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AN APPROACH TO VERSATILE INTERMEDIATES IN THE SYNTHESIS OF ANTHRACYCLINONE AGLYCONE ANALOGS

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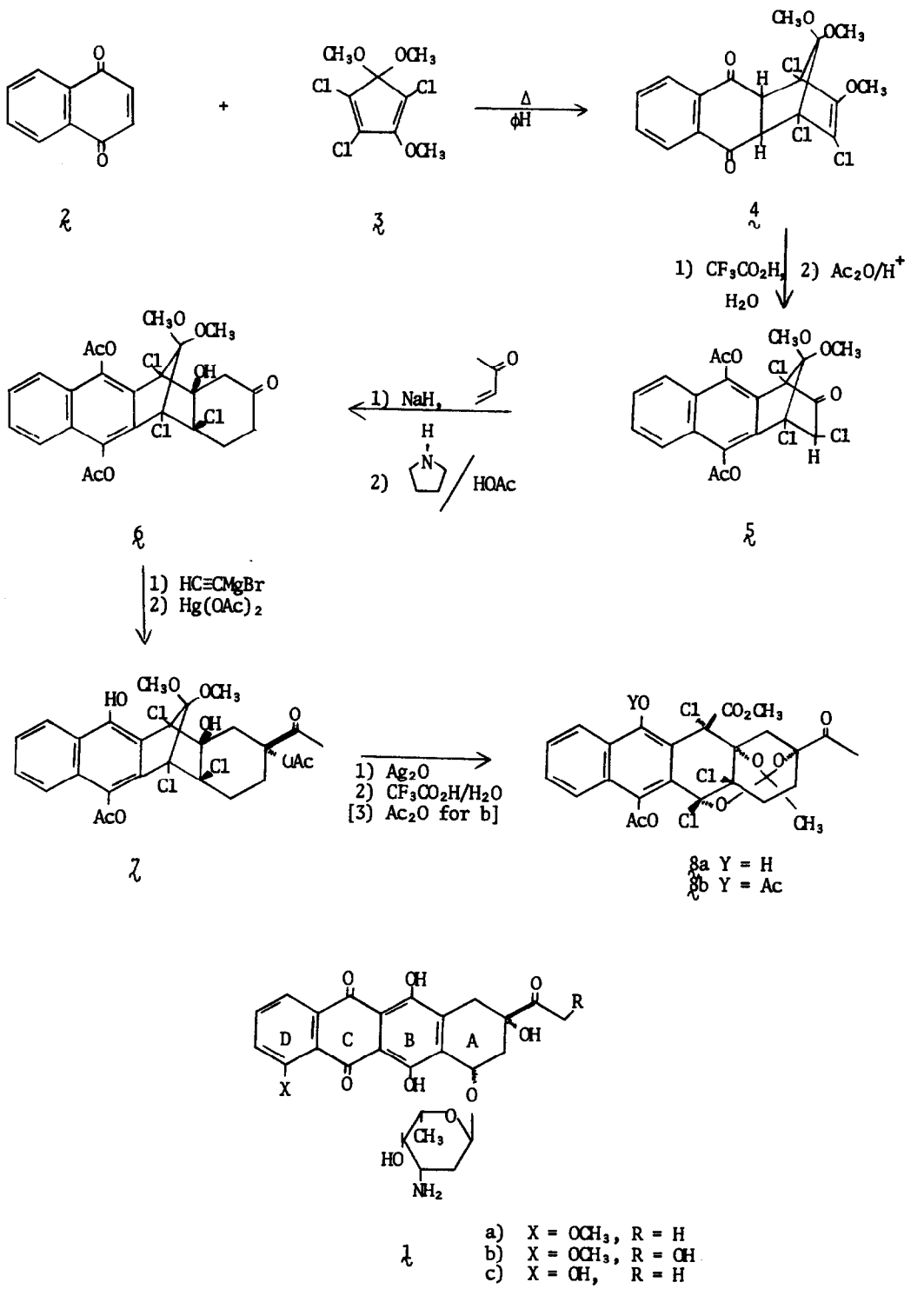
Daunorubicin,[1] adriamycin[2] and carminomycin[3] (1a-c) are powerful antitumor anthracyclines having very similar molecular structures. These broad spectrum anticancer agents[4] are presently prepared by microbiological fermentation methods but the yields of these reactions are very low thus making these drugs rather inaccessible and costly.[5] The need for a good chemical synthesis is apparent and recently several partial approaches to these problems have appeared.[6] These procedures have exclusively focused on the preparation of the aglycone (anthracyclinone) portion of the molecule, with the synthesis of the sugar (daunosamine) portion[7] and the coupling[8] of this sugar to the aglycone having been accomplished previously. None of these procedures has been aimed at the preparation of the aglycone analogs and thus we had planned to develop a route that could be used to prepare the parent compounds as well as analogs of these materials. As it turned out, the route developed into a potentially general synthesis of anthracyclinone and/or tetracycline type structures and we, therefore, present our preliminary results at this time.

The basic route that we have developed has enough flexibility so that 1) tetracyclic structures can be constructed easily and rapidly from readily available materials; 2) substituents on the tetracyclic structure can potentially be varied in a systematic and regiospecific fashion; and 3) all the rings of the tetracyclic structure can theoretically be altered in part or whole with few modifications in the general sequence. The route is shown in Scheme I for the specific example starting with naphthoquinone but in principle other quinones can be utilized.

The Diels-Alder reaction of naphthoquinone, 2, with 1,1,3-trimethoxy-2,4,5-trichlorocyclopentadiene,[9] 3, in refluxing benzene or xylene proceeded in better than 80% yield to produce the desired 4[10] (mp = 196-8°; NMR δ: 7.95 (m), 4H; 3.8 (s), 2H; 3.65 (s), 3H; 3.55 (s), 3H; 3.40 (s), 3H) Hydrolysis of 4 in CF_3CO_2H, with at least 1 equiv. of H_2O present, yielded an intermediate hydroquinone[10] in 80% yield (mp = 213-5°; NMR δ: 8.0 (m), 6H; 5.2 (s), 1H; 3.8 (s), 3H; 3.6 (s), 3H) which was quantitatively acetylated with acetic anhydride and a catalytic amount of H_2SO_4 to produce 5[10] (mp = 158-9°; NMR δ: 7.9 (m), 4H; 4.8 (s), 1H; 3.7 (s), 3H; 3.6 (s), 3H; 2.5 (s), 6H) Removal of the α-chloroketo proton with NaH in dry benzene and subsequent reaction with methyl vinyl ketone yielded an intermediate adduct[10] in 70% yield (mp = 212-4°; NMR δ: 7.9 (m), 4H; 3.7 (s), 3H; 3.5 (s), 3H; 2.9 (m), 4H; 2.55 (s), 3H; 2.50 (s), 3H; 2.15 (s), 3H) which could be condensed intramolecularly with pyrrolidine in glacial acetic acid to produce 6[10] in >90% yield (mp = 258° (d); NMR δ: 7.8 (m), 4H; 3.7 (s), 3H; 3.4 (s), 3H; 3.2 (m), 2H; 2.9 (s), 2H; 2.7 (m), 2H; 2.55 (s), 3H; 2.45 (s), 3H). Addition of ethynyl magnesium bromide to 6 resulted in a monoacetylated hydroquinone ethynyl derivative[10] in 70% yield (mp = 250-2°; NMR δ: 8.4 (m), 1H; 7.7 (m), 3H; 7.0 (s), 1H; 3.7 (s), 3H; 3.4 (s), 3H; 2.8 to 1.9 (m), 8H; 2.5 (s), 1H; 2.4 (s), 3H) which was hydrated and acetylated with mercuric acetate in ethyl acetate to produce 7[10] in 85% yield (mp = 180° (d); NMR δ: 8.3 (m), 1H; 7.6 (m), 3H; 7.1 (s), 1H; 3.8 (s), 3H; 3.5 (s), 3H;

Scheme I



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a) X = OCH_3, R = H
b) X = OCH_3, R = OH
c) X = OH, R = H

2.9-2.1 (m), 7H; 2.5 (s), 3H; 2.2 (s), 3H; 2.1 (s), 3H). Oxidation of 7 with Ag_2O in acetone produced a naphthoquinone[10] in 90% yield (mp = 149-51°; NMR δ: 8.5 (m), 1H; 7.6 (m), 3H; 3.7 (s), 3H; 2.8-1.9 (m), 7H; 2.4 (s), 3H; 2.1 (s), 3H; U.V. λ max = 410 nm) which could be hydrolyzed with aqueous trifluoroacetic acid to the tetracyclic structure, 8a[10] in 45% yield (mp = 234-5°; NMR δ: 8.3 (m), 1H; 7.6 (m), 3H; 7.2 (s), 1H; 3.8 (s), 3H; 2.8 (m), 3H; 2.6 (s), 4H; 2.4 (s), 4H; 2.1 (s), 3H; 1.9 (m), 1H; U.V. λ max = 260, 293, 305, 315 and 330 nm; mass spec. m/e: 584, 542, 482 and 455; I.R. ν: 3500, 1760, 1740 and 1735.) Other compounds of unknown structure are also obtained in this last reaction. They appear to be more highly aromatized tetracyclic structures, possibly derived from the hydrolyzed product of 8a. If 8a is treated with acetic anhydride and trifluoroacetic acid, 8b is obtained in quantitative yield. This diacetate is highly crystalline and a crystal structure is planned to substantiate the stereochemistry and positioning of the various functionalities.

The identity of the orthoacetate functionality[11] in 8 was proven in conjunction with CMR, LIS-NMR, high resolution mass spectra and model building. It is obvious from the models that the molecule is concave and the orthoacetate methyl group is thus in close proximity to the aromatic ring. This is apparently the reason for the low field resonance, δ 2.4, of these protons, as well as the decreased hydrolytic sensitivity of this functionality.[12]

The sequence outlined in Scheme I is a convenient one as readily available materials are used and the stereochemistry at each step is known. Potential modifications of the sequence are easily envisioned as taking place through the key intermediate 8. These modifications can take two forms: 1) Preparations of anthracyclinone analogs having altered substitution patterns in rings A, B or D; and 2) Syntheses of tetracycline derivatives having a variety of substituents in rings A, B or C. Conversion of 8 to the anthracyclinone natural products and their analogs is now in progress and these will be reported at a later date.

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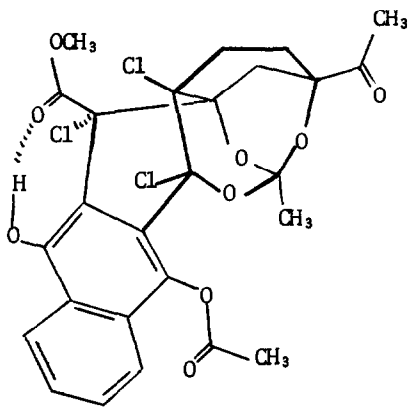

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