Tetrahedron Vol. 43, No. 1, pp 255 to 262, 1987
Printed in Great Britain

0040-4020/87 $5.00+.00
Pergamon Journals Ltd.

MITOMYCIN ANALOGS I. INDOLOQUINONES AS (POTENTIAL) BISALKYLATING AGENTS

E.A. OOSTVEEN and W.N. SPECKAMP

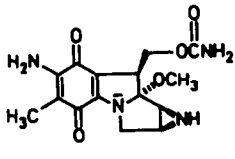
Laboratory for Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands.

(*Received in UK* 3 *October* 1986)

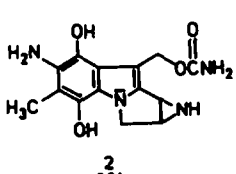
Abstract - Catalytic reduction (H_2, PtO_2-EtOH) of indoloquinones 7 affords indoloquinones 8. Depending on their leaving group ability one or both substituents X and Y can be eliminated. Evidence is provided, on carrying out the reduction reactions in EtOD, for the intermediacy of quinone methides 10, 12 and/or 13 and iminium derivatives 14.

In cancer chemotherapy there is an urgent need for hypoxia selective agents[1] in order to eradicate the hypoxic cells[2] of the slowly growing solid tumors, such as carcinomas of the lung, colon and breast, which constitute the major cause of mortality from cancer.

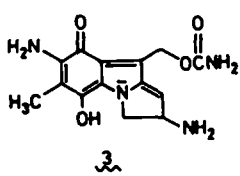
The quinone containing bioreductive alkylating agents[3] form an important class of compounds which are being developed and clinically used for targeting these cells. They require reductive biotransformation to exert their cytotoxic alkylating activity. It has been well established, that mitomycin C (MMC; 1)[4], the prototype of this class of anticancer drugs, upon reductive activation - either chemically or enzymatically - may bind via its C-1 atom covalently to suitable nucleophiles (e.g. DNA or RNA)[5,6]. It has also been observed, that MMC acts as a bisalkylating agent via its C-1 and C-10 carbon atom[6]. On interaction with DNA cross-linked adducts are formed in this manner[4,7]. Whether mono- or bisalkylation occurs is strongly dependent on the reducing conditions, the nature of the nucleophiles and the environmental pH.



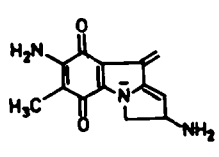
1



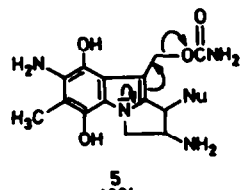
2



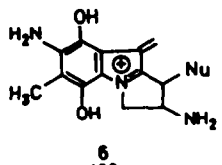
3



4



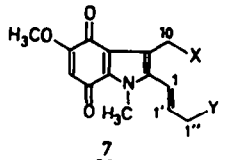
5



6

The first steps in the molecular activation sequence of MMC comprise its conversion into hydroquinone 2[3b,8]. The latter intermediate is structurally related to intermediates arising from the mitosenes[9] after reductive activation. The driving force for the activation of the C-1 position in preference to the C-10 position in MMC has to be ascribed to the opening of the aziridine ring thereby releasing the strain energy during the formation of quinone methide 3. Activation of the second electrophilic center (C-10) may take place via one of the following two ways: i. Conversion of the monoquinone methide 3 into bis-quinone methide 4 via elimination of the elements of $HOCONH_2$. ii. Nucleophilic trapping of quinone methide 3 and elimination of $HOCONH_2$ from the resulting adduct 5 affording iminium derivative 6, which may act as both an electrophilic or a nucleophilic trap. Hornemann c.s.[6a] and recently Kohn c.s.[10] have presented evidence favouring the iminium pathway. Finally, the dual reactivity of quinone methide 3 has also unequivocally been established[5a,5g,11].

As we felt that the results obtained so far on the (bio) reductive alkylation of MMC could be placed in a more general framework we became interested in the chemistry of indoloquinones 7. In this paper we wish to provide evidence for the intermediacy of reactive species from 7 similar to the quinone methides 3 and 4, and the iminium derivative 6.



7

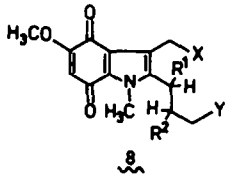
a. X = Y = $OCCH_3$ (O)

b. X = H ; Y = $OCCH_3$ (O)

c. X = OH ; Y = $OCCH_3$ (O)

d. X = $OCCH_3$ (O) , Y = OH

e. X = Y = OH



8

a. X = Y = R^1 = R^2 = H

b. X = Y = R^1 = R^2 = D

c. X = H ; Y = R^1 = R^2 = D

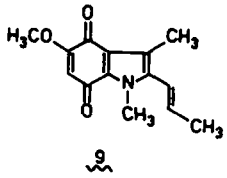
d. X = R^1 = R^2 = H ; Y = OH

e. X = R^1 = R^2 = D ; Y = OH

f. X = OH ; R^1 = R^2 = Y = H

g. X = Y = OH ; R^1 = R^2 = H

h. X = Y = OH ; R^1 = R^2 = D

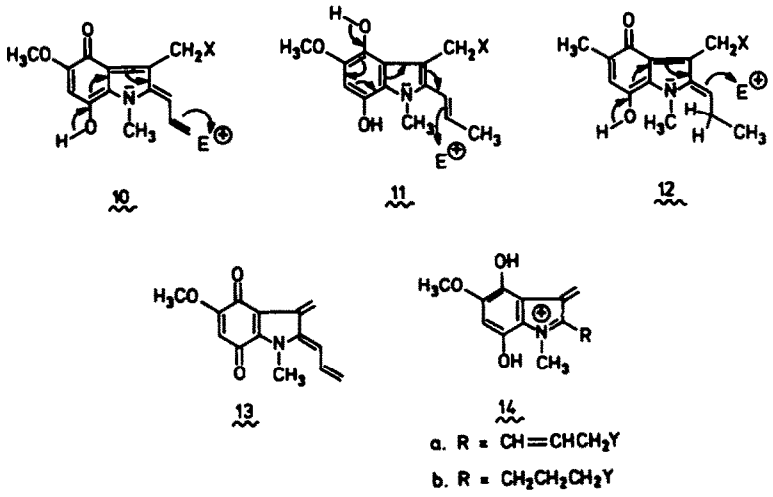


9

RESULTS and DISCUSSION

Treatment of an EtOH solution of indoloquinone 7b with PtO_2 and H_2 (25°C, 2h) in the presence of NEt_3 led to full conversion of the starting compound and to a reaction mixture, which yielded after oxidative work-up indoloquinone 8a. Evidence for the intermediacy of quinone methides 10 and 12 was obtained via the following two ways:

i. Oxidative work-up of the reaction mixture after 10 min yielded besides starting material and some unidentified material a mixture of the indoloquinones 8a and 9 (~1/1). ii. Carrying out the same reaction in EtOD afforded the trideuterioquinone 8c. The extent of deuterium incorporation amounted to more than 90% at all positions as has been established by ^1H NMR analysis. Due to coupling with the deuterium atoms the absorptions of all carbon atoms of the propyl side chain appear in the protondecoupled ^{13}C spectrum of 8c as triplets (J=19.4 Hz). These spectroscopic data and the almost complete built-in of deuterium atoms at the C-1, C-1' and C-1'' positions and not at e.g. the C-10 position exclude a catalytic solvent-exchange mechanism. The absence of such a secondary process has been



10 11 12

13 14

a. R = $CH{=}CHCH_2Y$

b. R = $CH_2CH_2CH_2Y$

verified experimentally on treating indoloquinone 8a with EtOD in the presence of NEt_3 and PtO_2. A similar type of reactivity was found in alcohol 7c which provided quinone 8f, without affecting the C-10 position.

Activation of both the C-1 and C-1'' carbon atoms and the C-10 carbon atom has been observed in the case of indoloquinone 7a. Upon use of H_2/PtO_2 and in the presence of $C_6H_5NH_2$* the fully hydrogenated indoloquinone 8a was obtained. Substantiation for the intermediacy of quinone methides 10 and 13 or iminium salt 14 and indoloquinones 10 and 12 was obtained by performing the reduction of 7a in EtOD. A considerable amount (65-70%) of deuterium incorporation into indoloquinone 8a at C-10, C-1, C-1' and at carbon atom C-1'' was observed. The mechanism of activation, either via 13 or 14, however, cannot be ascertained by this experiment.

Support for a mechanism of activation of C-10 independent from the fate of the leaving group Y in 7, under reducing conditions, has been obtained on treating indoloquinone 7d with H_2/PtO_2 in the presence of $C_6H_5NH_2$ using EtOD as solvent. Trideuterio alcohol 8e was formed, showing deuterium incorporation to a high extent (~70%) at all carbon atoms. The deuterium incorporation at C-1 and C-1' demonstrates the occurrence of a secondary activation process, which takes place after the first substitution at C-10.

The intimate connection between reduction and addition was finally illustrated in the reaction (PtO_2/H_2/EtOD) of the diol 7e. The isolation of dideuteriodiol 8h (80% built-in of deuterium at both C-1 and C-1') emphasized the overall activity pattern of the indoloquinone.

So far it has been assumed that for the formation of the quinone methides and the iminium compounds from 7 a 2 electron/$2H^+$ reduction sequence is required. The results presented herein, however, especially the formal hydrogenation of 7e indicate the occurrence of other reactive species. Presumably after the uptake of one electron, the semiquinone anion radicals formed, are inherently connected with the formation of the reduction products 8. One of the many representations for such a process is given in Fig. 1. Clear evidence for the latter activation process has been revealed recently[12] in the reduction of MMC and mitosenes.

* On the involvement of $C_6H_5NH_2$ in the activation sequence we will report in a separate paper.

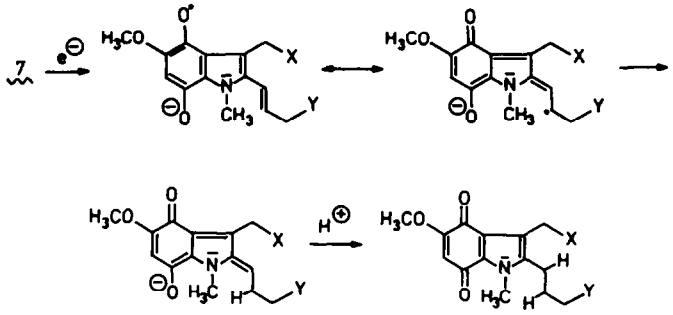


Fig. 1

CONCLUSIONS

The foregoing results emphasize the similarity of the reductive activation of indoloquinones 7 and the MMC activation cascade. Of foremost importance is the participation of additional unsaturated moieties in the reactive intermediates. The latter phenomenon in principle allows for a fine-tuning of bioactive mitomycin analogs. A further implication of this work is of more general interest. Since quinone methides are likely to be involved in the mechanism of action of the anthracycline antitumor antibiotics[13-16] the present results can also be accomodated to better understand the chemical basis of its mode of action.

Studies concerning the electrophilic character of the intermediates 10, 12 and 14, the electrochemical behaviour and biological activities of the new series of indoloquinones are in progress.

ACKNOWLEDGEMENT We are grateful for the financial support of this work by the "Koningin Wilhelmina Fonds". The authors wish to thank Messrs. R.C. van den Brink and R.H. Balk for the large scale preparations of some of the precursors of the starting indoloquinones. They further wish to express their gratitude to Dr. N.N.M. Nibbering and his co-workers and to Mr. C. Kruk and his staff for providing the mass spectra and NMR spectra respectively.

EXPERIMENTAL

Melting points were measured with a Leitz hot-stage microscope and are uncorrected. ^{1}H NMR spectra were recorded on Varian XL-100-12, Bruker WP-200 or Bruker WM-250 spectrometers. ^{13}C NMR spectra were taken with a Perkin-Elmer 257 spectrometer. Mass spectra were obtained with a Varian Matt 711 instrument[17]. Flash chromatography[18] was performed over silicagel (E. Merck, Kieselgel 60, 230-400 mesh).

Preparation of the indoloquinones 7a-7e

These were prepared according to reference 19. The synthesis of these compounds will be further described in a separate paper.

General procedure for the reduction of indoloquinones 7a-7e

Indoloquinones 7 (0.1 mmol) were reduced with H_2 at atmospheric pressure using a mixture of dry ethanol (10 ml) and either triethylamine (1 ml) or aminobenzene (0.2 g) as solvent and PtO_2 as catalyst. When the reaction proceeded, the colour of the solution turned from red or purple to light yellow or disappeared completely. The reduction was continued for two hours. To reoxidise the hydroquinone derivatives of 8 thus obtained, the reaction mixture was stirred in the air for 10 min. The resulting dark red solution was diluted with CH_2Cl_2 and filtered through high flow. Thereupon, depending on the nature of the solvent mixture, one of the following work-up methods were used.

Method A: on using $EtOH/NEt_3$ or EtOH as reaction medium.
The solvents were evaporated under reduced pressure yielding the crude products,

which were submitted to flash column chromatography and/or crystallization.
Method B: on using EtOH/$C_6H_5NH_2$ as reaction medium.
The filtrate was washed subsequently with 6N HCl (4 times) and sat. NaCl aq., and dried over $MgSO_4$. The residue obtained after evaporation of the solvent in vacuo, was purified by column chromatography and/or crystallization.

Reduction of indoloquinone 7a

Work-up (methode B) and crystallization from methanol yielded 8a or 8b as orange crystals (33%); m.p. 173-174°C.

a) *1,3-Dimethyl-5-methoxy-2-propyl-1H-indole-4,7-dione (8a)*

IR($CHCl_3$): 1630 and 1670 cm^{-1} (quinone CO); 1600 (quinone C=C); ^{1}H NMR δ($CDCl_3$): 5.55 (s, 1H, H-6); 3.86 (s, 3H); 3.77 (s, 3H), 2.53 (t, J=7.4 Hz, 2H, $-CH_2-Ar$), 2.24 (s, 3H, H_3C-Ar), 1.52 (m, 2H, $-H_2C-CH_3$); 0.95 (t, J=7.4 Hz, 3H, $-CH_2-CH_3$). ^{13}C NMR δ($CDCl_3$): 178.4 and 178.3 (s, C=O); 159.6, 139.2, 128.1, 121.9 and 118.9 (s, Ar); 106.8 (s, C-6), 56.2 (s, OCH_3); 32.3 (s, NCH_3); 25.2 (s, $-CH_2Ar$); 22.2 (s, $-CH_2-CH_3$); 13.7 (s, $-CH_2-CH_3$) and 10.0 (H_3C-Ar). An exact mass determination gave: 247.1213; $C_{14}H_{17}NO_3$ requires 247.1209 (1.6).

b) *5-Methoxy-1-Methyl-3[$^2H_1$]methyl-2-[1,2,3-$^2H_3$]propyl-1H-indole-4,7-dione (8b)*

^{1}H NMR ($CDCl_3$): 5.56 (s, 1H, H-6); 3.86 (s, 3H); 3.77 (s, 3H); 2.45-2.6 (m, 1H, $-CHD-Ar$); 2.24 (t, J=2.2 Hz, 2H, DH_2C-Ar); 1.4-1.6 (m, 1H, $-CHD-CH_2D$); 0.85-1.0 (m, 2H, $-CHD-CH_2D$).
^{13}C NMR δ($CDCl_3$): 178.5 and 178.3 (s, C=O); 159.7, 139.3, 128.2, 121.9 and 118.9 (s, Ar); 106.8 (s, C-6); 56.3 (s, OCH_3); 32.4 (s, NCH_3); 24.8 (t, J=19.5 Hz, $-CHDAr$); 21.7 (t, J=19.5 Hz, $-CHD-CH_2D$); 13.3 (t, J=19.5 Hz, $-CHD-CH_2D$); 9.9 (t, J=19.5 Hz, $ArCH_2D$). An exact mass determination gave: 251.1453; $C_{14}H_{13}D_4NO_3$ requires 251.1460 (2.4).

Reduction of Indoloquinones 7b

a) Work-up (method A) and purification by flash column chromatography (CH_2Cl_2/acetone: 9:1) of the reaction mixture obtained after 2h reduction afforded 8a or 8c as orange crystals (58%).

1,3-Dimethyl-5-methoxy-2-[1,2,3-$^2H_3$]propyl-1H-indole-4,7-dione 8c

^{1}H NMR δ($CDCl_3$): 5.55 (s, $0.2H^{20}$, H-6); 3.85 and 3.76 (s, 3H); 2.45-2.6 (m, 1H, $-CHD-Ar$); 2.23 (s, 3H, H_3C-Ar); 1.4-1.6 (m, 1H, $-HDC-CH_2D$); 0.85-1.0 (m, 2H, $-HDC-CH_2D$).
^{13}C NMR δ($CDCl_3$); 178.3 and 178.2 (s, C=O); 159.6, 159.5, 139.2, 128.1, 121.8 and 118.8 (s, Ar); 106.7 (s, C-6); 56.2 (s, OCH_3); 32.2 (s, NCH_3); 24.7 (t, J=19.4 Hz, $-CHD-Ar$); 21.6 (t, J=19.4 Hz, $-CHD-CH_2D$); 13.2 (t, J=19.4 Hz, $-CHD-CH_2D$); 10.0 (s, CH_3-Ar). Exact mass determination gave: i. 250.1391; $C_{14}H_{14}D_3NO_3$ requires 250.1396 (2.0); ii. 251.1468; $C_{14}H_{13}D_4NO_3$ requires 251.1459 (3.5).

b) Work-up and purification of the reaction mixture after a 10 min period of hydrogenation yielded an inseparable (~1/1) mixture of indoloquinones 8a and 9 (60-65%).

1,3-Dimethyl-5-methoxy-2[(E)-1-propenyl]-1H-indole-4,7-dione (9)

^{1}H NMR δ($CDCl_3$): 6.17 (d, J=16.5 Hz, 1H, $Ar-CH=CH-$); 6.0-6.15 (m, 1H, $ArCH=CH$); 5.58 (s, 1H, H-6); 3.88 and 3.77 (s, 3H); 2.34 (s, 3H, H_3C-Ar); 1.94 (d, J=6.1 Hz, 3H, $-CH=CHCH_3$).
^{13}C NMR δ($CDCl_3$): 178.6 and 178.2 (s, C=O); 159.7, 139.2, 127.9, 122.0, 119.8 (s, Ar); 133.8 (s, $ArCH=CH-$); 117.9 (s, $ArCH=CH-$); 107.1 (s, C-6); 56.3

(s, OCH_3); 32.9 (s, NCH_3); 19.3 (s, -CH=CH-$\underline{C}H_3$); 11.1 (s, Ar$\underline{C}H_3$). An exact mass determination gave: 245.1050; $C_{14}H_{15}NO_3$ requires 245.1052 (0.8).

Reduction of indoloquinone 7c

Work-up (method A) and purification of the reaction mixture by column chromatography (CH_2Cl_2/acetone: 7/3) afforded indoloquinone 8f as a red oil (45%).

[3-(5-Methoxy-1-methyl-2-propyl-1H-indole-4,7-dione)]methanol (8f)

IR($CHCl_3$): 3450 cm^{-1} (OH); 1660 and 1640 cm^{-1} (quinone C=O); 1600 cm^{-1} (quinone C=C).

^1H NMR δ($CDCl_3$): 5.62 (s, 1H, H-6); 4.58 (d, J=6.9 Hz, 2H, Ar-C$\underline{H}_2$OH); 4.04 (t, J=6.9 Hz, OH); 3.87 and 3.80 (s, 3H); 2.38 (t, J=7.6 Hz, 2H, -C$\underline{H}_2$-Ar); 1.45-1.6 (m, 2H, -C$\underline{H}_2$-CH_3); 0.94 (t, J=7.4 Hz, 3H, -CH_2-C$\underline{H}_3$).

^{13}C NMR ($CDCl_3$): 179.3 and 178.6 (s, C=O); 159.7, 138.7, 129.4, 123.1 and 122.1 (s, Ar); 107.2 (s, C-6); 56.5 (s, OCH_3); 55.9 (Ar$\underline{C}H_2$OH); 32.4 (s, NCH_3); 25.4 (s, -$\underline{C}H_2$AR); 22.8 (s, -$\underline{C}H_2$-CH_3); 13.6 (s, -$CH_2\underline{C}H_3$). An exact mass determination gave: 263.1143; $C_{14}H_{17}NO_4$ requires 263.1157 (4.2).

Reduction of indoloquinone 7d

Work-up (method B) and purification of the crude product by column chromatography (CH_2Cl_2/acetone: 8/2) afforded indoloquinones 8d or 8e as orange crystals (37%); m.p. 150-151°C.

a) *3-[2-(1,3-Dimethyl-5-methoxy-1H-indole-4,7-dione)]propan-1-ol (8d)*

IR($CHCl_3$): 3400 cm^{-1} (OH); 1660 and 1630 cm^{-1} (quinone C=O); 1595 cm^{-1} (quinone C=C).

^1H NMR δ($CDCl_3$): 5.59 (s, 1H, H-6); 3.91 and 3.79 (s, 3H); 3.68 (t, J=6 Hz, 2H, -C$\underline{H}_2$-OH), 2.72 (t, J=7.3 Hz, 2H, -C$\underline{H}_2$-Ar); 2.28 (s, 3H, $\underline{H}_3$C-Ar); 1.6-1.9 (m, 3H, -C$\underline{H}_2$-CH_2OH and OH).

^{13}C NMR δ($CDCl_3$): 178.5 and 178.3 (s, C=O); 159.7, 138.7, 128.3. 121.9 and 119.0 (s, Ar); 106.8 (s, C-6); 61.5 (s, -CH_2-$\underline{C}H_2$OH); 56.3 (s, OCH_3); 32.4 (s, NCH_3); 31.5 (s, -$\underline{C}H_2$Ar); 19.7 (s, -$\underline{C}H_2$-CH_2OH); 10.0 (s, Ar$\underline{C}H_3$).
An exact mass determination gave: 263.1154; $C_{14}H_{17}NO_4$ requires 263.1158 (1.5).

b) *3-[2-(5-Methoxy-1-methyl-3-[$^2H_1$]methyl-1H-indole-4,7-dione][1,2,3-$^2H_3$ propan-1-ol (8e)*

^1H NMR δ($CDCl_3$): 5.56 (s, 1H, H-6); 3.89 and 3.77 (s, 3H); 3.67 (d, J=6.1 Hz, 1H, -C$\underline{H}_2$OH); 2.6-2.7 (m, 1H, -C$\underline{H}$D-Ar); 2.24 (t, J=2.2 Hz, 2H, D$\underline{H}_2$C-Ar); 1.5-1.7 (m, 2H, -C$\underline{H}$D-CH_2OH and OH).

^{13}C NMR δ($CDCl_3$): 178.5 and 178.3 (s, C=O); 159.7, 138.7, 128.3, 121.9 and 119.0 (s, Ar); 106.8 (s, C-6); 61.4 (s, -CH_2-$\underline{C}H_2$OH); 56.3 (s, OCH_3); 32.4 (s, NCH_3); 31.0 (t, J=19.7 Hz, -CHDAr); 19.3 (t, J=19.7 Hz, -$\underline{C}$HD-CH_2OH); 9.8 (t, J=19.6 Hz, Ar$\underline{C}H_2$D). An exact mass determination gave: 266.1341; $C_{14}H_{14}D_3NO_4$ requires 246.1346 (2.0).

Reduction of indoloquinone 7e

The reduction was carried out using EtOH or EtOD as solvent. Work-up (method A) and purification of the reaction mixture by column chromatography (CH_2Cl_2/acetone: 7/3) afforded indoloquinones 8g and 8h as orange crystals (45%); m.p. 207-209°C (MeOH).

a) *3-[2-(3-Hydromethyl-1-methyl-5-methoxy-1H-indole-4,7-dione)]propan-1-ol (8g)*

IR($CHCl_3$): 3300 cm^{-1} (OH); 1665 and 1630 cm^{-1} (quinone C=O); 1590 (quinone C=C).

^{1}H NMR δ(DMSO-d_6/D_2O); 5.71 (s, 1H, H-6); 4.54 (s, 2H, ArC$\underline{H}_2$OH); 3.88 and 3.77 (s, 3H); 3.42 (t, J=6.0 Hz, 2H, CH_2-C$\underline{H}_2$OH); 2.72 (t, J=7.6 Hz, 2H, -CH_2-Ar); 1.55-1.75 (m, 2H, -C$\underline{H}_2$-CH_2OH).
^{13}C NMR (DMSO-d_6): 178.1 and 177.5 (s, C=O); 159.3, 140.8, 127.7, 121.9 and 120.6 (s, Ar); 106.7 (s, C-6); 59.7 (s, -CH_2-C$\underline{H}_2$OH; 56.4 (s, OCH_3); 53.1 (s, ArC$\underline{H}_2$OH); 32.1 (s, NCH_3); 31.8 (s, Ar-C$\underline{H}_2$-CH_2-); 19.5 (s, -C$\underline{H}_2$$CH_2$OH). An exact mass determination gave: 279.1094; $C_{14}H_{17}NO_5$ requires 279.1107 (4.7).

b) *3-[2-(3-Hydroxymethyl-5-methoxy-1-methyl-1H-indole-4,7 dione)][2,3-$^2H_2$]propan-1-ol (8h)*

^{1}H NMR δ(DMSO-d_6/D_2O); 5.68 (s, 1H, H-6); 4.53 (s, 2H, ArC$\underline{H}_2$OH); 3.81 and 3.72 (s, 3H); 3.40 (d, J=6.1 Hz, 2H, -CHD-C$\underline{H}_2$OH); 2.6-2.8 (m, 1H, -C$\underline{H}$D-Ar); 1.6-1.7 (m, 1H, -C$\underline{H}$D-CH_2OH).
^{13}C NMR (DMSO-d_6): 178.1 and 177.5 (s, C=O); 159.3, 140.8, 127.7, 121.9 and 120.6 (s, Ar); 106.7 (s, C-6); 59.7 (s, -CH_2-C$\underline{H}_2$OH); 56.4 (s, OCH_3); 53.1 (s, ArC$\underline{H}_2$OH); 32.1 (s, NCH_3); 31.2 (t, 19.5 Hz, ArC$\underline{H}_2$-CH_2-); 19.1 (t, 19.5 Hz, -C$\underline{H}_2$-CH_2OH). An exact mass determination gave 281.1230; $C_{14}H_{15}D_2NO_5$ requires 281.1233 (1.1).

REFERENCES

1 W.A. Wenny and W.R. Wilson, J.Med.Chem., 29, 879 (1986).
2a K.A. Kennedy, B.A. Teicher, S. Rockwell and A.C. Sartorelli, Biochem.Pharmac., 29, 1 (1980).
2b A.C. Sartorelli, Biochem.Pharmac., 35, 67 (1986).
3a A.J. Lin, L.A. Cosby, B.J. Lillis, C.W. Shansky and A.C. Sartorelli, J.Med.Chem., 16, 1268 (1973).
3b H.W. Moore, Science, 197, 527 (1977).
3c H.W. Moore and R. Czerniack, Med.Res.Rev., 1981, Vol.1, 249.
4a W.A. Remers, The Chemistry of Antitumor Antibiotics, Vol.1, John Wiley & Sons, New York, 1979, Ch.5, p.221.
4b S.K. Carter and S.T. Crooke (Eds), Mitomycin C - Current Status and New Developments, Academic Press, New York 1979.
4c M. Ogawa, M. Rosenczweig and M.J. Staquet (Eds), Mitomycin C - Current Impact on Cancer Chemotherapy, Excerpta Medica, Amsterdam, Princeton, Genova, Tokyo, 1982.
5a M. Tomasz and R. Lipman, Biochemistry, 20, 5056 (1981).
5b M. Tomasz, M. Jung, G. Verdine and K. Nakanishi, J.Am.Chem.Soc., 106, 7367 (1984).
5c Y. Hashimoto, K. Shudo and T. Okamoto, Chem.Pharm.Bull., 28, 1961 (1980).
5d Y. Hashimoto, K. Shudo and T. Okamoto, Tetrahedron Letters, 23, 677 (1982).
5e Y. Hashimoto, K. Shudo and T. Okamoto, Chem.Pharm.Bull., 31, 861 (1983).
5f Y. Hashimoto, K. Shudo and T. Okamoto, Acc.Chem.Res., 17, 403 (1984).
5g D.M. Peterson and J. Fisher, Biochemistry, 25, 4077 (1986).
6a U. Hornemann, P.J. Keller and J.F. Kozlowski, J.Am.Chem.Soc., 101, 7121 (1979).
6b U. Hornemann, K. Iguchi, P.J. Keller, H.M. Vu, J.F. Kozlowski and H. Kohn, J.Org.Chem., 48, 5026 (1983).
6c M. Bean and H. Kohn, J.Org.Chem., 48, 5033 (1983).
6d M. Bean and H. Kohn, J.Org.Chem., 50, 293 (1985).
7 S. Pan, T. Irachi and N.R. Bachur, Mol.Pharmac., 29, 622 (1986).
8a S.J. Danishefsky and M. Ciufolini, J.Am.Chem.Soc., 106, 6424 (1984).
8b S.J. Danishefsky and M. Egbertson, J.Am.Chem.Soc., 108, 4648 (1986).
9a W.S. Taylor, G. Leadbetter, D.L. Fost and W.A. Remers, J.Med.Chem., 20, 138 (1977).
9b J.C. Hodges and W.A. Remers, J.Med.Chem., 24, 1184 (1981).
9c M.L. Casner, W.A. Remers and W.T. Bradner, J. Med.Chem., 28, 921 (1985).
10 N. Zein and H. Kohn, J.Am.Chem.Soc., 108, 296 (1986).
11 H. Kohn and N. Zein, J.Am.Chem.Soc., 105, 4105 (1983).
12 P.A. Andrews, S. Pan and N.R. Bachur, J.Am.Chem.Soc., 108, 4158 (1986).
13a F. Arcamone, Doxorubicin Anticancer Antibiotics, Academic Press, New York 1981.
13b F. Arcamone, Med.Res.Rev., 1984, Vol.4, 153.
14a D.L. Kleyer and T.H. Koch, J.Am.Chem.Soc., 105, 2504 (1983).
14b D.L. Kleyer and T.H. Koch, J.Am.Chem.Soc., 105, 5154 (1983).
14c D.L. Kleyer and T.H. Koch, J.Am.Chem.Soc., 106, 2380 (1984).
14d D.J. Brand and J. Fisher, J.Am.Chem.Soc., 108, 3088 (1986).

15 A. Anne and J. Moiroux, Nouveau J. de Chimie, 9, 83 (1985).
16 K. Ramakrishnan and J. Fischer, J.Med.Chem., 29, 1215 (1986).
17 Figures given in parentheses after exact mass determinations give the absolute value of the difference between calculated and recorded masses (in ppm).
18 W.C. Still, M. Kahn and A. Mitra, J.Org.Chem., 43, 2923 (1978).
19 W.N. Speckamp and E.A. Oostveen. The indoloquinones, Brit.Pat.Appl. no 86.09369, 1986.
20 For the built-in of deuterium at this position reducing conditions are required as has been established on treating indoloquinone 8a with EtOD in the presence of NEt_3 and PtO_2.