Ring Closure of Enaminones via Intramolecular Electrophilic Arylation Involving Benzyne Intermediates and Its Use in the Synthesis of γ-Lycorane and Related Compounds

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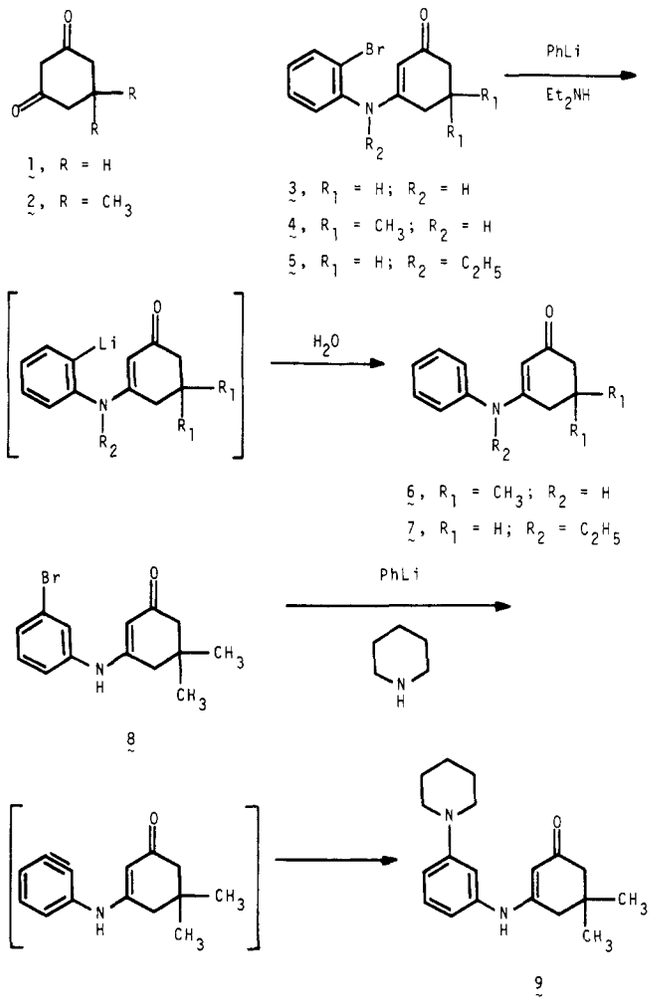
Reaction of a series of halo enaminones with lithium amide was investigated. Treatment of the *N*-phenyl enaminones with the ortho bromine atom (**4** and **5**) or the meta bromine atom (**8**) with phenyllithium and secondary amines resulted in halogen–metal exchange or benzyne formation followed by amination reaction, respectively. Upon similar treatment with lithium diethylamide, 3-(2-bromo-4,5-methylenedioxybenzyl)aminocyclohex-2-en-1-one (**17**) and its 5,5-dimethyl analogue **18** underwent intramolecular cyclization via benzyne intermediates to give the 3,4-dihydro-1(2*H*)-phenanthridone **20** and **21**, respectively. When this reaction was carried out with the *N*-ethyl derivative of **18** (i.e., **22**), the 3,4,5,6-tetrahydro-1(2*H*)-phenanthridone (**23**) was obtained. In the competing formation between five- and seven-membered rings on the benzyne cyclization using the *N*-phenethyl analogues **27** and **31** as substrates, *N*-arylation leading to the five-membered ring predominantly occurred to give the indoline derivatives **28** and **32**, respectively, rather than the azepine ring formation. The same result was obtained even if the *N*-ethyl derivative of **27** (i.e., **29**) was used, that being the simple indoline, 1-ethyl-5,6-dimethoxy-2,3-dihydroindole (**30**). In order to extend the synthetic utility of the benzyne cyclization, appropriate enaminones, 1-(2-halo-4,5-methylenedioxybenzyl)-1,2,3,3a,4,5-hexahydro-6*H*-indol-6-ones (**42a** and **42b**), were conveniently synthesized by the reaction of 3,3a,4,5-tetrahydro-6-methoxy-2*H*-indole (**35**) with respective 2-bromo- or 2-iodo-4,5-methylenedioxybenzyl chlorides. Upon treatment with lithium diethylamide, these halo enaminones were efficiently cyclized to 3,3a,4,5,6,7-hexahydro-9,10-methylenedioxypyrrolo[3,2,1-*de*]phenanthridin-1(2*H*)-one (**45**). Air oxidation of **45** provided 3,3a,4,5-tetrahydro-9,10-methylenedioxypyrrolo[3,2,1-*de*]phenanthridine-1,7(2*H*)-dione (**46**), which has been appreciated as a key intermediate to α-anhydrodihydrocaranine and γ-lycorane. On the other hand, reduction of **45** with lithium aluminum hydride afforded (±)-α-dihydrocaranone (**47**) and (±)-1-*epi*-γ-dihydrocaranine (**48**).

Enaminones,[1] in which the conjugation of the enamine system is extended by a carbonyl group, show in many cases different properties characteristic of enamines or ketones. Owing to their unique properties, they have received considerable attention in recent years in connection with chemical reactivity and versatility and also have been noted for potential physiological activity, e.g., as prodrugs.[2b] The enaminone system $N_c—C_e=C_b—C_d=O_a$ is tridentate (site a, b, and c) toward electrophiles and bidentate (site d and e) toward nucleophiles and thus opens the possibility of a wide variety of reactions which are interesting and sometimes complicated. Although chemical literature abounds with examples of alkylation and acylation on enaminones,[2] there appear to be no reports of arylation of enaminones.[3] Here we present a study of new intramolecular arylation of enaminones and the use of this reaction for the synthesis of γ-lycorane[4] and related compounds. Our procedure represents the crucial ring closure of enaminones utilizing an intramolecular reaction involving benzyne intermediates, which was hinted by a cyclization reaction via electrophilic attack by alkynes on the enaminone system.[5]

Benzyne Cyclization of N-Substituted Enaminones. An initial project focused on attempted intramolecular benzyne reaction of *N*-phenyl enaminones leading to carbazoles. Thus condensation of *o*-bromoaniline with cyclohexane-1,3-dione (**1**) or dimedone (**2**) gave **3** or **4**, respectively, the former of which was further treated with sodium hydride and ethyl iodide to give **5**. Upon treatment of **4** or **5** with phenyllithium and diethylamine, halogen–metal exchange[6] preferentially occurred to give the corresponding dehalogenated products **6** or **7**. On the other hand, when the *m*-bromo analogue **8** was treated with phenyllithium and piperidine, the amination reaction proceeded via benzyne formation to give the 3′-piperidino derivative **9**.[6] The lack of cyclization in the latter procedure may be attributed to reduction of the nucleophilicity of the α carbon (site b in the generalized formula cited above) by attachment of a benzyne substituent on nitrogen.

We then considered utilizing a series of *N*-benzyl enaminones as substrates for cyclization reactions involving benzyne intermediates because of their expected ease of cyclization.



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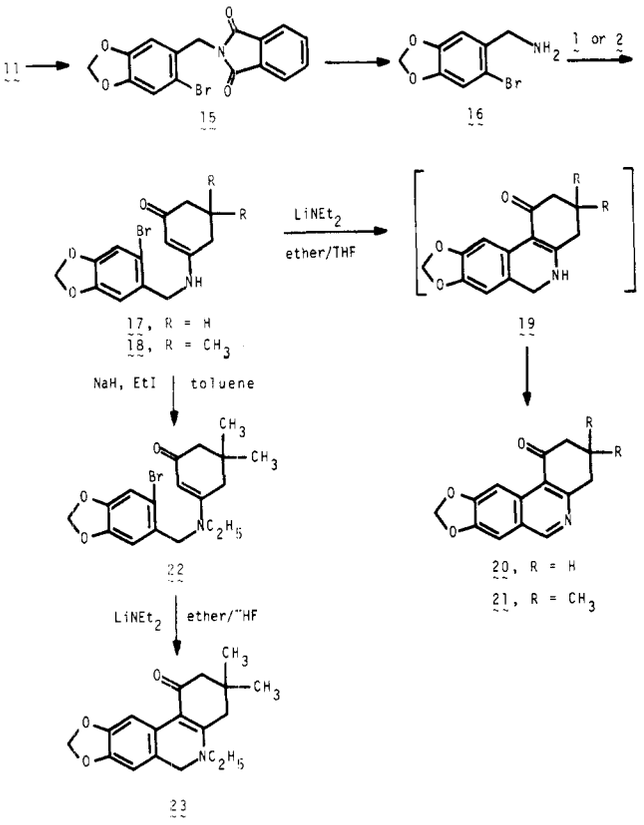
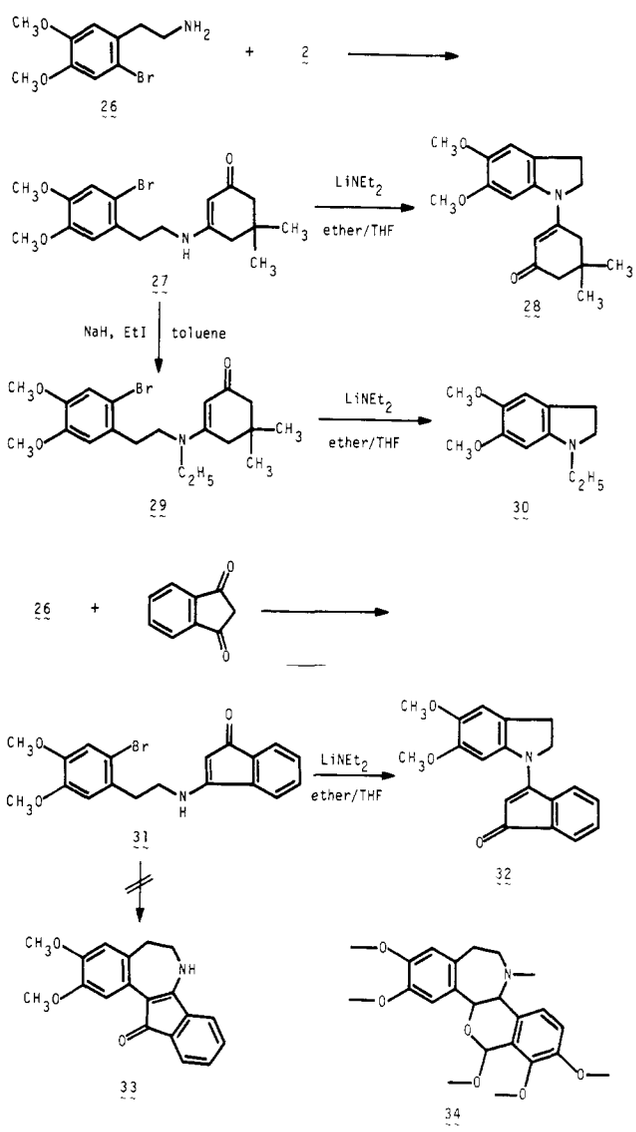
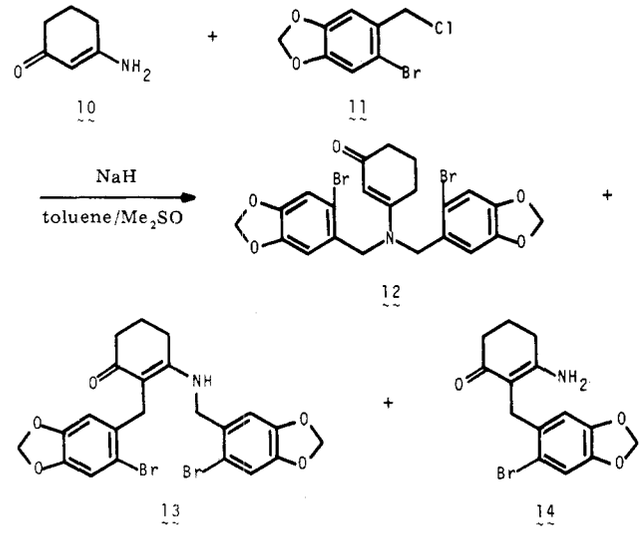
Scheme I



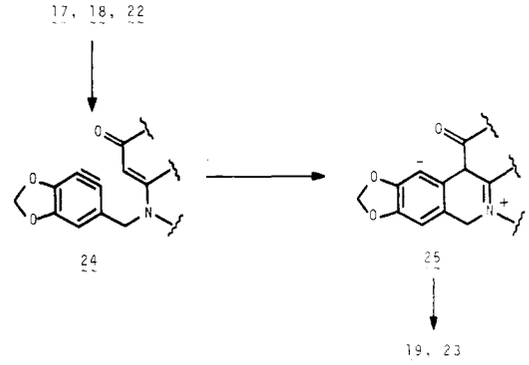
Scheme II



Our initial attempt to prepare the desired enaminone **17** using 3-aminocyclohex-2-en-1-one (**10**)[5a] as starting material was unsuccessful:[7] treatment of **10** with the benzyl chloride **11** in the presence of sodium hydride resulted in *N,N*- and *C,N*-dibenzylation to give **12** and **13**, respectively, and *C*-benzylation to give **14**. To obtain *N*-benzylated products, our attention then turned to utilizing 2-bromo-4,5-methylenedioxybenzylamine (**16**), readily available from **11** via a Gabriel synthesis, as shown in Scheme I. Condensation of **16** with **1** gave desired **17** in an excellent yield. Treatment of **17** with lithium diethylamide (LDEA) in ether–tetrahydrofuran at room temperature for 2 h gave the 3,4-dihydro-1(2*H*)-phenanthridone **20** in 24% yield. Similar treatment of **18**, prepared by condensation of **16** with **2**, gave **21** in 26% yield. These products may have arisen from initial intramolecular arylation of **17** and **18**, yielding **19** as intermediates, followed by oxidative aromatization. When the tertiary enaminone **22** was used as a substrate the cyclization reaction was accomplished more conveniently, affording **23** in 55% yield which contains the nonaromatized isoquinoline nucleus (Scheme I).

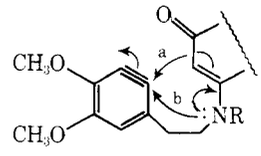


The formation of **19** (not isolated) and **23** can be best rationalized by a pathway involving benzyne (**24**) formation

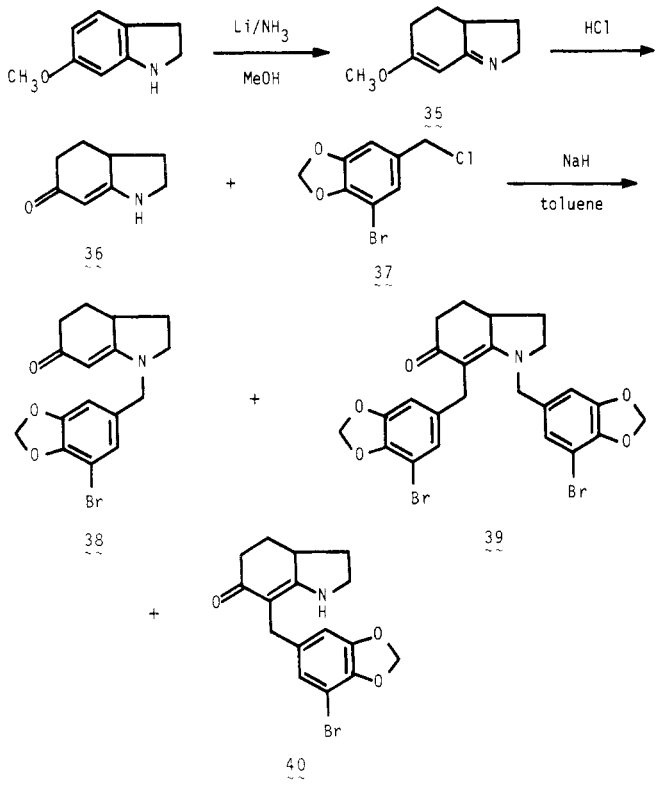


followed by cyclization to generate zwitterionic intermediate **25**, which is subsequently converted to the products via proton transfer.[8]

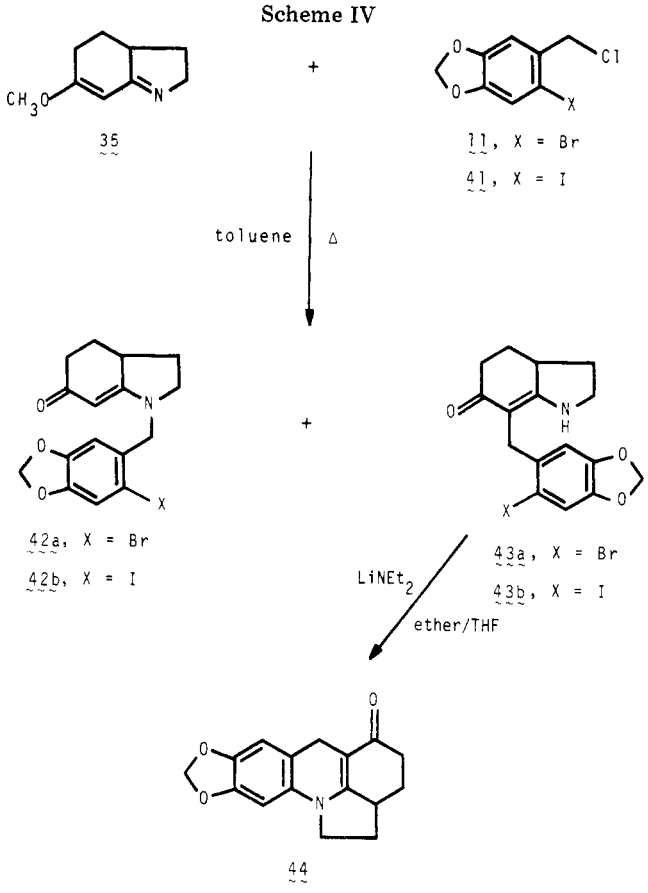
We next investigated the comparative ease of seven- (via path a) vs. five-membered ring (path b) on the competing



Scheme III



Scheme IV



cyclization involving benzyne intermediates. We therefore prepared the *N*-phenethyl enaminones **27** and **31** by reaction of the cyclic β-diketones **2** and 1,3-indanedione, respectively, with 2-bromo-4,5-dimethoxyphenethylamine (**26**) (Scheme II). Upon treatment of **27** with LDEA, *N*-arylation leading to a five-membered ring proceeded predominantly to give the indoline derivative **28** in 65% yield rather than the azepine ring formation, which is expected to arise from the *C*-arylation on the α position of the enaminone system. In anticipation of the synthesis of rheadan alkaloids **34**,[9] attempted preparation of the benzazepine **33** by similar treatment of **31** gave instead the indoline derivative **32**. The preferential formation of a five-membered ring via nucleophilic attack by the nitrogen onto the benzyne was not necessarily the expected result, since the nitrogen in the enaminones has unusually low nucleophilic character.[10] In an anticipation of obtaining the benzazepine, we then prepared the tertiary enaminone **29** from **27** as a substrate with no hydrogen on the nitrogen to replace. Treatment of **29** with LDEA resulted in *N*-arylation followed by C–N bond cleavage, affording the unexpected simple indoline **30** in 50% yield (Scheme II).

In conclusion, the individual halo enaminone behaved upon treatment with lithium reagents in distinctly different manners depending upon the chain lengths of the methylenes (0–2) linking to the nitrogens.

Synthesis of (±)-γ-Lycorane and Related Compounds. The synthetic utility of this methodology involving benzyne cyclization of enaminones was demonstrated by the synthesis of γ-lycorane and related compounds.

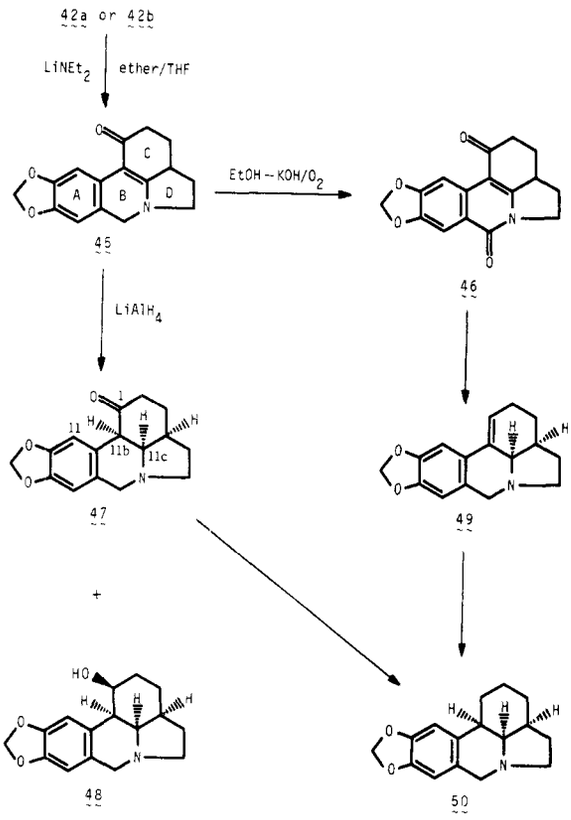
Preliminary experiments on synthesis of an appropriate enaminone required for construction of the pyrrolophenanthridine ring system were carried out. Upon treatment of 1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one (**36**),[4e] available from 6-methoxyindoline in two steps as shown in Scheme III, with 3-bromo-4,5-methylenedioxybenzyl chloride (**37**)[11] in a manner similar to that described for the alkylation of **10**, the *N*-benzyl enaminone **38** (29% yield) was obtained along the *C*,*N*-dibenzyl and *C*-benzyl enaminones (**39** and **40**) as side reaction products. To obtain the requisite halo enaminones, we then considered using the imino enol ether **35**, the precursor of **36**, as a starting material which is regarded as a structural equivalent of enaminones. Thus **35** was heated with the benzyl chloride **11** in the absence of catalyst to give the desired enaminone **42a** in an improved yield (51%) together with a very small yield (3%) of the *C*-benzylated enaminone **43a**. Similar treatment of **35** with 2-iodo-4,5-methylenedioxybenzyl chloride (**41**) yielded the corresponding *N*-benzyl enaminone **42b** in 50% yield and *C*-benzyl enaminone **43b** (3% yield) (Scheme IV).

The ring closure of the bromo enaminone **42a** was successfully carried out in a similar manner to that described for the benzyne reaction of **22** using lithium diethylamide (LDEA). The reaction proceeded to completion in 30 min at room temperature, furnishing the pyrrolophenanthridone **45** in 49% yield. In the same manner the cyclization of the iodo enaminone **42b** afforded **45** in 38% yield (Scheme V). Moreover upon treatment with LDEA at 40 °C for 24 h, the *C*-benzyl enaminone **43a** was cyclized to the pyrroloacridone **44** via *N*-arylation (Scheme IV).

The cyclization product **45** began to melt at 145 °C and completely liquefied at 252 °C, coinciding with the melting point reported for the keto lactam **46**, which has been obtained[12] from lycorine or caranine as degradation product, or synthesized[4e] by photochemical means. Accordingly, **45** was treated with oxygen in ethanol containing aqueous potassium hydroxide to give the keto lactam **46**. This material can be readily converted into γ-lycorane (**50**) via α-anhydrodihydrocaranine (**49**) according to a procedure previously reported.[4e]

On the other hand, reduction of **45** with lithium aluminum hydride via 1,4-addition stereoselectivity provided (±)-α-dihydrocaronone (**47**) and (±)-1-*epi*-γ-dihydrocaranine (**48**) in yields of 33 and 10%, respectively. In the NMR spectrum of **47** the C-11 aromatic proton (δ 6.59) was shifted markedly upfield compared to that in **45** (δ 8.92), consistent with the assigned structure: compound **47**, which lacks the conjugated enone system, is more flexible than is **45** so that the C-11 ar-

Scheme V



omatic proton in **47** must be sufficiently free from the deshielding effect due to the proximate C-1 carbonyl group. Furthermore the flexible structure for **47** was supported by the AB quartet attributed to the C-7 methylene protons occurring at δ 3.29 and 4.00 (J = 14 Hz), whereas the corresponding methylene protons in **45** appeared as a singlet at δ 4.53. That the B/C ring in **47** is cis-fused was supported by a doublet with coupling constant of 4 Hz, which is ascribed to the C-11b proton according to the decoupling experiment; irradiation of the C-11c proton (δ 2.73) caused the doublet at δ 3.47 to collapse to a singlet. The IR and NMR spectra of these products, (±)-α-dihydrocaranone (**47**) and (±)-1-*epi*-γ-dihydrocaranine (**48**), were agreement with reference spectra of authentic materials.[13] The conversion of α-dihydrocaranone (**47**) into γ-lycorane (**50**) was previously reported.[14,4a]

Experimental Section

General. All melting points were determined on a Yanagimoto micro apparatus and are uncorrected. Infrared spectra were determined on a Hitachi 215 spectrophotometer in $CHCl_3$ solutions. Nuclear magnetic resonance spectra were determined on Varian T-60 and JEOL JNM-PS-100 spectrometers in $CDCl_3$ (unless otherwise stated) with absorptions recorded in parts per million downfield from internal $(CH_3)_4Si$. Mass spectra were determined on a Hitachi RMU-7L spectrometer at 70 eV. All organic extracts were dried over $MgSO_4$ (unless otherwise stated).

3-(2-Bromoanilino)cyclohex-2-en-1-one (3). A mixture of *o*-bromoaniline (2.4 g, 0.0014 mol) and **1** (1.6 g, 0.0014 mol) was heated at 120–130 °C under nitrogen for 1 h. After cooling, the resulting yellow solid was crushed to a powder, washed with ether, and recrystallized from acetone–hexane to give **3** (3.3 g, 80%) as white needles: mp 167–168 °C; IR[15] ($CHCl_3$) 3380 (NH), 1620 (C=O), 1570 cm^{-1} (C=C); NMR[15] δ 1.86–2.92 (m, 6 H), 5.36 (s, 1 H, vinylic H), 6.46 (br s, 1 H, NH), 6.96–7.61 (m, 4 H, aromatic H).

Anal. Calcd for $C_{12}H_{12}BrNO$: C, 54.16; H, 4.54; N, 5.26. Found: C, 53.77; H, 4.47; N, 5.14.

3-(2-Bromoanilino)-5,5-dimethylcyclohex-2-en-1-one (4). A mixture of *o*-bromoaniline (2.4 g, 0.014 mol) and **2** (2.0 g, 0.014 mol) was treated under the identical condition stated above to give **4** (3.6 g, 86%) as white needles: mp 156–158 °C; IR ($CHCl_3$) 3380 (NH), 1620 (C=O), 1580 cm^{-1} (C=C); NMR δ 1.17 (s, 6 H, 2 CH_3), 2.20 and 2.36 (each s, 2 H, CH_2), 5.36 (s, 1 H, vinylic H), 5.26 (br s, 1 H, NH), 6.92–7.61 (m, 4 H, aromatic H).

Anal. Calcd for $C_{14}H_{16}BrNO$: C, 57.33; H, 5.48; N, 4.76. Found: C, 57.33; H, 5.46; N, 4.50.

3-(2-Bromo-*N*-ethylanilino)cyclohex-2-en-1-one (5). A mixture of sodium hydride [120 mg, 5.0 mmol (as 240 mg of a 50% dispersion in mineral oil)] and **3** (600 mg, 2.3 mmol) in dry toluene was heated under reflux with stirring for 1 h. After cooling to room temperature, ethyl iodide (360 mg, 2.3 mmol) was added and the reaction mixture was heated under reflux for 2 h. After cooling, the reaction mixture was poured into ice–water (~50 mL). The organic phase was separated and the aqueous phase was extracted with chloroform. The combined extracts were washed with water, dried, and evaporated at reduced pressure. Chromatography of residual oil on a silica gel column and elution with chloroform gave **5** (520 mg, 78%) as an orange–red oil: IR ($CHCl_3$) 1620 (C=O), 1550 cm^{-1} (C=C); NMR δ 1.20 (t, 3 H, J = 7 Hz, NCH_2CH_3), 1.79–2.28 (m, 6 H, 3 CH_2), 5.28 (s, 1 H, vinylic H), 7.03–7.73 (m, 4 H, aromatic H); mass spectrum *m/e* (rel intensity) 295 (M^+ + 2, 25), 293 (M^+, 25), 214 (M^+ − Br, 100), 186 (44).

Exact mass. Calcd for $C_{14}H_{16}{}^{79}BrNO$: 295.0395. Found: 295.0373.

3-(3-Bromoanilino)-5,5-dimethylcyclohex-2-en-1-one (8). A mixture of *m*-bromoaniline (2.4 g, 0.014 mol) and **2** (2.0 g, 0.014 mol) was treated in the same manner as that described for the preparation of **3**. The crude product was recrystallized from methanol–water to give **8** (3.6 g, 86%) as white needles: mp 160–161.5 °C; IR ($CHCl_3$) 3400 (NH), 1620 (C=O), 1570 cm^{-1} (C=C); NMR δ 1.07 (s, 6 H, 2 CH_3), 2.17 and 2.33 (each s, 2 H, CH_2), 5.48 (s, 1 H, vinylic H), 6.97–7.26 (m, 4 H, aromatic H), 7.49 (br s, 1 H, NH).

Anal. Calcd for $C_{14}H_{16}BrNO$: C, 57.16; H, 5.48; N, 4.76. Found: C, 57.22; H, 5.47; N, 4.68.

Reaction of 3-(2-Bromoanilino)-5,5-dimethylcyclohex-2-en-1-one (4) with Phenyllithium and Diethylamine. To a stirred solution of phenyllithium (8.0 mmol in 50 mL of ether) was added diethylamine (190 mg, 2.6 mmol) at ice-bath temperature in a nitrogen atmosphere. After approximately 20 min, a solution of **4** (750 mg, 2.6 mmol) in dry tetrahydrofuran (THF) (20 mL) was added and the mixture was heated under reflux for 20 h. After cooling, the reaction mixture was quenched by addition of ammonium chloride (0.5 g), the solvent was evaporated, and chloroform (70 mL) was added to the residue. The resulting solution was washed with water and dried. After evaporation of the solvent, the residue was chromatographed on a silica gel column using chloroform as eluent, affording the unchanged starting material (150 mg, 20%) and then 3-anilino-5,5-dimethylcyclohex-2-en-1-one (**6**, 24 mg, 44%): mp 181–182 °C (chloroform–hexane) (lit.[16] mp 181–182 °C). The NMR data of this sample were identical with those reported in the literature.[16]

Reaction of 3-(2-Bromo-*N*-ethylanilino)cyclohex-2-en-1-one (5) with Phenyllithium and Diethylamine. In the same manner described above for **4**, **5** (700 mg, 2.4 mmol) was treated with phenyllithium (8.5 mmol in 55 mL of ether) and diethylamine (180 mg, 2.5 mmol). After workup according to the above procedure, silica gel column chromatography eluting with chloroform gave the unchanged starting material (90 mg, 13%) and 3-(*N*-ethylanilino)cyclohex-2-en-1-one (**7**, 100 mg, 20%) as an oil: IR ($CHCl_3$) 1610 (C=O), 1560 cm^{-1} (C=C); NMR δ 1.17 (t, 3 H, J = 7 Hz, $NCH_2\mathbf{CH_3}$), 1.69–2.36 (m, 6 H, 3 CH_2), 5.68 (q, 2 H, J = 7 Hz, $NC\mathbf{H_2}CH_3$), 5.28 (s, 1 H, vinylic H), 7.00–7.40 (m, 5 H, aromatic H); mass spectrum *m/e* (rel intensity) 215 (M^+, 87), 214 (M^+ − 1, 50), 198 (81), 187 (100).

Exact mass. Calcd for $C_{14}H_{17}NO$: 215.1309. Found: 215.1311.

Reaction of 3-(3-Bromoanilino)-5,5-dimethylcyclohex-2-en-1-one (8) with Phenyllithium and Piperidine. A solution of **8** (750 mg, 2.6 mmol) in dry THF (40 mL) was treated with phenyllithium (8.0 mmol, in 50 mL of ether) and piperidine (230 mg, 2.7 mmol) in the same manner as described for **4**, except that the reaction time was 45 h. The crude product obtained by usual workup was recrystallized from benzene to give pure 3-(3-piperidylanilino)-5,5-dimethylcyclohex-2-en-1-one (**9**, 210 mg, 28%) as white prisms: mp 190–192 °C; IR ($CHCl_3$) 3320 (NH), 1610 (C=O), 1575 cm^{-1} (C=C); NMR δ 1.08 (s, 6 H, 2 CH_3), 1.56–1.72 (m, 6 H, 3 CH_2 in the piperidine ring), 2.24 (br s, 2 H, CH_2), 2.52 (s, 2 H, CH_2), 2.68–2.78 (m, 4 H, CH_2NCH_2), 5.80 (s, 1 H, vinylic H), 6.68 (br s, 1 H, NH), 7.00–7.36 (m, 4 H, aromatic H); mass spectrum *m/e* (rel intensity) 298 (M^+, 10), 241 (63), 214 (43), 199 (100).

Anal. Calcd for $C_{19}H_{26}N_2O\cdot\frac{1}{4}H_2O$: C, 75.31; H, 8.65; N, 9.25. Found: C, 75.44; H, 8.84; N, 9.10.

Benzylation of 3-Aminocyclohex-2-en-1-one (10). A stirred mixture of **10**[5a] (2.00 g, 0.018 mol) and sodium hydride [1.00 g, 0.042

mol (as 2.00 g of a 50% dispersion in mineral oil)] in toluene–dimethyl sulfoxide (Me_2SO) (5:1, 60 mL) was heated at 130–140 °C for 1 h. After cooling, to this mixture was added a solution of 2-bromo-4,5-methylenedioxybenzyl chloride (**11**, 4.50 g, 0.018 mol) and the mixture was heated at 130–140 °C with stirring for an additional 1 h. The reaction mixture was worked up in a similar manner as described for the preparation of **5** from **3** and the crude product was chromatographed on a silica gel column using chloroform as eluent. The first fractions contained 2-(2-bromo-4,5-methylenedioxybenzyl)-3-(2-bromo-4,5-methylenedioxybenzylamino)cyclohex-2-en-1-one (**13**, 0.15 g, 2%): mp 188–190 °C (acetone–hexane); IR ($CHCl_3$) 3380 (NH), 1610 (C=O), 1565 cm^{-1} (C=C); NMR δ 3.36 (s, 2 H, $PhCH_2C$), 4.26 (d, 2 H, J = 6 Hz, $PhCH_2N$), 5.86 and 5.91 (each s, 2 H, OCH_2O), 6.26, 6.59, 6.79, and 6.89 (each s, 1 H, aromatic H); mass spectrum m/e (rel intensity) 539 (M^+ + 4, 0.3), 537 (M^+ + 2, 0.8), 535 (M^+, 0.3), 456 (M^+ − Br, 63), 242 (61), 213 (100).

Anal. Calcd for $C_{22}H_{19}Br_2NO_5$: C, 49.19; H, 3.56; N, 2.61. Found: C, 49.05; H, 3.51; N, 2.68.

The second fractions contained 3-[*N*,*N*-bis(2-bromo-4,5-methylenedioxybenzyl)amino]cyclohex-2-en-1-one (**12**, 1.25 g, 13%): mp 130–132 °C (chloroform); IR ($CHCl_3$) 1610 (C=O), 1560 cm^{-1} (C=C); NMR δ 4.40 (s, 4 H, 2 $PhCH_2N$), 5.17 (s, 1 H, vinylic H), 5.93 (s, 4 H, 2 OCH_2O), 6.50 (s, 2 H, 2 6′-H), 6.94 (s, 2 H, 2 3′-H); mass spectrum m/e (rel intensity) 539 (M^+ + 4, 0.4), 537 (M^+ + 2, 0.7), 535 (M^+, 0.4), 456 (M^+ − Br, 46), 213 (100).

Anal. Calcd for $C_{22}H_{19}Br_2NO_5$: C, 49.19; H, 3.56; N, 2.61. Found: C, 49.06; H, 3.75; N, 2.56.

The last fractions contained 2-(2-bromo-4,5-methylenedioxybenzyl)-3-aminocyclohex-2-en-1-one (**14**, 0.30 g, 5%), which was recrystallized from dimethylformamide (DMF)–chloroform: mp 255–260 °C (sublimed); IR (Nujol) 3430 and 3330 (NH), 1650 (C=O), 1600 cm^{-1} (C=C); NMR ($CDCl_3$–Me_2SO-d_6) δ 3.36 (s, 2 H, $PhCH_2$), 5.83 (s, 2 H, OCH_2O), 6.03 (br s, 2 H, NH_2), 6.36 (s, 1 H, 6′-H), 6.89 (s, 1 H, 3′-H); mass spectrum m/e (rel intensity) 244 (M^+ − Br, 38), 130 (100).

Anal. Calcd for $C_{14}H_{14}BrNO_3$: C, 51.87; H, 4.35; N, 4.32. Found: C, 51.41; H, 4.31; N, 4.26.

***N*-(2-Bromo-4,5-methylenedioxybenzyl)phthalimide (15).** To a solution of **11** (18.2 g, 0.073 mol) in DMF (150 mL) was added potassium phthalimide (13.5 g, 0.073 mol) and the mixture was heated under reflux for 2 h. Most of the solvent was evaporated at reduced pressure, water (~100 mL) was added to the reaction mixture, and it was extracted with chloroform. The extract was washed with water, dried, and evaporated. Recrystallization from acetone–hexane gave **15** (13.9 g, 53%): mp 173–175 °C; IR ($CHCl_3$) 1770 and 1710 cm^{-1} (imide C=O); NMR δ 4.86 (s, 2 H, $PhCH_2$), 5.89 (s, 2 H, OCH_2O), 6.68 (s, 1 H, 6′-H), 6.96 (s, 1 H, 3′-H), 7.66–7.86 (m, 4 H, aromatic H).

Anal. Calcd for $C_{16}H_{10}BrNO_4$: C, 53.36; H, 2.80; N, 3.89. Found: C, 53.37; H, 2.74; N, 3.92.

2-Bromo-4,5-methylenedioxybenzylamine (16). A solution of **15** (11.0 g, 0.031 mol) and 100% hydrazine hydrate (2 mL) in methanol (75 mL) was heated under reflux for 1 h. After addition of water, the reaction mixture was evaporated under reduced pressure and concentrated hydrochloric acid (30 mL) was added to the residue. The reaction mixture was heated under reflux for 1 h and cooled in an ice–water bath and the resulting crystalline phthalhydrazide was removed by filtration. The filtrate was basified by addition of K_2CO_3 and extracted with chloroform. The extract was washed with water, dried over K_2CO_3, and evaporated. Distillation of the residue gave **16** (3.1 g, 44%) as a colorless oil: bp 90–91 °C (0.1 mm); IR (neat) 3360 and 3280 cm^{-1} (NH); NMR δ 1.56 (s, 2 H, NH), 3.40 (s, 2 H, $PhCH_2$), 5.87 (s, 2 H, OCH_2O), 6.79 (s, 1 H, 6′-H), 6.87 (s, 1 H, 3′-H).

Anal. Calcd for $C_8H_8BrNO_2$: C, 41.77; H, 3.51; N, 6.09. Found: C, 41.09; H, 3.47; N, 6.22.

3-(2-Bromo-4,5-methylenedioxybenzyl)aminocyclohex-2-en-1-one (17). A solution of **16** (3.10 g, 0.0135 mol) and **1** (1.51 g, 0.0135 mol) in benzene (50 mL) was refluxed with azeotropic removal of water using a Dean–Stark apparatus for 3 h. Evaporation of the solvent and recrystallization of the residue from DMF–chloroform gave **17** (3.76 g, 86%) as white needles: mp 241.5–243 °C; IR ($CHCl_3$) 3400 (NH), 1610 (C=O), 1580 cm^{-1} (C=C); NMR ($CDCl_3$–Me_2SO-d_6) δ 1.76–2.46 (m, 6 H, 3 CH_2), 4.13 (d, 2 H, J = 6 Hz, $PhCH_2$), 4.76 (s, 1 H, vinylic H), 5.96 (s, 2 H, OCH_2O), 6.74 (s, 1 H, 6′-H), 6.97 (s, 1 H, 3′-H), 7.26 (br s, 1 H, NH, disappears by addition of D_2O); mass spectrum m/e (rel intensity) 325 (M^+ + 2, 3), 323 (M^+, 3), 244 (M^+ − Br, 100), 213 (90), 188 (42).

Anal. Calcd for $C_{14}H_{14}BrNO_3$: C, 51.87; H, 4.35; N, 4.32. Found: C, 51.53; H, 4.26; N, 4.47.

3-(2-Bromo-4,5-methylenedioxybenzyl)amino-5,5-dimethylcyclohex-2-en-1-one (18). A solution of **16** (3.10 g, 0.0135 mol) and **2** (1.89 g, 0.0135 mol) was treated in the same manner as described above for the preparation of **17**. Recrystallization of the crude product from ethanol gave **18** (3.94 g, 83%) as white needles: mp 223–224 °C; NMR ($CDCl_3$–Me_2SO-d_6) δ 1.03 (s, 6 H, 2 CH_3), 2.00 and 2.26 (each s, 2 H, CH_2), 4.15 (d, J = 6 Hz, $PhCH_2$), 4.69 (s, 1 H, vinylic H). 6.00 (s, 2 H, OCH_2O), 6.76 (s, 1 H, 6′-H), 7.07 (s, 1 H, 3′-H), 7.33 (br s, 1 H, NH, disappears by addition of D_2O); mass spectrum m/e (rel intensity) 273 (M^+ + 1 − Br, 22), 272 (M^+ − Br, 100), 213 (24).

Anal. Calcd for $C_{16}H_{18}BrNO_3$: C, 54.56; H, 5.15; N, 3.97. Found: C, 54.38; H, 5.16; N, 3.74.

3-[(2-Bromo-4,5-methylenedioxybenzyl)-*N*-ethylamino]-5,5-dimethylcyclohex-2-en-1-one (22). A mixture of **18** (1.90 g, 0.0054 mol) and sodium hydride [0.25 g, 0.0010 mol (as 0.50 g of a 50% dispersion in mineral oil)] in dry toluene (50 mL) was treated in the same manner as described in the preparation of **5** from **3**. After addition of ethyl iodide (0.85 g, 0.0054 mol), the resulting mixture was heated under reflux for 1 h and worked up as for **3**. The crude product was recrystallized from acetone–ether giving **22** (1.65 g, 80%) as white prisms: mp 167–169 °C; IR ($CHCl_3$) 1610 (C=O), 1555 cm^{-1} (C=C); NMR δ 1.00 (s, 6 H, 2 CH_3), 1.10 (t, 3 H, J = 6 Hz, NCH_2CH_3), 2.07 and 2.20 (each s, 2 H, CH_2), 3.24 (q, 2 H, J = 6 Hz, NCH_2CH_3), 4.26 (s, 2 H, $PhCH_2$), 5.07 (s, 1 H, vinylic H), 5.84 (s, 2 H, OCH_2O), 6.35 (s, 1 H, 6′-H), 6.89 (s, 1 H, 3′-H); mass spectrum m/e (rel intensity) 381 (M^+ + 2, 5), 379 (M^+, 5), 300 (M^+ − Br, 100), 27 (37), 213 (49).

Anal. Calcd for $C_{18}H_{22}BrNO_3$: C, 56.85; H, 5.83; N, 3.68. Found: C, 56.91; H, 5.82; N, 3.50.

3,4-Dihydro-8,9-methylenedioxy-1(2*H*)-phenanthridone (20). A solution of **17** (700 mg, 2.16 mmol) in dry THF (30 mL) was treated with phenyllithium (6.3 mmol in 40 mL of ether) and diethylamine (160 mg, 2.2 mmol) in the same manner as described for **4**. The reaction mixture was stirred at room temperature under nitrogen for 2 h and worked up as for **4**. Column chromatography (silica gel, chloroform) and recrystallization from acetone–hexane gave **20** (125 mg, 24%) as pale yellow needles: mp 158–160 °C; IR ($CHCl_3$) 1665 (C=O), 1605 cm^{-1} (C=C); NMR δ 2.07–2.27, 2.62–2.83, and 3.14–3.33 (each m, 2 H, CH_2), 6.11 (s, 2 H, OCH_2O), 7.12 (s, 1 H, 7-H), 8.82 (s, 1 H, 6-H), 8.93 (s, 1 H, 10-H); mass spectrum m/e (rel intensity) 242 (M^+ + 1, 18), 241 (M^+, 100), 213 (84), 185 (39), 127 (26).

Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.59; N, 5.80. Found: C, 69.58; H, 4.70; N, 5.64.

3,4-Dihydro-3,3-dimethyl-8,9-methylenedioxy-1(2*H*)-phenanthridone (21). A solution of **18** (1050 mg, 2.98 mmol) in dry THF (35 mL) was treated with phenyllithium (9.0 mmol in 55 mL of ether) and diethylamine (220 mg, 3.01 mmol) in the same manner as described above for **17**. Column chromatography (silica gel, chloroform) and recrystallization (acetone–hexane) gave **21** (210 mg, 26%) as white prisms: mp 175–177 °C; IR ($CHCl_3$) 1660 cm^{-1} (C=O); NMR δ 1.13 (s, 6 H, 2 CH_3), 2.58 and 3.16 (each s, 2 H, CH_2), 6.05 (s, 2 H, OCH_2O), 7.06 (s, 1 H, 7-H), 8.73 (s, 1 H, 6-H), 8.86 (s, 1 H, 10-H); mass spectrum m/e (rel intensity) 270 (M^+ + 1, 19), 269 (M^+, 100), 213 (84), 185 (48).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.38; H, 5.54; N, 5.17.

5-Ethyl-3,4,5,6-tetrahydro-3,3-dimethyl-8,9-methylenedioxy-1(2*H*)-phenanthridone (23). In the same manner as described above for the preparation of **20** from **17**, a solution of **22** (760 mg, 2.00 mmol) in dry THF (30 mL) was treated with a mixture of phenyllithium (6.0 mmol in 35 mL of ether) and diethylamine (150 mg, 2.05 mmol), except that the reaction time was 30 min. Column chromatography (silica gel, chloroform) and recrystallization (acetone–hexane) gave **23** (330 mg, 55%) as white needles: mp 123–124 °C; IR ($CHCl_3$) 1715 (C=O), 1610 cm^{-1} (C=C); NMR δ 1.10 (s, 6 H, 2 CH_3), 1.24 (t, 3 H, J = 7 Hz, NCH_2CH_3), 2.30 and 2.38 (each s, 2 H, CH_2), 3.40 (q, 2 H, J = 7 Hz, NCH_2CH_3), 4.25 (s, 2 H, $PhCH_2$), 5.83 (s, 2 H, OCH_2O), 6.40 (s, 1 H, 7-H), 8.80 (s, 1 H, 10-H); mass spectrum m/e (rel intensity) 300 (M^+ + 1, 50), 299 (M^+, 100), 243 (21).

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.38; H, 7.01; N, 4.63.

3-[2-(2-Bromo-4,5-dimethoxyphenyl)ethylamino]-5,5-dimethylcyclohex-2-en-1-one (27). A solution of 2-(2-bromo-4,5-dimethoxyphenyl)ethylamine[17] (2.60 g, 10.0 mol) and **2** (1.40 g, 10.0 mol) in benzene (70 mL) was treated in the same manner as described for the preparation of **17** from **16**. Evaporation of the solvent and recrystallization of the residue from acetone–hexane gave **27** (3.10 g, 81%) as white needles: mp 167–168 °C; IR ($CHCl_3$) 3410 (NH), 1610 (C=O), 1580 cm^{-1} (C=C); NMR δ 1.06 (s, 6 H, 2 CH_3), 3.83 (s, 6 H, 2 OCH_3), 4.66 (br s, 1 H, NH, disappears by addition of D_2O), 5.13 (s, 1 H, vinylic H), 6.63 (s, 1 H, 6′-H), 6.96 (s, 1 H, 3′-H); mass spectrum m/e (rel intensity) 383 (M^+ + 2, 2), 381 (M^+, 2), 302 (M^+ − Br, 100), 242 (31), 152 (88).

Anal. Calcd for $C_{18}H_{24}BrNO_3$: C, 56.55; H, 6.33; N, 3.66. Found: C, 56.33; H, 6.21; N, 3.64.

3-[2-(2-Bromo-4,5-dimethoxyphenyl)ethylamino]indan-2-en-1-one (31). Treatment of 2-(2-bromo-4,5-dimethoxyphenyl)-ethylamine (950 mg, 3.65 mmol) with indan-1,3-dione (530 mg, 3.63 mmol) in the same manner as described above gave a badly colored solid which was washed with benzene and then recrystallized from acetone to yield **31** (410 mg, 29%) as yellow prisms: mp 205–207 °C; IR ($CHCl_3$) 3400 (NH), 1670 (C=O), 1570 cm^{-1} (C=C); NMR δ 2.89–3.87 (m, 4 H, $PhCH_2CH_2$), 3.76 and 3.84 (each s, 3 H, OCH_3), 4.97 (s, 1 H, vinylic H), 5.74 (br s, 1 H, NH), 6.66 (s, 1 H, 6′-H), 7.00 (s, 1 H, 3′-H), 7.25–7.40 (m, 4 H, aromatic H); mass spectrum *m/e* (rel intensity) 389 (M^+ + 2, 0.2), 387 (M^+, 0.2), 308 (M^+ − Br, 100), 229 (22), 158 (80).

Anal. Calcd for $C_{19}H_{18}BrNO_3$: C, 58.78; H, 4.67; N, 3.61. Found: C, 58.78; H, 4.72; N, 3.58.

3-[2-(2-Bromo-4,5-dimethoxyphenyl)-*N*-ethylethylamino]-5,5-dimethylcyclohex-2-en-1-one (29). Reaction of **27** (760 mg, 1.99 mmol) with sodium hydride [70 mg, 2.9 mmol (as 140 mg of a 50% dispersion in mineral oil)] and ethyl iodide (315 mg, 2.02 mmol) was conducted in the same manner as in the preparation of **5** from **3**, except that the reaction mixture was heated at 100 °C for 2 h. The product obtained by usual workup was then chromatographed on a silica gel column with chloroform to give **29** (605 mg, 74%) as an orange-red oil: IR ($CHCl_3$) 1610 (C=O), 1560 cm^{-1} (C=C); NMR δ 1.01 (s, 6 H, 2 CH_3), 1.11 (t, 3 H, J = 7 Hz, NCH_2CH_3), 2.08 and 2.18 (each s, 2 H, CH_2), 2.74–3.53 (m, 6 H, NCH_2CH_3 and $PhCH_2CH_2N$), 3.82 (s, 6 H, 2 OCH_3), 5.17 (s, 1 H, vinylic H), 6.59 (s, 1 H, 6′-H), 6.91 (s, 1 H, 3′-H); mass spectrum *m/e* (rel intensity) 411 (M^+ + 2, 2), 409 (M^+, 2), 330 (M^+ − Br, 100), 242 (24).

Exact mass. Calcd for $C_{20}H_{28}{}^{79}BrNO_3$: 409.1252. Found: 409.1205.

3-(5,6-Dimethoxy-2,3-dihydroindolo)-5,5-dimethylcyclohex-2-en-1-one (28). A solution of **27** (1.00 g, 0.0026 mol) in dry THF (50 mL) was treated with phenyllithium (0.0080 mol in 50 mL of ether) and diethylamine (0.20 g, 0.0027 mol) in the same procedure as described for the preparation of **20** from **17**, except that the reaction time was 1 h. After standard workup, the product solidified by trituration with ether was recrystallized from acetone–hexane to give **28** (0.51 g, 65%) as white prisms: mp 142–143 °C; IR ($CHCl_3$) 1720 (C=O), 1610 cm^{-1} (C=C); NMR δ 1.13 (s, 6 H, 2 CH_3), 2.21 and 2.61 (each s, 2 H, CH_2), 2.89–3.20 (m, 2 H, $PhCH_2CH_2N$), 3.72–4.04 (m, 2 H, $PhCH_2CH_2N$), 5.40 (s, 1 H, vinylic H), 6.72 (s, 2 H, aromatic H); mass spectrum *m/e* (rel intensity) 302 (M^+ + 1, 17), 301 (M^+, 100), 286 (74).

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.74; H, 7.69; N, 4.65. Found: C, 71.72; H, 7.77; N, 4.45.

3-(5,6-Dimethoxy-2,3-dihydroindolo)indan-2-en-1-one (32). Reaction of **31** (390 mg, 1.0 mmol) with phenyllithium (4.0 mmol in 25 mL of ether) and diethylamine (75 mg, 1.0 mmol) was conducted in the same manner as described for the preparation of **20**, except that the reaction time was 30 min. Standard workup and recrystallization from acetone–benzene gave **32** (150 mg, 49%) as an orange powder: mp 142–145 °C; IR ($CHCl_3$) 1650 (C=O), 1570 cm^{-1} (C=C); NMR δ 3.15 (t, 2 H, J = 8 Hz, $PhCH_2CH_2N$), 4.45 (t, 2 H, J = 8 Hz, $PhCH_2CH_2N$), 3.81 and 3.83 (each s, 3 H, OCH_3), 5.46 (s, 1 H, vinylic H), 6.75 (s, 1 H, 4-H), 6.85 (s, 1 H, 7-H), 7.17–7.38 (m, 4 H, aromatic H); mass spectrum *m/e* (rel intensity) 308 (M^+ + 1, 100), 307 (M^+, 87), 292 (87), 231 (22), 179 (78).

Exact mass. Calcd for $C_{17}H_{17}NO_3$: 307.1208. Found: 307.1195.

1-Ethyl-5,6-dimethoxy-2,3-dihydroindole (30). Reaction of **29** (1.00 g, 0.0024 mol) with phenyllithium (0.0080 mol in 50 mL of ether) and diethylamine (0.18 g, 0.0025 mol) was conducted as described for the preparation of **20**, except that the reaction time was 2.5 h. After standard workup, the crude reaction product was chromatographed on a silica gel column with chloroform to give **30** (0.25 g, 50%) as an oil: IR ($CHCl_3$) showed no absorptions characteristic for the enaminone moiety; NMR δ 1.17 (t, 3 H, J = 7 Hz, NCH_2CH_3), 3.77 and 3.83 (each s, 3 H, OCH_3), 6.18 (s, 1 H, 4-H), 6.73 (s, 1 H, 7-H); mass spectrum *m/e* (rel intensity) 207 (M^+, 62), 205 (M^+ − 2, 15), 192 (M^+ − 15, 100).

Exact mass. Calcd for $C_{12}H_{17}NO_2$: 207.1259. Found: 207.1229.

Reaction of 1,2,3,3a,4,5-Hexahydro-6*H*-indol-6-one (36) with 3-Bromo-4,5-methylenedioxybenzyl Chloride (37). Reaction of **36**[4e] (0.80 g, 0.0058 mol) with sodium hydride [0.35 g, 0.0015 mol (as 0.70 g of a 50% dispersion in mineral oil)] and **37**[11] (1.46 g, 0.0058 mol) in dry toluene (50 mL) was conducted in the same procedure as in the preparation of **5** from **3**, except that the reaction time was 1.5 h. The same workup as for **3** afforded the crude reaction product, which was chromatographed on a silica gel column with chloroform–ethyl acetate (90:10). The first fractions contained 1,7-bis(3-bromo-4,5-methylenedioxybenzyl)-1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one (**39**, 0.09 g, 3%): mp 130–132 °C (chloroform–hexane); IR ($CHCl_3$) 1610 (C=O), 1560 cm^{-1} (C=C); NMR δ 3.53 (br s, 2 H, $PhCH_2C$), 4.27 (br s, 2 H, $PhCH_2N$), 5.83 and 5.92 (each s, 2 H, OCH_2O), 6.30–6.50 (m, 4 H, aromatic H); mass spectrum *m/e* (rel intensity) 565 (M^+ + 4, 45), 563 (M^+ + 2, 84), 561 (M^+, 42), 349 (62), 348 (M^+ − 2 Br, 65), 213 (100).

The second fractions contained 7-(3-bromo-4,5-methylenedioxybenzyl)-1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one (**40**, 0.10 g, 5%): mp 231–233 °C (benzene–hexane); IR ($CHCl_3$) 3420 (NH), 1625 (C=O), 1580 cm^{-1} (C=C); NMR δ 3.43 (d, 2 H, J = 6 Hz, $PhCH_2C$), 5.00 (br s, 1 H, NH), 5.87 (s, 2 H, OCH_2O), 6.53 (d, 1 H, J = 1 Hz, 6′-H), 6.69 (d, 1 H, J = 1 Hz, 2′-H); mass spectrum *m/e* (rel intensity) 351 (M^+ + 2, 97), 349 (M^+, 100), 320 (11), 292 (26), 270 (54).

Anal. Calcd for $C_{16}H_{16}BrNO_3$: C, 54.87; H, 4.60; N, 3.99. Found: C, 55.10; H, 4.57; N, 4.19.

The third fractions contained 1-(3-bromo-4,5-methylenedioxybenzyl)-1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one (**38**, 0.60 g, 29%): mp 176–178 °C (chloroform–hexane); IR ($CHCl_3$) 1610 (C=O), 1580 cm^{-1} (C=C); NMR δ 4.32 (s, 2 H, $PhCH_2N$), 5.12 (d, 1 H, vinylic H), 6.00 (s, 2 H, OCH_2O), 6.56 (d, 1 H, J = 1 Hz, 6′-H), 7.26 (d, 1 H, J = 1 Hz, 2′-H); mass spectrum *m/e* (rel intensity) 351 (M^+ + 2, 30), 349 (M^+, 30), 321 (16), 213 (100).

Anal. Calcd for $C_{16}H_{16}BrNO_3$: C, 54.87; H, 4.60; N, 3.99. Found: C, 54.61; H, 4.53; N, 3.73.

1-(2-Bromo-4,5-methylenedioxybenzyl)-1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one (42a). A mixture of **35** (1.51 g, 0.0010 mol) and **11** (2.50 g, 0.0010 mol) in dry toluene (60 mL) was heated under reflux for 10 h. After evaporation of the solvent under reduced pressure, the residue was carefully chromatographed on a silica gel column using chloroform as eluent. The first elution afforded 7-(2-bromo-4,5-methylenedioxybenzyl)-1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one (**43a**, 0.09 g, 3%) as white needles: mp 201–202 °C (benzene–hexane); IR ($CHCl_3$) 3380 (NH), 1625 (C=O), 1570 cm^{-1} (C=C); NMR δ (3.59 (d, 2 H, J = 2 Hz, $PhCH_2C$), 5.23 (br s, 1 H, NH, disappears by addition of D_2O), 5.81 (s, 2 H, OCH_2O), 6.70 (s, 1 H, 6′-H), 6.81 (s, 1 H, 3′-H); mass spectrum *m/e* (rel intensity) 351 (M^+ + 2, 2), 349 (M^+, 2), 270 (M^+ − Br, 100), 213 (54), 135 (32).

Anal. Calcd for $C_{16}H_{16}BrNO_3$: C, 54.87; H, 4.60; N, 3.99. Found: C, 54.80; H, 4.57; N, 4.05.

Continued elution afforded **42a** (1.93 g, 55%) as white needles: mp 157–158 °C (chloroform–hexane); IR ($CHCl_3$) 1605 (C=O), 1580 cm^{-1} (C=C); NMR δ 4.40 (s, 2 H, $PhCH_2N$), 5.10 (s, 1 H, vinylic H), 5.98 (s, 2 H, OCH_2O), 6.59 (s, 1 H, 6′-H), 7.02 (s, 1 H, 3′-H); mass spectrum *m/e* (rel intensity) 351 (M^+ + 2, 9), 349 (M^+, 10), 270 (M^+ − Br, 100), 242 (47), 213 (68).

Anal. Calcd for $C_{16}H_{16}BrNO_3$: C, 54.87; H, 4.60; N, 3.99. Found: C, 54.66; H, 4.52; N, 3.82.

1-(2-Iodo-4,5-methylenedioxybenzyl)-1,2,3,3a,4,5-hexahydro-6*H*-indol-6- one (42b). In the same manner as described above, **35** (1.51 g, 0.0010 mol) was reacted with **41** (2.97 g, 0.0010 mol) to give **42b** (2.00 g, 50%): mp 173–174 °C; IR ($CHCl_3$) 1605 (C=O), 1580 cm^{-1} (C=C); NMR δ 4.39 (s, 2 H, $PhCH_2$), 5.09 (s, 1 H, vinylic H), 5.96 (s, 2 H, OCH_2O), 6.86 (s, 1 H, 6-H), 7.26 (s, 1 H, 3′-H); mass spectrum *m/e* (rel intensity) 397 (M^+, 2), 270 (M^+ − I, 100), 261 (48), 135 (63).

Anal. Calcd for $C_{16}H_{16}INO_3$: C, 48.42; H, 4.06; N, 3.28. Found: C, 48.38; H, 4.06; N, 3.52.

This reaction was accompanied by the formation of **43b** as a minor product: mp 209–211 °C (chloroform–hexane); IR ($CHCl_3$) 3370 (NH), 1620 (C=O), 1570 cm^{-1} (C=C); NMR δ 3.52 (d, 2 H, J = 2 Hz, $PhCH_2$), 5.10 (br s, 1 H, NH, disappears by addition of D_2O), 5.86 (s, 2 H, OCH_2O), 6.66 (s, 1 H, 6′-H), 7.13 (s, 1 H, 3′-H); mass spectrum *m/e* (rel intensity) 399 (M^+ + 2, 1), 397 (M^+, 1), 270 (M^+ − I, 100), 212 (31), 135 (48).

Anal. Calcd for $C_{16}H_{16}INO_3$: C, 48.48; H, 4.06; N, 3.52. Found: C, 48.43; H, 4.05; N, 3.57.

1,2,2a,3-Tetrahydro-8,9-methylenedioxy-6*H*-pyrrolo[3,2,1-*kl*]acridin-5(4*H*)-one (44). In a similar manner as described for **4**, a solution of **43a** (306 mg, 0.874 mmol) in dry THF (10 mL) was treated with phenyllithium (2.6 mmol in 15 mL of ether) and diethylamine (64 mg, 0.877 mmol) at 40 °C for 24 h. After usual workup, the resulting crude product was chromatographed on a silica gel column using chloroform as eluent to give the crystalline product which was recrystallized from chloroform–hexane, affording **44** (45 mg, 19%) as white needles: mp 195–197 °C; IR ($CHCl_3$) 1655 (C=O), 1595 cm^{-1} (C=C); NMR δ 3.52 (br s, 2 H, $PhCH_2$), 5.88 (s, 2 H, OCH_2O), 6.54 and 6.44 (each s, 1 H, aromatic H); mass spectrum *m/e* (rel intensity) 270 (M^+ + 1, 21), 269 (M^+, 100), 268 (M^+ − 1, 30), 241 (32), 240 (49), 213 (14).

3,3a,4,5,6,7-Hexahydro-9,10-methylenedioxypyrrolo[3,2,1-*de*]phenanthridin-1(2*H*)-one (45). Reaction of **42a** (1.40 g, 0.0040 mol) with phenyllithium (0.012 mol in 70 mL of ether) and diethylamine (0.30 g, 0.0041 mol) was conducted in the same manner as previously described for the preparation of **20** from **17**, except that the reaction time was 30 min. After normal workup, the resulting crude product was purified by rapidly passing through a column of silica gel with ethyl acetate and then recrystallization from ethyl acetate–hexane, yielding **45** (0.53 g, 49%) as white needles. This material showed no clear melting point; it began to melt at 145 °C with a final melting at 252 °C: IR ($CHCl_3$) 1610 (C=O), 1560 cm^{-1} (C=C); NMR δ 4.53 (s, 2 H, $PhCH_2$), 5.88 (s, 2 H, OCH_2O), 6.45 (s, 1 H, 8-H), 8.92 (s, 1 H, 11-H); mass spectrum *m/e* (rel intensity) 269 (M^+, 61), 268 ($M^+ - 1$, 100), 236 (11), 195 (18), 149 (56).

Exact mass. Calcd for $C_{16}H_{15}NO_3$: 269.1051. Found: 269.1066.

In the same manner as described above, **42b** (1.00 g, 0.0025 mol) was allowed to react with phenyllithium (0.0080 mol in 50 mL of ether) and diethylamine (0.19 g, 0.0026 mol) to afford **45** (0.26 g, 38%).

Air Oxidation of 3,3a,4,5,6,7-Hexahydro-9,10-methylenedioxypyrrolo[3,2,1-*de*]phenanthridin-1(2*H*)-one (45). A stirred solution of **45** (50 mg, 0.19 mmol) in ethanol (30 mL) including KOH (100 mg) was heated at 60 °C with bubbling of oxygen for 24 h. After removal of the solvent, the residue was diluted with water and extracted with chloroform. The extract was washed with water, dried, and evaporated. The residual crystalline product was recrystallized from chloroform–hexane to give 3,3a,4,5-tetrahydro-9,10-methylenedioxypyrrolo[3,2,1-*de*]phenanthridine-1,7(2*H*)-dione (**46**, 45 mg, 85%) as white plates: mp 252–253 °C (lit. mp 249–250 °C,[12a] 251.5–253 °C,[12b] 252–253 °C[4e]). This material obtained was identical in spectral respects with an authentic sample.[4e]

(±)-α-Dihydrocaranone (47) and (±)-1-*epi*-γ-Dihydrocaranine (48). To a stirred suspension of lithium aluminum hydride (250 mg) in dry THF (30 mL) was added dropwise a solution of **45** (250 mg, 0.93 mmol) under ice–water cooling over the period of 30 min. The mixture was stirred at room temperature for 2 h and quenched by addition of THF including a small amount of water. After filtration of the mixture through Celite, the filtrate was evaporated and the residue was dissolved in chloroform. The chloroform solution was washed with water and dried over K_2CO_3. Removal of the solvent and column chromatography on silica gel using chloroform as eluent afford **47** (83 mg, 33%) as white needles: mp 147–149 °C (methanol) (lit.[4a] mp 147.5–149.5 °C for the racemate); IR ($CHCl_3$) 1705 cm^{-1} (C=O); NMR δ 3.29 and 4.00 (AB q, 2 H, J = 14 Hz, $PhCH_2$), 3.47 (d, 1 H, J = 4 Hz, 12b-H), 5.89 (s, 2 H, OCH_2O), 6.49 (s, 1 H, 8-H), 6.59 (s, 1 H, 11-H); mass spectrum *m/e* (rel intensity) 271 (M^+, 75), 270 ($M^+ - 1$, 100), 254 (37), 242 (18), 149 (19).

Further elution with the same solvent gave **48** (25 mg, 10%) as white prisms: mp 130–132 °C (benzene–ether) (lit.[4a] mp 135.5–136.5 °C for the racemate); IR ($CHCl_3$) 3250 cm^{-1} (OH); NMR δ 3.28 and 4.04 (AB q, 2 H, J = 14 Hz, $PhCH_2$), 5.90 (s, 2 H, OCH_2O), 6.48 (s, 1 H, 8-H), 6.64 (s, 1 H, 11-H); mass spectrum *m/e* (rel intensity) 273 (M^+, 54), 272 ($M^+ - 1$, 100), 254 (18), 174 (25).

Both of the IR and NMR spectra of **47** and **48** were essentially superimposable on those of authentic specimens.[13]

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Registry No.—**1**, 504-02-9; **2**, 126-81-8; **3**, 68890-19-7; **4**, 68890-20-0; **5**, 68890-21-1; **6**, 18940-21-1; **7**, 51788-74-0; **8**, 68890-22-2; **9**, 68890-23-3; **10**, 5220-49-5; **11**, 64603-67-4; **12**, 68890-24-4; **13**, 68908-32-7; **14**, 68890-25-5; **15**, 68890-26-6; **16**, 67496-29-1; **17**, 68890-27-7; **18**, 67496-30-4; **20**, 68890-28-8; **21**, 67496-33-7; **22**, 67496-31-5; **23**, 67496-34-8; **27**, 68890-29-9; **28**, 68890-30-2; **29**, 68890-31-3; **30**, 68890-32-4; **31**, 68890-33-5; **32**, 68890-34-6; **35**, 59601-27-3; **36**, 64705-39-1; **37**, 65673-82-7; **38**, 65673-78-1; **39**, 68890-35-7; **40**, 68890-36-8; **41**, 65673-83-8; **42a**, 65673-79-2; **42b**, 65673-80-5; **43a**, 68890-37-9; **43b**, 68890-38-0; **44**, 68890-39-1; **45**, 67497-77-2; **46**, 54022-56-9; **47**, 67529-10-6; **48**, 67529-11-7; *o*-bromoaniline, 615-36-1; *m*-bromoaniline, 591-19-5; potassium phthalimide, 1074-82-4; piperidine, 110-89-4; 2-(2-bromo-4,5-dimethoxyphenyl)ethylamine, 63375-81-5; indan-1,3-dione, 606-23-5.

References and Notes

(1) For designation, "enaminone" has been recommended[2b] instead of enamino ketone or β-amino-α,β-unsaturated ketone, since the compounds rarely show the physical or chemical properties normally associated with ketones. This system can also be regarded as vinylogous amide.
(2) For reviews, see (a) T. Nishio, C. Kajima, and Y. Omote, *J. Synth. Org. Chem. Jpn.*, **34**, 526 (1976); (b) J. V. Greenhill, *Chem. Soc. Rev.*, **6**, 277 (1977).
(3) In the case of enamines, the arylation reaction has been attained when aryl halides with a halogen activated by strong electron-withdrawing groups such as 2,3-dinitrochlorobenzene were used; M. E. Kuehne, *J. Am. Chem. Soc.*, **84**, 837 (1962).
(4) For total syntheses of γ-lycorane, see (a) N. Ueda, T. Tokuyama, and T. Sakan, *Bull. Chem. Soc. Jpn.*, **39**, 2012 (1966); (b) H. Irie, Y. Nishitani, M. Sugita, and S. Uyeo, *Chem. Commun.*, 1313 (1970); (c) B. Ganem, *Tetrahedron Lett.*, 4105 (1971); (d) H. Hara, O. Hoshino, and B. Umezawa, *ibid.*, 5031 (1972); (e) H. Iida, S. Aoyagi, and C. Kibayashi, *J. Chem. Soc., Chem. Commun.*, 499 (1974); *J. Chem. Soc., Perkin Trans. 1*, 2502 (1975); (f) B. Umezawa, O. Hoshino, S. Sawaki, S. Sato, and N. Numao, *J. Org. Chem.*, **42**, 4272 (1977).
(5) (a) F. Zymalkowski and H.-J. Rimek, *Arch. Pharm.*, **294**, 759 (1961); (b) M. A. T. Sluyter, U. K. Pandit, W. N. Speckamp, and H. O. Huisman, *Tetrahedron Lett.*, (c) C. Ruangsiyanand, H.-J. Rimek, and F. Zymalkowski, *Chem. Ber.*, **103**, 2403 (1970).
(6) It has been reported that in the metalation reaction of 2,5-dibromonitrobenzene with alkyllithium the lithium atom in the product is preferentially located on the most electronegative carbon atom ortho to the nitro group: W. E. Parham and R. M. Piccirilli, *J. Org. Chem.*, **42**, 257 (1977). In light of this fact, it is considered that the bromine atoms in **4** and **5** are favorably exchangeable with lithium atom because of the presence of groups at the ortho position with strong inductive effect, which is presumably caused through the formation of lithium enolates. Thus on treatment of **4** and **5** with lithium reagent, halogen–metal exchange may precede benzyne formation to provide **6** and **7** (after water quench), respectively. By contrast, the meta analogue **8**, lacking the effect attributed to coordination of lithium with the ortho group containing unshared electrons, may predominantly undergo the amination reaction via a benzyne intermediate rather than halogen–metal exchange and thus is converted into **9**.
(7) The electrophilic alkylation of enaminones can occur on the carbon, nitrogen, and/or oxygen atoms. The mode of alkylation may depend on the reactivity of the alkylation agent, the structure of the substrate, and the polarity of the solvent. In contrast to the well-established investigations of the *C*- and *O*-alkylation of enaminones, only a limited number of reports of the *N*-alkylation have appeared in the literature: (a) H. Dugas, R. A. Ellison, Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Lett.*, 1279 (1965); (b) C. A. Grob and H. J. Willkens, *Helv. Chim. Acta*, **50**, 725 (1967).
(8) An alternative S_NAr mechanism might be also applicable in the intramolecular arylation of the halo enaminones **17**, **18**, and **22**, but the benzyne mechanism should be accepted by considering the reaction conditions adapted and the structure of these substrates with nonactivated aromatic rings.
(9) Cf. T. Kametani, "The Chemistry of the Isoquinoline Alkaloids", Vol. 2, The Sendai Institute of Heterocyclic Chemistry, Sendai, Japan, 1974, p 231.
(10) G. H. Alt in "Enamines: Synthesis, Structure, and Reactions", A. G. Cook, Ed., Marcel Dekker, New York, N.Y., 1969, p 116.
(11) Compound **37** was prepared by reduction of 3-bromo-4,5-methylenedioxybenzaldehyde [M. Tomita and Y. Aoyagi, *Chem. Pharm. Bull.*, **16**, 523 (1968)] with sodium borohydride, followed by treatment with thionyl chloride in a standard procedure.
(12) (a) From lycorine: K. Takeda and K. Kotera, *Chem. Pharm. Bull.*, **5**, 234 (1957). (b) From caranine: E. W. Warnhoff and W. C. Wildman, *J. Am. Chem. Soc.*, **79**, 2192 (1957).
(13) The IR and NMR spectra of **46** and **47** were kindly provided by Professor T. Sakan.
(14) K. Kotera, *Tetrahedron*, **12**, 248 (1961).
(15) Spectral analysis by IR, UV, and NMR has been proven to be effective for the determination of the enaminone structure.[7b]
(16) K. Kashima, M. Yamamoto, and N. Sugiyama, *J. Chem. Soc. C*, 111 (1970).
(17) R. Baltzy, V Dvorkovitz, and A. P. Phillips, *J. Am. Chem. Soc.*, **71**, 116 (1949).