While the mechanism of the significant inhibition by chloroquine and the naphthoquinone V of CoQ-enzymic systems remains a subject for further study, it is evident that this inhibition could be directly related to their antimalarial activity. However, the antimalarial activity need not be solely related to interference with the biosynthesis or with the function of CoQ but may involve binding to enzymes directly related to CoQ. However, partial reversal of *in vitro* inhibition is observed by CoQ. Chloroquine appears to have other modes of action in the body. Schueler and Cantrell[13] report that ferrihemic acid complexes with chloroquine, and that the complex is an antagonist of the antimalarial action of chloroquine. Hahn, *et al.*,[14] have evidence that chloroquine inhibits nucleic acid biosynthesis and that the mechanism of action is the formation of a molecular complex with DNA. However, complexes of chloroquine with DNA and ferrihemic acid are not known to be directly related to the antimalarial activity.

Emphasis can now be given to the organic synthesis of new antimalarials based on the interference with the fundamental role of CoQ in the electron-transfer process of *Plasmodium;* one group of new hydroxyquinones (X) which are apparent inhibitors of CoQ enzyme systems has been synthesized.[15]

Acknowledgment. Dr. Ronald S. Pardini held the Stanley E. Harris Postdoctoral Fellowship in Biomedical Research. He and Dr. Karl Folkers express their gratitude to Mr. Harris, of Woodside, Calif., for this fellowship.

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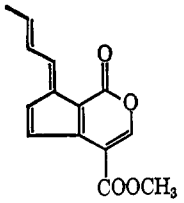
Frederick S. Skelton, Ronald S. Pardini
James C. Heidker, Karl Folkers
Stanford Research Institute
Menlo Park, California 94025
Received July 15, 1968

The Total Synthesis of Fulvoplumierin

Sir:

Fulvoplumierin (**1**), a constituent of *Plumeria acutifolia* with antibacterial activity, is a member of the small class of naturally occurring fulvenes.[1] Its structure was established by Schmid and coworkers,[2,3] and we now describe a total synthesis which confirms this structural assignment.



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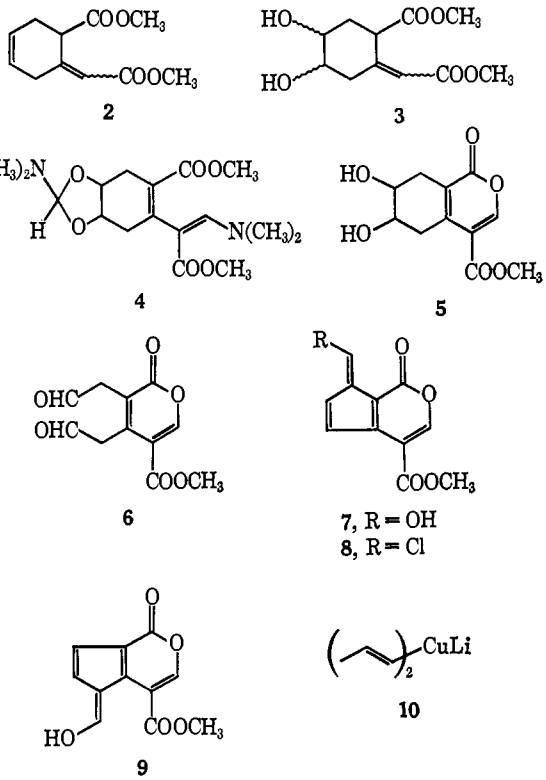
Condensation of dimethyl penta-2,3-dienedioate[4] with butadiene in benzene at 80° gave the adduct **2**, bp 78–80° (0.3 mm) (60%), which was oxidized in aqueous tetrahydrofuran at room temperature for 40 hr with potassium chlorate in the presence of a catalytic amount of osmium tetroxide[5] to a mixture of isomeric diols **3** (oil) (80%). Condensation with dimethylformamide dimethyl acetal[6] in dimethylformamide at 80° for 5 hr gave the dimethylaminomethylene compound **4** which, without purification, was hydrolyzed with dilute hydrochloric acid to the α-pyrone **5** (28%), mp 160–162°, ultraviolet absorptions at 253 (ϵ 7730) and 285 mμ (ϵ 4650) in ethanol and 251 mμ (ϵ 8850) in ethanol–NaOH. The latter was transformed with sodium periodate in aqueous methanol to the dialdehyde **6** and thence by cyclization with Amberlite IR 120 in dimethoxyethane at 78° for 4 hr to the yellow hydroxyfulvene **7** (61%), mp 162–163°, ultraviolet absorptions at 357 mμ (ϵ 7320) in ethanol and 304 (ϵ 9270) and 378 mμ (ϵ 24,100) in ethanol–NaOH.

The isomeric hydroxyfulvene **9** cannot be constructed with molecular scale models due to severe steric interaction between the hydroxymethylene and the carbomethoxy groups, and we consequently felt confident that the cyclization of the dialdehyde **6** had proceeded in the desired sense. Contrary to 6-hydroxyfulvene which is less stable than the tautomeric cyclopentadienaldehydes,[7] compound **7** exists entirely in the hydroxyfulvene form, and its nmr spectrum in $CDCl_3$ is characterized by two doublets, J = 14 Hz at δ 14 and 7.65, caused by the enolic and the adjacent vinylic hydrogen atoms, respectively.



(1) The structures of two other natural fulvenes were determined by D. J. Bertelli and J. H. Crabtree, *Tetrahedron*, **24**, 2079 (1968).
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(4) E. R. H. Jones, G. H. Mansfield, and M. C. Whiting, *J. Chem. Soc.*, 3208 (1954).
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(6) H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Ann.*, **641**, 1 (1961).
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When the hydroxyfulvene **7** was allowed to stand in oxalyl chloride solution at room temperature for 12 hr it was converted to the highly reactive, yellow chloride **8**, mp 126–127° (88%), ultraviolet absorptions at 234 (ϵ 5010), 314 (ϵ 10,300), 327 (ϵ 9700), and 343 mμ (ϵ 5140) in pentane. Condensation with lithium di(*trans*-1-propenyl)cuprate (**10**)[8] in ether solution at −25° gave a purple reaction mixture which was chromatographed on silicic acid. Elution with chloroform followed by crystallizations from chloroform–hexane gave the orange fulvoplumierin (**1**) (27%), mp 148–150°. Infrared,[2] ultraviolet,[2] and nuclear magnetic resonance[3] spectra of synthetic and natural fulvoplumierin were indistinguishable.

Acknowledgment. We are indebted to the National Institutes of Health for financial support.

(8) Prepared by the method of G. M. Whitesides, J. San Fillipo, Jr., C. P. Casey, and E. J. Panek, *J. Am. Chem. Soc.*, **89**, 5302 (1967). Lithium dimethylcopper has been condensed with a vinyl bromide by E. J. Corey and G. H. Posner, *ibid.*, **89**, 3911 (1967). Analogous coupling reactions were performed by H. O. House and W. F. Fischer (unpublished), while G. M. Whitesides and J. San Fillipo, Jr. (unpublished), have condensed vinyl cuprates with alkyl halides. We are indebted to the latter investigators for much unpublished information.

(9) National Institutes of Health Predoctoral Fellow, 1966–present.

G. Büchi, John A. Carlson[9]
Department of Chemistry, Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received August 2, 1968

The Synthesis of 6′-Deoxyhomonucleoside-6′-phosphonic Acids[1]

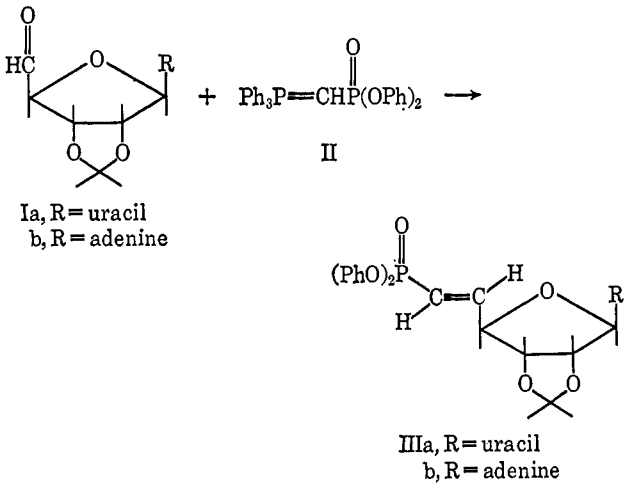
Sir:

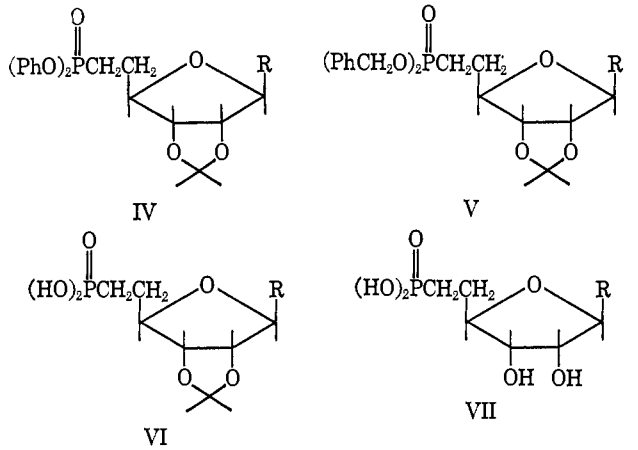
We have recently been involved in a general program on the utility, as synthetic intermediates, of nucleoside derivatives containing aldehydo[2] and keto[3] functions in the sugar moiety. In a separate paper[4] we describe the synthesis of the stabilized Wittig reagent diphenyl triphenylphosphoranylidenemethylphosphonate (II) and we here describe the reaction of this compound with protected nucleoside 5′-aldehydes (I) leading to 6′-deoxyhomonucleoside-6′-phosphonic acids.

Treatment of 2′,3′-O-isopropylideneuridine with dicyclohexylcarbodiimide and dimethyl sulfoxide in the presence of pyridinium trifluoroacetate led to the formation of the 5′-aldehyde Ia in high yield. This material was not isolated,[5] but rather was treated directly with II in DMSO at 37° for 20 hr. Chromatography on silicic acid then gave the crystalline α,β-unsaturated phosphonate IIIa in 58% yield, mp 146–147°.[6]

The 100-MHz nmr spectrum of IIIa showed the $C_{6'}$ proton as an octet at 6.13 ppm with $J_{6',5'}$ = 17 Hz, $J_{H,P}$ = 21 Hz, and $J_{6',4'}$ = 1.5 Hz. The $C_{5'}$ proton was located within the aromatic envelope. These data are consistent with a *trans* configuration for the vinyl phosphonate.[7] Hydrogenation of IIIa in methanol using a 5% palladium on barium sulfate catalyst proceeded readily and gave IVa in quantitative yield as a white foam with the expected nmr and ultraviolet spectra. Alkaline hydrolysis readily cleaved one phenyl ester and, following acidic removal of the isopropylidene group, the second could be removed enzymatically using the phosphodiesterase from *Crotalus adamanteus* venom[8] giving the free phosphonic acid VIIa.

Removal of the ester groups was, however, more readily achieved on a preparative scale by reaction of the diphenyl ester IVa with 4 equiv of sodium benzoxide in dimethyl sulfoxide at 20° for 5–15 min. Such treatment led to almost instantaneous transesterification with formation of the dibenzyl ester Va which was isolated in 83% yield by chromatography on silicic acid. Palladium-catalyzed hydrogenolysis of the benzyl esters of Va was rapid and gave the free phosphonic acid VIa which was treated with water at 100° for 1 hr to remove the isopropylidene groups, giving crystalline 6′-deoxy-





(1) This trivial nomenclature stresses the relationship of these compounds with the essentially isosteric nucleoside 5′-phosphates. Systematically they may be referred to as 5′-deoxy-5′-(dihydroxyphosphinylmethyl)nucleosides or as derivatives of phosphonic acids, *e.g.*, VIIa, being [1-(5′,6′-dideoxy-β-D-*ribo*-hexofuranosyl)uracil]-6′-phosphonic acid.

(2) (a) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **85**, 3027 (1963); (b) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 5661 (1965).

(3) A. F. Cook and J. G. Moffatt, *ibid.*, **89**, 2697 (1967).

(4) G. H. Jones and J. G. Moffatt, in preparation.

(5) See G. H. Jones, J. P. H. Verheyden, and J. G. Moffatt, XXIst International Congress of Pure and Applied Chemistry, Prague, 1967, Abstract N-26, for the problems associated with chromatographic isolation.

(6) All crystalline products have given satisfactory elemental analyses.

(7) C. E. Griffin and T. D. Mitchell, *J. Org. Chem.*, 30, 1935 (1965); L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 85.

(8) The close analogy between the homonucleoside phosphonates and natural nucleotides is emphasized by this enzymatic reaction which proceeded at roughly 20% the rate found using monophenyluridine 5′-phosphate.