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NEW CHEMISTRY OF MITOMYCIN C

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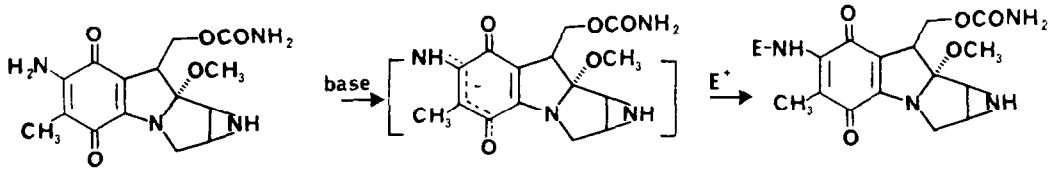
Abstract: Novel and significant analogues of mitomycin C were prepared based on new chemistry utilizing mitomycin C in its anion form.

In recent years there has been resurgence of interest in mitomycins.[1] Although these compounds have been known for approximately 30 years, new chemistry is still being discovered as exemplified by Danishefsky's recent finding on leucomitomycin B and C[2]. In this communication we report new chemistry of mitomycin C (1) developed by use of its anion.

It is well-established the C7 substituent of mitosane has a significant effect on the antitumor activity of the analogues.[3] Historically, N7-substituted mitomycin C analogues have been prepared by displacement of the methoxy group in mitomycin A.[3,4] Since mitomycin C is more easily obtained by fermentation than mitomycin A, use of the former as the starting material for the preparation of N7 substituted mitomycin C analogues appeared attractive. At the outset there was no method available to selectively derivatize the C7 amino group, as it had been reported that alkylation or acylation under standard conditions took place at the aziridine nitrogen.[5,6] Since the C7 amino group can be considered as a vinylogous amide, we sought to reverse the reactivity of the C7 amino group and the aziridine nitrogen by forming the anion at the former site. That is, if an anion such as 2 could be formed, addition of an electrophile should provide a new route to compounds of structure 3.[7]

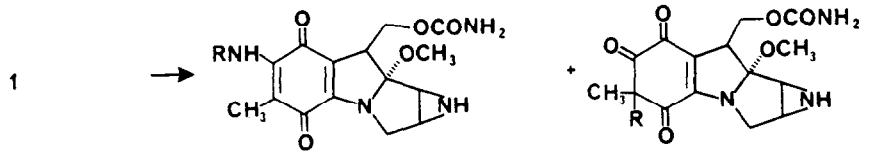


1 2 3

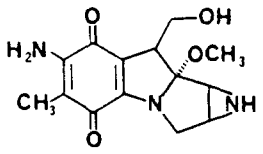
It has been reported the pKa of the C7 amino group of 1 in an aqueous solution is 12.44.[8] This suggested that deprotonation at this site should be relatively easy. Treatment of 1 with lithium diisopropylamide in tetrahydrofuran (THF) gave, after an aqueous workup, mainly decarbamoyl mitomycin C (4).[9] On the other hand treatment of 1a[10] with NaH in dimethylformamide (DMF) at room temperature produced a deep blue solution which upon addition of ethyl iodide at -20°C yielded, besides the starting material (15%), the desired N7-ethyl mitomycin C (5a, 11%) and 6a (6%).[11,12] Compound 6a was obtained as a single isomer but its stereochemistry at the newly-created quarternary center could not be determined since in NMR experiment no nOe was observed between the substituents at this center and the rest of the molecule. The formation of 6a indicated that the anion was extensively delocalized; however, no O-5 alkylation product was isolated.

Some examples of alkylating agents used and the product distribution are indicated in Figure 1. The low yields are due to the decomposition of the starting material under the reaction conditions. It was found that mesylates could be used as alkylating agents whereas secondary halides did not react.

Figure 1



RX				
EtI	5a	11%	6a 6%	15%
MeI	5b	22%	6b 5%	28%
CH_2=$CHCH_2Br$	5c	0%	6c 6%	dec.
$C_6H_5CH_2Cl$	5d	5%	6d 16%	60%
CH_3OCH_2OMs	5e	19%	6e 0%	9%



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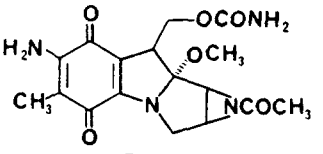

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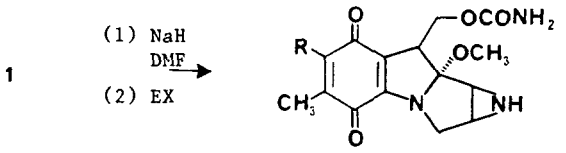
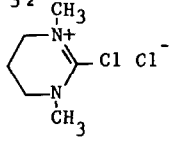
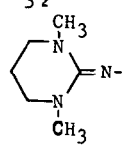
In the attempted acetylation of the C7 amino group, addition of acetyl chloride or acetic anhydride at -20°C to the anion solution mentioned above yielded predominantly the product acetylated on the aziridine (7, 50%). Alternatively, addition of N-hydroxysuccinimide ester of acetic acid gave N7-acetyl mitomycin C in 40% yield. Previously, there were no N7-acyl derivatives of mitomycin C reported.[14] The difference in regioselectivity might be explained by the HSAB principle.[15] Thus, reactive acylating

agents (hard acids) react at the aziridine nitrogen (hard base) whereas an activated ester (soft acid) reacts at the C7-amino group where electrons are quite diffused (soft base). Activated carbonates and isocyanates gave C7-carbamoyl- and C7-ureido-mitosanes, respectively. Some examples are shown in Figure 2.

A reaction of the mitomycin C anion with a formimidinium chloride or an amidinium chloride at -20°C yielded C7-amidino- or C7-guanidino-mitosane, respectively. The typical examples are shown in Figure 2. Compound 8f is currently in clinical trials.[16,17] Thus, this chemistry of mitomycin C anion provides new avenues to novel mitomycin analogues and it may be applicable to other natural products or semisynthetic natural products containing an aminoquinone moiety.[18]

Figure 2.



EX	R	Yield
HCO_2Ph	8a HCONH-	47%
CH_3CONSu	8b CH_3CONH-	40%
$CF_3CO_2PhNO_2$-p	8c CF_3CONH-	24%
$CH_3OCO_2PhNO_2$-p	8d CH_3OCONH-	38%
iPrN=C=O	8e iPrNHCONH-	17%
$(CH_3)_2N^+=CHClCl^-$	8f $(CH_3)_2NCH=N$-	43%
	8g 	40%

References and Notes

1. For a review see Remers, W.A. in "Chemistry of Antitumor Antibiotics"; Wiley-Interscience: New York, 1979; Vol. 1, pp. 221.
2. Danishefsky, S.; Ciufolini, M. J. Amer. Chem. Soc., 1984, 106, 6424.
3. Sami, S.M.; Iyengar, B.S.; Tarnow, S.E.; Remers, W.A.; Bradner, W.T.; Schurig, J.E. J. Med. Chem., 1984, 27, 701 and references therein.
4. An additional route is displacement of an acyloxy group at C7 with an amine, see: Saito, Y.; Shirahata, K.; Kawanishi, M. Japan Patent, 1981, S56-73085.
5. Matsui, M.; Yamada, Y.; Uzu, K.; Hirata, T. J. Antibiotics, 1968, 21, 189.

6. Sasaki, H.; Mukai, E.; Hashida, M.; Kimura, T.; Sezaki, H. Int. J. Pharm., 1983, 15, 49.
7. A search of the literature failed to give any precedents of this approach for the preparation of N-alkyl aminoquinones.
8. Underberg, W.J.M.; Lingeman, H. J. Pharm. Sci., 1983, 72, 533.
9. The solubility of mitomycin C in THF is limited and may be the cause of little observable reaction.
10. The anion appears to be stable at room temperature for at least 30 min.
11. The workup involves quenching of the reaction by addition of a small amount of dry ice followed by addition of 0.4M aq. solution of potassium biphthalate.
12. The structure of 5a was confirmed by comparison to the authentic sample prepared by the published route.[13] Compound 6a had the following spectroscopic data: nmr (pyridine-d_5) δ 0.81 (t, 3H, J=6.9 Hz), 1.50 (s, 3H), 1.88 (q, 2H, J=6.9 Hz), 2.79 (bd, 1H, J=4.5 Hz), 3.15 (s, 3H), 3.20 (d, 1H, J=4.5 Hz), 3.57 (bd, 1H, J=11.3 Hz), 4.04 (d, 1H, J=11.6 Hz), 4.07 (dd, 1H, J=9.0, 4.5 Hz), 5.05 (t, 1H, J=8.8 Hz), 5.49 (dd, 1H, J=8.8, 4.5 Hz); IR (KBr) 3460, 1730, 1700, 1640, 1562, 1456, 1340, 1020 cm^{-1}; UV λ_{max}^{MeOH} 238mμ(ε 8300), 368 mμ (ε 7300). Anal. calcd for $C_{17}H_{21}N_3O_6$: C, 54.83; H, 5.95, N, 11.28; found: C, 54.93, H, 6.11; N, 11.12.
13. Matsui, M.; Yamada, Y.; Uzu, K.; Hirata, T., J. Antibiotics, 1968, 21, 189.
14. Compound 8b was found to be much less myelosuppresive than mitomycin C, see: Schlein, A.; Schurig, J.E.; Rose, W.C.; Farwell, A.R.; Florczk, A.P.; Kaneko, T.; Wong, H.; Bradner, W.T. AACR Abstracts, 1985. The physiochemical data and the biological activity of new analogues will be reported in a full paper.
15. Ho, T.-L. "Hard and Soft Acids and Bases Principles in Organic Chemistry", Academic Press, New York, 1977.
16. Vyas, D.; Doyle, T.W.; Bradner, W.T.; Rose, W.C., 187th ACS Meet. Abstracts, 1984 MEDI 30.
17. Bradner, W.T.; Rose, W.C.; Schurig, J.E.; Huftalen, J.B.; Florczyk, A.F.; Vyas, D. AACR Abstracts, 1984, 1138.
18. For example, see: Marsili, L.; Franceschi, G.; Ballabio, M.; Oronzo, G.; Vigevani, A.; Ungheri, D.; Bruna, C.D.; Sanfilipo, A. J. Antibiotics, 1983, 36, 1495. Zmijewski, M.J.; Mikolajczak, M.J. J. Antibiotics, 1983, 36, 1767.

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