Synthesis of 2,5-Dihydroxy-3,6-bis-(2-hydroxybenzyl)pyrazine

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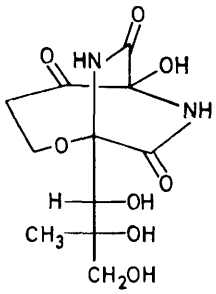
A short synthesis of the title compound, a model for investigating a proposed bicmimetic photo-oxygenation leading to a bicyclomycin analogue, is described. Photo-oxygenation studies proved to be impractical owing to the complete insolubility of this compound in appropriate solvents.

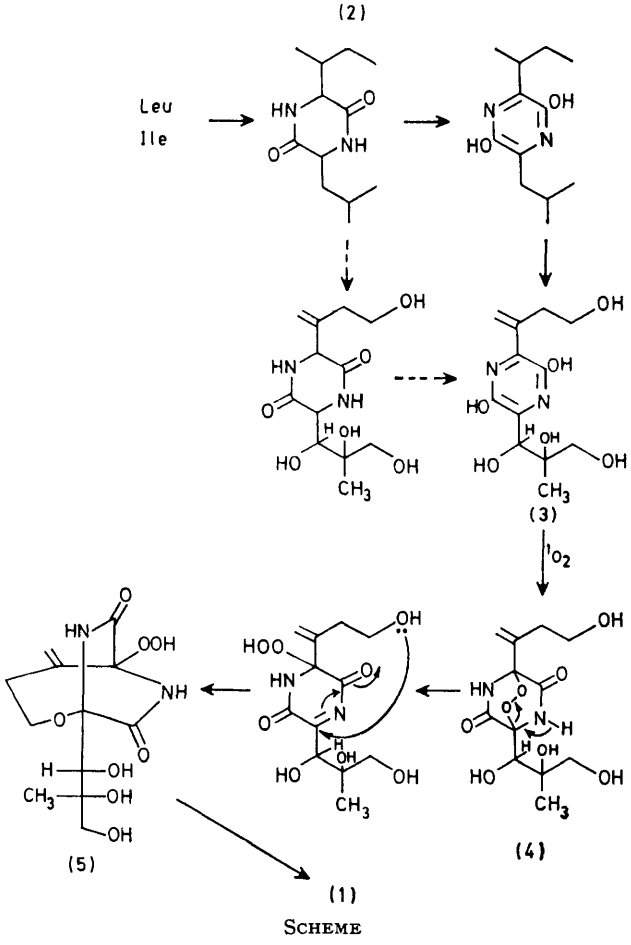
CONSIDERATION of the structure of the antibiotic [1] bicyclomycin (1) suggests that its biosynthesis proceeds by way of leucine and isoleucine, and preliminary feeding studies with the ^{14}C-labelled amino-acids [2] support this



(1)

view. Little is known concerning the subsequent stages, but precedent suggests [3] the initial formation of the dioxopiperazine *cyclo*(-Leu-Ile-) (2), followed by oxidation to the pyrazine (Scheme). Extensive oxidation of the side chains is then necessary to bring about the observed oxygenation pattern, and it would seem that a pyrazine such as (3) is probably involved in the late stages. 2,5-Dihydroxypyrazines are known [4,5] to undergo [4 + 2] cycloaddition reactions, and Sammes and Markham [6] have recently demonstrated that cycloaddition occurs with singlet oxygen to produce bicyclic peroxides, lending support to the involvement of intermediates such as (4). The conversion of (4) into bicyclomycin would then involve the expulsion of the peroxy-bridge, followed by cyclisation and reduction of the resultant hydroperoxide.

We were interested in the development of a model system to mimic the transformation of (3) through (4) to (5). Clearly an attempt to carry out such a transformation on a polyfunctional system such as (3), although possible *in vivo*, would prove impractical, and we therefore sought a simple model system with the inbuilt structural requirements to facilitate these transformations. The model which we chose was 2,5-dihydroxy-3,6-bis(2-hydroxybenzyl)pyrazine (6; X = OH, R = H), which meets three important criteria. First, its high symmetry should facilitate synthesis. This symmetry is important in that, regardless of the direction of ring opening of an oxygen-bridged intermediate such as (7), subsequent peroxide expulsion and recyclisation can only furnish a single product (8). Finally the phenolic



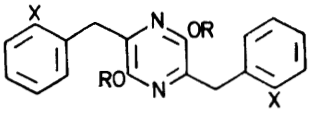
SCHEME

hydroxy-group was expected to be significantly more nucleophilic than the primary alcohol in *e.g.* (4); this would aid the cyclisation of (7) to (8).

Cyclodimerisation [7] of 2-hydroxyphenylalanine in refluxing ethylene glycol gave the dioxopiperazine (9; X = OH) in low but reproducible yields. The phenolic hydroxy-group was acetylated selectively by treatment with acetic anhydride in dry dimethyl sulphoxide in the presence of imidazole. Treatment of (9; X = OAc) with 4 equiv. of triethyloxonium tetrafluoroborate in dichloromethane gave the bis-imidate (10; X = OAc), which was oxidised [8] with dichlorodicyanobenzoquinone to (6; X = OAc, R = Et). In keeping with earlier observations,[8] the intermediates (9; X = OAc)

(9; X =OH), and (10; X = OAc) were mixtures of *cis*- and *trans*-diastereoisomers as evidenced by their n.m.r. spectra and t.l.c. behaviour.

The acetate (6; X = OAc, R = Et) was readily deacetylated with ethanolic KOH, but cleavage of the protecting ether groups proved difficult. Treatments with lithium iodide in collidine, refluxing aqueous



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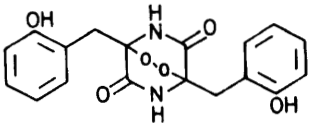

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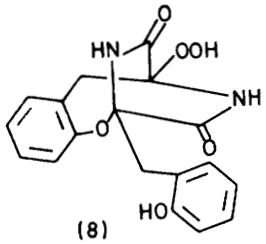

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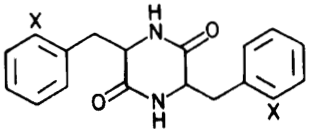

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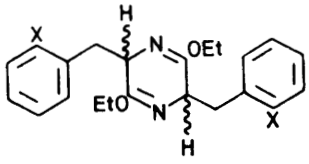

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hydrogen halides, boron tribromide, and iodotrimethylsilane [9] in dichloromethane failed, but cleavage was achieved by refluxing in neat iodotrimethylsilane.

The model compound (6; X = OH, R = H) proved virtually insoluble in all organic solvents tried. Proton n.m.r. spectra were obtained by use of trifluoroacetic acid, in which (6) is sparingly soluble. All attempts to prepare solutions of (6; X = OH, R = H) for photooxygenation studies failed.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 577, and ^{1}H n.m.r. spectra on a Perkin-Elmer R24 (60 MHz) or R32 (90 MHz) spectrometer.

3,6-*Bis*-(2-*hydroxybenzyl*)*piperazine*-2,5-*dione* (9; X = OH).—2-Hydroxyphenylalanine (210 g) suspended in ethylene glycol was refluxed for 18 h. The resulting suspension was filtered and the solid dried in a vacuum oven for 5 h at 100 °C. Recrystallisation from glacial acetic acid gave the *product* (41.7 g, 20%) as a colourless crystalline solid, m.p. 250—251 °C (decomp.); $\nu_{max.}$ (KBr) 3 500—2 800 and 1 690 cm^{-1}; δ [$(CD_3)_2SO$] 6.8 (8 H, m), 3.7 (2 H, m), and 2.9 (4 H, m) (Found: M^+, 326.1253. $C_{18}H_{18}N_2O_4$ requires M, 326.1267). T.l.c. in several solvent systems (ninhydrin as developing agent) showed the product to be an approximately 1 : 1 mixture of *cis*- and *trans*-diastereoisomers, R_f (butanol–acetic acid–water, 3 : 1 : 1) 0.7 and 0.77.

Acetylation of the Bis-phenol (9; X = OH).—The bisphenol (1.51 g) and imidazole (50 mg) were suspended in dry dimethyl sulphoxide (5 ml), acetic anhydride (10 ml) was added, and the mixture was stirred at room temperature for 18 h. After 2.5 h a clear solution was obtained, but slow precipitation of the product occurred over the remaining 15 h. Dry ether (200 ml) was added and the mixture was stored at −15 °C for 6 h. The resulting precipitate was filtered off, washed with dry ether, and air dried. The dried product was dissolved in refluxing methanol (100 ml) and the filtered solution was kept at −15 °C for 3 days. The resulting white crystalline solid was filtered off, washed with ether, and dried at 100 °C (KOH) at 1.0 Torr to yield the *acetate* (9; X = OAc) (1.21 g, 60%), m.p. (sealed tube) 211—217 °C; $\nu_{max.}$ (KBr) 3 500—2 800br, 1 750, and 1 690 cm^{-1}; δ [$(CD_3)_2SO$] 7.1 (8 H, m), 3.5 (2 H, m), 2.8 (4 H, m), and 2.2 (6 H, s) (Found: C, 64.2; H, 5.3; N, 6.8. $C_{22}H_{22}N_2O_6$ requires C, 64.4; H, 5.4; N, 6.8%). T.l.c. ($CDCl_3$–MeOH, 9 : 1) R_f 0.2 and 0.3 (diastereoisomers).

2,5-*Bis*-(2-*acetoxybenzyl*)-3,6-*diethoxy*-2,5-*dihydropyrazine* (10; X = OAc).—The acetylated dioxopiperazine (9; X = OAc) (0.386 g) was suspended in dry dichloromethane (5 ml) and stirred during the addition of triethyloxonium tetrafluoroborate (0.38 g) in dry CH_2Cl_2 (5 ml). The mixture was stirred at room temperature overnight, then more triethyloxonium tetrafluoroborate (0.38 g) was added and the mixture was stirred for a further 24 h, then poured onto saturated aqueous $NaHCO_3$ (10 ml). The dichloromethane phase was separated, the aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried ($MgSO_4$), filtered, and evaporated to yield the crude *product* (0.405 g, 87%), which was crystallised from ethyl acetate; m.p. 144—145 °C; $\nu_{max.}$ ($CHCl_3$) 2 990, 1 750, and 1 690 cm^{-1}; δ ($CDCl_3$) 7.2 (8 H, m), 4.2 (6 H, m), 3.0 (4 H, m), 2.4 (6 H, s) and 1.4 (6 H, t, J 7 Hz) (Found: C, 66.8; H, 6.3; N, 6.1%. $C_{26}H_{30}N_2O_6$ requires C, 66.9; H, 6.5; N, 6.0%).

2,5-*Bis*-(2-*acetoxybenzyl*)-3,6-*diethoxypyrazine* (6; X = OAc, R = Et).—The bis-imidate (10; X = OAc) (1.52 g) and 2,5-dichloro-3,6-dicyanobenzoquinone (0.88 g) were mixed in dry benzene (50 ml) and stirred overnight at room temperature. The solution was concentrated to a small volume and eluted through a short column of grade III neutral alumina (20 × 2 cm) with benzene (300 ml) and chloroform (70 ml). Concentration of the eluate gave the *product* (6; X = OAc, R = Et) (0.66 g, 44%), m.p. 83—84.5 °C (from EtOAc); $\nu_{max.}$ ($CHCl_3$) 2 980 and 1 780 cm^{-1}; δ ($CDCl_3$) 7.1 (8 H, m), 4.2 (4 H, q, J 7 Hz), 3.9 (4 H, s), 2.3 (6 H, s), and 1.3 (6 H, t, J 7 Hz) (Found: C, 67.1; H, 5.9; N, 5.8. $C_{26}H_{28}N_2O_6$ requires C, 67.2; H, 6.1; N, 6.0%).

Deacetylation of the Diacetate (6; X = OAc, R = Et).—The diacetate (0.9 g, 1.93 mmol) was added to ethanolic KOH (0.43 g in 10 ml) and the mixture stirred for 2 h. The solution was taken to dryness, acidified, and extracted into dichloromethane. The crude product was purified by p.l.c. (SiO_2 : toluene–MeOH, 95 : 5) to yield the *bis-phenol* (6; X = OH, R = Et) (0.68 g, 93%), m.p. 127—128 °C (from cyclohexane); $\nu_{max.}$ ($CHCl_3$) 3 500—3 100br, 2 990, and 1 590 cm^{-1}; δ ($CDCl_3$) 8.5 (2 H, br, s, exchangeable with D_2O), 6.9 (8 H, m), 4.2 (4 H, q, J 7 Hz), 3.85 (4 H, s), and 1.3 (6 H, t, J 7 Hz) (Found: C, 69.6; H, 6.2; N, 7.3%; M^+, 380.1736. $C_{22}H_{24}N_2O_4$ requires C, 69.45; H, 6.35; and N, 7.3%; M, 380.1840).

2,5-*Dihydroxy*-3,6-*bis*-(2-*hydroxybenzyl*)*pyrazine* (6; X = OH, R = H).—The bis-phenol (6; X = OH, R = Et) (0.1 g) was heated under reflux with iodotrimethylsilane (1 ml) for 4.5 h and allowed to cool to room temperature. Water (0.1 ml) and acetone (0.3 ml) were added and a yellow

solid precipitated. This was filtered off, washed with water and acetone, and dried to yield the title compound (0.066 g, 79%), m.p. 210.5—213 °C, $\nu_{max.}$ (KBr) 3 200—2 400 and 1460 cm^{-1}; δ (CF_3CO_2H), 6.9 (8 H, m), 4.8 (4 H, s), 8.7 (2 H, br, s), and 8.5 (2 H, br, s) (Found: C, 66.5; H, 4.7; N, 8.5. $C_{18}H_{16}N_2O_4$ requires C, 66.6; H, 4.9; N, 8.6%).

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