

The 1-arylpiperazine (0.10 mole) was thoroughly mixed with the 1,2-epoxide in an Erlenmeyer flask, and allowed to stand for from one to two days. Either a crystalline solid or a viscous liquid, which showed no tendency to flow, was formed. In some cases crystallization was induced by scratching the flask or by seeding. Purification of these products was extremely difficult. Ethanol proved to be the best crystallizing solvent for all the reported products except 1-(2-chlorophenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl] piperazine. It was crystallized from freshly distilled ethyl ether.

The omissions of certain members of series result from the fact that analytical samples of these members could not be obtained. Data concerning the new compounds prepared are given in Table I.

The 1,2-epoxydodecane was obtained from the Becco Chemical Division of Food Machinery Chemical Corp. The 1,2-epoxy-3-aryloxypropanes were prepared by Dr. Jaime B. Fernandez using the method of the Shell Development Co.¹⁵

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(15) Shell Development Co., Emeryville, Calif. Technical Booklet SC: 49-35, p. 18 (1949).

[CONTRIBUTION FROM JOHN HARRISON LABORATORY OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

A Procedure for Phthaloylation under Mild Conditions

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By allowing phthalic anhydride to react with a number of amino acids and related primary amines in refluxing nonpolar solvents in the presence of triethylamine and separating the water formed, the phthalimide derivative may be prepared in good yield and without racemization. Phthaloylation without racemization may also be carried out in *N,N*-dimethylformamide medium.

Sheehan, Chapman, and Roth³ have shown that phthaloylation by the fusion of an amino acid with phthalic anhydride can lead to racemization if the reaction temperature is higher than 150°. More recently it has been reported⁴ that some substituted amino acids like *N*-benzylcysteine undergo racemization if the fusion temperature exceeds 110°. Baker and co-workers⁵ have reported a mild two-step process for phthaloylation which involves the preparation of a phthalamic acid in the first step and its cyclization *via* a mixed anhydride in the second step. Evidently this process is suitable only for those amino compounds which do not also possess a free carboxyl group. Balenović and Gašpert⁴ have developed a two-step procedure applicable to amino acids which involves the cyclization of a phthalamic ester obtained by the reaction of an amino acid with *o*-carbethoxythiobenzoic acid.

We wish to report here a one-step process for phthaloylation that avoids high temperature.

This phthaloylation procedure consists in treating one equivalent of phthalic anhydride with an amino compound in a refluxing solvent (*e.g.*, toluene or benzene) in the presence of triethylamine, a water separator being used to remove the water formed in the reaction. In the phthaloylation of an amino acid the best yield is obtained when the quantity of triethylamine used is about one-tenth of an equivalent.

Using this method ethyl phthalimidoacetate was obtained from glycine ethyl ester hydrochloride in 96% yield when toluene was the reaction medium. When, however, a water separator was not used the yield was reduced to 50%; the rest of the glycine ester was presumably in the form of the corresponding phthalamic acid because on standing in a dilute hydrochloric acid solution, this material was slowly converted to ethyl phthalimidoacetate. Drefahl and Fischer⁶ have recently reported that mineral acids catalyze the dehydration of some phthalamic acids to phthalimide derivatives in the presence of an excess of water.

Due to the instability of aminoacetonitrile to heat, the fusion method is unsuitable for the phthaloylation of this compound. However, by treating aminoacetonitrile bisulfate with phthalic anhydride and triethylamine in benzene medium, phthal-

(1) Supported in part by U. S. Public Health Service Grant CY-2189.

(2) Supported in part by U. S. Public Health Service Grant CY-2790.

(3) J. C. Sheehan, D. W. Chapman, and R. W. Roth, *J. Am. Chem. Soc.*, **74**, 3822 (1952).

(4) K. Balenović and Gašpert, *Chem. & Ind. (London)*, 115 (1957).

(5) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).

(6) G. Drefahl and F. Fischer, *Ann.*, **610**, 166 (1957).

imidoacetonitrile was prepared in 81% yield. The yield dropped when a higher reaction temperature was provided by substituting toluene for benzene. Reaction of phthalic anhydride and aminoacetonitrile bisulfate in pyridine at 85–90° gave phthalimidoacetonitrile in 85.5% yield.

It has been reported⁷ that by treating phthalic anhydride with glycine in refluxing *p*-cymene (b.p. 177°) and separating the water formed, *N*-phthaloylglycine is obtained in 90% yield. We found that when refluxing toluene (b.p. 110°) was substituted for *p*-cymene, the water separated was 30% but the yield of phthaloylglycine was 70%. Addition of 3% of one equivalent of triethylamine led to 52% water separation and the formation of *N*-phthaloylglycine in 80% yield. The yield of the phthaloylated product rose to 90% when 10% of one equivalent of triethylamine was used. Excess triethylamine afforded the calculated amount of water but an 80% yield of phthaloylglycine. When toluene was replaced by benzene as the reaction medium, the yield of phthaloylglycine was lowered to 55%.

Fischer⁸ had prepared *N*-phthaloyl-L-alanine, $[\alpha]_D^{20} -17.8^\circ$, in 68% yield by fusing together phthalic anhydride and L-alanine for seven hours. Using our method *N*-phthaloyl-L-alanine was obtained in 91.3% yield in less than three hours and its rotation was found to be higher ($[\alpha]_D^{24} -24.2^\circ$) than that reported by Fischer.

Phthaloylation of D-phenylalanine by this method was found to proceed without racemization.

Reaction of an amino compound (without a free carboxyl group) with phthalic anhydride in chloroform medium has been used for obtaining the corresponding phthalamic acid in good yield.⁵ When, however, glycine and phthalic anhydride were heated in refluxing chloroform (b.p. 61°) for five hours, no water separated and phthalic anhydride was recovered in 89% yield. In the presence of triethylamine some water separated and *N*-phthaloylglycine was obtained in a fair yield (see Table 1). When triethylamine was used but the flask was not fitted with a water separator, very little phthaloylglycine was produced. Even with such a low boiling solvent as dichloromethane (b.p. 40°) as the reaction medium, phthaloylation proceeded to the extent of 44%. Thus, by a proper choice of solvent, phthaloylation can be carried out at any temperature and in one step. Furthermore, phthaloylamino acids obtained in this way are essentially pure as indicated by their melting points and need no recrystallization.

It is interesting to note that when triethylamine is present in the reaction mixture, the unreacted phthalic anhydride remains in aqueous solution during the working up. Even when two equivalents

of phthalic anhydride were used for one equivalent of an amino acid in the presence of an excess of triethylamine in chloroform, the water-insoluble product was an oil which partially crystallized on standing. The crystalline material was found to be quite pure phthaloylaminoacid.

Wanag and Veinbergs⁹ found that phthaloylation of α -aminoacids proceeds normally in acetic acid medium but the rate of reaction is slow—in some cases ten hours were required for completion of reaction.

The use of pyridine as the medium for the reaction of phthalic anhydride with α -aminoacids gives poor yield; *N*-phthaloyl-L-leucine prepared in this way showed no racemization.

Baker and co-workers¹⁰ have used boiling *N,N*-dimethylformamide (b.p. 153°) as the reaction medium for phthaloylating certain amino compounds.

We have found that phenylalanine or glycine and an equivalent of phthalic anhydride will react in dimethylformamide (at above 100°) to yield the phthaloyl derivative in more than 80% yield. If, however, the reaction temperature is below 100°, the yield is almost nil. Phthaloylation of D-phenylalanine by this method was found to take place without racemization.

Dioxane has been found to be a suitable medium for the phthaloylation of certain aminoacids.¹¹

Phthalimido-L-glutamic acid and phthalimido-L-aspartic acid have been prepared by the acid hydrolysis of the corresponding ethyl esters^{4,12–16} since direct phthaloylation of these free amino acids leads to racemization and side products.¹³ Two-^{4,16} or three-^{12,15} step methods have been used for converting diethyl L-glutamate hydrochloride and diethyl L-aspartate hydrochloride into the corresponding phthalimidoesters. Using the procedure described above, we have converted diethyl L-glutamate hydrochloride to *N*-phthalyl L-glutamic acid ethyl ester in one step in very good yield and without racemization.

EXPERIMENTAL¹⁷

Ethyl phthalimidoacetate. (a) A suspension of phthalic anhydride (1.5 g.) and glycine ethyl hydrochloride (1.4 g.) in 20 ml. of triethylamine was heated under reflux for 30 min.,

(9) G. Wanag and A. Veinbergs, *Ber.*, **75**, 1558 (1942).

(10) B. R. Baker, J. P. Joseph, and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5905 (1955).

(11) J. C. Sheehan, M. Goodman, and G. P. Hess, *J. Am. Chem. Soc.*, **78**, 1367 (1956).

(12) F. E. King and D. A. A. Kidd, *J. Chem. Soc.*, 3315 (1949).

(13) R. S. Tipson, *J. Org. Chem.*, **21**, 1353 (1956).

(14) J. W. Clark-Lewis and J. S. Fruton, *J. Biol. Chem.*, **207**, 477 (1954).

(15) R. E. King and D. A. A. Kidd, *J. Chem. Soc.*, 2978 (1951).

(16) K. Balenović, B. Gašpert, and N. Štimac, *Croatica Chemica Acta*, **29**, 93 (1957).

(17) All melting points are uncorrected.

(7) J. J. O'Neill, F. P. Veitch, and T. Wagner-Jauregg, *J. Org. Chem.*, **21**, 363 (1956).

(8) E. Fischer, *Ber.*, **40**, 498 (1907).

when a clear liquid and a gum were obtained. The liquid was poured into dilute hydrochloric acid, but no solid separated. On triturating with water, the gum gave 0.25 g. (11%) of colorless ethyl phthalimidoacetate, m.p. 111° (lit.,¹⁸ m.p. 112–113°). In another experiment, heating under reflux was continued for 6 hr., and then triethylamine was removed from the reaction mixture under reduced pressure. When the residue was extracted with ether and the ether solution was evaporated, 1.2 g. (51.5%) of colorless, crystalline material, m.p. 110°, was obtained.

(b) A suspension of phthalic anhydride (1.5 g.) and glycine ethyl ester hydrochloride (1.4 g.) in 10 ml. of triethylamine and 40 ml. of benzene was heated under reflux for 1 hr. On filtering the hot reaction mixture, the calculated amount of triethylammonium hydrochloride was obtained. When the filtrate was evaporated under reduced pressure, a pasty mass was obtained. On triturating this mass with 5 ml. of water, 1 g. (50% yield) of crystalline material, m.p. 107–109°, separated. The filtrate on standing for a few days afforded another 0.45 g. of the product.

(c) A mixture of phthalic anhydride (6.0 g.), glycine ethyl ester hydrochloride (5.6 g.), triethylamine (10 ml.), and toluene (200 ml.) was heated under reflux in a flask fitted with a Dean-Stark tube. The calculated amount of water separated in 2 hr. The hot reaction mixture was filtered and the filtrate further heated for 30 min. Evaporation gave an almost quantitative yield of colorless, crystalline material, m.p. 112–113°. In a second experiment, crystalline material, m.p. 108°, was obtained in 96% yield. Use of xylene in place of toluene gave an equally high yield, but the product was somewhat colored. When benzene was used as the solvent, the yield of material, m.p. 108–110°, was 62%.

Phthalimidoacetonitrile. (a) A mixture of 10 g. of aminoacetonitrile bisulfate, 10 g. of phthalic anhydride, 22 ml. of triethylamine, and 100 ml. of benzene was heated under reflux in a flask fitted with a water separator. All volatile material was removed from the reaction mixture in a steam bath under reduced pressure. The residue was treated with 200 g. of cracked ice. The slightly colored, crystalline solid that separated was collected by filtration, washed with cold water, and dried. The yield of phthalimidoacetonitrile so obtained, m.p. 124–126°, was 9.7 g. (81%).

When toluene was substituted for benzene the higher reaction temperature led to a low yield of highly colored material.

(b) Aminoacetonitrile bisulfate (30 g.) and phthalic anhydride (30 g.) were added to 60 ml. of dry pyridine with shaking. Some heat was evolved and most of the solid went into solution. The reaction mixture was then heated in an oil bath maintained at 90°, giving a clear solution which became dark. Heating was stopped after 1.5 hr. and the reaction mixture was poured over 200 g. of ice. Hydrochloric acid was added until the reaction mixture was acidic. The crystalline solid was collected, washed with 50 ml. of ice cold water, and dried. The yield of phthalimidoacetonitrile so obtained, m.p. 124–125° (after one recrystallization from ethanol, m.p. 127–128°), was 31 g. (85.5%).

Anal. Calcd. for C₁₀H₈N₂O₂: C, 64.51; H, 3.25; N, 15.05. Found: C, 64.73; H, 3.21; N, 14.87.

N-Phthaloylglycine. A mixture of glycine, an equivalent of phthalic anhydride, triethylamine, and a solvent was heated under reflux in a flask fitted with a water separator. At the end of the reaction all volatile matter was removed on a steam bath under reduced pressure and the residual sirup was triturated with dilute acid. The colorless crystalline material that separated was filtered, washed with cold water, and dried. The yields obtained under different reaction conditions are given in Table I. The melting point of the product in each case was very close to that reported,¹⁹ 191–192°.

(18) S. Gabriel, *Ber.*, **40**, 2649 (1907).

(19) E. Drechsel, *J. pract. Chem.*, (2) **27**, 418 (1883).

TABLE 1

REACTION BETWEEN GLYCINE AND AN EQUIVALENT OF PHTHALIC ANHYDRIDE

Reaction Medium	Triethylamine, Eq.	Reaction Time, Hr.	Water Separated, %	Yield of Phthaloylglycine, %
Toluene	...	2.5	30	70
Toluene	0.03	2.5	52	80
Toluene	0.10	2	97	90
Benzene	0.10	2.5	56	55
Toluene	Excess	2.5	100	80
Chloroform	...	5 ^a
Chloroform	Excess	2	...	2.5 ^b
Chloroform	Excess	5	ca. 25	57.5
Methylene dichloride	Excess	4.5	ca. 30	44
<i>N,N'</i> -Dimethylformamide	...	2 (at 110°)	...	83

^a Phthalic anhydride was recovered in 89% yield. ^b No water separator was used.

N-Phthaloyl-L-alanine. (a) A mixture of 1.78 g. of L-alanine (chromatographically pure, $[\alpha]_D^{25}$ 14.5° ($c = 2$ in 2*N* HCl); supplied by Mann Research Laboratories, New York, N. Y.), 3.05 g. of phthalic anhydride, 0.1 ml. of triethylamine, and 50 ml. of toluene was heated under reflux for 2.5 hr. The water separated amounted to 83%. On working up in the general manner indicated for phthaloylglycine, the yield of phthaloyl-L-alanine, m.p. 145–147° (lit.,⁸ m.p. 150–151° with softening starting at 139°) was 4 g. (91.3%). On recrystallization from acetone-petroleum ether mixture, the material was obtained as colorless crystals, m.p. 144–146°, $[\alpha]_D^{25}$ –24.2° ($c = 2.6$ ethanol) (lit.,⁸ $[\alpha]_D^{25}$ –17.8°).

(b) A suspension of 1 g. of L-alanine and 1.66 g. of phthalic anhydride in 10 ml. of *N,N*-dimethylformamide was heated on a water bath. In 45 min. a clear solution was obtained which was poured into water. There was no separation of any solid product. When 0.9 g. of L-alanine, 1.5 g. of phthalic anhydride and 10 ml. of dimethylformamide was heated at 110–115° for 13 hr. and the clear solution so obtained was poured into 90 ml. of water, an emulsion was obtained. On seeding with *N*-phthalyl-L-alanine, 0.7 g. (32% yield) of a crystalline solid, m.p. 144–145° was obtained. (The use of such a large volume of water may have reduced the yield.)

(c) A mixture of 1.8 g. (0.02 mole) of DL-alanine, 6 g. (0.04 mole) of phthalic anhydride, 10 ml. of triethylamine, and 150 ml. of chloroform was heated under reflux for 2.5 hr. Only a small amount of water separated. When all volatile matter was removed from the reaction mixture and dilute acid added, a yellow oil separated which partially crystallized on standing for several hours. The crystals were separated by filtration and washed several times with cold water and on drying 1 g. (23% yield) of phthaloyl-DL-alanine, m.p. 161.5–162.5° (lit.⁹ m.p., 164°) was obtained.

On substituting 1.5 g. of glycine for alanine in the above experiment, the water-insoluble product again was an oil which partially crystallized to afford 1.32 g. (32% yield) of phthaloylglycine, m.p. 191.5–192.5°.

N-Phthaloylphenylalanine. (a) D-phenylalanine (0.459 g.), phthalic anhydride (0.412 g.), triethylamine (2 ml.), and benzene (30 ml.) were heated together under reflux for 2 or 3 hr. On removing the solvent and adding dilute hydrochloric acid, an oil separated that crystallized on standing overnight. The yield was 0.75 g. (58%), m.p. 182–183°, $[\alpha]_D^{25}$ +213° (0.0491 g. in 4 ml. of ethanol) showing 100% optical purity (lit.,⁸ $[\alpha]_D^{25}$ –212° for phthaloyl-L-phenylalanine).

(b) A mixture of 3.02 g. of DL-phenylalanine, 3.00 g. of phthalic anhydride, 2.5 ml. of triethylamine, and 100 ml. of toluene was heated under reflux for 2.5 hr. in a flask fitted

with a water separator. On working up in the manner indicated for glycine, the yield of phthaloyl-DL-phenylalanine, m.p. 176.5–177.5° (lit.,²⁰ m.p. 174–175°), was 5.05 g. (90% yield).

(c) D-Phenylalanine (0.300 g.) and phthalic anhydride (0.254 g.) were heated in 10 ml. of refluxing dimethylformamide for 45 min. The product, isolated by pouring the reaction mixture into 30 ml. of ice and water, weighed 0.43 g. (83.5%) and melted at 175–177°. For a sample recrystallized from aqueous methanol, m.p. 182–183.5°, $[\alpha]_D^{20}$ was +211° (0.0566 g. in 3.5 ml. of ethanol), showing 100% optical purity.

N-Phthaloyl-L-leucine. L-Leucine and phthalic anhydride heated in pyridine at 100–105° for 1 hr. afforded *N*-phthaloyl-L-leucine in poor yield. A sample recrystallized from

(20) J. H. Billman and W. F. Harting, *J. Am. Chem. Soc.*, **70**, 1473 (1948).

aqueous methanol, m.p. 121–122°, showed $[\alpha]_D^{20}$ –25.5° (0.0915 g. in 3.5 ml. ethanol); (lit.,³ m.p. 118.5–119.5°, $[\alpha]_D^{25}$ –24°).

Diethyl N-phthaloyl-L-glutamate. A suspension of 12 g. of diethyl L-glutamate hydrochloride and 7.4 g. of phthalic anhydride in 10 ml. of triethylamine and 150 ml. of toluene was heated under reflux for 2.5 hr. in a flask fitted with a Dean-Stark tube. Nearly the calculated amount of water was collected. The reaction mixture was filtered and the filtrate was washed with dilute hydrochloric acid and then with water and dried over sodium sulfate. On removing the solvent from the dried solution, a light yellow colored, viscous oil was obtained (14.6 g., 88%). A sample was purified by distillation, giving close to quantitative recovery of nearly colorless distillate: n_D^{25} 1.5234; $[\alpha]_D^{25}$ –35.2° (ethanol) [lit.,¹² n_D^{25} 1.5220; $[\alpha]_D^{25}$ –33.5° (ethanol)].

PHILADELPHIA 4, PA.

[CONTRIBUTION FROM E. I. DU PONT DE NEMOURS & CO., INC., EASTERN LABORATORY]

Reaction of Cyclohexane with Nitrosyl Chloride

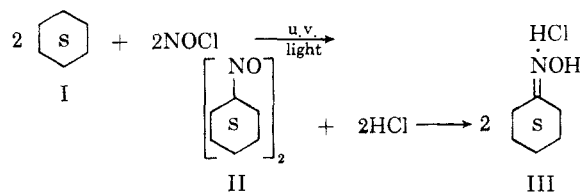
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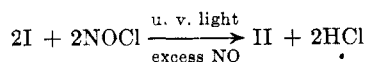
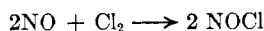
The preparation of nitrosocyclohexane dimer from cyclohexane and nitrosyl chloride is described. Data are presented which may explain the fact that, under the reaction conditions employed, the major reaction product is nitrosocyclohexane dimer and not cyclohexanone oxime hydrochloride.

The reaction of nitrosyl chloride with cyclohexane (I) in the presence of light to yield cyclohexanone oxime hydrochloride (III) has been known for many years.¹ More recently, Mueller and Metz-

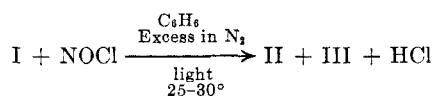
ger² found that they could prepare nitrosocyclohexane dimer (II) by the reaction of cyclohexane (I) with a mixture of nitric oxide and chlorine in the presence of light: Cyclohexyl nitrate and 1-chloro-1-



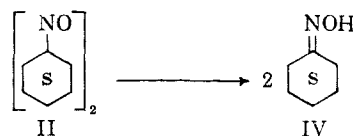
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nitrosocyclohexane were formed as by-products of the reaction. They used a nitric oxide-chlorine volume ratio of 8:1. It seemed logical that the flow of gas through the system resulted in the removal, by entrainment, of the hydrogen chloride formed before it could isomerize the nitroso compound (II)



action was carried out by entraining nitrosyl chloride, with a stream of dry nitrogen, into an irradiated solution of cyclohexane (I) in benzene. In this manner good yields (30–50%) of nitrosocyclohexane dimer (II) and small amounts of cyclohexanone oxime hydrochloride (III) were obtained. If the flow of the gas stream was slow, or if the gas stream was passed into the bottom of a container holding a benzene-cyclohexane solution of considerable depth, the major product was the oxime salt (III). These observations prompted us to measure the rate of isomerization of the nitroso dimer (II) to cyclohexanone oxime (IV) in various media. Table I



shows the results obtained from the measurement of the rate of isomerization of nitrosocyclohexane dimer to cyclohexanone oxime in cyclohexane and in the presence of several different catalysts.

Surprisingly, the data in Table I show that the nitroso dimer (II) did not isomerize to cyclohex-

(1) German Appln. **W5051** (1952), (to Matheson Chemical Corp.); *French Patent 992,772* (1951) (to Svit, Narodni Podnik). W. Zerneck and H. Ritter, (to Cassella Farberwerke Maunkur), Ger. Appln., **C, 2,405** (1952); B. B. Brown (to Olin Matheson), U. S. Patent **2,719,116** (1955); M. A. Naylor and A. W. Anderson, *J. Org. Chem.*, **18**, 115 (1953).

(2) E. Mueller and H. Metzger, *Chem. Ber.*, **88**, 165 (1955).