POLONOVSKI REACTIONS OF MITOSANE DERIVATIVES

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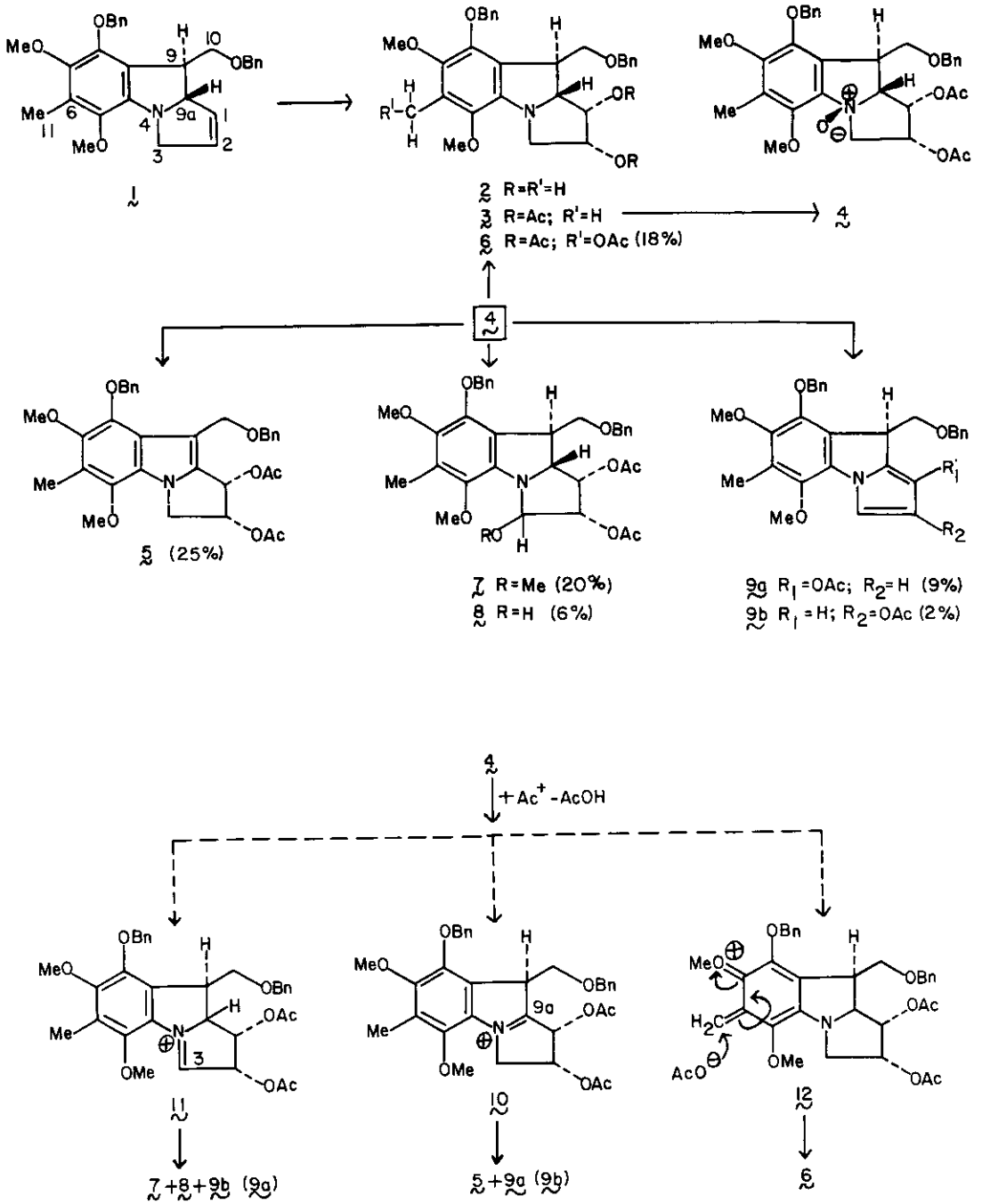
Abstract — Reaction of N-oxide **4** with acetic anhydride oxidizes carbons 3, 11 and 9a, thus providing a route to novel mitomycin congeners.

A concise route to compound **1**,[1] a potential precursor to mitomycin-like structures,[2] has been developed. Furthermore, a β-N-methylaziridino linkage has been stereospecifically installed at carbons 1 and 2 via diol **2**[1,3] which can be converted to diacetate **3** (87% from **1**). The introduction and maintenance of C_{9a} oxygen functionality is a long-term goal of the synthesis. The survival of any C_{9a} hetero function in the face of potential indolization would seem to demand[2] that the A ring be quinonoidal. Before dealing with that complicated problem, the feasibility of any constructive functionalization of C_{9a} in the presence of other competing sites was probed. To study this more general goal, the Polonovski reaction of N-oxide **4**[4] was investigated. In this Communication we report that C_{9a} functionalization is indeed possible (see compound **5**).

Reaction of **4** (Ac_2O (8 eq):methanol (8 eq)[5,6]-$CDCl_3$, r.t., 30 min) afforded, after purification (PTLC), compounds **3**,[7] **5**, **6**, **7**,[8] **8**,[8] **9a** and **9b** in the indicated approximate yields. It seems not unreasonable to formulate the genesis of compounds **5**–**9b** in terms of imminium ions **10** and **11** and delocalized oxonium ion, **12**.[9] By this view, ion **10** would suffer eventual conversion to **5**, whereas ion **11** could well give rise to compounds **7** and **8**. Furthermore, the origin of pyrroles **9a** and **9b** can be readily accommodated via either (or both) of these imminium ions. The formation of compound **6** can be rationalized via species **12** which would have arisen by deprotonation of the aromatic methyl group of an activated version of N-oxide **4**.[9]

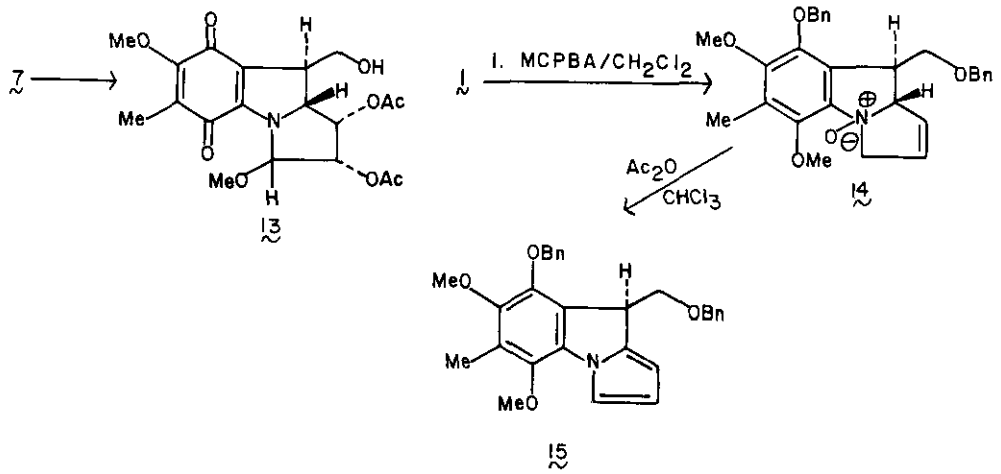
Dedicated to my friend and mentor, Gilbert Stork, in honor of his many accomplishments.



On the basis of many precedents in the mitomycin area,[2] cation **10** would be expected to undergo transformation to the indolic series. Prior to our own recent isolation of leucomitomycins[10] under carefully controlled conditions, all systems bearing a C_{9a} heterofunction in which the ring A is in the hydroquinonoidal oxidation level had suffered apparently very facile conversion to indolohydroquinones.

Predictably, the carbinolamine ether linkage of system **7** proved to be rather more rugged. Hydrogenolysis of **7** (H_2-Pd/C-methanol) afforded a phenolic alcohol which, upon oxidation with DDQ in 9:1 THF:H_2O,[1] gave rise to quinone **13**. This substance was fully characterized by spectroscopic methods.[7] It will be recognized that compound **13** is isomeric with the natural mitomycin series[2] in that the crucial carbinolamine-like linkage is situated at C_3 rather than at the usual C_{9a} site. The preparation and biological evaluation of "isomitomycin" congeners related to **7** and **8** which bear the 1,2-aziridino linkage and the carbamoyl side chain would be of considerable interest.

The Polonovski reaction[5] of N-oxide **14**[11] was also investigated. The required substrate was prepared by treatment of compound **1** with m-chloroperoxybenzoic acid. In this reaction there was no interference from the double bond. Treatment of **14** with acetic anhydride in chloroform resulted in a very clean reaction leading to a 77% yield of the homogeneous pyrroloindoline derivative, **15**.[7] Of course, the formation of **15** can be interpreted by deprotonation of either a C_{9a} (cf. **10**) or a C_3 (cf. **11**) imminium species.



In summary, it has been found that Polonovski reaction on certain fully synthetic mitosane N(4) oxides, accomplishes, albeit in modest yield, the crucial oxidation of the C_{9a} carbon. Left unanswered at this stage is the matter of stabilizing this C_{9a} functionality vis-a-vis indole formation.

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2. For key reviews of the chemistry and biology of mitomycins see: R. Franck. Fort. Chem. Org. Natur. 38, 1 (1979); W. Remers, "The Chemistry of Antitumor Antibiotics", Wiley Interscience: New York, New York, 1979, Vol. I, p. 221 ff.; and W. Remers, in "Anticancer Agents Based on Natural Product Models", Cassady, J.M., Douros, J.D., Eds., Academic Press: New York, New York, 1980, p. 131 ff.
3. The method used for incorporation was patterned after that of Kishi and collaborators in the **only** successful total syntheses of mitomycins. *For a review see:* Y. Kishi. J. Nat. Prod. 42, 549 (1979).
4. Prepared from the reaction of **3** with MCPBA in methylene chloride. The N-oxide was used in crude form. The stereochemistry shown for the N-oxide is not, in fact, rigorously known.
5. M. Polonovski, M. Polonovski. Bull. Soc. Chim. France. 41, 1190 (1927); W. Walter, M. Steffen, K. Heyns. Chem. Ber. 94, 2493 (1961); Ibid. 99, 3205 (1966); M. Lounasmaa, A. Koskinen. Heterocycles. 22, 1591 (1984).
6. The use of $CDCl_3$ and methanol was prompted by the isolation of an ethoxy-containing product when the reaction was carried out in commercial $CHCl_3$ (containing ethanol as a stabilizer).
7. The structures of all new compounds were in accord with their infrared, nmr (250 MHz), and mass spectral properties.
8. In this compound, the stereochemistry at C_3 is not determined.
9. Formally, loss of acetate from the acetylated N-oxide derived from **4** would produce a delocalized dication which, upon deprotonation of the aromatic methyl group, would give rise to delocalized monocation **12.** We emphasize that no concrete mechanistic information is available to determine, in a precise way, the origin of compound **6.**
10. S. Danishefsky, M. Ciufolini. J. Am. Chem. Soc. 106, 6424 (1984).
11. This experiment was first carried out by Dr. W.H. Pearson.

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