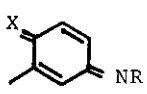
NEW SYNTHETIC STUDIES ON MITOMYCINS

Takeshi Ohnuma, Yasuo Sekine, and Yoshio Ban

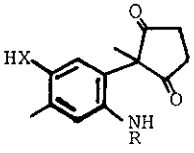
Faculty of Pharmaceutical Sciences, Hokkaido University, 060 Sapporo, Japan

The mitomycins of potent antitumor antibiotics, which contain several unique structural features including an aziridine group, were isolated by Hata and co-workers in 1956. Since their structures were determined by Webb, Tulinsky, and co-workers in 1962, a large number of the synthetic studies have been reported. Recently, Kishi and co-workers have succeeded in the first total synthesis of mitomycins.

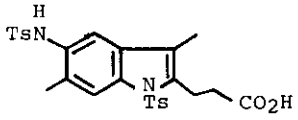
We now report the new synthetic approach which involves a retroaldol type of ring openning ractıon to obtain the benzazocinone 5 as a key intermediate of the synthesis. Under basic conditions, treatment of 2-methylcyclopentane-1,3-dione (1)with the toluquinonediimides 2 derived from 5-nitro-2-aminotoluene in three or four steps gave the desired Michael adducts 3a~c as a sole product in a high yield, respectively. On the other hand, Michael addition of the toluquinonemonoimide 2 (X=O) with 1 afforded the undesired C_3-adduct of monoimide 2. When the diketone 3a was treated with various acidic or basic conditions, elimination reaction via the indoline derivative took place to afford the indole 4 instead of retroaldol product. Transformation to the mitosane 6a, b (95%, 86% overall yield from 2b and 2c,respectively) was accomplished by hydrogenation of the diketone 3b and 3c over Pd/C followed by treatment with sodium hydride in tetrahydrofuran at room temperature. Oxidation of 6b with lead tetracetate in methanol gave the dehydrobenzazocinone 7 in a moderate yield.



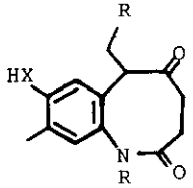
2



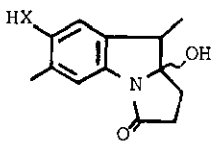
3a, X= tosyl, R= tosyl
b, X= tosyl, R= CO_2CH_2Ph
c, X= $NSO_2N(CH_3)_2$, R= CO_2CH_2Ph



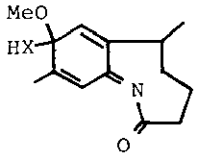
4



5



6a, X= tosyl
b, X= $NSO_2(CH_3)_2$



7, X= O, $NSO_2(CH_3)_2$