sodium acetate trihydrate was refluxed for two hours. The mixture was poured into cold water and the solid product was recrystallized from 95% ethanol to yield 20 g. (92% yield) of N-*p*-nitrophenylglycine ethyl ester, m.p. 132–134°.

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.50. Found: C, 53.64; H, 5.46; N, 12.2.

N-*p*-Nitrophenylglycine[12] was obtained from the ethyl ester in 90% yield by hydrolysis with refluxing 10% hydrochloric acid for a period of 30 minutes.

Experiments on the Acetylation of N-Phenylglycine at Room Temperature.—Parallel experiments were performed in which a 10-ml. portion of either acetyl chloride or acetic anhydride was added to a 2-g. portion of N-phenylglycine. In the acetyl chloride experiment bubbling of the liquid was noticed immediately and the yellow color of the undissolved solids became lighter. In the case of the acetic anhydride the mixture warmed perceptibly and the solids took on a more granular appearance. After each of the reaction mixtures had been allowed to stand for 10 minutes with intermittent agitation, the liquid was decanted from the solid and water (approximately 80 ml.) was added both to the residual solid and to the decanted liquid.

In the acetyl chloride experiment the solid dissolved in the added water, but in the acetic anhydride experiment solution did not occur until the mixture had been made alkaline by addition of sodium carbonate. The mixture from the acetyl chloride experiment was also made alkaline with sodium carbonate, and solutions from both experiments were then acidified to congo red with hydrochloric acid. The solution from the acetic anhydride experiment began at once to deposit crystals of N-acetyl-N-phenylglycine, and a yield of 1.4 g. (56%) of the product separated, m.p. 193–194°. After 3 days only 0.1 g. of crystals, m.p. 165–200°, had separated from the solution from the acetyl chloride experiment.

In neither experiment did more than a trace of precipitate result from the hydrolysis of the decanted liquid.

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PITTSBURGH 13, PENNSYLVANIA