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APPROACHES TO THE ISOQUINOLINE QUINONE ANTIBIOTICS.[1]

ADDITIONS OF AN AMINO ACID DERIVATIVE TO A QUINONE MONOACETAL.

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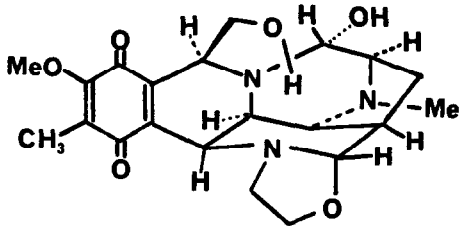
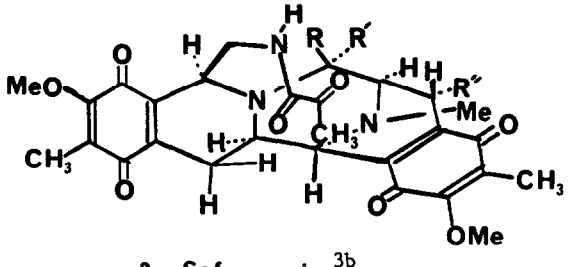
The addition of the benzylidine derivative of ethyl glycine to the enone system of a quinone monoacetal and subsequent aromatization provide a high yield preparation of intermediates for the synthesis of isoquinoline quinones.

The novel and diverse structures of the dimeric isoquinoline quinone antibiotics,[2,3] e.g., naphthyridinomycin (1)[3a] and the saframycins (2),[3b] invite the chemist to explore general approaches to their construction.[4]

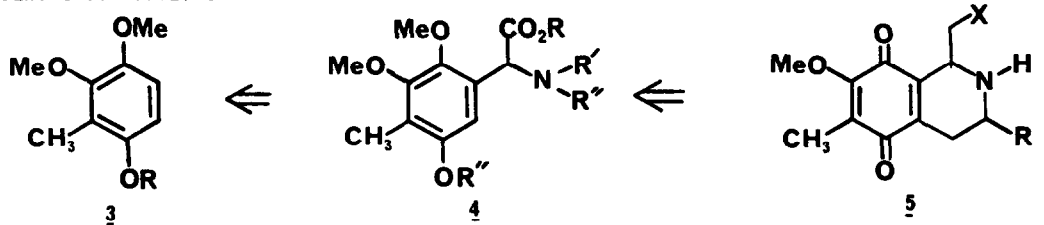


1, Naphthyridinomycin



2, Saframycins[3b]

Our strategy for building these molecules (Scheme I) begins with the regiospecific nucleophilic aromatic substitution[5] of a simple benzene derivative 3 to afford the substituted phenylglycine derivative 4 followed by elaboration of the tetrahydroisoquinoline system.[6] We have investigated the first conversion in this sequence and are pleased to report the facile synthesis of 13 (4, R=Et, R'=H, R''=COC_6H_5), as well as a fortuitous synthesis of an isoindole quinone derivative.

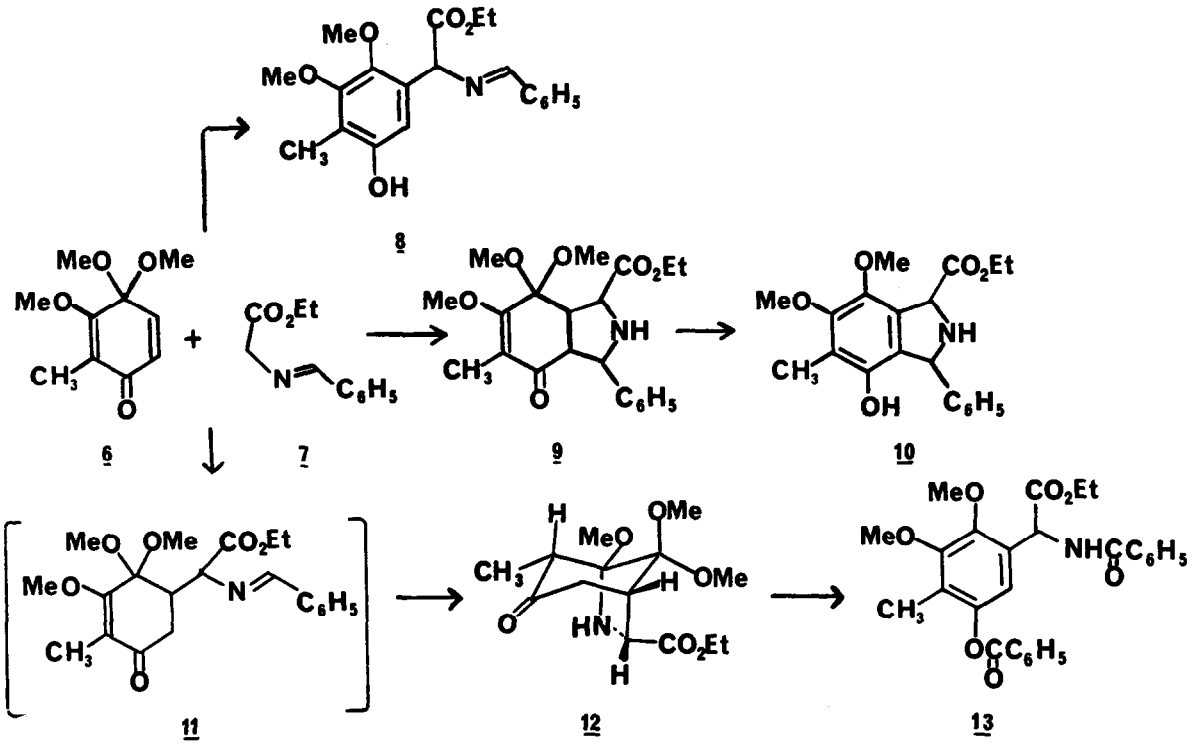


3 4 5

SCHEME I

The required starting material, quinone monacetal 6, is readily available in multigram quantities from 1,2,4-trimethoxy-3-methylbenzene (3, R=CH_3)[7] by Swenton's electrochemical oxidation sequence.[8]

The course of the addition of N-benzylidene glycine ethyl ester (7)[9] to this material was found to be markedly dependent on experimental conditions (Scheme II).



SCHEME II

Treatment of 6 with 7 in ethanol containing a catalytic amount of sodium ethoxide resulted in a complex mixture from which a low (5%, 2 steps) yield of the unstable phenol 8[10] could be isolated after acid treatment and chromatography.

When quinone monoketal 6 was treated with 7 in the presence of 1 equivalent of sodium hydride and excess 15-crown-5 in tetrahydrofuran, a rapid exothermic reaction took place. Isoindole 9 was isolated in 45% yield as a mixture of diastereomers.[10,11]

Aromatization of 9 with p-toluenesulfonic acid in refluxing benzene afforded phenol 10 as a single diastereomer (48%; stereochemistry not assigned)[10].

Reaction of 6 with 7 could be effected by a suspension of potassium t-butoxide in tetrahydrofuran at low temperature. The reaction mixture appears to contain the simple adduct 11 and the two starting materials. We were unable to purify 11; however, treatment of the crude reaction mixture with ammonium chloride in aqueous tetrahydrofuran results in a clean conversion to the stable, crystalline, bicyclo adduct 12.[12] Thus, removal of the hydrolytically labile benzylidene group from 11 allows a second, intramolecular Michael reaction to occur.[13] In an alternative procedure, ammonium chloride quench of the Michael reaction provided 12 directly in excellent yield (91% from 6).

The relative stereochemistry depicted in 12 was confirmed by a single crystal X-ray structure determination (Figure 1).[14]

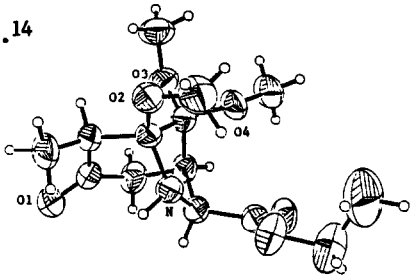


Figure 1

When compound 12 is heated with excess benzoyl chloride in dry pyridine for several hours, aromatized and derivatized 13[12] is formed in 85% yield. Studies on the conversion of 13 to synthetically useful tetrahydroisoquinolines are currently in progress.

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   (b) This work was presented at the 187th National Meeting of the American Chemical Society, April, 1984, St. Louis, MO.

2. The "monomeric" isoquinoline quinones have been prepared.
   (a) mimosamycin:
   Mishima, H., Fukumi, H., Kurihara, H., Heterocycles, 1977, 6, 1652. Fukumi, H., Kurihara, H., Mishima, H. Chem. Pharm. Bull., 1978, 26, 2175.
   (b) mimocin:
   Kubo, A., Nakahara, S., Iwata, R., Takahashi, K., Arai, T., Tetrahedron Lett., 1980, 21, 3207.
   (c) renierone
   Danishefsky, S., Berman, E., Cvetovich, R., Minamikawa, J., Tetrahedron Lett., 1980, 4819.

3. Leading references
(a) Naphthyridinomycin: Sygusch, J., Brisse, F., Hanessian, S., Kluepfel, D., Tetrahedron Lett., 1974, 4021; errata, 1975, no. 3. Kluepfel, D., Baker, H.A., Piattoni, G., Sehgal, S.N., Sidorowicz, A., Singh, K., Vezina, C., J. Antibiot., 1975, 28, 497.
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(b) Saframycins. A: R,R'=H,CN; R''=H. B: R,R',R''=H. C: R,R''=H; R'=OMe. S: R,R'=H,OH; R''=H. Arai, T., Takashi, K., Kubo, A. J. Antibiot., 1977, 30, 1015; Arai, T., Takahashi, K., Kubo, A., Nakahara, S., Sato, S., Aiba, K., Tamura, C., Tetrahedron Lett., 1979, 2355; Arai, T., Takahashi, K., Nakahara, S., Kubo, A., Experientia, 1980, 36, 1025; Arai, T., Takahashi, K., Ishiguro, K., Yazawa, K., J. Antibiot., 1980, 33, 951. Ishiguro, K., Takahashi, K., Yazawa, K., Sakiyama, S., Arai, T., J. Biol. Chem., 1981, 256, 2162. Ishiguro, K., Sakayama, S., Takahari, K., Arai, T., Biochem., 1978, 17, 2545.
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(e) Safracins: Ikeda, Y., Matsuki, H., Ogawa, T., Munakata, T., J. Antibiot., 1983, 36, 1284. Ikeda, Y. Shimada, Y., Honjo, K., Okumoto, T., Munakata, T., J. Antibiot., 1983, 36, 1290.

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10. Characterization: IR, ^{1}H NMR, MS, exact mass.

11. This transformation is reminiscent of the cycloaddition reactions of arylidene imines of amino acids with unsaturated esters and nitriles; see Grigg, R., Gunaratne, H. Q. N., J. Chem. Soc., Chem. Commun., 1982, 384 and Grigg, R., Kemp, J., Sheldrick, G., Trotter, J., J. Chem. Soc., Chem. Commun., 1978, 109. Also see Gilgen, P., Jackson, B., Hansen, H. J., Heimgartner, H., and Schmid, H., Helv. Chim. Acta, 1974, 57, 2634 and Myers, J.A., Moore, L.D., Whitter, W.L., Council, S.L., Waldo, R.M., Lanier, J.L., Omoji, B.U., J. Org. Chem., 1980, 45, 1202.

12. Characterization: IR, ^{1}H NMR, MS, elemental analysis.

13. Similar bicyclic compounds arise from related Michael adducts, see reference 5 above.

14. We thank Professor Paul G. Williard (Brown University) for performing this structure determination.

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