N-Phenylaminomaleimide (IId).—The procedure was similar to that of compound IIc except that 4 g. of Id[3] was employed. There was obtained 2.55 g. (94%) of IId. Dissolution in benzene at room temperature and reprecipitation with petroleum ether (b.p. 30–60°) gave m.p. 143–144° dec. The compound was very hygroscopic; on standing, the melting point decreased to 101–102° dec. Attempts to recrystallize IId from hot solvents resulted in its conversion to 2-phenyl-6-hydroxy-3(2H)-pyridazinone (IIId).

Anal. Calcd. for $C_{10}H_8O_2N_2 \cdot 4H_2O$: C, 46.15; H, 6.15; N, 10.76. Found: C, 46.42; H, 4.38; N, 10.59.

Rearrangement of N-aminomaleimides to N-substituted Maleic Hydrazides.—Typical procedures are described for the preparation of 2-(2,4-dinitrophenyl)-6-hydroxy-3(2H)-pyridazinone (IIIc) from IIc.

Method (a).—Four grams of IIc was refluxed for 24 hr. in 50 ml. of anhydrous acetic acid. Several successive freezings of the solution gave 2.12 g. of product and evaporation of the combined mother liquors left an oil which on treatment with ether gave an additional 0.62 g. (total yield, 68%) of material. Dissolution in benzene followed by reprecipitation with petroleum ether (b.p. 30–60°) gave IIIc, m.p. 230–232° dec.; $\gamma_{\max}^{\text{Nujol}}$ 5.79 μ (ring carbonyl).

Anal. Calcd. for $C_{10}H_6O_6N_4$: C, 43.17; H, 2.17; N, 20.14. Found: C, 43.25; H, 2.30; N, 20.44.

Method (b).—Four grams of IIc was heated for 24 hr. at 120° in anhydrous xylene. Work-up of the reaction mixture as described in method (a) gave a 60% yield of IIIc. A mixture melting point determination with an authentic sample of IIIc which was obtained by method (a) gave no depression and the infrared spectra were superimposable.

IIIc also was prepared in 91% yield by refluxing 1-(2,4-dinitrophenyl)-2-(3-carboxyacryloyl)hydrazine (Ic) for 5 hr. in glacial acetic acid.

2-Butyl-6-hydroxy-3(2H)-pyridazinone.—To 4.9 g. of maleic anhydride in 150 ml. of chloroform was added 8.0 g. of butylhydrazine oxalate at room temperature. The mixture was stirred for 5 hr. and then filtered to give 11.4 g. (88% yield) of 2-butyl-6-hydroxy-3(2H)-pyridazinone, m.p. 125–127° after recrystallization with ethanol. A mixture melting point determination with an authentic sample[4] was undepressed and the infrared spectra were superimposable.

Some Observations on the Synthesis of Phthaloylamino Acids

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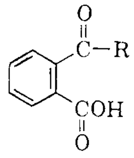
Received August 6, 1962

The synthesis of phthaloylamino acids by fusion of phthalic anhydride with an amino acid may lead to appreciable racemization.[1] Optically active phthaloyl-L-threonine and phthaloyl-O-acetyl-L-serine have been prepared in suspension of hot dioxane.[2] Other investigations have been carried out in order to establish optimal reaction conditions,[3] but the reported procedures do not seem to be satisfactory.[4] In order to obtain high yields without racemization it seems necessary to effect the synthesis of the phthaloylamino acids and their intermediate N-substituted phthalamic acids in solution and at moderate temperatures. The intermediate N-substituted phthalamic acids can be prepared in good yields at room temperature by stirring a solution of phthalic anhydride in an organic–water miscible solvent to which an equimolar aqueous solution of an amino acid and triethylamine has been added. During the course of the reaction one more equivalent of triethylamine is added to keep the solution at neutral pH. Under these conditions and with the quantities used (0.01–0.025 mole) the reaction is practically complete after forty-five minutes. Table I gives the phthalamic acids prepared and their yields and purities in terms of molecular weight calculated and determined by titration. Purification by recrystallization proved difficult because in boiling water hydrolysis is appreciable and in organic solvents of moderate boiling point (80–100°) partial cyclization to phthaloylamino acids seems to take place.

TABLE I

SYNTHESIS OF N-SUBSTITUTED PHTHALAMIC ACIDS



(Reaction solvent: tetrahydrofuran)

R	M.p., °C.	Mol. wt.		Yield,[a]
		Calcd.	Found	%
Glycine	100–102 (lit. 105–106)[b]	223	220	81
DL-Alanine	95–97	237	238	76
DL-Valine	170–171 dec.	265	270	74
DL-Phenylalanine	162–164 dec.	313	310	80

[a] These compounds are somewhat soluble in aqueous acidic solution and do not precipitate easily. Actual yields might therefore be higher since the phthaloylamino acids prepared from these solutions (Table II) give higher yields. [b] *Cf.* ref. 7.

Phthalamic acid itself is known to undergo hydrolysis in water at acidic pH and the reaction kinetics have been investigated.[5] It has also been reported that some phthalamic acids can be dehydrated to phthalimide derivatives in dilute aqueous solution under certain conditions.[6] It is therefore interesting to note that phthalamic acid itself as well as phthalanilic acid and the *N*-substituted phthalamic acids in Table I do undergo

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[1] J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley & Sons, Inc., New York, N. Y., 1961, p. 902.

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

[3] A. K. Bose, F. Greer, and C. C. Price, *J. Org. Chem.*, **23**, 1335 (1958).

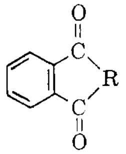
[4] F. Weygand and J. Kaelicke, *Ber.*, **95**, 1031 (1962).

[5] M. L. Bender, Y. Chow, and F. Chloupek, *J. Am. Chem. Soc.*, **80**, 5380 (1958).

[6] G. Drefahl and F. Fischer, *Ann.*, **610**, 166 (1957); F. Fischer, G. Preisser, and D. Strauss, *Ann.*, **643**, 110 (1961).

TABLE II

SYNTHESIS OF PHTHALOYLAMINO ACIDS



(Reaction solvent: dioxane)

R	Yield, %	M.p., °C.		Calcd.	Found	$[\alpha]^{29}D$	G./ml. sol.	Recryst. solvent
						(Solvent:	abs. ethanol)	
Glycine	81	196–197	C:	58.5	58.3			96% EtOH
		(lit. 191–192)[a]	H:	3.4	3.5			
			N:	6.8	6.8			
DL-Alanine	91.3	160–162	C:	60.2	60.0			Water
		(lit. 160–161)[a]	H:	4.1	4.2			
			N:	6.4	6.6			
DL-Valine	93	102	C:	63.1	63.2			Cyclohexane
		(lit. 101.5–102)[a]	H:	5.3	5.4			
			N:	5.7	5.8			
DL-Phenylalanine	95	181	C:	69.2	69.5			MeOH–water
		(lit. 174–175)[a]	H:	4.4	4.4			
			N:	4.7	4.7			
D-Alanine	85.5	146–147	C:	60.2	60.3	+25.4°	0.088	EtOH–water
			H:	4.1	4.0	(lit. −25.0°)[b]		
			N:	6.4	6.2			
L-Valine	90	116–117	C:	63.1	63.1	−69.4°	0.0647	Cyclohexane
		(lit. 114–115)[c]	H:	5.3	5.1	(lit. −68.5°)[c]		
			N:	5.7	5.6			
L-Phenylalanine	94	187	C:	69.2	69.3	−212°	0.0562	MeOH–water
		(lit. 183–185)[d]	H:	4.4	4.5	(lit. −212°)[d]		
			N:	4.7	4.6			

[a] *Cf.* ref. 8. [b] *Cf.* ref. 11. [c] *Cf.* ref. 9. [d] *Cf.* ref. 10.

cyclization to phthalimide, phthalanil, and phthaloylamino acids in dilute aqueous solutions at neutral pH. The phthalamic acid is dissolved for that purpose in water and neutralized with two equivalents of triethylamine and the solution subjected to slow distillation. Under these conditions triethylamine is distilled together with water formed in the proceeding cyclization reaction, and the solution is thus kept constantly at neutral pH. If, however, the distillation is continued until one equivalent of triethylamine is distilled (thus bringing the reaction theoretically to completion), it is found that the resultant phthaloylamino acid is already contaminated with phthalic acid, a sign that under prolonged distillation hydrolysis sets in. The extent of this hydrolysis varies with the nature of the phthaloylamino acid. Thus optimal yields of 95% for phthaloylglycine, 42% for phthaloyl-DL-alanine, 12.5% for phthalimide, and 25% for phthalanil were obtained.

For quantitative preparation of phthaloylamino acids the following experimental procedure was therefore adopted. After completion of the reaction, the original reaction solution of the N-substituted phthalamic acid was diluted with additional organic solvent and subjected to slow distillation. In this way water and triethylamine were distilled together with organic solvent until finally only pure organic solvent was left in the solution. By that time cyclization was complete and no hydrolysis or other side reaction were discernable. This procedure has been used for the phthaloylamino acids listed in Table II with good yields and no apparent racemization.

Experimental[12]

DL-N-(*o*-Carboxy)benzoylalanine.—A solution of 0.9 g. (0.01 mole) of DL-alanine in 10 ml. of water and 1 g. (0.01 mole) of triethylamine was added with stirring to a solution of 1.5 g. (0.01 mole) of phthalic anhydride in 30 ml. of tetrahydrofuran. During the addition the solution developed a slightly yellow color which vanished shortly afterward. It was then stirred at room temperature for 45 min. during which time one more gram of triethylamine was gradually added. The aqueous phase was then separated and the organic phase extracted with a minimum quantity of 30% sodium hydroxide so that the combined aqueous solution was distinctly alkaline. This aqueous solution was then extracted with ether, separated, freed from ether under vacuum and acidified with conc. hydrochloric acid. After cooling for 2 hr. the resultant precipitate was filtered and air dried. Yield 1.8 g. (76%), m.p. 95–97°.

N-Phthaloylglycine from N-(*o*-carboxy)benzoylglycine.—A 2.23-g. sample (0.01 mole) of N-(*o*-carboxy)benzoylglycine (prepared as above) was dissolved in 50 ml. of water together with 2 g. (0.02 mole) of triethylamine. The solution was subjected to distillation for 45 min. During this treat-

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(7) S. Gabriel and K. Kroseberg, *Ber.*, **22**, 426 (1889).

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

(9) M. Fling, F. N. Minard, and S. W. Fox, *ibid.*, **69**, 2466 (1947).

(10) J. C. Sheehan, D. W. Chapman, and R. W. Roth, *ibid.*, **74**, 3822 (1952).

(11) Found for N-phthaloyl-L-alanine, ref. 4.

(12) All melting points are uncorrected.

ment another 75 ml. of water was gradually added and the distillate collected in a solution of 100 ml. of 0.1 *N* hydrochloric acid until complete neutralization was effected. A total quantity of 97 ml. of liquid was thus distilled. The residual solution was cooled, acidified with concd. hydrochloric acid, and the resultant precipitate filtered and air dried. Yield, 1.94 g. (95%). It was recrystallized from boiling water and melted at 196°.

Anal. Calcd. for $C_{10}H_7O_4N$: C, 58.5; H, 3.4; N, 6.8%. Found: C, 58.4; H, 3.7; N, 7.2%.

N-Phthaloyl-L-valine.—A solution of 3 g. (0.0256 mole) of L-valine (Nutritional Biochemicals Corporation) and 2.6 g. of triethylamine in 40 ml. of water was added with stirring to a solution of 3.8 g. of phthalic anhydride in 130 ml. of dioxane. During the addition a small amount of precipitate was formed which dissolved again after 5 min. of vigorous stirring. The resultant homogenous solution was then stirred at room temperature for another 45 min. during which time an additional 2.6 g. of triethylamine was gradually added. Another 130 ml. of dioxane was then added and the solution was subjected to slow distillation for a period of 2 hr. During this time a total of 265 ml. of liquid was distilled and the temperature of the vapor rose slowly until finally the boiling point of pure dioxane was reached. The residual solvent was then evaporated *in vacuo* at room temperature and the resultant glassy residue treated with 10 ml. of pure concd. hydrochloric acid until complete crystallization set in. The precipitate was then filtered, washed with a little cold water, and air dried; yield, 5.7 g. (90%). It was twice recrystallized from cyclohexane. White needles were obtained which melted at 116–117° (for analysis and rotation, see Table II).

An Unusual Reaction of Thionyl Chloride Leading to 10-Dicyanomethyleneanthrone

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Received July 12, 1962

The unusually high electrical conductivities exhibited by several polycyano derivatives[1,2] have stimulated research in recent years on organonitrile compounds. As a part of the study of the electrical properties of organic compounds, 10-dicyanomethyleneanthrone has been synthesized. The reaction of thionyl chloride with anthrone, followed by a treatment with malononitrile, to yield the 10-substituted anthrone is described.

Anthrone was refluxed with excess thionyl chloride (1:10 molar ratio) and the resultant solution was treated with malononitrile (5 moles) in dioxane, producing 10-dicyanomethyleneanthrone (I) in 88% yield. Upon replacing dioxane with tetrahydrofuran as a solvent, only a small yield of I was obtained. Both chloroform and N,N-dimethylformamide failed to yield the dinitrile product. Infrared absorptions for I were observed at 4.48 (CN) and 5.98 μ (quinoid CO).[3]

The dinitrile (I) was recovered unchanged from heating in concentrated sulfuric acid. However, it was converted by hot 90% sulfuric acid, followed by hydrolysis, to 10 - (cyanocarbonamidomethylene)anthrone (II) in 42% yield. Infrared absorptions for II were noted in the 3- and 6-μ regions attributed to a primary amide[3] and carbonyl group, respectively. A nitrile absorption was also observed at 4.54 μ.

Catalytic hydrogenation of I and II yielded 10-dicyanomethylanthrone (III) and 10-(cyanocarbonamidomethyl)anthrone(IV), respectively. Infrared spectra of III and IV exhibited a band at 6.0 μ and a weak band at 4.45 μ. In addition, IV exhibited several bands in 3 μ (primary amide) region similar to that found in II. Hydrolyses of III and IV yielded anthraquinone as the only identifiable product.

The structural assignment of the dicyanomethylene group of I to the 10-position of anthrone was based on elemental analyses, spectral data, and the facile acid or base catalyzed conversions of I to anthraquinone, in yields of 75 and 80%, respectively.

In an effort to study the generality of the reactions leading to the synthesis of I, the anthrone–thionyl chloride reaction product was treated with two other compounds containing active methylene groups. Both ethyl cyanoacetate and phenylacetonitrile failed to yield the corresponding substituted methyleneanthrone derivative; anthraquinone was the only product isolated. Furthermore, the treatment of anthrone with phosphorus oxychloride or phosphorus trichloride followed by malononitrile in dioxane did not yield I. However, replacing thionyl chloride with sulfuryl chloride gave a low yield of I. It may be possible in the latter case that thionyl chloride was present in the sulfuryl chloride as an impurity.

To investigate the possibility that the reaction may be proceeding *via* anthraquinone, this quinone was refluxed with thionyl chloride and then treated with malononitrile in dioxane. The only crystalline compound isolated was the starting material, anthraquinone.

Upon treatment of the reaction product of anthrone and excess thionyl chloride with crushed ice, an unidentified product was obtained. Attempted purification of this product resulted in its decomposition to yield anthraquinone. Since 10,10-dichloroanthrone is reported[4] to be stable in ice-water under highly acidic conditions and is recrystallizable from aqueous ethanol, it appears reasonable that the dichloroanthrone is not an

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[1] D. S. Acker, R. J. Harder, W. R. Hertler, W. Mahler, L. R. Melby, R. E. Benson, and W. E. Mochel, *J. Am. Chem. Soc.*, **82**, 6408 (1960).

[2] R. G. Kepler, P. E. Bierstedt, and R. E. Merrifield, *Phys. Rev. Letters*, **5**, 503 (1960).

[3] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1954, chap. 9, 12, and 15.

[4] V. V. Kozlov, *Zh. Obshch. Khim.*, **18**, 757 (1948); *Chem. Abstr.*, **43**, 618^e.