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A BIOGENETICALLY MODELED SYNTHESIS OF ELEUTHERIN

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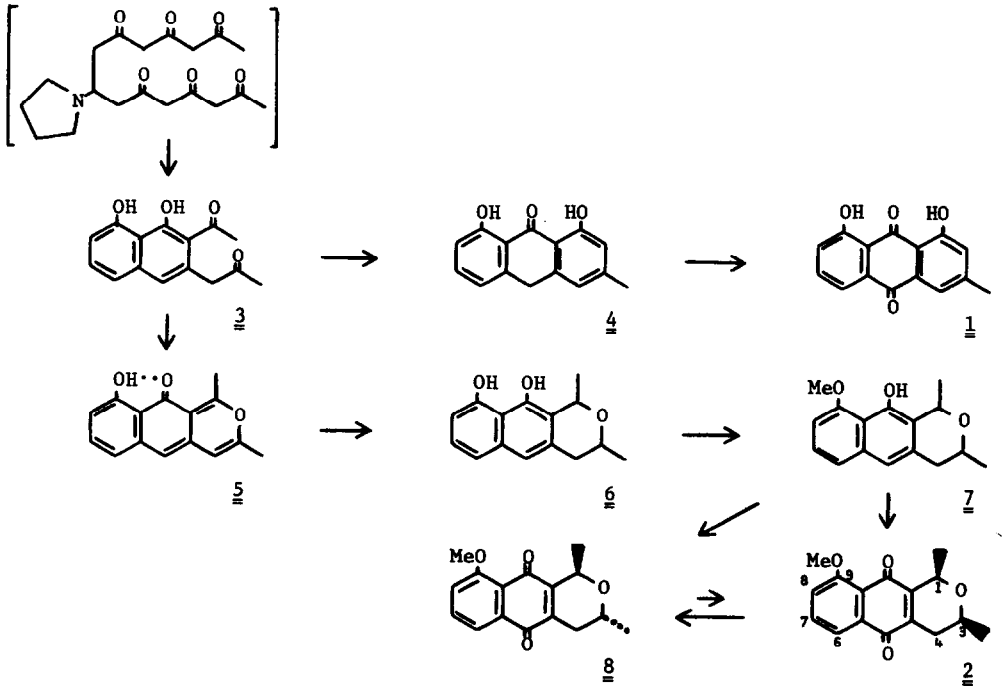
For some years we have been interested in biogenetically modeled syntheses of polyketide-type aromatic natural products from β-polycarbonyl compounds.[1] These studies have progressed to increasingly more complex metabolites, one of the most recent syntheses being that of the anthraquinone chrysophanol (1).[2] The three stages of cyclization of the polyketide precursor of 1 showed a degree of regiospecificity that is truly remarkable in view of the many cyclization products which are possible. We have now succeeded in diverting the final ring closure to give naphthopyran derivatives and, by capitalizing on this reaction, have developed a synthesis of the naphthoquinone eleutherin (2).



Whereas the final ring closure in the synthesis of chrysophanol involved treatment of naphthyl diketone 3 with base to give anthrone 4; compound 3 under acidic condition gives pyran 5 as dark red needles.[3] The cyclization occurred readily and was essentially quantitative within 3 hours in refluxing ethanol containing a catalytic amount of CF_3CO_2H. Even without acid catalysts ring closure could be observed; storage of 3 at ambient temperature led to gradual contamination of the yellow crystals of 3 with red pyran. In spite of this facile ring closure, 5 was unstable relative to anthrone 4. Treatment of 5 with HI for 5 hours in refluxing HOAc gave 4, presumably by the initial ring opening to give back 3, followed by the slower but thermodynamically favored carbocyclic ring closure.

The initial approach for conversion of 5 to 2 involved attempts to introduce the O-methyl group prior to reduction of the pyran ring. These efforts were frustrated by lack of reactivity of the hydroxyl group and by the greatly increased instability of the quinone methide once the hydrogen bond had been disrupted.[4] The alternative sequence, however, was successful; catalytic reduction of 5 (5% Pd/C in abs. EtOH at 26°C with H_2 at 1 atm) gave the highly air-sensitive naphthopyran 6.[5] Immediate treatment of 6 with excess ethereal CH_2N_2 gave monomethyl ether 7 in 87% yield. The nmr spectrum of 7 showed it to be a mixture of the cis and trans isomers with the former predominating.[6] The fraction of trans isomer was minimized by carrying out the reduction and methylation in the dark; the best cis:trans ratio obtained was ~9:1. Oxidation of the mixture of isomers of 7 with $(KSO_3)_2NO$ gave the corresponding quinones in 56% yield.[7] The cis isomer, dl-eleutherin (2), was still slightly contaminated by a second component of the same molecular weight. That the minor component was the stereoisomer of 2 (i.e., 8) rather than a structural isomer was demonstrated by isomerization of 2 in H_3PO_4 by the method[8] of Schmid and Ebnöther to give an equilibrium mixture containing mainly trans isomer 8, the nmr spectrum of which was identical with that of the minor component in the Fremy oxidation. Eleutherin has previously been synthesized by Eisenhuth and Schmid by a condensation of acetaldehyde with 3-(2-hydroxypropyl)-1,8-naphthalenediol.[9]

The synthesis of 2 is of interest because it provides a potential route to other naphtho[2,3-*c*]pyrans. Some of the most notable of these compounds are the pigments which have been obtained from aphids[10] and a neurotoxin recently obtained from the

range plant Karwinskia humboldtiana.[11] In both cases the natural products have oxy substituents at the 7 position. The new route to the naphtho[2,3-*c*]pyran ring system appears to be particularly applicable to synthesis of 7-methoxyeleutherin[11] and other more complex 7-oxygenated naphtho[2,3-*c*]pyran metabolites.

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(3) Compound 5: mp 221-223°C with sublimation; ir (Nujol) 1675 cm^{-1}; uv (95% EtOH) 363 (ε 7920), 345 (1170), 329 (1060), 270 (4460), 216 nm (1850); nmr (CF_3CO_2H) δ 2.67 (s, 3-CH_3), 3.46 (s, 1-CH_3), 7.12 (d, J = 8 Hz, 8-H), 7.23 (s, 4-H), 7.51 (s, 5-H), 7.55 (d, J = 8 Hz, 6-H), 7.84 (t, J = 8 Hz, 7-H); ms m/e 240 (P^+, 100%), 225 (4), 212 (3), 211 (5), 197 (8), 43 (46). Anal. Calcd for $C_{15}H_{12}O_3$: C, 75.12; H, 5.14. Found: C, 74.97; H, 5.03.

(4) A second tautomer with keto and hydroxyl groups transposed can be formulated for 5. Methylation of 5 could also give isomeric methyl ethers.

(5) Care must be taken to avoid hydrogenolysis of 6. Because of variability in the rate of reduction of 5, the best results were obtained by monitoring the extent of hydrogenation by periodically assaying (mass spectra) the reaction mixture. Compound 6: ms m/e 244 (P^+), 229, 215.

(6) Compound 7: mp 94-95°C; ir (Nujol) 3370, 1630, 1605 cm^{-1}; uv (95% EtOH) 323 (ε 8460), 308 (7150), 295 (5600), 284 (5100), 236 nm (79400); nmr ($CDCl_3$) δ [cis isomer] 1.27 (d, J = 6 Hz, 1-CH_3), 1.66 (d, J = 6 Hz, 3-CH_3), 5.11 (q, J = 6 Hz, 1-H), 9.38 (s, OH), [trans isomer] 1.26 (d, J = 6 Hz, 1-CH_3), 1.65 (d, J = 6 Hz, 3-CH_3), 5.18 (q, J = 6 Hz, 1-H), 9.30 (s, OH), [both isomers] 2.62 (m, CH_2), 3.72 (m, 3-CH), 3.75 (s, OCH_3), 6.39

(dxd, J = 7 + 1 Hz, 8-H), 6.79 (s, 5-H), 7.22 (m, 6-H and 7-H); ms m/e 258 (P^+, 16%), 243 (100), 229 (17). Calcd for $C_{16}H_{18}O_3$: m/e 258.12558. Found: 258.12538.

(7) Quinone 2, mp 154-156°C, was slightly contaminated with 8 after recrystallization from cold EtOH. All spectra of 2 were in agreement with reported values.[8]

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