of E values and the plausible presence of twofold rotational symmetry, and it was confirmed in the refinement of the structure. The diffraction data were collected at 24 °C ($4° \leq 2\theta \leq 45°$) with a Nicolet P3 automated diffractometer (Mo Kα, λ = 0.71073 Å). They were corrected for Lp effects and for absorption by an empirical ψ-scan technique (μ = 90.4 cm^{-1}, max/min transmission, 0.139/0.078). Of the 1412 reflections that were collected (no hkl, $h + k = 2n + 1$), 1236 of them were unique. The 1067 reflections which were considered observed [$F_o \geq 2.5\sigma(F_o)$] were employed in the solution and refinement of the structure. The direct-methods routine SOLV (SHELXTL, version 4.1) located the two unique Br atoms, and the phases generated from them located all of the non-hydrogen atoms in a subsequent difference Fourier synthesis. Following four cycles of blocked-cascade, least-squares refinement, the locations of all hydrogen atoms were found. The final cycles of refinement incorporated anisotropic parameters for all non-hydrogen atoms and isotropic parameters for the hydrogen atoms. It converged at R_F 0.0387, R_{wF} = 0.413, and GOF = 1.467. The highest peak in the final difference map was 0.67 e Å^{-3}, which was located 0.98 Å from Br(1), followed by a diffuse background at ca. 0.4 e Å^{-3}. The computer programs used in this study are contained in the P3, SHELXTL, and XP program packages that are distributed by the Nicolet Corporation. Additional information is available as supplementary material.

5,5',7-Tribromo[1]diadamantane (16). Alcohol 8 (30 mg, 0.11 mmol) was added to a solution containing 2.0 mL of bromine and 0.2 mL of a 0.96 M solution of aluminum bromide in dibromomethane, and the resulting reaction mixture was stirred at room temperature for 60 min under nitrogen. Workup of the reaction mixture by the general procedure provided 65 mg of a viscous oil. Analysis of this material by ^{13}C NMR spectroscopy showed that it contained **11** and **16** in an approximate ratio of 1:2, respectively.

When this reaction was repeated with a reaction time of 90 min, an approximately 1:1 mixture of **12** and **16** was obtained.

When this reaction was repeated with a reaction time of 120 min, the isolated material consisted of **12** and **16** in an approximate ratio of 2:1, respectively.

With the exception of the resonance for C-2, the ^{13}C NMR signals of **16** were apparent from these spectra: δ 64.5 (C-13), 61.5 (C-5 and C-7), 60.2 (C-6), 50.3 (C-14), 43.2 (C-12 and C-19), 41.4 (C-4 and C-10 or C-8 and C-9), 41.1 (C-4 and C-10 or C-8 and C-9), 38.2 (C-1 or C-3), 38.0 (C-1 or C-3), 35.0 (C-11 and C-17), 31.5 (C-15), 29.8 (C-16 and C-18).

Acknowledgment. This work was supported by grants from the United Parkinson Foundation and the University of Delaware Research Foundation. The acquisition of the Nicolet R3 X-ray crystallographic system was supported in part by a grant (CHE-82-05 589) from the National Science Foundation.

Supplementary Material Available: Tables of the experimental data for the crystallographic structural determination and an ORTEP drawing of **12** (3 pages). Ordering information is given on any current masthead page.

Synthesis of Mitomycin C Analogues. 1. Introduction of the Urethane Function at C-10 of the Pyrrolo[1,2-*a*]indole Skeleton

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α-(Alkoxymethylene)-2-(1-pyrrolidinyl)benzeneacetonitriles **5b–e**, prepared by condensation of 2-(1-pyrrolidinyl)benzeneacetonitrile with ethyl formate and subsequent alkylation of the sodium salt formed, cyclize thermally to the *trans*- and *cis*-9-(alkoxymethyl)pyrrolo[1,2-*a*]indoles **6b–e** and **7b–e**, respectively. Treatment of the sodium salt of **5a** with acetyl chloride or acetic anhydride affords the 1-alkylindoles **8a** and **8b**, respectively. The mechanisms of both types of reaction, which are examples of the "tertiary amino effect", are discussed. The CH_2OR group of the pyrrolo[1,2-*a*]indoles **6b,d,e** and **7b,d,e** is deprotected, dependent on the nature of R, by boron tribromide (R = CH_3), hydrobromic acid in acetic acid, and subsequent hydrolysis of the acetate formed (R = CH_2Ph) and by concentrated hydrochloric acid in methanol (R = CH_2OCH_3) to give the corresponding alcohols **6a** and **7a**, respectively. Treatment of the pyrrolo[1,2-*a*]indole **7b** with sodium in liquid ammonia yields a mixture of isomers of the 9-methylpyrrolo[1,2-*a*]indole **12b**; in addition to the cyano group at C-9 also the methoxy group has been removed. Under these conditions the alcohol **7a** affords a mixture of **12b** and the decyanated alcohols *cis*-**12c** and *trans*-**12c**. The alcohols **7a** and *trans*-**12c** are transformed to the corresponding urethanes **7g** and **12d**, respectively.

The mitomycins represent an important class of heterocyclic antitumor antibiotics that have a 2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole as the basic skeleton.[1a] Mitomycin C (**1**) is currently employed clinically, in spite of the relative high toxicity, for the treatment of solid tumors[1b] and consequently several groups are involved in the synthesis of less toxic analogues.[2,3] On the basis of structure–activity relationship studies it has been postulated that for cytotoxic activity three structural elements are required, viz., the quinone function which is possibly reduced in the cell, the urethane, and the aziridine moieties.[4] The proposed mechanism of action has been supported by several studies including the reaction of chemically reduced **1** with DNA,[5a–d] although it has to be noticed

(1) (a) "Mitomycin C: Current Status and new Developments"; Carter, S. T., Crooke, S. T., Alder, N. A., Eds.; Academic Press: New York, 1979. (b) Crooke, S. T. "Cancer Chemotherapy"; Crooke, S. T., Prestayko, A. W., Eds.; Academic Press: New York, 1981; Vol. 3, p 49.

(2) A total synthesis of mitomycin C has been performed by the group of Kishi in 47 steps starting from 2,6-dimethoxytoluene: Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549.

(3) For a few recent examples see: (a) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 1671. (b) Rebek, J., Jr.; Shaber, S. H.; Shue, Y.-K.; Gehret, J.-C.; Zimmerman, S. *J. Org. Chem.* **1984**, *49*, 5164. (c) Crenshaw, M. D.; Zimmer, H. *J. Heterocyclic Chem.* **1984**, *21*, 623. (d) Speckamp, W. N. *Heterocycles* **1984**, *21*, 211. (e) Flitsch, W.; Russkamp, P. *Heterocycles* **1984**, *21*, 541. Also see references cited in the above.

(4) (a) Franck, R. W. *Prog. Chem. Org. Nat. Prod.* **1979**, *38*, 1. (b) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249.

(5) (a) Danishefsky, S.; Ciufolini, M. *J. Am. Chem. Soc.* **1984**, *106*, 6424. (b) Tomasz, M.; Jung, M.; Verdine, G.; Nakanishi, K. *J. Am. Chem. Soc.* **1984**, *106*, 7367. (c) Hornemann, U.; Keller, P. J.; Takeda, K. *J. Med. Chem.* **1985**, *28*, 31. (d) Hashimoto, Y.; Shudo, K.; Okamoto, T. *Acc. Chem. Res.* **1984**, *17*, 403. (e) Bean, M.; Kohn, H. *J. Org. Chem.* **1985**, *50*, 293. Recent other references are contained herein.

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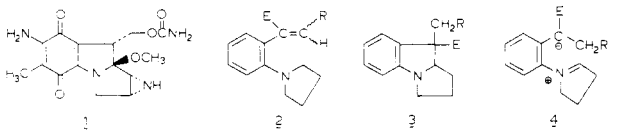
that there is experimental evidence that the urethane function at C-10 seems to be of less importance.[5e]

Our approach to the synthesis of less toxic analogues is based on a novel synthesis of 2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles (**3**) by thermal isomerization of 1-(1-pyrrolidinyl)-2-vinylbenzene derivatives **2**.[6] This isomerization takes place via two consecutive pericyclic reactions, viz., a [1,6] hydrogen transfer and subsequent 1,5-dipolar cyclization.[7] A prerequisite for this thermal isomerization is the stabilization of the negative charge by an electron-withdrawing substituent (E) in the 1,5-dipole **4**. A somewhat related intermediate, although fundamentally different, has been postulated for the formation of mitosane type of compounds by the groups of Akiba[8a] and Rapoport.[8b]



1 2 3 4

In order to enable us to use this novel reaction as a starting point for the synthesis of mitomycin analogues, three further modifications are required. Firstly the benzene ring must be converted into a quinone function. Secondly the aziridine or another strong alkylating function has to be introduced, and thirdly the urethane group has to be built in the molecule together with the removal of the electron-withdrawing group E.

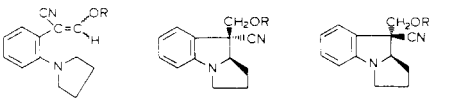
In this paper we describe the results of our work aimed at the introduction of a urethane group and the removal of the cyano group by using our methodology for the synthesis of 2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles.

Results and Discussion[9]

Synthesis and Thermal Rearrangement of α-(Alkoxymethylene)-2-(1-pyrrolidinyl)benzeneacetonitriles (5). Our approach for the introduction of a urethane function involved the cyclization of the enol ethers **5** and subsequent modification of the resulting pyrrolo[1,2-*a*]-indoles **6** and **7**. The starting materials **5** were prepared by using a method described a few years ago by Cariou[10] for α-(alkoxymethylene)benzeneacetonitrile derivatives.

The sodium salt of α-(hydroxymethylene)-2-(1-pyrrolidinyl)benzeneacetonitrile (**5a**) was prepared by condensation of 2-(1-pyrrolidinyl)benzeneacetonitrile[7] with ethyl formate and sodium hydride as a base in toluene and was obtained in a yield of 87%. This enolate was subsequently reacted with either dimethyl sulfate, 1-bromobutane, bromomethylbenzene, or chloromethoxymethane, respectively, in dimethyl formamide (DMF) as a solvent to give the corresponding α-(alkoxymethylene)-2-(1-pyrrolidinyl)benzeneacetonitriles **5b–e** as mixtures of *E* and *Z* isomers in yields of 85%, 71%, 74%, and 70%, respectively.

When **5b** was heated in mesitylene a mixture of the *trans*- and *cis*-tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles **6b** and **7b** was formed. After chromatography **6b** and **7b** were



5 6 7

a, R = H; b, R = CH_3; c, R = n-C_4H_9; d, R = CH_2Ph; e, R = CH_2OCH_3; f, R = $C(O)CH_3$; g, R = $C(O)NH_2$

isolated in yields of 13% and 48%, respectively. The structural assignment of these isomers[11] is based upon comparison of the characteristic NMR data (Table I) with those of *cis*- and *trans*-2,3,9,9a-tetrahydro-9-(methoxymethyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile,[7] the structure of which has unequivocally been determined via X-ray analysis of the cis isomer. When the isomerization of **5b** was carried out in 1-butanol a mixture of the pyrrolo[1,2-*a*]indoles **6b** and **6c** and the butyl ether **5c** was obtained. The formation of **6c** and **5c** is attributed to partial transetherification. The butyl ether **5c** afforded upon heating in mesitylene the *trans*- and *cis*-pyrrolo-[1,2-*a*]indoles **6c** and **7c** in yields of 12% and 56%, respectively. Heating of **5c** in 1-butanol yielded in addition to **7c** (9%) the trans isomer **6c** as the predominant reaction product (73%). The benzyl ether **5d** gave in refluxing mesitylene **6d** and **7d** in yields of 18% and 46%, respectively, whereas the methoxymethyl ether **5e** gave rise to a mixture of **6e** and **7e** (ratio 4:5) which could not be separated by chromatography, in a total yield of 78%.

The differences between the NMR spectral data of the trans and cis isomers **6** and **7**[11] are consistent with the results of earlier work.[7,8,12,13] In general the NCH and CH_2OR hydrogen atoms of the trans isomers absorb at lower field than those of the cis isomers and the CH_2OR hydrogen atoms of the trans isomers exhibit a greater diastereotopic effect. The CH_2OR carbon atoms of the trans isomers absorb at higher field than those of the cis isomers.

In agreement with the mechanism of the isomerization that we have discussed previously,[7,8] the formation of the trans isomers **6** is preferred when the reaction is carried out in a polar solvent (reaction of **5c** in 1-butanol), whereas the formation of the cis isomers **7** is predominant in an apolar solvent. The thermal cyclization reactions of **5b–e** require higher reaction temperatures compared with those of **2**. In our previous papers[7,8] we have discussed the role of the electron-withdrawing group at the α-position of the vinyl moiety in **2**. The OR group in **5** decreases the electron density at the adjacent carbon atom, making the [1,6] hydrogen shift (vide supra) less favourable, consequently the rate of the thermal isomerization of **5** will be lower than that of **2** (R = COOMe or phenyl).

In order to introduce a potential leaving group directly at the 10-position of the pyrrolo[1,2-*a*]indoles we decided to prepare the appropriate enol acetate **5f**. However, reaction of the sodium salt of **5a** with acetyl chloride in DMF afforded not the expected compound **5f**. In a yield of 65% a crystalline compound was isolated which showed characteristic absorptions in the ^1H NMR spectrum at δ 7.57 (s), 4.17 (t), and 3.51 (t) and in the ^{13}C NMR spectrum at δ 86.0 (s), 46.5 (t), and 44.0 (t). According to the mass

(6) Verboom, W.; Reinhoudt, D. N.; Visser, R.; Harkema, S. *J. Org. Chem.* **1984**, *49*, 269.

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

(8) (a) Akiba, M.; Ikuta, S.; Takada, T. *J. Chem. Soc., Chem. Commun.* **1983**, 817. (b) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 2404.

(9) The results of this investigation have been partly published in a preliminary communication. See: Dijksman, W. C.; Verboom, W.; Reinhoudt, D. N.; Hale, C. G.; Harkema, S.; van Hummel, G. J. *Tetrahedron Lett.* **1984**, *25*, 2025.

(10) Cariou, M. *Bull. Soc. Chim. Fr.* **1969**, 198.

(11) It has to be noticed that the nomenclature of the stereochemistry of the compounds **6** and **7** is just opposite as that of the previously reported pyrrolo[1,2-*a*]indoles (compare Section 203 of Appendix IV to the 1984 Chemical Abstracts Index Guide); the relative stereochemistry of H-9a and CH_2X is the same.

(12) Reinhoudt, D. N.; Geevers, J.; Trompenaars, W. P.; Harkema, S.; van Hummel, G. J. *J. Org. Chem.* **1981**, *46*, 424.

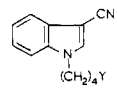
(13) Verboom, W.; Visser, G. W.; Trompenaars, W. P.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *Tetrahedron* **1981**, *37*, 3525.

Table I. Characteristic ^1H and ^{13}C NMR Chemical Shifts of Compounds 6 and 7

		^1H NMR ($CDCl_3$)				^{13}C NMR ($CDCl_3$), δ			
compd	R	δ NCH	J, Hz	δ CH_2OR (AB q)	J, Hz	C-4a (s)	CH_2OR (t)	C-9a (d)	C-9 (s)
6a	H	4.26 (dd)	5.5 and 9.9	4.20 and 3.88	11.2	154.0	64.2	73.0	48.6
6b	CH_3	4.22 (dd)	5.2 and 10.0	3.91 and 3.64	9.4	153.9	73.6	59.5	46.7
6c	n-C_4H_9	4.16 (dd)	5.3 and 10.1	3.90 and 3.63	9.5	153.9	71.8	73.4	46.8
6d[a]	CH_2Ph	4.23 (dd)	5.1 and 10.1	3.96 and 3.67	9.3	153.9	73.9[b] or 70.1	73.4	46.7
6e[c]	CH_2OCH_3	4.24 (dd)	4.8 and 9.6	4.08 and 3.79	9.6	153.9	68.5	73.3	46.4
7a	H	4.0–3.7 (m)		3.86 and 3.70	10.8	153.6	67.5	70.3	50.9
7b	CH_3	4.1–3.8 (m)		3.64 and 3.47	9.2	153.8	76.7	59.6	49.1
7c	n-C_4H_9	4.1–3.8 (m)		3.66 and 3.49	9.3	153.6	74.7 or 71.7	70.4	49.2
7d[d]	CH_2Ph	4.15–3.85 (m)		3.68 and 3.52	9.2	153.7	74.1[b] or 73.7	70.6	49.2
7e[c]	CH_2OCH_3	4.1–3.8 (m)		3.81 and 3.63	9.5	153.6	71.5	70.6	49.2
7f	$C(O)CH_3$	4.0–3.8 (m)		4.34 and 4.16	11.2	153.6	67.2	70.7	47.9
7g	$C(O)NH_2$	4.05–3.8 (m)		4.34 and 4.20	11.2	153.7	67.9	70.7	48.4

[a] ^1H NMR δ 4.73 and 4.56 (AB q, 2 H, J = 12.7 Hz, OCH_2Ph). [b] Together with the CH_2Ph absorption. [c] Spectral data obtained from a mixture of **6e** and **7e**. [d] ^1H NMR δ 4.59 (s, 2 H, OCH_2Ph).

spectrum and elemental analysis, the elemental composition of the reaction product was $C_{13}H_{13}N_2Cl$ indicating that the oxygen atom had been eliminated and a chlorine atom had been incorporated. Definite proof was provided by single-crystal X-ray analysis which revealed the structure to be 1-(4-chlorobutyl)-1*H*-indole-3-carbonitrile (**8a**).[9] The same product was obtained by reaction of the sodium salt of **5a** with (4-methylphenyl)sulfonyl chloride. Treatment of the sodium salt of **5a** with acetic anhydride afforded 1-[4-(acetyloxy)butyl]-1*H*-indole **8b** in a yield of 68%; the spectral data of **8b** correspond with those of **8a**.



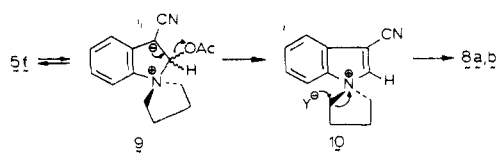
8

a, Y = Cl
b, Y = $OC(O)CH_3$

The formation of the 1-alkylindoles **8a,b** can be explained as depicted in Scheme I. In the initially formed enol acetate **5f** an intramolecular Michael addition of the tertiary amino group to the electron-deficient double bond takes place which is followed by elimination of the acetate ion leading to the spiro compound **10**. Finally, nucleophilic substitution of **10** by the stronger nucleophile (in the case of **8a** when both a chloride and an acetate ion are present, the chloride ion), gives the 1-alkylindole derivatives **8a,b**.

Recently[7] we have reported that 1-(1-pyrrolidinyl)-2-vinylbenzenes, e.g., **2**, can react in *two* different modes, depending on the position of the electron-withdrawing groups in the vinyl moiety, namely via a [1,5] or a [1,6] hydrogen transfer followed by C–C bond formation to either pyrrolo[1,2-*a*]quinolines or pyrrolo[1,2-*a*]indoles (as described above), respectively. The formation of **8a,b** represents the third possible reaction pathway of the 2-vinyl-*N*,*N*-dialkylanilines. These modes of reaction can be regarded as three variations of the so-called "tertiary amino effect".[14,15] It cannot be excluded that an intermediate such as **9** is formed in all three different reactions of 1-(1-pyrrolidinyl)-2-vinylbenzenes. However, in most cases the Michael addition cannot be followed by a subsequent elimination reaction, which renders the addition reversible. Only when a good leaving group is present at the β-position of the vinyl moiety, elimination of this group makes the equilibrium shift to the right.

Scheme I



9 **10**

Attempts to cyclize the free enol ether **5a**, prepared by acidification of the corresponding sodium salt, in refluxing 1-butanol did not yield the expected pyrrolo[1,2-*a*]indoles **6a** and **7a**; 2-(1-pyrrolidinyl)benzeneacetonitrile was isolated quantitatively.

Functionalization of the Pyrrolo[1,2-*a*]indoles at the 9-Position. For the synthesis of mitomycin analogues the 9-position of the pyrrolo[1,2-*a*]indoles **6b–e** and **7b–e** has to be modified. Firstly we have studied the "deprotection" of the CH_2OR group by cleavage of the ether function.[18]

When **7b** was reacted with at least 3 equiv of boron tribromide in dichloromethane,[19] the alcohol **7a** was obtained in a yield of 81%. Since this method will not be generally applicable, e.g., in systems containing an anisole moiety, we have investigated several alternative routes for the synthesis of 9-(hydroxymethyl)pyrrolo[1,2-*a*]indoles.

The benzyl group in **6d** and **7d** could not be removed with 5% palladium on carbon at hydrogen pressures up to 25 atm at room temperature.[20]

An effective method for the debenzylation appeared to be reaction with hydrobromic acid in acetic acid.[21] The corresponding acetate **7f**, isolated in a yield of 61%, was subsequently hydrolyzed with potassium hydroxide in methanol to afford **7a** (87%).

The methoxymethyl group in **6e** and **7e** (vide supra) could be removed by refluxing the mixture of isomers with concentrated hydrochloric acid in methanol.[22] The resulting mixture of alcohols could be separated by chromatography to give **6a** and **7a** in yields of 20% and 44%, respectively.

(14) Meth-Cohn, O.; Suschitzky, H. *Adv. Heterocycl. Chem.* **1972**, *14*, 211.

(15) For other recent applications of the "tertiary amino effect" in the preparation of [3,1]benzoxazine and [3,1]benzothiazine derivatives, see ref 16 and 17, respectively.

(16) Verboom, W.; van Dijk, B. G.; Reinhoudt, D. N. *Tetrahedron Lett.* **1983**, *24*, 3923.

(17) Verboom, W.; Hamzink, M. R. J.; Reinhoudt, D. N.; Visser, R. *Tetrahedron Lett.* **1984**, *25*, 4309.

(18) For a recent general review see: Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249.

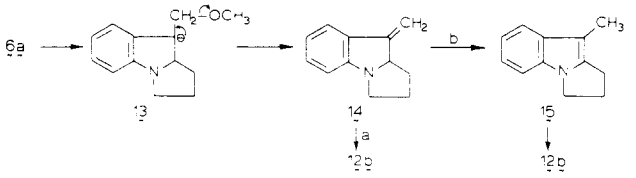
(19) McOmie, J. F. W.; Watts, M. L.; West, D. E. *Tetrahedron* **1968**, *24*, 2289. Blatchly, J. M.; Gardner D. V.; McOmie, J. F. W.; Watts, M. L. *J. Chem. Soc. C* **1968**, 1545.

(20) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746.

(21) Callahan, F. M.; Anderson, G. W.; Paul, R.; Zimmerman, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 201.

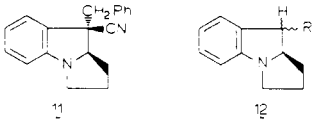
(22) Auerbach, J.; Weinreb, S. M. *J. Chem. Soc., Chem. Commun.* **1974**, 298.

Scheme II



The alcohol **7a** was converted in two subsequent steps, viz., reaction with phenyl chloroformate followed by treatment with ammonia,[23] into the urethane **7g** in an overall yield of 64%.

The second modification of compounds **6** (or **7**) is the removal of the cyano group at the 9-position *in such way that no double bond will be formed at the 9,9a-position.* A suitable method for the decyanation of tertiary nitriles is the treatment with an alkali metal in an appropriate solvent, e.g., sodium in liquid ammonia.[24] In a model reaction the pyrrolo[1,2-*a*]indole **11**[7] was reacted under these conditions to give a mixture of isomers (cis/trans ratio according to GLC about 5:1) of the decyanated compound **12a** in a yield of 83%. Using ^{1}H NOE difference spectroscopy revealed the cis/trans stereochemistry of these isomers.



a, R = CH_2Ph
b, R = CH_3
c, R = CH_2OH
d, R = $CH_2OC(O)NH_2$ (trans)

Reaction of **7b** with sodium in liquid ammonia under similar conditions afforded the pyrrolo[1,2-*a*]indole **12b** as a mixture of isomers (ratio about 1:3) in a yield of 66%. The major isomer was shown to have the trans stereochemistry by using the same NMR technique. Therefore in this case not only *the cyano but also the methoxy group had been removed.*

It is known that alkyl aryl ethers can be cleaved by reaction with sodium in liquid ammonia just as benzyl and trityl ethers because they form stable radicals.[25] To the best of our knowledge there is no report that dialkyl ethers can be cleaved in this way. Therefore the formation of **12b** may be explained as depicted in Scheme II. We assume that the decyanation is followed by a β-elimination in the intermediate **13** to give **14**; for further reaction two pathways are possible. According to path a reduction of the exocyclic double bond leads directly to formation of **12b**. In path b isomerization takes place to the more stable compound **15** which ultimately is reduced to **12b**.[26] We have no conclusive evidence which is the preferred pathway.

In order to prevent the above mentioned β-elimination the leaving group character of the substituent at the 10-position must be reduced. Decyanation of the alcohol **7a** resulted in the formation of a mixture of products. After chromatography, in addition to **12b** (cis/trans ratio about 1:3; yield 22%), the decyanated alcohols *cis*-**12c** and *trans*-**12c** were isolated in yields of 18% and 58%, respectively. The stereochemistry of *trans*-**12c** and *cis*-**12c** was assigned by comparison with the pyrrolo[1,2-*a*]indoles **6** and **7** (vide supra). In this particular case the position of the NCH hydrogen atom in the ^{1}H NMR spectra is very characteristic, viz., δ 3.85–3.65 and 4.15–3.85 (together with CH_2O) for *cis*-**12c** and *trans*-**12c**, respectively. In the ^{13}C NMR spectra the values for C-9 (δ 51.8) and C-10 (δ 66.1) for *cis*-**12c**, compared with δ 44.9 and 62.3, respectively, for *trans*-**12c** are significantly different. These differences between the spectral data of *trans*- and *cis*-**12c** are in agreement with those of **6** and **7** (compare Table I).

In the same way as described for **7a** (vide supra), the trans alcohol **12c** was converted into the trans urethane **12d** in an overall yield of 59%.

In summary, the present results show the usefulness of our novel synthesis of tetrahydro-1*H*-pyrrolo[1,2-*a*]indoles for the preparation of potential analogues of the mitomycins. With relative simple methods it is possible to introduce a urethane function at the 10-position. Further work on the other modifications, e.g., the introduction of a quinone function and a leaving group at C-1 such as an aziridine moiety 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 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.

All reactions were carried out under a nitrogen atmosphere.

Sodium Salt of α-(Hydroxymethylene)-2-(1-pyrrolidinyl)benzeneacetonitrile (5a). To a suspension of sodium hydride (1.79 g, 59.7 mmol) in toluene (200 mL) was added a solution of 2-(1-pyrrolidinyl)benzeneacetonitrile[7] (10.0 g, 53.7 mmol) in toluene (200 mL) 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 50–60 °C ethyl formate (19.5 mL, 240 mmol) was added dropwise whereupon the reaction mixture was heated at that temperature for 4 h. Upon cooling to room temperature dry diethyl ether (200 mL) was added. The resulting precipitate was filtered off and washed with diethyl ether (5 × 50 mL) to give the pure sodium salt of **5a** in a yield of 87%.

α-(Hydroxymethylene)-2-(1-pyrrolidinyl)benzeneacetonitrile (5a). To a suspension of the sodium salt of **5a** (0.46 g, 1.9 mmol) in tetrahydrofuran (50 mL) was added 5 drops of concentrated sulfuric acid. After stirring for 10 min water (50 mL) was added to the reaction mixture. The product was isolated by extraction with chloroform (3 × 30 mL). The combined extracts were washed with water (5 × 30 mL) and dried with $MgSO_4$, and then the solvent was removed under reduced pressure to give **5a** as an oil in quantitative yield: ^{1}H NMR δ 16.5–15.5 (br s, 1 H, OH), 7.8–7.5 (m, 2 H, Ar H), 7.35–7.05 (m, 2 H, Ar H), 7.28 (s, 1 H, =CH), 3.35–3.05 (m, 4 H, NCH_2), 2.2–1.9 (m, 4 H, CH_2); ^{13}C NMR δ 165.1 (d, =CH), 139.8 (s, C-2), 130.0 (s, C-1), 129.4, 127.4, 119.8, and 117.1 (d, Ar C), 121.9 (s, CN), 87.4 (s, =*C*CN), 52.8 (t, NCH_2), 23.5 (t, CH_2); IR (KBr) 3400 (OH) and 2195 (CN) cm^{-1}; mass spectrum, *m/e* 214.109 (M^+, calcd for $C_{13}H_{14}N_2O$ 214.111).

General Procedure for the Preparation of the α-(Alkoxymethylene)-2-(1-pyrrolidinyl)benzeneacetonitriles 5b–e. A solution of the sodium salt of **5a** (3.54 g, 15.0 mmol) and the alkylating reagent (17 mmol) in dry DMF (100 mL) was heated at 50 °C for 2 h. The products were isolated by pouring the reaction mixture into water (100 mL) and extraction with chloroform (3 × 50 mL). The combined extracts were washed thrice with a 10% HCl solution, twice with water, and dried with $MgSO_4$.

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(24) Arapakos, P. G.; Scott, M. K.; Huber, F. E., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 2059.
(25) Moore, D. R. *J. Org. Chem.* **1961**, *26*, 3596.
(26) Remers et al.[27] have described a similar reduction of such a double bond. 1-Methylindole was reduced to the corresponding indoline by lithium in ammonia.
(27) Remers, W. A.; Gibs, G. J.; Pidacks, C.; Weiss, M. J. *J. Org. Chem.* **1971**, *36*, 279.

After removal of the solvent under reduced pressure, the residue was purified as indicated to afford pure **5b–e** as *E*/*Z* mixtures (ratio about 1:1 except for the case of **5e**).

α-(Methoxymethylene)-2-(1-pyrrolidinyl)benzeneacetonitrile (5b) was prepared by reaction of the sodium salt of **5a** with dimethyl sulfate (2.14 g, 17.0 mmol). The resulting oil solidified upon standing and was subsequently purified by recrystallization from diisopropyl ether/petroleum ether (bp 60–80 °C): yield 85%; mp 88.5–90 °C; ^{1}H NMR δ 6.97 and 6.89 (s, 1 H, =CH), 3.88 and 3.80 (s, 3 H, OCH_3); ^{13}C NMR δ 161.7 and 158.5 (d, =CH), 94.7 and 92.9 (s, =CCN), 61.9 and 61.7 (q, OCH_3); mass spectrum, *m/e* 228.128 (M^+, calcd 228.126).

Anal. Calcd for $C_{14}H_{16}N_2O$ (M_r 228.296): C, 73.66; H, 7.06; N, 12.27. Found: C, 73.99; H, 7.20; N, 12.19.

α-(Butoxymethylene)-2-(1-pyrrolidinyl)benzeneacetonitrile (5c) was prepared by reaction of the sodium salt of **5a** with 1-bromobutane (2.33 g, 17.0 mmol). The crude reaction mixture was purified by column chromatography [silica gel, dichloromethane/petroleum ether (bp 40–60 °C), 1:1] to afford **5c** as a light yellow oil: yield 71%; ^{1}H NMR δ 7.03 and 6.92 (s, 1 H, =CH), 3.99 and 3.91 (t, 2 H, *J* = 6.1 Hz, OCH_2); ^{13}C NMR δ 161.0 and 157.7 (d, =CH), 94.4 and 92.6 (s, =CCN), 75.1 and 74.8 (t, OCH_2); mass spectrum, *m/e* 270.172 (M^+, calcd for $C_{17}H_{22}N_2O$ 270.173).

α-[(Phenylmethoxy)methylene]-2-(1-pyrrolidinyl)benzeneacetonitrile (5d) was obtained by reaction of the sodium salt of **5a** with (bromomethyl)benzene (2.91 g, 17.0 mmol). The crude mixture was purified by column chromatography (silica gel, chloroform) to afford after removal of the solvent a solid which after trituration with methanol gave pure **5d**:[28] yield 74%; mp 101–108 °C (methanol); ^{1}H NMR δ 7.06 and 7.00 (s, 1 H, =CH), 5.14 and 5.01 (s, 2 H, OCH_2); ^{13}C NMR δ 160.2 and 156.8 (d, =CH), 95.3 and 93.7 (s, =CCN), 76.1 and 75.7 (t, OCH_2); mass spectrum, *m/e* 304.158 (M^+, calcd for $C_{20}H_{20}N_2O$ 304.158).

α-[(Methoxymethoxy)methylene]-2-(1-pyrrolidinyl)benzeneacetonitrile (5e) was prepared by reaction of the sodium salt of **5a** with (chloromethoxy)methane (1.36 g, 16.9 mmol). The crude reaction mixture was purified by column chromatography (silica gel, chloroform) to afford **5e**, as an isomer mixture in a ratio of about 5:8, as a light yellow oil: yield 70%; ^{1}H NMR δ 7.23 and 7.14 (s, 1 H, =CH), 5.03 and 4.94 (s, 2 H, OCH_2O); ^{13}C NMR δ 158.0 and 155.0 (d, =CH), 97.9 and 97.6 (t, OCH_2O), 96.5 and 95.1 (s, =CCN); mass spectrum, *m/e* 258.139 (M^+, calcd for $C_{15}H_{18}N_2O_2$ 258.137).

General Procedure for the Preparation of the Pyrrolo[1,2-*a*]indoles 6b–e and 7b–e. A solution of the enol ethers **5b–e** (5 mmol) in the appropriate solvent (50 mL) was heated at reflux temperature. When the reaction was complete as followed from TLC, the solvent was removed under reduced pressure. Except for the case of **5e** the residue was separated by column chromatography [silica gel (0.015–0.040 mm), chloroform] to yield the pure pyrrolo[1,2-*a*]indoles. Characteristic ^{1}H and ^{13}C NMR data are summarized in Table I.

***trans*- and *cis*-2,3,9,9a-Tetrahydro-9-(methoxymethyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (6b and 7b). Reaction in Mesitylene.** Heating of **5b** for 4 days gave **6b** and **7b** in yields of 13% and 48%, respectively.

Reaction in 1-Butanol. After heating of **5b** for 2 days, in addition to **5c** (23%) a mixture of **6b** and **6c** was obtained (yield about 40%).

6b: mp 113.5–114.5 °C [diisopropyl ether/petroleum ether (bp 60–80 °C)]; mass spectrum, *m/e* 228.125 (M^+, calcd 228.126).

Anal. Calcd for $C_{14}H_{16}N_2O$ (M_r 228.296): C, 73.66; H, 7.06; N, 12.27. Found: C, 73.70; H, 7.14; N, 12.42.

7b: mp 37–38 °C [diisopropyl ether/petroleum ether (bp 60–80 °C)]; mass spectrum, *m/e* 228.125 (M^+, calcd 228.126).

Anal. Calcd for $C_{14}H_{16}N_2O$ (M_r 228.296): C, 73.66; H, 7.06; N, 12.27. Found: C, 73.75; H, 7.10; N, 12.26.

***trans*- and *cis*-2,3,9,9a-Tetrahydro-9-(butoxymethyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (6c and 7c). Reaction in Mesitylene.** Heating of **5c** for 6 days afforded **6c** and **7c** in yields of 12% and 56%, respectively.

Reaction in 1-Butanol. Heating of **5c** for 12 days gave **6c** and **7c** in yields of 73% and 9%, respectively.

6c: mp 46.5–48.0 °C [diisopropyl ether/petroleum ether (bp 60–80 °C)]; mass spectrum, *m/e* 270.172 (M^+, calcd 270.173).

Anal. Calcd for $C_{17}H_{22}N_2O$ (M_r 270.377): C, 75.52; H, 8.20; N, 10.36. Found: C, 75.48; H, 8.25; N, 10.21.

7c: oil; mass spectrum, *m/e* 270.174 (M^+, calcd for $C_{17}H_{22}N_2O$ 270.173).

***trans*- and *cis*-2,3,9,9a-Tetrahydro-9-[(phenylmethoxy)methyl]-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (6d and 7d)** were obtained after heating of **5d** in mesitylene for 3 days.

6d: yield 18%; oil; mass spectrum, *m/e* 304.159 (M^+, calcd for $C_{20}H_{20}N_2O$ 304.158).

7d: yield 46%; mp 91–93 °C (methanol); mass spectrum, *m/e* 304.160 (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, 78.87; H, 6.60; N, 9.13.

***trans*- and *cis*-2,3,9,9a-Tetrahydro-9-[(methoxymethoxy)methyl]-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (6e and 7e).** After refluxing of **5e** in mesitylene for 22 h the solvent was removed under reduced pressure. The residue was dissolved in chloroform (150 mL) and treated with activated coal under reflux (5 min). After filtration and removal of the solvent, the residue was purified by column chromatography (silica gel, chloroform) to give a mixture of **6e** and **7e** (ratio about 4:5) which could not be separated further: yield 78%; mass spectrum, *m/e* 258.138 (M^+, calcd for $C_{15}H_{18}N_2O_2$ 258.137).

1-(4-Chlorobutyl)-1*H*-indole-3-carbonitrile (8a). To a solution of the sodium salt of **5a** (1.18 g, 5.0 mmol) in dry DMF (20 mL) was added acetyl chloride (0.47 g, 6 mmol) whereupon the reaction mixture was heated at 60 °C for 2 h. After workup as described for compounds **5b–e** the resulting solid was recrystallized from diisopropyl ether/petroleum ether (bp 60–80 °C) to afford **8a** as colorless crystals: yield 65%; mp 48.0–48.5 °C; ^{1}H NMR δ 7.8–7.6 (m, 1 H, Ar H), 7.57 (s, 1 H, H-2), 7.5–7.1 (m, 3 H, Ar H), 4.17 (t, 2 H, *J* = 6.8 Hz, NCH_2), 3.51 (t, 2 H, *J* = 6.1 Hz, CH_2Cl), 2.25–1.5 (m, 4 H, CH_2); ^{13}C NMR δ 135.2 (s, C-7a), 134.3 (d, C-2), 127.9 (s, C-3a), 123.9, 122.2 and 120.0 (d, C-4,5,6), 115.7 (s, CN), 110.4 (d, C-7), 86.0 (s, C-3), 46.5 (t, NCH_2), 44.0 (t, CH_2Cl), 29.5 and 27.3 (t, CH_2); IR (KBr) 2205 (CN) cm^{-1}; mass spectrum, *m/e* 232.073 (M^+, calcd 232.077).

Anal. Calcd for $C_{13}H_{13}N_2Cl$ (M_r 232.711): C, 67.10; H, 5.63; N, 12.04. Found: C, 66.90; H, 5.55; N, 12.02.

1-[4-(Acetyloxy)butyl]-1*H*-indole-3-carbonitrile (8b). To a solution of the sodium salt of **5a** (1.50 g, 6.4 mmol) in dry DMF (20 mL) was added a solution of acetic anhydride (0.91 g, 8.9 mmol) in DMF (5 mL). The reaction mixture was heated at 50 °C for 1 h. After workup as described for compounds **5b–e** the crude reaction product was purified by column chromatography (silica gel, chloroform) to give pure **8b** as an oil which solidified on standing to an amorphous solid which could not be recrystallized: yield 68%; mp 40–42 °C; ^{1}H NMR δ 7.8–7.6 (m, 1 H, Ar H), 7.60 (s, 1 H, H-2), 7.5–7.2 (m, 3 H, Ar H), 4.20 (t, 2 H, *J* = 6.8 Hz, NCH_2), 4.08 (t, 2 H, *J* = 6.1 Hz, CH_2OAc), 2.03 (s, 3 H, CH_3), 2.0–1.5 (m, 4 H, CH_2); ^{13}C NMR δ 170.8 (s, C=O), 135.2 (s, C-7a), 134.3 (d, C-2), 127.8 (s, C-3a), 123.8, 122.1 and 119.8 (d, C-4,5,6), 115.8 (s, CN), 110.5 (d, C-7), 85.5 (s, C-3), 70.0 (t, CH_2OAc), 46.7 (t, NCH_2), 26.4 and 25.8 (t, CH_2), 20.8 (q, CH_3); IR (KBr) 2216 (CN) cm^{-1}; mass spectrum, *m/e* 256.125 (M^+, calcd for $C_{15}H_{16}N_2O_2$ 256.122).

***cis*-9-[(Acetyloxy)methyl]-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (7f).** A mixture of **7d** (0.80 g, 2.6 mmol) and 33% hydrobromic acid in acetic acid (3 mL) was stirred for 30 min. Thereupon pyridine (5 mL) was added to the reaction mixture. After cooling to room temperature water (100 mL) was added. The product was isolated by extraction with diethyl ether (3 × 40 mL). The combined organic layers were washed with water, a 10% HCl solution, and again with water and dried with $MgSO_4$. After removal of the solvent under reduced pressure the residue was purified by column chromatography (silica gel, chloroform) to afford pure **7f** as a light yellow oil: yield 61%; IR (NaCl) 2245 (CN) cm^{-1}; mass spectrum, *m/e* 256.121 (M^+, calcd for $C_{15}H_{16}N_2O_2$ 256.122). Characteristic ^{1}H and ^{13}C NMR spectral data are summarized in Table I.

***trans*- and *cis*-2,3,9,9a-Tetrahydro-9-(hydroxymethyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (6a and 7a). Reaction**

(28) No satisfatory elemental analysis could be obtained of the mixture of isomers of **5d**.

of 7b with Boron Tribromide. To a stirred solution of **7b** (1.34 g, 6.3 mmol) in dichloromethane (100 mL) boron tribromide (5.5 g, 6.3 mmol) was added at 0 °C. After stirring for 2 h at room temperature the solution was left standing overnight. Diluted hydrochloric acid was added to the reaction mixture to dissolve the complexes formed. After separation of the layers, the water layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed twice with a saturated $NaHCO_3$ solution and twice with water and dried with $MgSO_4$. After removal of the solvent under reduced pressure the residue, dissolved in chloroform, was passed through a short column of silica gel to give pure **7a** in a yield of 81%.

Saponification of 7f. To a solution of **7f** (0.48 g, 1.9 mmol) in methanol (25 mL) was added potassium hydroxide (1 g, 18 mmol). After stirring for 16 h at room temperature most of the methanol was removed under reduced pressure. To the residue water (100 mL) was added. The product was isolated by extraction with chloroform (3 × 75 mL). The combined extracts were washed twice with water and dried with $MgSO_4$. After further workup as described above pure **7a** was obtained in a yield of 87%.

Ether Cleavage of 6e and 7e. A solution of a mixture of **6e** and **7e** (12.1 g, 46.8 mmol) and concentrated hydrochloric acid (25 mL) in methanol (250 mL) was refluxed for 4 h. After removal of a part of the solvent under reduced pressure, the resulting reaction mixture was neutralized with a saturated $NaHCO_3$ solution. The products were isolated by extraction with ethyl acetate (2 × 100 mL). The combined extracts were washed twice with brine and dried with $MgSO_4$. After removal of the solvent under reduced pressure, the residue was separated by column chromatography [silica gel (0.015–0.040 mm), chloroform/ethyl acetate, 3:1] to afford **6a** and **7a** in yields of 20% and 44%, respectively. Characteristic ^1H and ^{13}C NMR data of **6a** and **7a** are summarized in Table I.

6a: mp 155–156 °C (methanol); IR (KBr) 3220 (OH) and 2226 (CN) cm^{-1}; mass spectrum, *m/e* 214.108 (M^+, calcd 214.111).

Anal. Calcd for $C_{13}H_{14}N_2O$ (M_r 214.269): C, 72.87; H, 6.59; N, 13.07. Found: C, 72.92; H, 6.78; N, 12.94.

7a: mp 127–128 °C (chloroform); IR (KBr) 3190 (OH) and 2238 (CN) cm^{-1}; mass spectrum, *m/e* 214.112 (M^+, calcd 214.111).

Anal. Calcd for $C_{13}H_{14}N_2O$ (M_r 214.269): C, 72.87; H, 6.59; N, 13.07. Found: C, 72.99; H, 6.59; N, 12.97.

[*cis*-2,3,9,9a-Tetrahydro-9-cyano-1*H*-pyrrolo[1,2-*a*]indol-9-yl]hydroxymethyl Carbamate (Ester) (7g). To a solution of **7a** (0.51 g, 2.0 mmol) in dry pyridine (10 mL) phenyl chloroformate (0.33 g, 2.0 mmol) was added at 0 °C. After stirring for 18 h water (10 mL) was added to the reaction mixture. The mixture was extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with water (2 × 75 mL) and dried with $MgSO_4$. After removal of the solvents under reduced pressure the residue was dissolved in dichloromethane (10 mL) whereupon dry liquid ammonia (75 mL) was added at about −40 °C. After refluxing for 6 h the ammonia was allowed to evaporate. The residue was dissolved in a mixture of chloroform (150 mL) and ethyl acetate (25 mL). The solution was washed with a 4% NaOH solution (100 mL) and brine (100 mL) and dried with $MgSO_4$. After removal of the solvents under reduced pressure, the resulting solid was triturated with diethyl ether to give pure **7g**: yield 64%; mp 179–180 °C (methanol); IR (KBr) 2240 (CN) and 1727 (C=O) cm^{-1}; mass spectrum, *m/e* 257.115 (M^+, calcd 257.116).

Anal. Calcd for $C_{14}H_{15}N_3O_2$ (M_r 257.295): C, 65.36; H, 5.88; N, 16.33. Found: C, 65.61; H, 6.20; N, 16.41.

Characteristic ^1H and ^{13}C NMR data are summarized in Table I.

General Procedure for the Decyanation of 11, 7b, and 7a. To a solution of the substrate in dry liquid ammonia (75 mL) were added small pieces of sodium at about −35 °C. When the reaction was complete as followed from TLC the reaction mixture was poured out in ice-cold diethyl ether (250 mL), whereupon the reaction mixture was quenched with crushed ice. After evaporation of the ammonia the layers were separated. The water layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with brine (2 × 100 mL) and dried with $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified as indicated.

***cis*- and *trans*-2,3,9,9a-Tetrahydro-9-(phenylmethyl)-1*H*-pyrrolo[1,2-*a*]indole (12a)** were prepared by reaction of **11** (0.80 g, 2.9 mmol) with sodium (0.20 g, 8.7 mmol) for 2 h. Column chromatography (silica gel, dichloromethane) of the crude reaction mixture afforded one fraction (210 mg) containing pure *cis*-**12a** (as followed from the ^{13}C NMR spectrum) and several fractions containing mixtures of *cis*- and *trans*-**12a**; total yield 83% (cis/trans ratio according to GLC about 5:1).

***cis*-12a**: oil; ^1H NMR δ 7.8–6.5 (m, 9 H, Ar H), 4.1–3.7 (m, 2 H, NCH and NC*H*H), 3.7–2.6 (m, 4 H, CH_2Ph, HC-9 and NCH*H*), 2.2–1.4 (m, 4 H, CH_2); ^{13}C NMR δ 154.7 (s, C-4a), 140.5 (s), 132.3 (s), 128.6 (d), 128.4 (d), 127.8 (d), 126.1 (d), 123.5 (d), 119.0 (d) and 110.4 (d) (Ar C), 70.0 (d, C-9a), 51.7 (t, C-3), 43.2 (d, C-9), 35.7 (t, C-10), 25.5 and 24.9 (t, C-1 and C-2); mass spectrum, *m/e* 249.150 (M^+, calcd for $C_{19}H_{19}N$ 249.152).

***trans*-12a**:[29] ^{13}C NMR δ 154.3 (s, C-4a), 71.0 (d, C-9a), 51.9 (t, C-3), 42.2 (d, C-9), 30.9 (t, C-10), 25.6 and 25.2 (t, C-1 and C-2).

***cis*- and *trans*-2,3,9,9a-Tetrahydro-9-methyl-1*H*-pyrrolo[1,2-*a*]indole (12b)** were prepared by reaction of **7b** (0.85 g, 3.7 mmol) with sodium (0.30 g, 13.0 mmol). Column chromatography (silica gel, dichloromethane) of the crude reaction mixture gave a mixture of *cis*- and *trans*-**12b** (ratio about 1:3) in a total yield of 66%. A part of this mixture was separated by preparative TLC [silica gel, ethyl acetate/petroleum ether (bp 60–80 °C), 15:85] to afford a fraction of pure *trans*-**12b**.

***cis*-12b**:[30] ^1H NMR δ 1.30 (d, 3 H, *J* = 7.1 Hz, CH_3); ^{13}C NMR δ 73.8 (d, C-9a), 52.0 (t, C-3), 41.4 (d, C-9), 31.0 and 25.8 (t, C-1 and C-2), 21.9 (q, CH_3).

***trans*-12b**: oil; ^1H NMR δ 7.2–6.9 (m, 2 H, Ar H), 6.85–6.5 (m, 2 H, Ar H), 4.05–3.7 (m, 1 H, NCH), 3.6–2.95 (m, 3 H, NCH_2 and H-9), 2.0–1.25 (m, 4 H, CH_2), 1.33 (d, 3 H, *J* = 7.1 Hz, CH_3); ^{13}C NMR δ 154.5 (s, C-4a), 134.1 (s, C-8a), 127.5, 123.2, 119.1 and 110.4 (d, Ar C), 71.1 (d, C-9a), 52.2 (t, C-3), 36.6 (d, C-9), 25.7 and 25.0 (t, C-1 and C-2), 13.8 (q, CH_3); mass spectrum, *m/e* 173.120 (M^+, calcd for $C_{12}H_{15}N$ 173.120).

***cis*- and *trans*-2,3,9,9a-Tetrahydro-1*H*-pyrrolo[1,2-*a*]indole-9-methanol (12c)** were prepared by reaction of **7a** (1.28 g, 6.0 mmol) with sodium (0.41 g, 18.0 mmol) for 0.5 h. The crude reaction mixture was separated by column chromatography [silica gel (0.015–0.040 mm), chloroform/ethyl acetate, 3:2] to give **12b** (cis/trans ratio about 1:3), *cis*-**12c**, and *trans*-**12c** in yields of 22%, 18%, and 58%, respectively.

***cis*-12c**: oil; ^1H NMR (200 MHz) δ 7.2–7.05 (m, 2 H, H-6 and H-8), 6.78 (dt, 1 H, *J* = 0.8 and 7.4 Hz, H-7), 6.62 (d, 1 H, *J* = 7.7 Hz, H-5), 3.85–3.65 (m, 1 H, NCH), 3.75 (d, 2 H, *J* = 6.5 Hz, CH_2O), 3.5–3.3 (m, 2 H, NCH_2), 3.2–3.05 (m, 1 H, H-9), 2.39 (br s, 1 H, OH), 2.0–1.8 (m, 3 H, CH_2), 1.45–1.25 (m, 1 H, CH_2); ^{13}C NMR δ 155.0 (s, C-4a), 69.0 (d, C-9a), 66.2 (t, CH_2O), 52.0 (t, C-3), 49.4 (d, C-9); IR (KBr) 3360 (OH) cm^{-1}; mass spectrum, *m/e* 189.115 (M^+, calcd for $C_{12}H_{15}NO$ 189.115).

***trans*-12c**: oil; ^1H NMR (200 MHz) δ 7.15–7.05 (m, 2 H, H-6 and H-8), 6.76 (dt, 1 H, *J* = 0.8 and 7.4 Hz, H-7), 6.60 (d, 1 H, *J* = 7.8 Hz, H-5), 4.15–3.85 (m, 3 H, NCH and CH_2O), 3.65–3.4 (m, 2 H, NCH_2), 3.2–3.05 (m, 1 H, H-9), 2.42 (br s, 1 H, OH), 1.95–1.7 (m, 3 H, CH_2), 1.55–1.35 (m, 1 H, CH_2); ^{13}C NMR δ 155.0 (s, C-4a), 129.6 (s, C-8a), 128.2, 123.8 and 119.2 (d, Ar C), 110.7 (d, C-5), 68.8 (d, C-9a), 62.7 (t, CH_2O), 51.8 (t, C-3), 45.0 (d, C-9), 26.1 and 25.0 (t, C-1 and C-2); IR (KBr) 3380 (OH) cm^{-1}; mass spectrum, *m/e* 189.116 (M^+, calcd for $C_{12}H_{15}NO$ 189.115).

[*trans*-2,3,9,9a-Tetrahydro-1*H*-pyrrolo[1,2-*a*]indol-9-yl]methyl carbamate (ester) (12d) was prepared from *trans*-**12c** (0.18 g, 1.0 mmol) and phenyl chloroformate (0.18 g, 1.14 mmol) at the same manner as described for **7g**: yield 59%; mp 177–181 °C dec (methanol); ^1H NMR δ 7.4–7.0 (m, 2 H, Ar H), 7.0–6.4 (m, 2 H, Ar H), 5.1–2.9 (m, 8 H, NCH, NCH_2, H-9, CH_2O and NH_2), 2.1–0.8 (m, 4 H, CH_2); ^{13}C NMR δ 156.6 and 154.9 (s, C=O and C-4a), 128.9 (s, C-8a), 128.4, 124.0, 119.2 and 110.7 (d, Ar C), 68.6 (d, C-9a), 64.9 (t, CH_2O), 51.7 (t, C-3), 41.8 (d, C-9), 26.0 and 25.1 (t, C-1 and C-2); IR (KBr) 1728 (C=O) cm^{-1}; mass spectrum, *m/e* 232.121 (M^+, calcd 232.121).

Anal. Calcd for $C_{13}H_{16}N_2O_2$ (M_r 232.285): C, 67.22; H, 6.94; N, 12.06. Found: C, 67.21; H, 7.27; N, 11.77.

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(29) From a mixture of *cis*-**12a** and *trans*-**12a** only the ^{13}C NMR spectrum exhibited relevant information about *trans*-**12a**.

(30) Spectral data determined from a mixture of *cis*- and *trans*-**12b**.

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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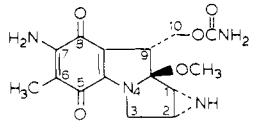
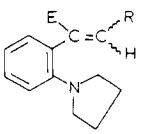
2-(2,5-Dihydro-1*H*-pyrrol-1-yl)-α-(phenylmethylene)benzeneacetonitriles **6a,b** cyclize thermally in aprotic solvents to the *cis*- and/or *trans*-9,9a-dihydro-3*H*-pyrrolo[1,2-*a*]indoles **7a,8a** and **7b,8b**, respectively. Reaction in methanol affords the 2-(1*H*-pyrrol-1-yl)benzeneacetonitriles **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.

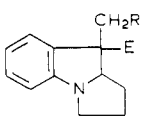
The mitomycins represent an important class of antitumor antibiotics of which mitomycin C (**1**) is used for the treatment of several solid tumors.[2-4] On the basis of structure–activity relationship studies it has been established that three structural elements are required for biological activity,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



1



2



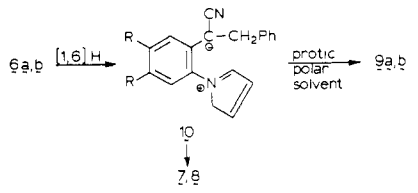
3

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



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