H-11), 7.32 (d, 1, J = 7 Hz, H-9), 7.47 (d, 1, J = 7 Hz, H-12), 7.58 (s, 1, H-17); exact mass, m/e 394.1890 (calcd for $C_{23}H_{26}O_4N_2$ m/e 394.1891).

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"*tert*-Amino Effect" in Heterocyclic Synthesis. The Effect of a *p*-Quinone Moiety on the [1,6] H-Transfer and 1,5-Electrocyclization Reactions

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(Dialkylamino)benzo*quinone* **15** and (dialkylamino)naphtho*quinones* **32** and **34–37** undergo a thermal cyclization to the corresponding pyrrolo[1,2-*a*]indoles **41**, **43**, and **45–47** and to the pyrido[1,2-*a*]indole **44**, respectively. A corresponding *hydroquinone*, viz. (*E*/*Z*)-2,5-dimethoxy-α-(phenylmethylene)-3,6-di(1-pyrrolidinyl)benzeneacetonitrile (**18**), cyclizes only slowly to pyrrolo[1,2-*a*]indole **42**. The naphtho*hydroquinones* **38–40** do not undergo a thermal rearrangement. The results demonstrate the accelerating effect of the *quinone* function on the rate of the reaction, as a result of stabilization of the "*negative* end" of the intermediate 1,5-dipole. The presence of an electron-donating group at the β-carbon atom of the vinyl moiety lowers the rate of the reaction. Moreover, this influence is demonstrated by oxidation of one of the sulfur atoms in **35** to the ketene dithioacetal *S*-monooxide **36**, which undergoes a fast thermal isomerization to **47**. Cyclization of the pyrrolidinylnaphthoquinones **32**, **34**, and **35** yielded exclusively products in which H-11a and CN have a trans relationship, while in the case of piperidinylnaphthoquinone **37** predominantly *trans*-1*H*-benzo[*f*]pyrido[1,2-*a*]indole **44a** was formed. The trans stereochemistry of **43** was determined by single-crystal X-ray analysis. Heating of (dialkylamino)naphthoquinone **33** afforded the indoline **50** in low yield.

Introduction

In our studies on the "*tert*-amino effect" in heterocyclic chemistry[1,2] we have shown that 1-(1-pyrrolidinyl)-2-vinylbenzene derivatives **1** (Chart I) rearrange thermally to 2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles **2**.[3] This isomerization proceeds via two consecutive pericyclic reactions, viz. a [1,6] hydrogen transfer to give the 1,5-dipole **3** which undergoes a concerted 1,5-dipolar cyclization.[4] A prerequisite for this thermal isomerization is the stabilization of the negative charge in the 1,5-dipole **3** by an electron-withdrawing group (EWG). Furthermore, we have demonstrated the effect of both the substituent R and of different dialkylamino groups on the [1,6] hydrogen transfer and subsequent 1,5-electrocyclization.[5] Intermediates related to **3** in the formation of pyrrolo[1,2-*a*]indoles have been postulated by several other groups.[6,7]

The main reason for our current interest in the *tert*-amino effect is the possible application in the synthesis of isomitosanes,[8] analogues of the antitumor antibiotic mitomycin C.[5,9,10] In mitomycin C the basic skeleton contains a *p-quinone* function and therefore we have studied the influence of this oxidation state of 1-(1-pyrrolidinyl)-2-vinylbenzene derivatives on the rate of the thermal cyclization.

Previously, we reported the formation of the Michael adduct **4** in the reaction of 5,5-dimethyl-3-(1-pyrrolidinyl)-2-cyclohexen-1-one and dimethyl acetylenedicarboxylate (DMAD).[11] However, **4** could not be isomerized thermally into the corresponding pyrrolizine.[12] This lack of reactivity might be attributed to the less reactive "vinylogous amide" structure in **4**. On the other hand, 5,10-dioxo-1*H*-benzo[*f*]pyrrolo[1,2-*a*]indole **5** is formed by

Chart I

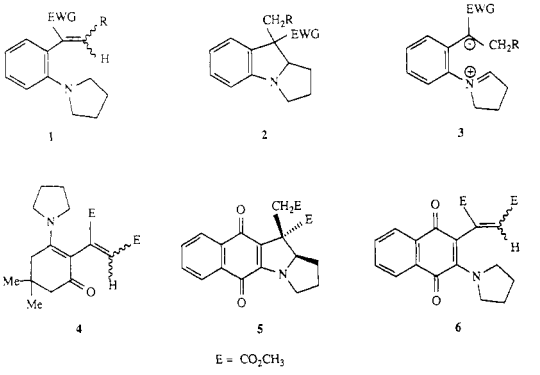
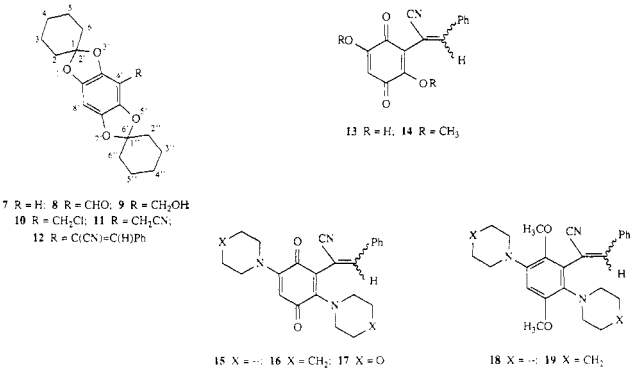


Chart II



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a reaction of 2-(1-pyrrolidinyl)-1,4-naphthoquinone with DMAD in 1-butanol at 70 °C, most likely via the Michael adduct **6**.[9] Since in **6** the nitrogen lone pair also constitutes part of a vinylogous amide system we decided to investigate the influence of both a benzo- and a naphthoquinone system on the rate of the 1,5-dipolar cyclization more systematically. This paper describes the synthesis and the thermal isomerization of *p*-quinones containing different *N,N*-dialkylamino groups and different electron-donating substituents at the β-carbon atom of the vinyl moiety.

Results

Synthesis of Starting Materials. The starting (dialkylamino)benzoquinones **15–17** were prepared in several steps from the known bisketal **7**.[13] Monolithiation of **7**,[13,14] using *n*-butyllithium (*n*-BuLi), followed by quenching of the anion with *N,N*-dimethylformamide (DMF) gave the *mono*formylated product **8** in a good yield (Chart II). Upon reduction with sodium borohydride ($NaBH_4$) the resulting benzyl alcohol **9**[15] was converted into the corresponding benzyl chloride **10**, under essentially neutral conditions, by refluxing **9** in carbon tetrachloride in the presence of excess of tri-*n*-butylphosphine [$(n\text{-Bu})_3P$].[16] Conversion of **10** into the corresponding benzyl cyanide **11** was accomplished by refluxing **10** in the presence of potassium cyanide (KCN) and 18-crown-6 in acetonitrile. Finally, the α-phenylmethylene group was introduced by condensation of the benzyl cyanide **11** with benzaldehyde in methanol with sodium methoxide as a base. During this reaction one isomer precipitated and after prolonged[17] reaction this isomer could be isolated in a yield of 77%; in addition a mixture of *E/Z* isomers was obtained as an oil in a yield of 8%. The stereochemistry of the isomers has not been determined, because it is not relevant for further reaction. Treatment of **12** with boron tribromide (BBr_3) in dichloromethane resulted in deketalization. Oxidation of the resulting tetrahydroxybenzene derivative with air, followed by methylation of the intermediate dihydroxy quinone **13** using diazomethane produced the dimethoxy quinone **14** in an overall yield of 55%.[18–21] Compound **14** was obtained as a mixture of *E/Z* isomers, as was demonstrated among others by a signal for =C*H*Ph at δ 6.99 (minor isomer) in the ^1H NMR spectrum, while that of the major isomer overlapped with the multiplet for =C(H)Ph*H* at δ 7.9–7.1. The dimethoxy quinone **14** is a suitable starting material for further conversion into amino quinones. Treatment of **14** with an excess of the appropriate amine in methanol afforded the disubstituted amino quinones **15–17** in excellent yields. With piperidine and morpholine mixtures of *E/Z* isomers were obtained; these were not separated. The reaction of **14** with pyrrolidine also afforded a mixture of *E/Z* isomers, from which a single isomer partially precipitated. The structures of the (dialkylamino)benzoquinones **15–17** were proven among others by ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum of one isomer of **15** showed two pyrrolidinyl moieties, i.e. signals at δ 4.2–3.0 (m, 8 H, NCH_2) and 2.1–1.7 (m, 8 H, CH_2), in addition to singlets at δ 6.74 [=C*H*(Ph)] and 5.32 (H-4). The spectra of **16** and **17** were very similar.

15 was converted by reductive methylation,[7a] i.e. via catalytic hydrogenation in the presence of dimethyl sulfate and $Ba(OH)_2{\cdot}8H_2O$, to **18** in order to study the influence of a quinone function on the thermal isomerization. Starting from a single isomer of dipyrrolidinyl quinone **15**

Chart III

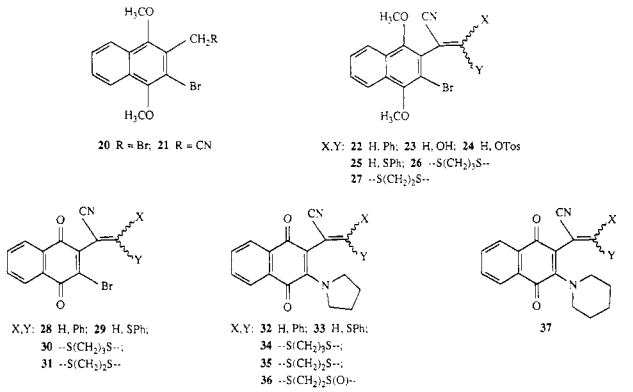
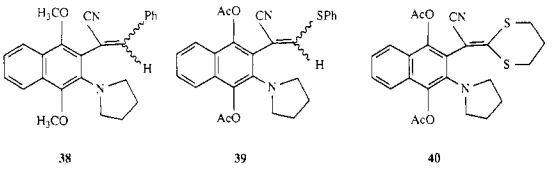


Chart IV



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(15) When we tried to prepare the tosylate of **9** using tosyl chloride and triethylamine in dichloromethane, we obtained the benzyl chloride **10** in a yield of 49%. We assume that the initially formed tosylate is substituted by the chloride ion produced.

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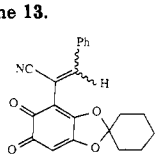
(17) After 4 h the reaction was complete and the precipitated isomer could be obtained in a yield of 57%, while in addition a mixture of *E/Z* isomers was isolated as an oil in a yield of 28%.

(18) Under hydrolytic conditions (4 M HCl/1,4-dioxane/40 °C) **12** decomposed and since the corresponding *o*-quinone might be a suitable precursor for the desired *p*-quinone **13**,[19,20] we prepared this *o*-quinone by reacting the bis(cyclohexylidene) ketal **12** with ceric ammonium nitrate (CAN).[19] Unfortunately, we were not able to convert this *o*-quinone into the corresponding *p*-quinone **13**.



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(21) Other methods to methylate **13** by using Me_2SO_4 or MeI failed. On a larger scale the methylation gave yields ranging from 30% to 37%.

the corresponding dimethyl hydroquinone **18** was obtained as a mixture of E/Z isomers in a yield of 50%. The ^1H NMR spectrum of **18** revealed among other signals at δ 6.39 and 6.34 (s, Ar H), 3.80, 3.56, and 3.51 (s, 3 H, 6 H, and 3 H, respectively, OCH_3), and 3.5–3.0 (m, NCH_2). The dimethyl dipiperidinyl hydroquinone **19** was prepared analogously as a single isomer in a yield of 49%.

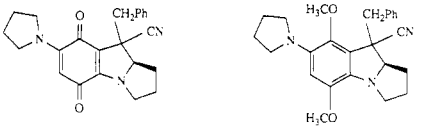
The starting amino quinones **32–37** in the naphthoquinone series were prepared in several steps from the known dibromide **20**.[22,23] Treatment of **20** with KCN and 18-crown-6 in refluxing acetonitrile gave the benzyl cyanide **21**, which was used as a starting material in all condensation reactions (Chart III). The α-phenylmethylene group was subsequently introduced by a reaction with benzaldehyde in methanol using sodium methoxide as a base; the overall yield of both reactions was 70%. Compound **22** was obtained as a mixture of E/Z isomers, which could be separated by chromatography to afford one isomer as a solid, while the other was isolated as an oil. Both isomers of **22** underwent oxidative demethylation upon treatment with ceric ammonium nitrate (CAN) in acetonitrile–water to afford the corresponding isomer of quinone **28** in a yield of 65%. In the case of the solid isomer of **28** the presence of a C=O function was clearly demonstrated by an absorption at 1680 cm^{-1} in the IR spectrum and by signals at δ 182.8 (s) and 178.9 (s) in the ^{13}C NMR spectrum. The bromine atom in quinone **28** was easily substituted by pyrrolidine, giving a mixture of E/Z isomers[24] of the pyrrolidinyl quinone **32** in a yield of 80%. The ^1H NMR spectrum of **32** revealed signals at δ 8.15–7.25 [m, 10 H, Ar H, Ph H, and =C*H*Ph (major isomer)], 6.99 [s, =C*H*Ph (minor isomer)], 3.9–3.6 [m, NCH_2 (major isomer)], 3.55–3.25 [m, NCH_2 (minor isomer)]. The piperidinyl quinone **37** was prepared in an analogous way to afford a mixture of E/Z isomers[24] in a yield of 80%.

The amino naphthoquinone **32** was converted into the corresponding dimethyl hydroquinone **38** (Chart IV) by reductive methylation in the same way as dipyrrolidinyl quinone **15** (vide supra). The E and Z isomers of **38** could be separated by chromatography, but the individual structures of the isomers have not been determined.

In order to study the influence of electron-donating substituents at the β-carbon atom of the vinyl moiety, we have prepared several substituted naphthohydroquinones (**23**, **25–27**). The sodium salt of α-(hydroxymethylene)-benzeneacetonitrile **23** was synthesized by condensation of benzeneacetonitrile **21** with ethyl formate and sodium hydride as a base in toluene[25] in a yield of 84%. Since neither α-(hydroxymethylene)benzeneacetonitrile **23** nor the corresponding methyl enol ether[26,27] could be transformed into the corresponding p-quinone, we decided to prepare the thio enol ether **25**. Starting from α-(hydroxymethylene)benzeneacetonitrile **23**, obtained after acidification of its sodium salt, the phenylthio enol ether **25** could be synthesized in pyridine using tosyl chloride and thiophenol.[28] After workup, in addition to the desired thio enol ether **25**, which was obtained in 70% yield, 5% of the tosylate intermediate **24** was also isolated. Proof for the structure of **24** was obtained from the spectroscopic data. The IR spectrum showed absorptions at 2210 cm^{-1} (CN) and at 1350 and 1180 cm^{-1} (OSO_2). In addition, the ^1H NMR spectrum exhibited signals at δ 8.2–7.9 and 7.8–7.25 (m, Ar H, Ph H and =C*H*Ph), 3.93 and 3.78 (s, OCH_3), and 2.47 (s, CH_3). Phenylthio enol ether **25** was isolated as a mixture of E/Z isomers, as shown by absorptions in the ^1H NMR spectrum at δ 4.03, 3.98, and 3.95 (s, 3 H, 6 H, and 3 H, respectively, OCH_3) and by two signals of the CN group at 2250 and 2210 cm^{-1} in the IR spectrum. The hydroquinone **25**, containing a phenylthio enol ether moiety, was converted into the corresponding p-quinone **29** by using CAN. Subsequent treatment of this unstable bromo quinone **29** with pyrrolidine in benzene–ethanol, in the same way as described for the synthesis of **32** (vide supra), gave the pyrrolidinyl quinone **33** as one isomer in an overall yield of 34%. The synthesis of the protected hydroquinone derivative **39** was accomplished by reductive acylation using zinc dust in acetic anhydride in the presence of triethylamine as a base[29] to give a mixture of E and Z isomers of 1,4-bis(acetyloxy)naphthaleneacetonitrile **39** in 41% yield. Condensation of benzyl cyanide **21** with carbon disulfide in the presence of potassium *tert*-butoxide[30] in THF, followed by dialkylation with 1,3-dibromopropane or 1,2-dibromoethane, gave the ketene dithioacetals **26** and **27**, respectively. Oxidative demethylation of these dimethyl hydroquinones **26** and **27** using CAN gave the corresponding quinones **30** and **31**, respectively. Substitution of the bromine atom in **30** by pyrrolidine afforded **34**. In the same way, we prepared **35** from **31**. Since electron-donating substituents at the β-carbon atom of the vinyl moiety lower the rate of the thermal isomerization,[5] we also converted **35** into the ketene dithioacetal S-monooxide **36** by careful oxidation with *m*-chloroperbenzoic acid.[31] The presence of the electron-withdrawing sulfoxide in **36** should enable a faster 1,5-electrocyclization. In analogy with the reductive acylation of the phenylthio enol ether **33**, we converted ketene dithioacetal **34** into the corresponding diacetate **40**.

Thermal Cyclization. Heating of the dipyrrolidinyl *quinone* **15** in toluene or in 1-butanol gave a mixture of *cis*- and *trans*-2,3,5,8,9,9a-hexahydro-5,8-dioxo-9-(phenylmethyl)-7-(1-pyrrolidinyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (**41a** and **41b**), respectively (Chart V). The ratio of cis and trans isomers **41a** and **41b** depends on the solvent. In 1-butanol the reaction proceeded at 100 °C in 3 h to give a mixture of **41a** and **41b** in a ratio of about

Chart V



41a α-CN
41b β-CN
42a α-CN
42b β-CN

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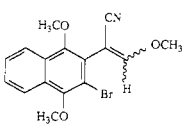
(26) A reaction of the sodium salt of **23** with dimethyl sulfate in acetonitrile gave the corresponding α-(methoxymethylene)benzeneacetonitrile. However, this methylated hydroquinone could not be converted into the corresponding p-quinone. Oxidative demethylation using CAN, Fremy's salt, argentic oxide,[27] or silver(II) dipicolinate[22] only gave decomposition.



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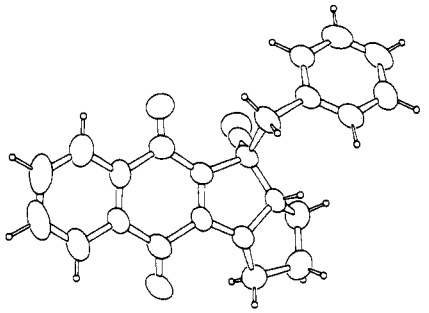


Figure 1. X-ray crystal structure of **43**.

2:1. In toluene a complete conversion of starting material **15** was accomplished at 100 °C in 8 h, giving **41a** and **41b** in a ratio of about 1:2. The assignment of the stereochemistry of the isomers is based upon comparison of the characteristic NMR data, i.e. the CH_2Ph hydrogen atoms and NCH and the CH_2Ph carbon atoms, with those of the *trans*-naphthoquinone **43** (vide infra), the structure of which has been unequivocally determined by X-ray analysis. In the ^1H NMR spectrum the CH_2Ph absorptions of **41a** (cis) are present at δ 4.02 and 2.95 (AB q, J = 15.0 Hz), while those of **41b** are situated at approximately δ 3.9[32] and 3.00 (AB q, J = 13.7 Hz). In addition, the ^{13}C NMR spectra of **41** exhibited CH_2Ph and NCH signals of **41a** at δ 37.8 and 75.0, respectively, and CH_2Ph and NCH signals of **41b** at δ 42.1 and 72.5, respectively.

Conversion of the E/Z mixture of the corresponding dipyrrolidinyl hydroquinone **18**[33] required refluxing in 1-butanol for 116 h.[34] After chromatography the *cis*- and *trans*-tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles (**42a** and **42b**) were isolated in yields of 85% and 5%, respectively. The structural assignment of these isomers is based upon comparison of the characteristic NMR data, i.e. the CH_2Ph hydrogen atoms and the NCH and CH_2Ph carbon atoms, with those of similar tetrahydro-1*H*-pyrrolo[1,2-*a*]-indoles.[3,10b] In the ^1H NMR spectrum of **42a** the CH_2Ph absorptions are present at δ 4.10 and 3.13 (AB q, J = 15.2 Hz), while those of **42b** are situated at approximately δ 4.2[32] and 2.78 (AB q, J = 13.4 Hz). In addition, the ^{13}C NMR spectrum of cis isomer **42a** exhibited CH_2Ph and NCH signals at δ 39.3 and 74.4, respectively, while the corresponding absorptions of **42b** are situated at δ 45.2 and 73.0, respectively.[35] The dipiperidinyl and dimorpholinyl quinones **16** and **17**, respectively, could not be thermally isomerized due to decomposition when heated.

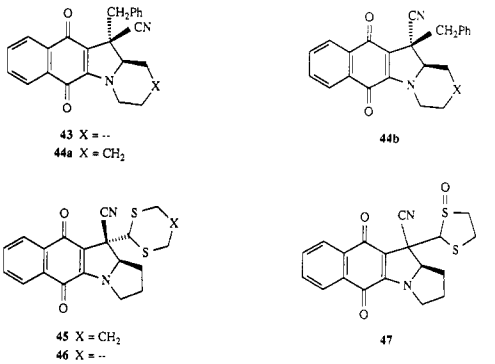
Refluxing naphthoquinone **32** in 1-butanol for 3 h gave only one isomer of 1*H*-benzo[*f*]pyrrolo[1,2-*a*]indole **43** in a yield of 70%. From the characteristic absorptions at δ 3.86 and 3.10 (AB q, J = 13.9 Hz, CH_2Ph) in the ^1H NMR spectrum and at δ 71.5 (NCH) and 42.2 (CH_2Ph) in the ^{13}C NMR spectrum a definite assignment of the stereochemistry was not possible. However, the definite structure proof was given by X-ray analysis (Figure 1), which revealed that **43** has the trans configuration. When the amino quinone **32** was refluxed in toluene for 8 h, again the trans isomer was obtained as the single cyclization product but only in a yield of 33%. Thermal cyclization of piperidinyl quinone **37** in refluxing 1-butanol gave after 3 h in 25% overall yield a mixture of the *trans*- and *cis*-1*H*-benzo[*f*]pyrido[1,2-*a*]indoles **44a** and **44b**, respectively, in a ratio of 20:1 (Chart VI). Since a considerable amount of decomposition was observed in this reaction, we decided to investigate the stability of the products formed by refluxing for an additional 3 h in 1-butanol. Both products remained stable and therefore we concluded that only the starting amino quinone **37** decomposes under the conditions used in the cyclization. The structural assignment of the *trans*- and *cis*-1*H*-benzo[*f*]pyrido[1,2-*a*]indoles **44a** and **44b** is based upon comparison of the characteristic NMR data with those of *trans*-1*H*-benzo[*f*]pyrrolo[1,2-*a*]indole **43**. In the ^1H NMR spectrum of the trans isomer **44a**, the NCH signals are present at δ 4.8–4.55 (m) and the CH_2Ph absorptions at δ 3.53 and 3.11 (AB q, J = 13.9 Hz), while for the cis isomer **44b** these absorptions are situated at δ 5.1–4.8 (m) and 3.35–3.0 (m), respectively. The trans isomer **44a** exhibited absorptions at δ 67.9 (NCH) and 41.7 (CH_2Ph) in the ^{13}C NMR spectrum, while the corresponding signals of the cis isomer **44b** are found at δ 72.0 and 36.7.

The corresponding dimethoxynaphthalene **38** did not cyclize in 1-butanol or mesitylene upon refluxing for 14 days; only decomposition of **38** was observed.

Heating of quinone **33** in 1-butanol[36] for 8 h at 90 °C gave in addition to starting material (10%) the indoline **50** in a yield of 20%. The mass spectrum of **50** revealed a ($M^+ - 2$) peak for $C_{27}H_{26}N_2O_3S$, i.e. the sum of the molecular formula of starting compound **33** ($C_{23}H_{18}N_2O_2S$) and 1-butanol minus 2 H. The ^1H NMR spectrum exhibited among others multiplets at δ 4.8–4.7 (1 H, CHCN), 3.9–3.75 (1 H, NCHS), 3.7–3.2 (6 H, 2 × OCH_2 and NCH_2) and 2.25–1.15 (8 H, CH_2). The corresponding diacetate **39**, in which the quinone function is absent, failed to undergo thermal isomerization.

Refluxing the ketene dithioacetal **34** for 10 days in 1-butanol gave the cis isomer **45**[37] in 80% yield. The

Chart VI

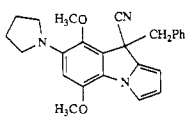


(32) This part of the AB system overlapped with the signals of the NCH_2 moiety.

(33) When a mixture of E/Z isomers of the dipiperidinyl hydroquinone **19** was heated in 1-butanol or toluene decomposition occurred.

(34) In refluxing toluene or mesitylene no cyclization took place.

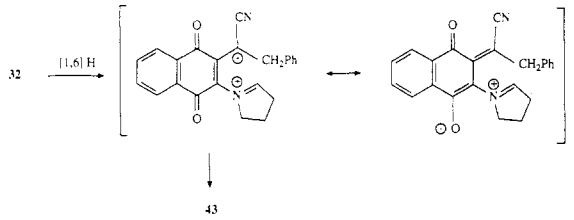
(35) Oxidative demethylation of the hydroquinone **42** with CAN gave a red compound in low yield (18%). The M^+ value 399.192 (M^+, calcd for $C_{25}H_{25}N_3O_2$ 399.195) is in agreement with 5,8-dimethoxy-9-(phenylmethyl)-7-(1-pyrrolidinyl)-9*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (vide infra) and in the ^1H NMR spectrum typical absorptions, which correspond with those of the previously described 5-amino-7-methoxy-6-methyl-9-(phenylmethyl)-9*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile,[10b] are located at δ 6.25–6.15 (m, H-2) and at δ 5.88 (dd, J = 3.7 and 1.0 Hz, H-1). Previously, we have reported[10b] that a similar pyrrolo[1,2-*a*]indole underwent aromatization under oxidative conditions, i.e. using Fremy's salt.



(36) In DMSO or toluene at 90 °C only decomposition of starting material took place.

(37) It should be noticed that the nomenclature of the stereochemistry of compound **45** is just opposite that of the other pyrrolo[1,2-*a*]indoles, e.g. **43** (compare Section 203 of Appendix IV to the 1984 Chemical Abstracts Index Guide); the relative stereochemistry of C-1 and CN is the same.

Scheme I



structural assignment of **45** is based on comparison of the characteristic ^{13}C NMR data with those of *trans*-1*H*-benzo[*f*]pyrrolo[1,2-*a*]indole **43**, more specifically the C-11 and NCH absorptions of **45** which are situated at δ 52.3 and 70.1, respectively. In toluene the cyclization took place in low yield (10%) to the cis isomer. The ketene dithioacetal **35** was converted very slowly into *cis*-1*H*-benzo[*f*]-pyrrolo[1,2-*a*]indole **46**, after 30 days of refluxing in 1-butanol only 40% had reacted. The assignment of the stereochemistry of **46** is based on comparison of the characteristic NMR data with those of **45** and **43**. In case of the ketene dithioacetal *S*-monooxide **36**, in which one of the sulfur atoms is oxidized, the thermal rearrangement to **47** in refluxing 1-butanol was very fast (1.5 h). The resulting reaction mixture contained several isomers of **47**, which were not separated.[38] The corresponding ketene dithioacetal diacetate **40** did not undergo cyclization either in mesitylene or in DMSO.

Discussion

Despite the fact that in the (dialkylamino) quinones, e.g. **15** and **32**, the nitrogen lone pair constitutes part of a vinylogous amide system, which might render [1,6] hydrogen transfer unfavorable due to a lower electron density at the nitrogen atom, experimentally a very fast cyclization is observed. Therefore we conclude that the predominant effect of a quinone function is the stabilization of the *negative* end of the 1,5-dipole that is formed upon a thermal antarafacial[39] [1,6] hydrogen transfer (Scheme I).

This is clearly demonstrated when we compare the rates of the thermal isomerization of the dipyrrolidinyl *hydroquinone* **18** and the corresponding dipyrrolidinyl *quinone* **15**, which cyclizes with a rate that is about 42 times faster.[40] Of the examples described in the present study dipyrrolidinyl hydroquinone **18** is the only *hydroquinone* which undergoes a thermal rearrangement, in contrast to the cyclization of most of the *quinones*. Since we have proven that the [1,6] hydrogen transfer comprises the rate-determining step in the thermal isomerization,[4] groups stabilizing the 1,5-dipole will lower the activation energy. In the case of **18**, which lacks the stabilizing effect of a quinone function, additional stabilization of the *positive* end of the 1,5-dipole is provided by the field and inductive (−I) effects of the pyrrolidinyl group in the para position.

Stabilization of the intermediate iminium ion in the 1,5-dipole is mainly dependent on the efficiency of the overlap between the lone pair of the nitrogen atom and the π-system of the aromatic ring.[3,41] This effect may be the reason why dipiperidinyl *hydroquinone* **19** and both the quinones **16** and **17** do not undergo a thermal rearrangement. On the other hand, piperidinyl *naphthoquinone* **37** isomerizes thermally to the 1*H*-benzo[*f*]-pyrido[1,2-*a*]indole **44**. A comparison of the cyclization rates of pyrrolidinyl naphthoquinones **32** to **43** and piperidinyl naphthoquinone **37** to **44**, however, is complicated by the fact that extensive decomposition of **37** occurs on heating. The reason why piperidinyl*naphthoquinone* **37** cyclizes to **44** while both dipiperidinyl- and dimorpholinyl*benzoquinone* (**16** and **17**) do not rearrange thermally may be that **37** possesses more "enamine character" which renders a [1,6] hydrogen transfer more facile.[42,43] In agreement with earlier studies[5] the presence of an electron-donating group at the β-carbon atom of the vinyl moiety lowers the rate of cyclization, because a decrease of the electron density at the adjacent carbon atom will make the [1,6] hydrogen shift less favorable. Due to the *quinone* moiety in **34** this compound undergoes a thermal rearrangement to the 1*H*-benzo[*f*]pyrrolo[1,2-*a*]-indole **45**, despite of the fact that two "destabilizing substituents" of a ketene dithioacetal moiety are present at the β-carbon atom of the vinyl group. In analogy with the thermal isomerization of **34** to **45**, the ketene dithioacetal derivative **35**, containing a five-membered ring, also cyclizes to the 1*H*-benzo[*f*]pyrrolo[1,2-*a*]indole **46**, although much slower than the ketene dithioacetal **34**. The explanation for this difference may be found in the relative torsional strain in the two systems, according to the concept of I strain.[44-47] A conversion of the sp^2-hybridized carbon atom in the five-membered ketene dithioacetal to sp^3 increases the number of eclipsing interactions. A similar process in the six-membered ketene dithioacetal leads to a completely staggered arrangement of bonds. In addition, the effect of an electron-donating group at the β-carbon atom of the vinyl moiety is clearly demonstrated by comparing the rates of cyclization of **32** with **34** and **35**, i.e. 3 h for **32**, 10 days for **34**, and about 75 days for **35**. Moreover, this influence is shown by oxidation of one of the sulfur atoms in **35** to the ketene dithioacetal *S*-monooxide **36**. As a result **36** cyclizes in 1.5 h to **47**.

Our work on the thermal rearrangement of 1-(1-pyrrolidinyl)-2-vinylbenzene derivatives **1** has revealed the crucial role of the solvent both on the rate of the cyclization and on the stereochemistry of the products **2**.[3,5,10b] In apolar solvents the 1,5-dipolar intermediate, e.g. **3**, is not stabilized and stereomutation does not occur, resulting in the formation of the trans isomer. In polar solvents stereomutation of the 1,5-dipolar intermediates generally occurs,[4] as a result of a better solvation of the intermediate, to give the cis isomer. However, it appears that in the pyrrolidinyl naphthoquinones **32**, **34**, and **35** the solvent has *no influence* on the stereochemistry of the product.

(38) The isomers could be partly separated by chromatography (EtOAc). The overall yield of the oxidation reaction of **35** and the thermal isomerization of **36** was 50%. Mass spectrum of **47**, *m/e* 484.058 (M^+, calc for $C_{19}H_{16}N_2O_3S_2$ 484.060). Characteristic ^1H NMR data of three isomers ($CDCl_3$, δ):

	CHSO (s)	NCH [AB q, *J* (Hz)]	CH_2SO (m)
A	6.00	4.67 4.62 (5.8)	3.75–3.6 2.8–2.6
B	5.59	4.87 4.82 (6.0)	3.7–3.55 3.0–2.75
C	4.19	4.84 4.79 (5.8)	3.7–3.55 3.0–2.8

(39) (a) This shift is electronically equivalent with a [1,7] hydrogen shift in an all carbon system[39b] since the lone pair of the nitrogen atom contributes two π-electrons. (b) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 2511.

(40) In refluxing 1-butanol dipyrrolidinyl quinone **15** cyclizes in about 2 h and 45 min.

(41) Effenberger, F.; Fischer, P.; Schoeller, W. V.; Stohrer, W.-D. *Tetrahedron* **1978**, *34*, 2409.

(42) E.g. 2-(1-pyrrolidinyl)-1,4-*naphthoquinone* reacts with DMAD in 1-butanol at 70 °C,[9] while 2-(1-pyrrolidinyl)-1,4-*benzoquinone* derivatives do not react with DMAD at all.[43]

(43) Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 199.

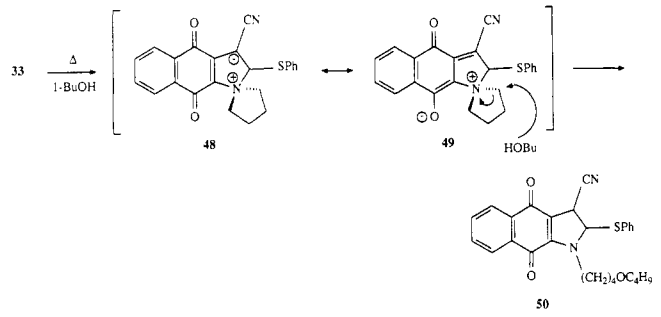
(44) Pasto, D. J.; Gontarz, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 6909.

(45) Brown, H. C. *J. Org. Chem.* **1957**, *22*, 439.

(46) Brown, H. C.; Brewster, J. H.; Shechter, H. *J. Am. Chem. Soc.* **1954**, *76*, 467.

(47) Brown, H. C. *Tetrahedron* **1957**, *1*, 221.

Scheme II



In a polar solvent like 1-butanol or in apolar solvents like toluene or mesitylene, the relative stereochemistry of H-11a and CN in the 1*H*-benzo[*f*]pyrrolo[1,2-*a*]indoles **43**, **45**, and **46** is the same, i.e. trans. Most likely, the quinone function fixes the intermediate formed by the concerted [1,6] hydrogen shift (Scheme I). The results of the thermal isomerization of **15** show that the trans isomer is the major isomer when toluene is used as a solvent, while in 1-butanol the cis isomer is the major product.[48] When dipyrrolidinyl hydroquinone **18** is refluxed in *1-butanol* the cis isomer **42a** is formed predominantly, in agreement with the mechanism of the concerted disrotatory 1,5-electrocyclization, which we have discussed previously.[3,4]

Finally, the formation of indoline **50** represents another variation of the "*tert*-amino effect".[5] We assume that a spiro intermediate such as **48** is formed, which is stabilized by resonance (**49**); subsequently, a nucleophilic attack by a solvent molecule yields indoline **50** (Scheme II).

We are aware that the formation of **50** is not in agreement with Baldwin's rules, i.e. the conversion of **33** into **50** is an example of a 5-*Endo-Trig* ring closure.[49-51] However, the formation of **50** is not the only example of a 5-*Endo-Trig* reaction pathway we have found, because previously we reported[5] the synthesis of 1-alkylindoles, that represents a similar variation of the "*tert*-amino effect".

Conclusion

We can conclude that a *quinone function* has an accelerating effect on the 1,5-electrocyclization and it appears that the rate of [1,6] hydrogen transfer is most influenced by the stabilization of the *negative* end of the intermediate 1,5-dipole. The use of this principle constitutes a simple method for the synthesis of pyrrolo[1,2-*a*]indoles containing a *p*-quinone function. Further work on the synthesis of isomitosanes using this methodology is in progress.

Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^{1}H NMR spectra ($CDCl_3$) were recorded with a Bruker WP-80 spectrometer and ^{13}C NMR spectra ($CDCl_3$) were recorded with a Nicolet MT 200 spectrometer (Me_4Si as an internal standard). Mass spectra were recorded with a Varian MAT 311A spectrometer and IR spectra with a Perkin-Elmer 257 spectrophotometer. Elemental analyses were carried out by E. Hoogendam and A. Christenhusz of the Laboratory of Chemical Analysis of the University of Twente.

CH_2Cl_2 was distilled from P_2O_5; THF from sodium/benzophenone ketyl. Petroleum ether refers to the fraction with bp 60–80 °C.

Column chromatography was performed with silica gel.

All reactions were carried out under a nitrogen atmosphere.

Dispiro[cyclohexane-1,2′-benzo[1,2-*d*:4,5-*d*′]bis[1,3]dioxole-6′,1″-cyclohexane]-4′-carboxaldehyde (8). To a solution of **7**[13,14] (6.04 g, 20.0 mmol) in THF (85 mL) was added *n*-BuLi (16.3 mL, 22.0 mmol, 1.35 M solution in hexane) at 0 °C, while the temperature was kept below 5 °C. Subsequently, the mixture was stirred for 30 min at 0 °C, 2 h at room temperature, and 10 min at 35 °C. The solution was cooled to 0 °C followed by the addition of DMF (3.04 g, 40.0 mmol) at such a rate that the temperature did not rise above 10 °C. Subsequently, the reaction mixture was allowed to warm to room temperature. After being stirred for 17 h, the resulting solution was concentrated to 30 mL, water (50 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 100 mL). The combined organic layers were washed with a saturated NH_4Cl solution (100 mL) and water (100 mL), dried with $MgSO_4$, and evaporated. The crude residue was triturated with MeOH to give pure **8**: yield 83%; mp 154–156 °C (MeOH); ^{1}H NMR δ 10.11 (s, 1 H, CHO), 6.53 (s, 1 H, Ar H), 2.1–1.3 (m, 20 H, CH_2); ^{13}C NMR[52] δ 185.4 (d, CHO), 140.8 (s, C-3′a), 120.9 (s, C-4′), 106.5 (s, C-1), 98.3 (d, C-8′), 43.9 (t, C-2), 24.5 (t, C-4), 23.2 (t, C-3); IR (KBr) 1695 (C=O) cm^{-1}; mass spectrum, *m/e* 330.145 (M^+, calcd 330.147).

Anal. Calcd for $C_{19}H_{22}O_5$ (M_r 330.382): C, 69.07; H, 6.71. Found: C, 68.81; H, 6.66.

Dispiro[cyclohexane-1,2′-benzo[1,2-*d*:4,5-*d*′]bis[1,3]dioxole-6′,1″-cyclohexane]-4′-methanol (9). To a solution of **8** (5.51 g, 17.0 mmol) in a mixture of THF, MeOH, and water (6:1:1, total volume 640 mL) was added a portion of $NaBH_4$ (1.30 g, 34.2 mmol). After stirring for 1.5 h, another portion of $NaBH_4$ (0.50 g, 13.2 mmol) was added and stirring was continued for 1.5 h. Subsequently, the reaction mixture was concentrated to 150 mL and the resulting solution was extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with a saturated NH_4Cl solution (2 × 150 mL) and water (100 mL), dried with $MgSO_4$, and evaporated. The crude compound was purified by chromatography ($CHCl_3$) to afford an oil, which crystallized upon adding some drops of petroleum ether: yield 86%; mp 126–127 °C (petroleum ether); ^{1}H NMR δ 6.28 (s, 1 H, Ar H), 4.66 (s, 2 H, CH_2O), 2.0–1.3 (m, 20 H, CH_2); ^{13}C NMR[52] δ 140.1 and 138.4 (s, C-3′a and C-8′a), 118.9 (s, C-4′), 107.0 (s, C-1), 92.2 (d, C-8′), 55.9 (t, CH_2O), 34.9 (t, C-2), 24.6 (t, C-4), 23.3 (t, C-3); mass spectrum, *m/e* 332.161 (M^+, calcd 332.163).

Anal. Calcd for $C_{19}H_{24}O_5$ (M_r 332.398): C, 68.66; H, 7.28. Found: C, 68.52; H, 7.29.

4′-(Chloromethyl)dispiro[cyclohexane-1,2′-benzo[1,2-*d*:4,5-*d*′]bis[1,3]dioxole-6′,1″-cyclohexane] (10). A solution of **9** (2.23 g, 6.7 mmol) and $(n\text{-Bu})_3P$ (2.71 g, 13.4 mmol) in CCl_4 (100 mL) was refluxed for 24 h, whereupon another portion of $(n\text{-Bu})_3P$ (1.00 g, 5.0 mmol) was added slowly at room temperature and refluxing was continued for 48 h. After cooling to room temperature, water (75 mL) was added and the mixture was stirred overnight. Subsequently, the layers were separated, and the organic layer was dried with $MgSO_4$ and passed through a short column of silica gel, using an additional 200 mL of $CHCl_3$. After evaporation of the solvent the resulting solid was triturated with MeOH to give pure **10**: yield 95%; mp 122–124 °C (MeOH); ^{1}H NMR δ 6.31 (s, 1 H, Ar H), 4.54 (s, 2 H, CH_2Cl), 2.1–1.3 (m, 20 H, CH_2); ^{13}C NMR[52] δ 140.1 and 139.1 (s, C-3′a and C-8′a), 119.3 (s, C-4′), 103.9 (s, C-1), 93.2 (d, C-8′), 35.3 (t, CH_2Cl), 34.9 (t, C-2), 24.6 (t, C-4), 23.2 (t, C-3); mass spectrum, *m/e* 350.129 (M^+, calcd 350.129).

Anal. Calcd for $C_{19}H_{23}ClO_4$ (M_r 350.844): C, 65.05; H, 6.61. Found: C, 65.21; H, 6.68.

Dispiro[cyclohexane-1,2′-benzo[1,2-*d*:4,5-*d*′]bis[1,3]dioxole-6′,1″-cyclohexane]-4′-acetonitrile (11). A mixture of **10** (1.43 g, 4.1 mmol), KCN (1.33 g, 20.4 mmol), and 18-crown-6 (0.40 g, 1.9 mmol) in acetonitrile (50 mL) was refluxed for 5 h. After cooling to room temperature, the salts were filtered off, and the filtrate was concentrated. The residue was taken up in $CHCl_3$ (150 mL) and washed with water (2 × 100 mL). After drying the organic layer with $MgSO_4$ and evaporation of the solvent **11** was obtained in a quantitative yield: mp 124–126 °C (MeOH); ^{1}H

(48) The reason why stereomutation occurs during the thermal isomerization of **15** may be attributed to the presence of the *p*-amino group, which may compensate for the effect of fixation of the quinone function.

(49) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(50) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.

(51) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738.

(52) The bisketals **8–12** are symmetrical, therefore we have assigned the absorptions in the ^{13}C NMR spectrum to only one carbon atom.

NMR δ 6.30 (s, 1 H, Ar H), 3.56 (s, 2 H, CH_2CN), 2.1–1.3 (m, 20 H, CH_2); ^{13}C NMR[52] δ 140.2 and 138.8 (s, C-3′a and C-8′a), 119.6 and 116.4 (s, C-4′ and CN), 95.7 (s, C-1), 92.8 (d, C-8′), 34.9 (t, C-2), 24.6 (t, C-4), 23.2 (t, C-3), 12.8 (t, CH_2CN); IR (KBr) 2260 (CN) cm^{-1}; mass spectrum, *m/e* 341.165 (M^+, calcd 341.163).

Anal. Calcd for $C_{20}H_{23}NO_4$ (M_r 341.408): C, 70.36; H, 6.79; N, 4.10. Found: C, 70.48; H, 6.89; N, 3.92.

(*E,Z*)-α-(Phenylmethylene)dispiro[cyclohexane-1,2′-benzo[1,2-*d*:4,5-*d*′]bis[1,3]dioxole-6′,1″-cyclohexane]-4′-acetonitrile (12). Cyanide **11** (0.60 g, 1.8 mmol) was added to a solution of sodium methoxide (0.13 g Na, 5.7 mmol) in MeOH (30 mL). After the reaction mixture was heated for 35 min at 40–50 °C, freshly distilled benzaldehyde (0.56 g, 5.3 mmol) was added and the solution was refluxed for 7 h. After cooling to 0 °C the precipitate was filtered off to afford one isomer of **12** in a yield of 77%. The filtrate was concentrated to 10 mL, $CHCl_3$ (30 mL) was added, and the resulting solution was washed thoroughly with a 15% $NaHSO_3$ solution (3 × 75 mL), $NaHCO_3$ solution (75 mL), and water (75 mL). After drying with $MgSO_4$ and removal of the solvent the resulting crude compound was purified by chromatography ($CHCl_3$:petroleum ether = 3:1) to give a mixture of *E/Z* isomers as an oil in 8% yield. Only the data of the major isomer are given.

Major isomer: mp 171–172 °C (MeOH); ^1H NMR δ 8.0–7.8 and 7.6–7.4 (m, 5 H, Ph H), 7.70 (s, 1 H, =CH), 6.36 (s, 1 H, H-8′), 2.1–1.3 (m, 20 H, CH_2); ^{13}C NMR[52] δ 146.5 (d, =CH), 140.7 and 137.8 (s, C-3′a and C-8′a), 119.5 and 116.7 (s, C-4′ and CN), 103.1 and 102.5 [s, C-1 and =*C*(CN)], 93.4 (d, C-8′), 34.9 (t, C-2), 24.6 (t, C-4), 23.3 (t, C-3); IR (KBr) 2210 (CN) cm^{-1}; mass spectrum, *m/e* 429.190 (M^+, calcd 429.194).

Anal. Calcd for $C_{27}H_{27}NO_4$ (M_r 429.517): C, 75.50; H, 6.34; N, 3.26. Found: C, 75.64; H, 6.35; N, 3.16.

(*E,Z*)-2,5-Dimethoxy-3,6-dioxo-α-(phenylmethylene)-1,4-cyclohexadiene-1-acetonitrile (14). To a solution of **12** (0.40 g, 0.9 mmol) in CH_2Cl_2 (20 mL) was added a solution of BBr_3 (2.39 g, 9.3 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After stirring for 1.5 h at 0 °C, water (30 mL) was slowly added at such a rate that the temperature did not rise above 25 °C. Subsequently, the pH of the water layer was set to 9 by adding a 2 M NaOH solution and the mixture was stirred in open air for 1.5 h, followed by the addition of a 4 M HCl solution to adjust the pH to 1. The layers were separated and the water layer was extracted with CH_2Cl_2 (6 × 40 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated to afford crude **13**, which was used without purification: ^1H NMR (DMSO-d_6) δ 9.3 (br s, 2 H, OH), 7.9–7.2 (m, 6 H, =CH and PhH), 5.80 (s, 1 H, H-4); mass spectrum, *m/e* 267.052 (M^+, calcd for $C_{15}H_9NO_4$ 267.053).

To a solution of crude **13** in CH_2Cl_2 (50 mL) was added a solution of CH_2N_2 (2.0 mmol) in Et_2O (6 mL) and the whole was stirred for 5 min. Subsequently, acetic acid was added to destroy the excess of CH_2N_2, whereupon the resulting solution was washed with a $NaHCO_3$ solution (50 mL) and water (50 mL). After drying with $MgSO_4$ and removal of the solvent the resulting crude compound was purified by chromatography (EtOAc) to give **14** as a mixture of *E/Z* isomers as an oil in a yield of 55% (from **12**): ^1H NMR δ 7.9–7.1 (m, 6 H, PhH and =CH of the major isomer), 6.99 (s, 1 H, =CH), 5.83 (s, 1 H, H-4), 4.22, 4.00, 3.83, and 3.61 (s, 3 H, OCH_3); IR (KBr) 2210 and 2200 (CN) cm^{-1}; mass spectrum, *m/e* 295.085 (M^+, calcd for $C_{17}H_{13}NO_4$ 295.084).

General Procedure for the Synthesis of the (Dialkylamino)benzoquinones 15–17. To a solution of **14** (1.00 g, 3.4 mmol) in MeOH (80 mL) was added the amine (10.2 mmol) at room temperature and stirring was continued for 1.5 h. In the case of **15** the precipitate was filtered off and washed with MeOH to give one pure isomer in a yield of 57%, while the filtrate was evaporated and subjected to chromatography (EtOAc) to afford an oil containing a 1:1 mixture of *E/Z* isomers in a yield of 38%. In the case of the dipiperidinyl quinone **16** and the dimorpholinyl quinone **17** the solvent and excess amine were evaporated, and the residue was subsequently purified by chromatography (EtOAc).

(*E*)- or (*Z*)-3,6-Dioxo-α-(phenylmethylene)-2,5-di(1-pyrrolidinyl)-1,4-cyclohexadiene-1-acetonitrile (15). Major isomer: mp 175–176 °C (EtOH); ^1H NMR δ 7.9–7.8 and 7.6–7.3 (m, 5 H, Ph H), 6.74 (s, 1 H, =CH), 5.32 (s, 1 H, H-4), 4.2–3.0 (m, 8 H, NCH_2), 2.1–1.7 (m, 8 H, CH_2); ^{13}C NMR δ 181.2 (s, C=O), 151.8 and 149.8 (s, C-2 and C-5), 145.8 (d, =CH), 118.6 (s, CN), 107.1 [s, =*C*(CN)], 98.4 (d, C-4), 54.8 (t, NCH_2), 25.4 (t, CH_2); IR (KBr) 2200 (CN), 1615 (C=O) cm^{-1}; mass spectrum, *m/e* 373.178 (M^+, calcd 373.179).

Anal. Calcd for $C_{23}H_{23}N_3O_2$ (M_r 373.456): C, 73.97; H, 6.21; N, 11.25. Found: C, 73.95; H, 6.14; N, 11.26.

(*E,Z*)-3,6-Dioxo-α-(phenylmethylene)-2,5-di(1-piperidinyl)-1,4-cyclohexadiene-1-acetonitrile (16): yield 93%; oil; isomer ratio = 7:3; ^1H NMR δ 8.0–7.7 and 7.6–7.2 (m, 5 H, Ph H), 6.98 and 6.92 (s, 1 H, =CH), 5.61 and 5.55 (s, 1 H, H-4), 3.8–3.2 (m, 8 H, NCH_2), 2.0–1.2 (m, 12 H, CH_2); IR (KBr) 2230 and 2210 (CN), 1630 (C=O) cm^{-1}; mass spectrum, *m/e* 401.212 (M^+, calcd for $C_{25}H_{27}N_3O_2$ 401.210).

(*E,Z*)-3,6-Dioxo-2,5-di(4-morpholinyl)-α-(phenylmethylene)-1,4-cyclohexadiene-1-acetonitrile (17): yield 91%; oil; isomer ratio = 2:1; ^1H NMR δ 7.9–7.75 and 7.7–7.1 (m, 5 H, Ph H), 7.19 and 7.00 (s, 1 H, =CH), 5.82 and 5.63 (s, 1 H, H-4), 4.0–3.3 (m, 16 H, NCH_2 and OCH_2); IR (KBr) 2220 (CN), 1630 (C=O) cm^{-1}; mass spectrum, *m/e* 405.165 (M^+, calcd for $C_{25}H_{27}N_3O_2$ 405.169).

(*E,Z*)-2,5-Dimethoxy-α-(phenylmethylene)-3,6-di(1-pyrrolidinyl- and 1-piperidinyl)benzeneacetonitrile (18 and 19). Hydrogen was bubbled through a solution of **15/16** (0.6 mmol) in dry DMF (20 mL) to which was added 5% Pd/C (0.10 g) until the solution was colorless (1.5 h). Then $Ba(OH)_2 \cdot 8H_2O$ (0.92 g, 3.0 mmol) and dimethyl sulfate (0.37 g, 3.0 mmol) were added and slow hydrogen bubbling was continued for 24 h. Subsequently, EtOAc (50 mL) was added and the reaction mixture was filtered through hyflo. The hyflo was eluted with EtOAc (150 mL) and the combined organic layers were washed with a NH_4Cl solution (6 × 100 mL). Drying ($MgSO_4$) and evaporation of the solvent gave the methylated hydroquinones.

18: yield 50%; oil; isomer ratio = 2:1; ^1H NMR δ 8.0–7.8 and 7.5–7.1 (m, 6 H, =CH and Ph H), 6.39 and 6.34 (s, 1 H, H-4), 3.80, 3.56, and 3.51 (s, 3 H, 6 H, and 3 H, respectively, OCH_3), 3.5–3.0 (m, 8 H, NCH_2), 2.0–1.8 (m, 8 H, CH_2); IR (KBr) 2220 and 2210 (CN) cm^{-1}; mass spectrum, *m/e* 403.228 (M^+, calcd for $C_{25}H_{29}N_3O_2$ 403.226).

In the case of **19** only one isomer was obtained after trituration with diisopropyl ether: yield 49%; mp 146–147 °C (diisopropyl ether); ^1H NMR δ 7.28 (s, 6 H, =CH and Ph H), 6.51 (s, 1 H, H-4), 4.02 and 3.81 (s, 3 H, OCH_3), 3.5–2.65 (m, 8 H, NCH_2), 2.0–1.4 (m, 12 H, CH_2); ^{13}C NMR δ 155.4 (d, =CH), 144.2, 144.1, 138.3, and 133.4 (s, C-2, C-3, C-5, and C-6), 118.8 (s, CN), 103.2 (d, C-4), 58.7 and 55.4 (q, OCH_3), 51.8 and 51.6 (t, NCH_2); IR (KBr) 2210 (CN) cm^{-1}; mass spectrum, *m/e* 433.272 (M^+, calcd 433.273).

Anal. Calcd for $C_{27}H_{35}N_3O_2$ (M_r 433.596): C, 74.79; H, 8.14; N, 9.69. Found: C, 74.90; H, 8.09; N, 9.63.

3-Bromo-1,4-dimethoxy-2-naphthaleneacetonitrile (21) was prepared starting from **20** (3.60 g, 10.0 mmol) analogously to **11** and purified by flash chromatography (petroleum ether:EtOAc = 3:1): yield 77%; mp 112–114 °C (MeOH); ^1H NMR δ 8.2–8.0 and 7.7–7.5 (m, 4 H, Ar H), 4.08 (s, 2 H, CH_2CN), 4.03 and 4.00 (s, 3 H, OCH_3); ^{13}C NMR δ 151.6 and 150.8 (s, C-1 and C-4), 117.2 (s, CN), 63.0 and 61.5 (q, OCH_3), 19.1 (t, CH_2CN); IR (KBr) 2240 (CN) cm^{-1}; mass spectrum, *m/e* 305.004 (M^+, calcd 305.005).

Anal. Calcd for $C_{14}H_{12}BrNO_2$ (M_r 306.159): C, 54.92; H, 3.95; N, 4.58. Found: C, 54.66; H, 3.89; N, 4.49.

(*E,Z*)-3-Bromo-1,4-dimethoxy-α-(phenylmethylene)-2-naphthaleneacetonitrile (22) was prepared starting from **21** (3.06 g, 10.0 mmol) analogously to **12** and purified by chromatography (CH_2Cl_2:petroleum ether = 3:1) to give one isomer as a solid and the other as an oil (in a ratio of 5:4) in a total yield of 81%.

Solid isomer: mp 139–140 °C (MeOH); ^1H NMR δ 8.25–7.9 and 7.7–7.3 (m, 9 H, Ar H and Ph H), 7.21 (s, 1 H, =CH), 4.02 and 3.96 (s, 3 H, OCH_3); ^{13}C NMR δ 151.9 and 150.6 (s, C-1 and C-4), 149.6 (d, =CH), 117.7 (s, CN), 62.4 and 61.5 (q, OCH_3); IR (KBr) 2205 (CN) cm^{-1}; mass spectrum, *m/e* 393.035 (M^+, calcd 393.037).

Anal. Calcd for $C_{21}H_{16}BrNO_2$ (M_r 394.268): C, 63.97; H, 4.09; N, 3.55. Found: C, 63.71; H, 4.04; N, 3.73.

Minor isomer: oil; ^1H NMR δ 8.25–8.05 and 7.7–7.5 (m, 4 H, Ar H), 7.56 (s, 1 H, =CH), 7.25–7.0 (m, 5 H, Ph H), 3.99 and 3.91 (s, 3 H, OCH_3); ^{13}C NMR δ 151.6 and 151.2 (s, C-1 and C-4), 147.5 (d, =CH), 119.3 (s, CN), 62.5 and 61.6 (q, OCH_3); IR (KBr) 2210

(CN) cm^{-1}; mass spectrum, m/e 393.035 (M^+, calcd for $C_{21}H_{16}BrNO_2$ 393.037).

Sodium Salt of 3-Bromo-α-(hydroxymethylene)-1,4-dimethoxy-2-naphthaleneacetonitrile (23). To a suspension of 80% NaH (0.36 g, 12.0 mmol) in toluene (50 mL) was added **21** (3.06 g, 10.0 mmol) at room temperature. Heating of the reaction mixture for 2 h at 110 °C resulted in the formation of a grey precipitate. Upon cooling to 50 °C ethyl formate (3.3 mL, 40.0 mmol) was added dropwise, whereupon the reaction mixture was heated at that temperature for 15 h. Upon cooling **23** precipitated, was filtered off, and was washed with dry diethyl ether (3 × 50 mL) to give the sodium salt of **23** in a yield of 84%.

(*E*)- or (*Z*)-3-Bromo-1,4-dimethoxy-α-[[[(4-methylphenyl)sulfonyl]oxy]methylene]-2-naphthaleneacetonitrile (24) and (*E*/*Z*)-3-Bromo-1,4-dimethoxy-α-[(phenylthio)methylene]-2-naphthaleneacetonitrile (25). To a suspension of the sodium salt of **23** (2.41 g, 6.8 mmol) in THF (150 mL) and water (10 mL) was added concentrated sulfuric acid (3 mL). After stirring for 10 min, water (100 mL) was added to the reaction mixture. Compound **23** was isolated by extraction with $CHCl_3$ (3 × 150 mL). The combined extracts were washed with water (3 × 100 mL) and dried with $MgSO_4$. Removal of the solvent under reduced pressure gave **23** as an oil in quantitative yield, which was used without purification. To a solution of **23** (2.26 g, 6.8 mmol) in pyridine (15 mL) was added tosyl chloride (1.33 g, 7.0 mmol) at 0 °C. Stirring was continued for 30 min at this temperature, whereupon thiophenol (0.7 mL, 7.0 mmol) was added. After stirring for 48 h at room temperature the solution was poured into 1% NaOH (50 mL) and extracted with Et_2O (4 × 75 mL). The combined organic layers were washed with water (100 mL), 25% KOH (100 mL), and water (100 mL) and dried with $MgSO_4$. Evaporation of the solvent gave an oil which was subjected to chromatography (petroleum ether:EtOAc = 3:1) to afford **25** (70%) and **24** (5%).

24: mp 132–134 °C (CCl_4); ^1H NMR δ 8.2–7.9 and 7.8–7.25 (m, 9 H, Ar H, TosH, and =CH), 3.93 and 3.78 (s, 3 H, OCH_3), 2.47 (s, 3 H, CH_3); ^{13}C NMR δ 152.1 and 150.6 (s, C-1 and C-4), 149.2 (d, =CH), 118.8 (s, CN), 62.5 and 61.5 (q, OCH_3), 21.8 (q, CH_3); IR (KBr) 2210 (CN), 1350 and 1180 (OSO_2) cm^{-1}; mass spectrum, m/e 487.010 (M^+, calcd 487.009).

Anal. Calcd for $C_{22}H_{18}BrNO_5S$ (M_r 488.356): C, 54.11; H, 3.72; N, 2.87. Found: C, 53.97; H, 3.70; N, 2.79.

25: oil; isomer ratio = 1:1; ^1H NMR δ 8.25–8.0 and 7.75–7.2 (m, 10 H, Ar H, Ph H, and =CH), 4.03, 3.98, and 3.95 (s, 3 H, 6 H, and 3 H, respectively, OCH_3); IR (KBr) 2250 and 2210 (CN) cm^{-1}; mass spectrum, m/e 425.004 (M^+, calcd for $C_{21}H_{16}BrNO_2S$ 425.009).

General Procedure for the Synthesis of the Ketene Dithioacetals 26 and 27. To a suspension of KO-*t*-Bu (6.16 g, 55.0 mmol) in THF (50 mL) was added a solution of **21** (8.00 g, 25.0 mmol) and CS_2 (2.0 mL, 27.0 mmol) in THF (70 mL) over a period of 1 h at room temperature. After stirring for an additional hour at room temperature, the precipitate was filtered off and washed with Et_2O (100 mL). Subsequently, this dipotassium salt was dissolved in a mixture of MeOH (100 mL) and water (40 mL), whereupon 1,3-dibromopropane or 1,2-dibromoethane (27.0 mmol) was added and the resulting solution was refluxed for 2 h. After cooling to room temperature NH_4Cl (1.5 g) was added and the mixture was extracted with EtOAc (3 × 150 mL). The combined EtOAc layers were washed with a saturated NaCl solution (450 mL) and dried with $MgSO_4$. After removal of the solvent under reduced pressure, the residue was subjected to chromatography (CH_2Cl_2) to give pure **26** and **27**.

3-Bromo-1,4-dimethoxy-α-1,3-dithian-2-ylidene-2-naphthaleneacetonitrile (26): yield 50%; mp 143–145 °C (EtOAc/MeOH); ^1H NMR δ 8.2–8.0 and 7.7–7.5 (m, 4 H, Ar H), 3.99 and 3.96 (s, 3 H, OCH_3), 3.3–2.8 (m, 4 H, SCH_2), 2.4–2.0 (m, 2 H, CH_2); ^{13}C NMR δ 162.4 (s, $=CS_2$), 152.5 and 150.5 (s, C-1 and C-4), 116.8 (s, CN), 62.8 and 61.5 (q, OCH_3), 29.0 and 28.9 (t, SCH_2), 22.9 (t, CH_2); IR (KBr) 2200 (CN) cm^{-1}; mass spectrum, m/e 420.978 (M^+, calcd 420.981).

Anal. Calcd for $C_{18}H_{16}BrNO_2S_2$ (M_r 422.363): C, 51.19; H, 3.82; N, 3.32. Found: C, 51.30; H, 3.70; N, 3.25.

3-Bromo-1,4-dimethoxy-α-1,3-dithiolan-2-ylidene-2-naphthaleneacetonitrile (27): yield 61%; mp 152–154 °C (EtOAc/petroleum ether); ^1H NMR δ 8.2–8.0 and 7.65–7.5 (m, 4 H, Ar H), 4.00 and 3.99 (s, 3 H, OCH_3), 3.7–3.4 (m, 4 H, SCH_2); ^{13}C NMR δ 174.6 (s, $=CS_2$), 152.1 and 150.5 (s, C-1 and C-4), 117.8 (s, CN), 62.9 and 61.5 (q, OCH_3), 39.7 and 39.5 (t, SCH_2); IR (KBr) 2200 (CN) cm^{-1}; mass spectrum, m/e 406.966 (M^+, calcd 406.965).

Anal. Calcd for $C_{17}H_{14}BrNO_2S_2$ (M_r 408.336): C, 50.00; H, 3.46; N, 3.43. Found: C, 49.90; H, 3.50; N, 3.39.

General Procedure for the Synthesis of the Bromo Quinones 28–31. To a solution of **22**, **25**, **26**, or **27** (2.0 mmol) in a mixture of acetonitrile and water (54 and 6 mL, respectively) was added a solution of CAN (2.70 g, 5.0 mmol) in water (7 mL) at 0 °C over a period of 30 min. After being stirred for an additional 1.5 h at room temperature, the reaction mixture was poured into water (200 mL) and extracted with $CHCl_3$ (3 × 250 mL). The combined extracts were washed with water (3 × 200 mL) and dried with $MgSO_4$. Removal of the solvent under reduced pressure gave the crude bromo quinones **28–31**, which were purified by flash chromatography (petroleum ether:EtOAc = 3:1).

(*E*)- or (*Z*)-3-Bromo-1,4-dihydro-1,4-dioxo-α-(phenylmethylene)-2-naphthaleneacetonitrile (28) was obtained as a solid[53] (starting from the solid isomer of **22**): yield 65%; mp 156–158 °C (EtOH); ^1H NMR δ 8.2–8.1 and 8.0–7.9 (m, 4 H, Ar H), 7.9–7.75 and 7.6–7.45 (m, 5 H, Ph H), 7.28 (s, 1 H, =CH); ^{13}C NMR δ 182.8 and 178.9 (s, C=O), 151.6 (d, =CH), 117.7 (s, CN); IR (KBr) 2210 (CN), 1680 (C=O) cm^{-1}; mass spectrum, m/e 362.990 (M^+, calcd for $C_{19}H_{10}BrNO_2$ 362.990).

The other isomer of **28** was obtained as an oil (starting from the other isomer of **22**): yield 65%; ^1H NMR δ 8.4–8.0 and 7.95–7.7 (m, 4 H, Ar H), 7.66 (s, 1 H, =CH), 7.6–7.1 (m, 5 H, Ph H); ^{13}C NMR δ 181.5 and 178.0 (s, C=O), 150.0 (d, =CH), 116.8 (s, CN); IR (KBr) 2210 (CN), 1680 (C=O) cm^{-1}; mass spectrum, m/e 362.990 (M^+, calcd for $C_{19}H_{10}BrNO_2$ 362.990).

(*E*/*Z*)-3-Bromo-1,4-dihydro-1,4-dioxo-α-[(phenylthio)methylene]-2-naphthaleneacetonitrile (29): yield 48%; oil; isomer ratio = 1:1; ^1H NMR δ 8.25–8.0 and 7.9–7.25 (m, 10 H, Ar H, Ph H, and =CH); IR (KBr) 2210 and 2205 (CN), 1685 and 1675 (C=O) cm^{-1}; mass spectrum, m/e 394.962 (M^+, calcd for $C_{19}H_{10}BrNO_2S$ 394.980).

3-Bromo-1,4-dihydro-1,4-dioxo-α-1,3-dithian-2-ylidene-2-naphthaleneacetonitrile (30): yield 39%; mp 212–214 °C (EtOAc/petroleum ether); ^1H NMR δ 8.4–8.0 and 7.95–7.7 (m, 4 H, Ar H), 3.3–2.9 (m, 4 H, SCH_2), 2.45–2.1 (m, 2 H, CH_2); ^{13}C NMR δ 179.0 and 177.2 (s, C=O), 166.7 (s, $=CS_2$), 114.4 (s, CN); IR (KBr) 2200 (CN), 1680 and 1665 (C=O) cm^{-1}; mass spectrum, m/e 390.930 (M^+, calcd 390.934).

Anal. Calcd for $C_{16}H_{10}BrNO_2S_2$ (M_r 392.293): C, 48.99; H, 2.57; N, 3.57. Found: C, 48.76; H, 2.53; N, 3.54.

3-Bromo-1,4-dihydro-1,4-dioxo-α-1,3-dithiolan-2-ylidene-2-naphthaleneacetonitrile (31): yield 42%; mp 200–210 °C dec (toluene); ^1H NMR δ 8.25–8.0 and 7.95–7.7 (m, 4 H, Ar H), 3.65–3.6 (m, 4 H, SCH_2); IR (KBr) 2200 (CN), 1680 (C=O) cm^{-1}; mass spectrum, m/e 376.921 (M^+, calcd 376.918).

Anal. Calcd for $C_{15}H_8BrNO_2S_2$ (M_r 378.266): C, 47.63; H, 2.13; N, 3.70. Found: C, 47.60; H, 2.07; N, 3.58.

General Procedure for the Synthesis of the Amino Quinones 32–35 and 37. To a solution of bromo quinone **28–31** (3.3 mmol) in a mixture of benzene and ethanol (80 and 10 mL, respectively) was added dropwise a solution of the amine (8.3 mmol) in benzene (3 mL) at 0 °C and stirring was continued for 1 h at that temperature. Subsequently, EtOAc (50 mL) was added and the remaining solution was washed with 0.5 N HCl (3 × 75 mL) and water (200 mL). After drying with $MgSO_4$ and evaporation of the solvent the crude **32–35** and **37** were obtained and purified as follows: **32** and **37** by flash chromatography (petroleum ether:EtOAc = 3:1), **33** by chromatography (petroleum ether: EtOAc = 1:1), and **34** and **35** by recrystallization from EtOAc/petroleum ether and ethanol, respectively.

(*E*/*Z*)-1,4-Dihydro-1,4-dioxo-α-(phenylmethylene)-3-(1-pyrrolidinyl)-2-naphthaleneacetonitrile (32): yield 80%; oil; isomer ratio =7:3; ^1H NMR δ 8.15–7.25 (m, 10 H, Ar H, Ph H, and =CH of the major isomer), 6.99 (s, 1 H, =CH), 3.9–3.6 [m, 4 H, NCH_2 (major isomer)], 3.55–3.25 [m, 4 H, NCH_2 (minor isomer)], 2.05–1.8 (m, 4 H, CH_2); IR (KBr) 2220 (CN), 1680 (C=O)

(53) No satisfactory elemental analyses were obtained for this compound, on account of instability.

Table I. Melting Points, Formation Times, Yields, Characteristic ^1H and ^{13}C NMR Spectral Data, and Molecular Ion Values of Compounds 41–46[a]

	mp (°C) (solvent)	time, (h)	yield (%)	^1H NMR ($CDCl_3$), δ				^{13}C NMR ($CDCl_3$), δ				MS (M^+)	
				CH_2Ph/CHS_2	J, Hz	NCH (m)	NCH_2 (m)	CN (s)	NCH (d)	C-9/C-11	CH_2Ph/CHS_2	found	(calcd)
41a[b]	151–155 (c)	2.45[d]	58	4.02 and 2.95	15.0	4.5–4.2	4.1–3.2	118.4	75.0	45.0	37.8	373.178	(373.179)
41b[b]	151–155 (c)	2.45[d]	29	3.9[e] and 3.00	13.7	4.5–4.2	4.1–3.2	118.4	72.5	47.5	42.1	373.178	(373.179)
42a	oil[f]	116	85	4.10 and 3.13	15.2	4.3–4.1	3.6–2.9	123.8	74.4	47.2	39.3	403.222	(403.226)
42b	oil[f]	116	5	4.2[e] and 2.78	13.4	4.3–4.1	3.6–2.9	122.8	73.0	49.6	45.2	403.222	(403.226)
43	164–166 (c)	3[g]	70	3.86 and 3.10	13.9	4.14[h]	3.7–3.5	118.4	71.5	47.5	42.2	354.137	(354.137)
44a	180–182 (i)	3	24	3.53 and 3.11	14.2	4.8–4.55	3.9–3.7	117.2	67.9	48.5	41.7	368.154	(368.152)
44b	214–216 (i)	3	1	3.35–3.0[j]		5.1–4.8	3.85–3.65	118.2	72.0	45.7	36.7	368.154	(368.152)
45	214–215 (i)	240	80	5.36[k]		4.60[l]	3.85–3.6	116.0	70.1	52.3	52.0	382.080	(382.081)
46	232–234 (i)	1800	70	5.91[k]		4.41[m]	3.9–3.5	117.2	70.3	52.0	58.7	368.060	(368.065)

[a] All compounds, except **42a** and **42b**, gave satisfactory elemental analyses. [b] Data concern a mixture of **41a** and **41b**. [c] Diisopropyl ether. [d] In refluxing toluene t = 8 h, **41a**:**41b** = 1:2, total yield 81%. [e] This part of the AB system overlaps with the signals of the NCH_2 moiety. [f] Both **42a** and **42b** could not be crystallized. [g] In refluxing toluene (t = 8 h) **43** was obtained in a yield of 33%. [h] t, J = 7.6 Hz. [i] EtOAc/petroleum ether. [j] m. [k] s. [l] t, J = 6.6 Hz. [m] t, J = 6.8 Hz.

cm^{-1}; mass spectrum, m/e 354.137 (M^+, calcd for $C_{23}H_{18}N_2O_2$ 354.137).

(*E*)- or (*Z*)-1,4-Dihydro-1,4-dioxo-α-[(phenylthio)methylene]-3-(1-pyrrolidinyl)-2-naphthaleneacetonitrile (33): yield 71%; mp 176–178 °C (EtOAc/petroleum ether); ^1H NMR δ 8.2–7.9 and 7.8–7.6 (m, 4 H, Ar H), 7.5–7.2 (m, 5 H, Ph H), 6.96 (s, 1 H, =CH), 3.7–3.4 (m, 4 H, NCH_2), 2.1–1.75 (m, 4 H, CH_2); ^{13}C NMR δ 181.8 and 181.2 (s, C=O), 152.6 (d, =CH), 119.3 (s, CN), 48.1 (t, NCH_2), 25.2 (t, CH_2); IR (KBr) 2190 (CN), 1660 (C=O) cm^{-1}; mass spectrum, m/e 386.106 (M^+, calcd 386.109).

Anal. Calcd for $C_{23}H_{18}N_2O_2S$ (M_r 386.473): C, 71.48; H, 4.69; N, 7.25. Found: C, 71.38; H, 4.69; N, 7.15.

1,4-Dihydro-1,4-dioxo-α-1,3-dithian-2-ylidene-3-(1-pyrrolidinyl)-2-naphthaleneacetonitrile (34): yield 65%; mp 185–187 °C (EtOAc/petroleum ether); ^1H NMR δ 8.2–7.4 (m, 4 H, Ar H), 3.9–3.4 (m, 4 H, NCH_2), 3.2–2.8 (m, 4 H, SCH_2), 2.4–1.7 (m, 4 H, CH_2); ^{13}C NMR δ 184.2 (s, C=O), 156.6 (s, $=CS_2$), 117.3 (s, CN), 53.3 (t, NCH_2), 29.3 and 29.0 (t, SCH_2), 25.6 and 23.1 (t, CH_2); IR (KBr) 2200 (CN), 1675 (C=O) cm^{-1}; mass spectrum, m/e 382.078 (M^+, calcd 382.081).

Anal. Calcd for $C_{20}H_{18}N_2O_2S_2$ (M_r 382.504): C, 62.80; H, 4.74; N, 7.32. Found: C, 62.71; H, 4.77; N, 7.25.

1,4-Dihydro-1,4-dioxo-α-1,3-dithiolan-2-ylidene-3-(1-pyrrolidinyl)-2-naphthaleneacetonitrile (35): yield 65%; mp 214–215 °C (ethanol); ^1H NMR δ 8.15–7.55 (m, 4 H, Ar H), 3.7–3.4 (m, 8 H, NCH_2 and SCH_2), 2.1–1.65 (m, 4 H, CH_2); IR (KBr) 2200 (CN), 1670 (C=O) cm^{-1}; mass spectrum, m/e 368.065 (M^+, calcd 368.065).

Anal. Calcd for $C_{19}H_{16}N_2O_2S_2$ (M_r 368.477): C, 61.93; H, 4.38; N, 7.60. Found: C, 62.08; H, 4.50; N, 7.48.

(*E*/*Z*)-1,4-Dihydro-1,4-dioxo-α-(phenylmethylene)-3-(1-piperidinyl)-2-naphthaleneacetonitrile (37): yield 80%; oil; isomer ratio = 1:1; ^1H NMR δ 8.25–7.0 (m, 10 H, Ar H, Ph H, and =CH), 3.65–3.45 and 3.4–3.2 (m, 8 H, NCH_2), 2.0–1.2 (m, 12 H, CH_2); IR (KBr) 2220 and 2210 (CN), 1680 (C=O) cm^{-1}; mass spectrum, m/e 368.154 (M^+, calcd for $C_{24}H_{20}N_2O_2$ 368.152).

(*E*,*Z*)-1,4-Dimethoxy-α-(phenylmethylene)-3-(1-pyrrolidinyl)-2-naphthaleneacetonitrile (38) was prepared analogously to 18 and 19 starting from **32** (3.54 g, 10.0 mmol) in a yield of 50%. The major isomer could be isolated as an oil in a yield of 30% after chromatography ($CHCl_3$). Major isomer: ^1H NMR δ 8.3–7.8 and 7.7–7.0 (m, 10 H, Ar H, Ph H, and =CH), 3.85 and 3.83 (s, 3 H, OCH_3), 3.6–3.3 (m, 4 H, NCH_2), 2.1–1.9 (m, 4 H, CH_2); ^{13}C NMR δ 150.8 and 148.8 (s, C-1 and C-4), 145.4 (d, =CH), 118.8 (s, CN), 62.1 and 61.9 (q, OCH_3), 50.7 (t, NCH_2), 26.0 (t, CH_2); IR (KBr) 2210 (CN) cm^{-1}; mass spectrum, m/e 384.180 (M^+, calcd for $C_{25}H_{24}N_2O_2$ 384.182).

General Procedure for the Synthesis of the 1,4-Bis(acetyloxy)naphthaleneacetonitrile Derivatives 39 and 40. A mixture of **33**, **34** (0.6 mmol), triethylamine (0.19 g, 1.9 mmol), zinc powder (0.05 g, 0.8 mmol) and acetic anhydride (2 mL, 21.0 mmol) was refluxed for 20 min. After being cooled to room temperature, the reaction mixture was poured into water (10 mL) and the resulting suspension was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water (3 × 100 mL) and dried with $MgSO_4$. Evaporation of the solvent gave the crude **39** and **40**, which were purified as follows: **39** by flash chromatography ($CHCl_3$:EtOAc = 25:1) and **40** by trituration with diisopropyl ether.

(*E*,*Z*)-1,4-Bis(acetyloxy)-α-[(phenylthio)methylene]-3-(1-pyrrolidinyl)-2-naphthaleneacetonitrile (39): yield 41%; isomer ratio = 1:1; ^1H NMR δ 7.9–6.7 (m, 4 H, Ar H), 7.18 and 7.17 (s, 5 H, Ph H), 6.95 and 6.50 (s, 1 H, =CH), 3.5–3.25 and 3.2–2.8 (m, 4 H, NCH_2), 2.47, 2.45, 2.42, and 2.38 (s, 3 H, CH_3), 1.9–1.6 (m, 12 H, CH_2); IR (KBr) 2240 (CN), 1700 (C=O) cm^{-1}; mass spectrum, m/e 472.142 (M^+, calcd for $C_{27}H_{24}N_2O_4S$ 472.146).

1,4-Bis(acetyloxy)-α-1,3-dithian-2-ylidene-3-(1-pyrrolidinyl)-2-naphthaleneacetonitrile (40): yield 43%; mp 167–168 °C (EtOAc/petroleum ether); ^1H NMR δ 7.8–7.6 and 7.5–7.3 (m, 4 H, Ar H), 3.45–3.25 (m, 4 H, NCH_2), 3.2–2.75 (m, 4 H, SCH_2), 2.43 (s, 3 H, CH_3), 2.35–1.8 (m, 4 H, CH_2); ^{13}C NMR δ 169.1 and 168.4 (s, C=O), 161.6 (s, $=CS_2$), 116.5 (s, CN), 49.9 (t, NCH_2), 29.2 and 29.1 (t, SCH_2), 26.0 and 22.9 (t, CH_2), 20.7 and 20.5 (q, CH_3); IR (KBr) 2200 (CN), 1700 (C=O) cm^{-1}; mass spectrum, m/e 468.109 (M^+, calcd 468.112).

Anal. Calcd for $C_{24}H_{24}N_2O_4S_2$ (M_r 468.594): C, 61.52; H, 5.16; N, 5.98. Found: C, 61.71; H, 5.10; N, 5.93.

General Procedure for the Preparation of the Pyrrolo[1,2-*a*]indoles 41 and 42, the Benzo[*f*]pyrrolo[1,2-*a*]indoles 43, 45, and 46, and Pyrido[1,2-*a*]indole 44. A solution of **15**, **18**, **32**, **34**, **35**, or **37** (5.0 mmol) in 1-butanol (50 mL) was heated at reflux temperature. When the reaction was complete as followed from TLC, the solvent was removed under reduced pressure (except in the case of **45**). The compounds **41** and **42** were purified by chromatography, using EtOAc (**41**) and $CHCl_3$:EtOAc 10:1 (**42**) as eluents, and the compounds **43** and **44** were purified by flash chromatography, using CH_2Cl_2:EtOAc = 97:3 (**43**) and CH_2Cl_2 (**44**) as eluents. Compound **41** was obtained as a mixture of cis and trans isomers, which could not be separated. Compound **45** crystallized upon cooling and was isolated after filtration and trituration with MeOH (50 mL). The melting points, formation times, yields, and the characteristic NMR data and molecular ion values of **41–46** are given in Table I.

1-(4-Butoxybutyl)-2,3,4,9-tetrahydro-4,9-dioxo-2-(phenylthio)-1*H*-benz[*f*]indole (50). A solution of **33** (0.05 g, 0.1 mmol) in 1-butanol (2 mL) was heated for 8 h at 90 °C. After removal of the solvent under reduced pressure the crude residue was subjected to flash chromatography ($CHCl_3$:EtOAc = 4:1) to give **50** as an oil in a yield of 20%: ^1H NMR δ 8.2–7.95 and 7.85–7.6 (m, 4 H, Ar H), 7.5–7.2 (m, 5 H, Ph H), 4.8–4.7 (m, 1 H, CHCN), 3.9–3.75 (m, 1 H, NCHS), 3.7–3.2 (m, 6 H, 2 × OCH_2 and NCH_2), 2.25–1.15 (m, 8 H, CH_2), 1.1–0.7 (m, 3 H, CH_3); ^{13}C NMR δ 179.2 and 178.4 (s, C=O), 118.6 (s, CN), 95.2 (d, C-2), 72.0 (d, C-3), 67.4 and 67.3 (t, OCH_2), 47.2 (t, NCH_2), 31.6, 30.9, 22.8, and 19.3 (t, CH_2), 13.9 (q, CH_3); IR (KBr) 2210 (CN) cm^{-1}; mass spectrum, m/e 458.167 (M^+ − 2, calcd for $C_{27}H_{26}N_2O_3S$ 458.166).

X-ray Crystal Structure Determination of 43. Crystals of **43** belong to the monoclinic space group $P2_1/n$, with cell constants a = 11.135 (3), b = 12.083 (6), and c = 26.624 (6) Å, β = 93.76 (4)°, d_c = 1.326 g cm^{-3}, and Z = 8. Intensities were measured with an Enraf-Nonius CAD 4 diffractometer at 293 K by using graphite-monochromated Mo K_α radiation [ω −2θ scan mode; scan width (ω) (1.2 + 0.3 tan ω)°; 3 < ω < 20°). A total of 2174 reflections with $I > 3\sigma(I)$ have been used in the refinement[54] and

solution[55] of the structure. The structure contains two molecules in the asymmetric unit. Both molecules have the same overall conformation but differ somewhat in the orientation of the phenyl group. Hydrogen atoms have been treated as riding atoms with fixed thermal parameters (B = 5.0 Å^2). The remaining atoms have been refined with anisotropic thermal parameters (no. of parameters 380). The final R factor was 4.1%.

(54) B. A. Frenz and Associates Inc. (1983), Structure Determination Package, College Station, Texas, and Enraf-Nonius, Delft.
(55) Germain, P.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *A27*, 368.

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Supplementary Material Available: Lists of positional and thermal parameters, bond lengths, and bond angles (8 pages). Ordering information is given on any current masthead page.

Electroreductive Cyclization. Ketones and Aldehydes Tethered to α,β-Unsaturated Esters (Nitriles). Fundamental Investigations

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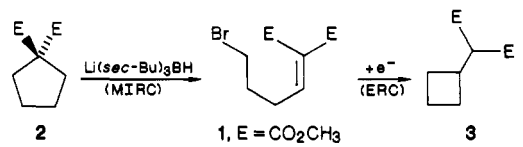
The intramolecular electrochemically initiated cyclization of a variety of α,β-unsaturated esters and one nitrile, each of which is tethered to an aldehyde or a ketone, has been investigated. Good yields (70–79%) of mono- and bicyclic products, resulting from closure between the β-carbon of the α,β-unsaturated unit and the aldehyde or ketone carbonyl carbon, were obtained. Cyclic voltammetry was used to determine that the α,β-unsaturated unit corresponded to the electrophore. In all but one instance, cyclization favored formation of the product wherein the hydroxy and (methoxycarbonyl)methyl units were trans to one another. The stereoselectivity was studied as a function of temperature, nature of the proton donor, proton availability, and percent conversion (i.e., as a function of time). Attempts to use the reaction to synthesize the marine natural product ambliol A were unsuccessful. A mechanistic scheme in which a reversible cyclization of the initially formed radical anion is followed by an irreversible proton transfer is suggested to account for the experimental observations.

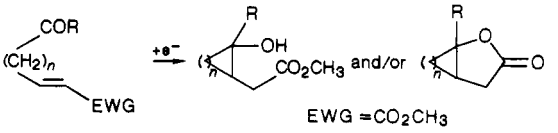
Introduction. Electroreductive Cyclization (ERC) Reactions. The conjugate addition of lithium *sec*-butylborohydride to the alkylidenemalonate **1**, leading to the formation of the cyclopentyl diester **2**, constitutes one example of what we have previously referred to as a MIRC (Michael-Initiated Ring Closure) reaction.[1-4] In contrast, an electrochemically initiated reduction of the same substrate afforded the cyclobutyl diester **3** in a reaction involving closure between the β (rather than the α) carbon of the starting material and the bromine-bearing carbon. Once reduced, an umpolung occurs and the formerly electrophilic β carbon becomes nucleophilic. In general, MIRC reactions and electroreductive cyclizations complement one another and allow the construction of rings of size n and $n - 1$, respectively.[5]



2 **1**, E = CO_2CH_3 **3**

(1) Little, R. D.; Dawson, J. R. *Tetrahedron Lett.* **1980**, *21*, 2609. Technically, the term Michael reaction refers to carbon-centered nucleophiles. See: Bergmann, E. D.; Ginsburg, D. *Organic Reactions*; Wiley: New York, 1959; Vol. 10, Chapter 3.
(2) For a discussion of the development of and application to total synthesis of the tandem Michael-Michael-Ring Closure (MIMIRC) reaction, refer to: Posner, G.; Mallamo, J. P.; Black, A. L. *Tetrahedron* **1981**, *37*, 3921.
(3) Little, R. D.; Dawson, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 4607.
(4) Little, R. D.; Verhé, R.; Monte, W. T.; Nugent, S.; Dawson, J. R. *J. Org. Chem.* **1982**, *47*, 362.

Aldehydes and Ketones Tethered to α,β-Unsaturated Esters (Nitriles). Encouraged by these results, we elected to explore use of electroreductive cyclization (ERC) methodology for the construction of a variety of different ring systems and first decided to use substrates wherein a carbonyl unit was tethered to an α,β-unsaturated ester or nitrile. The successful implementation of the plan would lead to the formation of γ-hydroxy esters (nitriles) which could, either in situ or in a follow-up step, lead to the production of bi- or tricyclic lactones.[6]



EWG = electron-withdrawing group

A variety of substrates was examined; the results are illustrated in Table I. In each case, the electroreductive cyclization reactions were carried out at controlled potential in 10% aqueous acetonitrile with Et_4NOTs as the supporting electrolyte. A standard H-cell, a mercury pool cathode, and a saturated calomel reference electrode (SCE) were used; the course of each reaction was monitored as a function of time by coulometry and thin layer chromatography. Each of the examples, except the last, illustrates that the reaction stereoselectively affords products wherein

(5) Nugent, S. T.; Baizer, M. M.; Little, R. D. *Tetrahedron Lett.* **1982**, *23*, 1339.
(6) Fox, D. P.; Little, R. D.; Baizer, M. M. *J. Org. Chem.* **1985**, *50*, 2202.

0022-3263/88/1953-2287$01.50/0