Synthesis of 9,10-Dihydroanthracen-9,10-imines

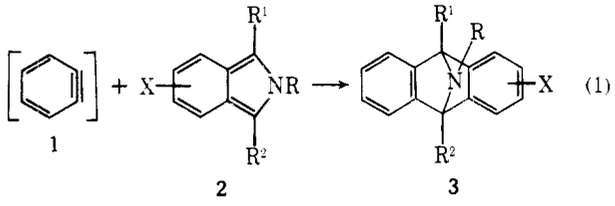
Paul S. Anderson, Marcia E. Christy, C. Dylion Colton, Wasyl Halczenko, Gerald S. Ponticello, and Kenneth L. Shepard*

Department of Medicinal Chemistry, Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania 19486

Received September 22, 1978

The cycloaddition of benzynes with isoindoles to generate 9,10-dihydroanthracen-9,10-imines has been examined in detail. A versatile synthesis of these ring-strained heterocycles based on a detailed analysis of the 2,3-dihydro-1*H*-isoindol-1-one (phthalimidine) approach to the prerequisite isoindoles is presented. A variety of synthetic methods to phthalimidines were evaluated and developed including (1) reductive amination of *o*-acylbenzoic acids, (2) amidoalkylation of benzoic acids, (3) halogenation and amination of *o*-alkylbenzoic acids, and (4) reduction of phthalimides. In addition, generation of benzynes from chlorobenzenes and lithium tetramethylpiperidide greatly increases the scope of the Diels–Alder reaction to form the desired products.

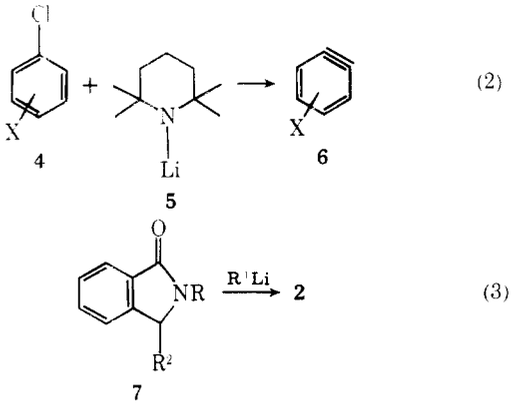
Cycloaddition of benzynes (**1**) to isoindoles (**2**) constitutes



(1)

(eq 1) the only known synthetic route to the 9,10-dihydroanthracen-9,10-imine ring system (**3**).[1] In view of the transient nature of benzyne and the chemical sensitivity of isoindoles,[2] it is not surprising that among the few derivatives of this ring system which have been reported most are derived from the stable 1,3-diphenylisoindoles (**2**, $R^1 = R^2 = C_6H_5$).[3-10] Set forth here is a broader analysis of the Diels–Alder approach to these heterocyclic compounds which demonstrates that cycloaddition has considerable utility when the methods of benzyne and isoindole generation are appropriately selected and combined. Emphasis is placed on the use of readily available precursors for **1** and **2**, the generation of **1** and **2** in a reaction medium compatible with subsequent cycloaddition, and the ability to prepare nuclear substituted derivatives of **3** in an efficient manner such that mixtures of isomers are avoided when possible. These points are illustrated in detail below.

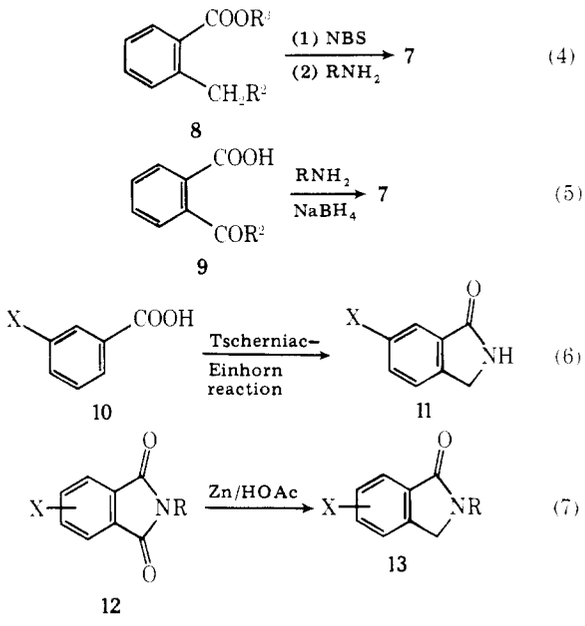
In order to broaden the scope of the cycloaddition, conditions were needed such that the transient benzyne **1** could be efficiently generated in the presence of a chemically reactive isoindole. Furthermore, a method for generating the isoindole from an available intermediate so that storage and purification of this reactive species would be minimal also was desirable. We have found that the action of lithium tetramethylpiperidide on chlorobenzenes as the source of benzyne (eq 2)[11] coupled with conversion of phthalimidines to isoindoles on



(2)

(3)

exposure to alkyllithium reagents (eq 3)[12-15] provided the most efficient solution to these problems. Thus, substituted chlorobenzenes are readily available in comparison with the corresponding precursors needed for other benzyne generation methods, and phthalimidines are prepared easily from *o*-alkylbenzoates (eq 4),[16] *o*-acylbenzoic acids (eq 5),[17] *m*-halo- and *m*-alkylbenzoic acids (eq 6),[18] and phthalimides (eq 7).[19]



(4)

(5)

(6)

(7)

Furthermore, when isoindoles are prepared from phthalimidines via the alkyllithium route, the product is suitable for use in the cycloaddition reaction with only minimal workup and no further purification.

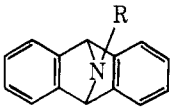
The examples below illustrate and further elaborate these points as they relate to the scope of the cycloaddition method. It should be noted that injudicious use or combination of the previously described methods in many situations would produce isomeric products as well as involve unnecessary synthetic effort.

Discussion

Since a major portion of the work described here required flexibility in the choice of R, R^1, and R^2 in structure **2**, and thus **3** (see Tables I–V), an important objective was to examine the scope of available isoindole syntheses in meeting this condition. Although a number of synthetic approaches to isoindoles have been described, few offer any degree of versatility for the substituents on the isoindole nucleus.[2-10] Of these methods, only two, the α,α^1-dibromo-*o*-xylene synthesis

0022-3263/79/1944-1519$01.00/0

Table I



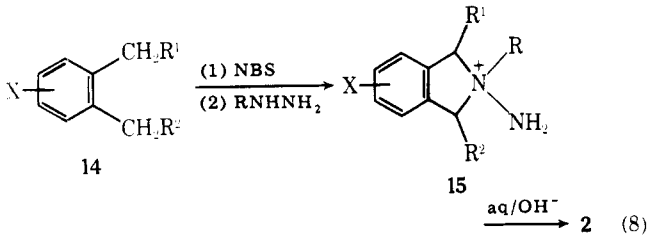
I

compd	R	substituent(s)	mp, °C	yield, %	isoindole method[a]	benzyne precursor	registry no.	method[b]	^{1}H NMR, δ	C, calcd/obsd	H, calcd/obsd	N, calcd/obsd
Ia[c]	CH_3	1,3-di-F	151–153 dec	5	A	1,3,5-F_3 2-Br	2367-76-2	F	2.70 (d, J = 6 Hz, 3 H) 6.10 (s, 1 H) 6.30 (s, 1 H)[x]	61.26/ 61.60	3.93/ 4.21	4.20/ 4.23
Ib[c]	CH_3	2,3-di-F	168–169 dec	9	A	1-Br 2,4,5-F_3[m]		F	3.17 (d, J = 4 Hz, 3 H) 6.50 (s, 2 H)[x]	61.26/ 60.93	3.93/ 4.13	4.20/ 4.26
Ic[c]	CH_3	1-CH_3, 6-F; 1-CH_3, 7-F mix.	94–114	30	$A_{(F)}$	1-CH_3 2-Br 3-Cl	69190-56-3	G	2.17 (s, 3 H) 2.20 (s, 3 H) 2.60 (s, 3 H) 2.63 (s, 3 H) 5.96 (s, 1 H) 6.10 (s, 1 H)[x]	63.89/ 63.83	5.07/ 4.88	4.14/ 4.03
Id[c]	CH_3	2-CF_3, 6-F; 2-CF_3, 7-F mix.	153–155 dec	19	$A_{(F)}$	1-Cl 2-Br 4-CF_3	454-78-4	F	3.40 (s, 3 H) 3.43 (s, 3 H) 6.83 (s, 4 H)[x]	56.40/ 56.78	3.42/ 3.81	3.65/ 3.61
Ie	CH_3	2-Cl, 6-OCH_3; 2-Cl, 7-OCH_3 mix.	bp 136–140 (0.2 mm)	18	$A_{(Cl)}$	1-Br 2-I 4-OCH_3[n]	4897-68-1	G	2.3 (s, 3 H) 3.8 (s, 3 H) 4.9 (2, 2 H) 6.4–7.4 (m, 6 H)[y]	70.70/ 70.90	5.15/ 5.45	5.15/ 4.97
If[c]	CH_3	2,7-di-Cl; 2,6-di-Cl mix.	176–183	26	$A_{(Cl)}$	1-F 2-Br 4-Cl[n]	1996-30-1	F	2.4 (s, 3 H) 5.6 (s, 2 H) 7.2–7.8 (m, 6 H)[w]	55.74/ 56.16	3.58/ 3.87	3.82/ 3.92
Ig[d]	CH_3	2-Cl, 6-F; 2-Cl, 7-F mix.	70–75	27	$A_{(Cl)}$	2-Br 1,4-F_2[o]	399-94-0	F	2.2 (s, 3 H) 5.2 (s, 2 H) 6.8–7.6 (m, 6 H)[w]	60.72/ 60.37	4.02/ 4.02	3.73/ 3.71
Ih	CH_3	2-OCH_3	~96	21	A	1-Br 2-I 4-OCH_3[n]		G	2.3 (s, 3 H) 3.8 (s, 3 H) 4.9 (s, 2 H) 6.6–7.4 (m, 7 H)[y]	80.01/ 80.24	6.37/ 6.49	5.90/ 5.89
Ii[d]	CH_3	2-Cl	90–92	11	A	1-I 2-Br 4-Cl[p]	31928-44-6	G	2.16 (s, 3 H) 5.17 (s, 2 H) 6.95–7.6 (m, 7 H) 12.1 (br s, 2 H)[w]	63.78/ 63.67	4.51/ 4.84	3.91/ 3.70
Ij[c]	CH_3	1-Cl	176–178	14	A	1,3-Cl_2 2-Br[q]	19393-91-1	G	2.18 (s, 3 H) 5.16 (s, 2 H) 7.28 (s, 3 H) 6.95–7.55 (m, 7 H) 12.2 (br s, 3 H)[u]	58.64/ 59.87	4.22/ 4.39	3.26/ 3.21
Ik[e]	CH_3	2-F	150–152	15	A	2-Br 1,4-F_2[o]		G	2.2 (s, 3 H) 5.18 (s, 2 H) 6.67 (s, 3 H) 6.5–7.6 (m, 7 H) 12.5 (s, 3 H)[w]	63.15/ 63.18	4.54/ 4.65	3.50/ 3.38
Il[e]	CH_3	1-F	163–164	9	A	1,3-F_2 2-Br[r]	64248-56-2	G	2.18 (s, 3 H) 5.2 (m, 1 H) 5.3 (s, 1 H) 6.68 (s, 3 H) 6.8–7.6 (m, 7 H) 12.75 (s, 3 H)[w]	63.15/ 62.73	4.54/ 4.64	3.50/ 3.39
Im[e]	CH_3	2-CH_3	143–144	13	A	1-F 2-Br 4-CH_3[n]	452-62-0	G	2.2 (s, 3 H) 2.22 (s, 3 H) 4.8 (s, 2 H) 6.6–7.4 (m, 7 H)[y]	66.77/ 66.66	5.35/ 5.40	3.54/ 3.21

Table I (*Continued*)

compd	R	substituent(s)	mp °C	yield, %	isoindole method[a]	benzyne precursor	registry no.	method[b]	^{1}H NMR, δ	C, calcd/obsd	H, calcd/obsd	N, calcd/obsd
In[e]	CH_3	1-CH_3	172–173	8	A	1-CH_3 2-Br 3-Cl		G	2.22 (s, 3 H) 2.29 (s, 3 H) 4.9 (m, 2 H) 6.65–7.45 (m, 7 H)[y]	66.77/66.80	5.35/5.43	3.54/3.44
Io[e]	CH_3	2-Br	168–170	16	$A_{(Br)}$	1-Br 2-F		G	2.25 (s, 3 H) 4.8 (2, 2 H) 6.7–7.4 (m, 7 H)[y]	54.79/54.97	3.94/4.12	3.04/2.87
Ip[f]	CH_2-C_6H_5	2-F	100–110	11	*k*	2-Br 1,4-F_2[o]		G	4.5 (s, 2 H) 4.88 (s, 2 H) 6.4–7.5 (m, 12 H)[y]	67.27/67.16	5.65/5.71	2.62/2.42
Iq	CH_3	1,2,4-F_3	bp 100–104 (0.2 mm)	9	A	1-Br 2,3,5,6-F_4	1559-88-2	G	2.25 (s, 3 H) 5.2 (m, 2 H) 6.2–7.8 (m, 5 H)[y]	68.96/67.19	3.85/3.93	5.36/5.47
Ir	CH_3		159–161	53[i]	A	Cl		H				

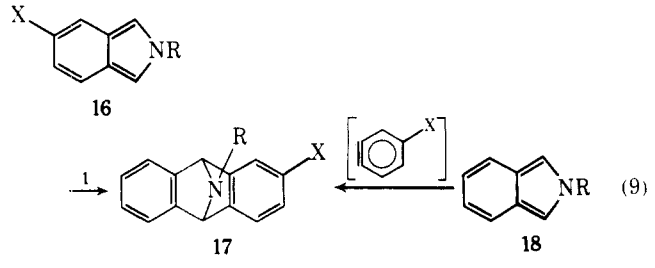
[a] Method A is the hydrazine procedure, see eq 8. Since organolithium reagent addition to phthalimidine forms isoindoles, the other methods refer to the preparation of the phthalimidine: method B, see eq 7; method C, see eq 6; method D, see eq 4; method E, see eq 5. Element in parentheses indicates that the substituent was introduced through isoindole. [b] Refers to the method of benzyne generation from described precursor: method F, BuLi (−70 °C); method G, Mg, THF (65 °C); method H, lithium tetramethylpiperidide, or butyllithium, THF (65 °C). [c] Hydrogen oxalate. [d] Hydrogen fumarate. [e] 1.5 g fumarate. [f] 1.5 g fumarate, 2-propanol solvate. [g] Hydrogen oxalate hydrate. [h] Bis oxalate. [i] Reference 41. [j] 33% by method G. [k] Reference 20. [l] Reference 26. [m] Reference 34. [n] Reference 36. [o] Reference 37. [p] Reference 38. [q] Reference 39. [r] Reference 40. [s] Reference 26. [t] Reference 43. [u] Reference 35. [v] Reference 44. [w] Me_2SO-d_6, salt. [x] D_2O, salt. [y] $CDCl_3$, base.



(8)

of Zeeh and König[6] (eq 8) and the phthalimidine method[2] (eq 3), appeared attractive. The utilization of these routes for the synthesis of anthracen-9,10-imines is described in detail in the following examples.

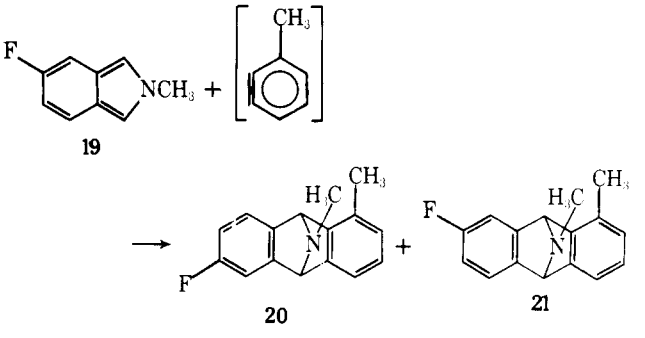
9,10-Unsubstituted Derivatives (Table I). The least complicated situation is the synthesis of an N-substituted-9,10-dihydroanthracen-9,10-imine (**17**, X = H). The appropriate hydrazine with α,α′-dibromo-*o*-xylene generates the necessary isoindole, and benzyne may be generated by a variety of techniques. In derivatives of this type where only one of the aromatic rings is substituted, clearly the substituent(s) could be introduced via either the isoindole or the benzyne precursor (eq 9). Routes to the requisite isoindoles, however,



(9)

have more limitations than those to the benzynes. For example, the use of the substituted hydrazine procedure (eq 8) is limited by the availability of the substituted *o*-xylene and the required hydrazine.[6,20] While lithium aluminum hydride reduction of an appropriate N-substituted phthalimidine as a source of the isoindole circumvents the hydrazine problem,[2] it also is limited by the compatibility of substituents with this reducing agent. The recent discovery that benzyne generated from chlorobenzene by lithium tetramethylpiperidide could be trapped in a Diels–Alder reaction, and the fact that this method is compatible with the isoindole nucleus,[11] allows a variety of substituents to be introduced readily through the benzyne component (vide infra). Since certain substituted *o*-dihalobenzenes are also available (commercially or synthetically), the aromatic substituent(s) may be introduced through the benzyne component using the conventional magnesium (method G) or butyllithium (method F) benzyne generation methods. These combinations have the further advantage that a single isoindole (**18**) can serve as precursor for a number of final products as demonstrated in Table I.

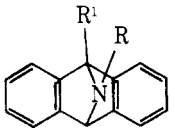
Where substituents in both aromatic rings are desired, the problem of isomer production arises. Using 5-fluoro-2-methylisoindole (**19**) in combination with 3-methylbenzyne, no selectivity was observed and the isomers **20** and **21** were



produced in essentially equivalent amounts. Similar findings with a number of analogues of this type are recorded in Tables I and III.

9- or 10-Substituted Derivatives (Table II). An added degree of complexity is introduced when a substituent is desired at only one bridgehead position, i.e., 9- or 10-substituted-9,10-dihydroanthracen-9,10-imines (**23**). The compounds are best approached by deriving the required 1,2-disubstituted isoindole (**22**) from an alkyllithium reagent

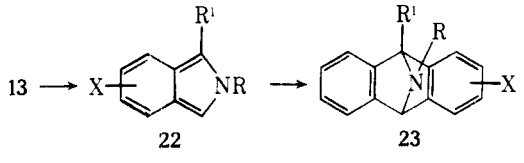
Table II[a]



II

compd	R	R¹	substituent(s)	mp, °C	yield, %	isoindole method[a]	benzyne precursor	method[b]	¹H NMR, δ	C, calcd/obsd	H, calcd/obsd	N, calcd/obsd
IIa[c]	CH_3	CH_3		139–140	16	B	1-Br 2-F	G	1.97 (s, 3 H) 2.30 (s, 3 H) 5.73 (s, 1 H)[w]	69.44/69.50	5.50/5.72	4.50/4.58
IIb[d]	CH_3	CH_3	2-Cl[y]	154–156	15	C	1-Br 2-F	G	1.73 (s, 3 H) 2.00 (s, 3 H) 5.05 (s, 1 H)[w]	64.60/64.84	4.88/5.18	3.77/3.73
IIc[e]	CH_3	CH_3	3-CH_3	125–127	4.5	B	1-Br 2-F	G	1.80 (s, 3 H) 2.10 (s, 3 H) 2.20 (s, 3 H) 5.70 (s, 1 H)[w]	67.46/67.34	5.66/5.89	3.42/3.47
IId[e]	CH_3	CH_3	2-CH_3	131–136	15	C	1-Br 2-F	G	1.87 (s, 3 H) 2.17 (s, 6 H) 5.38 (s, 1 H)[w]	67.46/67.53	5.66/5.78	3.42/3.36
IIe[e]	CH_2-C_6H_5	CH_3		110–114 turns red 191–194 decn eff	12	B	1-Br 2-F	G	1.83 (s, 3 H) 3.37 (s, 2 H) 4.83 (s, 1 H[w])	71.32/71.18	5.34/5.40	2.97/2.85
IIf[e]	CH_3	C_2H_5		>153 (grad)	14	B	1-Br 2-F	G	1.07 (t, J = 6 Hz, 3 H) 2.07 (s, 3 H) 2.27 (m, 2 H) 5.27 (s, 1 H)[w]	67.47/67.87	5.66/5.81	3.42/3.39
IIg[d]	C_2H_5	CH_3		132–134	15	B	1-Br 2-F	G	1.03 (t, J = 6 Hz, 3 H) 1.83 (s, 3 H) 2.33 (m, 2 H) 5.45 (s, 1 H)[w]	71.78/71.39	6.02/6.21	3.99/3.94
IIh[c]	CH_3	CH_3	2,3-di-Cl	153–155	19	B	1-Br 2-F	G	1.92 (s, 3 H) 2.23 (s, 3 H) 5.53 (s, 1 H) 7.05–7.55 (m, 4 H) 7.62 (s, 1 H) 7.68 (s, 1 H)[w]	56.86/56.42	3.98/3.94	3.68/3.62

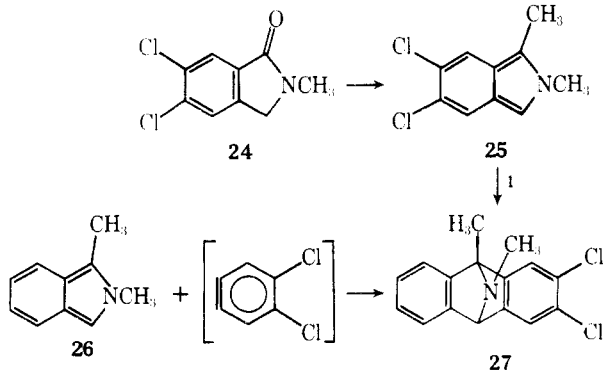
[a] See corresponding footnotes in Table I. [z] Cl: calcd 9.54; obsd 9.34.



22 23

addition to a phthalimidine.[12-15] The N-substituted phthalimidines (**13**) are readily accessible from phthalic anhydride by conversion to phthalimides (**12**)[21] followed by reduction with zinc in acetic acid[15] (eq 7). These products may also be prepared by the reductive amination of 2-carboxybenzaldehyde with the appropriate primary amine and sodium cyanoborohydride (eq 5, R^2 = H).[17] In addition, these phthalimidines can be generated from methyl *o*-toluate by benzylic bromination (NBS) followed by condensation with the required amine as described by Danishefsky[16] (eq 4).

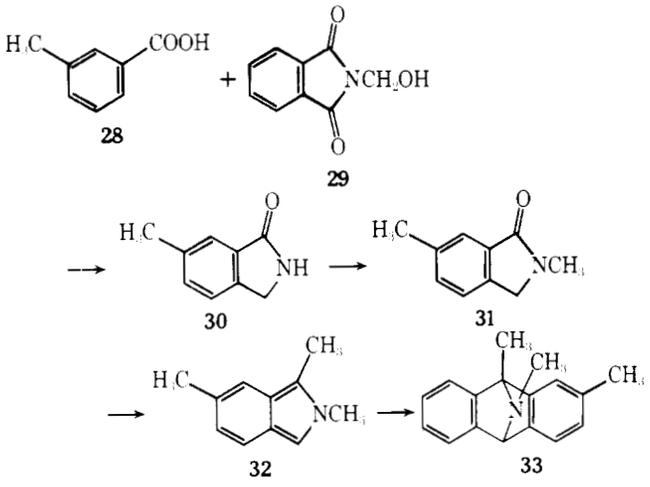
The synthesis of compounds of this type having aromatic substituents significantly complicates the required methodology. In the simplest situation where two identical substituents are desired on the same aromatic ring in the 1 and 4 or 2 and 3 positions, isomeric products do not arise and the problem reduces to choosing whether the isoindole or the benzyne should be the source of these substituents. As indicated, we have carried out both synthetic routes to the dichloro product **27** to illustrate this principle. 4,5-Dichlorophthalic anhydride was converted to *N*-methyl-4,5-dichlorophthalimide and reduced with zinc and acetic acid to **24.** Treatment with methyllithium generated **25,** and condensation with benzyne (*o*-bromofluorobenzene, method G) gave **27.** Preparation of **26** followed by cycloaddition with 4,5-dichlorobenzyne produced the same product (**27**). The most important criteria in the route to analogous products would be the availability of either intermediate.



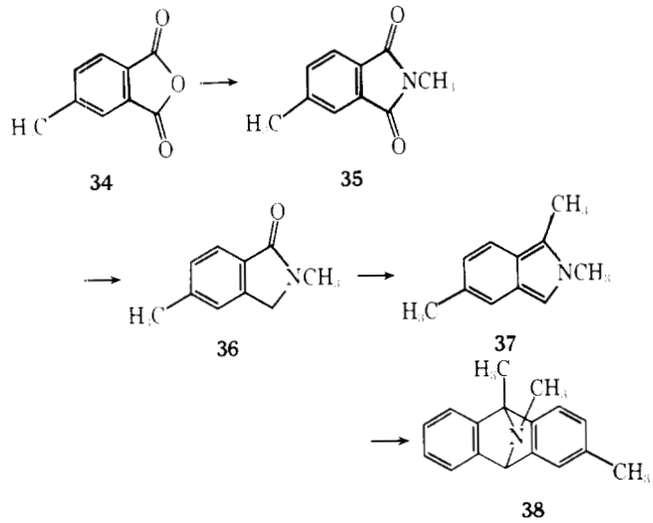
24 25 26 27

In the case of 9- or 10-substituted-9,10-dihydroanthracen-9,10-imines with a single aromatic substituent, designing a scheme to avoid the synthesis of a mixture of isomeric products becomes the principal concern. As suggested earlier, the lack of selectivity in the cycloaddition required that the substituent be introduced via the isoindole. The phthalimidine route to the desired isoindoles is preferred since procedures can be chosen to provide pure substituted isoindoles as illustrated below for the synthesis of 2,9,11- and 3,9,11-trimethyl-9,10-dihydroanthracen-9,10-imines.

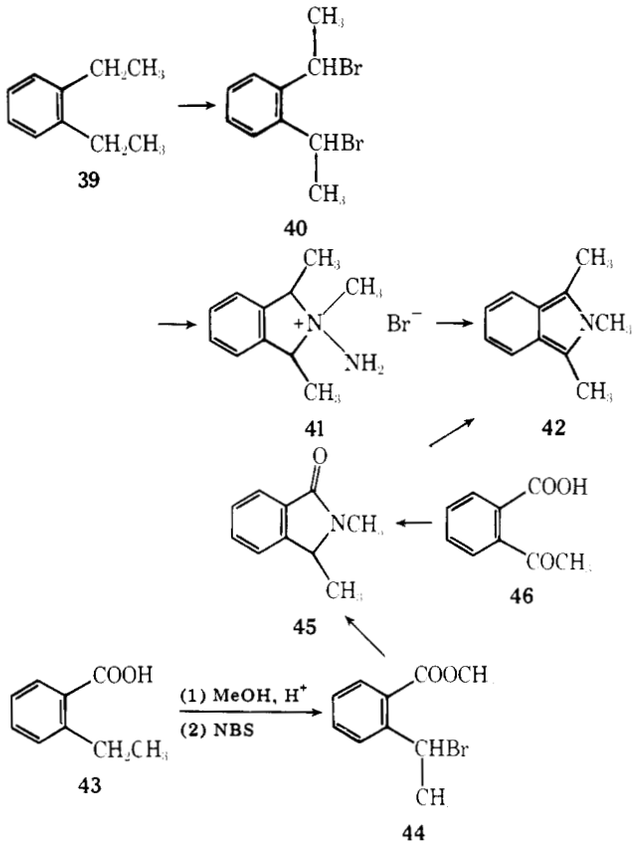
The 2,9,11-trimethyl isomer (**33**) requires 2,6-dimethylphthalimidine (**31**) as the precursor to the generation of 1,2,6-trimethylisoindole (**32**). Amidoalkylation[18] (e.g., eq 6) of *m*-toluic acid (**28**) with *N*-(hydroxymethyl)phthalimide in sulfuric acid produced 6-methylphthalimidine (**30**) directly. Alkylation of the amide nitrogen (NaH, CH_3I, DMF) gave the 2,6-dimethylphthalimidine (**31**). Addition of methyllithium followed by condensation with benzyne produced the 2,9,11-trimethyl isomer (**33**). In contrast, 2,5-dimethyl-



phthalimidine (**36**) is the necessary precursor for the 1,2,5-trimethylisoindole (**37**) that is required for the 3,9,11-trimethyl derivative (**38**). 4-Methylphthalic anhydride (**34**) was converted to 2,4-dimethylphthalimide (**35**), which, utilizing the principle of selective reductions of 4-substituted phthalimides,[22] was reduced (Zn, HOAc) to the requisite phthalimidine (**36**). The 1,2,5-trimethylisoindole (**37**) was generated by addition of methyllithium, and cycloaddition with benzyne gave the 3,9,11-trimethyl isomer (**38**).



9,10-Disubstituted Derivatives (Tables III and IV). In the synthesis of 9,10-disubstituted derivatives, three methods (A, D, and E) were employed to synthesize isoindole intermediates. Of these, the reductive amination procedure is superior in all respects. As an illustration, *o*-diethylbenzene (**39**) was dibrominated followed by treatment with methylhydrazine and hot aqueous base to give 1,2,3-trimethylisoindole (**42**,

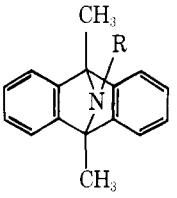


26% yield). The same isoindole was prepared from *o*-ethylbenzoic acid (**43**) by conversion to the methyl ester, bromination (NBS), amination (CH_3NH_2), and addition of methyllithium (76%). Using *o*-acetylbenzoic acid (**46**) in the reductive amination procedure followed by addition of methyllithium, the isoindole **42** was formed in better than 90% yield. Although all of these sequences provide the desired compound, the most accessible starting material is an acylbenzoic acid such as **46**. These derivatives are readily available from the action of organocadmium reagents on phthalic anhydrides, and their use allows a broader versatility of the substituents in the isoindole (**2**). Thus, in a 1,2,3-trisubstituted isoindole, one substituent would derive from the organocadmium reagent, one from the amine employed in the reductive amination, and the third from the organolithium reagent used to convert the phthalimidine to the target isoindole.

In those nuclear substituted anthracenimines where both bridgehead substituents are methyl, or other identical groups, the problem of isomeric synthesis is equivalent to those products that contain hydrogen at these positions. Therefore, the choice of synthetic method depends upon whether a nuclear substituent could be introduced best via the isoindole or the benzyne. In general, the latter alternative usually is the better choice as described earlier.

However, where the appropriate phthalic anhydride is available, nuclear substituents can be selectively introduced by method E. For example, 4-methylphthalic anhydride (**34**), when treated with dimethylcadmium, gives a mixture of acetyltoluic acids **47** and **48**. Reductive amination with methylamine maintains a mixture of products at the phthalimidine stage (**49** and **50**), but addition of methyllithium generates a single isoindole (**51**). Condensation of this isoindole with benzyne produces a product (**52**) identical with that from 1,2,3-trimethylisoindole (**42**) and 4-methylbenzyne.

Table III[a]



III

compd	R	substituent(s)	mp, °C	yield, %	isoindole method[a]	benzyne precursor	registry no.	method[b]	^{1}H NMR, δ	C, calcd/obsd	H, calcd/obsd	N, calcd/obsd
IIIa[e]	CH_3		169–172	52[j]	A, D, E	Cl		H	1.80 (s, 6 H) 2.00 (s, 3 H)[w]	67.47/ 67.66	5.66/ 5.86	3.44/ 3.36
IIIb[e]	CH_3	2-CH_3	153 dec	28	A	1-F 2-Br 4-CH_3[n]		G	1.83 (s, 6 H) 2.07 (s, 3 H) 2.25 (s, 3 H)[w]	68.07/ 68.43	5.95/ 6.13	3.31/ 3.18
IIIc[g]	CH_3	2-Cl	118–130	16	D, E	1-I 2-Br 4-Cl[p]		G	1.97 (s, 6 H) 2.23 (s, 3 H)[w]	60.40/ 60.40	5.34/ 5.01	3.71/ 3.67
IIId[c]	CH_3	1-F	191–193	24	A	1,3-F_2 2-Br[r]		G	1.93 (s, 3 H) 2.07 (s, 3 H) 2.20 (s, 3 H)[w]	66.65/ 66.75	5.30/ 5.62	4.09/ 4.10
IIIe[g]	CH_3	2-OCH_3	116–122 dec		A	1-Br 2-I 4-OCH_3[n]		G	2.00 (s, 6 H) 2.30 (s, 3 H) 3.70 (s, 3 H)[w]	64.33/ 64.18	6.21/ 6.26	3.75/ 3.64
IIIf	CH_3	1-Cl	98–100 base	9.5	D	1,3-Cl_2 2-Br		G	1.80 (s, 3 H) 2.03 (s, 3 H) 2.07 (s, 3 H)[y]	75.69/ 75.72	5.98/ 6.36	5.19/ 5.33
IIIg[e]	CH_3	1-OCH_3	168–169	17	D	1-OCH_3 2-Cl		G	1.97 (s, 3 H) 2.07 (s, 3 H) 2.27 (s, 3 H) 3.73 (s, 3 H)[w]	67.59/ 67.89	5.96/ 6.34	3.94/ 3.96
IIIh	CH_3	2-CH_3, 6-F 2-CH_3, 7-F mix.		9	E	2-Br 1,4-F_2[o]		G	1.80 (s, 6 H) 2.03 (s, 3 H) 2.27 (s, 3 H)[y]	65.56/ 65.46	5.78/ 5.77	3.82/ 3.84
IIIi	CH_2-C_6H_5	1,4-di-CH_3	153–155 base	50	*l*	1-Br 2-F		G	1.83 (s, 6 H) 2.27 (s, 6 H) 3.53 (s, 2 H) 6.63 (s, 2 H)[y]	88.45/ 88.28	7.42/ 7.47	4.13/ 3.96
IIIj	CH_3	1,4-di-CH_3	101–105 base	15	*l*	1-Br 2-F		G	1.90 (s, 6 H) 2.10 (s, 3 H) 2.27 (s, 6 H) 6.53 (s, 2 H)[y]	86.65/ 87.03	8.04/ 8.28	5.32/ 5.41
IIIk[g]	CH_3	2-SCH_3	108–114	5.5	D	1-SCH_3 4-Cl[s]	123-09-1	H	1.95 (s, 6 H) 2.23 (s, 3 H) 2.42 (s, 3 H)[w]	61.67/ 62.07	5.95/ 6.02	3.60/ 3.74
IIIl	CH_3	1-CH-$(CH_3)_2$ 2-CH-$(CH_3)_2$ mix.	80 °C (0.1 mm) short-path	33	D	1-CH-$(CH_3)_2$ 3- and 4-Cl	52944-34-0 57430-24-7	H	1.3 (d, J = 6 Hz, 6 H) 1.85 (s, 3 H) 2.05 (s, 3 H) 2.10 (s, 3 H)[y]	86.59/ 86.23	8.36/ 8.71	5.05/ 5.00
IIIm[c]	CH_3	2-SO_2N-$(CH_3)_2$	178–180	5	D	1-SO_2N-$(CH_3)_2$ 4-Cl[t]		H	1.93 (s, 6 H) 2.13 (s, 3 H) 2.57 (s, 6 H)[u]	58.32/ 58.53	5.60/ 5.92	6.48/ 6.54
IIIn[d]	CH_3	1-CH_3, 2-Cl	196–199	1.8	E	1-CH_3 2,6-Cl_2		H	1.90 (s, 3 H) 2.10 (s, 3 H) 2.20 (s, 3 H) 2.40 (s, 3 H) 6.60 (s, 3 H) 7.2 (m, 6 H)[w]	62.95/ 63.22	5.28/ 5.51	3.05/ 2.92
IIIo[g]	CH_3	2-CHO	120	15	D	1-CH-$(OEt)_2$[u] 4-Cl		H	1.83 (s, 6 H) 2.03 (s, 3 H) 2.03 (s, 3 H) 9.70 (s, 1 H)[y]	64.68/ 64.68	5.70/ 6.08	3.77/ 3.63
IIIp[c]	CH_3	2,3-di-F	182–184 dec	8	A	1-Br 2,4,5-F_3[m]		F	2.0 (m, 9 H)[u]	63.15/ 63.41	4.74/ 4.93	3.88/ 3.68
IIIq[h]	CH_3	1,3-di-Cl	120–125	11	E	1,3,5-Cl_3	108-70-3	H	1.87 (s, 3 H) 2.02 (s, 3 H) 2.13 (s, 3 H) 7.03–7.50 (m, 6 H)[w]	52.07/ 52.01	3.95/ 4.01	2.89/ 2.77

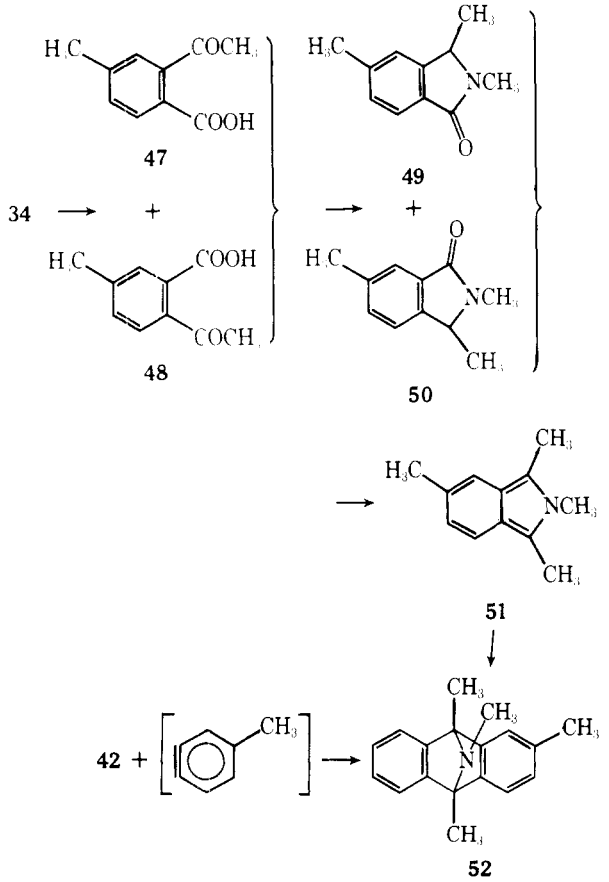
Table III (*Continued*)

compd	R	substituent(s)	mp, °C	yield, %	isoindole method[a]	benzyne precursor	registry no.	method[b]	^{1}H NMR, δ	C, calcd/obsd	H, calcd/obsd	N, calcd/obsd
IIIr[c]	CH_3	1-CH_3	184–185 dec	19	A	1-CH_3 2-Br 3-Cl		G	1.97 (s, 3 H) 2.13 (s, 3 H) 2.30 (s, 3 H) 2.32 (s, 3 H)[w]	70.78/71.09	6.24/6.42	4.13/4.02
IIIs[g]	CH_3	2-CF_3	124–127	4	A	1-Cl 2-Br 4-CF_3		F	1.97 (s, 6 H) 2.17 (s, 3 H) ^{19}F 60.1 ppm (s)[w]	58.39/58.30	4.90/4.95	3.41/3.12
IIIt[e]	CH_3	2-F	162 dec	10	A	1-Br 2,4-F_2	348-57-2	G	1.80 (s, 6 H) 2.0 (s, 3 H)[y]	64.62/64.71	5.19/5.30	3.28/3.00
IIIu[g]	CH_3	2-Br[z]	114–134	20	$A_{(Br)}$	1-Br 2-F		F	2.23 (s, 6 H) 2.60 (d, J = 2 Hz, 3 H)[x]	54.04/54.04	4.77/5.02	3.32/3.54
IIIv	CH_2-C_6H_5		152.5–154.5	35	D	1-Br 2-F		G	1.70 (s, 6 H) 3.40 (s, 2 H)[y]	88.71/88.73	6.80/7.11	4.50/4.50
IIIw	CH_2-C_6H_5	2-CH_3	133–137	20	D	1-Cl 2-Br 4-CH_3[c]	57310-39-1	F	1.70 (s, 6 H) 2.27 (s, 3 H) 3.42 (s, 2 H)[y]	88.57/88.84	7.12/7.40	4.30/4.45
IIIx	CH_2-C_6H_5	2-F	150–151	27	E	2-Br 2,4-F_2		G	1.65 (s, 6 H) 3.35 (s, 2 H)[y]	83.86/83.57	6.12/6.18	4.25/4.31
IIIy[c]	C_2H_5		143–145	49	D	1-Br 2-F		G	1.13 (t, J = 6 Hz, 3 H) 2.03 (s, 6 H) 2.63 (q, J = 6 Hz,[w] 2 H)	70.78/71.13	6.24/6.30	4.13/4.24
IIIz[c]	CH_2–◁		147 dec	32	D	1-Br 2-F		G	0.4 (m, 5 H) 2.07 (s, 6 H) 2.43 (d, J = 6 Hz, 2 H)[w]	72.31/72.55	6.34/6.34	3.83/3.78
IIIaa[c]	C_4H_9-t		>280	18	D	1-Br 2-F		G	1.03 (s, 9 H) 2.27 (s, 6 H)[y]	71.91/71.77	6.86/7.09	3.81/3.85
IIIbb[g]	CH_2CH_2-C_6H_5		100 dec	38	D	1-Br 2-F		G	2.07 (s, 6 H) 2.60 (m, 4 H)[w]	72.03/72.10	6.28/5.98	3.23/3.04
IIIc	$CH_2C_6H_4$-p-OCH_3		122–124	12	D	1-Br 2-F		G	1.70 (s, 6 H) 3.30 (s, 2 H) 3.70 (s, 3 H)[y]	84.42/84.01	6.79/7.14	4.10/3.97
IIIdd	$(CH_2)_3OH$		116–118	26	D	1-Br 2-F		G	1.70 (m, J = 6 Hz, 2 H) 1.90 (s, 6 H) 2.40 (t, J = 6 Hz, 2 H) 3.70 (t, J = 6 Hz, 2 H) 4.70 (s, 1 H)[y]	81.68/81.71	7.58/7.89	5.01/4.99
IIIee[c]	◁		165 dec	45	D	1-Br 2-F		G	0.50 (m, 4 H) 1.53 (m, 1 H) 1.93 (s, 6 H)[w]	71.78/71.41	6.02/6.42	3.99/4.05
IIIff[c]	◁	2-Cl	150–151 dec	16	D	1,4-Cl_2	106-46-7	H	0.50 (m, 4 H) 1.40 (m, 1 H) 1.97 (s, 6 H)[y]	65.36/65.08	5.23/5.41	3.63/3.58
IIIgg[c]	C_3H_7-n		156 dec	17	D	1-Br 2-F		G	0.80 (t, J = 6 Hz, 3 H) 2.0 (s, 6 H)[w]	71.37/71.81	6.56/6.97	3.96/4.13
IIIhh[aa]	C_3H_7-n	2-Cl	HCl	40	D	1,4-Cl_2		H	1.0 (t, J = 6 Hz, 3 H) 2.35 (s, 6 H)[x]	68.26/67.77	6.33/6.27	4.19/4.01
IIIii[c]	C_4H_9-n		150 dec	42	D	1-Br 2-F		G	0.8–1.8 (m, 7 H) 2.03 (s, 6 H) 2.60 (m, 2 H)[w]	71.91/71.94	6.86/6.75	3.81/3.69
IIIjj	CH_2CH=CH_2		132–134 dec[c] 110–112 base	20	D	1-Br 2-F		G	2.27 (s, 6 H) 3.50 (d, J = 6 Hz, 2 H) 5.50 (m, 3 H)[x]	87.31/86.73	7.33/7.32	5.36/5.37
IIIkk[d]	CH_3	2-I	180–184	29	E	1-Cl 4-I	637-87-6	H	1.8 (s, 6 H) 2.0 (s, 3 H) 6.9–7.5 (m, 7 H) 6.6 (s, 2 H) fumaric acid[w]			
IIIll	CH_3	1,2,3,4-F_4	96–98	32	E	F_5	363-73-4	F	2.0 (s, 6 H) 2.2 (s, 3 H) 7–7.3 (m, 4 H)[y]	66.44/66.73	4.26/4.34	4.55/4.43

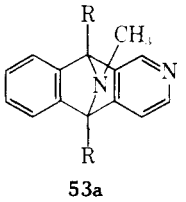
Table III (*Continued*)

compd	R	substituent(s)	mp, °C	yield, %	isoindole method[a]	benzyne precursor	registry no.	method[b]	^{1}H NMR, δ	C, calcd/obsd	H, calcd/obsd	N, calcd/obsd
IIImm	H		100–105	21					1.97 (s, 6 H) 3.30 (s, 1 H)[y]	86.84/ 86.39	6.83/ 6.84	6.33/ 6.29
IIInn	H	1,4-di-CH_3	114–116	97					2.00 (s, 6 H) 2.27 (s, 6 H) 3.13 (s, 1 H) 6.43 (s, 2 H)[x]	86.70/ 86.68	7.68/ 7.65	5.62/ 5.52
IIIoo[cc]	C_2H_5	1,4-di-CH_3	219.5–221.5 dec	20					1.47 (t, J = 6 Hz, 3 H) 2.33 (s, 6 H) 2.40 (s, 6 H) 3.07 (q, J = 6 Hz,[x] 2 H)	71.97/ 72.07	6.86/ 6.92	3.81/ 3.65
IIIpp[bb]	$(CH_2)_3$-$N(CH_3)_2$		172–174	40					1.95 (s, 6 H) 2.75 (s, 6 H)[x]	73.56/ 71.72	7.94/ 8.06	8.17/ 7.84
IIIqq	$(CH_2)_3Br$								2.46 (s, 6 H)[y]			
IIIrr	$-(CH_2)_3-^+Br^-$[cc]		182–183						2.23 (s, 6 H)[x]	63.34/ 63.56	6.16/ 5.99	3.89/ 3.78
IIIss	CH_3	2-CH=NOH	108–130	69					1.87 (s, 6 H) 2.07 (s, 3 H) 7.94 (s, 1 H)[y]			
IIItt[a]	CH_3	2-CN	100–115	35					2.28 (d, J = 2 Hz, 6 H) 2.66 (s, 3 H)[x]	63.65/ 63.97	5.61/ 5.08	7.42/ 7.61

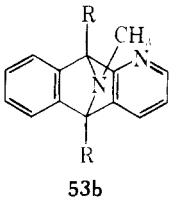
[a] See corresponding footnotes in Table I. [z] Br: calcd 18.92, obsd 18.89. [aa] Hydrochloride. Cl: calcd 21.21; obsd 21.21. [bb] Hydrochloride. Cl: calcd 10.34; obsd 10.57. [cc] Br: calcd 22.18; obsd 22.35.



Benzyne Generation. The aforementioned procedures have been primarily concerned with the preparation of the intermediate isoindoles. Having succeeded in our quest of making isoindoles readily available for subsequent synthetic studies, we turned our attention to the benzyne generation step. Most of the known methods of producing benzynes for Diels–Alder reactions utilize an ortho-disubstituted precursor.[23] Where additional substitution is desired or required, it is necessary to obtain a multisubstituted benzene as starting material. Many of these products are not available or must be synthesized. However, there are a great many substituted chlorobenzenes that are commercially available. Prompted by the observation that benzyne could be generated from chlorobenzene and trapped in a Diels–Alder reaction,[11] it was of interest to determine what functional groups were compatible with this process. Substituents that could be introduced in this manner include methylthio, *N,N*-dimethylsulfamoyl, isopropyl, dichloro, chloro, formyl (through acetal), methoxy, and iodo (see eq 2). This latter product was prepared from *p*-chloroiodobenzene, and although the product was contaminated with a small amount of the chloro derivative the major product contained iodine. There is apparently selectivity of halogen removal utilizing lithium tetramethylpiperidide, and the predominating factor would appear to be the acidity of adjacent protons. Attempts to introduce cyano, nitro, and methylsulfonyl by this method were unsuccessful. We attribute this to a greater acidity of the protons adjacent to these groups and subsequent failure to eliminate chloride. It is noteworthy that treatment of 3-bromopyridine with lithium tetramethylpiperidide produces the 3,4-pyridyne that was trapped by *N*-methylisoindole and 1,2,3-trimethylisoindole to generate the 2-aza analogues (**53a**) of the anthracenimines. To our knowledge this is the first reported example of a pyridyne generated from a monohalopyridine by a strong base undergoing a Diels–Alder condensation. Derivatives of the 1-aza system (**53b**) were prepared from 3-bromo-2-chloropyridine utilizing butyllithium (−78 °C, method F) (Table V).

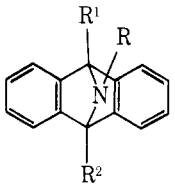


53a



53b

Table IV[a]

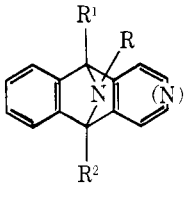


IV

compd	R	R^1	R^2	mp, °C	yield, %	isoindole method[a]	benzyne precursor	method[b]	^{1}H NMR, δ	C, calcd/obsd	H, calcd/obsd	N, calcd/obsd
IVa[e]	CH_3	CH_3	C_2H_5	179–180	30	E	1-Br 2-F	G	1.27 (t, J = 7 Hz, 3 H) 2.20 (s, 3 H) 2.50 (s, 3 H) 2.92 (q, J = 7 Hz, 2 H)[x]	68.07/68.32	5.95/6.00	3.31/3.32
IVb	CH_3	CH_3	C_4H_9-n	88–90	20	E	1-Br 2-F	G	0.8–2.6 (m, 9 H) 1.87 (s, 3 H) 2.00 (s, 3 H)[y]	86.59/86.67	8.36/7.97	5.05/4.88
IVc[e]	CH_3	CH_3	CH=CH_2	154–156 dec	2	E	1-Br 2-F	G	1.80 (s, 3 H) 1.97 (s, 3 H) 6.0 (m, 2 H) 6.7 (m, 1 H)[w]	68.40/68.30	5.50/5.72	3.32/3.19
IVd[d]	CH_3	C_2H_5	C_2H_5	173–175	13	A	1-Br 2-F 2-F	G	1.34 (t, J = 6 Hz, 6 H) 2.50 (s, 3 H) 2.0–3.3 (m, 4 H)[x]	72.80/72.65	6.64/6.96	3.69/3.68
IVe	CH_2-C_6H_5	C_3H_7-n	C_3H_7-n	197–200	18	E	1-Br 2-F	G	0.8 (t, J = 6 Hz, 6 H) 3.3 (s, 2 H)[y]	88.23/88.43	7.95/8.12	3.81/3.83

[a] See corresponding footnotes in Table I.

Table V[a]



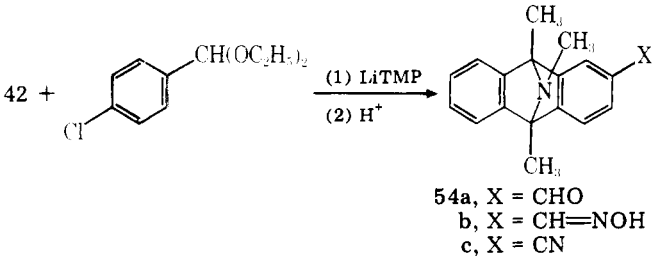
V

compd	R	R^1	R^2	(N)	mp, °C	yield, %	isoindole method[a]	substd pyridine	method[b]	^{1}H NMR, δ	C, calcd/obsd	H, calcd/obsd	N, calcd/obsd
Va[d]	CH_3	H	H	1	168–170	24	A	2-Cl 3-Br	F	2.15 (s, 3 H) 5.05 (s, 1 H) 5.25 (s, 1 H) 6.65 (s, 4 H) 6.8–8.2 (m, 7 H) 12.7 (s, 4 H)[w]	59.99/60.15	4.53/4.70	6.36/6.43
Vb[e]	CH_3	H	H	2	149–151	8	A	3-Br[z]	F	2.10 (s, 3 H)	62.82/62.43	4.74/5.09	7.32/6.93
						12		4-Cl	H	5.2 (br s, 2 H) 6.7 (s, 3 H) 6.9–8.7 (m, 7 H)			
						12		3-Br	H	12.5 (br s, 3 H)[w]			
Vc	CH_3	CH_3	CH_3	2	67–71	8	D-E	3-Br[aa]	H		81.32/81.43	6.83/6.91	11.86/7.83
Vd[c]	CH_3	CH_3	CH_3	1	178–179	2	A	2-Cl 3-Br	F	2.07 (s, 3 H) 2.17 (s, 3 H) 2.60 (s, 3 H)[x]	66.24/66.13	5.56/5.54	8.58/8.44

[a] See the corresponding footnotes in Table I. [z] Registry no., 36953-42-1. [aa] Registry no., 626-55-1.

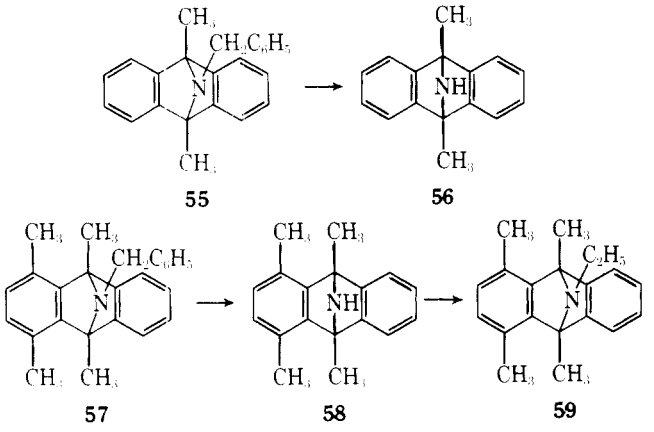
Chemistry of 9,10-Dihydroanthracen-9,10-imines. Although most of the anthracen-9,10-imines reported here are listed as salts, the majority are stable in both the salt and base forms. To decide the usefulness of these products to further transformations, some investigations were made concerning their chemical reactivity. The carboxaldehyde **54a** could be converted to an oxime (**54b**) and dehydrated to the corresponding nitrile (**54c**).

Thus, anthracenimines containing substituents not compatible with the benzyne generation step may be synthesized



54a, X = CHO
b, X = CH=NOH
c, X = CN

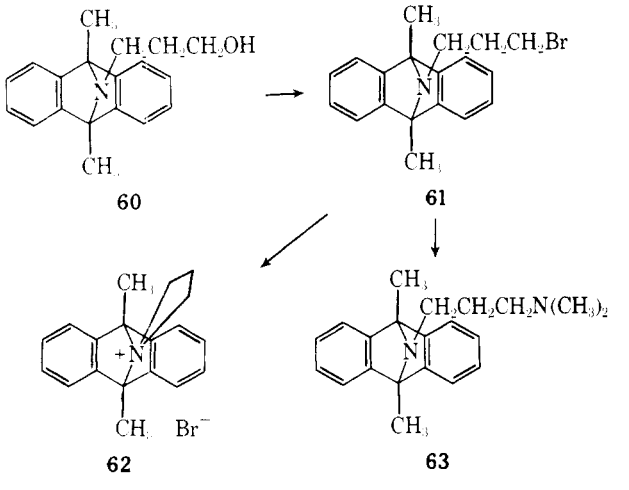
by subsequent transformation of a substituent which is compatible. In contrast to the oxidative instability of these compounds,[24] certain derivatives were capable of smooth catalytic reduction. Debenzylation of **55** to the amine **56** over



55 **56**

57 **58** **59**

Pd/C in acetic acid was accomplished, but the yield was low and unreproducible. However, the tetramethyl product **57**[25] was debenzylated in 97% yield (Pd/C, acetic acid, atmospheric pressure). The resulting secondary amine (**58**) could be converted to its *N*-ethyl derivative (**59**) in a reductive amination sequence with acetaldehyde ($NaCNBH_3$). Thus, although our general synthetic approach to anthracenimines led only to tertiary amines, secondary amines can be derived subsequently from the *N*-benzyl compounds. The 3-hydroxypropyl analogue **60** was converted to the corresponding bromide **61**

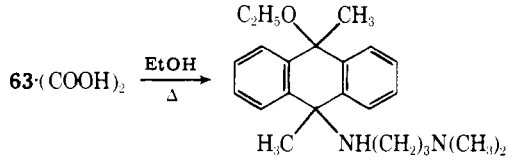


60 **61**

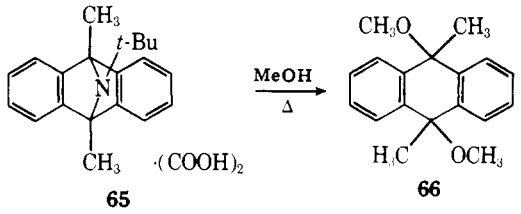
62 **63**

(NBS, $(C_6H_5)_3P$), and this product was treated with dimethylamine (in situ) to form the (dimethylamino)propyl compound **63.** This result illustrated that substituents which could not be carried through the isoindole synthesis step may be subsequently prepared from a group that is compatible with this step. The intermediate bromide underwent facile cyclization to the quaternary salt **62** on attempted isolation.

In contrast to the marked stability of most of these products, two proved to be exceptionally labile as their acid addition salts. The hydrogen oxalate salt of **63** solvolyzed upon hot ethanol recrystallization to yield the dihydroanthracene derivative **64.**[3] Attempted recrystallization of the hydrogen oxalate salt of **65** from hot methanol resulted in solvolysis with deamination to the 9,10-dihydroanthracene **66.** Both of these



64



65 **66**

salts could be recrystallized from cold solvents with no decomposition.

Summary

It is thus apparent from the foregoing discussion that a variety of substituted 9,10-dihydroanthracen-9,10-imines are readily available in reasonable yield (see Tables I–V). Except for oxidative instability, the products are stable and capable of further chemical transformations.

As indicated earlier, the preparation of anthracenimines requires the synthesis of isoindoles in sufficient quantity and purity and a benzyne generation method compatible with the isoindole nucleus. We have examined the scope of the reaction whereby isoindoles can be generated for subsequent synthetic operations from phthalimidines. Phthalimidines are best prepared via the versatile reductive amination method from *o*-acylbenzoic acids, which allows introduction of a variety of N and potential bridgehead substituents. The generation of benzynes from chlorobenzenes and 3,4-pyridyne from 3-bromopyridine using lithium tetramethylpiperidide and subsequent Diels–Alder addition with isoindoles establish the fact that substituted benzynes and pyridyne are more readily available for these types of reactions than heretofore believed.

Experimental Section

Essentially all reactions were run under dry nitrogen. ^1H NMR spectra were run in the solvents indicated on a Varian A60A or T60 instrument, and chemical shifts (δ) are measured from internal tetramethylsilane (Me_4Si) as reference. Infrared spectra were recorded on a Perkin-Elmer Infracord. GLC analyses were determined on an F & M 810 flame ionization instrument. All melting points were taken in open capillaries (Thomas Hoover apparatus) and are uncorrected values.

The synthesis of 9,10-dihydroanthracen-9,10-imines is separated into two stages. Methods A–E depict the isoindole preparation, and methods F–H refer to the benzyne generation/Diels–Alder step.

Preparation of Isoindoles. Method A. (All isoindoles in Table I were prepared by method A.) **1,2,3-Trimethylisoindole (2, R = R^1 = R^2 = CH_3, X = H).** A mixture of *o*-diethylbenzene (50 g, 0.374 mol), *N*-bromosuccinimide (146 g, 0.82 mol), benzoyl peroxide (0.1 g), and CCl_4 (800 mL) was heated under reflux with stirring and ultraviolet irradiation until the reaction was complete. The precipitated succinimide was filtered and washed with CCl_4, and the filtrate was concentrated to dryness. The residual oil was dissolved in absolute Et_2O (800 mL). To the stirred solution under N_2 was added, dropwise, a solution of methylhydrazine (40 g, 0.87 mol) in Et_2O (50 mL). After stirring for 3 h and standing overnight, the Et_2O was decanted from the precipitated solid. The residue was dissolved in H_2O (625 mL) and treated with 40% NaOH solution (375 mL), and the mixture was stirred at reflux for 1.5 h. After being cooled, the precipitate of crude

product was collected, washed with H_2O, and dissolved in Et_2O (600 mL). The Et_2O solution was washed repeatedly with H_2O and dried over $MgSO_4$ with stirring and cooling in an ice bath. The filtered solution was evaporated under reduced pressure, and the residual solid was triturated with petroleum ether, filtered, and dried in vacuo to yield 15.6 g (26%) of 1,2,3-trimethylisoindole.

5-Bromo-2-methylisoindole (2, R = CH_3, R^1 = R^2 = H, X = 5-Br). Step A. 4,α,α-Tribromo-*o*-xylene (14, R = R^1 = Br, X = 4-Br). Bromine (180 g, 1.15 mol) was added dropwise with stirring under ultraviolet irradiation at 125 °C to 4-bromo-*o*-xylene (92.5 g, 0.5 mol). After the addition was complete, the mixture was heated for 1 h at 125 °C and distilled to give 151 g (87%) of 4,α,α-tribromo-*o*-xylene, bp 130–145 °C (0.3 mm).

Step B. To a solution of 4,α,α-tribromo-*o*-xylene (151 g, 0.44 mol) in Et_2O (900 mL) was added dropwise methylhydrazine (60 g, 1.3 mol) over a period of 4 h at room temperature. After stirring overnight, a 40% NaOH solution (800 mL) was added with stirring. The Et_2O was removed by distillation, and H_2O (800 mL) was added to the resulting suspension. The solution was refluxed for 3 h, cooled, and extracted with $CHCl_3$ (3 × 300 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was distilled to give 30 g (33%): bp 126–128 °C (0.3 mm); ^1H NMR ($CDCl_3$) δ 3.60 (s, 3 H, NCH_3).

5-Fluoro-2-methylisoindole (19): 28%; bp 90–100 °C (1 mm); mp 60–65 °C.

5-Chloro-2-methylisoindole (2, R = CH_3, R^1 = R^2 = H, X = 5-Cl).

1,3-Diethyl-2-methylisoindole (2, R = CH_3, R^1 = R^2 = C_2H_5, X = H) was prepared from *o*-di-*n*-propylbenzene[45] using the procedure outlined for 1,2,3-trimethylisoindole: 23%; oil.

5-Bromo-1,2,3-trimethylisoindole (2, R = R^1 = R^2 = CH_3, X = 5-Br): 35%; solid; ^1H NMR ($CDCl_3$) δ 2.43 (s, 6 H, $ArCH_3$), 3.63 (s, 3 H, NCH_3).

2-Methylisoindole[6] (2, R = CH_3, R^1 = R^2 = X = H) was prepared from *o*-xylene: 81%; waxy solid.

Methods B, C, D, and E utilize the addition of an organolithium reagent to a phthalimidine for generation of the isoindole. The various methods thus reflect alternate procedures for preparation of the requisite phthalimidine. All of the new phthalimidines are listed prior to the listing of the isoindoles. Although only one method may be described for a specific isoindole, when it may be prepared by method E, that is the method of choice.

Method B (Table II). 2-Methylphthalimidine (13, R = CH_3, X = H). Phthalic anhydride (40 g) and methylamine hydrochloride (40 g) were added to glacial AcOH (750 mL) and stirred for 5 min. Sodium acetate (anhydrous, 48.6 g) and additional AcOH (250 mL) were added, and the mixture was heated to reflux for 2 h. The hot mixture was filtered and the filtrate was cooled to 70 °C. Zinc dust (95 g) was added rapidly with stirring, and the resulting mixture was heated to reflux for an additional 4 h. The mixture was filtered while hot, and most of the solvent was removed in vacuo. Saturated $NaHCO_3$ solution (700 mL) was added cautiously to the milky residue. The resulting mixture was extracted with $CHCl_3$ (4 × 200 mL). The combined extracts were washed with saturated $NaHCO_3$ solution, H_2O, and saturated NaCl solution and dried ($MgSO_4$). Removal of the $CHCl_3$ in vacuo gave 35.3 g of an off-white solid, mp 102–112 °C. Recrystallization from cyclohexane gave material with mp 112–115 °C (lit.[19] mp 114.5–115 °C).

2-Benzylphthalimidine (13, R = $CH_2C_6H_5$, X = H): using phthalic anhydride and benzylamine hydrochloride; mp 88–90 °C (ligroine) (lit.[27] mp 89–90 °C).

2-Ethylphthalimidine (13, R = C_2H_5, X = H): from phthalic anhydride and ethylamine hydrochloride as above; bp 88–91 °C/0.07 mm (lit.[28] mp 45 °C).

2,5-Dimethylphthalimidine (36): from 4-methylphthalic anhydride and methylamine hydrochloride as above; mp 38–47 °C; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3 H, $ArCH_3$), 3.1 (s, 3 H, NCH_3), 4.23 (s, 2 H, $-CH_2N<$).

5,6-Dichloro-2-methylphthalimidine (24): from 4,5-dichlorophthalic anhydride and methylamine hydrochloride; mp 183–186 °C (EtOAc); ^1H NMR ($CDCl_3$) δ 3.13 (s, 3 H, *n*-CH_3), 4.30 (s, 2 H, $-CH_2N<$), 7.53 (s, 1 H, ArH, O- to $-CH_2N<$), 7.83 (s, 1 H, ArH, O- to -CO-).

Method C (Table II). 2,6-Dimethylphthalimidine (31). Step A. 6-Methylphthalimidine (30). *m*-Toluic acid (**28**, 27.24 g, 0.20 mol) and *N*-(hydroxymethyl)phthalimide (35.44 g, 0.20 mol) were heated with concentrated H_2SO_4 (200 mL) on a steam bath for 24 h. The cooled reaction mixture was poured over ice (1 kg) and stirring was continued for several hours. The tacky brown solid was filtered and suspended in 5% aqueous sodium hydroxide solution (200 mL). The resulting tan solid was filtered and recrystallized from benzene: 10.0 g; mp 203–205 °C (lit.[29] mp 205 °C). This product could be prepared similarly using *N*-(hydroxymethyl)chloroacetamide. However, an additional hydrolytic step was required to remove the protecting group and close the lactam ring.

Step B. 2,6-Dimethylphthalimidine (31). Sodium hydride (4.95 g, 0.115 mol, 57% oil dispersion) was added to a stirred solution of 6-methylphthalimidine (**30**; 14.3 g, 0.097 mol) and methyl iodide (40 g) in DMF (400 mL). After the initial exothermic reaction had subsided, the mixture was stirred at 25 °C for 18 h. The solvent was removed in vacuo, and the residue was dissolved in H_2O (400 mL) and extracted with $CHCl_3$ (4 × 100 mL). After being dried (Na_2SO_4), the solvent was removed and the residue was triturated with ether (25 mL). Filtration and drying produced 7.2 g, mp 81–84.5 °C. Another 1.5 g, mp 75–81 °C, was obtained from the filtrate. A sample recrystallized from ethyl acetate/hexane had mp 85–88 °C; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3 H, $ArCH_3$), 3.10 (s, 3 H, $>NCH_3$), 4.23 (s, 2 H, $-CH_2N<$).

6-Chloro-2-methylphthalimidine (13, R = CH_3, X = 6-Cl). Step A. Using *m*-chlorobenzoic acid as above, 6-chlorophthalimidine (42%) was obtained, mp 250–254 °C. Further recrystallization from 2-propanol raised the melting point to 255–257.5 °C. Anal. Calcd (C_8H_6ClNO): C, 57.33; H, 3.61; N, 8.36. Found: C, 56.68; H, 3.56; N, 8.06.

Step B. Alkylation with methyl iodide was performed as indicated above: 58%; mp 82–88 °C. Recrystallization from CCl_4/hexane gave mp 95–98 °C; ^1H NMR ($CDCl_3$) δ 3.13 (s, 3 H, $>NCH_3$), 4.30 (s, 2 H, $-CH_2NCO-$).

Method D (Tables III, IV, and V). 2-Cyclopropyl-3-methylphthalimidine (7, R = $-CH(CH_2)_2$, R^2 = CH_3). Step A. Methyl 2-Ethylbenzoate (8, R^2 = R^3 = CH_3). A solution of 2-ethylbenzoic acid[30] (37.09 g, 0.247 mol) in CH_3OH (80 mL) was treated cautiously with concentrated H_2SO_4 (7.8 mL) and heated to reflux. After 3.5 h, the mixture was poured onto ice and the resulting mixture was extracted with Et_2O (3 × 100 mL). The organic layer was washed (H_2O, saturated $NaHCO_3$ solution, H_2O) and dried ($MgSO_4$). Evaporation of the filtered extract left 38 g (93.5%) of colorless oil.

Step B. Methyl 2-(1-Bromoethyl)benzoate. Methyl 2-ethylbenzoate (38 g, 0.231 mol), *N*-bromosuccinimide (41.2 g, 0.231 mol), and a catalytic amount of benzoyl peroxide were stirred and heated under reflux in CCl_4 (480 mL) until reaction was complete (~2 h). The precipitated succinimide was filtered from the cooled mixture. Evaporation of the filtrate left 56 g (quantitative) of yellow oil.

Step C. 2-Cyclopropyl-3-methylphthalimidine. To a stirred solution of methyl 2-(1-bromoethyl)benzoate (18.0 g, 0.074 mol) in CH_3OH (110 mL) was added rapidly from a dropping funnel a solution of cyclopropylamine (9 g, 0.158 mol) in CH_3OH (10 mL). After being stirred overnight, the solvent was stripped and the residue was triturated with $CHCl_3$. The precipitate of cyclopropylamine hydrobromide was filtered. The washed and dried filtrate was concentrated to dryness. Distillation of the residue gave 10.7 g (77%) of a colorless oil: bp 120 °C (0.2 mm); ^1H NMR ($CDCl_3$) δ 0.90 (m, 4 H, cyclopropyl), 1.50 (d, J = 7 Hz, 3 H, $>CHCH_3$), 2.60 (m, 1 H, $-NCHCH_2CH_2$), 4.47 (q, J = 7 Hz, 1 H, $>CHCH_3$).

The following phthalimidines were prepared using this general procedure and substituting the appropriate amine for cyclopropylamine in step C.

2,3-Dimethylphthalimidine:[31] 68%; see method E also.

2-Benzyl-3-methylphthalimidine:[32] 61%; bp 158–162 °C (0.1 mm); IR (KBr) 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.45 (d, J = 6 Hz, 3 H, CH_3), 4.32 (d, J = 14 Hz, 1 H, benzylic), 4.43 (q, J = 6 Hz, 1 H, $>CHCH_3$), 5.41 (d, J = 14 Hz, 1 H, benzylic).

2-Ethyl-3-methylphthalimidine: 84%; bp 97–105 °C (0.1 mm); ^1H NMR ($CDCl_3$) δ 1.2 (t, J = 6 Hz, $-CH_2CH_3$), 1.4 (d, J = 6 Hz, 3 H, $-CHCH_3$), 3.3 (m, 1 H, NCH_2-), 3.9 (m, 1 H, NCH_2-), 4.6 (q, J = 6 Hz, 1 H, $>CHCH_3$), 7.4 (m, 3 H, aromatic), 7.8 (m, 1 H, aromatic).

2-(Cyclopropylmethyl)-3-methylphthalimidine: 71%; bp 131–133 °C (0.1 mm); GLC 93%; ^1H NMR ($CDCl_3$) δ 0.8 (m, 5 H, cyclopropyl), 1.5 (d, J = 7 Hz, 3 H, CH_3), 3.0 (dd, J = 6 and 14 Hz, 1 H, NCH_2-), 4.0 (dd, J = 6 and 14 Hz, 1 H, NCH_2-), 4.75 (q, J = 7 Hz, 1 H, $>CHCH_3$), 7.5 (m, 3 H, aromatic), 7.9 (m, 1 H, aromatic).

3-Methyl-2-*tert*-butylphthalimidine: 46%; bp 90–100 °C (0.1 mm); GLC homogeneous; ^1H NMR ($CDCl_3$) δ 1.5 (d, J = 6 Hz, 3 H, $>CHCH_3$), 1.57 (s, 9 H, *t*-Bu), 4.75 (q, J = 6 Hz, 1 H, $>CHCH_3$), 7.4 (m, 3 H, aromatic), 7.7 (m, 1 H, aromatic).

3-Methyl-2-phenethylphthalimidine: 88%; bp ~180 °C (0.1 mm); GLC homogeneous; ^1H NMR ($CDCl_3$) δ 1.33 (d, J = 6 Hz, 3 H, CH_3) 2.75–4.5 (overlapping signals, 5 H, NCH_2CH_2- and $>CHCH_3$), 7.3 (m, 8 H, aromatic), 7.77 (m, 1 H, aromatic).

3-Methyl-2-(4-methoxybenzyl)phthalimidine: 84%; bp 192–197

°C (0.15 mm); GLC, 97%; ^{1}H NMR ($CDCl_3$) δ 1.40 (d, J = 6 Hz, 3 H, >CHC**H**$_3$), 3.73 (s, 3 H, OCH_3), 4.2 (d, J = 14 Hz, 1 H, benzylic), 4.37 (q, J = 6 Hz, 1 H, >C**H**CH$_3$), 5.3 (d, J = 14 Hz, 1 H, benzylic), 7.15 (m, 7 H, aromatic), 7.85 (m, 1 H, aromatic).

2-(3-Hydroxypropyl)-3-methylphthalimidine: 64%; bp 172–175 °C (0.2 mm); ^{1}H NMR ($CDCl_3$) δ 1.5 (d, J = 6 Hz, 3 H, CH_3), 1.9 (m, 2 H, $NCH_2C\mathbf{H}_2CH_2OH$), 3.8 (overlapping signals, 5 H, NCH_2, $-CH_2OH$), 4.57 (q, J = 6 Hz, 1 H, >C**H**CH$_3$), 7.5 (m, 3 H, aromatic), and 7.8 (m, 1 H, aromatic).

3-Methyl-2-propylphthalimidine: 71%; bp 98–104 °C (0.1 mm); GLC, 99%; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7 Hz, 3 H, $-CH_2C\mathbf{H}_3$), 1.45 (d, J = 7 Hz, 3 H, >CHC**H**$_3$), 1.8 (m, 2 H, $-C\mathbf{H}_2CH_3$), 3.15 (m, 1 H, NCH_2–), 3.8 (m, 1 H, NCH_2–), 4.5 (q, J = 7 Hz, 1 H, >C**H**CH$_3$), 7.4 (m, 3 H, aromatic), 7.75 (m, 1 H, aromatic).

2-Butyl-3-methylphthalimidine: 79%; bp 109–114 °C (0.1 mm); GLC homogeneous; ^{1}H NMR ($CDCl_3$) δ 1.35 (m, 7 H, $-CH_2CH_2CH_3$), 1.4 (d, J = 6 Hz, 3 H, >CHC**H**$_3$), 3.3 (m, 1 H, NCH_2), 4.0 (m, 1 H, NCH_2), 4.6 (q, J = 6 Hz, 1 H, $-C\mathbf{H}CH_3$), 7.5 (m, 3 H, aromatic), 7.9 (m, 1 H, aromatic).

2-Allyl-3-methylphthalimidine: 74%; bp 102–104 °C (0.15 mm); GLC homogeneous; ^{1}H NMR ($CDCl_3$) δ 1.45 (d, J = 6 Hz, 3 H, CH_3), 3.6–6.3 (overlapping signals, 6 H, allyl and >C**H**CH$_3$), 7.5 (m, 3 H, aromatic), 7.9 (m, 1 H, aromatic).

2-(2-Chlorobenzyl)-3-methylphthalimidine: 98%; bp 185 °C (0.05 mm); ^{1}H NMR ($CDCl_3$) δ 1.4 (d, J = 6 Hz, 3 H, CH_3), 4.4 (q, J = 6 Hz, 1 H, >C**H**CH$_3$), 4.55 (d, J = 16 Hz, 1 H, benzylic), 5.25 (d, J = 16 Hz, 1 H, benzylic), 7.3 (m, 7 H, aromatic), 7.85 (m, 1 H, aromatic).

Method E. This method has been published; see ref 17.

Isoindoles. Organolithium General Procedure. To a stirred solution of the phthalimidine (25 mmol) in dry Et_2O (150 mL) under nitrogen was added dropwise CH_3Li (15 mL, 1.8 M in Et_2O, 27 mmol). The mixture was stirred at room temperature for 16 h, cooled, and treated with H_2O (20 mL). The Et_2O phase was separated, washed (H_2O), and dried ($MgSO_4$), keeping it ice-cold and under nitrogen as much as possible. The filtered extract was evaporated, and the residue was dried at 0.1 mm and protected from light.

Isoindoles (Table II). 1,2-Dimethylisoindole[12] (22, R = R^1 = CH$_3$): from 2-methylphthalimidine and CH_3Li; 78%; yellow-orange low-melting solid; ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3 H, $ArCH_3$), 3.47 (s, 3 H, $>NCH_3$).

6-Chloro-1,3-dimethylisoindole (2, R = R^1 = CH$_3$, R^2 = H, X = 6-Cl): from 6-chloro-2-methylphthalimidine and CH_3Li; 72%; oil; ^{1}H NMR ($CDCl_3$) δ 2.3 (s, 3 H, $ArCH_3$), 3.6 (s, 3 H, $>NCH_3$).

1,2,5-Trimethylisoindole (37): from 2,5-dimethylphthalimidine and CH_3Li; 79%; oil; ^{1}H NMR ($CDCl_3$) δ 2.3 (s, 3 H, $ArCH_3$), 2.4 (s, 3 H, $ArCH_3$), 3.67 (s, 3 H, $>NCH_3$).

1,2,6-Trimethylisoindole (32): from 2,6-dimethylphthalimidine and CH_3Li; 91%; yellow-orange powder; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 6 H, $ArCH_3$), 3.53 (s, 3 H, $>NCH_3$).

2-Benzyl-1-methylisoindole (2, R = CH$_2$C$_6$H$_5$, R^1 = CH$_3$, R^2 = X = H): from 2-benzylphthalimidine and CH_3Li; 98%; ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3 H, $ArCH_3$), 5.05 (s, 2 H, $>NCH_2Ar$).

1-Ethyl-2-methylisoindole[13] (2, R = CH$_3$, R^1 = C$_2$H$_5$, R^2 = X = H): from 2-methylphthalimidine and C_2H_5Li; 95%; oil; ^{1}H NMR ($CDCl_3$) δ 1.12 (t, 3 H, J = 7 Hz, $-CH_2C\mathbf{H}_3$), 2.83 (q, 2 H, J = 7 Hz, $-C\mathbf{H}_2CH_3$), 3.53 (s, 3 H, $>NCH_3$).

2-Ethyl-1-methylisoindole (2, R = C$_2$H$_5$, R^1 = CH$_3$, R^2 = X = H): from 2-ethylphthalimidine and CH_3Li; 95%; oil.

5,6-Dichloro-1,2-dimethylisoindole (25): from 5,6-dichloro-2-methylphthalimidine (24) and CH_3Li; crude product, containing unreacted phthalimidine, was used directly in cycloaddition with benzyne.

6-Amino-1,2-dimethylisoindole (2, R = R^1 = CH$_3$, R^2 = H, X = 6-NH$_2$): from 6-amino-2-methylphthalimidine[33] and CH_3Li; crude yield 53%; mp 76–87 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (3 H, s, $ArCH_3$), 3.30 (2 H, broad, exchangeable, $-NH_2$), 3.57 (3 H, s, NCH_3).

Isoindoles (Tables III–V). 2-Benzyl-1,3-dimethylisoindole: from 2-benzyl-3-methylphthalimidine and CH_3Li; 97%; solid; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 6 H, CH_3), 5.33 (s, 2 H, benzylic).

2-Ethyl-1,3-dimethylisoindole: from 2-ethyl-3-methylphthalimidine and CH_3Li; 94%; oil; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7 Hz, 3 H, $-CH_2C\mathbf{H}_3$), 2.47 (s, 6 H, $ArCH_3$), 4.03 (q, J = 7 Hz, 2 H, $-C\mathbf{H}_2CH_3$).

2-(Cyclopropylmethyl)-1,3-dimethylisoindole: from 2-(cyclopropylmethyl)-3-methylphthalimidine and CH_3Li; 98%; oil; ^{1}H NMR ($CDCl_3$) δ 0.47 (m, 5 H, cyclopropyl), 2.53 (s, 6 H, $ArCH_3$), 4.00 (m, 2 H, NCH_2).

2-*tert*-Butyl-1,3-dimethylisoindole: from 2-*tert*-butyl-3-methylphthalimidine and CH_3Li; 100%; yellow solid; ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 9 H, *t*-Bu), 2.70 (s, 6 H, $ArCH_3$).

1,3-Dimethyl-2-phenethylisoindole: from 3-methyl-2-phenethylphthalimidine and CH_3Li; 100%; oil; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 6 H, $ArCH_3$), 2.97 (t, J = 6 Hz, 2 H, $-CH_2C_6H_5$), 4.30 (t, J = 6 Hz, 2 H, NCH_2).

1,3-Dimethyl-2-(4-methoxybenzyl)isoindole: from 2-(4-methoxybenzyl)-3-methylphthalimidine and CH_3Li; oil; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 6 H, $ArCH_3$), 3.57 (s, 3 H, OCH_3), 5.10 (s, 2 H, benzylic).

1,3-Dimethyl-2-[3-(tetrahydropyranyloxy)propyl]isoindole: oil; ^{1}H NMR ($CDCl_3$) δ 1.0–2.3 (overlapping signals, 8 H, THP ring and $-NCH_2C\mathbf{H}_2CH_2$–), 2.47 (s, 6 H, $ArCH_3$), 3.4–4.6 (overlapping signals, 7 H, NCH_2–, OCH, $-OCH_2$–).

1,3-Dimethyl-2-propylisoindole: from 3-methyl-2-propylphthalimidine and CH_3Li; 98%; oil; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 6 Hz, 3 H, $-CH_2CH_3$), 1.50, (m, 2 H, $-C\mathbf{H}_2CH_3$), 2.47 (s, 6 H, $ArCH_3$), 4.0 (t, J = 6 Hz, 2 H, NCH_2).

2-Butyl-1,3-dimethylisoindole: from 2-butyl-3-methylphthalimidine and CH_3Li; oil; ^{1}H NMR ($CDCl_3$) δ 0.9–1.9 (overlapping signals, 7 H, C_3H_7), 2.50 (s, 6 H, $ArCH_3$), 4.10 (t, J = 6 Hz, 2 H, NCH_2–).

2-Allyl-1,3-dimethylisoindole: from 2-allyl-3-methylphthalimidine and CH_3Li; 98%; oily solid; ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 6 H, $ArCH_3$), 4.43–5.30 (overlapping signals, 5 H, allyl).

2,3-Dimethyl-1-ethylisoindole: from 2,3-dimethylphthalimidine and C_2H_5Li; oil; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3 H, $-CH_2C\mathbf{H}_3$), 2.48 (s, 3 H, $ArCH_3$) 2.97 (q, J = 7 Hz, 2 H, $ArCH_2$–), 3.67 (s, 3 H, NCH_3).

1-Butyl-2,3-dimethylisoindole: from 2,3-dimethylphthalimidine and *n*-C_4H_9Li; oil; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6 Hz, 3 H, $-CH_2C\mathbf{H}_3$), 1.40 (m, 2 H, $-C\mathbf{H}_2C\mathbf{H}_2CH_2CH_3$), 2.43 (s, 3 H, $ArCH_3$), 3.0 (t, J = 6 Hz, 2 H, $ArCH_2$–), 3.63 (s, 3 H, NCH_3).

2,3-Dimethyl-1-vinylisoindole: from 2,3-dimethylphthalimidine and vinyllithium; oil; ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 3 H, $ArCH_3$), 3.13 (s, 3 H, NCH_3), 4.5–5.25 (overlapping signals, 3 H, vinyl).

2-Benzyl-1,3-dipropylisoindole: from 2-benzyl-3-propylphthalimidine and *n*-C_3H_7Li; oil; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6 Hz, 6 H, aliphatic CH_3), 1.63 (m, 4 H, $-C\mathbf{H}_2CH_3$), 2.87 (t, J = 7 Hz, $ArCH_2$–), 5.37 (s, 2 H, NCH_2–).

2-Cyclopropyl-1,3-dimethylisoindole (2, R = $-\overline{CHCH_2}\overline{CH_2}$, R^1 = R^2 = CH$_3$, X = H): from 2-cyclopropylphthalimidine and CH_3Li; 99%; oily dark yellow solid; ^{1}H NMR ($CDCl_3$) δ 1.08 (m, 5 H, cyclopropyl), 2.57 (s, 6 H, CCH_3).

Preparation of 9,10-Dihydroanthracen-9,10-imines. Specific examples of each method of synthesis are described below. All products were prepared using these procedures and the isoindoles and benzyne precursors as noted in the tables. The numbers associated with these products refer to the table containing the specific derivative.

Method F. 2,3-Difluoro-11-methyl-9,10-dihydroanthracen-9,10-imine. (Ib). To 30 mL of a 2.2 M solution of *n*-BuLi in hexane under nitrogen and cooled to −70 °C was added dropwise a solution of 1-bromo-2,4,5-trifluorobenzene[34] (13.7 g, 65 mmol) in Et_2O (10 mL), followed by a solution of 2-methylisoindole (8.5 g, 65 mmol) in Et_2O (125 mL). The mixture was stirred at room temperature for 16 h and then partitioned between Et_2O and H_2O. The Et_2O solution was dried and evaporated to a dark oil that was triturated with hexane. The insoluble material was filtered. Evaporation of the filtrate left a dark yellow oil that was dissolved in Et_2O and added to a solution of maleic acid (5 g) in EtOH (20 mL). Removal of solvent left a dark oil that was triturated with H_2O (3 × 200 mL). The aqueous solution was neutralized with Na_2CO_3 and extracted with benzene. Evaporation of the washed and dried extract gave the crude product as a dark yellow oil. This oil was converted into the hydrogen oxalate salt in EtOH/Et_2O. Recrystallization from EtOH gave 1.8 g (9%), mp 168–169 °C dec.

5,10-Dihydro-5,10,11-trimethylbenzo[*g*]quinolin-5,10-imine (Vd). Dry Et_2O (30 mL) and 2.2 M *n*-BuLi in hexane (19.5 mL, 0.0429 mol) were added to a dry flask under N_2 and cooled to −70 °C. To this solution was added dropwise a solution of 3-bromo-2-chloropyridine (8.15 g, 0.042 mol) in Et_2O (40 mL) followed by a solution of 1,2,3-trimethylisoindole (6.15 g, 0.0386 mol) in Et_2O (60 mL). After the addition, the mixture was warmed rapidly to 20 °C and allowed to stir overnight at room temperature. The cooled reaction mixture was added to H_2O (200 mL), and the Et_2O layer was separated, filtered, washed, and dried ($MgSO_4$). Evaporation under reduced pressure gave a dark oily residue that was triturated with hexane and filtered from the insoluble material. Evaporation of the filtrate under reduced pressure yielded 3.1 g of crude product. This residue was chromatographed on alumina (activity I, 200 g), and the product was eluted with

1:1 MeOH/$CHCl_3$. Evaporation of the solvent gave a 6% yield of Vd. An analytical sample was prepared by crystallization of Vd as the oxalate salt from 95% EtOH/Et_2O. Recrystallization from acetone gave off-white crystals, mp 178–179 °C.

Method G. 11-Cyclopropyl-9,10-dimethyl-9,10-dihydroanthracen-9,10-imine (IIIee). Magnesium turnings (0.7 g, 29 mmol), a few drops of 2-bromofluorobenzene, and dry THF (10 mL) were stirred and heated to reflux under nitrogen. The Grignard reaction was initiated, and a solution of 2-bromofluorobenzene (4.8 g, 0.0274 mol) and 2-cyclopropyl-1,3-dimethylisoindole (4.6 g, 0.0249 mol) in dry THF (40 mL) was added dropwise. After the resulting mixture was stirred at reflux for 1 h, all of the Mg was consumed. The reaction mixture was cooled and treated with H_2O (20 mL). Filtration and evaporation of the filtrate gave an oily residue which was taken up in C_6H_6/Et_2O (2:1). The washed and dried extract was evaporated to obtain a dark oil that was triturated with hexane. The insoluble material was filtered and the filtrate was evaporated to give an oily yellow solid that was sublimed at 80 °C (0.1 mm): 3.1 g (45%); white crystals; mp 98–101 °C. A sample for analysis was prepared by conversion into the hydrogen oxalate salt in acetone, mp 165 °C dec.

9,11-Dimethyl-9,10-dihydroanthracen-9,10-imine (IIa). To a warm mixture of magnesium turnings (2.0 g, 0.082 g-atm) and crude 1,2-dimethylisoindole (12.53 g, 0.085 mol) in THF (50 mL) was added, in portions, a solution of *o*-bromofluorobenzene (13 g, 0.074 mol) in THF (50 mL). After initiation of the Grignard reaction and complete addition of bromofluorobenzene solution, the mixture was refluxed for 2 h. The reaction mixture was cooled to 20–25 °C and poured into saturated NH_4Cl solution (150 mL, 1 mL of concentrated NH_4OH added). The layers were separated, and the aqueous phase was extracted with THF (3 × 100 mL). The combined organic extracts were dried (K_2CO_3) and evaporated to a dark red-black oil, 20.3 g. A solution of the oil in IPA (250 mL) was mixed with a solution of oxalic acid (9.0 g) in IPA (250 mL). The resulting blue-green solution was diluted to 1000 mL with EtOAc and placed in a freezer overnight. The mixture was concentrated (30 °C) to half-volume, and the pale blue solid was filtered and dried: 4.38 g (16%); mp 134–136 °C. Recrystallization from acetone and subsequent treatment with Darco produced a white powder, mp 139–140 °C.

Method H. 1,2,3-Trimethyl-9,10-dihydroanthracen-9,10-imine (IIIa). A stirred solution of 2,3-dimethylphthalimidine (1.5 g, 0.0093 mol) in Et_2O (100 mL) was treated dropwise with 1.8 M CH_3Li in Et_2O (7 mL). After 14 h, H_2O (75 mL) and Et_2O (75 mL) were added and the Et_2O solution was separated and washed with H_2O (2 × 50 mL). The Et_2O solution was dried over anhydrous $MgSO_4$ and filtered and the filtrate was evaporated. The residue (1,2,3-trimethylisoindole) was dissolved in THF (20 mL) containing chlorobenzene (0.74 g, 0.0065 mol). To this solution at room temperature was added dropwise a solution of 2.1 M *n*-C_4H_9Li in hexane (3.2 mL). After being heated under reflux for 1 h, the reaction mixture was poured into aqueous NH_4Cl solution and extracted with Et_2O (3 × 100 mL). The combined extracts were dried over anhydrous $MgSO_4$ and filtered and the filtrate was evaporated. The concentrate was extracted with hot hexane (150 mL). The extract was cooled and filtered and the filtrate was evaporated. The residue (1.5 g) was chromatographed on silica gel. Elution with $CHCl_3$ gave crystalline product (0.8 g, 52%). This product was dissolved in EtOAc and added to fumaric acid (0.59 g) in hot IPA. Cooling and filtration gave 1.2 g (45%) of fumarate, mp 179–181 °C.

12-Chloro-1,9,10,11-tetramethyl-9,10-dihydroanthracen-9,10-imine (IIIn). A THF (25 mL) solution of 1,2,3-trimethylisoindole was prepared as previously described from 2,3-dimethylphthalimidine (6.0 g, 0.037 mol) and 1.7 M CH_3Li in Et_2O (30 mL). A solution of 2,6-dichlorotoluene (6.0 g, 0.037 mol) in THF (5 mL) was added followed by dropwise addition of a solution prepared by adding 1.7 M CH_3Li in Et_2O (23 mL) to 2,2,6,6-tetramethylpiperidine (5.3 g, 0.037 mol) in THF (10 mL). The reaction mixture was heated under reflux for 6 h and then poured into aqueous NH_4Cl solution. The aqueous mixture was extracted with Et_2O (3 × 100 mL), the combined extracts were dried over anhydrous $MgSO_4$ and filtered, and the filtrate was evaporated. The residue was extracted with hot hexane (350 mL). The extract was cooled and filtered and the filtrate was evaporated. The residue was chromatographed on silica gel. Elution with $CHCl_3$ gave 5 g of crude product which was dissolved in EtOAc and added to a solution of fumaric acid (3.0 g) in hot IPA (150 mL). The solvent was evaporated and the residue was triturated with Et_2O to yield 6.3 g of solid. Recrystallization from acetone gave the fumarate: 4.8 g (18%); mp 196–199 °C.

9,10-Imino-9,10,11-trimethyl-9,10-dihydroanthracene-2-carboxaldehyde (IIIo). To a stirred solution of 2,2,6,6-tetramethylpiperidine (5.64 g, 0.040 mol) in dry THF (25 mL) under nitrogen was added dropwise 23.4 mL of a 1.8 M solution of CH_3Li in Et_2O. The resulting solution was added dropwise to a stirred solution of 1,2,3-trimethylisoindole (6.2 g, 0.039 mol) and the diethyl acetal of 4-chlorobenzaldehyde[35] (8.58 g, 0.040 mol) in dry THF (40 mL) at room temperature and under nitrogen. The mixture was stirred at reflux for 16 h, cooled, and poured into saturated NH_4Cl (150 mL) containing concentrated NH_4OH (2 mL). The resulting mixture was extracted with Et_2O. Removal of solvent left a dark oil that was triturated with hexane (3 × 200 mL). After standing, the insoluble material was removed by filtration and the filtrate was passed through a column of silica gel (300 g). Elution with 2% $CH_3OH/CHCl_3$ gave the crude diethyl acetal of the product as a yellow oil. The oil was dissolved in a solution of oxalic acid (0.8 g) in acetone (25 mL). Water (1.5 mL) was added and the solution was heated to boiling to effect hydrolysis of the acetal. Dilution with Et_2O precipitated the hydrogen oxalate hydrate salt, and recrystallization from acetone gave 2.2 g (15%), mp 120 °C.

2-Cyano-9,10,11-trimethyl-9,10-dihydroanthracen-9,10-imine (IIItt). Step A. 9,10-Imino-9,10,11-trimethyl-9,10-dihydroanthracene-2-carboxaldehyde Oxime (IIIss). To a stirred solution of the hydrogen oxalate hydrate salt of 9,10-imino-9,10,11-trimethyl-9,10-dihydroanthracene-2-carboxaldehyde (IIIo; 2.5 g, 6.72 mmol) in 95% EtOH (50 mL) was added a solution of hydroxylamine hydrochloride (0.6 g, 8.4 mmol) in H_2O (10 mL) followed by a solution of NaOH (0.8 g, 20 mmol) in H_2O (12 mL). The mixture was stirred at room temperature for 3 h and poured onto ice and H_2O (300 mL). After adjusting the pH to weakly basic, the off-white precipitate was collected and dried: 1.25 g (69%); mp 108–130 °C.

Step B. 2-Cyano-9,10,11-trimethyl-9,10-dihydroanthracen-9,10-imine (IIItt). Trifluoroacetic anhydride (1.6 g, 7 mmol) was added dropwise to a stirred and ice-cooled solution of the oxime from step A (1.8 g, 6.5 mmol) in pyridine (7 mL). After an overnight period at room temperature, the solution was evaporated to dryness and the residue was partitioned between Et_2O and H_2O. The aqueous phase was separated, made basic with aqueous NaOH, and reextracted with Et_2O. The combined Et_2O extracts were washed (aqueous NaOH, H_2O) and dried (Na_2SO_4). Removal of solvent left 1.7 g (quantitative) of yellow glass. This was dissolved in a solution of oxalic acid (0.6 g) in acetone (12 mL). The solid that separated (1.15 g), mp 70–100 °C dec, was recrystallized twice from acetone to yield the hydrogen oxalate sesquihydrate: 0.85 g; mp 100–115 °C dec.

9,10-Dimethyl-9,10-dihydroanthracen-9,10-imine (IIImm). 11-Benzyl-9,10-dimethyl-9,10-dihydroanthracen-9,10-imine (IIIv; 2.3 g, 7.4 mmol) was dissolved in glacial HOAc (25 mL) and hydrogenated at 1 atm and 25 °C over 5% Pd/C (200 mg) until uptake ceased. The mixture was filtered and evaporated. The residual oily solid was dissolved in C_6H_6/Et_2O (1:1) and extracted with 0.5 M citric acid. The aqueous acid phase was separated, made basic with aqueous NaOH, and extracted with Et_2O. Evaporation of the washed and dried extract left an oily solid that was sublimed at 70 °C (0.05 mm) to yield white crystals: 350 mg (21%); mp 100–105 °C.

1,4,9,10-Tetramethyl-9,10-dihydroanthracen-9,10-imine (IIInn). 11-Benzyl-1,4,9,10-tetramethyl-9,10-dihydroanthracen-9,10-imine (IIIi; 8.3 g, 24.1 mmol) was dissolved in glacial HOAc (100 mL) and hydrogenated at 1 atm and 25 °C over 10% Pd/C (1.0 g) until uptake ceased. The mixture was filtered and evaporated to yield white crystalline solid: 5.85 g (97%); mp 113–116 °C. A sample for analysis was obtained by sublimation at 85 °C (0.1 mm), mp 114–116 °C.

11-Ethyl-1,4,9,10-tetramethyl-9,10-dihydroanthracen-9,10-imine (IIIoo). To a stirred solution of 1,4,9,10-tetramethyl-9,10-dihydroanthracen-9,10-imine (1.0 g, 4 mmol) and acetaldehyde (1.8 g, 40 mmol) in H_3CCN (20 mL) was added $NaCNBH_3$ (0.75 g, 12 mmol). Glacial HOAc (0.5 mL) was added in portions over 10 min. The mixture was stirred at room temperature for 2 h. Another 0.5 mL of glacial HOAc was added, and stirring was continued overnight. The bulk of the solvent was evaporated, and the residue was partitioned between 5% aqueous NaOH and Et_2O. The Et_2O extract was washed with H_2O and saturated NaCl and dried (Na_2SO_4). Removal of solvent left 0.65 g of the oily base. This was dissolved in a solution of oxalic acid (0.2 g) in EtOH (4 mL). The solid that separated (0.45 g), mp 208–212 °C dec, was recrystallized twice from EtOH to yield the purified hydrogen oxalate, mp 218–220 °C dec.

11-[3-(Dimethylamino)propyl]-9,10-dimethyl-9,10-dihydroanthracen-9,10-imine (IIIpp). *N*-Bromosuccinimide (0.95 g, 5.35 mmol) was added in portions to a stirred mixture of 11-(3-hydroxypropyl)-9,10-dimethyl-9,10-dihydroanthracen-9,10-imine (IIIdd; 1.45 g, 5.2 mmol), triphenylphosphine (1.4 g, 5.35 mmol), and dry C_6H_6 (17 mL) at room temperature and under nitrogen. Stirring was continued for 6 h as a fine white precipitate slowly separated. After being cooled in an ice bath, the mixture was saturated with dimethylamine

and stirring was continued overnight at room temperature. Solvent was evaporated and the residue was triturated with Et_2O. The precipitate of succinimide was filtered, and the filtrate was evaporated. The residue was triturated with boiling hexane, and this mixture was chilled. After filtration of the precipitate of triphenylphosphine oxide, evaporation of the hexane filtrate left 1.5 g of oil. Short-path distillation at 95–105 °C (0.2 mm) yielded 0.9 g (56%) of viscous yellow oil. This was dissolved in EtOH (5 mL)/Et_2O (10 mL), treated with 6.9 N HCl (EtOH) (0.45 mL), and diluted with Et_2O. Filtration gave 0.78 g of solid that was recrystallized from cold EtOH/Et_2O to yield 0.68 g of the hygroscopic white crystalline hydrochloride, mp 172–174 °C.

In a previous conversion of the alcohol IIIdd to the bromide by the above procedure, the reaction was worked up after 6 h by filtration, evaporation of the filtrate, and trituration of the residue with hexane. After filtration of the triphenylphosphine oxide, evaporation of the hexane filtrate left an oily solid that was triturated with $CHCl_3$ to yield a white crystalline solid, mp 180–185 °C dec. Recrystallization from water gave the quaternary bromide IIIrr hydrate, mp 182–183 °C dec.

***N*-[3-(Dimethylamino)propyl]-9,10-dimethyl-10-ethoxy-9,10-dihydroanthracen-9-amine (64).** A solution of 11-[3-(dimethylamino)propyl]-9,10-dimethyl-9,10-dihydroanthracen-9,10-imine (IIIpp; 800 mg, 2.6 mmol) in acetone (10 mL) was treated with oxalic acid (450 mg, 5 mmol) in 95% EtOH (1 mL). The oxalate that crystallized (930 mg, mp 128–130 °C dec) was recrystallized from hot EtOH (10 mL). The solid that separated (750 mg, mp ~185 °C dec) failed to redissolve in hot EtOH and was converted to the base by partitioning the solid between 5% aqueous NaOH and hexane. Evaporation of the washed and dried extract left the oily base that was purified by short-path distillation (95 °C, 0.1 mm) to yield 140 mg of **64** as a colorless, viscous oil: ^1H NMR ($CDCl_3$) δ 1.1 (t, J = 7 Hz, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3), 2.17 (s, 6 H, $-N(CH_3)_2$), 2.83 (q, J = 7 Hz, 2 H, $-OCH_2-$); IR (neat) λ 3250 cm^{-1} (NH). Anal. Calcd ($C_{23}H_{32}N_2O$): C, 78.36; H, 9.15; N, 7.95. Found: C, 78.21; H, 9.10; N, 7.84.

9,10-Dimethoxy-9,10-dimethyl-9,10-dihydroanthracene (66). A solution of 11-*tert*-butyl-9,10-dimethyl-9,10-dihydroanthracen-9,10-imine (IIIaa; 6.6 g, 23.75 mmol) in acetone (50 mL) was treated with oxalic acid (2.38 g, 26.4 mmol) in acetone (15 mL). The oxalate that crystallized (7.8 g, mp >260 °C) was recrystallized from hot MeOH (90 mL). The white crystalline solid that separated was collected to obtain **66**: 4.18 g; mp 190 °C; ^1H NMR ($CDCl_3$) δ 1.63 and 1.70 (two s, 6 H, 9- and 10-CH_3), 2.8 (s, 6 H, 9- and 10-OCH_3); MS *m/e* 268 (M^+), 253 ($M - CH_3$), 237 ($M - OCH_3$), 207 ($M - (OCH_3)_2$). Anal. Calcd ($C_{18}H_{20}O_2$): C, 80.56; H, 7.51. Found: C, 79.52, 79.36; H, 7.67, 7.45.

Acknowledgment. We would like to express our appreciation to Mr. W. Riley McGaughran for certain ^1H NMR spectra, to Mr. Robert E. Rhodes for mass spectral data, to Mr. Albert Augenblick for GLC data, and to Dr. W. C. Randall for combustion analyses. We also would like to thank Dr. Edward L. Engelhardt for many helpful discussions and his generous support of this work.

Registry No.—Ia, 69190-19-8; Ib, 69190-21-2; Ic (1-CH_3, 6-F), 69190-23-4; Ic (1-CH_3, 7-F), 69190-25-6; Id (2-CF_3, 6-F), 69190-27-8; Id (2-CF_3, 7-F), 69190-29-0; Ie (2-Cl, 6-OCH_3), 69190-30-3; Ie (2-Cl, 7-OCH_3), 69190-31-4; If (2,7-di-Cl), 69190-33-6; If (2,6-di-Cl), 69190-35-8; Ig (2-Cl, 6-F), 69190-37-0; Ig (2-Cl, 7-F), 69225-06-5; Ih, 69190-38-1; Ii, 69190-40-5; Ij, 69190-42-7; Ik, 69190-44-9; Il, 69190-46-1; Im, 69190-48-3; In, 69190-50-7; Io, 69190-52-9; Ip, 69190-54-1; Iq, 69190-55-2; Ir, 62209-89-6; IIa, 69205-03-4; IIb, 69189-94-2; IIc, 58083-54-8; IId, 69189-96-4; IIe, 69189-98-6; IIf, 69190-00-7; IIg, 69205-01-2; IIh, 69190-02-9; IIIa, 69190-03-0; IIIb, 69225-08-7; IIIc, 69190-05-2; IIId, 69204-99-5; IIIe, 69190-07-4; IIIf, 69190-08-5; IIIg, 69190-10-9; IIIh (2-CH_3, 6-F), 69190-11-0; IIIh (2-CH_3, 7-F), 69190-12-1; IIIi, 69190-13-2; IIIj, 69190-14-3; IIIk, 69190-16-5; IIIl [1-$CH(CH_3)_2$], 69190-17-6; IIIl [2-$CH(CH_3)_2$], 69189-63-5; IIIm, 69189-65-7; IIIn, 69189-67-9; IIIo, 69189-69-1; IIIp, 69205-05-6; IIIq, 69189-71-5; IIIr, 69189-73-7; IIIs, 69189-75-9; IIIt, 69225-13-4; IIIu, 69189-77-1; IIIv, 58083-49-1; IIIw, 69189-78-2; IIIx, 69189-79-3; IIIy, 69189-81-7; IIIz, 69189-83-9; IIIaa, 69189-84-0; IIIbb, 69189-86-2; IIIcc, 69189-87-3; IIIdd, 58083-64-0; IIIee, 69189-88-4; IIIff, 69225-12-3; IIIgg, 69225-10-1; IIIhh, 69189-89-5; IIIii, 69189-91-9; IIIjj, 69189-92-0; IIIkk, 69189-43-1; IIIll, 69189-44-2; IIImm, 58083-50-4; IIInn, 58083-47-9; IIIoo, 69189-45-3; IIIpp, 58083-66-2; IIIqq, 69189-46-4; IIIrr, 69189-47-5; IIIss, 69189-48-6; IIItt, 69189-50-0; IVa, 69189-52-2; IVb, 69189-53-3; IVc, 69225-15-6; IVd, 69189-55-5; IVe, 69189-56-6; Va, 69189-58-8; Vb, 69189-60-2; Vc, 69189-61-3; Vd, 69189-62-4; **2** (R = R^1 = R^2 = CH_3, X = H), 58083-43-5; **2** (R = CH_3, R^1 = R^2 = H, X = 5-Br), 69189-32-8; **2** (R = CH_3, R^1 = R^2 = H, X = 5-Cl), 69189-33-9; **2** (R = CH_3, R^1 = R^2 = C_2H_5, X = H), 69189-34-0; **2** (R = R^1 = R^2 = CH_3, X = 5-Br), 69189-35-1; **2** (R = CH_3, R^1 = R^2 = X = H), 33804-84-1; **2** (R = R^1 = CH_3, R^2 = H, X = 6-Cl), 69189-36-2; **2** (R = $CH_2C_6H_5$, R^1 = CH_3, R^2 = X = H), 58083-61-7; **2** (R = CH_3, R^1 = C_2H_5, R^2 = X = H), 58083-60-6; **2** (R = C_2H_5, R^1 = CH_3, R^2 = X = H), 58083-62-8; **2** (R = R^1 = CH_3, R^2 = H, X = 6-NH_2), 69189-37-3; **7** (R = $CH(CH_2)_2$, R^2 = CH_3), 58083-37-7; **7** (R = R^2 = Me), 58083-35-5; **7** (R = $CH_2C_6H_5$, R^2 = CH_3), 1726-16-5; **7** (R = $CH_2CH(CH_2)_2$, R^2 = CH_3), 58083-42-4; **7** (R = Bu-*t*, R^2 = CH_3), 69189-38-4; **7** (R = $(CH_2)_2C_6H_5$, R^2 = CH_3), 69189-39-5; **7** (R = *p*-$OCH_3C_6H_4$, R^2 = CH_3), 69189-40-8; **7** (R = $(CH_2)_3OH$, R^2 = CH_3), 58083-38-8; **7** (R = $CH(CH_3)_2$, R^2 = CH_3), 58083-39-9; **7** (R = Bu, R^2 = CH_3), 58083-40-2; **7** (R = $CH_2CH{=}CH_3$, R^2 = CH_3), 58083-41-3; **7** (R = C_6H_4-*o*-Cl, R^2 = CH_3), 69189-41-9; **8** (R = R^3 = CH_3), 50604-01-8; **11** (X = Cl), 58083-59-3; **13** (R = $CH_2C_6H_5$, X = H), 13380-32-0; **13** (R = C_2H_5, X = H), 23967-95-5; **13** (R = CH_3, X = 6-Cl), 58141-51-8; **13** (R = CH_3, X = H), 5342-91-6; **14** (R^1 = R^2 = CH_3, X = H), 135-01-3; **14** (R^1 = R^2 = Br, X = 4-Br), 69189-19-1; **19**, 69189-20-4; **22**, 58083-58-2; **24**, 69189-21-5; **25**, 69189-22-6; **28**, 99-04-7; **29**, 118-29-6; **30**, 58083-55-9; **31**, 58083-56-0; **32**, 58083-57-1; **36**, 58083-51-5; **37**, 58083-52-6; **63**, 69189-23-7; **64**, 69189-24-8; **65**, 69189-25-9; **66**, 6321-63-7; benzylamine hydrochloride, 3287-99-8; ethylamine hydrochloride, 557-66-4; 4-methylphthalic anhydride, 4792-30-7; 4,5-dichlorophthalic anhydride, 942-06-3; methyl iodide, 74-88-4; cyclopropylamine, 765-30-0; 6-amino-2-methylphthalimidine, 69189-26-0; 2-benzyl-1,3-dimethylisoindole, 69189-27-1; 2-ethyl-1,3-dimethylisoindole, 69189-28-2; 2-(cyclopropylmethyl)-1,3-dimethylisoindole, 69189-29-3; 2-*tert*-butyl-1,3-dimethylisoindole, 69189-30-6; 1,3-dimethyl-2-phenethylisoindole, 69189-08-8; 1,3-dimethyl-2-(4-methoxybenzyl)isoindole, 69189-09-9; 1,3-dimethyl-2-[3-(tetrahydropyranyloxy)propyl]isoindole, 69189-10-2; 1,3-dimethyl-2-propylisoindole, 69189-11-3; 2-butyl-1,3-dimethylisoindole, 69189-12-4; 2-allyl-1,3-dimethylisoindole, 69189-13-5; 2,3-dimethyl-1-ethylisoindole, 69189-14-6; 1-butyl-2,3-dimethylisoindole, 69189-15-7; 2,3-dimethyl-1-vinylisoindole, 69189-16-8; 2-benzyl-1,3-dipropylisoindole, 69189-17-9; 2-cyclopropyl-1,3-dimethylisoindole, 69189-18-0; 2-cyclopropylphthalimidine, 69225-16-7; 1-bromo-2,4,5-trifluorobenzene, 327-52-6; 3-bromo-2-chloropyridine, 52200-48-3; 2-bromofluorobenzene, 1072-85-1; chlorobenzene, 108-90-7; 2,6-dichlorotoluene, 118-69-4; diethyl acetal of 4-chlorobenzaldehyde, 2403-61-4; acetonitrile, 75-05-8; methylhydrazine, 60-34-4; 4-bromo-*o*-xylene, 583-71-1; phthalic anhydride, 85-44-9; methylamine hydrochloride, 593-51-1; methyl 2-(1-bromoethyl)-benzoate, 16281-95-1.

References and Notes

(1) L. J. Kricka and J. M. Vernon, *Adv. Heterocycl. Chem.*, **16**, 87 (1974).
(2) J. D. White and M. F. Mann, *Adv. Heterocycl. Chem.*, **10**, 113 (1969).
(3) J. Bornstein, D. E. Remy, and J. E. Shields, *J. Chem. Soc., Chem. Commun.*, 1149 (1972).
(4) G. M. Priestley and R. N. Warrener, *Tetrahedron Lett.*, 4295 (1972).
(5) B. Jacques and R. G. Wallace, *J. Chem. Soc., Chem. Commun.*, 397 (1972).
(6) B. Zeeh and K. H. König, *Synthesis*, 45 (1972).
(7) M. J. Huddadin and N. C. Chelhot, *Tetrahedron Lett.*, 5185 (1973).
(8) R. Bonnett, R. F. C. Brown, and R. G. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1432 (1973).
(9) R. Kreher and K. J. Herd, *Angew. Chem., Int. Ed. Engl.*, **13**, 739 (1974).
(10) J. Bornstein, D. E. Remy, and J. E. Shields, *Tetrahedron Lett.*, 4247 (1974).
(11) K. L. Shepard, *Tetrahedron Lett.*, 3371 (1975).
(12) G. Wittig and H. Streib, *Justus Liebigs Ann. Chem.*, **584**, 1 (1953).
(13) W. Theilacker and H. Kalenda, *Justus Liebigs Ann. Chem.*, **584**, 87 (1953).
(14) W. Theilacker and W. Schmidt, *Justus Liebigs Ann. Chem.*, **597**, 95 (1955).
(15) W. Theilacker and W. Schmidt, *Justus Liebigs Ann. Chem.*, **605**, 43 (1957).
(16) S. Danishefsky, T. A. Bryson, and J. Puthenpurayil, *J. Org. Chem.*, **40**, 796 (1975).
(17) P. S. Anderson, M. E. Christy, C. D. Colton, and K. L. Shepard, *J. Org. Chem.*, **43**, 3719 (1978).
(18) H. E. Zaugg and W. B. Mentin, *Org. React.*, **14**, 52 (1965).
(19) J. H. Brewster, A. M. Fusco, L. E. Carosino, and B. G. Corman, *J. Org. Chem.*, **28**, 498 (1963).
(20) R. Kreher and J. Seubert, *Angew. Chem.*, **76**, 682 (1964).
(21) E. J. Alford and K. Schofield, *J. Chem. Soc.*, 1811 (1953).
(22) E. J. Cornish, G. E. Lee, and W. R. Wragg, *J. Pharm. Pharmacol.*, **18**, 65 (1966).
(23) R. W. Hoffman, "Dehydrobenzene and Cycloalkynes", Academic Press, New York, 1967.
(24) G. W. Gribble, R. W. Allen, P. S. Anderson, M. E. Christy, and C. D. Colton, *Tetrahedron Lett.*, 3673 (1976).

(25) In our hands, the reaction of 2-benzyl-1,3,4,7-tetramethylisoindole[26] with slightly less than 1 equiv of benzyne produced **57** in relatively good yield. This result is in contrast to that reported by Kricka and Vernon [*J. Chem. Soc., Perkin Trans. 1*, 766 (1973)], who obtained only mass spectral evidence for the presence of **57** in this Diels–Alder reaction. Their major product was a triptycene derivative resulting from further deaminative attack of benzyne on the anthracenimine.
(26) C. O. Bender and R. Bonnett, *J. Chem. Soc. C*, 3036 (1968).
(27) H. Gilman and L. A. Woods, *J. Am. Chem. Soc.*, **65**, 33 (1943).
(28) C. Graebe and A. Pietet, *Justus Liebigs Ann. Chem.*, **247**, 305 (1888).
(29) Henri de Diesback, *Helv. Chim. Acta*, **23**, 1232 (1940).
(30) J. Kollonitsch, H. E. Mertel, and V. F. Verdi, *J. Org. Chem.*, **27**, 3362 (1962).
(31) S. Gabriel and G. Giebe, *Chem. Ber.*, **29**, 2518 (1896).
(32) A. H. Lewin, J. Lipowitz, and T. Cohen, *Tetrahedron Lett.*, 1241 (1965).
(33) W. Borsch, K. Diacont, and H. Hanan, *Chem. Ber.*, **67B**, 675 (1934).
(34) G. C. Finger, F. H. Reed, D. M. Burness, D. M. Fort, and R. R. Blough, *J. Am. Chem. Soc.*, **73**, 145 (1951).
(35) T. H. Fife and L. K. Jao, *J. Org. Chem.*, **30**, 1492 (1965).
(36) H. Tanida, R. Muneyuki, and T. Tsumi, *Bull. Chem. Soc. Jpn.*, **37**, 40 (1964).
(37) R. Muneyuki and H. Tanida, *J. Org. Chem.*, **31**, 1988 (1966).
(38) J. F. Bunnett and C. E. Moyer, Jr., *J. Am. Chem. Soc.*, **93**, 1183 (1971).
(39) P. S. Anderson, M. E. Christy, E. L. Englehardt, G. F. Lundell, and G. S. Ponticello, *J. Heterocycl. Chem.*, **14**, 213 (1977).
(40) G. Wittig and W. Merkle, *Chem. Ber.*, **75**, 1491 (1942).
(41) G. Wittig, E. Knauss, and K. Niethammer, *Justus Liebigs Ann. Chem.*, **630**, 10 (1960), report a 54% yield using method G, mp 159–160.5 °C.
(42) L. M. Yagupolskii and M. S. Marenets, *Zh. Obshch. Khim.*, **29**, 278 (1959).
(43) J. R. Geigy, A-G., Swiss Patent 245 679, Aug 1, 1947; *Chem Abstr.*, **43**, 5802b (1949).
(44) J. B. Cohen and H. S. Roper, *J. Chem. Soc.*, 1269 (1904).
(45) B. B. Elsner and H. E. Strauss, *J. Chem. Soc.*, 583 (1957).

Synthesis of 8-Phenyl-1,2,3,4-tetrahydroisoquinolines

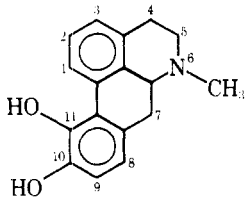
Charles R. Ellefson

Searle Laboratories, Chicago, Illinois 60680

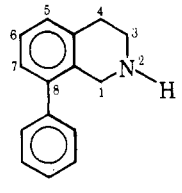
Received December 5, 1978

A general synthesis for the preparation of previously unreported 8-phenyl-1,2,3,4-tetrahydroisoquinolines is described. The directing properties of aryloxazolines were used for an unambiguous route to appropriate 1,2,3-trisubstituted benzenes (2,6-disubstituted aryloxazolines). Hydrolysis of the oxazolines produced 8-phenylisocoumarins, which were readily converted into the 8-phenylisoquinoline derivatives.

Although many methods[1] are available for the synthesis of isoquinolines and tetrahydroisoquinolines, none are satisfactory for the synthesis of 8-phenylisoquinoline derivatives. 8-Phenyl-1,2,3,4-tetrahydroisoquinoline is interesting because it possesses the basic structural features of the apomorphine ring system without the C-7 methylene bridge which holds the two aromatic rings in a nearly planar configuration. Only one synthesis of 8-phenylisoquinoline has appeared,[2] and no reports of its tetrahydro derivative have been described. Attempts to produce 8-phenylisoquinoline by the Pomeranz–



apomorphine



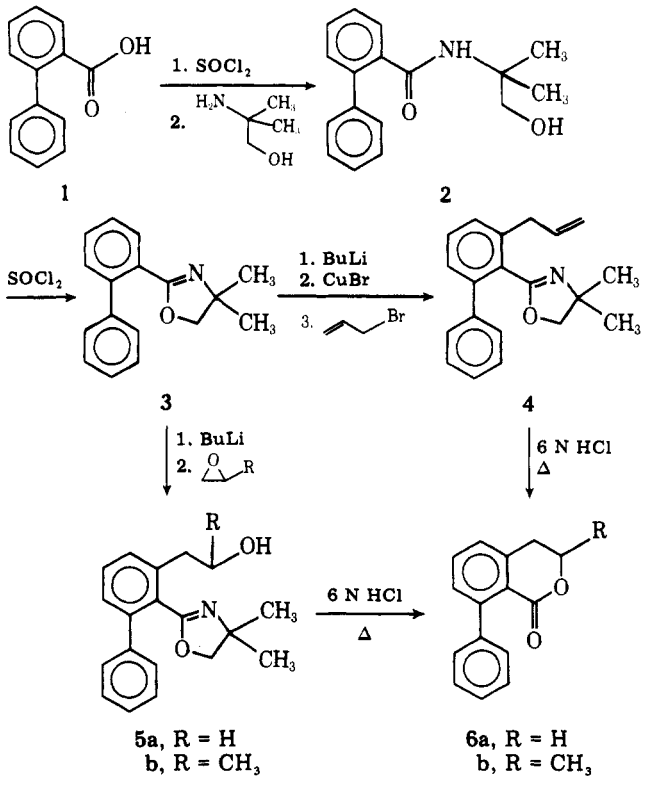
8-phenyltetrahydroisoquinoline

Fritsch reaction failed,[2] and the Bischler–Napieralski reaction gave 6- or 7-phenyl isomers but no 8-phenylisoquinoline derivatives.[3]

This report describes a general synthesis that has been successfully utilized for the preparation of 8-phenyl-1,2,3,4-tetrahydroisoquinoline and a 3-alkyl derivative, 3-methyl-8-phenyl-1,2,3,4-tetrahydroisoquinoline. Using aryloxazoline chemistry developed by Meyers[4] and Gschwend[5] et al., an unambiguous route (Scheme I) to an appropriate 1,2,3-trisubstituted benzene has been used to prepare 8-phenylisocoumarins, the key intermediates for further elaboration to tetrahydroisoquinolines.

Biphenyl-2-carboxylic acid (1) was converted to the acid chloride and reacted with 2-amino-2-methylpropanol, producing the hydroxyamide **2**, which on treatment with thionyl chloride cyclized to the aryloxazoline **3**.[6] The directing properties of the oxazoline[4,5] were used to functionalize the ortho position of the benzene ring. When **3** was metalated with *n*-

Scheme I



butyllithium followed by reaction with allyl bromide, a mixture was produced from which **4** was obtained in only 19% yield along with recovered **3** (39%) and 34% of product[7] arising from subsequent alkylation at the activated methylene of **4**. This problem was resolved when the lithiated intermediate was first converted to the organocopper reagent with cuprous bromide; alkylation with allyl bromide then gave a 71% yield of **4** after LC. Using this methodology it should be possible to

0022-3263/79/1944-1533$01.00/0