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A BIOGENETICALLY PATTERNED CONCEPT FOR THE LABORATORY SYNTHESIS OF CYCLIC COMPOUNDS

William S. Johnson and Russell A. Bell

Department of Chemistry, University of Wisconsin,

Madison, Wisconsin

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THE key step in the polymerization of isopentenyl pyrophosphate, namely the C-C bond-forming stage, has been depicted[1] as a process involving alkylation of an isolated olefinic bond with an allylic cation-forming species (3,3-dimethylallyl pyrophosphate) under non-acidic ("physiological") conditions. There appears to be no in vitro precedent for the occurrence of such a reaction under neutral conditions. In biological systems the matter of unprecedented behavior can be dismissed by attributing special catalytic properties to the enzyme surface. But it is surely more attractive to hope to find some new chemical behavior, and in this case we chose to consider the hypothesis that the alkylation step is anchimerically assisted by participation of the pyrophosphate residue as indicated in the accompanying flow sheet. The tertiary alkyl phosphate linkage of the cyclized form would

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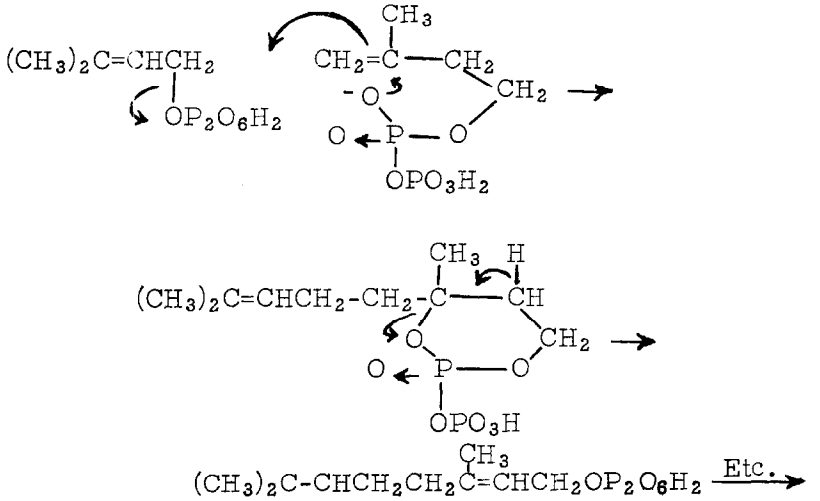
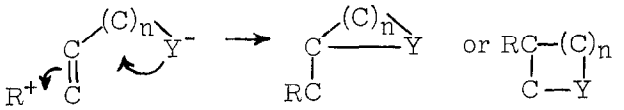
[1] F. Lynen, H. Eggerer, U. Henning and I. Kessel, Angew. Chem. 70, 739 (1958); H.C. Rilling and K. Bloch, J. Biol. Chem. 234, 1424 (1959); J.W. Cornforth, Tetrahedron Letters No. 19, 29 (1959).



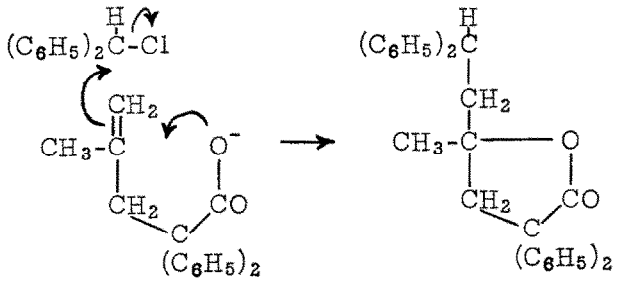
be expected to be unstable and collapse as indicated.

In considering models to test this hypothesis, we discovered that we were dealing with an apparantly unprecedented general reaction of the following type where Y^- is a nucleophilic function such as phosphate, amino, O of carbonyl, alkoxide O^-, carboxylate O^-, S^-, $^-CH(COOEt)_2$, etc.; and R^+ is a cationic species which might be derived from an alkyl halide, acid chloride, epoxide, C of carbonyl, etc., including vinylogous systems such as α,β-unsaturated ketones:



To test the premise, as well as to set up a model for the biochemical hypothesis, we chose to examine a case where $Y^- = COO^-$. When sodium 4-methyl-4-pentenoate was treated with simple alkyl halides it was not surprising to

find that only the ester was produced. In order to sterically inhibit alkylation of the carboxylate ion we turned to an extreme case, namely the reaction of sodium 2,2-diphenyl-4-methyl-4-pentenoate (I) with benzhydryl chloride. When a solution of these reactants in dimethyl formamide was allowed to stand at room temperature for four days, a γ-lactone, m.p. 128-129°,



I II

λ_{max} 5.72 μ, was isolated in over 60% (crude) yield. This substance was different from the known lactone,[2] m.p. 106-107°, λ_{max} 5.72 μ of the starting acid. That it was indeed the lactone of 2,2,6,6-tetraphenyl-4-methyl-4-hydroxy-hexanoic acid (II) followed from the analysis (Calc. for $C_{31}H_{28}O_2$: C, 86.08; H, 6.53. Found: C, 86.15; H, 6.62), the extinction coefficient of 890 at 261 mμ showing the presence of four phenyl groups, and the unique nmr spectrum, at 60 mc/sec which showed (CS_2 solution) a sharp singlet at -60.4 cps (relative to tetramethyl silane) corresponding to the 3 protons of the methyl group sttached to C_4; a doublet at -137.2 and -144 cps corresponding to two equivalent protons (at C_5) split (J = 6.8) by a single adjacent proton (at C_6); signals at -156.3 and -158.6 cps corresponding to two non-equivalent protons at C_3 and a well defined triplet at -232.4, -239.2 and

[2] P.N. Craig and I.H. Witt, J. Amer. Chem. Soc. 72, 4925 (1950).

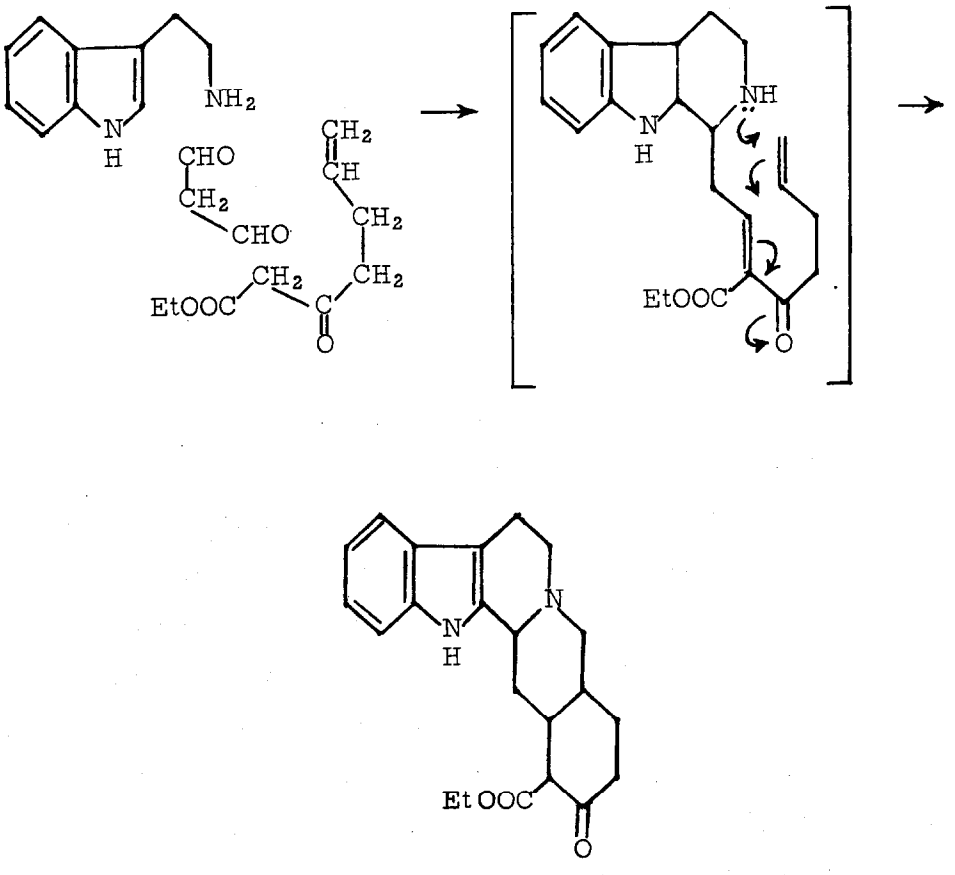
-246.0 cps, corresponding to a single proton (at C_6) split (J = 6.8) by two adjacent protons (at C_5). In addition to the aromatic proton absorption, a very weak band was found at -169.5 cps which corresponds to part of a quartet arising from spin-spin coupling (J = 12 cps) of the nonequivalent protons at C_3. The fourth (weak band) of the quartet, which would absorb at -145.5 cps is masked by the strong signal due to the C_5 protons.

The production of the lactone II as described above bears a formal resemblance to the reaction of halogen with the sodium salt of a γ,δ-unsaturated acid to produce a δ-halo-γ-lactone, e.g. the reaction of bromine with I to produce the bromo lactone II (Br in place of benzhydryl).[2] The reaction with benzhydryl chloride, however, is basically different in that production of a new C-C bond is involved. Even if this type of reaction may have been carried out before, the general principle for thus producing new C-C bonds has not, to our knowledge, hitherto been recognized.

The scope of the concept is yet to be determined. An obvious limitation is the competing reaction involving interaction of R^+ directly with Y^- (ester formation in the example above), which can easily constitute the major course of the reaction. This difficulty promises to be obviated by a modification of the general scheme depicted above to include systems where R^+, as well as Y^-, is incorporated in the same molecule in such a way that their interaction is precluded, but so that they are juxtaposed, relative to the olefinic bond, for ring formation, viz.

$$^{+}R(C)_mC{=}C(C)_nY^{-} \longrightarrow \overbrace{R(C)_mC\text{-}C(C)_nY} \text{ or } \overbrace{R(C)_mC\text{-}\underbrace{C(C)_nY}}$$

The following hypothetical scheme illustrates this modification and suggests its potential versatility:



It should be emphasised that this example is meant to serve only as a schematic illustration of the principle rather than as a proposed synthesis. The acid-catalyzed cyclization of certain polyenes[3] can be considered as a special case in this class, where the carbonium ion center is produced by

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3 G. Stork and A.W. Burgstahler, J. Amer. Chem. Soc. 77, 5068 (1955); P.A. Stadler, A. Eschenmoser, H. Schinz and G. Stork, Helv. Chim. Acta 40, 2191 (1957).

protonation of one olefinic bond, and another serves as the nucleophilic center. Our present study suggests that appropriate selection of functional groups may permit realization of cyclizations under neutral or even basic conditions to produce a wide variety of structures.

Another variation in the general concept, is the case where R^+, instead of Y^-, is incorporated in the olefinic portion of the molecule. Acid-catalyzed cyclizations of certain olefinic compounds may be considered as belonging to this class, e.g. the cyclization of butenyl-methylcyclohexene with sulfuric-acetic acid and acetic anhydride to give 9-methyldecalyl acetate,[4] but important variations under neutral conditions may now be anticipated.

It still remains to be shown whether the reaction of I with benzhydryl chloride is truly anchimerically assisted by the carboxylate group, or whether this anion serves to capture the carbonium ion formed by a rate-controlling attack of the benzhydryl cation on the olefinic bond, in which case the cyclization process still appears to play an important role in deciding the fate of the carbonium ion in a clean and selective manner. In any case our findings suggest the intermediacy of a cyclic form in the polymerization of isopentenyl pyrophosphate, and further studies of the general cyclization concept are indicated.[5]

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[4] V.C.E. Brunop and R.P. Linstead, J. Chem. Soc. 720 (1940).

[5] Acknowledgment is made to the Wisconsin Alumni Research Foundation, the U.S. Public Health Service, and the National Science Foundation for support of this project.