Methodology for the Synthesis of the Spiro[4.4]nonane System: An Approach for the Total Synthesis of Fredericamycin A

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A convenient approach for building the spiro[4.4]nonane system present in fredericamycin A, an antitumour antibiotic, is described and the *X*-ray crystal structure presented.

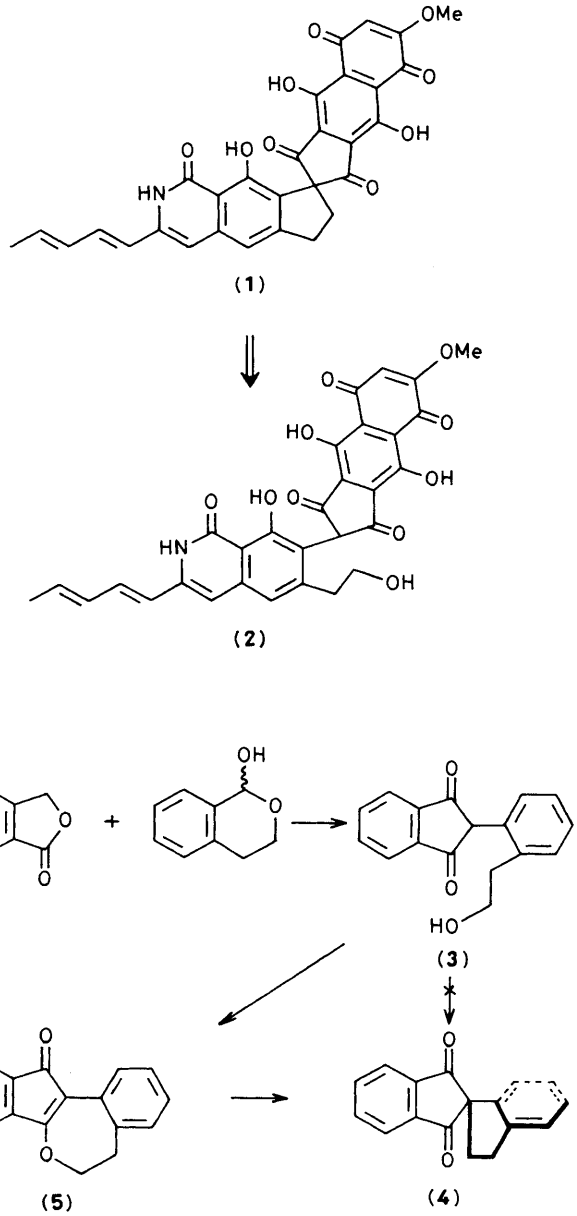
Fredericamycin A (**1**),[1] an antitumour antibiotic produced by *Streptomyces griseus*, possesses an entirely novel spiro[4.4]nonane system which has not been observed in any other types of antibiotics. It has certain interesting spacial characteristics (the two aromatic portions are nearly at right angles to each other) which may be important in determining its biological activity. We have recently undertaken the total synthesis of fredericamycin A and completed the general methodology for building the spiro[4.4]nonane system.

Synthetic analysis of (**1**) suggests that it can be made first by obtaining (**2**) and then by building the spiro system. This strategy was utilised by making 2-[2-(hydroxyethyl)-phenyl]indan-1,3-dione (**3**), *cf.* (**2**), and converting it into (**4**), *cf.* (**1**).

Dieckmann condensation[2] of phthalide with 1-hydroxy-isochroman[3] [*o*-(2-hydroxyethyl)benzaldehyde] in the presence of sodium methoxide in methanol as base and ethyl propionate as scavenger afforded (**3**),† [65% yield, pale yellow crystals, m.p. 101—103 °C; i.r. (Nujol): 1718 (C=O), 1750 (C=O), and 3540 cm^{-1} (OH); ^1H n.m.r. δ($CDCl_3$), 2.3 (br. s, 1H, D_2O exchangeable), 3.0 (t, 2H, *J* 7 Hz, $ArCH_2$), 3.90 (t, 2H, *J* 7 Hz, $-CH_2O$), 4.75 (s, 1H, –CH), 6.6—6.8 (m, 1H, ArH), 7.0—7.4 (m, 3H, ArH), and 7.8—8.1 (m, 4H, ArH); ^{13}C n.m.r. δ($CDCl_3$), 199.3 (2C), 143.2 (2C), 139.4, 136.2 (2C), 133.3, 131.0, 128.6, 128.4, 127.3, 124.0 (2C), 63.7, 57.8, and 36.9; *m/z* 266].

Our attempts to convert (**3**) into the spiro system (**4**) *via* the corresponding bromo (PBr_3–CH_2Cl_2–room temp.) or tosyl derivative (Na_2CO_3–toluene-*p*-sulphonyl chloride) resulted mostly in the formation of 5,6-dihydro-12*H*-benz[*d*]indeno[1,2-*b*]oxepin-12-one (**5**)‡ and no detectable amounts of (**4**). This seems to be the first report of the preparation of the oxepine ring system (**5**). The conversion of (**3**) into (**5**) appears to be rapid and can be best obtained by treating (**3**) with a catalytic amount of toluene-*p*-sulphonic acid in CH_2Cl_2 for 30 min at room temperature resulting in the exclusive formation of (**5**), [95% yield, bright orange crystals, m.p. 89—91 °C; i.r. (Nujol): 1707 (C=O), 1630 cm^{-1} (–C=C–O); ^1H n.m.r. δ($CDCl_3$), 3.15 (t, 2H, *J* 5 Hz, $ArCH_2$–), 4.65 (t, 2H, *J* 5 Hz, $-CH_2O$–), 7.0—7.5 (m, 7H, ArH), and 7.8—8.1 (m, 1H, ArH); ^{13}C n.m.r. δ($CDCl_3$), 194.1, 171.7, 140.0, 139.2, 132.9 (2C), 130.9, 130.3, 128.8, 128.6, 127.0, 126.4, 121.4, 118.8, 108.4, 73.6, and 37.9; *m/z* 248].

Since we could not convert (**3**) into (**4**) by usual chemical transformations, we resorted to the thermal isomerization of (**5**) to (**4**). Thus heating (**5**) to 290—300 °C for 5 h followed by crystallisation of the product from hexane furnished the spiro compound (**4**), (40% yield, colourless crystals, m.p. 131—133 °C). The i.r. spectrum of (**4**) shows, as expected, –C=O absorptions at 1755 and 1715 cm^{-1}, as in the 2-substituted indan-1,3-dione spectrum. The ^1H n.m.r. spectrum is also in agreement with the assigned structure (**4**), [δ($CDCl_3$), 2.50 (t, 2H, *J* 7.5 Hz, $-CH_2$–), 3.28 (t, 2H, *J* 7.5 Hz, $-CH_2$–), 6.5—6.7 (m, 1H, ArH), 6.8—7.4 (m, 3H, ArH), and 7.8—8.1 (m, 4H, ArH)]. Thus the two methylene groups are seen as triplets at 3.28 and 2.50 accounting for the benzylic $-CH_2$– and –C–CH_2– groups respectively. The corresponding values for the two methylene groups in fredericamycin A (**1**), are seen at 3.29 (t, *J* 7.5 Hz, $-CH_2$–) and 2.58 (t, *J* 7.5 Hz, $-CH_2$–). The ^{13}C



† All the new compounds showed spectral data consistent with the proposed structures and gave satisfactory elemental analyses.

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n.m.r. spectrum of (**4**) [δ($CDCl_3$), 201.5 (2C), 145.8, 142.9 (2C), 142.1, 130.2 (2C), 128.5, 127.0, 125.4, 124.1 (2C), 123.0, 68.2, 32.8, and 32.2] is also in agreement with the assigned structure. The formation of (**4**) from (**5**) would be concerted or biradical, although the latter may be preferred. We have thus demonstrated for the first time a novel approach for the construction of the spiro[4.4]nonane system present in fredericamycin A. This strategy is being pursued not only for the total synthesis of fredericamycin A but also for other simple analogues having the spiro system, to assess their antitumour activity.

An *X*-ray crystallographic determination of compound (**4**) indicated that the two aromatic portions are placed nearly at right angles to each other as in the case of fredericamycin A. The crystals of (**4**) belong to the space group $P2_1/n$ with a = 12.544(2), b = 7.507(1), c = 13.480(2) Å and β = 97.09(1)°. The intensity data (2219 reflections) were collected on a CAD4F-11M diffractometer with Mo-K_α radiation (λ = 0.7107 Å) using the ω/2θ scan technique. The structure was solved by direct methods. The refinement has resulted in a final R value of 0.052 for 651 reflections with $|F_o| > 3\sigma|F_o|$. Several interesting and noteworthy features of this *X*-ray crystal structure study will be detailed elsewhere.§

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