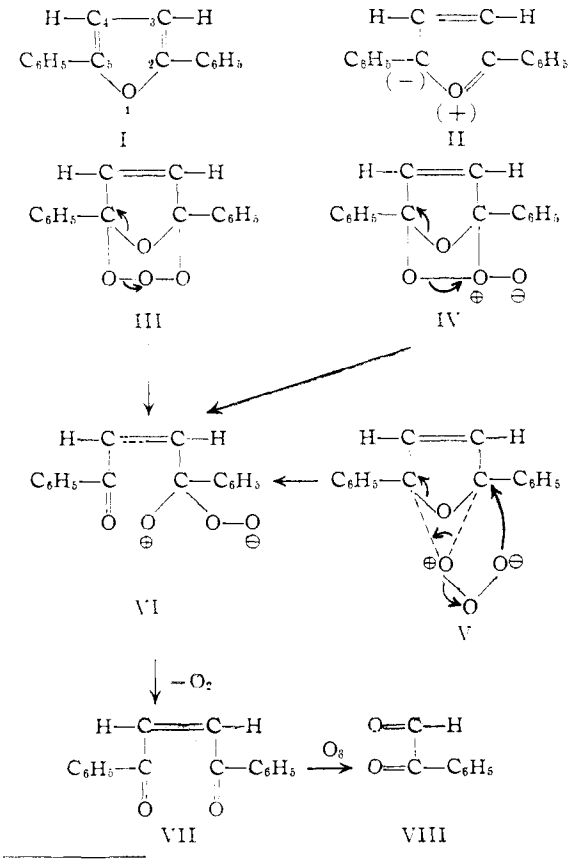
COMMUNICATIONS TO THE EDITOR

1,4-ADDITION OF OZONE TO FURANS AND PYRROLES

Sir:

Wibaut and co-workers[1,2] have obtained products from the ozonolyses of methylated pyrroles and furans which cannot be accounted for by cleavage of the double bonds in the normal structures of these substances. Similarly, we have obtained a 14% yield of phenylglyoxal (VIII) from ozonolysis of 2,5-diphenylfuran (I). The solvent was a methanol–acetone mixture, the temperature was −40°, two mole equivalents of ozone were absorbed, the peroxidic ozonolysis products were reduced with hydrogen over palladium catalyst and the other major product was benzoic acid (81% yield).

Wibaut and co-workers[1,2] have explained "abnormal" results such as these as being reactions of ionic structures such as II. It hardly seems likely, however, that ozone would polarize the molecule to, and attack, such an unstable structure as II, especially since the reactive positions of the furan and pyrrole ring systems are 2 and 5.[3] We have felt that the "abnormal" reactions are the result of the 1,4-addition of ozone. We wish now to report confirmatory evidence for this.



When the ozonolysis just described was stopped after the absorption of one mole equivalent of ozone and the reaction mixture was partially evaporated, a 12% yield of *cis*-1,2-dibenzoylethylene (VII) precipitated (m.p. 130–135°, identification by a mixture melting point with an authentic sample[4]) Similar results were obtained using a mixture of ozone and nitrogen instead of ozone and oxygen, showing definitely that the reaction is one of ozone and not of oxygen.

This material cannot arise from ozonolysis of II. The furan ring has been cleaved but the 3,4 bond is still intact. The *cis* configuration, which is that of the labile isomer,[5] proves that the double bond at the 3 and 4 positions was formed before the ring was cleaved. This can occur only by a 1,4-addition of ozone to the conjugated system of the furan. Any one of structures III, IV or V could have been the intermediate.

We believe a similar mechanism holds true for the reactions of Wibaut and co-workers.[1,2] Further, we believe ozone will attack the ends of other conjugated systems, if the ends are spatially close together. We have found previously that this holds true with anthracene.[6]

We wish to thank the University of Texas Research Institute and the Research Corporation for grants which made this work possible.

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(2) J. P. Wibaut, paper presented at International Ozone Conference, Chicago, Illinois, November 28–30, 1956.

(3) R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, Chapters 4 and 6.

(4) (a) J. B. Conant and R. E. Lutz, THIS JOURNAL, **45**, 1303 (1923); (b) R. E. Lutz and F. N. Wilder, *ibid.*, **56**, 978 (1934).

(5) L. R. Kuhn, R. E. Lutz and C. R. Bauer, *ibid.*, **72**, 5058 (1950).

(6) P. S. Bailey and J. B. Ashton, *J. Org. Chem.*, **22**, 98 (1957).

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ISOLATION AND BEHAVIOR OF *spiro*[2,5]OCTA-1,4-DIENE-3-ONE

Sir:

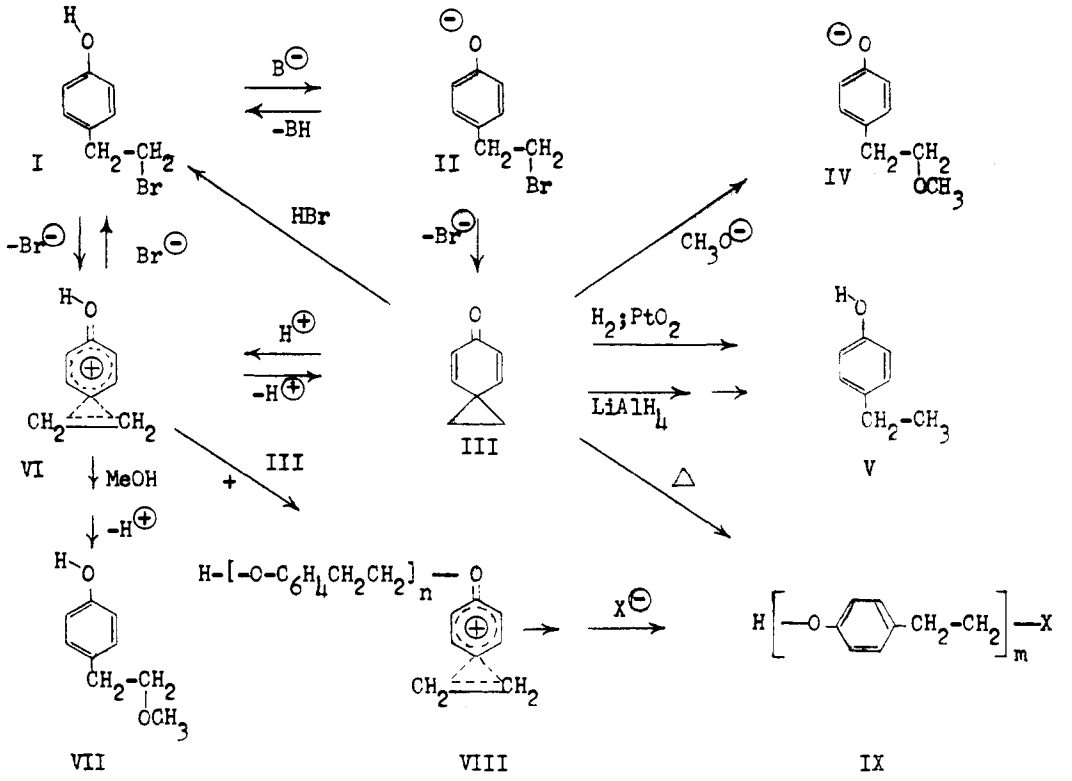
Recently[1] spectroscopic evidence was reported for the formation of *spiro*[2,5]octa-1,4-diene-3-one (III) as a transient intermediate in solvolytic reactions of 2-*p*-hydroxyphenyl-1-ethyl bromide (I). We now report the successful isolation of this interesting reactive molecular species.

Passage of an ethereal solution of 2-*p*-hydroxyphenyl-1-ethyl bromide (I) through a column of a basic alumina[2] gives a *ca.* 10^{-3} *M* solution of *spiro*[2,5]-octa-1,4-diene-3-one (III) free from phenolic species.

If carefully treated glassware is employed, so as to ensure a dry neutral glass surface, ether solutions of this species can be evaporated at reduced pressure to give a crystalline solid, soluble in most

(1) S. Winstein and R. Baird, THIS JOURNAL, **79**, 756 (1957).

(2) J. Castells and G. A. Fletcher, *J. Chem. Soc.*, 3245 (1956).



common solvents. Recrystallization from ether–pentane at low temperatures gives crystals, m.p. 43–46°, with the correct carbon–hydrogen analysis for dienone III, and which show strong absorption maxima for a highly conjugated carbonyl in the infrared at 1650 cm.$^{-1}$ in carbon disulfide and at 1640 cm.$^{-1}$ in chloroform. In the ultraviolet strong maxima are observed at 261 mμ in ether, 271 mμ in *t*-butyl alcohol. 274 mμ in methanol and *ca.* 282 mμ in water, the maxima in methanol and *t*-butyl alcohol being identical with those obtained previously.[1]

The dienone III at low concentrations reacts with a variety of reagents to open the 3-ring and restore the phenolic system. Reduction of the dienone III with lithium aluminum hydride or by catalytic hydrogenation gives *p*-ethylphenol (V) in good yield.

Solvolytic opening of the 3-ring occurs under basic, neutral and acidic conditions, a few spectroscopically measured rate constants being summarized in Table I. The rate of disappearance in methanol with added methoxide is within one per-

TABLE I

FIRST ORDER RATE CONSTANTS FOR SOLVOLYTIC CLEAVAGE OF DIENONE III AT 25°

Solvent	Added solute	10^4k (sec.$^{-1}$)
HOH	...	34.2
MeOH	...	3.87
MeOH	0.01 *N* NaOMe	9.14
MeOH	10^{-5} *N* $HClO_4$	>700

cent. of that reported previously[1] for the transient intermediate observed spectroscopically.

The opening of the dienone III is especially sensitive to acid catalysis, the half-life of III at 25° in 10^{-5} *M* methanolic perchloric acid being less than ten seconds. Under these conditions, and at least partly under neutral conditions, the solvolysis presumably involves the bridged-ion VI, also an intermediate in the solvolysis of suitable 2-*p*-hydroxyphenyl-1-ethyl derivatives.

The ion VI is attacked not only by solvent species, but by other nucleophiles such as bromide ion. Thus, treatment of the dienone III with excess ethereal hydrogen bromide gives rise to the parent bromoethylphenol I, m.p. and mixed m.p. with authentic I, 89–91.5°.

Although ether solutions of dienone III as concentrated as 5×10^{-3} *M* can be kept for about a week, the solid seldom is stable for more than 20 to 30 minutes, probably due to the presence of traces of stray catalysts. On standing, or more rapidly on warming above its m.p., dienone III is converted to a material melting in the range 160–200°, which is insoluble in the common solvents. The infrared spectrum (KBr), quite different from that of dienone III, resembles that of 2-*p*-anisylethyl bromide, especially with respect to the aromatic substitution patterns and the strong aromatic ether absorption band at 1235 cm.$^{-1}$. These data, along with carbon–hydrogen analyses, suggest the polymeric ether structure IX.

With respect to ionic mechanisms for polymerization of dienone III, different processes may be visualized which involve either attack of a growing aryloxide ion on dienone III, or attack of dienone III on a growing cation of the type of VIII. The

latter type is presumably involved in the stannic chloride-catalyzed polymerization of dienone III in ether.

(3) National Science Foundation Predoctoral Fellow, 1953–1955, 1956–1957.

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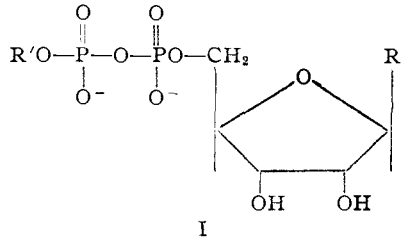
RECEIVED JUNE 19, 1957

THE PREPARATION OF NUCLEOSIDE 5′-PHOSPHORAMIDATES AND THE SPECIFIC SYNTHESIS OF NUCLEOTIDE COENZYMES

Sir:

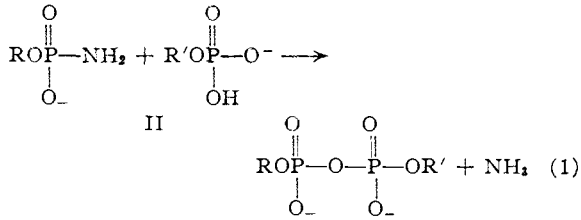
While the carbodiimide method[1] has been applied successfully to the syntheses of certain nucleotide coenzymes[2] (General Formula I) in good yield, the method is often unsatisfactory owing to its lack of specificity in effecting condensation between two dissimilar phosphate esters and frequently, to competing intramolecular cyclic phosphate formation.[3] In seeking to devise more specific methods for the synthesis of compounds of the type I, we have recently investigated[4] the use of phosphoramidates in reactions represented by equation 1. The application of this promising



I

R = Purine or Pyrimidine
R′ = Sugar, etc.

approach to the practical synthesis of nucleoside



R = nucleoside
R′ = H, sugar, etc.

pyrophosphate derivatives (I) was limited, however, by the relative inaccessibility of the key intermediates, nucleoside 5′-phosphoramidates[4] (II) and more direct methods for the preparation of these derivatives were, therefore, sought. In the present communication we outline a convenient one-step preparation of these compounds and record their use in highly improved syntheses of the unsymmetrical pyrophosphates, adenosine 5′-diphosphate (I, R = adenine; R′ = H; ADP) and uridine diphosphate glucose[5,6] (I, R = uracil; R′ = glucose; UDPG).

The direct preparation of nucleoside 5′-phosphoramidates by the condensation of readily available nucleoside 5′-phosphates with ammonia in the presence of an excess of dicyclohexyl carbodiimide (DCC) was examined and it was found that by the proper choice of reaction conditions, quantitative conversion of the nucleotides to the corresponding amidates could indeed be realized. Under the reaction conditions used, 1,3-dicyclohexylguanidine also is formed and the nucleoside 5′-phosphoramidates finally were obtained as the guanidinium salts. The general procedure may be illustrated by the preparation of adenosine 5′-phosphoramidate (AMP–NH_2): a mixture of adenosine 5′-phosphoric acid (3 mmoles), ammonia (7.5 ml. of 2*N*), formamide (5 ml.), *tert*-butyl alcohol (18 ml.) and DCC (3.0 g.) was heated at 80° for three hours. Paper chromatography at this stage showed a single strong spot corresponding to AMP–NH_2.[4] After a simple work up, which included removal of dicyclohexyl urea, ether extraction and subsequent evaporation, AMP–NH_2 was obtained as the crystalline dicyclohexylguanidinium salt (m.p. 240–241°, dec.) from formamide–acetone in 92% yield. *Anal.* Calcd. for $C_{23}H_{40}N_9O_6P\cdot 1H_2O$: C, 47.05; H, 7.21; N, 21.46; P, 5.27. Found: C, 47.46; H, 6.98; N, 21.92; P, 5.20; adenine phosphorus, 1.02. The addition of lithium hydroxide to an aqueous solution of the salt liberated the theoretical amount of free dicyclohexylguanidine (m.p. 181–182°; reported m.p. 182°).[7] Acidification of the above salt with hydrochloric acid liberated dicyclohexyl guanidinium hydrochloride; m.p. 296–297°, dec.

By the same procedure we have prepared the dicyclohexylguanidinium salts of the amidates derived from uridine 5′-phosphoric acid (75%) and monophenylphosphoric acid (68%).

In the previously reported experiments[4] on the synthesis of pyrophosphates from the phosphoramidic acids, formamide solutions of the free acids were used. In the present work, AMP–NH_2 reacted with orthophosphoric acid in *o*-chlorophenol to give 60% yield of ADP, which is easily separated from the other products of the reaction, AMP and orthophosphate, by ion exchange chromatography.[8] This new procedure should lead to more satisfactory syntheses of all the nucleoside 5′-diphosphates.[9] For the synthesis of the nucleoside pyrophosphate esters, it has now been found that pyridine solutions may be employed. In model experiments, dicyclohexylguanidium salts of uridine 5′- and adenosine 5′-phosphoramidates reacted in anhydrous pyridine with monophenylphosphoric acid to give, respectively, 87 and 70% yields of the corresponding pyrophosphates (I, R = uracil or adenine; R′ = phenyl). The application of this technique

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(2) E. P. Kennedy, *J. Biol. Chem.*, **222**, 185 (1956).

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(4) R. W. Chambers and H. G. Khorana, *Chemistry and Industry*, 1022 (1956).

(5) R. Caputto, L. F. Leloir, C. E. Cardini and A. C. Paladini, *J. Biol. Chem.*, **184**, 333 (1950).

(6) For earlier syntheses of this substance see: (a) G. W. Kenner, A. R. Todd and R. F. Webb, *J. Chem. Soc.*, 2843 (1954); (b) A. M. Michelson and A. R. Todd, *ibid.*, 3459 (1956).

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(8) In a recent paper, Clark, *et al.*, describe the use of monobenzylphosphoramidic acid in the synthesis of ADP and ATP: V. M. Clark, G. W. Kirby and A. R. Todd, *J. Chem. Soc.*, 1497 (1957).

(9) Experiments in the uridine and cytidine series are in progress