We express our gratitude to Dr. R. Visser for performing the ^1H NOE experiments. We also acknowledge J. M. Visser and J. L. M. Vrielink for recording the NMR and T. W. Stevens for recording the mass spectra.

Registry No. **5a**, 97721-21-6; **5a**·Na, 91147-57-8; (*E*)-**5b**, 91147-58-9; (*Z*)-**5b**, 91147-59-0; (*E*)-**5c**, 91147-60-3; (*Z*)-**5c**, 91147-61-4; (*E*)-**5d**, 91147-62-5; (*Z*)-**5d**, 91147-63-6; (*E*)-**5e**, 97721-22-7; (*Z*)-**5e**, 97721-23-8; **6a**, 97721-38-5; **6b**, 91147-64-7; **6c**, 91147-65-8; **6d**, 91147-66-9; **6e**, 97721-24-9; **7a**, 91147-70-5; **7b**, 91147-67-0; **7c**, 91147-68-1; **7d**, 91147-69-2; **7e**, 97721-25-0; **7f**, 97721-28-3; **7g**, 97721-29-4; **7** (R = CO_2Ph), 97721-30-7; **8a**, 97721-26-1; **8b**, 97721-27-2; **11**, 87711-10-2; *cis*-**12a**, 97721-31-8; *trans*-**12a**, 97721-32-9; *cis*-**12b**, 97721-33-0; *trans*-**12b**, 97721-34-1; *cis*-**12c**, 97721-35-2; *trans*-**12c**, 97721-36-3; *trans*-**12d**, 97721-37-4; 2-(1-pyrrolidinyl)benzeneacetonitrile, 87698-85-9; ethyl formate, 107-31-3; phenyl chloroformate, 1885-14-9.

Synthesis of Mitomycin C Analogues. 2.[1] Introduction of a Leaving Group at C-1 and Oxidation of the Aromatic Ring in 2,3,9,9a-Tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles

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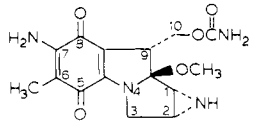
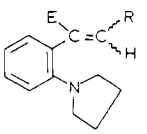
Received March 28, 1985

2-(2,5-Dihydro-1*H*-pyrrol-1-yl)-α-(phenylmethylene)benzeneacetonitriles **6a,b** cyclize thermally in aprotic solvents to the *cis*- and/or *trans*-9,9a-dihydro-3*H*-pyrrolo[1,2-*a*]indoles **7a,8a** and **7b,8b**, respectively. Reaction in methanol affords the 2-(1*H*-pyrrol-1-yl)benzeneacetonitriles **9a,b** as the main products. The appropriate double bond in **8a,b** reacts with osmium tetraoxide to give exclusively the cis-vicinal diols **15** and **13**, respectively. The stereochemistry of the former has been determined with single-crystal X-ray analysis. The (4,)5-substituted-α-(phenylmethylene)-2-(1-pyrrolidinyl)benzeneacetonitriles **6d–f** react in refluxing 1-butanol to give mixtures of the corresponding *cis*- and *trans*-(6,)7-substituted-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles **22b–d** and **23b–d**, respectively. The rate of cyclization is dependent on the nature of the substituents. Nitration of **22c,23c** affords the 5-nitro-1*H*-pyrrolo[1,2-*a*]indoles **25a** and **25b**, respectively, in low yield. The corresponding 8-nitro-1*H*-pyrrolo[1,2-*a*]indoles **28a,b** are prepared via cyclization of the appropriate 6-nitro-α-(phenylmethylene)-benzeneacetonitriles **27**. Reduction of **25a,b** and **28a** and subsequent oxidation of the corresponding anilines **25c,d** and **28c** with Fremy's salt do not give the desired *p*-quinones; in the case of **25a,b** a 9*H*-pyrrolo[1,2-*a*]indole (**29**) is isolated.

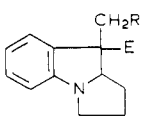
The mitomycins represent an important class of antitumor antibiotics of which mitomycin C (**1**) is used for the treatment of several solid tumors.[2-4] On the basis of structure–activity relationship studies it has been established that three structural elements are required for biological activity, viz., a quinone, a strongly alkylating function at C-1, e.g., an aziridine, and a urethane function at C-10.[5]



1



2



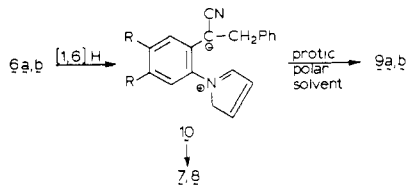
3

E = $COOCH_3$, CN
R = CH_2Ph, alkoxy, $COOCH_3$

Our approach to the synthesis of less toxic analogues of the mitomycins is based on our current studies of the "tertiary amino effect" in heterocyclic chemistry,[6] viz., the thermal rearrangement of the 1-(1-pyrrolidinyl)-2-vinylbenzene derivatives **2** to 2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles **3** (the mitosane basic skeleton) and the subsequent introduction of the required functional groups.

Previously[7] we have described the introduction of the urethane moiety. This paper deals with our work aimed at the introduction of the two other functions, viz., the quinone and a strongly alkylating group at C-1. As model compounds we have used appropriate pyrrolo[1,2-*a*]indoles all possessing a benzyl and a cyano group at C-9.

Scheme I



[†] Laboratory of Organic Chemistry.
[‡] Laboratory of Chemical Physics.

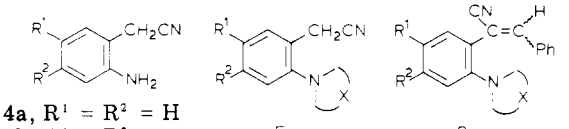
(1) For part 1 see ref 7.
(2) Carter, S. K.; Crooke, S. T. "Mitomycin C-Current Status and New Developments"; Academic Press: New York, 1979.
(3) Remers, W. A. In "Anticancer Agents Based on Natural Product Models"; Cassady, J. M., Duoros, J. D., Eds.; Academic Press: New York, 1980; p 131.
(4) Crooke, S. T. In "Cancer Chemotherapy"; Crooke, S. T., Prestayko A. W., Eds.; Academic Press: New York, 1981; Vol. 3, p 49.
(5) (a) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249. (b) Moore, H. W.; West, K. F.; Srinivasacher, K.; Czerniak, R. In "Structure-activity Relationships of Anti-tumour Agents"; Reinhoudt, D. N., Connors, T. A., Pinedo, H. M., van de Poll, K. W., Eds.; Martinus Nijhoff: The Hague, 1983; p 93.
(6) For leading references see: (a) Verboom, W.; Reinhoudt, D. N.; Visser, R.; Harkema, S. *J. Org. Chem.* **1984**, *49*, 269. (b) Verboom, W.; van Dijk, B. G.; Reinhoudt, D. N. *Tetrahedron Lett.* **1983**, *24*, 3923. (c) Verboom, W.; Hamzink, M. R. J.; Reinhoudt, D. N.; Visser, R. *Tetrahedron Lett.* **1984**, *25*, 4309.
(7) Dijksman, W. C.; Verboom, W.; Egberink, R. J. M.; Reinhoudt, D. N. *J. Org. Chem.*, previous paper in this issue.

0022-3263/85/1950-3797$01.50/0

Results and Discussion

Synthesis and Functionalization of the 9,9a-Dihydro-3*H*-pyrrolo[1,2-*a*]indoles at the 1-Position. Our approach to introduce a leaving group at the 1-position in 2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles involves the synthesis of 9,9a-dihydro-3*H*-pyrrolo[1,2-*a*]indoles **7** and **8** and subsequent functionalization of the appropriate double bond. To the best of our knowledge in the literature such transformations have only been reported for the heteroaromatic 5,6,7,8-tetrahydro-3*H*-pyrrolo[1,2-*a*]-indoles.[8]

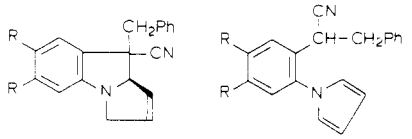
The 9,9a-dihydro-3*H*-pyrrolo[1,2-*a*]indoles **7** and **8** could be synthesized by using the same methodology as described for the 2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles **3**.[6a,7] Reaction of the benzeneacetonitriles **4a,b** with (*Z*)-1,4-dichloro-2-butene in the presence of ethyldiisopropylamine as a base and potassium iodide as a catalyst in refluxing toluene afforded the N,N-dialkylated benzeneacetonitriles **5a,b** in yields of 87% and 86%, respectively. Subsequently, a condensation reaction of **5a,b** with benzaldehyde in the presence of sodium hydroxide as a base in ethanol at room temperature gave one isomer of the α-(phenylmethylene)benzeneacetonitriles **6a,b** in yields of 45% and 70%, respectively; the stereochemistry of which has not been determined. The relatively low yield of **6a** is due to aromatization of the 2,5-dihydropyrrole moiety during the chromatographic purification on silica gel. Heating of **6a,b** in refluxing toluene gave exclusively the *trans*-9,9a-dihydro-3*H*-pyrrolo[1,2-*a*]indoles **7b** and **8b**, respectively, both in a yield of 86%. When the reaction was performed in refluxing acetonitrile in the presence of zinc chloride,



4a, $R^1 = R^2 = H$
b, $R^1 = R^2 =$ OCH_3
c, $R^1 = OCH_3$; $R^2 = H$
d, $R^1 = OCH_3$; $R^2 = CH_3$

5
a, $R^1 = R^2 = H$; X = HC=CH
b, $R^1 = R^2 = OCH_3$; X = HC=CH
c, $R^1 = R^2 = H$; $X = H_2CCH_2$
d, $R^1 = OCH_3$; $R^2 = H$; $X = H_2CCH_2$
e, $R^1 = OCH_3$; $R^2 = CH_3$; $X = H_2CCH_2$
f, $R^1 = R^2 = OCH_3$; $X = H_2CCH_2$

6



7a, R = H (α-CN)
7b, R = H (β-CN)
8a, $R = OCH_3$ (α-CN)
8b, $R = OCH_3$ (β-CN)

9a, R = H
b, $R = OCH_3$

6a was converted into a mixture of the cis and trans isomers **7a** and **7b** (ratio 3.5:1, total yield 58%). The cis isomer **7a** was isolated after chromatography in a yield of 30%. Compound **6b** reacted in a similar way to give a mixture of the cis and trans isomers **8a** and **8b** (ratio 1.8:1, total yield 53%). The cis isomer **8a** could be obtained in a pure state in a yield of 16%. Heating of **6a** in a *protic polar* solvent such as methanol gave, in addition to a mixture of **7a** and **7b** (ratio 1.2:1, yield 25%), another isomer in a yield of 45%. In the ^1H NMR spectrum of this product characteristic signals were present at δ 6.7–6.5 (m), 6.45–6.3 (m), 3.96 (t), and 2.95 (d). The ^{13}C NMR spectrum exhibited in the high field region only absorptions at δ 41.8 (t) and 34.8 (d). On the basis of these and other spectroscopic data we concluded that the reaction product was α-(phenylmethyl)-2-(1*H*-pyrrol-1-yl)benzeneacetonitrile (**9a**). Compound **6b** reacted similarly; in addition to a mixture of **8a** and **8b** (ratio 1.4:1, yield 22%), **9b** was obtained in a yield of 45%.

The assignment of the stereochemistry of the isomers **7** and **8** is based upon comparison of the characteristic NMR data with those of the corresponding 2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles, the structure of which has been established by X-ray analysis.[6a,7]

The formation of the (1*H*-pyrrol-1-yl)benzeneacetonitriles **9**, in addition to the 9,9a-dihydro-3*H*-pyrrolo[1,2-*a*]indoles **7** and **8**, can be explained as depicted in Scheme I. In both cases the first step comprises a thermal antarafacial [1,6] hydrogen shift to yield the 1,5-dipole **10**. In a protic polar solvent protonation and deprotonation of the 1,5-dipole will be faster than in an apolar solvent. Therefore, in addition to 1,5-dipolar electrocyclization to yield **7** and **8**, aromatization to **9** takes place. The formation of the pyrrolo[1,2-*a*]indoles and the influence of the solvent upon the stereochemistry has been discussed extensively in previous papers.[6a,9]

Subsequently we studied the possibility of the introduction of a leaving group at C-1 (e.g., the aziridine moiety) via an addition reaction to the double bond in **8a,b** as the most suitable model compounds. However, treatment of **8b** with the usual reagents for aziridine formation such as *N*-bromosuccinimide/sodium azide/lithium aluminum hydride,[10] iodine isocyanate,[11] or iodine azide/lithium aluminum hydride[12] all gave mixtures of starting material and the 9*H*-pyrrolo[1,2-*a*]indole **11**. The formation of the latter can be explained by an elimination reaction of the initially formed adduct, the aromatization to a pyrrole derivative being the driving force. In order to prevent this we prepared the *N*-oxide **12** by treatment of **8b** with hydrogen peroxide[13] in acetic acid. Additional treatment of **12** with hydrogen peroxide or 3-chlorobenzenecarboperoxoic acid did not result in epoxidation of the double bond.[14,16] Reaction of **12** with the reagents generally applied for aziridine formation mentioned above yielded complicated reaction mixtures in which only the 9*H*-pyrrolo[1,2-*a*]indole **11** could be detected.

(8) (a) Hirata, T.; Yamada, Y.; Matsui, M. *Tetrahedron Lett.* **1969**, 19; **1969**, 4107. (b) Franck, R. W.; Auerbach, J. *J. Org. Chem.* **1971**, *36*, 31. (c) Siuta, G. J.; Franck, R. W.; Kempton, R. J. *Ibid.* **1974**, *39*, 3739. (d) Rebek, J., Jr.; Shaber, S. H.; Shue, Y.-K.; Gehret, J.-C.; Zimmerman, S. *Ibid.* **1984**, *49*, 5164. (e) Danishefsky, S.; Berman, E. M.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891.

(9) Reinhoudt, D. N.; Visser, G. W.; Verboom, W.; Benders, P. H.; Pennings, M. L. M. *J. Am. Chem. Soc.* **1983**, *105*, 4775.

(10) (a) Van Ende, D.; Krief, A. *Angew. Chem.* **1974**, *86*, 311. (b) Chiu, I.-C.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 2857.

(11) Hassner, A.; Lorber, M. E.; Heathcock, C. *J. Org. Chem.* **1967**, *32*, 540.

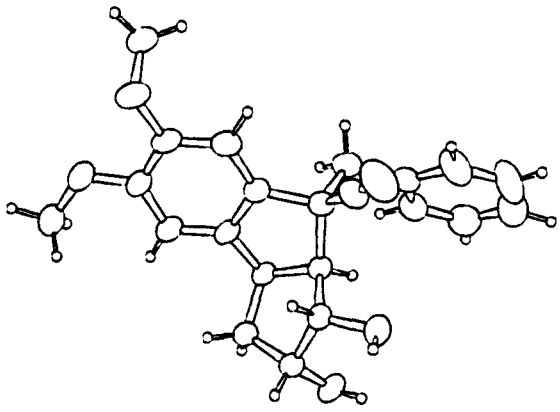
(12) (a) Hassner, A.; Matthews, G. J.; Fowler, F. W. *J. Am. Chem. Soc.* **1969**, *91*, 5046. (b) Cambie, R. C.; Hayward, R. C.; Rutledge, P. S.; Smith-Palmer, T.; Swedlund, B. E.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1980.

(13) Another method of preparation will be treatment with 3-chlorobenzenecarboperoxoic acid in dichloromethane. However, we found that during the workup under the influence of a $NaHSO_3$ solution, the *N*-oxide is converted into starting material.

(14) Ittah et al.[15] reported the conversion of an epoxide into an aziridine ring.

(15) Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* **1978**, *43*, 4271.

(16) A similar observation has been made by Chaudhuri et al. in the case of pirprofen: Chaudhuri, N. K.; Ball, Th. *J. Org. Chem.* **1982**, *47*, 5196.



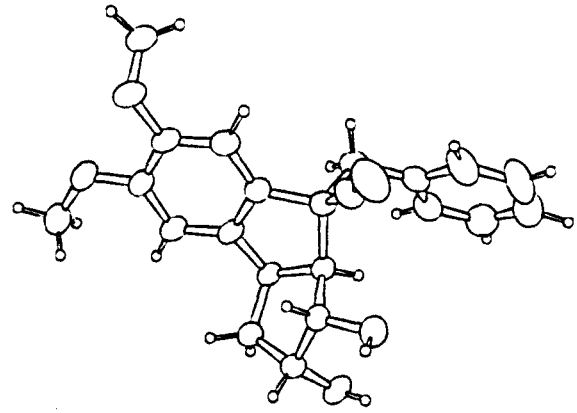
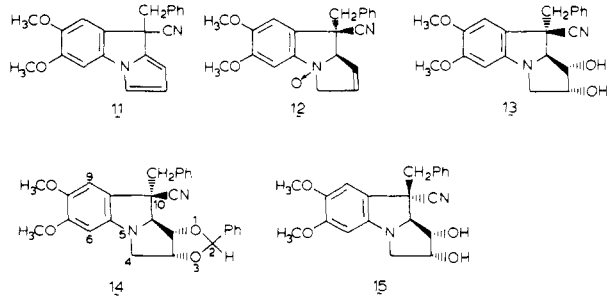
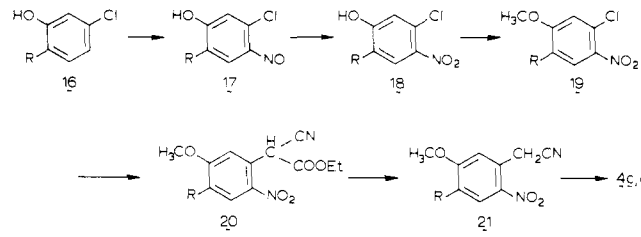


Figure 1. Stereoscopic view of **13**.



Scheme II[a]



[a] a, R = H; b, R = CH_3.

Reaction of **8b** with a stoichiometric amount[17] of osmium tetraoxide[19,20] in pyridine afforded one isomer of a cis-vicinal diol in a yield of 45%. Single-crystal X-ray analysis (Figure 1) revealed the compound to be the diol **13** which means that the cis-hydroxylation had taken place stereoselectively with the reagent approaching from the least hindered side. A Dreiding model of **8b** clearly shows that one side of the double bond is shielded by the cyano group. The diol **13** was transformed by reaction with benzaldehyde in the acetal **14** which was obtained in a yield of 54%. Treatment of the *cis*-pyrrolo[1,2-*a*]indole **8a** with osmium tetraoxide gave exclusively the cis-vicinal diol **15** which was isolated in a yield of 36%.

From our results it will be clear that in contrast to 3*H*-pyrrolo[1,2-*a*]indoles[8] it is difficult to functionalize 9,9a-dihydro-3*H*-pyrrolo[1,2-*a*]indoles via addition reactions to the double bond because of the facile aromatization to a pyrrole derivative. The aromatization is suppressed only when poor leaving groups such as a hydroxyl function are present.

On the other hand the synthesis of potential mitomycin analogues is not limited to compounds with an aziridine ring as the leaving group at C-1. In the literature several active mitosenes containing another *moderately good* leaving group (e.g., an acetyloxy function) at the 1-position have been reported.[21]

Synthesis and Oxidation of (6,)7-Substituted-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles. In the literature an established method for the introduction of a quinone function involves the nitration of aromatic compounds with appropriate substituents, reduction of the nitro group and subsequent oxidation of the resulting aniline derivative by Fremy's salt.[22] Therefore we decided to prepare the substituted tetrahydro-1*H*-pyrrolo[1,2-*a*]-indoles **22** and **23** and to perform the above mentioned reactions for the introduction of the quinone function which is present in the mitomycins.

The preparation of the starting aniline derivatives **4c,d** is depicted in Scheme II. Since in our hands direct nitration of the phenol **16a**[23] as well as **16b**[24] gave the corresponding nitro compounds **18a** and **18b**, respectively, in low yields, we decided to prepare **18a,b** via an alternative route. Nitrosation[25] of **16a,b** and subsequent oxidation of the nitroso compounds **17a,b**[26] with potassium ferricyanide[27] afforded **18a** and **18b** in overall yields of 57% and 52%, respectively. After methylation of **18a,b** a nucleophilic aromatic substitution reaction of **19a,b** with ethyl cyanoacetate in *N,N*-dimethylformamide (DMF) and sodium hydride as a base yielded **20a,b**[28] which were decarboxylated in a sodium carbonate solution to give the benzeneacetonitriles **21a,b**. Subsequent reduction with hydrogen and 5% palladium on carbon as a catalyst ultimately afforded the aniline derivatives **4c,d**.

Dialkylation of **4b–d** with 1,4-dibromobutane in refluxing toluene in the presence of ethyldiisopropylamine gave **5d–f**. Subsequent condensation with benzaldehyde in the presence of sodium ethoxide in ethanol afforded the α-(phenylmethylene)benzeneacetonitriles **6d–f**, respec-

(17) Reaction with a catalytic amount[18] of osmium tetraoxide in the presence of a regenerator was unsuccessful.

(18) See for instance: (a) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973. (b) Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, *98*, 1986.

(19) For very recent applications of the osmium tetraoxide method in the mitomycin field, see ref 8d and 8e.

(20) For a general review see: Schröder, M. *Chem. Rev.* **1980**, *80*, 187.

(21) See for instance: (a) Nakano, K. *Heterocycles* **1979**, *13*, 373. (b) Hodges, J. C.; Remers, W. A.; Bradner, W. T. *J. Med. Chem.* **1981**, *24*, 1184.

(22) See for instance: Ihara, M.; Takahashi, K.; Kigawa, Y.; Ohsawa, T.; Fukumoto, K.; Kametani, T. *Heterocycles* **1977**, *6*, 1658.

(23) (a) Ungnade, H. E.; Ortega I. *J. Org. Chem.* **1952**, *17*, 1475. (b) Jucker, E.; Vogel, A. *Helv. Chim. Acta* **1963**, *46*, 727.

(24) Cason, J.; Harman, R. E.; Adam, P. T.; Goodwin, S. *J. Org. Chem.* **1954**, *16*, 328.

(25) Kraaijeveld, A.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1954**, *73*, 537.

(26) The compounds **17a,b** will also be present in the oxime form.[25]

(27) Hodgson, H. H.; Moore, F. M. *J. Chem. Soc.* **1925**, *127*, 1599.

(28) For a corresponding reaction of 1-chloro-2-nitrobenzene in the presence of potassium *tert*-butoxide as a base in *tert*-butyl alcohol see: Grob, C. A.; Weissbach, O. *Helv. Chim. Acta* **1961**, *44*, 1748.

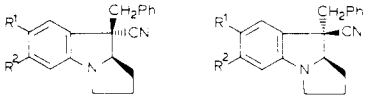
Table I. Conditions and Yields of the Thermal Rearrangement of 6d–f

starting compd	react[a] time, days	isolated products[b] (%)
6d	4.5	**6d** (13), **22b** (36), **23b** (25)
6e	9	**6e** (15), **22c** (36), **23c** (36)
6f	3.5	**6f** (6), **22d** (31), **23d** (37)

[a] Heating in 1-butanol at 118 °C. [b] Yields after separation of the crude reaction mixture with chromatography.

tively, as mixtures of *E*/*Z* isomers from which one isomer could be isolated as yellow solid compounds. The stereochemistry of the individual isomers has not been determined.

In a similar way as described for the unsubstituted α-(phenylmethylene)benzeneacetonitrile **6c**,[6a] compounds **6d–f** were converted into the corresponding *cis*- and *trans*-(6,)7-substituted-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles **22b–d** and **23b–d**, respectively. The conditions and yields are summarized in Table I.

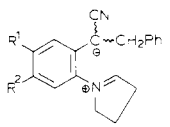


22 23

a, $R^1 = R^2 = H$
b, $R^1 = OCH_3$, $R^2 = H$
c, $R^1 = OCH_3$, $R^2 = CH_3$
d, $R^1 = R^2 = OCH_3$

In order to study the influence of the substituents R^1 and R^2 the rates of the thermal rearrangement of **6c–f** were measured by using HPLC and monitoring the decrease of the amount of the starting compounds **6c–f**. The conversion of **6c–f** fits first-order kinetics for at least 3 half-lives; the reaction rate constants are summarized in Table II.

Previously[9] we have proven that for such thermal isomerization reactions the [1,6] hydrogen transfer (vide supra), in this case the formation of the 1,5-dipole **24**, is the rate-determining step in the overall reaction. The fact that **6d** reacts about 7.5 times faster than **6c** can be explained by the stabilization of the positive charge of the 1,5-dipole **24** by the negative inductive (–I) effect of the methoxy group (R^1). The differences between the rate constants of **6d–f** can be explained in the following way. In all three cases there is the same –I effect of the methoxy group (R^1). However, in the sequence **6ef** the negative charge of the 1,5-dipole **24** is more destabilized by the +I effect of the methyl group (R^2) and the positive resonance (+R) effect of the methoxy group (R^2), respectively.



24

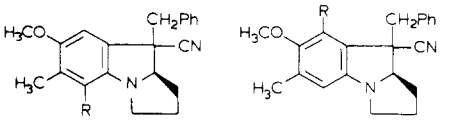
Nitration of the 2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles **22b,d** and **23b,d** under several conditions gave complicated reaction mixtures in which the desired product could not be identified. However, reaction of **22c** and **23c** with nitric acid in dichloromethane at 0 °C afforded the 2,3,9,9a-tetrahydro-5-nitro-1*H*-pyrrolo[1,2-*a*]indoles **25a** and **25b**, respectively, which both were isolated in a yield of 20%. The position of the nitro group followed from the ^{1}H NMR spectra of **25a** and **25b** which in both cases revealed the absence of a small coupling at the methyl signal at δ 2.16 and 2.19, respectively (vide infra).

In the literature[22] only 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]-

Table II. Rate Constants for the Thermal Rearrangement of 6c–f

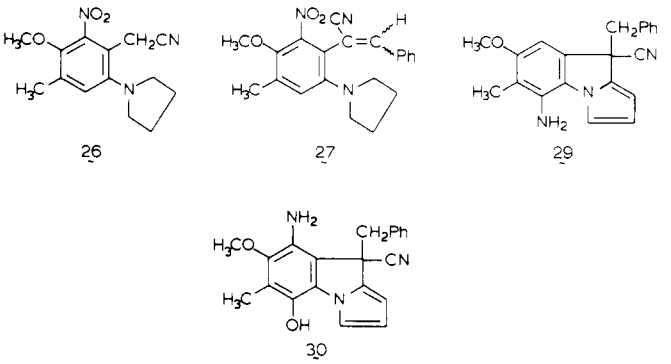
compd	R^1	R^2	10^5k, s^{-1}
6c	H	H	1.38 ± 0.02
6d	OCH_3	H	10.6 ± 0.5
6e	OCH_3	CH_3	9.1 ± 0.5
6f	OCH_3	OCH_3	2.6 ± 0.1

indoles in which the nitrogen lone pair constitutes part of an aromatic system have been nitrated. In these cases the nitro group is introduced at C-8, because the methoxy group at C-7 will be the strongest ortho-directing group. However, in compounds **22c** and **23c** the *N*,*N*-dialkylamino group renders the nitration to take place at C-5.



25 28

a, R = NO_2 (α-CN)
b, R = NO_2 (β-CN)
c, R = NH_2 (α-CN)
d, R = NH_2 (β-CN)



26 27 29

30

Because of the low yield of **25a,b** we decided to introduce the nitro group before the thermal rearrangement is carried out. Nitration of **5e** with concentrated nitric acid in sulfuric acid gave compound **26** in a yield of 36%. In this case nitration takes place ortho to the methoxy substituent as could be concluded from the broadened singlet at δ 2.35 of the methyl group in the ^{1}H NMR spectrum. The selective introduction of the nitro group at C-2 is due to protonation of the nitrogen atom of the pyrrolidinyl moiety in strong acid which means that in addition to the ortho-directing methoxy group a meta-directing protonated pyrrolidinyl moiety is present. Condensation of **26** with benzaldehyde in the presence of sodium ethoxide in ethanol afforded a mixture of (*E*/*Z*)-**27** in a yield of 20%. This low yield might be due to reaction of the nitro group with strong base. The latter could be avoided by the use of piperidine. Although in this case the reaction is very slow, after refluxing for 8 days in ethanol, in addition to starting material (51%), one isomer of the expected compound **27** and the pyrrolo[1,2-*a*]indole **28a** were obtained in yields of 29% and 10%, respectively. Cyclization of the *E*/*Z* mixture of **27** in refluxing 1-butanol gave a mixture of the *cis*- and *trans*-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles **28a** and **28b**, which were isolated in yields of 67% and 18%, respectively. The ^{1}H NMR spectrum of both compounds exhibited a doublet for the methyl group at δ 2.32. This observation served also as a definite proof of the structures of **25a** and **25b** that are formed by nitration of **22c** and **23c**, respectively (vide supra).

Reduction of **25a** and **28a** with iron powder in 50% aqueous acetic acid and of **25b** with hydrogen and 5%

palladium on carbon as a catalyst[29] afforded the corresponding aniline derivatives **25c**, **28c**, and **25d** in yields of 87%, 64%, and 40%, respectively. However, oxidation of both **25c** and **25d** with Fremy's salt under standard conditions did not produce the corresponding *p*-quinones. In a very low yield of 8% only compound **29** could be identified. The corresponding reaction of **28c** with Fremy's salt gave a complicated reaction mixture in which a trace of **30** could be detected. Therefore the structural assignment of **30** is based upon the mass spectrum only.

These results show that starting from tetrahydropyrrolo[1,2-*a*]indoles it is not possible to synthesize the corresponding *p*-quinones with the standard methodology for 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles. The nitro group can be introduced and reduced but the oxidation of the anilines with Fremy's salt affords complicated mixtures in which only the presence of the 9*H*-pyrrolo[1,2-*a*]indoles **29** (and **30**) could be proven. A somewhat related reaction is the aromatization of 2,3-dihydroindoles under the influence of Fremy's salt as reported by Teuber and Staiger.[30] Our results show that there is a fundamental difference between the synthesis of *mitosenes*[21a,22] and *mitosanes*[21a] in the oxidation step. Further work on the synthesis of tetrahydro-5,8-dioxopyrrolo[1,2-*a*]indoles with our methodology will concentrate on the introduction of a protected hydroquinone function in an earlier stage of the synthesis.

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 obtained with a Varian MAT 311A spectrometer and IR spectra with a Perkin-Elmer 257 spectrophotometer. Elemental analyses were carried out by E. Hoogendam of the Laboratory of Chemical Analysis of the Twente University of Technology and by the Element Analytical Section of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands, under the supervision of G. J. Rotscheid.

Petroleum ether refers to the fraction with bp 60–80 °C unless stated otherwise.

All reactions were carried out under a nitrogen atmosphere.

2-Amino-5-methoxybenzeneacetonitrile (4c) was obtained by reduction of **21a** with hydrogen (~50 psi) in the presence of 5% Pd/C as described:[31] yield 91%; mp 87.5–89 °C (ethanol) (lit.[31] mp 85–86 °C); ^{1}H NMR δ 6.85–6.65 (m, 3 H, Ar H), 3.76 (s, 3 H, OCH_3), 3.56 (s, CH_2CN), 3.39 (br s, 2 H, NH_2).

2-Amino-5-methoxy-4-methylbenzeneacetonitrile (4d). A solution of **21b** (3.78 g, 18.3 mmol) in a mixture of ethyl acetate (45 mL) and ethanol (45 mL) was hydrogenated in the presence of 5% Pd/C (0.25 g) at atmospheric pressure at room temperature. After 24 h, when the reaction was complete as followed from TLC, the solution was filtered through hyflo. After removal of the solvents under reduced pressure the resulting crude compound was purified by flash chromatography[32] (silica gel, dichloromethane/ethyl acetate, 92:8) to afford pure **4d**: yield 90%; mp 132–133.5 °C (methanol); ^{1}H NMR δ 6.68 and 6.57 (s, 1 H, H-3 and H-6), 3.77 (s, 3 H, OCH_3), 3.54 (s, 2 H, CH_2CN), 3.23 (br s, 2 H, NH_2), 2.15 (s, 3 H, CH_3); ^{13}C NMR δ 152.7 (s, C-5), 134.1 (s, C-2), 128.1 (s, C-4), 121.3 (d, C-3), 117.2 and 114.8 (s, C-1 and CN), 111.5 (d, C-6), 55.9 (q, OCH_3), 20.3 (t, CH_2CN), 15.9 (q, CH_3); IR (KBr) 3390 and 3250 (NH_2), 2250 (CN) cm^{-1}; mass spectrum, *m/e* 176.095 (M$^+$, calcd 176.095).

Anal. Calcd for $C_{10}H_{12}N_2O$ (M_r 176.220): C, 68.16; H, 6.84; N, 15.90. Found: C, 68.29; H, 6.83; N, 15.89.

General Procedure for the Preparation of 2-(2,5-Dihydro-1*H*-pyrrol-1-yl)- and 4,5-Dimethoxy-2-(2,5-dihydro-1*H*-pyrrol-1-yl)benzeneacetonitriles (5a and 5b). A solution of **4a**,[33] **4b**[34] (40 mmol), (*Z*)-1,4-dichloro-2-butene (4.93 g, 40 mmol), ethyldiisopropylamine (12.9 g, 0.1 mol), and a catalytic amount of KI (~0.5 g) in toluene (50 mL) was heated at 110 °C for 1.5 h and 4 h, respectively. Upon cooling the salts were filtered off. The filtrate was washed with water (2 × 50 mL) and brine and subsequently dried with $MgSO_4$. In the case of **4a** the toluene solution was passed through a short column of florisil[35] which after removal of the solvent under reduced pressure gave pure **5a**. In the case of **4b** the crude reaction mixture was separated by column chromatography (silica gel, chloroform) to afford pure **5b**.

5a: yield 87%; oil; ^{1}H NMR δ 7.5–6.9 (m, 4 H, Ar H), 5.89 (br s, 2 H, HC=), 4.08 (s, 4 H, NCH_2), 3.80 (s, 2 H, CH_2CN); ^{13}C NMR δ 149.0 (s, C-2), 126.5 (d, HC=), 58.8 (t, NCH_2), 21.3 (t, CH_2CN); mass spectrum, *m/e* 184.096 (M$^+$, calcd for $C_{12}H_{12}N_2$ 184.100).

5b: yield 86%; mp 74.5–75.5 °C (methanol); ^{1}H NMR δ 6.88 and 6.78 (s, 1 H, H-3 and H-6), 5.89 (br s, 2 H, HC=), 4.00 (s, 4 H, NCH_2), 3.88 and 3.85 (s, 3 H, OCH_3), 3.79 (s, 2 H, CH_2CN); ^{13}C NMR δ 149.7 (s, C-2), 146.1 and 143.1 (s, C-4 and C-5), 126.9 (d, HC=), 60.4 (t, NCH_2), 56.4 and 56.1 (q, OCH_3), 19.8 (t, CH_2CN); mass spectrum, *m/e* 244.123 (M$^+$, calcd 244.121).

Anal. Calcd for $C_{14}H_{16}N_2O_2$ (M_r 244.294): C, 68.83; H, 6.60; N, 11.47. Found: C, 68.87; H, 6.23; N, 11.47.

General Procedure for the Preparation of the 2-(1-Pyrrolidinyl)benzeneacetonitriles 5d–f. A solution of **4b–d**,[34] (0.10 mol), 1,4-dibromobutane (21.6 g, 0.10 mol), and ethyldiisopropylamine (32.3 g, 0.25 mol) in toluene (150 mL) was heated at 110 °C for 3, 4.5, and 5 h, respectively. Upon cooling the salts were filtered off. The filtrate was washed with water (3 × 100 mL) and dried with $MgSO_4$. After removal of the solvent under reduced pressure the residue was purified as indicated.

5-Methoxy-2-(1-pyrrolidinyl)benzeneacetonitrile (5d). The residue was purified by column chromatography (silica gel, chloroform/ethyl acetate, 9:1) to give **5d** as an oil which was subsequently distilled: yield 87%; bp 132 °C (0.08 mm); ^{1}H NMR δ 7.20 (d, 1 H, J_{ortho} = 8.5 Hz, H-3), 6.98 (d, 1 H, J_{meta} = 2.9 Hz, H-6), 6.83 (dd, 1 H, J_{ortho} = 8.5 Hz, J_{meta} = 2.9 Hz, H-4), 3.79 (s, 5 H, OCH_3 and CH_2CN), 3.15–2.85 (m, 4 H, NCH_2), 2.1–1.8 (m, 4 H, CH_2); ^{13}C NMR δ 155.6 and 142.3 (s, C-2 and C-5), 128.5 (s, C-1), 120.8, 114.8 and 114.1 (d, C-3, C-4, and C-6), 118.7 (s, CN), 55.5 (q, OCH_3), 52.8 (t, NCH_2), 24.7 (t, CH_2), 20.1 (t, CH_2CN); IR (KBr) 2245 (CN) cm^{-1}; mass spectrum, *m/e* 216.127 (M$^+$, calcd for $C_{13}H_{16}N_2O$ 216.126).

5-Methoxy-4-methyl-2-(1-pyrrolidinyl)benzeneacetonitrile (5e). The residue, dissolved in dichloromethane, was passed through a short column of silica gel to afford pure **5e**: yield 87%; mp 61–63 °C (methanol); ^{1}H NMR δ 6.95 (br s, 1 H, H-3), 6.86 (s, 1 H, H-6), 3.82 (s, 3 H, OCH_3), 3.78 (s, 2 H, CH_2CN), 2.19 (br s, 3 H, CH_3); ^{13}C NMR δ 122.4 (d, C-3), 110.9 (d, C-6), 55.7 (q, OCH_3), 52.8 (t, NCH_2), 19.9 (t, CH_2CN), 16.1 (q, CH_3); IR (KBr) 2240 (CN) cm^{-1}; mass spectrum, *m/e* 230.146 (M$^+$, calcd 230.142).

Anal. Calcd for $C_{14}H_{18}N_2O$ (M_r 230.310): C, 73.01; H, 7.88; N, 12.16. Found: C, 72.94; H, 8.07; N, 12.09.

4,5-Dimethoxy-2-(1-pyrrolidinyl)benzeneacetonitrile (5f). The resulting solid was triturated with methanol to give pure **5f**: yield 69%; mp 87–88.5 °C (diisopropyl ether); ^{1}H NMR δ 6.89 and 6.72 (s, 1 H, H-3 and H-6), 3.87 (s, 6 H, OCH_3), 3.75 (s, 2 H, CH_2CN); ^{13}C NMR δ 112.7 (d, C-6), 104.1 (d, C-3), 56.3 and 56.0 (q, OCH_3), 52.7 (t, NCH_2), 19.6 (t, CH_2CN); IR (KBr) 2237 (CN) cm^{-1}; mass spectrum, *m/e* 246.135 (M$^+$, calcd 246.137).

Anal. Calcd for $C_{14}H_{18}N_2O_2$ (M_r 246.312): C, 68.27; H, 7.37; N, 11.37. Found: C, 68.32; H, 7.49; N, 11.32.

General Procedure for the Preparation of 2-(2,5-Dihydro-1*H*-pyrrol-1-yl)- and 2-(2,5-Dihydro-1*H*-pyrrol-1-yl)-4,5-dimethoxy-α-(phenylmethylene)benzeneacetonitriles (6a and 6b). To a solution of **5a,b** (25.0 mmol) in dry ethanol (50 mL) was added NaOH pellets (0.8 g, 20 mmol) which partly dissolved. After the mixture stirred for 15 min, freshly distilled benzaldehyde (2.87 g, 27.0 mmol) was added, whereupon the

(29) On account of the small scale and the simple workup procedure the reduction was carried out by this method.
(30) Teuber, H. J.; Staiger, G. *Chem. Ber.* **1954**, *87*, 1251; **1956**, *89*, 489; **1965**, *98*, 2648.
(31) Piozzi, F.; Umani Ronchi, A. *Gazz. Chim. Ital.* **1963**, *93*, 3.
(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(33) Rousseau, V.; Lindwall, H. G. *J. Am. Chem. Soc.* **1950**, *72*, 3047.
(34) Walker, G. N. *J. Am. Chem. Soc.* **1955**, *77*, 3844.
(35) The use of silica gel gave rise to partial aromatization of the 2,5-dihydropyrrole moiety.

reaction mixture was stirred for 15 h at room temperature. After the addition of water (50 mL) the mixture was extracted with chloroform (3 × 50 mL). The combined extracts were washed with a $NaHSO_3$ solution, water, and brine and dried with $MgSO_4$, whereupon the solvent was removed under reduced pressure. In the case of **5a** the crude reaction mixture was purified by chromatography (silica gel, chloroform) through a short column to give **6a** as an oil which solidified upon the addition of a few drops of diisopropyl ether. Trituration of the yellow solid with the same solvent afforded pure **6a**. In the case of **5b** trituration of the resulting yellow solid with diisopropyl ether gave pure **6b**.

6a: yield 45%; mp 93.5–94 °C (ethanol); ^1H NMR δ 8.0–7.7 (m, 2 H, Ar H), 7.55–7.1 [m, 6 H, 5 Ar H and =C(Ph)*H*], 6.95–6.7 (m, 2 H, Ar H), 5.83 (br s, 2 H, HC=), 4.19 (s, 4 H, NCH_2); ^{13}C NMR δ 146.7 (s, C-2), 144.6 [d, =*C*(Ph)H], 125.9 (d, HC=), 111.8 [s, =*C*(CN)], 57.5 (t, NCH_2); IR (KBr) 2198 (CN) cm^{-1}; mass spectrum, *m/e* 272.129 (M^+, calcd 272.131).

Anal. Calcd for $C_{19}H_{16}N_2$ (M_r 272.351): C, 83.79; H, 5.92; N, 10.29. Found: C, 83.68; H, 6.00; N, 10.28.

6b: yield 70%; mp 141–142 °C (diisopropyl ether); ^1H NMR δ 8.0–7.7 (m, 2 H, Ar H), 7.65–7.3 (m, 3 H, Ar H), 7.17 [s, 1 H, =C(Ph)*H*], 6.83 and 6.58 (s, 1 H, H-3 and H-6), 5.86 (br s, 2 H, HC=), 4.15 (s, 4 H, NCH_2), 3.91 and 3.86 (s, 3 H, OCH_3); ^{13}C NMR δ 150.6, 143.1 and 142.3 (s, C-2, C-4 and C-5), 144.1 [d, =*C*(Ph)H], 126.4 (d, HC=), 111.5 [s, =*C*(CN)], 58.3 (t, NCH_2), 56.7 and 56.0 (q, OCH_3); IR (KBr) 2200 (CN) cm^{-1}; mass spectrum, *m/e* 332.149 (M^+, calcd 332.153).

Anal. Calcd for $C_{21}H_{20}N_2O_2$ (M_r 332.403): C, 75.88; H, 6.06; N, 8.43. Found: C, 75.92; H, 6.06; N, 8.59.

General Procedure for the Preparation of the (4,)5-Substituted-α-(phenylmethylene)-2-(1-pyrrolidinyl)benzeneacetonitriles 6d–f. 5d–f (50 mmol) was added to a solution of sodium ethoxide [prepared by dissolving sodium (1.5 g, 65 mmol) in ethanol (250 mL)] at room temperature. After stirring for 5 min at 40 °C freshly distilled benzaldehyde (6.4 g, 60 mmol) was added to the reaction mixture which was subsequently refluxed for 3 h. Upon cooling most of the solvent was removed under reduced pressure. The residue, suspended in chloroform (150 mL), was stirred with a $NaHSO_3$ solution. After separation of the layers, the organic layer was washed with water and brine and dried with $MgSO_4$. After removal of the solvent under reduced pressure the residue was purified as indicated. Only the spectral data of the isolated crystalline isomer are given. The ratio of the *E/Z* mixtures could not be determined with ^1H NMR spectroscopy.

5-Methoxy-α-(phenylmethylene)-2-(1-pyrrolidinyl)-benzeneacetonitrile (6d). The resulting solid was triturated with diisopropyl ether to afford one isomer of **6d** as a yellow solid (8.4 g, 55%). The filtrate, dissolved in chloroform, was passed through a short column of silica gel to give a *E/Z* mixture of **6d** (3.5 g, 23%) as a yellow oil.

Crystalline isomer: mp 132–138 °C dec (diisopropyl ether); ^1H NMR δ 7.95–7.75 (m, 2 H, Ar H), 7.6–7.25 (m, 4 H, 3 Ar H and =CH), 7.0–6.8 (m, 3 H, H-3, H-4, and H-6), 3.78 (s, 3 H, OCH_3), 3.25–3.0 (m, 4 H, NCH_2), 2.0–1.75 (m, 4 H, CH_2); ^{13}C NMR δ 153.6 (s, C-2), 144.6 (d, =CH), 142.4 (s, C-5), 118.0, 115.7 and 115.4 (d, C-3, C-4, and C-6), 111.7 [s, =*C*(CN)], 55.7 (q, OCH_3), 51.6 (t, NCH_2); IR (KBr) 2204 (CN) cm^{-1}; mass spectrum, *m/e* 304.159 (M^+, calcd 304.158).

Anal. Calcd for $C_{20}H_{20}N_2O$ (M_r 304.394): C, 78.92; H, 6.62; N, 9.20. Found: C, 79.11; H, 6.65; N, 9.18.

5-Methoxy-4-methyl-α-(phenylmethylene)-2-(1-pyrrolidinyl)benzeneacetonitrile (6e). Purification by column chromatography (silica gel, chloroform) gave one isomer of **6e** as a yellow solid (8.15 g, 51%) and a *E/Z* mixture of **6e** (3.20 g, 20%) as a yellow oil.

Crystalline isomer: mp 123–125 °C (diethyl ether/petroleum ether); ^1H NMR δ 7.6–7.2 (m, 6 H, Ar H and =CH), 6.84 (br s, 1 H, H-3), 6.78 (s, 1 H, H-6), 3.82 (s, 3 H, OCH_3), 3.2–3.0 (m, 4 H, NCH_2), 2.22 (br s, 3 H, CH_3), 2.0–1.8 (m, 4 H, CH_2); ^{13}C NMR δ 151.9 (s, C-2), 144.0 (d, =CH), 143.9 (s, C-5), 119.7 and 112.3 (d, C-3 and C-6), 111.6 [s, =*C*(CN)], 55.9 (q, OCH_3), 51.6 (t, NCH_2), 16.3 (q, CH_3); IR (KBr) 2190 (CN) cm^{-1}; mass spectrum, *m/e* 318.174 (M^+, calcd 318.173).

Anal. Calcd for $C_{21}H_{22}N_2O$ (M_r 318.421): C, 79.21; H, 6.96; N, 8.80. Found: C, 79.40; H, 7.00; N, 9.06.

4,5-Dimethoxy-α-(phenylmethylene)-2-(1-pyrrolidinyl)-benzeneacetonitrile (6f). The resulting solid was triturated with methanol to yield one isomer of **6f** as a yellow solid (7.45 g, 45%). Column chromatography (silica gel, chloroform) of the filtrate afforded another crop of the crystalline isomer (2.02 g, 12%) and a *E/Z* mixture of **6f** (3.08 g, 18%) as a yellow oil.

Crystalline isomer: mp 127–137 °C dec (methanol); ^1H NMR δ 8.1–7.8 (m, 2 H, Ar H), 7.65–7.2 (m, 4 H, 3 Ar H and =CH), 6.85 and 6.57 (s, 1 H, H-3 and H-6), 3.91 and 3.86 (s, 3 H, OCH_3), 3.4–3.1 (m, 4 H, NCH_2), 2.2–1.8 (m, 4 H, CH_2); ^{13}C NMR δ 150.1 (s, C-2), 143.5 (d, =CH), 114.1 (d, C-6), 111.5 [s, =*C*(CN)], 100.9 (d, C-3), 56.5 and 55.8 (q, OCH_3), 51.6 (t, NCH_2); IR (KBr) 2207 (CN) cm^{-1}; mass spectrum, *m/e* 334.166 (M^+, calcd 334.168).

Anal. Calcd for $C_{21}H_{22}N_2O_2$ (M_r 334.421): C, 75.42; H, 6.63; N, 8.38. Found: C, 75.31; H, 6.65; N, 8.30.

Thermal Rearrangements of 6a. Formation of 7a,b and 9a. Reaction in Toluene. A solution of **6a** (1.00 g, 3.67 mmol) in toluene (20 mL) was heated at 110 °C for 18 h. After removal of the solvent under reduced pressure, the resulting residue was purified by column chromatography (silica gel, chloroform) to afford an oil which solidified upon the addition of a few drops of diisopropyl ether. Trituration of the solid with this solvent gave pure **7b** in a yield of 86%.

Reaction in Methanol. A solution of **6a** (0.50 g, 1.84 mmol) in methanol (10 mL) was heated at 65 °C for 18 h. After removal of the solvent under reduced pressure, the residue was separated by column chromatography (silica gel, chloroform) to give **9a** as a white solid and a mixture of **7a** and **7b** (ratio about 1.2:1) in yields of 45% and 25%, respectively.

Reaction in Acetonitrile. A mixture of **6a** (1.25 g, 4.60 mmol) and zinc chloride (1.25 g, 9.17 mmol) in acetonitrile (20 mL) was heated at 81 °C for 3 h. After removal of the acetonitrile under reduced pressure, diethyl ether (100 mL) was added to the residue. The solution was washed with water (2 × 75 mL) and dried with $MgSO_4$ whereupon the solvent was removed under reduced pressure. The residue (the ^1H NMR spectrum of which showed the ratio of **7a/7b** 3.5:1) was separated by column chromatography [silica gel (0.015–0.040 mm), dichloromethane/petroleum ether, 2:1] to afford pure **7a** (0.37 g, 30%) and a mixture of **7a** and **7b** (0.35 g, 28%).

***cis*-9,9a-Dihydro-9-(phenylmethyl)-3*H*-pyrrolo[1,2-*a*]-indole-9-carbonitrile (7a)**: mp 88–90 °C (chloroform/petroleum ether); ^1H NMR δ 7.5–6.9 (m, 6 H, Ar H), 6.85–6.25 (m, 3 H, Ar H), 5.9 (br s, 2 H, HC=), 5.4–5.2 (m, 1 H, NCH), 4.35–3.75 (m, 2 H, NCH_2), 3.07 and 2.67 (AB q, 2 H, *J* = 13.6 Hz, CH_2Ph); ^{13}C NMR δ 152.2 (s, C-4a), 80.5 (d, C-9a), 59.7 (t, C-3), 48.4 (s, C-9), 43.1 (t, CH_2Ph); IR (KBr) 2230 (CN) cm^{-1}; mass spectrum, *m/e* 272.132 (M^+, calcd 272.131).

Anal. Calcd for $C_{19}H_{16}N_2$ (M_r 272.351): C, 83.79; H, 5.92; N, 10.29. Found: C, 83.75; H, 5.83; N, 10.21.

***trans*-9,9a-Dihydro-9-(phenylmethyl)-3*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (7b)**: mp 82.5–83 °C (diisopropyl ether); ^1H NMR δ 7.45–7.1 (m, 6 H, Ar H), 7.0–6.65 (m, 3 H, Ar H), 5.9 (br s, 2 H, HC=), 4.85–4.65 (m, 1 H, NCH), 4.1–3.9 (m, 2 H, NCH_2), 3.27 and 3.09 (AB q, 2 H, *J* = 16 Hz, CH_2Ph); ^{13}C NMR δ 153.7 (s, C-4a), 78.5 (d, C-9a), 61.2 (t, NCH_2), 49.6 (s, C-9), 46.0 (t, CH_2Ph); IR (NaCl) 2230 (CN) cm^{-1}; mass spectrum, *m/e* 272.128 (M^+, calcd 272.131).

Anal. Calcd for $C_{19}H_{16}N_2$ (M_r 272.351): C, 83.79; H, 5.92; N, 10.29. Found: C, 83.45; H, 5.87; N, 10.09.

α-(Phenylmethyl)-2-(1*H*-pyrrol-1-yl)benzeneacetonitrile (9a): mp 109–110.5 °C (ethanol); ^1H NMR δ 7.8–6.75 (m, 9 H, Ar H), 6.7–6.5 (m, 2 H, NCH=), 6.45–6.3 (m, 2 H, HC=), 3.96 (t, 1 H, *J* = 7.2 Hz, CHCN), 2.95 (d, 2 H, *J* = 7.2 Hz, CH_2Ph); ^{13}C NMR δ 122.1 (d, NC=), 109.8 (d, HC=), 41.8 (t, CH_2Ph), 34.8 (d, CHCN); IR (KBr) 2235 (CN) cm^{-1}; mass spectrum, *m/e* 272.130 (M^+, calcd 272.131).

Anal. Calcd for $C_{19}H_{16}N_2$ (M_r 272.351): C, 83.79; H, 5.92; N, 10.29. Found: C, 83.66; H, 6.00; N, 10.27.

Thermal Rearrangements of 6b. Formation of 8a,b and 9b. Reaction in Toluene. A solution of **6b** (5.70 g, 17.16 mmol) in toluene (60 mL) was heated at 110 °C for 18 h. After removal of the solvent under reduced pressure, the remaining solid was triturated with diisopropyl ether to give pure **8b** in a yield of 86%.

Reaction in Methanol. A solution of **6b** (0.60 g, 1.81 mmol) in methanol (10 mL) was heated at 65 °C for 18 h. After removal of the solvent under reduced pressure, the residue was separated

by column chromatography (silica gel, chloroform) to give **9b** as a white solid and a mixture of **8a** and **8b** (ratio about 1.4:1) in yields of 45% and 22%, respectively.

Reaction in Acetonitrile. A mixture of **6b** (1.60 g, 4.81 mmol) and zinc chloride (1.60 g, 11.74 mmol) in acetonitrile (50 mL) was heated at 81 °C for 2.75 h. After removal of the acetonitrile under reduced pressure, chloroform (150 mL) was added to the residue. The solution was washed with water (2 × 100 mL) and dried with $MgSO_4$ whereupon the solvent was removed under reduced pressure. The residue (the ^1H NMR spectrum of which showed the ratio of **8a**/**8b** 1.8:1) was separated by column chromatography [silica gel (0.015–0.040 mm), chloroform] to afford pure **8a** (0.25 g, 16%) and a mixture of **8a** and **8b** (0.60 g, 37%).

***cis*-9,9a-Dihydro-6,7-dimethoxy-9-(phenylmethyl)-3*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (8a):** mp 69–72 °C (chloroform/petroleum ether); ^1H NMR δ 7.5–7.1 (m, 5 H, Ar H), 6.38 and 5.78 (s, 1 H, H-5 and H-8), 6.0 (br s, 2 H, HC=), 5.5–5.3 (m, 1 H, NCH), 4.1–3.75 (m, 2 H, NCH_2), 3.86 and 3.48 (s, 3 H, OCH_3), 3.13 and 2.59 (AB q, 2 H, J = 13.6 Hz, CH_2Ph); ^{13}C NMR δ 150.9 (s, C-4a), 146.2 and 143.4 (s, C-6 and C-7), 109.4 (d, C-8), 98.1 (d, C-5), 81.5 (d, C-9a), 60.3 (t, C-3), 56.0 and 55.9 (q, OCH_3), 48.9 (s, C-9), 43.7 (t, CH_2Ph); IR (KBr) 2230 (CN) cm^{-1}; mass spectrum, m/e 332.151 (M^+, calcd 332.153).

Anal. Calcd for $C_{21}H_{20}N_2O_2$ (M_r 332.405): C, 75.88; H, 6.06; N, 8.43. Found: C, 75.52; H, 5.97; N, 8.36.

***trans*-9,9a-Dihydro-6,7-dimethoxy-9-(phenylmethyl)-3*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (8b):** mp 154–155 °C (diisopropyl ether); ^1H NMR δ 7.4–7.1 (m, 5 H, Ar H), 6.38 and 6.24 (s, 1 H, H-5 and H-8), 5.9 (br s, 2 H, HC=), 4.85–4.7 (m, 1 H, NCH), 4.1–3.95 (m, 2 H, NCH_2), 3.86 and 3.65 (s, 3 H, OCH_3), 3.28 and 3.05 (AB q, 2 H, J = 18.4 Hz, CH_2Ph); ^{13}C NMR δ 151.1 (s, C-4a), 147.8 and 144.3 (s, C-6 and C-7), 108.4 (d, C-8), 98.1 (d, C-5), 79.9 (d, C-9a), 61.6 (t, C-3), 56.3 and 56.1 (q, OCH_3), 50.0 (s, C-9), 46.5 (t, CH_2Ph); IR (KBr) 2215 (CN) cm^{-1}; mass spectrum, m/e 332.152 (M^+, 332.153).

Anal. Calcd for $C_{21}H_{20}N_2O_2$ (M_r 332.405): C, 75.88; H, 6.06; N, 8.43. Found: C, 75.90; H, 6.18; N, 8.48.

4,5-Dimethoxy-α-(phenylmethyl)-2-(1*H*-pyrrol-1-yl)-benzeneacetonitrile (9b): mp 123–125 °C (diisopropyl ether); ^1H NMR δ 7.5–7.1 (m, 5 H, Ar H), 6.93 and 6.78 (s, 1 H, H-3 and H-6), 6.65–6.5 (m, 2 H, NCH=), 6.4–6.2 (m, 2 H, HC=), 3.91 and 3.85 (s, 3 H, OCH_3), 3.87 (t, 1 H, J = 7.2 Hz, CHCN), 2.97 (d, 2 H, J = 7.2 Hz, CH_2Ph); ^{13}C NMR δ 122.5 (d, NC=), 111.0 and 110.2 (d, C-3 and C-6), 109.6 (d, HC=), 56.3 and 56.2 (q, OCH_3), 41.8 (t, CH_2Ph), 34.4 (d, CHCN); IR (KBr) 2235 (CN) cm^{-1}; mass spectrum, m/e 332.151 (M^+, calcd 332.153).

Anal. Calcd for $C_{21}H_{20}N_2O_2$ (M_r 332.405): C, 75.88; H, 6.06; N, 8.43. Found: C, 75.56; H, 6.06; N, 8.34.

***trans*-9,9a-Dihydro-6,7-dimethoxy-9-(phenylmethyl)-3*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile 4-Oxide (12).** A solution of **8b** (0.20 g, 0.60 mmol) and 30% hydrogen peroxide (10 mL) in acetic acid (10 mL) was stirred at room temperature for 2 days. The reaction mixture was made alkaline with a NH_4OH solution and subsequently extracted with chloroform (3 × 20 mL). The combined extracts were washed twice with water and brine and dried with $MgSO_4$. Removal of the solvent under reduced pressure afforded pure **12** as an oil in quantitative yield: ^1H NMR δ 7.4–7.2 (m, 5 H, Ar H), 7.28 (s, 1 H, H-5), 6.40 (s, 1 H, H-8), 6.1–5.6 (m, 2 H, HC=), 5.35–5.2 (m, 1 H, NCH), 4.9–4.65 (m, 2 H, NCH_2), 3.95 and 3.77 (s, 3 H, OCH_3), 3.64 and 3.38 (AB q, 2 H, J = 13.5 Hz, CH_2Ph); ^{13}C NMR δ 128.2 and 127.0 (d, HC=), 105.7 and 101.4 (d, C-5 and C-8), 95.4 (d, C-9a), 61.5 (t, C-3), 56.6 and 56.3 (q, OCH_3), 50.1 (s, C-9), 45.3 (t, CH_2Ph); mass spectrum, m/e 330.140 ($M^+ - H_2O$, calcd for $C_{21}H_{18}N_2O_2$ 330.139).

(1α,2α,9β,9aα)-2,3,9,9a-Tetrahydro-1,2-dihydroxy-6,7-dimethoxy-9-(phenylmethyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (13)[36] was prepared starting from **8b** (300 mg, 0.90 mmol) and osmium tetraoxide (240 mg, 0.94 mmol) in pyridine (24 mL) in a similar way as described for **15**: yield 45%; mp 184–187 °C (chloroform/petroleum ether); ^1H NMR δ 7.5–7.1 (m, 5 H, 366.159 H), 6.23 and 6.12 (s, 1 H, H-5 and H-8), 4.4–4.15 (m, 1 H, NCH), 4.1–3.8 (m, 2 H, CHOH), 3.86 and 3.60 (s, 3 H, OCH_3), 3.24 and 3.01 (AB q, 2 H, J = 13.6 Hz, CH_2Ph), 2.45 (br s, 2 H, OH); ^{13}C NMR δ 151.5 (s, C-4a), 147.5 and 143.5 (s, C-6 and C-7), 109.4 (d, C-8), 96.2 (d, C-5), 75.7 (d, C-9a), 73.3 and 72.4 (d, C-1 and C-2), 58.6 (t, C-3), 56.6 and 56.2 (q, OCH_3), 48.0 (s, C-9), 46.2 (t, CH_2Ph); IR (KBr) 3700–3100 (OH) and 2235 (CN) cm^{-1}; mass spectrum, m/e 366.159 (M^+, calcd 366.158).

Anal. Calcd for $C_{21}H_{22}N_2O_4$ (M_r 366.421): C, 68.84; H, 6.05; N, 7.65. Found: C, 68.94; H, 6.35; N, 7.59.

3a,10,10a,10b-Tetrahydro-7,8-dimethoxy-2-phenyl-10-(phenylmethyl)-4*H*-1,3-dioxolo[3,4]pyrrolo[1,2-*a*]indole-10-carbonitrile (14). A mixture of **13** (0.15 g, 0.41 mmol), benzaldehyde (60 mg, 0.57 mmol), *p*-toluenesulfonic acid (~0.1 g), and $MgSO_4$ (~1 g) in chloroform (5 mL) was heated at 61 °C for 20 h. Upon cooling the $MgSO_4$ was filtered off whereupon the filtrate was concentrated under reduced pressure. The residue was separated by column chromatography (silica gel, chloroform) to give pure **14** as a white solid: yield 54%; mp 166–167 °C (methanol/chloroform); ^1H NMR δ 7.6–7.1 (m, 10 H, Ar H), 6.30 and 6.21 (s, 1 H, H-6 and H-9), 5.96 (s, 1 H, HCPh), 4.9–4.65 (m, 2 H, H-3a and H-10b), 4.1–3.9 (m, 1 H, NCH), 3.87 and 3.63 (s, 3 H, OCH_3), 3.8–3.4 (m, 2 H, NCH_2), 3.22 and 3.04 (AB q, 2 H, J = 13.4 Hz, CH_2Ph); ^{13}C NMR δ 151.2 (s, C-5a), 145.7 and 143.7 (s, C-7 and C-8), 108.1 (d, C-2), 83.2 and 81.6 (d, C-3a and C-10b), 78.6 (d, C-10a), 56.8 (t, C-4), 48.7 (s, C-10), 45.1 (t, CH_2Ph); IR (KBr) 2235 (CN) cm^{-1}; mass spectrum, m/e 454.190 (M^+, calcd 454.189).

Anal. Calcd for $C_{28}H_{26}N_2O_4$ (M_r 454.530): C, 73.99; H, 5.77; N, 6.16. Found: C, 73.58; H, 5.95; N, 5.95.

(1α,2α,9α,9aα)-2,3,9,9a-Tetrahydro-1,2-dihydroxy-6,7-dimethoxy-9-(phenylmethyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (15).[36] **8a** (620 mg, 1.87 mmol) was added to a solution of osmium tetraoxide (470 mg, 1.85 mmol) in pyridine (47 mL). After the brown reaction mixture stirred for 1.25 h, a 10% $NaHSO_3$ solution (150 mL) was added, whereupon stirring was continued for 30 min. After addition of another portion of a 10% $NaHSO_3$ solution (100 mL), the product was isolated by extraction with chloroform (3 × 150 mL). The solvent (and pyridine) of the combined extracts were removed under reduced pressure. The residue, dissolved in chloroform (150 mL), was washed with 2 N HCl (200 mL), water (100 mL), and dried with $MgSO_4$, whereupon the solvent was removed under reduced pressure. The residue was separated by preparative TLC (silica gel, ethyl acetate/chloroform, 1:1) to afford pure **15**: yield 36%; mp 95–97 °C (ethanol); ^1H NMR δ 7.5–7.0 (m, 5 H, Ar H), 6.23 and 6.03 (s, 1 H, H-5 and H-8), 4.6–3.95 (m, 3 H, 2 × CHOH and NCH), 3.80 and 3.51 (s, 3 H, OCH_3), 3.36 (br s, 2 H, OH), 3.65 and 3.10 (AB q, 2 H, J = 13.6 Hz, CH_2Ph); ^{13}C NMR δ 151.3 (s, C-4a), 146.9 and 143.5 (s, C-6, C-7 and C-9a), 109.4 (d, C-8), 96.1 (d, C-5), 72.4 and 71.6 (d, C-1 and C-2), 58.0 (t, C-3), 56.3 and 56.1 (q, OCH_3), 46.1 (s, C-9), 39.6 (t, CH_2Ph); IR (KBr) 3700–3100 (OH) and 2230 (CN) cm^{-1}; mass spectrum, m/e 366.160 (M^+, calcd 366.158).

Anal. Calcd for $C_{21}H_{22}N_2O_4$ (M_r 366.421): C, 68.84; H, 6.05; N, 7.65. Found: C, 68.48; H, 6.01, N, 7.53.

3-Chloro-4-nitrophenol (18a) was prepared by nitrosation of 3-chlorophenol (**16a**, 0.5 mol) according to Kraaijeveld and Havinga[25] and subsequent oxidation of the nitroso compound **17a** with potassium ferricyanide according to Hodgson and Moore[27] in an overall yield of 57% [mp 120–124 °C (benzene) (lit.[23a] mp 120–120.5 °C, lit.[23b] mp 118–120 °C, lit.[27] mp 121 °C)]; ^1H NMR acetone-d_6) δ 9.76 (s, 1 H, OH), 7.97 (d, 1 H, J = 8.8 Hz, H-5), 7.2–6.8 (m, 2 H, H-2 and H-6).

5-Chloro-2-methyl-4-nitrophenol (18b). The starting 5-chloro-2-methylphenol (**16b**) was prepared by diazotization of 5-chloro-2-methylaniline according to a slightly modified method of Ungnade and Orwell[37]: yield 78%; mp 72–74 °C [petroleum ether (bp 40–60 °C)] (lit.[38] mp 73–74 °C). Starting from **16b** (0.5 mol) **18b** was prepared analogously as described for **18a**: yield 52%; mp 144–145 °C (toluene) (lit.[39] mp 144–145 °C); ^1H NMR δ 7.70 (br s, 1 H, H-3), 6.80 (s, 1 H, H-6), 3.30 (s, 1 H, OH), 2.10 (s, 3 H, CH_3).

General Procedure for the Preparation of 2-Chloro-4-

(36) For the nomenclature compare Section 203 of Appendix IV to the 1984 Chemical Abstracts Index Guide.

(37) Ungnade, H. E.; Orwell, E. F. *J. Am. Chem. Soc.* **1943**, *65*, 1736.
(38) Zincke, Th.; Reiss, O. *Liebigs Ann. Chem.* **1918**, *417*, 207.
(39) Auwers, K. V.; Schornstein, W. *Fortschr. Chem. Phys. Phys. Chem.* **1924/1926**, *18*, 71.

methoxy-1-nitro- and 1-Chloro-5-methoxy-4-methyl-2-nitrobenzene (19a and 19b). To a suspension of 80% sodium hydride (45 g, 1.5 mol) in tetrahydrofuran (750 mL) was added phenol **18a,b** (0.50 mol) in portions at 0 °C. After the addition of dimethyl sulfate (189 g, 1.5 mol) the reaction mixture was heated at reflux temperature for 3 h. Upon cooling the reaction mixture was poured carefully onto a mixture of crushed ice and a NH_4OH solution (100 mL). The product was isolated by extraction with diethyl ether (3 × 350 mL). The combined extracts were washed thrice with a NH_4OH solution and water and dried with $MgSO_4$, whereupon the solvent was removed under reduced pressure. Pure **19a** was obtained after trituration of the crude product with petroleum ether and pure **19b** after recrystallization from methanol.

19a: yield 92%; mp 56.5–57.5 °C (diisopropyl ether) (lit.[23a] mp 53–55 °C); ^1H NMR δ 7.98 (d, 1 H, J_{ortho} = 9.0 Hz, H-6), 7.00 (d, 1 H, J_{meta} = 2.7 Hz, H-3), 6.85 (dd, 1 H, J_{ortho} = 9.0 Hz, J_{meta} = 2.7 Hz, H-5), 3.90 (s, 3 H, OCH_3).

19b: yield 81%; mp 87–88.5 °C (methanol); ^1H NMR δ 7.83 (br s, 1 H, H-6), 6.89 (s, 1 H, H-3), 3.91 (s, 3 H, OCH_3), 2.22 (d, 3 H, J = 0.5 Hz, CH_3); ^{13}C NMR δ 127.9 (d, C-6), 112.6 (d, C-3), 56.3 (q, OCH_3), 15.7 (q, CH_3); mass spectrum, m/e 201.018 (M^+, calcd 201.019).

Anal. Calcd for $C_8H_8ClNO_3$ (M_r 201.609): C, 47.66; H, 4.00; N, 6.95. Found: C, 47.59; H, 4.13; N, 6.93.

5-Methoxy-2-nitrobenzeneacetonitrile (21a). To a suspension of 80% sodium hydride (16.0 g, 0.53 mol) in DMF (500 mL) was added a solution of ethyl cyanoacetate (33.2 g, 0.29 mol) in DMF (200 mL) at 0 °C. After addition of **19a** (25.0 g, 0.13 mol) the mixture was heated at 70 °C for 3.5 h. Upon cooling the mixture was poured into a 10% KOH solution and subsequently extracted with diethyl ether (3 × 10 mL) to remove any starting material. The water layer was acidified with a 10% HCl solution and subsequently extracted with diethyl ether (3 × 150 mL). The combined extracts were washed with a $NaHCO_3$ solution and water and dried with $MgSO_4$. After removal of the solvent under reduced pressure ethyl α-cyano-5-methoxy-2-nitrobenzeneacetate (**20a**) (33.5 g) was obtained as an oil which was not purified further: ^1H NMR δ 8.27 (d, 1 H, J_{ortho} = 9.0 Hz, H-3), 7.19 (d, 1 H, J_{meta} = 2.7 Hz, H-6), 7.04 (dd, 1 H, J_{ortho} = 9.0 Hz, J_{meta} = 2.7 Hz, H-4), 5.65 [s, 1 H, $HC(CN)COOC_2H_5$], 4.30 (q, 2 H, J = 7.3 Hz, OCH_2), 3.95 (s, 3 H, OCH_3), 1.32 (t, 3 H, J = 7.3 Hz, OCH_2CH_3). The crude **20a** was decarboxylated in a 1 N Na_2CO_3 solution (2 L) at 40 °C for 5 days. The separated solid was filtered off, washed with water, and dried. Trituration with diisopropyl ether afforded pure **21a**: yield 65% (calculated on **19a**); mp 84–85 °C (ethanol) (lit.[40] mp 84 °C, lit.[41] mp 82–84 °C); ^1H NMR δ 8.25 (d, 1 H, J_{ortho} = 9.3 Hz, H-3), 7.23 (d, 1 H, J_{meta} = 2.7 Hz, H-6), 6.97 (dd, 1 H, J_{ortho} = 9.3 Hz, J_{meta} = 2.7 Hz, H-4), 4.24 (s, 2 H, CH_2CN), 3.95 (s, 3 H, OCH_3).

5-Methoxy-4-methyl-2-nitrobenzeneacetonitrile (21b). Starting from **19b** (30.0 g, 0.15 mol) **20b** was prepared in an analogous way as described for **20a**: ^1H NMR δ 7.97 (br s, 1 H, H-3), 6.95 (s, 1 H, H-6), 5.57 [s, 1 H, $HC(CN)COO_2H_5$], 4.20 (q, 2 H, J = 7.3 Hz, OCH_2), 3.93 (s, 3 H, OCH_3), 2.25 (s, 3 H, CH_3), 1.27 (t, 3 H, J = 7.3 Hz, OCH_2CH_3). The crude **20b** was decarboxylated in a 1.5 N Na_2CO_3 solution (2 L) at 40 °C for 7 days. The separated solid was filtered off, washed with water, and dried. Subsequent recrystallization from methanol gave pure **21b**: yield 40% (calculated on **19b**); mp 103–106 °C (methanol); ^1H NMR δ 8.06 (br s, 1 H, H-3), 7.05 (s, 1 H, H-6), 4.24 (s, 2 H, CH_2CN), 3.99 (s, 3 H, OCH_3), 2.27 (br s, 3 H, CH_3); ^{13}C NMR δ 162.1 (s, C-5), 139.7 (s, C-2), 128.4 (d, C-3), 128.3 and 126.0 (s, C-1 and C-4), 116.7 (s, CN), 111.2 (d, C-6), 56.2 (q, OCH_3), 23.3 (t, CH_2CN), 15.8 (q, CH_3); IR (KBr) 2245 (CN) cm^{-1}; mass spectrum, m/e 206.070 (M^+, calcd 206.070).

Anal. Calcd for $C_{10}H_{10}N_2O_3$ (M_r 206.204): C, 58.25; H, 4.89; N, 13.59. Found: C, 58.26; H, 4.97; N, 13.56.

General Procedure for the Preparation of the *cis*- and *trans*-(6,)7-Substituted-pyrrolo[1,2-*a*]indoles (22b–d and 23b–d). A solution of **6d–f** (10 mmol) in 1-butanol (75 mL) was heated at 118 °C. In the case of **6d** the crude reaction mixture was separated by medium pressure chromatography (silica gel, dichloromethane) and in the cases of **6e** and **6f** by column chromatography (silica gel) with dichloromethane/ethyl acetate, 97:3, and chloroform/ethyl acetate, 20:1, respectively, as the eluents. The reaction times and the yields are summarized in Table I and the melting points and characteristic NMR data in Table III.

Kinetic Studies of the Thermal Rearrangement of 6c–f. A solution of **6c–f** (1.00 g) in 1-butanol (100 mL) was heated at 118 °C. At regular intervals aliquots were taken for HPLC analysis (column, Nucleosil 5-8; eluent, methanol/water, 80:20; detection, UV 254 nm). The rate of conversion was monitored by measuring the decrease of the amount of the starting compounds **6c–f**. All the reactions fitted first-order kinetics; the calculated rate constants are summarized in Table II.

***cis*- and *trans*-2,3,9,9a-Tetrahydro-7-methoxy-6-methyl-5-nitro-9-(phenylmethyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (25a and 25b).** To a solution of **22c,23c** (0.636 g, 2.0 mmol) in dichloromethane (100 mL) was added 65% HNO_3 (10 drops) at 0 °C. After the mixture stirred for 3 min, ice-cooled water (100 mL) was added. After separation of the layers, the aqueous layer was extracted with chloroform (3 × 20 mL). The combined organic layers were washed with a $NaHCO_3$ solution and water and dried with $MgSO_4$. After removal of the solvents under reduced pressure, the residue was separated by flash chromatography[32] (silica gel, petroleum ether/ethyl acetate, 85:15) to give pure **25a,b**.

The melting point and characteristic NMR data of both compounds are summarized in Table III.

25a: yield 20%; IR (KBr) 2230 (CN) cm^{-1}; mass spectrum, m/e 363.160 (M^+, calcd 363.158).

25b: yield 20%; IR (KBr) 2280 (CN) cm^{-1}; mass spectrum, m/e 363.158 (M^+, calcd 363.158).

***cis*-5-Amino-2,3,9,9a-tetrahydro-7-methoxy-6-methyl-9-(phenylmethyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (25c).** A solution of **25a** (0.46 g, 1.27 mmol) in 50% acetic acid (50 mL) was heated in the presence of iron powder (0.9 g, 16 mmol) at 80 °C for 2 h. After filtration the reaction mixture was extracted with dichloromethane (3 × 30 mL). The combined extracts were washed with water, a $NaHCO_3$ solution, and brine and dried with $MgSO_4$. After removal of the solvent under reduced pressure, the residue was separated by column chromatography (silica gel, dichloromethane/ethyl acetate, 1:1) to give **25c**: yield 64%; mass spectrum, m/e 333.183 (M^+, calcd for $C_{21}H_{23}N_3O$ 333.184).

The melting point and NMR data are summarized in Table III.

***trans*-5-Amino-2,3,9,9a-tetrahydro-7-methoxy-6-methyl-9-(phenylmethyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (25d).** A solution of **25b** (15 mg, 0.04 mmol) in a mixture of ethyl acetate/ethanol, 1:1 (5 mL), was hydrogenated in the presence of 5% Pd/C (15 mg) at atmospheric pressure at room temperature for 22 h. After removal of the catalyst, the crude reaction mixture was separated by preparative TLC (silica gel, chloroform) to afford **25d**: yield 40%; mass spectrum, m/e 333.182 (M^+, calcd for $C_{21}H_{23}N_3O$ 333.184). The ^1H NMR data are summarized in Table III.

3-Methoxy-4-methyl-2-nitro-6-(1-pyrrolidinyl)benzeneacetonitrile (26). **5e** (230 mg, 1.00 mmol) was dissolved in concentrated H_2SO_4 (5 mL) at −5 °C. To this solution was added slowly a mixture of concentrated HNO_3 (170 mg) and concentrated H_2SO_4 (400 mg) at ≤0 °C. The dark purple mixture was stirred at 0 °C for 15 min and then poured into ice water (200 mL). After neutralization with a NH_4OH solution, the mixture was extracted with chloroform (3 × 30 mL). The combined extracts were washed with water and dried with $MgSO_4$ whereupon the solvent was removed under reduced pressure. The remaining brown oil was separated by flash chromatography[32] (silica gel, petroleum ether/ethyl acetate, 85:15) to give pure **26**: yield 36%; mp 98–99 °C (methanol); ^1H NMR δ 7.08 (br s, 1 H, H-3), 3.82 (s, 3 H, OCH_3), 3.70 (s, 2 H, CH_2CN), 3.2–3.0 (m, 4 H, NCH_2), 2.35 (br s, 3 H, CH_3), 2.2–1.8 (m, 4 H, CH_2); ^{13}C NMR δ 146.1 and 144.9 (s, C-2 and C-5), 123.7 (d, C-3), 62.4 (q, OCH_3), 52.7 (t, NCH_2), 25.0 (t, CH_2), 16.3 (q, CH_3), 16.1 (t, CH_2CN): IR (KBr) 2250 (CN) cm^{-1}; mass spectrum, m/e 275.126 (M^+, calcd 275.127).

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Table III. Melting Points and Characteristic NMR Data of Compounds 22b–d, 23b–d, 25a–d, and 28a–c

		^{1}H NMR ($CDCl_3$)						^{13}C NMR ($CDCl_3$), δ		
compd	mp, °C[a] (solvent)	δ H-5 (*J*, Hz)	δ H-8 (*J*, Hz)	δ NCH	*J*, Hz	δ CH_2Ph (AB q) (*J*, Hz)	δ CH_3 (*J*, Hz)	C-9a (d)	C-9 (s)	CH_2Ph (t)
22b	106–107 (diisopropyl ether)	6.58 (d) (8.5)	6.54 (d) (2.4)	4.10 (dd)	6.2 and 9.1	3.44 and 3.14 (14.3)		74.9	46.9	39.3
22c	169–171.5 (diisopropyl ether)	6.50 (br s)	6.37 (s)	4.15 (dd)	6.4 and 9.0	3.39 and 3.15 (14.2)	2.18 (br s)	74.8	47.0	39.6
22d	148–149 (methanol)	6.27, 6.37 (s)		4.18 (dd)	6.1 and 9.0	*b*		75.0	46.9	39.9
23b	99–101 (methanol)	6.57 (d) (8.6)	6.36 (d) (2.4)	3.86 (dd)	6.4 and 9.3	3.12 (s)		73.5	49.3	45.5
23c	138–140 (diisopropyl ether)	6.49 (br s)	6.20 (s)	4.0–3.75 (m)		3.11 (s)	2.19 (br s)	73.8	49.4	45.7
23d	127–127.5 (methanol)	6.20, 6.27 (s)		4.1–3.8 (m)		*c*		74.1	49.2	45.8
25a	154–155 (methanol)		6.05 (s)	4.64 (dd)	6.6 and 8.2	3.26 and 2.87 (13.7)	2.16 (s)	75.5	47.1	41.1
25b	161–162.5 (methanol)		6.31 (s)	4.2–3.9 (m)		3.16 (br s)	2.19 (s)	74.6	48.7	46.0
25c	158–160 dec (methanol)		5.45 (s)	4.7–4.5 (m)		3.25 and 2.81 (13.2)	2.00 (s)	75.8	49.5	42.1
25d	oil		6.06 (s)	4.2–3.9 (m)		3.27 and 2.98 (13.5)	2.04 (s)	*d*	*d*	*d*
28a	148–150 (methanol)	6.61 (d) (0.7)		4.1–3.8 (m)		3.57 and 2.92 (14.4)	2.32 (d) (0.7)	75.3	46.4	35.7
28b	125–126 (methanol)	6.57 (br s)		3.91 (dd)	6.3 and 9.3	3.69 and 2.98 (13.9)	2.32 (d) (0.7)	72.2	48.1	43.3
28c	oil	5.88 (br s)		4.24 (t)	7.5	3.56 and 3.08 (14.6)	2.21 (br s)	74.3	46.3	39.1

[a] Satisfactory elemental analyses (±0.4% for C, H, and N) were obtained for all crystalline compounds except for **25c**.
[b] Partly hidden under the multiplet at δ 3.5–3.0 (4 H, NCH_2 and CH_2Ph).
[c] Partly hidden under the multiplet at δ 3.6–3.2 (4 H, NCH_2 and CH_2Ph).
[d] Because of the small amount no ^{13}C NMR spectrum was recorded.

Anal. Calcd for $C_{14}H_{17}N_3O_3$ (M_r 275.311): C, 61.08; H, 6.22; N, 15.26. Found: C, 61.13; H, 6.21; N, 15.40.

3-Methoxy-4-methyl-2-nitro-α-(phenylmethylene)-6-(1-pyrrolidinyl)benzeneacetonitrile (27). Sodium Ethoxide as a Base. Reaction of **26** (0.135 g, 0.49 mmol) with benzaldehyde (0.130 g, 1.22 mmol) in the presence of sodium ethoxide (4 mmol) in ethanol (3 mL) was performed as described for **6d–f**. The crude reaction mixture was separated by column chromatography (silica gel, dichloromethane) to give a *E*/*Z* mixture of **27** in a yield of 20%.

Piperidine as a Base. A mixture of **26** (0.55 g, 2.0 mmol), benzaldehyde (0.318 g, 3.00 mmol), and piperidine (5 drops) in ethanol (15 mL) was heated at 78.5 °C for 8 days. After 4 days an additional amount of benzaldehyde was added. After evaporation of the ethanol, the residue was dissolved in diethyl ether (50 mL). The resulting solution was washed with a $NaHSO_3$ solution, 2 N HCl, and water and dried with $MgSO_4$. After removal of the solvent under reduced pressure, the residue was separated by column chromatography (silica gel, dichloromethane) to give one isomer of **27**, starting material **26**, and ring closed product **28a** in yields of 29%, 51%, and 10%, respectively.

27 (one isomer): oil; ^{1}H NMR δ 7.9–7.6 (m, 2 H, Ar H), 7.5–7.3 (m, 3 H, Ar H), 7.14 (s, 1 H, =CH), 6.75 (br s, 1 H, H-3), 3.78 (s, 3 H, OCH_3), 3.4–3.2 (m, 4 H, NCH_2), 2.33 (d, 3 H, J = 0.7 Hz, CH_3), 2.0–1.8 (m, 4 H, CH_2); ^{13}C NMR δ 147.9 (d, =CH), 118.7 (d, C-3), 62.5 (q, OCH_3), 51.2 (t, NCH_2), 16.4 (q, CH_3); IR (NaCl) 2220 (CN) cm^{-1}; mass spectrum, *m*/*e* 229.111 (M^+, calcd for $C_{14}H_{15}NO_2$ 229.110).

***cis*- and *trans*-2,3,9,9a-Tetrahydro-7-methoxy-6-methyl-8-nitro-9-(phenylmethyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (28a and 28b).** A solution of **27** (0.33 g, 0.91 mmol) in 1-butanol (5 mL) was heated at 118 °C for 6 days. After removal of the solvent under reduced pressure, the residue was separated by column chromatography (silica gel, dichloromethane) to give pure **28a** and **28b**. The melting points and characteristic NMR data are summarized in Table III.

28a: yield 67%; IR (KBr) 2235 (CN) cm^{-1}; mass spectrum, *m*/*e* 363.155 (M^+, calcd 363.158).

28b: yield 18%; IR (KBr) 2238 (CN) cm^{-1}; mass spectrum, *m*/*e* 363.161 (M^+, calcd 363.158).

***cis*-8-Amino-2,3,9,9a-tetrahydro-7-methoxy-6-methyl-9-(phenylmethyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (28c)** was prepared by reaction of **28a** (0.20 g, 0.55 mmol) with iron powder (0.40 g, 7.2 mmol) in a similar way as described for **25c**: yield 87%; mass spectrum, *m*/*e* 333.184 (M^+, calcd for $C_{21}H_{23}N_3O$ 333.184). The NMR data are summarized in Table III.

5-Amino-7-methoxy-6-methyl-9-(phenylmethyl)-9*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (29). A solution of crude **25c** (60 mg, 0.18 mmol) in acetone (7.5 mL) was added to a stirred solution of Fremy's salt (250 mg, 0.93 mmol) in a mixture of water (5 mL) and 0.167 M potassium dihydrogen phosphate (2.5 mL). The resulting solution was stirred at room temperature for 18 h and then diluted with water (100 mL) and subsequently extracted with dichloromethane (3 × 20 mL). The combined extracts were dried with $MgSO_4$ whereupon the solvents were removed under reduced pressure. The residue was separated by preparative TLC (silica gel, dichloromethane) to give several small fractions from which the first could be identified as **29**: yield 5 mg (8%); oil; ^{1}H NMR δ 7.3–7.1 (m, 5 H, Ar H), 7.08 (dd, 1 H, J = 1.0 and 2.7 Hz, H-3), 6.34 (dd, 1 H, J = 2.7 and 3.6 Hz, H-2), 6.32 (s, 1 H, H-8), 6.02 (dd, 1 H, J = 1.0 and 3.6 Hz, H-1), 3.75 (s, 3 H, OCH_3), 3.34 and 3.14 (AB q, 2 H, J = 13.3 Hz, CH_2Ph), 2.12 (s, 3 H, CH_3); ^{13}C NMR δ 112.8, 112.5, 104.3 and 99.4 (d, C-1, C-2, C-3 and C-8), 56.1 (q, OCH_3), 45.6 (t, CH_2Ph), 9.3 (q, CH_3); IR (KBr) 2220 (CN) cm^{-1}; mass spectrum, *m*/*e* 329.155 (M^+, calcd for $C_{21}H_{19}N_3O$ 329.153).

X-ray Structure Determination of 13. Crystals of **13** ($C_{21}H_{22}N_2O_4$) belong to the monoclinic space group $P2_1/c$, with cell constants a = 10.489 (1) Å, b = 8.923 (1) Å, c = 20.158 (3) Å, β = 98.82 (2), Z = 4, d_c = 1.32 g cm^{-3}. X-ray intensities were measured at 274 K with a Philips PW1100 diffractometer using graphite monochromated Mo Kα radiation [ω – 2θ scan mode, scan width (ω) 1.7°, scan speed (ω) 0.05° s^{-1}, 4 < ω < 20°, number of reflexions measured 2440, number of reflexions with $I > \sigma(I)$ 2052]. The structure was solved by direct methods.[42] Refinements were done by a local block-diagonal version of ORFLS.[43] Hydrogen atoms were found from difference Fourier syntheses. The final R factor was 3.9%. The number of parameters refined was 333 [scale factor, isotropic extinction correction, positional parameters of all atoms, thermal parameters (isotropic for hydrogen atoms, anisotropic for others)]. The drawing of the molecule was made by ORTEP.[44]

Acknowledgment. We are grateful for the financial support of this work by the "Koningin Wilhelmina Fonds" and by the Netherlands Foundation for Technical Research (STW), future Technical Science Branch/Division of the Netherlands Organization for the Advancement of Pure Research (ZWO). We express our gratitude to D. Hazelaar, B. G. van Hees, and T. J. Hesp for their contributions to parts of the work. We also acknowledge J. M. Visser and J. L. M. Vrielink for recording the NMR, T. W. Stevens for recording the mass spectra, and H. Bevers for the HPLC analyses.

Registry No. **4a**, 2973-50-4; **4b**, 50546-80-0; **4c**, 90557-38-3; **4d**, 96631-78-6; **5a**, 97655-15-7; **5b**, 97655-16-8; **5d**, 97655-17-9; **5e**, 97673-92-2; **5f**, 97655-18-0; **6a**, 97655-19-1; **6b**, 97655-20-4; (*E*)-**6d**, 97655-21-5; (*Z*)-**6d**, 97655-22-6; (*E*)-**6e**, 97655-23-7; (*Z*)-**6e**, 97655-24-8; (*E*)-**6f**, 97655-26-0; (*Z*)-**6f**, 97655-25-9; *cis*-**7a**, 97655-27-1; *trans*-**7a**, 97655-28-2; *cis*-**8a**, 97655-30-6; *trans*-**8a**, 97655-31-7; **9a**, 97655-29-3; **9b**, 97655-32-8; **12**, 97655-33-9; **13**, 97655-34-0; **14**, 97655-35-1; **15**, 97718-52-0; **16a**, 108-43-0; **16b**, 5306-98-9; **17a**, 40140-91-8; **18a**, 491-11-2; **18b**, 97655-36-2; **19a**, 28987-59-9; **19b**, 97655-37-3; **20a**, 97655-38-4; **20b**, 97655-39-5; **21a**, 89302-15-8; **21b**, 97655-14-6; **22b**, 97655-40-8; **22c**, 97655-41-9; **22d**, 97655-42-0; **23b**, 97655-43-1; **23c**, 97655-44-2; **23d**, 97655-45-3; **25a**, 97655-46-4; **25b**, 97655-47-5; *cis*-**25c**, 97655-48-6; *trans*-**25c**, 97655-49-7; **26**, 97655-50-0; (*E*)-**27**, 97655-51-1; (*Z*)-**27**, 97655-52-2; **28a**, 97655-53-3; **28b**, 97655-54-4; **28c**, 97655-55-5; **29**, 97655-56-6; (*Z*)-$ClCH_2CH{=}CHCH_2Cl$, 1476-11-5; $Br(CH_2)_4Br$, 110-52-1; PhCHO, 100-52-7; $NCCH_2COOEt$, 105-56-6.

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond distances, and bond angles including all atoms (5 pages). Ordering information is given on any current masthead page.

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