determined by gas chromatography.

D. Decyl Chloride/Tetraethylene Glycol. Solvent extraction as described for butyl chloride/tetraethylene glycol gave clean separation of monoether and diether and decyl halide. Distillation gave pure monoether, bp 155–165 °C (30 μm).

E. Docosyl Bromide/Tetraethylene Glycol. The crude product from reaction of 0.05 mol of $C_{22}H_{45}Br$ with 0.10 mol of tetraethylene glycol was dissolved in CH_2Cl_2, and an aliquot was chromatographed on 100–200 mesh silica gel. Elution with $CHCl_3$ gave a mixture of docosyl bromide and docosene in about 10% yield. The next compound eluted was docosyl ether, formed in about 10% yield, identified tentatively by NMR and IR spectra. Next was eluted the diether, mp 69–70 °C (ether), 39% yield; identified by IR, NMR, and mass spectra. Anal. Calcd for $C_{52}H_{106}O_5$: C, 77.0; H, 13.2. Found: C, 77.3; H, 13.0. Elution with 70/30 $CHCl_3$/MeOH gave the monoether: mp 59–60 °C (hexane); 38% yield; IR ν_{max} 3480 and 1120 cm^{-1} (melt); ^1H NMR τ 6.33 (18 H, m), 8.70 (40 H, s), and 9.13 (3 H, t). Field ionization mass spectrometry showed a molecular ion at m/e 502 ± 1. Anal. Calcd for $C_{30}H_{62}O_5$: C, 71.7; H, 12.4. Found: C, 71.6; H, 12.6.

F. Docosyl Bromide/Hexaethylene Glycol. Reaction of $C_{22}H_{45}Br$ (0.11 mol), hexaethylene glycol (1.1 mol), 50% NaOH (0.56 mol), and Bu_4NHSO_4 (0.01 mol) in THF (250 mL) was carried out for 48 h at reflux. An additional 0.005 mol of catalyst was added and the reaction continued for 22 h. After the solution was cooled, extraction with ether and crystallization from ether gave 51.6 g of the monoether, mp 38–42 °C (80%). Further recrystallization gave mp 57–8 °C; IR ν_{max} 3460 and 1115 cm^{-1} (neat melt); ^1H NMR τ 6.32 (24 H, m), 6.54 (2 H, t, J = 6.5 Hz), 8.73 (40 H, m), and 9.12 (3 H, t). Chemical ionization mass spectrometry showed an $(M + 1)^+$ ion at m/e 592. Anal. Calcd for $C_{34}H_{70}O_7$: C, 69.1; H, 11.9. Found: C, 69.7; H, 11.9.

Registry No. Butyl chloride, 109-69-3; diethylene glycol, 111-46-6; diethylene glycol monobutyl ether, 112-34-5; diethylene glycol dibutyl ether, 112-73-2; tetraethylene glycol, 112-60-7; tetraethylene glycol monobutyl ether, 1559-34-8; tetraethylene glycol dibutyl ether, 112-98-1; decyl chloride, 1002-69-3; diethylene glycol monodecyl ether, 23238-41-7; diethylene glycol didecyl ether, 72659-41-7; tetraethylene glycol monodecyl ether, 5703-94-6; tetraethylene glycol didecyl ether, 51750-96-0; decyl bromide, 112-29-8; docosyl bromide, 6938-66-5; tetraethylene glycol monodocosyl ether, 72659-42-8; tetraethylene glycol didocosyl ether, 72659-43-9; hexaethylene glycol, 2615-15-8; hexaethylene glycol monodocosyl ether, 72659-44-0; butyl bromide, 109-65-9; butyl alcohol, 71-36-3.

Studies on the Synthesis of Substituted Phenanthrenoids

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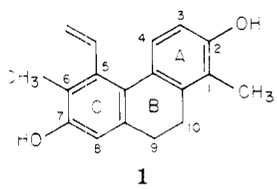
Highly regioselective reactions for the construction of polysubstituted benzenes **18**, **19**, **20**, **22**, **24**, and **44–47** are described, including some remarkable site-selective halogenations. These have been employed in the synthesis of halo-, nitro-, amino-, and urethane-substituted stilbenes **37**, **38**, and **51–56**. Ideas for thermal as well as photochemical cyclizations are presented and explored. Stilbene **54** led to the formation of phenanthrenes **57**, **58**, and **62**; likewise **55** furnished two new tricyclics, **60** and **61**, whereas irradiation of **52** in *tert*-butyl alcohol captured solvent to produce phenanthrenes **63** and **64**. Strategies for the total synthesis of juncusol (**1**), a cytotoxic phytoalexin, are considered.

Of the many defense mechanisms employed by plant populations against pathogens and herbivores, the induced phytoalexin response is an area of active investigation among ecologists and biochemists. Phytoalexins are specific antifungal agents which materialize in appreciable quantities postinfection, and are often present in low levels within the living cells of healthy plants.[2]

A large fraction of the known phytoalexin structures falls in the class of alkyl- and hydroxyl-substituted 9,10-dihydrophenanthrenes, one representative of which is juncusol (**1**), a cytotoxic constituent of the estuarine marsh



1

plant *Juncus roemerianus*.[3] Although a considerable body of preparative phenanthrene chemistry has been developed[4] which pertains to the synthesis of these natural products, the particular nature and degree of functionalization in structures like **1** pose a considerable challenge to existing methodology and have renewed interest in alternative approaches to such polycyclic dihydroaromatics.

Two independent syntheses of juncusol have recently been published,[5,6] and a full experimental account of the first[5b] describes the unexpected complexity of some classical methods when applied to **1**. In view of these disclosures we wish now to report our own work in this area which focuses first on the matter of polyfunctional benzene construction and then on the design of new phenanthrene-forming cyclizations.

Stilbene Photocyclization. The retrosynthetic analysis of juncusol shown in Scheme I suggested that the C5 vinyl substituent might be introduced late in the synthesis at the stage of a 9,10-dihydrophenanthrene by means of a metal–halogen exchange on bromide **5**. Addition of acetaldehyde to aryllithium **4** would furnish alcohol **3**, ultimately destined for dehydration. Since selective reduction of the 9,10 double bond in phenanthrenes is generally feasible,[7] we felt that phenanthrene **6** might be an attractive synthetic intermediate which, in turn, would be

(1) Fellow of the Alfred P. Sloan Foundation, 1978–1980; Camille and Henry Dreyfus Teacher-Scholar Grant Awardee, 1978–1983.
(2) Levin, D. A. *Annu. Rev. Ecol. Syst.* **1976**, *7*, 121–159.
(3) (a) Miles, D. H.; Bhattacharyya, J.; Mody, N. V.; Atwood, J. L.; Black, S.; Hedin, P. A. *J. Am. Chem. Soc.* **1977**, *99*, 618–620. (b) Miles, D. H.; Pelletier, S. W.; Bhattacharyya, J.; Mody, N. V.; Hedin, P. A. *J. Org. Chem.* **1978**, *43*, 4371–4373.
(4) Floyd, A. J.; Dyke, S. F.; Ward, S. E. *Chem. Rev.* **1976**, *76*, 509–562.
(5) (a) Kende, A. S.; Curran, D. P. *Tetrahedron Lett.* **1978**, 3003–3006. (b) Kende, A. S.; Curran, D. P. *J. Am. Chem. Soc.* **1979**, *101*, 1857–1864.
(6) McDonald, E.; Martin, R. T. *Tetrahedron Lett.* **1978**, 4723–4726.
(7) (a) Letcher, R. M.; Nhamo, L. R. M. *J. Chem. Soc., Perkin Trans.* **1973**, 1263–1265. (b) Stoessi, A.; Rock, G. L.; Fisch, M. H. *Chem. Ind. (London)* **1974**, 703–704.

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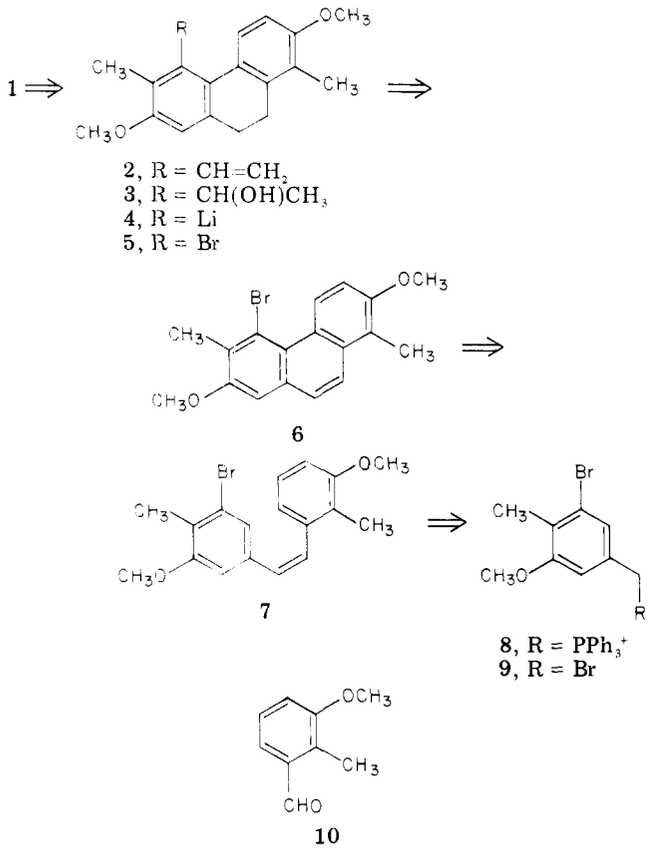
Scheme I



2, R = $CH{=}CH_2$
3, R = $CH(OH)CH_3$
4, R = Li
5, R = Br

6

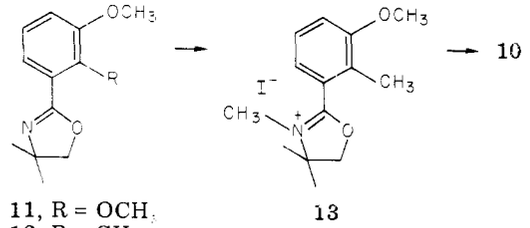
7

8, R = PPh_3^+
9, R = Br

10

readily accessible from the pentasubstituted stilbene **7**. While the oxidative photolysis of stilbenes is a well-known route to phenanthrenes,[8] two regioisomeric products may arise from **7**, and the substantial body of literature on this topic suggested that the two resulting phenanthrenes would likely form at comparable rates.[9] Nevertheless the highly convergent nature of this approach and the ease with which stilbene **7** could likely be prepared more than compensated for the nonselective photocyclization we anticipated.

The Wittig reaction of phosphonium salt **8** and aldehyde **10** was chosen to make a cis/trans mixture of **7**, and the synthesis of these benzenoid subunits became our first experimental goal. For ring A, 3-methoxy-2-methylbenzaldehyde was prepared from commercially available 2,3-dimethoxybenzoic acid via oxazoline **11** in 81% overall

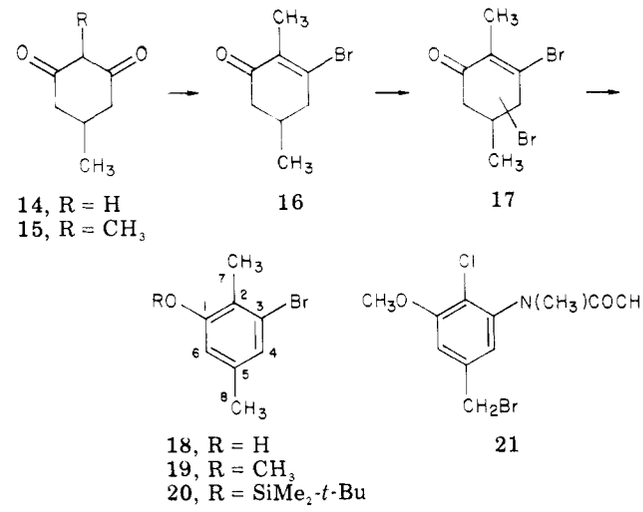


11, R = OCH_3
12, R = CH_3

13

yield as follows. First, reaction of **11** with CH_3MgBr in tetrahydrofuran (THF) afforded methyl-substituted oxazoline **12** in 99% yield.[10] **12** was heated with iodomethane in nitromethane to furnish the oxazolinium salt **13**, isolated in 98% yield, which could then be reduced using $NaBH_4$

Scheme II



14, R = H
15, R = CH_3

16

17

18, R = H
19, R = CH_3
20, R = $SiMe_2$-*t*-Bu

21

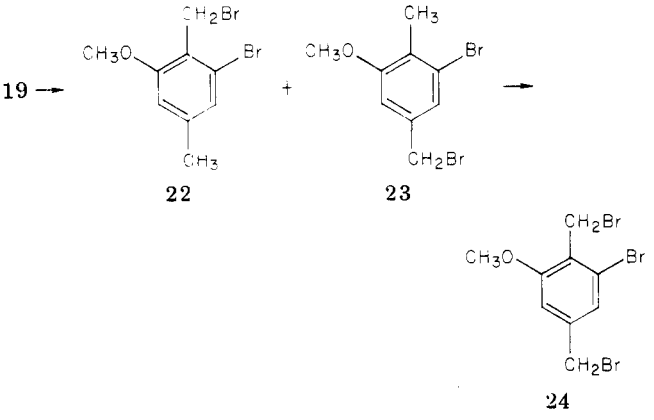
in ethanol.[11] Acidic workup cleanly gave **10** which was used in subsequent steps without further purification.

Phosphonium salt **8** was envisioned to arise from bromide **9**, a more complex, tetrasubstituted benzene which might be assembled in a variety of different ways. In synthetic studies on maytansine we had earlier addressed a similar problem in preparing arene **21** (Scheme II) as a building block for the "western zone" of this macrocycle.[12] In that work we first positioned the appropriate substituents in an alicyclic precursor and then oxidized the ring to an arene under mild conditions. This approach seemed amenable to the problem at hand and was all the more attractive since the projected starting material, 5-methylcyclohexane-1,3-dione (**14**), was readily available in our laboratory. The synthesis of 3-bromo-2,5-dimethylanisole (**19**) is depicted in Scheme II.

Treatment of the sodium enolate of **14** with methyl iodide in dioxane–water at reflux yielded 48% of **15**. A benzene solution of **15** in the presence of triphenylphosphine dibromide[13] and triethylamine smoothly formed β-bromo enone **16** (97%). Bromination of this enone with 1 equiv of Br_2 in $CHCl_3$ gave a dibromide, **17**, of undetermined structure which with *p*-toluenesulfonic acid–benzene underwent elimination and aromatization to 2,5-dimethyl-3-bromophenol (**18**) in 72% yield (from **16**). Finally, the conversion of **18** to its methyl ether **19** was effected (93%) with K_2CO_3–CH_3I in methanol.

As in the very clean, high-yield *N*-bromosuccinimide (NBS) bromination which produced maytansine intermediate **21** from its toluene precursor,[12] we hoped that benzylic bromination of **19** would prevail over ring halogenation and that it would also predominate at the more accessible C8 position, even though oxidation of C7 generates stabilized radical character in the transition state. We were unable to find precedent for any such selective brominations in aromatic systems;[14] consequently we undertook a short study on this system. In this event, NBS oxidation of **19** first occurred almost exclusively at C7, indicating a far greater sensitivity to electronic rather than steric factors. This was true even in the case of the highly hindered *tert*-butyldimethylsilyl ether **20**. Moreover a second equivalent of NBS acting on **22** furnished the crystalline tribromide **24** in 80% yield (mp 122–126 °C). As expected, phenol **18** underwent exclusive ring substi-

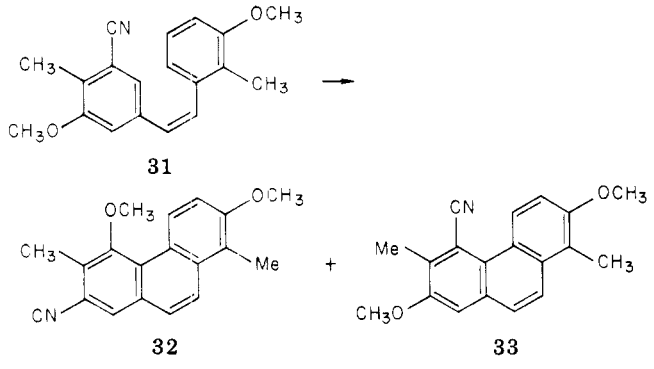
(8) Stermitz, F. R. In "Organic Photochemistry"; Chapman, O. L., Ed.; Marcel Dekker: New York, 1967; Vol. 1, p 247.
(9) Mallory, F. B.; Mallory, C. W. *J. Am. Chem. Soc.* **1972**, *94*, 6041–6048.
(10) Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383–7385.
(11) Nordin, I. C. *J. Heterocycl. Chem.* **1966**, *3*, 531–534.
(12) Foy, J. E.; Ganem, B. *Tetrahedron Lett.* **1977**, 775–776.
(13) Piers, E.; Nagakura, I. *Synth. Commun.* **1975**, *5*, 193–199.
(14) Djerassi, C. *Chem. Rev.* **1948**, *43*, 271–317.



tution with NBS, producing a dibromide tentatively identified as **30** (mp 85–90 °C) on the basis of its NMR spectrum. Table I describes a series of halogenations which support our conclusions and, moreover, confirm the hypothesis that relative to NBS, *N*-chlorosuccinimide (NCS) oxidations proceed via an early transition state.[15]

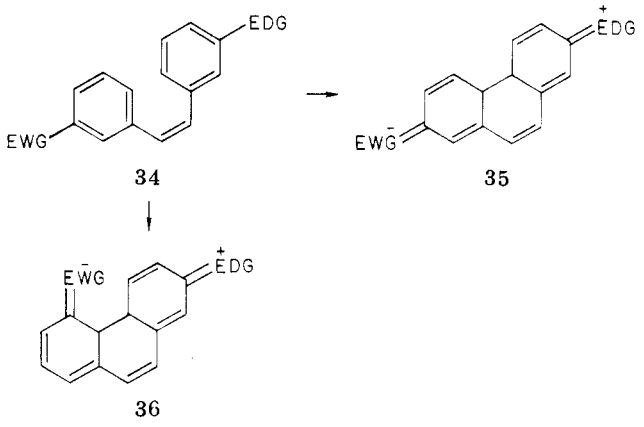
^{13}C NMR proved invaluable in elucidating the structures of the various isomeric benzylic halides. For instance, in the undecoupled spectrum of monobromide **18** the C7 methyl appeared as a simple quartet whereas the "unhindered" C8-methyl signal was split into a quartet of triplets due to coupling with the adjacent ortho hydrogens. After exposure to 1 equiv of NBS, the product **22** showed a triplet in place of a quartet for C7, but retained the quartet of triplets for C8. Tribromide **24** exhibited the expected triplet and triplet-of-triplets pattern for the alkyl substituents.

As we considered an alternative approach to phosphonium salt **8**, the first total synthesis of juncusol was published by Kende and Curran[5a] wherein the photocyclization of cyanostilbene **31** was described. Contrary to an expected



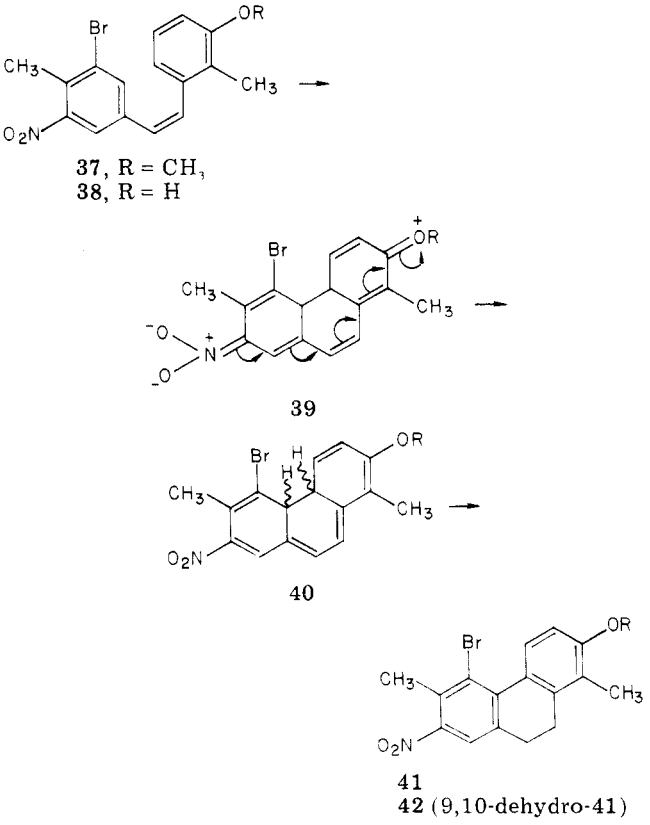
product ratio near unity,[9] a 7:1 mixture of tricyclics **32** (undesired) to **33** (desired) was obtained. This surprising and disappointing result caused us to abandon our route toward the functionally similar stilbene **7** and explore instead a different rationale for the preparation of substituted phenanthrenes.

Nitrostilbene Cyclizations. In principle the formation of a tricyclic phenanthrenoid skeleton ought to be possible in systems like **34** where a "push-pull" mechanism or charge-stabilized Michael-type cyclization would form the central biphenyl linkage. Such a process might be thermal or acid/base catalyzed and could produce regioisomers **35** and **36** depending on the proportion of ortho or para attack by the nucleophilic ring.



cis-Stilbene itself does not undergo thermal closure, for which the activation enthalpy has been calculated to be ca. 38 kcal/mol[16] or some 3 kcal/mol higher than the $\Delta H^{\ddagger}$ for *cis*- → *trans*-stilbene.[17] However we felt that the presence of additional electron-withdrawing groups (EWG) and electron-donating (EDG) groups as in **34** ought to reduce the activation enthalpies both for stilbene isomerization and ring closure so that a rate-determining cyclization might occur at a reasonable temperature. Moreover rough estimates of the π-electron energies of **35** and **36** based on the corresponding phenanthroquinodimethanes suggest that substantial quantities of both ortho and para coupling products should arise.

With this rationale, we envisioned that thermolysis of nitrostilbenes **37** or **38** could give rise to phenanthrene **42** after air oxidation or, in the ideal situation, might afford 9,10-dihydrophenanthrene **41** directly after two 1,3-sigmatropic shifts shown below.

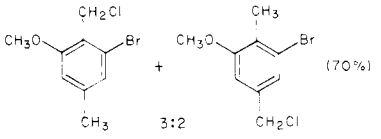
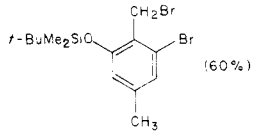
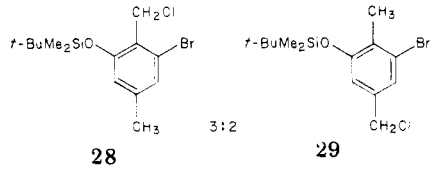
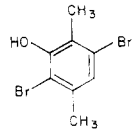


(15) (a) Streitweiser, A., Jr.: Heathcock, C. H. "Introduction to Organic Chemistry"; Macmillan: New York, 1976; pp 82–93, especially p 87. (b) Pryor, W. A. "Introduction to Free Radical Chemistry"; Prentice-Hall: Englewood Cliffs, NJ, 1966; pp 68–69.

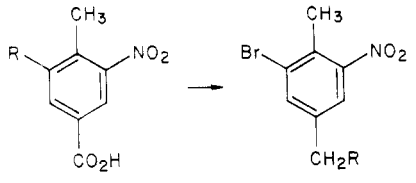
(16) Wilcox, C. F., Jr.; Carpenter, B. K. *J. Am. Chem. Soc.* **1979**, *101*, 3897–3905. We thank Professor Carpenter for performing this calculation.

(17) Willcott, M. R.; Cargill, R. L.; Sears, A. B. *Prog. Phys. Org. Chem.* **1972**, *9*, 25–98.

Table I. Benzylic Halogenations of Ethers of 18

substrate	conditions	products
19	1.0 equiv of NBS, CCl_4, $h\nu$, 0 °C, 3.5 h	22 (82%) + 23 (trace)
	2.0 equiv of NBS, CCl_4, $h\nu$, 0 °C, 3.5 h	24 (80%)
	1.0 equiv of NCS, CCl_4, $h\nu$, reflux, 30 h (70% complete)	 3:2 (70%) 25 26
	1.0 equiv of *t*-BuOCl, CCl_4, $h\nu$, 28 °C, 24 h (25% complete)	25:26 (20%) 11:3
20	1.0 equiv of NBS, CCl_4, $h\nu$, 0 °C, 3 h (65% complete)	 (60%)
	1.0 equiv of NCS, CCl_4, $h\nu$, reflux, 120 h	 3:2 28 29
18	1.0 equiv of NBS, CCl_4, $h\nu$, 0 °C, 3.5 h	 30 (90%)

Scheme III

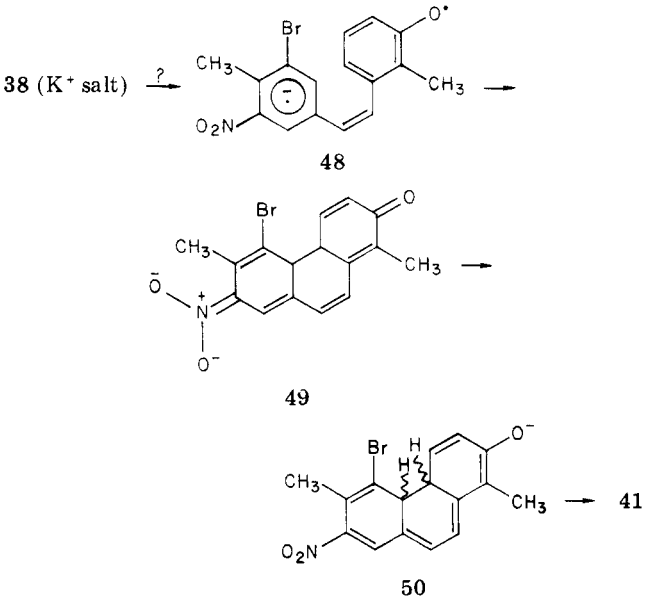


43, R = H
44, R = Br

45, R = OH
46, R = Br
47, R = $PPh_3^+Br^-$

47 + 10 → 37 → 38

Scheme IV



The eventual conversion of **41** or **42** into juncusol would necessitate a well-precedented nitroarene → phenol transformation in addition to the originally planned vinylation. The synthetic sequence which we adopted for nitrostilbenes **37** and **38** is summarized in Scheme III.

Nitrotoluic acid **43** was brominated in 98% yield using dibromoisocyanuric acid in concentrated H_2SO_4, an extremely effective reagent for difficult brominations.[18] Hydroboration of **44** led to alcohol **45** (96%) which could be transformed into its bromide **46** with thionyl bromide. In xylene at reflux **46** reacted with triphenylphosphine to afford phosphonium salt **47** (92% overall yield from **45**). Deprotonation of **47** using *n*-butyllithium in ether and condensation of the resulting phosphorane with aldehyde **10** produced a 1:1 mixture (81%) of *cis*- and *trans*-**37** which was separable by preparative TLC. The isomeric stilbenes were routinely used as a mixture and were demethylated by using trimethylsilyl iodide under carefully controlled conditions.[19]

Methoxystilbene **37** could be heated in boiling xylene for 6 days or in dimethylformamide (DMF) at 115 °C for 4 days without appreciable change. The corresponding phenol (**38**) also failed to cyclize in triethylamine at reflux (72 h). Alkali metal salts of **38** (aqueous KOH–reflux; NaH, DMF, 120 °C) decomposed upon heating, and no characterizable intermediate products were detected.

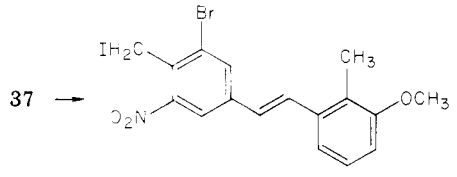
One last attempt to induce thermal cyclization in this series involved irradiation of the potassium salt of **38** in liquid ammonia. It was hoped that an initial photochemical redox reaction might produce anion diradical **48**, reminiscent of the reactive species in $S_{RN}1$ processes proposed by Bunnett[20] (Scheme IV). If para coupling were faster than ejection of bromide,[20] a pair of subsequent

(18) Gottardi, W. *Monatsh. Chem.* **1968**, *98*, 507–512.
(19) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761–3764.
(20) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413–420.

[1,3]-H shifts would afford dihydrophenanthrene **41**.

In the event, photolysis through quartz of the deep purple potassium phenolate with a medium-pressure Hanovia lamp consumed all but 10% of the starting material and produced only an intractable tar. This may have arisen by loss of bromide from **48** and polymerization of the resulting diradical.

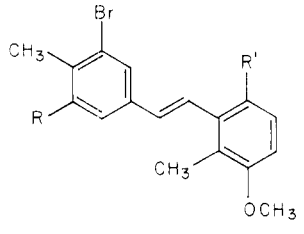
Stilbenes bearing aryl nitro substituents are well-known to resist photocyclization,[4,21] and **37** proved to be no exception to this rule. In benzene containing iodine, the photolysis of **37** furnished biphenyl and a new *trans*-stilbene tentatively identified as **51** on the basis of spectral



51

data and its behavior in solution (rapid evolution of iodine). No phenanthrenes were detected.

With substantial quantities of nitrostilbene **37** and its building blocks **10** and **47** still at hand, two more ideas appeared to be worth exploring and called for experiments with three new stilbenes. First, we decided to vary the nature of the nitrogen substituent at C5 and explore specifically the photolysis of **52**, since urethane function-



52, R = $NHCO_2Et$, R' = H
53, R = NH_2, R' = H
54, R = NO_2, R' = I
55, R = $NHCO_2Et$, R' = I
56, R = NH_2, R' = I

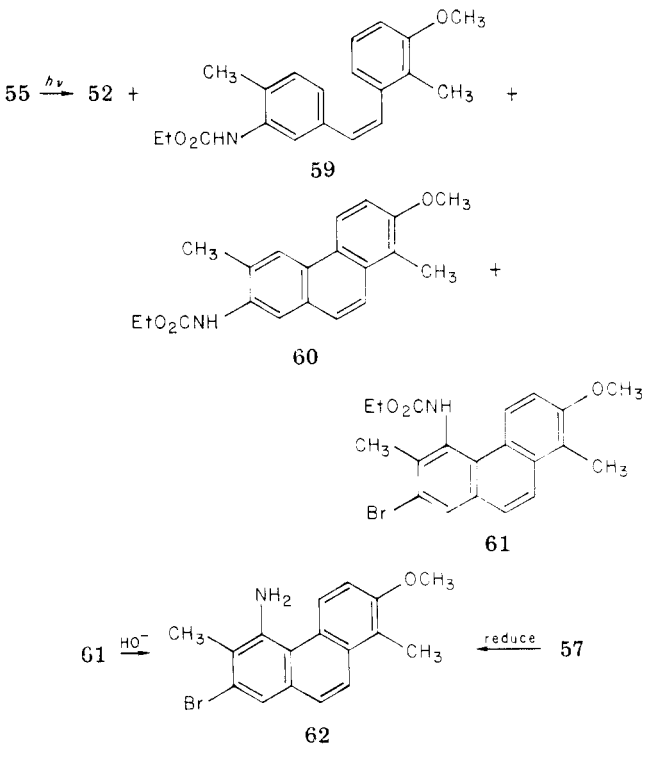
ality is compatible with the stilbene–phenanthrene isomerization.[22] A complementary approach was based on the fact that 2-iodostilbenes cyclize directly upon irradiation to phenanthrenes by loss of HI. This process occurs even in the presence of a nitro group[4] and suggests that photolysis of nitro iodide **54** could furnish **42**. A combination of these two strategies led us also to consider iodourethane **55** as a potential juncusol precursor.

Urethane **52** was prepared by reduction of nitrostilbene **37** with sulfurated sodium borohydride[23] and acylation of the intermediate amine **53** with ethyl chloroformate in 64% overall yield.

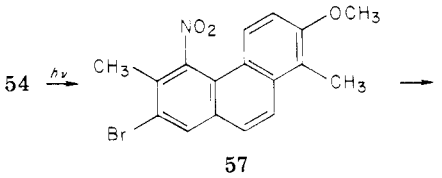
Nitro iodide **54** was synthesized in 76% yield by the Wittig condensation of **47** with 6-iodo-2-methoxy-3-methylbenzaldehyde.[5b] Reduction and carboethoxylation in the same manner as for **37** gave iodourethane **55** in 67% overall yield.

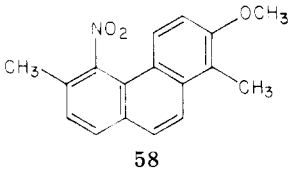
Irradiation of nitroiodostilbene **54** in *t*-BuOH–CH_2Cl_2 (0.002 M) under N_2 formed a single new photoproduct which was isolated in up to 12% yield by preparative TLC.

Scheme V



Its ^1H NMR spectrum indicated that the expected 1,2,5,6,7-substituted phenanthrene had been formed; however, spectral data did not enable a distinction between the 5-bromo-7-nitro and 5-nitro-7-bromo regioisomers. The new phenanthrene was identified as the undesired regioisomer **57** by reduction with *t*-butyllithium in THF at





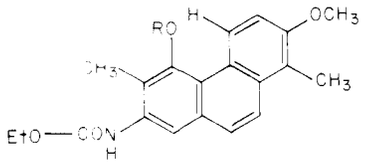
−90 °C. The debrominated product clearly displayed six nonoverlapping doublets in the aromatic region and is compatible only with structure **58**.

We next studied the photolysis of iodourethane **55** (0.002 M in *t*-BuOH–CH_2Cl_2) which led to a much more complicated mixture (see Scheme V). In addition to recovered **55** and its deiodination product (**52**) there were present two new phenanthrenes and yet another stilbene. The stilbene was assigned structure **59** on the basis of its NMR and mass spectra and indicated that a competitive photochemical debromination was occurring. One of the two new phenanthrenes (~8–10%) had also lost bromine, and spectral data suggested structure **60** for it. The remaining phenanthrene, produced in 15% yield, was a pentasubstituted tricyclic containing one bromine. However a doublet at δ 8.95 in the proton NMR spectrum hinted, by analogy with the δ 9.6 doublet observed in **32**,[5b] that the urethane substituent was located at C5 as shown in **61**, the undesired regioisomer. Additional support for this last, crucial assignment came from a correlation with the phenanthrene **57** from iodonitrostilbene photolysis. Re-

(21) Mallory, F. B.; Wood, C. S. *J. Am. Chem. Soc.* **1964**, *86*, 3094–3102.
(22) (a) Cava, M. P.; Mitchell, M. J.; Havlicek, S. C.; Lindert, A.; Spangler, A. *J. Org. Chem.* **1970**, *35*, 175–179. (b) Cava, M. P.; Havlicek, S. C. *Tetrahedron Lett.* **1967**, 2625–2627.
(23) Lalancette, J. M.; Brindle, J. R. *Can. J. Chem.* **1971**, *49*, 2990–2995.

duction of **57** using sulfurated $NaBH_4$ produced an amine which was identical with **62**, the hydrolysis product of **61** (NaOH, ethanol).

Turning to urethane **52**, irradiation in benzene containing iodine gave a mixture of starting material, **60**, and **61** which was similar to that obtained from **55**. However in *tert*-butyl alcohol, photolysis led to the formation of two new products which resulted from debromination and solvent capture. In addition to **61** (23%), *tert*-butoxy- and hydroxy-substituted phenanthrenes **63** (6%) and **64** (14%)



63, R = *t*-Bu
64, R = H

were isolated by preparative TLC. Both of these structures showed downfield doublets at δ 9.49 and 9.57, respectively, for the C4 hydrogen.

Experimental Section

Apparatus. The ^1H NMR spectra of deuteriochloroform solutions were recorded on Varian Model A60-A or EM-390 spectrometers; chemical shifts are expressed in parts per million downfield (δ) from internal tetramethylsilane. Infrared spectra were recorded on Perkin-Elmer Model 137 or 337 spectrometers and were calibrated by the 6.24-μm line of polystyrene. Mass spectral data were obtained on either an Associated Electrical Industries Model MS-902 spectrometer or a Finnigan Model 3300 gas chromatograph–mass spectrometer equipped with Systems Industries Datasystem 150. Preparative layer chromatography was performed on 20 × 20 cm glass plates coated with either a 1.0 or 2.0 mm thick layer of silica gel (Analtech) containing 1% zinc sulfide fluorescent indicator, with visualization by ultraviolet light.

Reagents. All solvents and reagents not listed below were ACS reagent grade and were not purified unless specifically indicated. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride under nitrogen immediately before use. Dimethylformamide (DMF) was distilled from barium oxide under nitrogen and stored over 4-Å molecular sieves. Dichloromethane was dried over activated 4-Å molecular sieves. Benzene was washed sequentially with concentrated sulfuric acid, 10% potassium hydroxide, and brine, dried over magnesium sulfate, and distilled from calcium hydride under nitrogen. *tert*-Butyl alcohol was distilled from calcium hydride. Triethylamine was dried over potassium hydroxide. Butyllithium was titrated according to the method of Watson and Eastham[24] before use. All organic extracts were dried over anhydrous magnesium sulfate.

2-(3′-Methoxy-*o*-tolyl)-4,4-dimethyl-2-oxazoline (12). A solution of methylmagnesium bromide (156 mmol, 8 equiv) in ether (60 mL) was added to a solution of 2-(2,3-dimethoxyphenyl)-4,4-dimethyl-2-oxazoline (5.00 g, 19.5 mmol) in THF (100 mL) with stirring at room temperature. The ether was distilled from the reaction mixture at aspirator vacuum and 60 mL collected in a calibrated cold trap. The solution was then stirred at room temperature for 7 days and quenched by the slow addition of 5% aqueous HCl with ice cooling. The bulk of THF was removed under vacuum and the residual acidic aqueous solution washed once with ether and then made basic by cautious addition of solid $NaHCO_3$. The aqueous layer was extracted three times with ether and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to yield a slightly pink liquid. Kugelrohr distillation (0.2 torr, 90–100 °C) gave 4.607 g (99%) of **12**: IR λ_{max} (film) 3.40, 6.10, 6.30 μm; NMR δ 6.65–7.4 (m, 3 H), 3.95 (s, 2 H), 3.7 (s, 3 H), 2.45 (s, 3 H), 1.3 (s, 6 H).

2-(3′-Methoxy-*o*-tolyl)-4,4-dimethyl-*N*-methyl-2-oxazolinium Iodide (13). Iodomethane (0.47 mL, 7.5 mmol, 1.55 equiv) was added to a solution of **12** (1.059 g, 4.83 mmol) in nitromethane (2.0 mL) in a flask equipped with an efficient condenser. The solution was warmed in a 70 °C oil bath for 22 h and then cooled to room temperature. Ether (2.0 mL) was added and the solution left standing in the freezer (–20 °C) overnight. The crystals which separated were collected by vacuum filtration and dried to yield 1.702 g (98%) of **13**: mp 155–155.5 °C; NMR δ 7.70 (dd, 1 H, J = 2 and 8 Hz), 7.45 (t, 1 H, J = 8 Hz), 7.20 (dd, 1 H, J = 2 and 8 Hz), 5.25 (s, 3 H), 3.90 (s, 2 H), 3.40 (s, 3 H), 2.25 (s, 3 H), 1.90 (s, 6 H).

3-Methoxy-2-methylbenzaldehyde (10). Sodium borohydride (0.045 g, 1.19 mmol, 1.2 equiv) was added portionwise over 30 min to a stirred slurry of **13** (0.360 g, 0.995 mmol) in absolute ethanol (4.0 mL) under nitrogen. Cooling was provided by a room temperature water bath. After the addition was complete, the resulting clear solution was stirred for 2 h, 2 N HCl (10 mL) was added, and stirring was continued overnight. The solution was partitioned between ether (50 mL) and water (50 mL) and the aqueous layer was extracted twice more with ether (20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and vacuum-dried for a short period to give 0.142 g (95%) of **10** as a pale yellow oil: NMR δ 10.30 (s, 1 H), 7.20 (m, 3 H), 3.80 (s, 3 H), 2.50 (s, 3 H); IR λ_{max} (film) 5.90, 7.95, 6.80, 8.10 μm.

2,5-Dimethyl-1,3-cyclohexanedione (15). Iodomethane (11.2 mL, 0.18 mol, 1.5 equiv) was added to a solution of 5-methyl-1,3-cyclohexanedione (15.0 g, 0.119 mol) in 4 N aqueous sodium hydroxide (30 mL, 1.0 equiv of NaOH). The solution was boiled for 12 h and cooled first to room temperature and then with an ice bath for 2 h. The crystals which formed were collected by vacuum filtration and dried to yield 8.06 g (48%) of **15**: mp 170–172 °C; NMR (Me_2SO-d_6) δ 2.15 (br m, 5 H), 1.55 (s, 3 H), 1.0 (br m, 3 H); IR λ_{max} (Nujol) 6.35 μm.

3-Bromo-2,5-dimethyl-2-cyclohexen-1-one (16). Triethylamine (12.0 mL, 86 mmol, 1.2 equiv) was added to a mechanically stirred slurry of triphenylphosphine dibromide (36.2 g, 86 mmol, 1.2 equiv) in benzene (300 mL) at room temperature. Dione **15** (10.0 g, 71.3 mmol) was immediately added and the reaction mixture was stirred for 47 h, at which point TLC analysis showed no **15** remaining. The slurry was filtered to remove triethylamine hydrobromide and rinsed well with fresh benzene. The filtrate was concentrated at aspirator vacuum with minimal heating and chromatographed (150 g of SiO_2, benzene) to furnish 4.06 g (97%) of pure **16**: NMR δ 2.6–2.95 (m, 2 H), 2.15–2.5 (m, 3 H), 1.95 (m, 3 H), 1.0–1.5 (m, 3 H); IR λ_{max} (film) 5.95, 6.15, 7.75 μm.

3-Bromo-2,5-dimethylphenol (18). Bromine (1.86 mmol, 1.05 equiv) in $CHCl_3$ (2.5 mL) was added over 15 min with stirring to a $CHCl_3$ solution of **16** (0.359 g, 1.77 mmol) in $CHCl_3$ (3 mL). After an additional 15 min, *p*-toluenesulfonic acid (0.050 g) was added and stirring continued for 72 h. More $CHCl_3$ (15 mL) was added and the solution washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to an oil. Column chromatography (SiO_2, CH_2Cl_2) gave 0.257 g (72%) of pure **18**: mp 85–88 °C; NMR δ 6.95, 6.45 (two d, 2 H, J = 1.5 Hz), 2.25, 2.20 (two s, 6 H); ^{13}C NMR δ 15.02 (q, J = 128 Hz), 20.50 (q of t, J = 127, 4.8 Hz); IR λ_{max} (KBr) 3.05 μm.

3-Bromo-2,5-dimethylanisole (19). A solution of **18** (2.204 g, 11.0 mmol), K_2CO_3 (9.12 g, 66.0 mmol, 6 equiv), and CH_3I (5.0 mL, 81.0 mmol, 7.4 equiv) in methanol (25 mL) was heated at reflux for 3 days. Excess CH_3I and solvent were removed under reduced pressure and the residue was partitioned between $CHCl_3$ and water. The aqueous layer was acidified to pH 3 by addition of 5% aqueous HCl and was extracted with three portions of $CHCl_3$. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Kugelrohr distillation (0.1 torr, 50–60 °C) gave 2.12 g (93%) of **19**: NMR δ 6.90, 6.50 (two d, 2 H, J = 1.5 Hz), 3.70 (s, 3 H), 2.25 (s, 6 H); ^{13}C NMR δ 15.11 (q, J = 129 Hz), 20.83 (q of t, J = 132, 4.5 Hz); IR λ_{max} (film) 6.25, 6.40 μm. Anal. ($C_9H_{11}BrO$).

3-Bromo-2,5-dimethylphenyl *tert*-Butyldimethylsilyl Ether (20). A solution of **18** (0.140 g, 0.698 mmol), imidazole (0.119 mg, 1.75 mmol, 2.5 equiv), and *tert*-butyldimethylchlorosilane (0.126 g, 0.836 mmol, 1.2 equiv) in dimethylformamide (2.0 mL) was stirred at room temperature for 24 h. The solution was diluted with 7 mL of water and extracted with three 30-mL portions of ether. The combined ether layers were washed with

(24) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–168.

water (3 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to give 0.218 g (99%) of **20** as a clear liquid; NMR δ 6.90, 6.50 (two d, 2 H, J = 1.5 Hz), 2.25 (s, 3 H), 2.20 (s, 3 H), 1.0 (s, 9 H), 0.2 (s, 6 H).

3-Bromo-2-bromomethyl-5-methylanisole (22). *N*-Bromosuccinimide (0.108 g, 0.60 mmol) and **19** (0.130 g, 0.61 mmol) were combined in CCl_4 (6 mL) and thoroughly purged with N_2 by repeated evacuation. The mixture was irradiated at 0 °C with a sunlamp for 3.5 h and then filtered to remove succinimide. The filtrate was washed with water, dried ($MgSO_4$), and concentrated under vacuum to a constant weight of 0.146 g (82%) that consisted of nearly pure **22**: NMR δ 6.95, 6.60 (two d, 2 H, J = 1 Hz), 4.70 (s, 2 H), 3.85 (s, 3 H), 2.30 (s, 3 H); ^{13}C NMR δ 21.27 (q of t, J = 132, 4.5 Hz), 28.45 (t, J = 156 Hz). Anal. ($C_9H_{10}Br_2O$).

3-Bromo-2,5-bis(bromomethyl)anisole (24). *N*-Bromosuccinimide (0.323 g, 1.82 mmol) and **19** (0.195 g, 0.91 mmol) were mixed in CCl_4 (9 mL) and thoroughly purged with N_2 by repeated evacuation. The mixture was irradiated at 0 °C with a sunlamp for 3.5 h and then filtered to remove succinimide. The filtrate was washed with water, dried ($MgSO_4$), and concentrated under vacuum to a constant weight (0.349 g). The crude product containing some succinimide and ca. 20% of **19** was crystallized from hexane–CH_2Cl_2 to afford 0.176 g (52%) of pure **24**: mp 122–126 °C; NMR δ 7.25, 6.85 (two d, 2 H, J = 1.5 Hz), 4.70 (s, 2 H), 4.40 (s, 2 H), 3.90 (s, 3 H); ^{13}C NMR δ 27.54 (t, J = 156 Hz), 31.78 (t of t, J = 154, 5.4 Hz). Anal. ($C_9H_9Br_3O$).

NCS Chlorination of 19: Preparation of 3-Bromo-2-(chloromethyl)-5-methylanisole (25) and 3-Bromo-5-(chloromethyl)-2-methylanisole (26). Following the same procedure used to make **22** and **24**, we photolyzed a solution of **19** (0.156 g, 0.73 mmol) in CCl_4 (8 mL) in the presence of NCS (0.097 g, 0.73 mmol) at reflux for 30 h. Workup afforded an oil containing starting material (60%) and a 3:2 mixture of **25**:**26**.

25: NMR δ 7.05, 6.70 (two d, 2 H, J = 1.5 Hz), 4.75 (s, 2 H), 3.75 (s, 3 H), 2.30 (s, 3 H).

26: NMR δ 7.05, 6.72 (two d, 2 H, J = 1.5 Hz), 4.60 (s, 2 H), 3.70 (s, 3 H), 2.35 (s, 3 H).

5-Bromo-4-methyl-3-nitrobenzoic Acid (44). A solution of dibromoisocyanuric acid[18] (8.606 g, 0.03 mol) in concentrated sulfuric acid (160 mL) was added over 30 min to a stirred solution of nitrotoluic acid **43** (10.87 g, 0.06 mol) in concentrated sulfuric acid (60 mL). After stirring 3.5 h at room temperature the solution was poured over 350 g of crushed ice. The precipitate was removed by suction filtration and resuspended in 500 mL of freshly prepared saturated $NaHCO_3$ solution. The undissolved solid (cyanuric acid) was filtered away, rinsed with a small portion of aqueous $NaHCO_3$, and discarded. The filtrate was extracted with eight 100-mL portions of ether and made strongly acidic by cautious addition of 35% sulfuric acid (ice cooling). The resulting precipitate was extracted into four 100-mL portions of ether which were then combined, washed with brine, dried ($MgSO_4$), and concentrated to yield 15.26 g (98%) of 5-bromo-4-methyl-3-nitrobenzoic acid **44**: mp 184.5–185.5 °C; NMR δ 8.2 (s, 2 H), 2.55 (s, 3 H); IR λ_{max} (Nujol mull) 3.30, 5.80 μm; mass spectrum, m/e 259, 261 (M^+), 242 (base).

3-Bromo-5-(hydroxymethyl)-2-methylnitrobenzene (45). Diborane (16.8 mmol, 1 M in THF, Aldrich) was added to a solution of **44** (4.161 g, 16.0 mmol) in THF (24 mL) and stirred at room temperature for 24 h. The solution was then poured into saturated aqueous $NaHCO_3$ and extracted with three portions of ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to yield 3.765 g (96%) of **45**: mp 62.5–63.5 °C; NMR (acetone-d_6) δ 7.85 (s, 1 H), 7.75 (s, 1 H), 4.70 (s, 2 H), 2.45 (s, 3 H); IR λ_{max} (Nujol) 3.0 μm. Anal. ($C_8H_8BrNO_3$).

3-Bromo-5-(bromomethyl)-2-methylnitrobenzene (46) and Triphenyl(3-bromo-4-methyl-5-nitrobenzyl)phosphonium Bromide (47). Thionyl bromide (1.5 mL, 19.3 mmol, 4.7 equiv) was added to a solution of **45** (1.00 g, 4.06 mmol) in benzene (8 mL) and stirred for 24 h at room temperature. Evaporation of the solvent and excess thionyl bromide gave 1.269 g of **46** as an orange solid, mp 71–78 °C. This crude dibromide was dissolved in xylenes (13.5 mL) with triphenylphosphine (1.40 g, 5.34 mmol, 1.3 equiv) and the solution was boiled for 15 h. The phosphonium salt which precipitated was collected by suction filtration, rinsed with fresh xylenes, and dried in a vacuum oven (0.02 torr, 60 °C). Crystallization from CH_2Cl_2–THF gave 2.127 g (92%) of **47**: mp >280 °C; NMR δ 7.40–8.10 (br m, 17 H), 6.00 (d, 2 H, J = 15 Hz), 2.35 (d, 3 H, J = 2 Hz).

3-Bromo-3′-methoxy-2′,4-dimethyl-5-nitrostilbenes (*cis*- and *trans*-37). *n*-Butyllithium in hexane (2.4 M, 1.0 mmol) was added to a −10 °C suspension of finely powdered **47** (0.571 g, 1.0 mmol) in anhydrous ether (10 mL). After 1 h at −10 °C the solid had completely dissolved, giving a deep orange solution to which was then added aldehyde **10** (0.142 g, 1.0 mmol) in ether (1 mL). After being warmed to room temperature and stirred for 21 h, the reaction mixture was acidified with 5% aqueous HCl and extracted three times with ether. The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The solid residue was purified by preparative TLC using multiple developments (three elutions with 2:1 hexane–CH_2Cl_2) to separate the cis and trans isomers of **37**. Band 1, having R_f 0.52 (3:1 hexane–CH_2Cl_2), was eluted to furnish 0.150 g of *cis*-**37**; NMR δ 6.90, 6.45 (AB q, J = 8 Hz), 3.80 (s, 3 H), 2.45 (s, 3 H), 2.10 (s, 3 H). Band 2, having R_f 0.42 (3:1 hexane–CH_2Cl_2), was eluted to furnish 0.144 g of *trans*-**37**: mp 140–145 °C; NMR δ 7.45, 6.86 (AB q, J = 13 Hz), 3.85 (s, 3 H), 2.55 (s, 3 H), 2.30 (s, 3 H). Anal. ($C_{17}H_{16}BrNO_3$).

3-Bromo-3′-hydroxy-2′,4-dimethyl-5-nitrostilbene (*cis*- and *trans*-38). According to the general procedure of Jung and Lyster,[19] a solution of **37** (0.050 g, 0.14 mmol) in $CDCl_3$ (ca. 0.4 mL) was placed in a 5-mm NMR tube under nitrogen while trimethylsilyl iodide (distilled from copper powder onto copper powder under nitrogen; 0.1 mL, 0.7 mmol) was added to give a deep red solution. The tube was then capped, sealed with Teflon tape, and heated in a 50 °C oil bath for 28.5 h, at which time ^1H NMR analysis indicated the absence of the $-OCH_3$ absorbance at 3.85 ppm. The mixture was poured into 2 mL of methanol and concentrated by rotary evaporation. The residue was partitioned between ether and $NaHSO_3$ solution, and the organic layer was washed sequentially with $NaHCO_3$ solution and brine, dried, and concentrated to give **38** as a yellow semisolid (0.053 g, 100%): NMR (acetone-d_6) δ 7.93, 7.53 (two d, total 1 H, J = 2 Hz), 7.85, 7.42 (two d, total 1 H, J = 2 Hz), 7.20–6.60 (m, 5 H), 2.52, 2.45 (two s, total 3 H), 2.33, 2.15 (two s, total 3 H).

Failure to exclude moisture rigorously by flushing with N_2 or use of undistilled trimethylsilyl iodide resulted in the formation of various undesired products.

Photolysis of 37: Preparation of *trans*-3-Bromo-4-iodomethyl-3′-methoxy-2′-methyl-5-nitrostilbene (51). A solution of **37** (0.211 g, 0.58 mmol) and iodine (0.140 g, 0.55 mmol) in benzene (300 mL) was placed in a 350-mL immersion well equipped with a N_2 inlet, a gas bubbler outlet, and a 450-W Hanovia lamp contained in a water-cooled quartz housing and degassed for 15 min. The solution was irradiated for a total of 25 h. Analytical TLC (2:1 hexane–CH_2Cl_2) showed the presence of starting material (R_f 0.52) and new material (R_f 0.85 and 0.42) after 7 and 18 h. The resulting dark brown solution was washed four times with $NaHSO_3$ solution and concentrated, and the residue was partitioned between ether and brine. The organic layer was dried and concentrated to leave a dark brown powder (0.245 g). Preparative layer chromatography (three elutions with 2:1 hexane–CH_2Cl_2) gave three fractions, the first of which (0.010 g) contained a solid which was identified by comparison with an authentic sample as biphenyl. Band 2 (0.041 g) contained starting material by analytical TLC. Band 3 (0.056 g) contained a substance which evolved a red color on standing in solution over silica gel and streaked on analytical TLC. The compound was tentatively identified as **51**: NMR δ 8.30 (br s), 7.90 (d, 1 H, J = 2 Hz), 7.81 (d, 1 H, J = 2 Hz), 7.58 (d, 1 H, J = 17 Hz), 7.17 (m, 1 H), 6.85 (m, 2 H), 6.84 (s, 1 H, J = 17 Hz), 5.43 (s, 1 H), 3.83 (s, 3 H), 2.30 (s, 3 H). The material decomposed to a viscous brown oil on standing.

Reduction of Nitrostilbene 37: Preparation of 5-Amino-3-bromo-3′-methoxy-2′,4-dimethylstilbene (*cis*- and *trans*-53). Sulfurated sodium borohydride was prepared according to the procedure of Lalancette and Brindle[23] by the additon of THF (17 mL) to a stirred mixture of sulfur (0.097 g, 3.0 mmol) and $NaBH_4$ (0.038 g, 1.0 mmol) under N_2. The bright yellow solution was stirred for 15 min at 25 °C, at which time stilbene **37** (0.181 g, 0.5 mmol) in THF (5 mL) was added dropwise. The mixture was heated at reflux and turned brown after 24 h, whereupon it was

concentrated in vacuo. The residue was stirred with 10% aqueous HCl (40 mL) for 1 h and filtered. The collected solid was dissolved in 5% NaOH solution and extracted three times with CH_2Cl_2 to afford, after concentration, a semisolid (0.160 g) which could be purified by preparative TLC (three elutions with 7:3 pentane–ether). The less polar cis isomer of **53** was eluted first (0.104 g): NMR δ 6.32–7.17 (m, 7 H), 3.80 (s, 3 H), 3.40 (br s, 2 H), 2.12 (s, 6 H); IR λ_{max} ($CHCl_3$) 2.80, 2.90 μm. A band at lower R_f contained the trans isomer (0.024 g): NMR δ 7.29, 6.14 (AB q, 2 H, J = 17 Hz), 6.77, 7.20 (two m, 5 H), 3.80 (s, 3 H), 3.40–3.80 (br s, 2 H), 2.24, 2.27 (two s, 6 H); mass spectrum (EI), m/e 331, 333 (M^+, 100%), 252, 237. The overall yield of **53** was 77%.

Acylation of 53: Preparation of *cis*- and *trans*-3-Bromo-5-[(ethoxycarbonyl)amino]-3′-methoxy-2′,4-dimethylstilbene (52). A mixture of *cis*- and *trans*-**53** (0.120 g, 0.36 mmol), ethyl chloroformate (0.1 mL, 1.0 mmol), and anhydrous K_2CO_3 (0.138 g, 1.0 mmol) in $CHCl_3$ (10 mL) was heated at reflux for 9 h under N_2. After the suspension was partitioned between 10% HCl and CH_2Cl_2, the organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated to afford **52** as a pale brown solid (0.120 g, 83%): NMR δ (acetone-d_6) 7.65 (m, 1 H), 6.50–6.35 (m, 7 H), 4.10 (q, 2 H, J = 7 Hz), 3.80 (s, 3 H), 2.27 (s, 3 H), 2.10 (s, 3 H), 1.20 (t, 3 H, J = 7 Hz); IR λ_{max} (CH_2Cl_2) 2.90, 5.75 μm.

3-Bromo-6′-iodo-3′-methoxy-2′,4-dimethyl-5-nitrostilbene (*cis*- and *trans*-54). Lithium diisopropylamide was prepared by the addition of *n*-butyllithium (2.61 M in hexane, 0.7 mL, 1.8 mmol) to a solution of diisopropylamine (0.5 mL, 3.5 mmol) in THF (10 mL) at 0 °C under N_2. After stirring for 15 min, the solution was transferred dropwise by cannula to a flask containing a stirred suspension of **47** (0.830 g, 1.45 mmol) in THF (20 mL) at −15 °C under N_2. The resulting deep reddish brown suspension was stirred at −15 °C for 45 min and then 6-iodo-3-methoxy-2-methylbenzaldehyde[5b] (0.372 g, 1.35 mmol) in THF (3 mL) was added over 1 min. The reaction mixture was stirred for 48 h at 25 °C and then partitioned between 5% HCl and ether. The aqueous layer was extracted twice with ether and the combined organic layers were washed with 10% HCl and brine, dried ($MgSO_4$), filtered, and concentrated to give a brown semisolid (1.30 g). Column chromatography (silica gel 60, 70–230 mesh, 10–25% CH_2Cl_2–hexane) gave **54** as a pale yellow powder (0.500 g, 76%): NMR δ 6.44–8.0 (complex m, 6 H), 3.79, 3.81 (two s, total 3 H), 2.46, 2.55 (two s, total 3 H), 2.03, 2.27 (two s, total 3 H). A pure sample of the trans isomer was obtained by preparative TLC; NMR δ (C_6D_6) 7.91, 7.83 (AB q, 2 H, J = 2 Hz), 7.67, 6.52 (AB q, 2 H, J = 9 Hz), 7.08, 6.43 (AB q, 2 H, J = 17 Hz), 3.83 (s, 3 H), 2.58 (s, 3 H), 2.26 (s, 3 H). Anal. ($C_{17}H_{15}BrINO_3$).

5-Amino-3-bromo-6′-iodo-3′-methoxy-2′,4-dimethylstilbene (*cis*- and *trans*-56). A solution of iodonitrostilbenes **54** (0.159 g, 0.33 mmol) in THF (3 mL) was added over 1 min to a solution of sulfurated sodium borohydride, prepared as described above from sulfur (0.072 g, 2.25 mmol) and $NaBH_4$ (0.029 g, 0.75 mmol) in THF (15 mL), and the mixture was heated at reflux for 24 h under N_2. The reaction mixture was worked up as described previously to give 0.186 g of crude **56**, R_f 0.4 (1:4 ether–hexane). Pure **56** was isolated as a mixture of cis and trans isomers (0.104 g, 69%) by preparative TLC (two elutions, 3:7 ether–pentane): NMR δ 7.72 (d, 1 H, J = 9 Hz), 6.20–7.15 (m, 5 H), 3.80 (s, 3 H), 3.40–3.85 (br s, 2 H), 2.02, 2.16, 2.27 (three s, total 6 H); IR λ_{max} ($CHCl_3$) 2.80, 2.90 μm; mass spectrum (CI), m/e 458 (M + 1), 459 (base).

3-Bromo-5-[(ethoxycarbonyl)amino]-6′-iodo-3′-methoxy-2′,4-dimethylstilbene (*cis*- and *trans*-55). A mixture of iodoaminostilbenes **56** (0.164 g, 0.36 mmol), ethyl chloroformate (0.1 mL, 1.0 mmol), anhydrous K_2CO_3 (0.138 g, 1.0 mmol), and $CHCl_3$ (10 mL) was heated at reflux for 8.5 h under N_2. The suspension was partitioned between dichloromethane and 10% HCl, and the organic layer was washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), filtered, and concentrated to afford **55** as an off-white powder (0.185 g, 97%): NMR δ 6.30–7.90 (m, 6 H), 4.20 (q, 2 H, J = 7 Hz), 3.77, 3.79 (two s, total 3 H), 2.02, 2.23, 2.26, 2.34 (four s, total 6 H), 1.28 (t, 3 H, J = 7 Hz); IR λ_{max} (CH_2Cl_2) 2.85, 5.75 μm. Anal. ($C_{20}H_{21}BrINO_3$).

Photolysis of 54. A solution of **54** (0.090 g, 0.18 mmol) in *t*-BuOH (80 mL) and CH_2Cl_2 (5 mL) was placed in a 250-mL flask equipped with a water-cooled condenser and deaerated with N_2 for 15 min. A 450-W Hanovia lamp, contained in a water-cooled quartz housing, was positioned ca. 4-in. away from the flask and the contents was irradiated with stirring under nitrogen for 16 h. The resulting dark red mixture was concentrated in vacuo and the residue partitioned between ether and $NaHSO_3$ solution. The organic layer was washed with $NaHCO_3$ solution and brine, dried, and concentrated to leave a dark red semisolid. Preparative TLC (4–6 elutions with 2:1 pentane–CH_2Cl_2) gave photoproduct **57** as a bright yellow solid (0.008 g, 12%) along with recovered **54** (0.031 g, 35%). Phenanthrene **57** was less polar and could be purified by chromatography: NMR δ 8.16 (s, 1 H), 8.12, 8.05, 7.58, 7.25 (four d, 4 H, J = 9 Hz), 3.95 (s, 3 H), 2.57 (s, 3 H), 2.53 (s, 3 H); mass spectrum (EI), m/e 359, 361 (M^+, base), 331, 329, 318, 316.

Debromination of 57. To a solution of phenanthrene **57** (0.015 g, 0.04 mmol) in THF (8 mL) at −90 °C under N_2 was added *t*-BuLi (1.14 M in hexane, 0.1 mL, 0.11 mmol) to give a brown solution. The reaction mixture was held at −90 °C for 3 h and then acidified with CH_3OH (0.25 mL). The yellow solution was poured into brine and extracted three times with ether. The combined organic layers were dried ($MgSO_4$) and concentrated to a bright yellow solid (0.017 g). Preparative TLC (four elutions with 2:1 pentane–CH_2Cl_2) gave recovered **57** (15 mg) and debrominated phenanthrene **58** (3 mg): NMR δ 8.11, 7.21 (AB q, 2 H, J = 9.5 Hz), 7.95, 7.65 (AB q, 2 H, J = 10 Hz), 7.82, 7.38 (AB q, 2 H, J = 8.5 Hz), 3.93 (s, 3 H), 2.57 (s, 3 H), 2.48 (s, 3 H); mass spectrum (EI), m/e 281 (M^+), 266, 264, 252, 251, 189 (base).

Reduction of the Nitro Group in 57: Preparation of 62. Sulfurated $NaBH_4$ was prepared from sodium borohydride (0.008 g, 0.2 mmol) and sulfur (0.020 g, 0.6 mmol) in THF (6 mL) at 25 °C under N_2. Phenanthrene **57** (0.015 g, 0.05 mmol) in THF (2 mL) was then added and the mixture was heated at reflux for 23 h under N_2. The milky white solution was concentrated in vacuo and the residue partitioned between ether and 10% HCl. The organic layer was washed with $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated to a brown semisolid (0.042 g). Preparative TLC (three elutions with 1:1 CH_2Cl_2–pentane) gave 5-aminophenanthrene **62** (0.005 g), identical with the sample described below from **61**.

Photolysis of 55: Preparation of Stilbenes 52 and 59 and Phenanthrenes 60 and 61. A solution of iodourethane **55** (0.086 g, 0.16 mmol) and triethylamine (0.2 mL) in *tert*-butyl alcohol (80 mL) and CH_2Cl_2 (10 mL) in a 250-mL flask equipped with a N_2 inlet and water-cooled condenser was deaerated for 15 min and then irradiated for 8 h with a 450-W Hanovia lamp housed in a water-cooled quartz container located ca. 4 in. from the flask. The yellow solution was concentrated by rotary evaporation and the residue was partitioned between CH_2Cl_2 and $NaHSO_3$ solution. The organic layer was washed with $NaHCO_3$ and brine and dried. The aqueous layer was back-extracted with ether and the organic layer was washed with brine and dried. The combined organic layers were concentrated to leave a yellow solid (0.095 g). Preparative TLC (two elutions with CH_2Cl_2) gave three fractions. Band 1 (in order of elution; 0.024 g) contained *cis*- and *trans*-iodourethanes **55** and urethane **52** by comparison with authentic samples, as well as some phenanthrene product (singlets at 2.49 and 2.56 ppm; vide infra).

Band 2 (0.011 g, white solid, pure by analytical TLC) contained one or more stilbenes including urethane **52** and a new phenanthrene, tentatively identified as **60** by spectral analysis. Integration of the respective ArCH_3 peaks indicated a 2:1 ratio of **60**:**52**. **60**: NMR δ 8.50 (br s), 8.35 (br m), 7.81 (d, 1 H, J = 9 Hz), 7.65 (d, 1 H, J = 9 Hz), 7.20 (m), 6.55 (m), 4.24 (q, 2 H, J = 7 Hz), 3.93 (s, 3 H), 2.47, 2.53 (two s, 6 H), 1.25 (t, 3 H, J = 7 Hz); mass spectrum (EI), m/e 323 (M^+, base).

Band 3 (0.010 g, white solid, pure by analytical TLC, R_f 0.43 in CH_2Cl_2) contained another new phenanthrene identified as **61**: NMR δ 8.95, 7.21 (AB q, 2 H, J = 10 Hz), 8.02 (s, 1 H), 7.85, 7.51 (AB q, 2 H, J = 9 Hz), 6.47 (br s, 1 H), 4.00–4.50 (m, 2 H), 3.95 (s, 3 H), 2.56 (s, 6 H), 1.35 (m, 3 H); IR λ_{max} (CH_2Cl_2) 2.85, 5.80, 6.05 μm; mass spectrum (EI), m/e 401, 403 (M^+, base), 355, 357, 328, 330.

Hydrolysis of Phenanthrene 61: Preparation of 62. A mixture of **61** (0.017 g, 0.04 mmol), 5% aqueous NaOH (3 mL), ethanol (10 mL), and THF (1 mL) was boiled for 22 h and concentrated in vacuo. The residue was partitioned between ether and water and the aqueous layer reextracted with ether. The

combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford **62** (0.015 g) as a pale brown solid: R_f 0.39 in 1:1 hexane–CH_2Cl_2; NMR δ 8.95, 7.42 (AB q, 2 H, J = 9 Hz), 7.79, 7.19 (AB q, 2 H, J = 10 Hz), 7.51 (s, 1 H), 4.45 (br s, 2 H), 3.93 (s, 3 H), 2.55 (s, 3 H), 2.50 (s, 3 H); IR λ_{max} ($CHCl_3$) 2.92, 2.95 μm; mass spectrum (EI), m/e 329, 331 (M^+, base), 314, 316, 286, 288.

Photolysis of 52 in *tert*-Butyl Alcohol: Preparation of Phenanthrenes 63 and 64. A solution of **52** (0.229 g, 0.57 mmol) and iodine (ca. 0.010 g) in *tert*-butyl alcohol (120 mL) and CH_2Cl_2 (5 mL) was prepared in a 250-mL flask equipped with a stir bar, water-cooled condenser, and calcium sulfate drying tube. It was irradiated for 23.5 h with a 450-W Hanovia lamp contained in a water-cooled quartz housing located ca. 4 in. from the flask. The resulting dark red solution was concentrated in vacuo and the residue partitioned between ether and $NaHSO_3$ solution. The aqueous layer was reextracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried, filtered, and concentrated. Preparative TLC (two elutions with CH_2Cl_2) gave three fractions.

Band 1 (0.040 g) contained a TLC-inseparable mixture of starting material **52** and a new phenanthrene **64** (14% yield): NMR δ 9.57, 7.08 (AB q, 2 H, J = 10 Hz), 8.08 (s, 1 H), 7.81, 7.10 (AB q, 2 H, J = 9 Hz), 6.60 (br s, 1 H), 6.40–6.80 (m), 4.25 (q, 2 H, J = 7 Hz), 3.95 (s, 3 H), 2.57, 2.60 (two s, 6 H), 1.35 (t, 3 H, J = 7 Hz). Anal. ($C_{20}H_{21}NO_4$).

Band 2 contained another new phenanthrene tentatively identified as **63** (0.015 g): NMR δ 9.49, 7.17 (AB q, 2 H, J = 10 Hz), 8.09 (s, 1 H), 7.80, 7.58 (AB q, 2 H, J = 10 Hz), 6.55 (br s, 1 H), 4.25 (q, 2 H, J = 7 Hz), 3.95 (s, 3 H), 2.55 (s, 3 H), 2.40 (s, 3 H), 1.33 (t, 3 H, J = 7 Hz), 1.17 (s, 9 H); IR λ_{max} ($CHCl_3$) 2.85, 5.80 μm; mass spectrum (EI), m/e 395 (M^+), 339 (base).

Band 3 contained 0.053 g (23%) of **61** which was identical with a sample prepared from stilbene **55**.

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General Synthetic Route to Malonamic Acids and 3-Thiomalonamic Acids. Amidations and Thioamidations of α Anions of Carboxylate Salts with Alkyl and Aryl Isocyanates and Isothiocyanates[1]

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Treatment of α anions of carboxylate salts **2** with alkyl or aryl isocyanates and isothiocyanates leads to substituted malonamic acids (**4**, X = O) and 3-thiomalonamic acids (**4**, X = S), respectively. Lithium naphthalenide is utilized as the base in the formation of the α anions **2** in order to circumvent the problem of a competitive reaction involving diisopropylamine (if lithium diisopropylamide is used to generate **2**) and the highly electrophilic isocyanates and isothiocyanates. A study of the generality of this type of reaction and a comparison of the two base systems are made.

During the past decade, α anions of carboxylate salts have found many synthetic applications.[2] As part of our continued interest in the synthetic uses of these α anions,[3] the present research was undertaken to investigate the reaction of carboxylic acids (via their α anions) with alkyl or aryl isocyanates and isothiocyanates as a possible general route to malonamic acids and 3-thiomalonamic acids, respectively.

The Ivanov reagent, $C_6H_5CH(MgCl)CO_2MgCl$, prepared from phenylacetic acid and isopropylmagnesium chloride, reacts with isocyanates to yield N-substituted malonamic acids.[4] However, treatment of this Ivanov reagent with isothiocyanates leads to decarboxylated products. This method suffers from the limitation that it cannot be applied to aliphatic and alicyclic carboxylic acids.

Malonamic acids have been prepared from amide α anions by treatment with CO_2,[5] from arylamines and diethyl malonate,[6] from acylals derived from substituted malonic acids,[7] from half-acid acyl chlorides,[8] by hydrolysis of spiro-1,3-oxazinones,[9] and by hydrogenation of a 1,3-oxazine-4,6-dione.[10]

(1) Presented in part at the 176th National Meeting of the American Chemical Society, Miami Beach, FL, Sept 11–15, 1978; Abstr. ORGN 13.
(2) Krapcho, A. P.; Kashdan, D. S.; Jahngen, E. G. E., Jr.; Lovey, A. J. *J. Org. Chem.* **1977**, *42*, 1189 and references cited therein.
(3) Creger, P. L. "Annual Reports in Medicinal Chemistry", Vol. 12, Academic Press, New York, 1977, Chapter 12. Creger presents an excellent review of the synthetic applications of metalated carboxylic acids.
(4) Blicke, F. F.; Zinnes, H. *J. Am. Chem. Soc.* **1955**, *77*, 4849.
(5) Yamada, S.; Kuramoto, M.; Yaso, M. Japan Kokai 74 116 019, 1974; *Chem. Abstr.* **1975**, *82*, 170074n.
(6) Patel, G. H.; Mehta, C. M. *J. Sci. Ind. Res., Sect. B* **1960**, *19*, 436; *Chem. Abstr.* **1961**, *55*, 9401. Substantial diamide is also formed.
(7) Loev, B.; Macko, E.; Fried, I. M. *J. Med. Chem.* **1969**, *12*, 854. Only one substituted malonamic acid is reported.
(8) (a) Palomo, A. L.; Torrens, E. *Afinidad* **1972**, *29*, 981; *Chem. Abstr.* **1973**, *79*, 5290. (b) Ramontian, E.; Voinescu, V. *Rev. Chim. (Bucharest)* **1976**, *27*, 106; *Chem. Abstr.* **1976**, *85*, 32372.
(9) Ziegler, E.; Brus, G. *Monatsh. Chem.* **1967**, *98*, 1100.
(10) Martin, J. C.; Gott, P. G. U.S. Patent 3 394 132, 23 Ju, 1968; *Chem. Abstr.* **1968**, *69*, 59256.

0022-3263/80/1945-1106$01.00/0