Preliminary experiments have shown that this method is applicable to a wide variety of molecules in photoexcited triplet states and should be of general value in photochemistry. For example it is possible to use photosensitization to produce the triplet state of a molecule whose line broadening is of interest as has been shown for the naphthalenebenzophenone system, where little broadening is observed on direct irradiation of naphthalene in the absence of benzophenone. The application of this method to determine hyperfine interactions and thus structural information as well as relative triplet energies for biologically important molecules such as chlorophyll will be reported shortly.

References and Notes

- (1) Supported by NSF Grant GP-37481 and equipment Grants NSF GP-33116 and The University of Chicago Cancer Center Grant CA-14599. For a review see R. W. Kreilick, *Adv. Magn. Reson.*, **6**, 141 (1973). M. Cocivera, *Chem. Phys. Lett.*, **2**, 529 (1968).

- (4) Bromobenzene as solvent is reported to retard the dimerization of anthracene: see E. J. Bowen, Adv. Photochem., 1, 36 (1963)
- (5) R. H. Clarke and C. A. Hutchison, Jr., J. Chem. Phys., 54, 2962 (1971); a_β was not determined; the value used here is for the anthracene cation; see A. Carrington and A. D. McLachlin, "Introduction to Magnetic Resonance", Harper and Row, New York, N.Y., 1967, p 90.
- (6)Cocivera³ came to the same conclusion by comparing the measured diamagnetic lifetime with that extrapolated from the intersystem crossing yield, and estimated light flux and triplet excitation lifetime.
- The concentration of anthracene in these experiments was high enough over the range studied so that the number of light quanta absorbed did not change significantly. (8) This equation is strictly valid only for one nuclear spin.² However, for
- systems where the nuclear spin-spin coupling constants are small compared to chemical shift differences, it provides a good approximation to the line widths obtained from a solution of the equation of motion of the total density matrix for the coupled system.
- (9) Best fit curves were obtained by a direct search method using "Subroutine Stepit" written by J. P. Chandler and available from the Quantum Chemistry Program Exchange. (10) Another computer fitting was attempted in which the *a*/s were also
- treated as variables. It is interesting to note that the program converged to values which deviate by less than 15% from the known ais,⁵ and the remaining three parameters determined by the more restricted search procedure. Of course, the determination of both hyperfine coupling constants and τ_p is only possible if T_{1e} is comparable to or smaller than τ_p .
- (11) The value of k corresponds to a diffusion rate constant of 2k since the naximum probability for degenerate exchange is 0.5.
- (12) ANL-AEC Laboratory Graduate participant.

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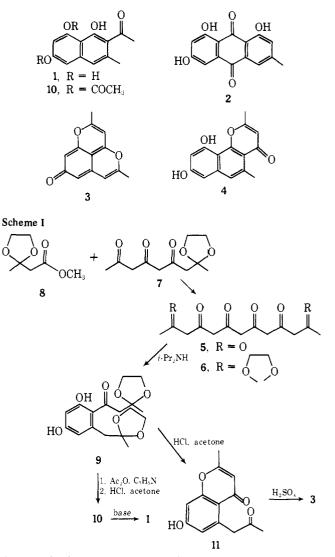
Department of Chemistry, The University of Chicago Chicago, Illinois 60637 Received January 25, 1975

Biogenetic-Type Syntheses of Polycyclic Polyketide Metabolites Using Partially Protected β -Hexa- and β -Heptaketones: 6-Hydroxymusizin, Barakol, Emodin, and Eleutherinol

Sir:

Biogenetically modeled syntheses of polyketide-type aromatic natural products have recently attracted attention.¹ Numerous syntheses of monocyclic compounds have been reported which involve free or partially protected β -tetracarbonyl compounds as precursors, but the corresponding use of higher polycarbonyl compounds or their derivatives has not, as yet, led to any naphthalenoid or anthracenoid natural products.² We now report biogenetic-type syntheses of 6-hydroxymusizin (1) and emodin (2), as well as the related heterocyclic metabolites barakol (3) and eleutherinol (4). The present approach involves polyketones having the two terminal carbonyl groups protected as ketals; these facilitate synthesis of the polycarbonyl compounds and direct their subsequent cyclizations.

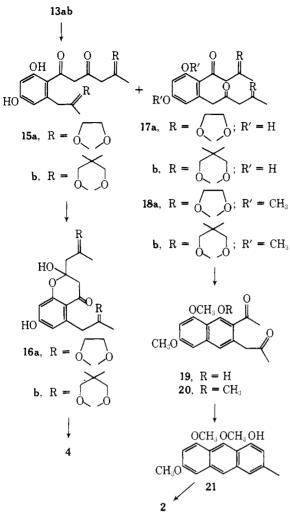
Bis(ethylene ketal) 6^3 of hexaketone 5 was employed for the synthesis of 1 and 3 and was prepared by acylation



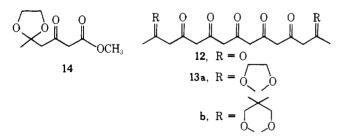
(30-45%) of the trilithium salt (0.03 mol, prepared with i- Pr_2NLi) of protected tetraketone $7^{3,4}$ with ester 8 (0.015) mol) in THF at -78° (Scheme I). The only cyclization pathway readily available to 6 is formation of resorcinol 9; an 80% yield of 9^3 was obtained when 6 was treated with *i*- Pr_2NH (C₆H₆, reflux, 0.5 hr). After acetylation (Ac₂O, C_6H_5N , 25°, 40 hr) of 9, the ketal groups were removed, and the second ring was closed to give naphthol 10^3 (55%) by treatment with 1:40 hydrochloric acid-acetone (25°, 10 hr). Saponification of 10 under N₂ (4 M KOH, 25°, 25 min) gave 70% of 6-hydroxymusizin (1), identical with an authentic sample.⁵

If 9 was not acylated prior to removal of the ketal groups, chromone 11 was formed instead (87%). Chromone 11, on treatment with concentrated H_2SO_4 (1 hr, 25°), cyclized further to give barakol (3, 80%), which was identical with an authentic sample.^{6,7} Both 3 and 11 are constituents of Cassia siamea.8

The initial approach to 2 involved bis(ethylene ketal) 13a of heptaketone 12 (Scheme II). Acylation of the trilithium salt (0.03 mol, formed with i-Pr₂NLi) of 7 with the sodium salt (0.015 mol, formed with NaH) of ester 14^{3,9} gave 13a (THF, 18 hr, 25°, 17%),¹⁰ which, although relatively stable at ambient temperature, could not be purified fully by chromatography on silica gel. Cyclization of 13a could give either resorcinol 15a or 17a, but under all conditions examined 15a was the major product, only traces of 17a being formed. For example, treatment with Et₃N in toluene (3 min, reflux) gave 57% of 15a (which cyclized spontaneously



to hemiketal $16a^3$) and 3% of 17a (isolated as dimethyl ether 18a (CH₂N₂, Et₂O-MeOH)). The quantity of 18awhich could be prepared was inadequate to justify completion of the emodin synthesis using this intermediate. However, isomeric 16a is a potential precursor of eleutherinol (4). Treatment of 16a with a 0.5:6:14 mixture of hydrochloric acid, water, and acetone (8 hr, 25°) followed by *i*-Pr₂NH (benzene, 5 min, 25°) closed the naphthalene ring; subsequent treatment with CF₃CO₂H (0.5 hr, 25°) closed the pyrone ring to give 4^{11} (19% from 16a).



For the synthesis of emodin, the relative proportion of attack at the 6 vs. the 4 position of heptaketone 12 was increased by using the more bulky ketals of 2,2-dimethyl-1,3-propanediol. Diprotected heptaketone 13b, prepared analogously (11%) to 13a, cyclized (*i*-Pr₂NH, toluene, reflux, 3 min) to give 54 and 10% yields of resorcinols 15b and 17b, with the former cyclizing spontaneously to 16b and the latter being isolated as dimethyl ether 18b³ (CH₂N₂, Et₂O-MeOH). Further cyclization of 18b under more basic conditions (NaOMe, MeOH, 50°, 2 hr), followed by acid-catalyzed deketalization (0.4:6:14 hydrochloric acid, H₂O, and acetone, 25°, 16 hr) gave dimethoxynaphthol **19**, which, when it failed to undergo further aldol cyclization, was methylated (Me₂SO₄, K₂CO₃, acetone, reflux, 2 hr) to give trimethyl ether **20**.³ The latter cyclized readily in the presence of NaOMe (MeOH, 60°, 0.5 hr) to anthracene **21**, which by treatment with HI in acetic acid (3 hr, reflux) and then with CrO₃ in aqueous acetic acid (5 min, 50°) gave emodin (**2**) (20% yield based on **18b**).^{11,12}

In the present study, the terminal carbonyl groups were protected because model studies¹³ had indicated that in polyketones **5** and **12** these groups would be too susceptible to intramolecular attack. The approach is highly effective for the synthesis of 6-hydroxymusizin, barakol, and eleutherinol but only marginally useful for emodin because the wrong initial cyclization predominates. We are currently investigating an alternate approach to direct the cyclizations, namely, the use of ketals to prevent participation of the adjacent methylene groups in aldol reactions. Hopefully through use of a combination of these protective devices, pretetramid and other complex polyketide metabolites can be synthesized.

Acknowledgment. We thank Drs. U. Weiss and B. W. Bycroft for helpful discussions and Dr. R. L. Foltz of the Battelle Mass Spectroscopy Laboratory for determining the chemical ionization spectrum. This research was supported by the U.S. Public Health Service (Research Grant GM-12848).

References and Notes

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- (3) This compound gave satisfactory elemental analyses and spectra consistent with the assigned structure.
- (4) Prepared in high yield by condensation of dilithioacetylacetone with ester 8.
- (5) We wish to thank Dr. U. Weiss and K. S. Brown for this sample; see K. S. Brown, D. W. Cameron, and U. Weiss, *Tetrahedron Lett.*, 471 (1969).
- (6) We thank Dr. B. W. Bycroft for providing a sample of 3; see B. W. Bycroft, A. Hassaniali-Walji, A. W. Johnson, and T. J. King, J. Chem. Soc. C, 1686 (1970).
- (7) Barakol crystallizes as a hydrate, which was assigned by the original workers⁵ as *i* rather than as a solvate of **3**. Electron impact and chemical ionization mass spectra of barakol which had been carefully freed of chromone 11 support a molecular weight of 214 for **3**, not 232 for *i*; the uv spectrum (λ_{MAX} 384 nm in EtOH and 408 nm in CHCl₃) and the lemon yellow color of crystalline material further argue against the original assignmént.



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 (12) Identified by comparison with authentic material.
- (12) identified by comparison with authentic material.(13) Unpublished results, P. J. Wittek and T. M. Harris.

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