layer chromatography was run on precoated silica gel plates (Merck, GF_{254}) using the following systems: A, benzene–ethyl acetate–acetic acid–water (10:10:2:1, v/v); B, 1-butanol–acetic acid–water (4:1:1, v/v); C, chloroform–methanol–acetic acid (85:10:31, v/v).

The Merrifield resin (IV) (chloromethylated copolystyrene, 1% divinylbenzene, 0.9 mequiv/g, 200–400 mesh) was purchased from Bio-Rad Laboratories.

***p*-Cyanophenyl Resin (V).** Merrifield resin (IV, 20 g, 18 mmol) in 200 ml of dry diglyme was treated with 14.28 g (120 mmol) of *p*-cyanophenol and 6.48 g (120 mmol) of $NaOCH_3$ at 60° for 2 hr. The resin was collected and washed with DMF, dioxane, CH_2Cl_2, and methanol to give 21.4 g of V. The resin absorbed strongly at 2250 cm^{-1}.

***p*-Alkoxybenzylamine Resin (VI).** A solution of 2.28 g (60 mmol) of $LiAlH_4$ in 60 ml of dry ether was placed in a three-necked flask. A suspension of the *p*-cyanophenyl resin (20 g) in 100 ml of dry ether was added from a dropping funnel. The mixture was then stirred for 6 hr under dry ammonia stream. The resin was then filtered and washed with ethyl acetate, methanol, and CH_2Cl_2 to give a grayish product. The colored matter was removed by stirring in 500 ml of a 1:1 mixture of acetic acid and 1 *N* HCl for 15 min. The product was washed with 10% (v/v) triethylamine in $CHCl_3$ to convert the hydrochloride to the free amine, $CHCl_3$, and CH_2Cl_2, and dried under vacuum at 30° to give 18.4 g of the *p*-alkoxybenzylamine resin (VI). The ir showed a broad absorption at 3500–3100 cm^{-1} and no cyano band. The capacity, determined by the Esko procedure,[7] was in the range of 0.6 mequiv of NH_2/g of polymer.

Ppoc-Glycyl-*p*-alkoxybenzylamine Resin (VII). The amino resin VI (10 g, 6 mmol) was washed several times with ethanol and methylene chloride and then treated with 2.84 g (12 mmol) of Ppoc-Gly and 2.48 g (12 mmol) of DCC for 120 min. After washings with CH_2Cl_2, $CHCl_3$–MeOH (1:1 v/v), and CH_2Cl_2, the resin was suspended in 100 ml of CH_2Cl_2 and then allowed to react with acetic anhydride (2 ml) for 30 min in the presence of a catalytic amount of 4-dimethylaminopyridine.[8] After washings with CH_2Cl_2, 11.2 g of resin was obtained; it contained no detectable amount of free amino group. Amino acid analysis indicated that there was 0.42 mmol of glycine/g of resin.

Ppoc-Met Resin (VIII) and Ppoc-Val Resin (IX). The amino resin VI was treated with Ppoc-Met or Ppoc-Val in the same manner as above yielding respectively Ppoc-Met resin (VIII) and Ppoc-Val resin (IX).

The resin VIII was found to have 0.47 mmol/g of methionine; the resin IX was found to have 0.39 mmol/g of valine.

Stability of the *p*-Alkoxybenzylamide Anchoring Bond. Several samples of resin VII (150 mg) were placed in test tubes and suspended in 1% TFA in CH_2Cl_2 (5 ml). The tubes were stoppered and the reaction was allowed to proceed for the desired time at 23°. Then the samples were taken, filtered, and washed with 2 ml of CH_2Cl_2. The liberated glycine amide was separated by thin layer chromatography on silica gel using the system B; the spots were detected with ninhydrin–cadmium acetate (0.2% v/v)[9] and evaluated by densitometry.[10]

Results of such experiments showed that there was 8% loss of the anchoring bond in 12 hr. In the case of polymers VIII and IX a loss of 7.7 and 7.2 was found in 12 hr.

Cleavage Experiments. Small samples of the resins VII, VIII, and IX were treated with 50% v/v TFA in methylene chloride for 30 min. The filtrates were concentrated and chromatographed. Gly-NH_2, Phe-NH_2, and Met-NH_2 were found in presence of traces of the free amino acids.

The results confirmed that the conversion of the amino resin VI into resins VII, VIII, and IX had proceeded satisfactorily.

Z-Pro-Leu-Gly-NH_2 (I). Solid phase synthesis was carried out on 5 g (2.1 mmol) of resin VII with a threefold excess of amino acid derivatives and DCC in each cycle. The tripeptide released (720 mg) was twice crystallized from methanol, yield 491 mg (56%), mp 161–162° (lit.[11] mp 162–163°).

Z-Ala-Phe-Gly-Leu-Met-NH_2 (II). Solid phase synthesis of this protected amide was carried out similarly starting from resin VIII, yield 32%, mp 222–223° from methanol, $[\alpha]^{25}\mathrm{D}$ −29.54° (*c* 1, DMF). It gave corrected amino acid analysis upon acid hydrolysis: $Ala_{1.02}Gly_{1.00}Leu_{1.03}Met_{0.92}Phe_{1.06}$.

Anal. Calcd for $C_{33}H_{46}N_6O_7S$ (670.8): C, 59.03; H, 6.85; N, 16.69. Found: C, 59.51; H, 6.92; N, 16.58.

Z-Gln(Dmb)-Gly-Leu-Val-NH_2 (III). Resin IX (5 g, 1.95 mmol) was placed in the peptide synthesis flask and the synthesis was carried out with fourfold excess of amino acid derivatives and DCC in each cycle. Ppoc-Leu (2.28 g), Ppoc-Gly (1.84 g), and Z-Gln(Dmb) [*N*-benzyloxycarbonyl-N^{γ}-(2,4-dimethoxybenzyl)-L-glutamine] (4.76 g) were sequentially coupled to the resin to give 6.2 g of the protected tetrapeptide polymer. The peptide was then released from the polymer by stirring in 100 ml of 50% (v/v) trifluoroacetic acid in methylene chloride for 30 min. After filtration and evaporation, the residue was treated with ethyl acetate–petroleum ether. The solid obtained (0.920 g) was crystallized from ethyl acetate: yield 0.734 g (54%); mp 246–248°; $[\alpha]^{25}\mathrm{D}$ +62.07° (*c* 1.5, DMF). On acid hydrolysis, the compound gave the correct amino acid analysis: $Gly_{1.04}Glu_{1.02}Leu_{1.02}Val_{0.97}$.

Anal. Calcd for $C_{35}H_{50}N_6O_9$ (698.6): C, 60.12; H, 7.22; N, 12.02. Found: C, 59.87; H, 7.35; N, 12.12.

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Registry No.—I, 14485-80-4; II, 56195-91-6; III, 56195-92-7.

References and Notes

(1) This work was supported by Grant 73.01069.03 from the Italian Research Council.

(2) P. G. Pietta and G. R. Marshall, *Chem. Commun.*, 650 (1970).

(3) P. G. Pietta, P. F. Cavallo, K. Takahashi, and G. R. Marshall, *J. Org. Chem.*, **39**, 44 (1974).

(4) S. S. Wang and R. B. Merrifield, *J. Am. Chem. Soc.*, **91**, 6488 (1969).

(5) B. E. B. Sandberg and U. Ragnarsson, *Int. J. Protein Res.*, **6**, 111 (1974).

(6) S. S. Wang, *J. Am. Chem. Soc.*, **95**, 1328 (1973).

(7) K. Esko, S. Karlsson, and J. Porath, *Acta Chem. Scand.*, **22**, 3342 (1968).

(8) W. Steglich and G. Hofle, *Angew. Chem.*, **81**, 1001 (1969).

(9) J. G. Heathcote and C. Haworth, *Biochem. J.*, **114**, 667 (1969).

(10) J. G. Heathcote and C. Haworth, *J. Chromatogr.*, **43**, 84 (1969).

(11) T. Mizoguchi, K. Shigezane, and N. Tamura, *Chem. Pharm. Bull.*, **18**, 1465 (1970).

Condensations of Phthalaldehydic and *o*-Acetylbenzoic Acids with Naphthalenes[1]

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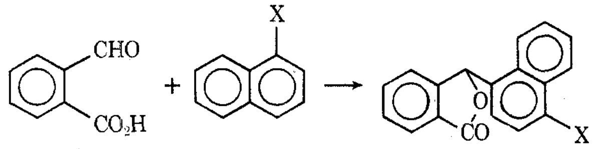
The acid-catalyzed condensation of phthaldehydic acid (1) with benzene and halogenated benzenes to produce 3-phenylphthalides[4] **2**, and of *o*-acetylbenzoic acid (3) with 1,2-dimethoxynaphthalene[5] have been reported. Because of the utility of this type of reaction in the synthesis of benz[*a*]anthracenes of interest in the field of cancer research we report herein on the condensations of phthaldehydic and *o*-acetylbenzoic acids with substituted naphthalenes.

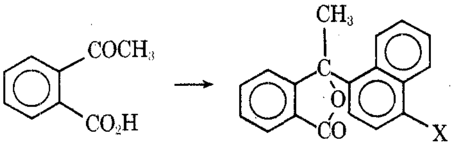
In the condensation of **1** with benzene and halogenated benzenes, Floutz used concentrated sulfuric acid, or 20% oleum, at room temperature to obtain almost quantitative yields of 3-phenylphthalides,[4] **2**. However, we have found that such strong acid is not advisable for the condensation of **1** or **3** with naphthalene derivatives because sulfonation and/or oxidation occurs. In studies with naphthalenes and **1**, 90–100% methanesulfonic acid[6] proved superior as no sulfonation or oxidation occurred in 20–24 hr at room temperature and almost quantitative yields of 3-(4-X-1-naphthyl)phthalides, **2**, were attained. With the more reactive 1-methoxynaphthalene, the reaction was complete in 3 hr. In this case 90% methanesulfonic acid was preferable to 100% acid because the latter caused some demethylation.

When *o*-acetylbenzoic acid (**3**) (see Experimental Section for an improved synthesis of **3**) was used in place of **1** a different technique was required because of the tendence of **3** to self condense in acidic media.[7] In these cases the best results were obtained when a solution of **3** in sulfolane[8] was slowly added to a stirred solution of the substrate in 100% methanesulfonic acid at room temperature. In this way a 94% yield of 3-methyl-3-(4-methoxy-1-naphthyl)phthalide (**4d**) was obtained. Lower yields, 55, 72, and 20%, of **4a, 4b,** and **4c,** respectively, were obtained.



1

2a, X = H
b, X = F
c, X = Br
d, X = OCH_3



3

4

The above route to the phthalides, **4**, is an attractive alternate to the route in which a 4-substituted naphthylmagnesium bromide is allowed to react with phthalic anhydride to yield a 2-(4-X-1-naphthoyl)benzoic acid[9] which is then treated with methylmagnesium halide to yield a substituted phthalide, **4**.[10] In the first place, 1-substituted naphthalenes are much easier to come by than 1-bromo-4-substituted naphthalenes. Secondly, the yields of **4** involving the acid-catalyzed route are superior to the yields obtained by the route involving two successive Grignard reactions. In spite of the only fair yields in the syntheses of **4a** and **4b,** this route is preferable to the double Grignard route[9,10] for **4a, 4b,** and **4d.** However, conditions for the attainment of acceptable yields for **4c** by this method have not been found.

The preparation of **3** has most often been carried out by heating a mixture of phthalic anhydride and malonic acid in pyridine on a steam bath for several hours,[11] although other methods for the synthesis of **3** have been described.[12] The best reported yield of **3** which we have found is 58%, obtained after a tedious and time-consuming work-up.[11b] By reaction of phthalic anhydride with malonic acid in triethylamine at 75–80° and isolation of **3** by continuous extraction we have obtained pure **3** in 89% yield.

Experimental Section[13]

***o*-Acetylbenzoic Acid (3).** A stirred mixture of 148 g (1 mol) of finely powdered phthalic anhydride, 125 g (1.2 mol) of malonic acid (dried at 100° for 2 hr), and 200 ml of freshly distilled triethylamine (cooling at the start) in a 1-l. three-necked flask was warmed to 80°, at which temperature gas evolution was fairly rapid. After 2.5 hr (no more gas evolution) the cooled dark red solution was poured into 1 l. of water and 1 l. of 20% hydrochloric acid was stirred in. The organic acids were continuously extracted with ether for 2 days (no shorter time was tried). The ether solution (final volume about 700 ml) was washed with a small amount of saturated salt solution and then dried over anhydrous Na_2SO_4. Removal of ether from the dried solution yielded 161 g of solid which was extracted with 1 l. of hot benzene, the insoluble phthalic acid (6.8 g) being filtered. Concentration and crystallization afforded crude **3**. A second crystallization from benzene afforded 147 g (90%) of **3**, mp 110–112°, of off-white acid suitable for the condensations described below.

Condensations of Phthaldehydic Acid[14] (1) with Naphthalenes. A mixture of 4.5 g (0.03 mol) of **1**, 30 ml of 100% methanesulfonic acid,[6] and 7.3 g (0.05 mol) of 1-fluoronaphthalene[15] was stirred at room temperature until homogeneous. After 20 hr the brown solution was poured into 600 ml of ice water and the solid was collected by filtration and washed well with ice water. On trituration with cold ether (to remove excess fluoronaphthalene which was recovered in larger runs) 8.36 g (99%) of colorless 3-(4-fluoro-1-naphthyl)phthalide (**2b**), mp 151–153°, ir 5.7 *μ*, suitable for further use, was obtained. Recrystallization from benzene–petroleum ether yielded a purer sample, mp 153–154° (lit.[16] mp 154–154.5°). A similar result was obtained in a run ten times as large.

Pure 3-(1-naphthyl)phthalide (**2a**), mp 137–138°, was prepared similarly in almost quantitative yield when naphthalene was used in place of fluoronaphthalene.

Anal. Calcd for $C_{18}H_{12}O_2$: C, 83.1; H, 4.6. Found: C, 82.9; H, 4.8.

In a similar way, a nearly quantitative yield of colorless 3-(4-bromo-1-naphthyl)phthalide (**2c**), mp 207–209°, ir 5.7 *μ*, was obtained using 1-bromonaphthalene.

Anal. Calcd for $C_{18}H_{11}BrO_2$: C, 63.7; H, 3.3; Br, 23.4. Found: C, 64.1; H, 3.2; Br, 23.5.

In a reaction involving 0.30 mol of **1**, 0.50 mol of 1-methoxynaphthalene, and 300 ml of 90% methanesulfonic acid for 3 hr at room temperature there was obtained an almost quantitative yield of **2d.** Recrystallization from benzene–petroleum ether afforded pure 3-(4-methoxy-1-naphthyl)phthalide (**2d**), mp 199–200°, ir 5.7 *μ*, in 98% yield.

Anal. Calcd for $C_{19}H_{14}O_3$: C, 78.7; H, 4.9. Found: C, 78.3; H, 5.0.

Condensations of *o*-Acetylbenzoic Acid (3) with Naphthalenes. A solution of 65.6 g (0.40 mol) of **3** in 400 ml of sulfolane was added dropwise during 24 hr to a stirred solution at room temperature of 104 g (0.66 mol) of methyl 1-naphthyl ether in 400 ml of 100% methanesulfonic acid[6] in a 2-l. three-necked flask protected from moisture. After 6 hr more the dark red solution was poured into 3 l. of ice water. After the dark oil which separated was washed with several portions of ice water and triturated with ether, filtration afforded 114.5 g (94%) of 3-methyl-3-(4-methoxyl-1-naphthyl)phthalide (**4d**), mp 138–140°, suitable for further work. A pure sample of **4d**, mp 142–143° (lit.[17] mp 139–140°), was obtained with little loss by recrystallization from benzene.

In similar reactions 1-fluoronaphthalene was converted into 3-methyl-3-(4- fluoro-1-naphthyl)phthalide (**4b**), mp 142–143° (lit.[18] a, mp 140°; b, 143–144°), in 72% yield and naphthalene into 3-methyl-3-(1-naphthyl)phthalide (**4a**), mp 149–151° (lit.[19] mp 154.5–155.0°), in 55% yield.[20] No pure product was isolated when similar, or other, reactions were tried on bromonaphthalene.

Registry No.—**1,** 119-67-5; **2a,** 56282-14-5; **2b,** 27525-72-0; **2c,** 56282-15-6; **2d,** 40893-29-6; **3,** 577-56-0; **4a,** 56282-16-7; **4b,** 2968-71-0; **4d,** 56282-17-8; phthalic anhydride, 85-44-9; malonic acid, 141-82-2; 1-fluoronaphthalene, 321-38-0; naphthalene, 91-20-3; 1-bromonaphthalene, 90-11-9; 1-methoxynaphthalene, 2216-69-5.

References and Notes

(1) This research was supported by Grant CA-07394 from the National Cancer Institute.
(2) Postdoctoral Research Associate.
(3) Postdoctoral Research Associate, 1974.
(4) V. W. Floutz, *J. Org. Chem.*, **25**, 643 (1960), and references cited therein.
(5) M. S. Newman and C. C. Davis, *J. Org. Chem.*, **32**, 66 (1967).
(6) We thank the Pennwalt Co. for generous gifts of 70% methanesulfonic acid. By vacuum distillation 100% methanesulfonic acid, bp 130–132° (0.2 mm), is readily obtained.
(7) The structures of two self-condensation products have been determined by P. Kolsaker and E. Berner, *Tetrahedron*, **29**, 1095 (1973).
(8) We thank the Phillips Petroleum Co., Borger, Texas 79007, for generous gifts of sulfolane.
(9) See, for example, M. S. Newman, D. MacDowell, and S. Swaminathan, *J. Org. Chem.*, **24**, 509 (1959).
(10) For a similar reaction, see M. S. Newman, *J. Am. Chem. Soc.*, **59**, 1004 (1937).
(11) (a) H. L. Yale, *J. Am. Chem. Soc.*, **69**, 1547 (1947); (b) R. Riemschneider and H.-G. Kassahn, *Ber.*, **92**, 1705 (1959).
(12) For example see (a) G. Glebe, *Ber.*, **29**, 2533 (1896); (b) P. R. Jones and S. L. Conydon, *J. Am. Chem. Soc.*, **81**, 4291 (1959).
(13) All melting points are uncorrected. Analyses are by the Galbraith Laboratories, Knoxville, Tenn., and M-H-W Laboratories, Garden City, Mich. 48135.
(14) Used as obtained from the Aldrich Co.
(15) Fluoronaphthane, Columbia Organic Chemicals Co., was redistilled before use.
(16) M. S. Newman and Z. ud Din, *J. Org. Chem.*, **36**, 966 (1971), used a solution of slightly diluted methanesulfonic acid (400 ml of CH_3SO_3H and 13.6 ml of H_2O) with similar results.
(17) W. M. Smith, Jr., E. F. Pratt, and H. J. Creech, *J. Am. Chem. Soc.*, **73**, 319 (1951).
(18) (a) E. D. Bergman and J. Blum, *J. Org. Chem.*, **27**, 527 (1962); (b) M. S. Newman and K. Naiki, *ibid.*, **27**, 863 (1962).
(19) M. S. Newman, *J. Am. Chem. Soc.*, **59**, 1003 (1937).
(20) All yields of phthalides cited are based on the use of **1** or **3**.