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A MANNICH-LIKE APPROACH TO NAPHTHYRIDINOMYCIN

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Summary: A concise route to a potential tetracyclic precursor of the title compound is described. The key step is the intramolecular interpolation of a formyl equivalent between an N-methyl group and a carbon atom α-to a ketone.

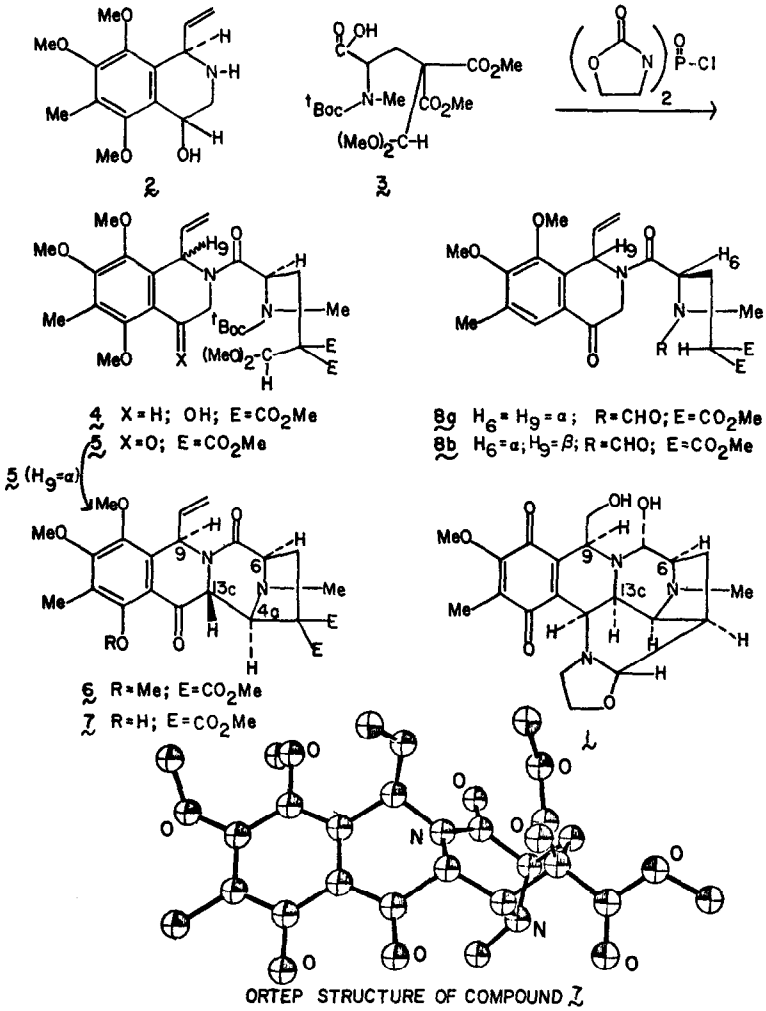
In the preceding Letter[1] we described the synthesis of the tetrahydroisoquinolinol, **2**, and the carboxyglutamyl derivative, **3**. The results of explorations of using these compounds in a projected synthesis of naphthyridinomycin (**1**)[2] are described herein.

The only effective method which we could find for establishing the amide bond was that of Palomo-Coll.[3] The crude acylation product, presumed to be **4**, was oxidized with Collins reagent to afford a 57% overall yield of **5**. Since two racemates were coupled it seemed likely[4] that ketoamide **5** was in fact a mixture of diastereomers. A chloroform solution of **5** was treated with excess borontrifluoride etherate and heated under reflux. Chromatography on silica gel allowed for the isolation of two homogeneous products. A tetracyclic product, mp 131-133°, was isolated in ca. 30% yield (i.e. ca. 60% of theory assuming that **5** is, in fact, a 1:1 mixture).

A second product, obtained in lower and variable yield, is the N-formyl compound **8b** (vide infra). Thus, the two components of the mixture **5** undergo strikingly different reactions. **Only the one in which the relative configurations at C_9 and C_6 correspond to that of naphthyridinomycin leads to tetracyclic product.**

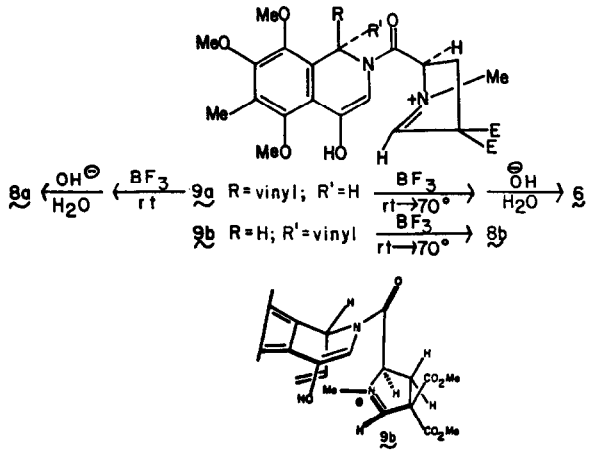
The stereochemistry of the tetracyclic product was undetermined at this stage. Upon treatment with BBr_3 in methylene chloride, it underwent clean conversion to phenol **7**, mp 175-176°, whose structure was established by an X-ray crystallographic determination.[5] The ORTEP drawing of **7**, shown below, reveals that the relative configurations at C_9 and C_6 (and C_{4a}) are those required for **1**, but that the configuration at C_{13c} is epimeric with that of the natural product. The initial tetracyclic

product is, accordingly, established to be **6**.



It was of interest to probe the course of events in greater detail. Stereoisomer mixture **5**[4] was treated with borontrifluoride etherate in methylene chloride from -25° to room temperature, for 7 hours. These conditions were substantially the same as those described above, **except that there was no heating.** Aqueous workup afforded a product mixture which contained no tetracyclic product, **6.** Rather, it seemed to be comprised of the formyl transfer products **(8a** and **8b) from both stereoisomers.**[6] A reasonable interpretation of these events invokes the intermediacy of "imminium-enol" isomers

9a and **9b**. Stereoisomer **9a** does not react at room temperature, but does cyclize at some point between room temperature and 70° C to produce compound **6**. However, stereoisomer **9b** does not undergo cyclization even at the higher temperature. Qualitatively at least, the greater propensity for cyclization of **9a** relative to **9b** can be rationalized. The pre-cyclization conformer of **9b** would suffer from a very serious steric crowding between the α-disposed vinyl group and the imminium ring attacking the enol from its α-face (see picture below). This destabilizing feature is absent in the corresponding structure required to go from **9a**→**6**.[7]



A convergent scheme leading to intermediate **6**, which corresponds to a significant subsection of the target system, **1**, has thus been developed. Of course, to reach the intended final goal, it would be necessary to achieve inversion of stereochemistry at C_{13c}. Studies bearing on this possibility will be described in due course.

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References

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2. K. Kluepfel, H.A. Baker, G. Piattoni, S.N. Sehgal, A. Sidorowicz, K. Singh, C. Vezing. J. Antibiot. 28, 497 (1975).
3. J. Cabre-Castellvi, A. Palomo-Coll, A.C. Palomo-Coll. Synthesis. 616 (1981).
4. Nmr analysis of the situation at this point was severely complicated by the multiplicities arising from amide rotamers. Only at the stage of compounds **6** and **7** were the nmr spectra helpful. The nmr spectra of the formyl transfer products **8a** and **8b** were complicated for the same reason.
5. The X-ray determination was carried out in Rahway. The refinement was to an unweighted residual of 0.070. Fractional coordinates, bond distances and bond angles are available from the Ph.D. *Dissertation of B.T. O'Neill, Yale University (1984).*
6. The conversion of the hypothetical **9** structures to compounds **8a** and **8b** would involve hydration of the imminium linkage, followed by retro-aldol cleavage of the carbon-carbon bond leading to the malonate. Thus, compound **8** could be the kinetically-derived product of aqueous workup of **9** or might be produced by a subsequent C→N transfer of a formyl malonate system.
7. The observed stereochemical outcome at C_{13c} may be rationalized. The imminium electrophile attacks the enol linkage in **9** from its axial face. Therefore, at the stage of cyclization, the B:C system is generated as in the "cis quinolizidone" sense. In the epimer wherein the C_{13c} hydrogen would be α, a very severe interaction between the endo ester and the concave face of the "cisoid" bicyclic system would result. In the observed product **6**, the ethano bridge emerges on the convex and less kindered face of this "cisoid" system.

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