dried, and concentrated and gave 2.10 g of a yellow oil, GLC analysis of which revealed at least 20 components, many of them minor. The major component (~30% relative peak area), 3-carbomethoxy-3-benzylnortricyclene (**9**), was collected in small quantity from the GLC column, and eventually it solidified (mp 38.0–39.5 °C). A sample of analytical purity was obtained by distillation of the crude product (~40 °C 0.05 mm) which yielded a white semisolid. The distilled material was vacuum pumped (room temperature, 0.05 mm) in a sublimator, and that semisolid which remained in the sublimator gave the correct CH analysis.

Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.34; H, 7.43. Found: C, 79.01; H, 7.58.

Spectroscopic Data for 9. Ir (neat) 3.32 (sh, cyclopropyl CH), 3.44 (CH), 5.77 (C=O), 12.40 μ (nortricyclene skeleton); NMR ($CDCl_3$, 300 MHz) δ 1.07–1.43 (complex multiplet, 6 H), four sharp resonances at 1.85, 1.88, 2.05, 2.16 (2 H), 2.78 (AB quartet, $-CH_2-$ adjacent to an asymmetric center), 3.50 (s, $O{=}COCH_3$), 6.97–7.27 (complex aromatic multiplet, 5 H). Minor impurites were observed in the spectrum.

Registry No.—**3**, 24161-47-5; **4**, 57951-46-9; **6**, 57951-47-0; **7**, 57951-48-1; **8**, 57951-49-2; **9**, 57951-50-5; lithium iodide, 10377-51-2; iodomethane, 74-88-4; benzyl iodide, 620-05-3.

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Preparation of Aroylbenzoic Acid. Reaction of Aryllithium Reagents with Phthalic Anhydride[1]

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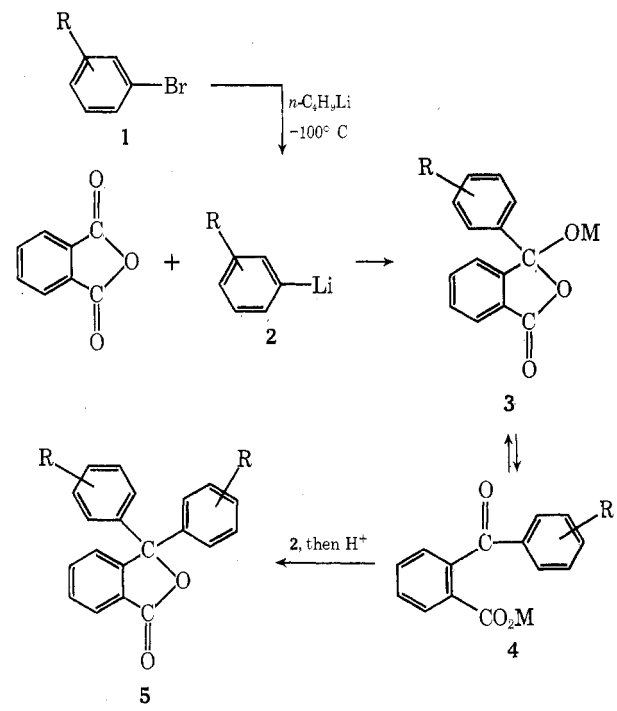
The preparation of a benzoylbenzoic acid by reaction of Grignard reagents with phthalic anhydride[2-4] offers advantages over the usual synthesis involving phthalic anhydride, aromatic hydrocarbons, and aluminum chloride in that isomers can be obviated when substituted aromatic compounds are employed. The method is limited, however, since Grignard reagents cannot be employed if the aromatic system contains functional groups that react with Grignard reagents. Since it has been shown[5-8] that organolithium reagents can be prepared at low temperature by halogen–metal exchange of aryl bromides substituted with groups normally reactive toward Grignard reagents (COO^-, CN, NO_2), the reaction of aryllithium reagents with phthalic anhydride has been examined as a route to *o*-benzoylbenzoic acids substituted with cyano functions. Previously, there has been little work related to the reaction of aryllithium with phthalic anhydride. Wittig and Leo report[9] that the reaction of phenyllithium with phthalic anhydride gives only a resinous compound and triphenylcarbinol, while Wilson reported an unworkable oil from which some diphenylphthalide[10] was isolated by distillation.

The reaction of organometallic reagents with phthalic anhydride is thought to proceed as shown in Scheme I. The products are generally *o*-benzoylbenzoic acids (**4**) and/or phthalides (**5**). Initially it was hoped that at low temperature, the equilibrium between the lithium salts **3** and **4** might favor **3**, which would obviate the necessity of employing inverse addition and/or an excess of phthalic anhydride to minimize phthalide (**5**) formation.[3] However, preliminary experiments using phenyllithium showed that this was not the case. When phthalic anhydride (1 equiv) was added to phenyllithium (1 equiv) at −78 °C the yield of phthalide **5a** was 78% base on phenyllithium. When the same ratios were maintained but the order of addition reversed, the yield of isolated phthalide **5a** was 9% while the yield of *o*-benzoylbenzoic acid was 35%. Furthermore, the yield of *o*-benzoylbenzoic acid was further increased (55%) when excess (2 equiv) of phthalic anhydride was employed.

In subsequent experiments, the aryllithium reagent was added rapidly to 2 equiv of phthalic anhydride in tetrahydrofuran at −100 °C. Reasonably good yields of substituted benzoylbenzoic acids were obtained; the results are summarized in Table I.

Scheme I



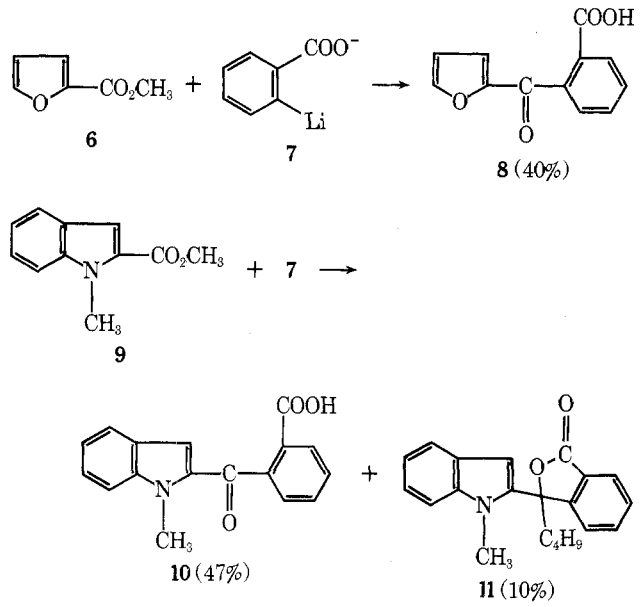
a, R = H
b, R = OCH_3 (ortho)
c, R = CN (ortho)
d, R = CN (meta)
e, R = CN (para)
f, R = NO_2 (ortho)

Table I. Reactions of Aryllithium Derivatives with Phthalic Anhydride

Aryl halide	Product[f]	Yield, %	Mp, °C
o-$CH_3OC_6H_4Br$ (**1b**)	**4b** (M = H)	70	142–144[a]
o-NCC_6H_4Br (**1c**)	**4c** (M = H)	87	146–147[b]
m-NCC_6H_4Br (**1d**)	**4d** (M = H)	60	175–176[c]
p-NCC_6H_4Br (**1e**)	**4e** (M = H)	71	179–186[d]
o-$O_2NC_6H_4Br$ (**1f**)	**4f** (M = H)	43	174–176[e]

[a] Lit.[4] 145–146 °C from CH_3COOH. [b] From H_2O. [c] From ethanol. [d] From ethanol–water. [e] From $CHCl_3$. [f] Satisfactory analytical data (±0.3% for C, H, N) for all new compounds were submitted for review.

Scheme II



Incidental to this study certain heterocyclic analogues of *o*-benzoylbenzoic acid were conveniently prepared by adaptation of the method previously described[7] for benzoylbenzoic acid as shown in Scheme II.[11]

The combination of these two methods provides considerable flexibility for the synthesis of *o*-aroylbenzoic acids not easily available by other routes.

Experimental Section

General Procedure. Aryllithium derivatives **2** were prepared from the corresponding aryl halides **1** (0.02 mol) in tetrahydrofuran (80 ml distilled from $LiAlH_4$) with *n*-butyllithium (9 ml of 2.3 M solution in hexane, 0.02 mol) at −100 °C as previously described[6,7] and were added (pumped by nitrogen pressure) as rapidly as possible to a solution of phthalic anhydride (0.04 mol) in 125 ml of dry tetrahydrofuran at −100 °C. The mixture was maintained at −100 °C for 1 h and then allowed to warm to room temperature. Tetrahydrofuran was removed (in vacuo) and the solid residue shaken with a mixture of ether (60 ml) and water (100 ml). The aqueous solution was made acidic with hydrochloric acid and was extracted with ether. The ether was extracted with saturated sodium bicarbonate to remove acid. Phthalides **5** were obtained from the ether layer. The alkaline extract was acidified and the solid was collected and recrystallized as described in Table I.

2-(2-Furoyl)benzoic acid (8) was prepared from lithium *o*-lithiobenzoate (from 0.05 mol of *o*-bromobenzoic acid) as described[6] and 2-methylfuroate. After warming the mixture to room temperature, the tetrahydrofuran was removed in vacuo and water (250 ml) was added to the residue. The aqueous solution was washed with ether, acidified with hydrochloric acid, and extracted with ether (3 × 30 ml). The dried ($MgSO_4$) ether extracts were evaporated in vacuo to give the crude acid as an oil which crystallized when treated with ethyl acetate followed by evaporation of all solvent (5.5 g, 52% yield, mp 150–153 °C, mp 154–156 °C from ethyl acetate); $\nu C{=}O$ 1660, 1700 cm^{-1}.

Anal. Calcd for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.50; H, 3.95.

2-(1-Methyl-2-indoloyl)benzoic acid (10) was prepared from methyl 1-methylindole-2-carboxylate (0.03 mol) essentially as described for **8**. Tetrahydrofuran was removed from the crude reaction mixture in vacuo and water (250 ml) was added to the residue. The resulting mixture was extracted with ether. From the ether extract there was obtained 0.38 g (7%) of starting ester. The mixture of acids obtained by acidification of the alkaline layer was collected (ether extraction) and recrystallized from benzene to give 4.00 g (47% yield) of pure 2-(1-methyl-2-indoloyl)benzoic acid (**10**), mp 164–165 °C.

Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.10; H, 4.69; N, 5.01. Found: C, 72.97; H, 4.62; N, 4.91.

Evaporation of the benzene from which **10** was crystallized gave a semisolid to which some cold ether was added. The resulting solid was collected and recrystallized from ethyl acetate to give 0.88 g (mp 131–132 °C 10% yield) of lactone **11**.

Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.96; H, 6.62; N, 4.38. Found: C, 78.93; H, 6.50; N, 4.34.

Registry No.—**1b**, 578-57-4; **1c**, 2042-37-7; **1d**, 6952-59-6; **1e**, 623-00-7; **1f**, 577-19-5; **4b**, 1151-04-8; **4c**, 57901-51-6; **4d**, 57901-52-7; **4e**, 20643-60-1; **4f**, 57901-53-8; **6**, 611-13-2; **8**, 57901-54-9; **9**, 37493-34-8; **10**, 57901-55-0; **11**, 57901-56-1; phthalic anhydride, 85-44-9; lithium *o*-lithiobenzoate, 57901-57-2.

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(11) Lactone **11** is assumed to have been formed as a consequence of the slight excess of *n*-butyllithium used for preparation of **7** from *o*-bromobenzoic acid. Analogous products have been reported (see ref 7).

Side Reactions in Peptide Synthesis. III.[1] Intermolecular Acylation by an Unprotected Side Chain Carboxyl Group[2]

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In a recent communication[1] we reported a side reaction in the preparation of the pentapeptide derivative *tert*-butyloxycarbonylglycyl-L-tryptophyl-L-methionyl-L-aspartyl-L-phenylalaninamide (I, Chart I), an intermediate in the syntheses of gastrin,[3] cholecystokinin[1], and caerulein.[4] The conditions of the reaction suggested the mixed anhydride II as the reactive intermediate leading—through *intramolecular* acylation—to the by-product III, a succinimide derivative. Our conclusion that the unprotected carboxyl of the aspartyl residue can compete with the amino group in the nucleophilic attack on an active ester, particularly when the latter is present in excess, is now further supported by the isolation of a second by-product.

During recrystallization of samples of compound I from 95% ethanol, small amounts of a crystalline material, insoluble even in the hot solvent, were obtained. Amino acid analysis of this new by-product revealed the amino acid constituents of I, but in the molar ratio Asp 2, Gly 1, Met 2, Phe 2, Trp 2. This immediately suggested that the nonapeptide derivative IV was in hand, formed via the same mixed anhydride (II)[5] but in an *intermolecular* reaction with the amino component, a tetrapeptide amide (as shown in Chart I).

The structure proposed for compound IV was supported by its degradation (after deblocking) with cyanogen bromide[6] and with aminopeptidase M[7] (Chart II).

The unexpected[8] formation of a nonapeptide derivative (IV) during the preparation of a blocked pentapeptide (I) suggests that the protection of carboxyl groups has to be