HETEROCYCLES, Vol. 6, Nos. 9, 10, 1977

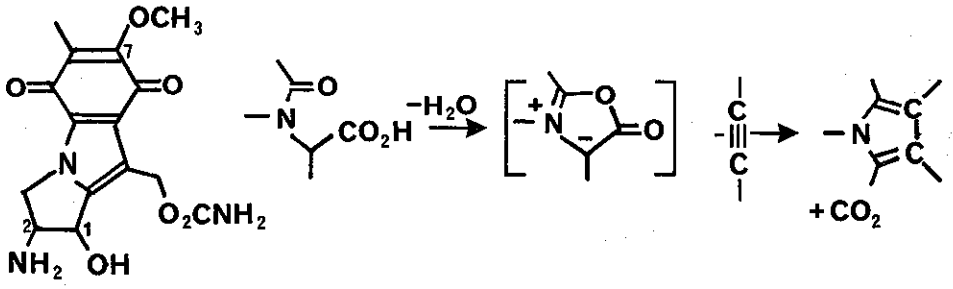
PROGRESS ON THE SYNTHESIS OF MITOSENES

Julius Rebek and Jean-Claude Gehret

Department of Chemistry, University of Pittsburgh

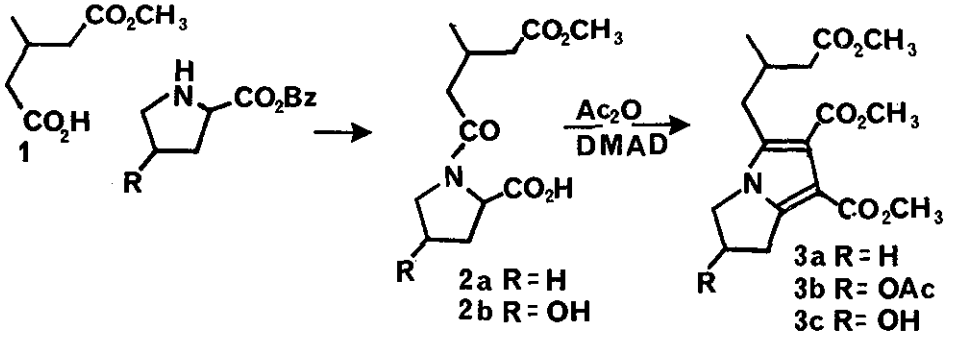
Pittsburgh, Pennsylvania 15260

Chemical degredation of the mitomycins with dilute acids yields a family of compounds known as mitosenes.[1] These substances have become attractive synthetic targets since they retain some of the antibacterial and antineoplastic activity of the mitomycins.[2] We have devised a rapid construction of the ring system based on Huisgen's facile pyrrole synthesis[3] from münchnones. These mesionic structures, generated by dehydration of acylamino acids, participate in 1,3 dipolar additions with acetylenes then extrude CO_2 to form pyrroles.

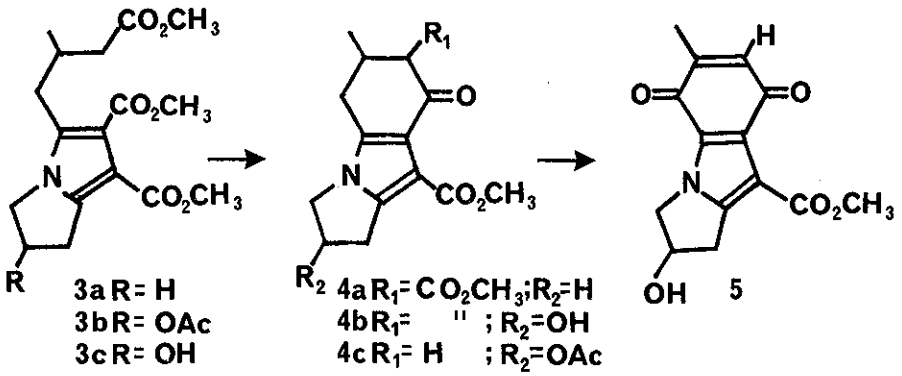


The generality of this pyrrole synthesis suggested that acyl (glutaric derivative 1), amino acid (proline) and acetylene (dimethyl acetylene dicarboxylate, DMAD) could be selected in such a manner that assembly of the remaining rings would be easily accomplished.[4]

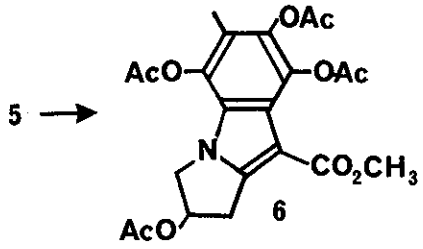
Consequently, 1 was condensed with proline benzyl ester (mixed anhydride, carbodiimide or acid chloride procedures) then hydrogenated (Pd/C) to give the acid 2, characterized as its DCHA salt. A solution of 2 in Ac_2O containing 1.5 eq. DMAD released the expected quantity of CO_2 within 2 hrs and gave, after evaporation of the volatiles, the crystalline triester 3a. The overall yields from proline were consistently 80-85%. A parallel series of reactions, using hydroxy proline as starting material gave the mixture of diastereomers 3b, (70% overall) from which one isomer was obtained in crystalline form.



Dieckmann cyclization of 3a proceeded without event (KH/THF 25°) to yield the tricyclic diester 4a in 80% yield. The availability of this material in quantity lured us into model studies aimed at the oxidation of the 6-ring to its required hydroxyquinone level, however, several attempts to replace the carbomethoxy group of the keto ester with oxidized nitrogen functions were thwarted by ring opening reactions. For example, coupling[5] of 4a with benzene diazonium fluoborate gave the azo compound, but this substance, on treatment with NaOMe, cleaved at the ketone carbonyl despite the latter's low (<1700 cm^{-1}) ir stretching frequency.



These difficulties led us to examine more reliable, if lengthier, methods for the oxidation procedures. Meanwhile, considerable experimentation had been required to effect the Dieckmann cyclization of the pyrrole derived from hydroxy proline. Only low (35%) yields of crystalline 4b were obtained from 3c on KOtBu/THF treatment, even though nmr showed the mother liquors to be rich in tricyclic products (probably diastereomers). Careful saponification, then re-esterification (CH_2N_2) and acetylation of the partially purified Dieckmann product gave the ketone 4c in 50% overall yield from 3b. Oxidation (DDQ) gave the phenol, which on deacylation (K_2CO_3/MeOH) and exposure to excess Fremy's salt yielded the orange, crystalline quinone in >90% yield from 4c. We have successfully performed Thiele acylation (Ac_2O/H_2SO_4) of the quinone at this writing, and are optimistic that the tetraacetate 6 shall provide us access to the mitosenes.



Acknowledgement

We thank the A. P. Sloan Foundation for support of this research.

References

1) Nomenclature for these substances is provided by J. S. Webb, et al , J. Amer. Chem. Soc., 84, 3185 (1962). The structure shown is derived from mitomycin A and is 1-hydroxy-2-amino-7-methoxy mitosene.

2) For biological activity of the mitosenes and other syntheses see W. G. Taylor, G. Leadbetter, D. L. Fost and W. A. Remers, J. Med. Chem., 20, 138 (1977) and references cited therein.

3) R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schafer, Chem. Ber., 103, 2611 (1970).

4) A practically identical selection has been described: F. M. Hershenson, J. Org. Chem., 40, 1260 (1975).

5) Organic Reactions, Vol. X, Chapt. 1 & 2, J. Wiley, New York, 1959.