(*E*)-3-Benzylidenephthalides

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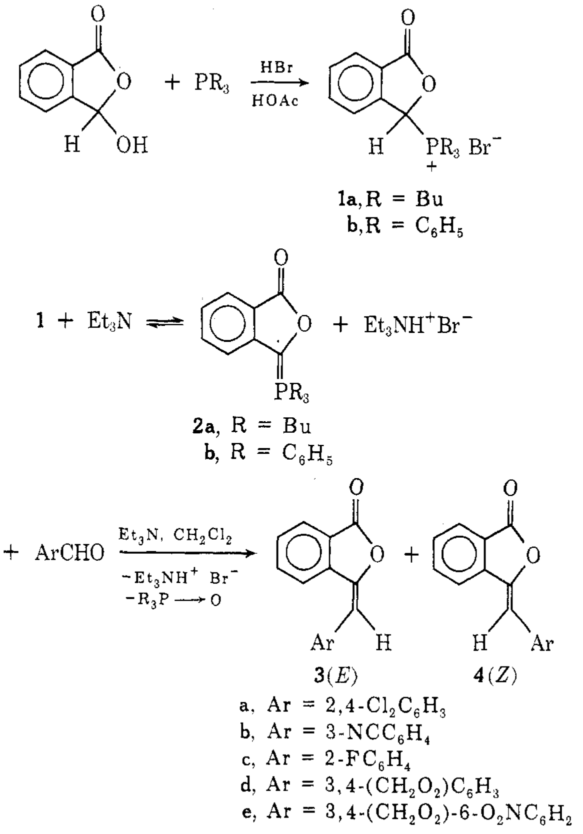
Tributyl(3-phthalidyl)phosphonium bromide (**1a**) and triphenyl(3-phthalidyl)phosphonium bromide (**1b**) were prepared from 3-hydroxyphthalide, the appropriately substituted phosphine, and hydrogen bromide in acetic acid. Triethylamine-catalyzed Wittig reactions of **1a** with aromatic aldehydes in methylene chloride solution produced, in nearly quantitative yields, *E–Z* mixtures of 3-benzylidenephthalides in which the *E* isomers predominated (80–91%). Pure *E* isomers **3a–e** were obtained in 40–49% yields by simple fractional crystallization procedures. This method constitutes the first practical synthesis of (*E*)-3-benzylidenephthalides. Triethylamine-catalyzed reaction of **1a** with aromatic nitroso compounds resulted in 3-aryliminophthalides **5a** (73% yield) and **5b** (82% yield).

(*E*)-3-Benzylidenephthalides have been the subject of numerous publications throughout the years. These compounds have served extensively as intermediates for syntheses of drug candidates.[1] Generally, 3-benzylidenephthalides are prepared by condensation of phthalic anhydride with arylacetic acids at 230–250°, a method that leads very predominantly to the *Z* isomers.[1b,g,2–4] Recently, a new synthesis was reported in which (*Z*)-3-benzylidene-6-nitrophthalides were prepared by condensation of diphenyl 6-nitrophthalide-3-phosphonate and aromatic aldehydes using sodium hydride in *N*,*N*-dimethylformamide.[5] (*E*)-3-Benzylidenephthalides have appeared only rarely in the chemical literature[3b,4] and have been isolated with difficulty from *E–Z* mixtures in which the more stable *Z* isomers predominated. No preparative method for synthesis of the *E* isomers appears to have been reported previously. We describe here a practical method of wide scope for the preparation of (*E*)-3-benzylidenephthalides.

The phthalidylphosphonium salts **1a** and **1b** were prepared as shown in Scheme I. These salts are remarkably acidic. Treatment of **1a** with 1 equiv of triethylamine in methylene chloride results in *ca.* 10–20% formation of yellow ylide **2a** and triethylammonium bromide, based on the intensity of the $Et_3NH^+Br^-$ ir bands at 3.85 and 4.05 μ. Inductive effects undoubtedly play a major role in the acidity of **1a**; however, extended conjugation through the π electron system of the ylide lactone ring may also be a contributing factor.

SCHEME I



1a, R = Bu
b, R = C_6H_5

2a, R = Bu
b, R = C_6H_5

a, Ar = $2,4\text{-}Cl_2C_6H_3$
b, Ar = $3\text{-}NCC_6H_4$
c, Ar = $2\text{-}FC_6H_4$
d, Ar = $3,4\text{-}(CH_2O_2)C_6H_3$
e, Ar = $3,4\text{-}(CH_2O_2)\text{-}6\text{-}O_2NC_6H_2$

Dropwise addition of 1 equiv of triethylamine to **1a** and 2,4-dichlorobenzaldehyde in methylene chloride resulted with each drop in a fleeting yellow color that rapidly discharged as the yellow ylide **2a** reacted with the aldehyde. After 1.5 hr at 23°, ir analysis of the solution revealed that all the aldehyde was consumed and that 1 equiv of triethylammonium bromide had formed. Extraction of the solution with water and nmr analysis of the aqueous extracts, using DMSO as a quantitative internal standard, revealed that triethylammonium bromide had formed in 96% yield. Quantitative gc analysis of the methylene chloride solution revealed that tributylphosphine oxide had formed in 100% yield and that a 91:9 mixture of (*E*)- and (*Z*)-3-(2,4-dichlorobenzylidene)phthalides had been produced in 98% yield. Similar reaction of **1b** with 2,4-dichlorobenzaldehyde gave triphenylphosphine oxide in 95.5% yield and an 87:13 mixture of (*E*)- and (*Z*)-3-(2,4-dichlorobenzylidene)phthalides in 93% yield.

The reaction appears general for aromatic aldehydes as demonstrated by the preparation of **3a–e** from **1a**.[6] With 3-cyanobenzaldehyde, an 86:14 mixture of **3b** and **4b** was obtained. 2-Fluorobenzaldehyde gave an 83:17 mixture of **3c** and **4c**. From piperonal, an 80:20 mixture of **3d** and **4d** was obtained. Use of 6-nitropiperonal resulted in formation of a mixture of **3e** and **4e** in which the *E* isomer amounted to ≥85%.

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[1] (a) U. S. Patent 3,274,185 (1966); (b) Z. J. Vejdelek, O. Nemecek, V. Musil, and A. Simek, *Collect. Czech. Chem. Commun.*, **29**, 776 (1964); (c) Swiss Patent 356,759 (1961); *Chem Abstr.*, **59**, 5104 (1963); (d) Czechoslovakian Patent 102,062 (1961); *Chem. Abstr.*, **57**, 16521 (1962); (e) P. Hrnciar and V. Kovalcik, *Chem. Zvesti*, **16**, 96, 200 (1959); *Chem. Abstr.*, **59**, 2731 (1963); (f) East German Patent 17,075 (1961); *Chem. Abstr.*, **55**, 2700 (1961); (g) C. van der Stelt, A. F. Harms, and W. T. Nauta, *J. Med. Pharm. Chem.*, **4**, 335 (1961).

[2] According to recent nomenclature rules [*J. Org. Chem.*, **35**, 2849 (1970)], the old cis and trans steroisomeric terms[3b,4] for 3-benzylidenephthalides are to be replaced by *E* and *Z* descriptors, respectively.

[3] (a) R. Weiss, *Org. Syn.*, **13**, 10(1933); (b) G. Berti, *Gazz. Chim. Ital.*, **86**, 655 (1956); *Chem Abstr.*, **52**, 1958 (1958).

[4] J. Rigaudy and P. Derible, *Bull. Soc. Chim. Fr.*, 3047 (1965).

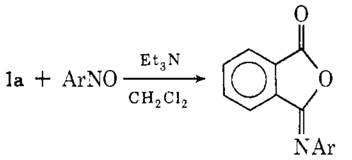
[5] A. Yamaguchi and M. Okazaki, *Nippon Kagaku Kaishi*, 110 (1973).

[6] Attempts to condense the ylide with acetone and with acetophenone were unsuccessful.

Compounds **3a–e** were each obtained in 100% purity by fractional crystallizations. Yields of pure *E* isomers **3a–e** ranged from 40 to 49%.

Pure samples of the *Z* isomers **4a–e** were prepared by iodine-catalyzed isomerizations of the corresponding *E* isomers. Compounds **4a**,[1b] **4c**,[7] and **4d**[8] have been prepared previously. Correspondence of the physical properties of our samples of **4a**, **4c**, and **4d** with the literature values for these compounds and conversion of the *E* isomers to the *Z* isomers adds confirmation to the nmr and ir spectral assignments for the structures of the (*E*)-benzylidenephthalides **3a–e**.

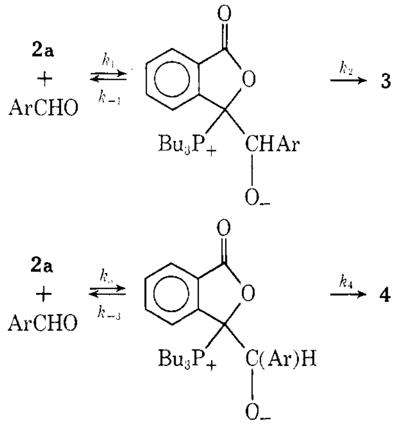
Ylide **2a** reacts very rapidly (5–15 min at 10–30°) with aromatic nitroso compounds to produce 3-aryliminophthalides in good yields (73% for **5a**, 82% for **5b**).[9] The very mild reaction conditions involved in this reaction allow isolation of these somewhat unstable materials that are prone toward isomerization[10] to *N*-arylphthalimides.



5a, Ar = C_6H_5
b, Ar = $2\text{-}CH_3C_6H_4$

The stereochemical outcome of any Wittig reaction depends on the interactions of several factors, including the ratio of epimeric betaine intermediates formed, the rates of reversion of the betaines to starting materials, and the rates of conversion of the epimeric betaines to *E* and *Z* olefins. In most cases of the phosphonate version of the Wittig reaction with aldehydes, these factors combine in such a fashion as to produce predominantly the more stable olefin.[11] In the reaction of phosphonium ylides with aldehydes, the betaine that produces the less stable olefin is formed predominantly, for reasons that are not entirely clear, under conditions of kinetic control.[11] When these conditions prevail and, in addition, when the epimeric phosphonium betaines collapse to olefin products faster than they revert to starting materials, the less stable olefin is produced predominantly.[11] Such appears to be the case in the reactions of **2a** and **2b** with aromatic aldehydes; restated, $k_1 > k_3$ and $k_2 > k_{-1}$ in Scheme II.[12,12a]

Scheme II



Neither the triethylamine nor the product triethylammonium bromide appears to influence significantly the stereochemical results of the reaction of **2a** with aldehydes as determined from an experiment in which a solution of **1a** and 2,4-dichlorobenzaldehyde in methylene chloride was shaken with excess aqueous sodium hydroxide at 0–5°. Reaction was nearly instantaneous under these conditions, in which ylide **2a** presumably is generated in the presence of the aldehyde and in the absence of any salts. Products **3a** and **4a** were obtained in a 93:7 ratio in 94% total yield.

Experimental Section[13]

Tributyl(3-phthalidyl)phosphonium Bromide (1a).—A mixture of 30 g (0.20 mol) of 2-carboxybenzaldehyde, 57 g (0.211 mol of HBr) of 30% HBr in acetic acid, and 40.4 g (0.20 mol) of tributylphosphine was stirred under N_2 at 90° for 22 hr and then was concentrated under vacuum. The residue was stirred with 250 ml of ether, and seed crystals were added. The resultant semisolid was triturated with 250 ml of fresh ether to give 75.8 g of pale yellow solid, mp 135–146°. The solid was crystallized from CH_3CN-EtOAc to give 34.6 g of white solid, mp 151–152.5°. An additional 18.1 g of solid, mp 149–151°, was obtained from the filtrate. The total yield was 63.5%: ir (mineral oil mull) 5.61 μ; nmr ($CDCl_3$) δ 7.9 (m, 5, ArH + ArCHP), 2.68 (m, 6, PCH_2), 1.50 (m, 12, $PCH_2CH_2CH_2CH_3$), 0.91 (m, 3, CH_3).

Anal. Calcd for $C_{20}H_{32}BrO_2P$: C, 57.83; H, 7.77. Found: C, 57.61; H, 7.82.

Triphenyl(3-phthalidyl)phosphonium Bromide (1b).—A solution of 45 g (0.30 mol) of 2-carboxybenzaldehyde, 78.6 g (0.30 mol) of triphenylphosphine, 81.0 g (0.30 mol of HBr) of 30% HBr in acetic acid, and 60 ml of acetic acid was stirred at 90° under N_2 for 48 hr. The reaction mixture was allowed to cool and was seeded with pure product obtained from an aliquot. The resultant 106.6 g of solid was boiled with 1400 ml of CH_3CN, and the mixture was allowed to cool and was filtered to give 64.6 g of white solid, mp 258–260°. An additional 37.7 g of solid, mp 258–260°, was obtained from the filtrate (72% total yield): ir (mineral oil mull) 5.65 μ.

Anal. Calcd for $C_{26}H_{20}BrO_2P$: C, 65.70; H, 4.24. Found: C, 65.86; H, 4.22.

(*E*)-3-(2,4-Dichlorobenzylidene)phthalide (3a).—To a solution of 4.15 g (0.010 mol) of tributyl(3-phthalidyl)phosphonium bromide and 1.75 g (0.010 mol) of 2,4-dichlorobenzaldehyde (recrystallized) in 60 ml of CH_2Cl_2 was added dropwise with stirring 1.01 g (0.010 mol) of triethylamine. The solution was stirred for 1.5 hr, and then 40 ml of CH_2Cl_2 was added. The solution was extracted with three 50-ml portions of water. The aqueous layers were combined, and 0.010 mol of DMSO was added. Nmr analysis of this solution, using the DMSO as a quantitative internal standard, indicated a 96% yield of triethylammonium bromide. Gc analysis of the CH_2Cl_2 solution using bis(*p*-bromophenyl) ether as an internal standard revealed that tributyl-

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(7) U. S. Patent 3,641,153 (1972).

(8) M. Furdik and I. Pastorek, *Acta Fac. Rerum Natur. Univ. Comenianae, Chim.*, No. 11, 47 (1966); *Chem. Abstr.*, **68**, 12742 (1968).

(9) Condensation of diphenyl 6-nitrophthalide-3-phosphonate with aromatic nitroso compounds using sodium hydride in *N*,*N*-dimethylformamide led to *N*-arylphthalimides, presumably *via* intermediate 3-arylimino-6-nitrophthalides which rearranged under the reaction conditions: ref 5.

(10) M. L. Ernst and G. L. Schmir, *J. Amer. Chem. Soc.*, **88**, 5001 (1966).

(11) M. Schlosser in "Topics in Stereochemistry," Vol. 5, E. Eliel and N. Allinger, Ed., Wiley-Interscience, New York, N. Y., 1970, pp 1–30.

(12) Similar results have been found in the reaction of certain carbonyl-stabilized phosphonium ylides with phthalic anhydride: P. S. Chopard, R. F. Hudson, and R. J. G. Searle, *Tetrahedron Lett.*, 2357 (1965).

(12a) Note Added in Proof.—In a recent paper, E. Vedejs and K. A. J. Snoble [*J. Amer. Chem. Soc.* **95**, 5778 (1973)] have provided direct evidence for the intermediacy of oxaphosphetanes in the Wittig reactions of certain nonstabilized phosphonium ylides with aldehydes. Possible betaine intermediates were not detected (<1%) and were considered to be considerably less stable than the cyclic oxaphosphetanes. Vedejs and Snoble proposed that the oxaphosphetane is formed by concerted $\pi 2_s + \pi 2_a$ cycloaddition of ylide and aldehyde; predominant cycloaddition *via* the least hindered orientation of ylide and aldehyde would lead directly to the most hindered oxaphosphetane and thus would result in selective cis olefin formation. This mechanism could account quite nicely for our results in the phthalidyl system.

(13) Melting points were taken in open capillaries in a Mel-Temp apparatus and are corrected.

phosphine oxide had formed in 100% yield and a mixture of (*E*)- and (*Z*)-3-(2,4-dichlorobenzylidene)phthalides was formed in 98% yield (analysis on a 2-ft column of 10% SE-30 at 230°). Gc analysis on a 2-ft column of 2% XE-60 at 220° (injector port at 250°) indicated the *E* to *Z* ratio to be 91:9 (under these latter gc conditions <1% isomerization of *E* to *Z* isomer occurred). Nmr analysis of the CH_2Cl_2 solution indicated a 92:8 *E* to *Z* isomer ratio by comparison with a standard 92:8 mixture prepared from the pure isomers. The analysis was made possible by the fact that the *Z* isomer has a one-proton doublet at δ 8.25 that is at lower field than the rest of the proton signals of the *E* and *Z* isomers.

The CH_2Cl_2 solution was concentrated under vacuum to 5.0 g of solid (98% of theory for tributylphosphine oxide plus the phthalides). The solid was treated twice with hot hexane. The undissolved solid, 1.8 g (62% yield), mp 143–144°, was >98% pure (*E*)-3-(2,4-dichlorobenzylidene)phthalide (ir analysis). Two crystallizations of the solid from ethanol gave 1.22 g (42% yield) of 100% pure *E* isomer (nmr, ir, and gc analyses): mp 145.5–146°; ir (mineral oil mull) 5.62 (s), 6.02 (w), 6.31 μ (w); nmr ($CDCl_3$) δ 7.93 (m, 1, ArH), 7.53 (m, 6, ArH), 6.78 (s, 1, ArCH=C).

Anal. Calcd for $C_{15}H_8Cl_2O_2$: C, 61.88; H, 2.77. Found: C, 61.97; H, 2.78.

A similar reaction in which triphenyl(3-phthalidyl)phosphonium bromide was employed gave triphenylphosphine oxide in 95.5% yield and an 87:13 mixture of (*E*)- and (*Z*)-3-(2,4-dichlorobenzylidene)phthalides in 93% yield.

(*Z*)-**3-(2,4-Dichlorobenzylidene)phthalide (4a).**—A solution of 1.1 g of (*E*)-3-(2,4-dichlorobenzylidene)phthalide and *ca.* 10 mg of I_2 in 20 ml of nitrobenzene was held at reflux under N_2 for 30 min. Methylene chloride was added, and the solution was washed twice with dilute sodium thiosulfate solution. Gc analysis indicated a 5:95 ratio of *E* to *Z* isomers. The solution was concentrated under vacuum to a brown solid, which was crystallized from methylcyclohexane (charcoal) to give 0.63 g of solid, mp 180–181° (lit.[1b] mp 181°), which was 100% pure (gc assay) *Z* isomer: ir (mineral oil mull) 5.60 (s), 6.02 (w) 6.32 μ (w); nmr ($CDCl_3$) δ 8.25 (d, 1, *J* = 8 Hz, 6-H of 2,4-$Cl_2C_6H_3$ ring), 8.0–7.2 (m, 6, ArH), 6.80 (s, 1, ArCH=C).

(*E*)-**3-(*m*-Cyanobenzylidene)phthalide (3b).**—To a solution of 5.15 g (0.0393 mol) of 3-cyanobenzaldehyde and 16.3 g (0.0393 mol) of **1a** in 150 ml of CH_2Cl_2 stirred under N_2 was added 3.97 g (0.0393 mol) of triethylamine during 5 min. The resultant mixture was stirred for another 15 min and then was diluted to 600 ml to obtain a homogeneous solution. The solution was washed with water and was analyzed by gc (2-ft 2% XE-60 column at 250°); the ratio of *E* and *Z* isomers was 86:14. The solvent was removed under vacuum and the residue was triturated with 125 ml of hexane to remove tributylphosphine oxide. The hexane-insoluble solid, 9.40 g (97%), was dissolved in hot $CHCl_3$, and the solution was allowed to cool and was seeded with pure *Z* isomer. After needles of the *Z* isomer formed, the mixture was rapidly filtered. The filtrate was reheated to boiling, was allowed to cool somewhat, was seeded with pure *E* isomer, and was diluted to *ca.* four times the volume with CCl_4. The mixture was filtered rapidly after two minutes to give *E*-rich solid. Recrystallizations of this material from $CHCl_3$–CCl_4 gave pure *E* isomer. In this way, a total of 4.27 g (44%) of 100% pure (gc assay) (*E*)-3-(*m*-cyanobenzylidene)phthalide, mp 206–207°, was obtained: ir (mineral oil mull) 4.50, 5.64 μ; nmr ($CDCl_3$) δ 8.07–7.3 (m, 8, ArH), 6.83 (s, 1, ArCH=C).

Anal. Calcd for $C_{16}H_9NO_2$: C, 77.72; H, 3.70. Found: C, 77.90; H, 3.81.

A total of 0.63 g (6.5%) of fairly pure *Z* isomer **4b**, mp 247–249°, was also obtained.

(*Z*)-**3-(*m*-Cyanobenzylidene)phthalide (4b).**—A solution of 2.0 g of **3b** and 20 mg of I_2 in 20 ml of nitrobenzene was held at reflux under N_2 for 30 min and then was allowed to cool. The resultant solid was collected, washed with methanol, and crystallized twice from 1,2 dichloroethane to give 1.54 g (77%) of 100% pure (gc assay) *Z* isomer **4b**: mp 249–250°; ir (mineral oil mull) 4.50, 5.58 μ; nmr ($CDCl_3$) δ 8.13–7.43 (m, 8, ArH), 6.37 (s, 1, ArCH=C).

Anal. Calcd for $C_{16}H_9NO_2$: C, 77.72; H, 3.70. Found: C, 77.92; H, 3.78.

(*E*)-**3-(*o*-Fluorobenzylidene)phthalide (3c).**—A solution of 4.96 g (0.040 mol) of *o*-fluorobenzaldehyde, 16.6 g (0.040 mol) of **1a**, and 4.04 g (0.040 mol) of triethylamine in 200 ml of CH_2Cl_2 was stirred under N_2 for 44 hr and then was washed with water. Gc analysis of the solution revealed an 83:17 mixture of *E* and *Z* isomers. The solvent was removed under vacuum, and the residue was triturated with two 50-ml portions of hexane. The hexane-insoluble solid, 7.60 g (79%), was crystallized from 600 ml of hexane to give 4.2 g (44%) of 100% pure *E* isomer **3c** as white needles, mp 119–120°. An additional 0.43 g (4.5%) of **3c**, mp 119–120°, was recovered from the hexane extracts and filtrate: ir (mineral oil mull) 5.60 μ; nmr ($CDCl_3$) δ 8.07–7.10 (m, 8, ArH), 6.78 (s, 1, ArCH=C).

Anal. Calcd for $C_{15}H_9FO_2$: C, 75.00; H, 3.78. Found: C, 75.22; H, 3.90.

(*Z*)-**3-(*o*-Fluorobenzylidene)phthalide (4c).**—Iodine-catalyzed isomerization of 1.5 g of **3c** in nitrobenzene at reflux under N_2 for 45 min and crystallization of the product from ethanol gave 0.63 g (42%) of **4c** as yellow needles: mp 151–152.5° (lit.[7] mp 148–151°); ir (mineral oil mull) 5.58 μ; nmr ($CDCl_3$) δ 8.53–7.0 (m, 8, ArH), 6.71 (s, 1, ArCH=C).

(*E*)-**3-Piperonylidenephthalide (3d).**—A solution of 8.30 g (0.020 mol) of **1a**, 3.0 g (0.020 mol) of piperonal, and 2.02 g (0.020 mol) of triethylamine in 120 ml of CH_2Cl_2 was stirred under N_2 for 29 hr, was diluted to 150 ml with CH_2Cl_2, and was washed with water. Gc analysis of the solution revealed the *E* to *Z* product ratio to be 82:18. The solution was concentrated under vacuum, and the solid residue was triturated with 50 ml of hexane. The hexane-insoluble solid, 5.0 g (94%), was crystallized from 30 ml of $CHCl_3$ at 5° (seeding with pure *Z* isomer) to give 0.59 g of 96% *Z* isomer, mp 196–200°. Recrystallization of this solid from 1,2-dichloroethane gave 0.42 g (8%) of pure *Z* isomer **4d**, mp 202–204° (lit.[8] mp 206–207.5°).

The $CHCl_3$ filtrate was concentrated somewhat and was cooled in ice to give 2.33 g of 96% *E* isomer, mp 137–140°. The filtrate was diluted with CCl_4 and was seeded with *Z* isomer to give 0.17 g of *E–Z* mixture. Concentration of the filtrate and seeding with *E* isomer gave 0.33 g of 95% *E* isomer. The 2.66 g (50%) of *E* isomer was dissolved in hot CCl_4. The solution was seeded with *E* isomer and was cooled rapidly to 20°. The resultant 2.31 g of 98% *E* isomer, mp 137–139°, was recrystallized in the same way to give 2.11 g (40%) of pale yellow solid, mp 139–140°, that was 100% pure *E* isomer **3d**: ir (mineral oil mull) 5.65 μ; nmr ($CDCl_3$) δ 7.87 (m, 1), 7.7–7.43 (m, 3), 6.90 (s, 3), 6.80 (s, 1, ArCH=C), 6.03 (s, 2, OCH_2O).

Anal. Calcd for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79. Found: C, 71.98; H, 3.84.

(*Z*)-**2-Piperonylidenephthalide (4d).**—A solution of 1.0 g of *ca.* 82:18 *E*:*Z* mixture of 3-piperonylidenephthalide and a few milligrams of iodine in 25 ml of nitrobenzene was held at reflux for 45 min and was concentrated under vacuum. The residue was triturated with methanol to give 0.90 g (90%) of solid, mp 201–203°. Recrystallization of this material from 1,2-dichloroethane gave 0.74 g of 100% pure *Z* isomer **4d** as a beige solid: mp 202.5–204° (lit.[8] mp 206–207.5°); ir (mineral oil mull) 5.63 and 5.68 μ; nmr ($CDCl_3$) δ 8.0–7.2 (m, 6), 6.82 (d, 1, *J* = 8 Hz, 5-H of piperonyl ring), 6.33 (s, 1, ArCH=C), 6.00 (s, 2, OCH_2O).

(*E*)-**3-(6-Nitropiperonylidene)phthalide (3e).**—A solution of 4.15 g (0.010 mol) of **1a**, 1.95 g (0.010 mol) of 6-nitropiperonal, and 1.01 g (0.010 mol) of triethylamine in 50 ml of CH_2Cl_2 was stirred under nitrogen for 30 hr, and the resultant mixture was diluted to 220 ml with CH_2Cl_2 to obtain a homogeneous solution. The solution was washed with water and was dried ($CaSO_4$). An aliquot was concentrated under vacuum, and the residue was dissolved in $CDCl_3$ for an nmr assay, which revealed that there was less than 15% of the *Z* isomer in the *E* product.

The $CDCl_3$ solution was combined with the CH_2Cl_2 solution, and the solvents were removed under vacuum to give a yellow solid. The solid was crystallized from 1,2-dichloroethane–hexane to give 2.73 g (88%) of solid, mp 197–201°. This material was fractionally recrystallized from 1,2 dichloroethane to give 1.36 g (44%) of pure *E* isomer **3e**: mp 203–204° (above 204°, the solid recrystallizes and then decomposes at 262–264° owing to isomerization to the *Z* isomer); ir (mineral oil) mull) 5.65 μ; nmr ($CDCl_3$) δ 8.0–6.9 (m, 7), 6.20 (s, 2, OCH_2O).

Anal. Calcd for $C_{16}H_9NO_6$; C, 61.74; H, 2.91. Found: C, 61.56; H, 2.93.

(*Z*)-**3-(6-Nitropiperonylidene)phthalide (4e).**—A solution of 0.50 g of **3e** and *ca.* 1 mg of iodine in 10 ml of nitrobenzene was held at reflux for 5 min under nitrogen and then was concentrated under vacuum. The residue was triturated with methanol to give 0.47 g (94%) of solid, mp 266–267° dec. This material was recrystallized from 1,2-dichloroethane to give 0.34 g (68%) of **4e** as a yellow solid: mp 269.5–270°; ir (mineral oil mull) 5.60 μ; nmr ($CDCl_3$) δ 8.1–7.4 (m, 6), 7.05 (s, 1, ArCH=C), 6.13 (s, 2, OCH_2O).

Anal. Calcd for $C_{16}H_9NO_6$: C, 61.74; H, 2.91. Found: C, 61.58; H, 2.83.

3-(Phenylimino)phthalide (5a).—To a solution of 4.15 g (0.010 mol) of **1a** and 1.07 g (0.010 mol) of nitrosobenzene in 30 ml of CH_2Cl_2 was added dropwise, during 3 min, 1.01 g (0.010 mol) of triethylamine with stirring at 25 ± 2° (ice-bath cooling required). The solution was stirred another 7 min at 10–25°, and then 20 ml of CH_2Cl_2 was added. The solution was extracted with three 25-ml portions of ice water, dried ($CaSO_4$), and concentrated under vacuum at 20° to 4.5 g of yellow solid. The solid was stirred with 15 ml of methanol, collected, and washed with 5 ml of methanol. The resultant 2.83 g of pasty solid was dissolved in 45 ml of CH_3CN, the solution was filtered, and 25 ml of ice water was added to the filtrate to give 1.63 g (73% yield) of yellow solid: mp 120–121.5° (lit.[10] mp 119–120°, lit.[14] mp 120–122°); ir (mineral oil mull) 5.60, 5.89 μ.

In preliminary experiments, crystallizations of the product from hot hexane gave solid of constant mp 114–115.5°. Examination of the ir spectrum of this material revealed weak extraneous absorptions at 7.26, 8.98, 11.33, and 13.89 μ due to small amounts of *N*-phenylphthalimide.

3-(*o*-Tolylimino)phthalide (5b).—To a solution of 8.30 g (0.020 mol) of **1a** and 2.42 g (0.020 mol) of 2-nitrosotoluene in 60 ml of CH_2Cl_2 was added dropwise, during 4 min, 2.02 g (0.020 mol) of triethylamine with stirring at 25–30° (ice-bath cooling). The solution was stirred for another 15 min at 5–15°, and then 40 ml of CH_2Cl_2 was added. The solution was extracted with three 50-ml portions of ice water, dried ($CaSO_4$), and concentrated under vacuum at 20° to a yellow solid. The solid was swirled with methanol and collected to give 3.90 g (82% yield) of yellow solid: mp 136–138° (lit.[15] mp 136–137°, lit.[16] mp 136°); ir (mineral oil mull) 5.51 (sh), 5.60, 5.88 μ. There was no trace of the isomeric phthalimide present as judged from the absence of absorptions at 11.65 and 13.89 μ, bands that are strong in the spectrum of *N*-(*o*-tolyl)phthalimide.

Reaction of 1a and 2,4-Dichlorobenzaldehyde Using Sodium Hydroxide as the Base.—A solution of 4.15 g (0.010 mol) of **1a** and 1.75 g (0.010 mol) of 2,4-dichlorobenzaldehyde in 60 ml of methylene chloride was extracted at 0–5° with two 20-ml portions of 0.5 *M* aqueous sodium hydroxide and 20 ml of water. The very pale, yellow-green methylene chloride solution was dried ($CaSO_4$) and analyzed by ir within 5 min; no residual aldehyde was present. Gc analysis of the solution indicated that **3a** and **4a** had formed in a 93:7 ratio in 94% total yield.

Registry No.—**1a**, 42116-85-8; **1b**, 42116-86-9; **3a**, 42086-67-9; **3b**, 42086-68-0; **3c**, 42086-69-1; **3d**, 42086-70-4; **3e**, 42086-71-5; **4a**, 42086-72-6; **4b**, 42086-73-7; **4c**, 42086-74-8; **4d**, 42086-75-9; **4e**, 42086-76-0; **5a**, 487-42-3; **5b**, 42116-88-1; 2-carboxybenzaldehyde, 119-67-5; tributylphosphine, 998-40-3; triphenylphosphine, 603-35-0; 2,4-dichlorobenzaldehyde, 874-42-0; 3-cyanobenzaldehyde, 24964-64-5; *o*-fluorobenzaldehyde, 446-52-6; piperonal, 120-57-0; 6-nitropiperonal, 712-97-0.

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11-Aminoacridizinium Derivatives[1]

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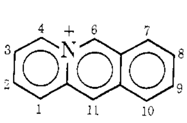
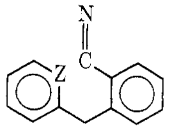
Acid-catalyzed cyclization of the 1-benzyl-2-cyanopyridinium ion and its congeners has provided a means for the synthesis of some 11-aminoacridizinium salts. Hydrolysis of the 11-aminoacridizinium ion afforded the 11-hydroxyacridizinium ion while diazotization effected ring opening and closing to form a 3-*v*-triazolo[1,5-*a*]pyridine derivative.

The relatively large number of acridizinium derivatives (**1**) which have been synthesized[2] includes only one amine, the 6-aminoacridizinium ion, obtained by the cyclization of *o*-(2-pyridylmethyl)benzonitrile (**2**).[3]



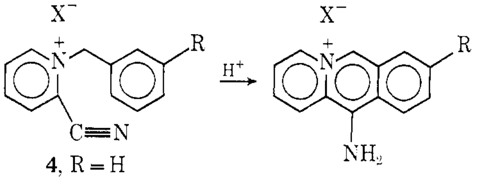
1



2, Z = N
3, Z = CH

This nitrile cyclization as well as the earlier cyclization[4] of *o*-benzylbenzonitrile (**3**) suggested that 11-aminoacridizinium salts (**6**) might be obtained by acid-catalyzed cyclization of 1-benzyl-2-cyanopyridinium salts (**4**).

While a variety of acidic cyclization reagents, including trifluoroacetic acid, polyphosphoric acid, fluorosulfonic acid, and hydrogen chloride in acetic acid, were tried, under a variety of conditions, nothing appeared superior to concentrated sulfuric acid (at 100° for 15 min) and yields of **6** did not surpass 35%. An important side reaction was cleavage of the quaternary salt **4**; for example, the cyclization attempt using hydrogen chloride afforded a good yield of 2-picolinamide hydrochloride.



4, R = H
5, R = OCH₃

7, R = H
6, R = OCH₃

Since the cyclization reaction can be regarded as an internal Hoesch[5] reaction, it is not surprising that introduction of a methoxyl group para to the position of expected cyclization (**5**) resulted in an improved (70%) yield. Efforts to prepare benzologs of **6** by the cyclization of 1α- or 1β-naphthylmethyl-2-cyanopyridinium salts failed.

An alternate approach to the synthesis of benzologs of the 11-aminoacridizinium system **6** was through the

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