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PREPARATION OF SOME NOVEL RIFAMYCINS BY A FACILE INTRAMOLECULAR DEHYDRATION

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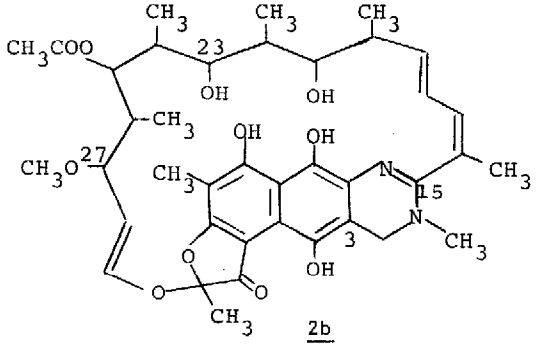
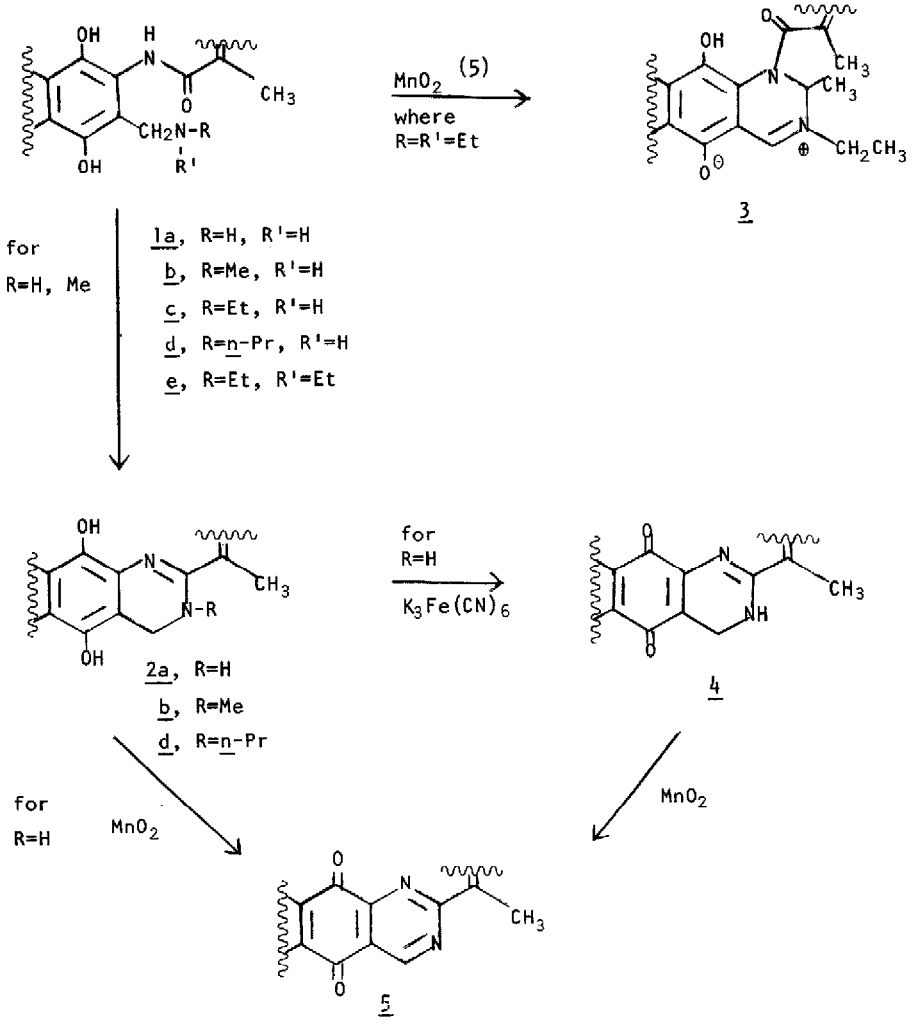
Recently, 3-alkylaminomethylrifamycins have attracted the attention of biologists because of the ability of certain derivatives in this series to interrupt oncornavirus replication in infected 3T3 cell cultures.[1] In the course of developing a synthetic procedure[2] suitable for obtaining gram quantities of some of these derivatives[3] for in vivo testing, we observed that 3-methylaminomethylrifamycin SV (1b)[2] was quantitatively transformed into a new crystalline material (crystallized from MeOH) on standing several days in chloroform at room temperature. The transformation of 1b can be effected in 15 hours at room temperature with a catalytic amount of glacial acetic acid. The structure assigned this new rifamycin, on the basis of spectral and chemical evidence, is N,15-didehydro-15-deoxo-3,15-epi(methano(methylimino))-rifamycin SV (2b).[4] This finding represents the second example of anomalous chemistry of the amide moiety of the rifamycin molecule. Maggi, Gallo, and Vigevani[5] isolated a zwitterionic dihydroquinazolinium rifamycin (3) from a MnO_2 oxidation of 3-diethylaminomethylrifamycin SV (1e).



2b

Comparison of the ir, pmr, and uv-visible spectra of 1b with 2b confirms the structure of the dihydropyrimidine 2b. The uv-visible absorption spectrum of 1b shows maxima at the same values as for known rifamycin Mannich bases[1] [λ (MeOH) (max) 447 (ε 13,350) and 314 (ε 17,400)]. However, the uv-visible spectrum of 2b is quite different and characteristic for this series,

namely, λ (MeOH) (max) 457 (ε 16,200), 374 (ε 9,400), 317 (ε 16,600), 282 (ε 12,600) and 271 (ε 12,700) nm, indicating that the chromophoric portion of the molecule has been altered. The ir (Nujol) of the dihydropyrimidine 2b shows the absence of both the amide and amino NH bands, which appear as sharp spikes at 3300 and 3135 cm^{-1} in amine 1b. The pmr spectrum (90 MHz, $CDCl_3$) of 3-methylaminomethylrifamycin SV (1b) has a broad singlet at δ 8.2, indicative of an amide NH, which is absent in the pmr spectrum of 2b.



Additional proof for the structural assignment of the cyclic rifamycin 2b comes from the transformation of 3-aminomethylrifamycin SV (1a)[3] into a new product, 2a, and the subsequent transformation of 2a into the pyrimidinorifamycin 5. The cyclization of 1a to dihydropyrimidine 2a does not proceed as readily as did the cyclization of 1b to 2b. It requires two days in refluxing 1,2-dichloroethane in the presence of a catalytic amount of glacial acetic acid. The product 2a (from MeOH when very pure) has the same uv-visible spectrum as 2b. Oxidation

of 2a to the quinone 4 was accomplished with potassium ferricyanide. Compound 4 was isolated as fine green crystals from ether, λ (MeOH) (max 439 (ε 8,000), 375 (ε 7,300), 303 sh (ε 14,100), and 272 (ε 7,400) nm. The pmr spectrum ($CDCl_3$) of 4 exhibited a well defined AB-system centered at δ 4.7 (J_{AB} = 19 Hz, Δν=67 Hz at 90 MHz[7]) corresponding to the two methylene protons adjacent to the 3 position. Treatment of the quinone 4 or hydroquinone 2a with activated manganese dioxide[8] in refluxing methanol for three hours gave N,1,4,15-tetradehydro-1,4,15-trideoxy-1,4-dihydro-1,4-dioxopyrimidino(4,5-b)rifamycin SV (5), (75%, from ether) λ (MeOH) (max) 410 (ε 7,400), 280 (ε 20,700), 265 (ε 20,600) nm. The pmr spectrum ($CDCl_3$) exhibited a sharp singlet at δ 9.50 corresponding to the aromatic pyrimidine proton.

Attempts to cyclize 3-ethylaminomethylrifamycin S (1c)[3] and the corresponding n-propyl analog (1d) were unsuccessful. Problems were encountered because of concomitant acid catalyzed loss of the 27-methoxy group and formation of a tetrahydropyran ring, between the 23 and 27 positions on the ansa chain. However, a small quantity of the cyclic propyl analog (2d), mp 184-7° (dec) (from EtOAc) λ (MeOH) (max) 454 (ε 17,000), 375 (ε 8,600), 316 (ε 17,700), 281 (ε 13,650), and 268 (ε 13,800) nm, was isolated from the reductive amination of rifaldehyde using Borch's reagent[9] and n-propylamine when the reaction was allowed to proceed 25 days at room temperature. Additional anomalous chemistry at the 15-amido position in rifamycins will be reported elsewhere.

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