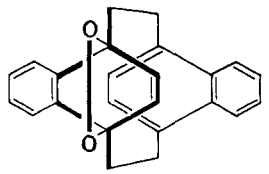
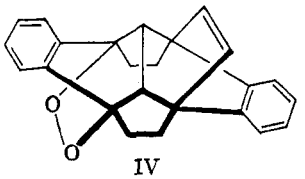
system. A second-stage internal Diels–Alder reaction would lead to IV which is transformed by solvolysis in methanol to II.



III



IV

Further investigations on the reactions of singlet oxygen with strained aromatic systems are in progress.

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Harry H. Wasserman, Philip M. Keehn
Department of Chemistry, Yale University
New Haven, Connecticut
Received August 1, 1966

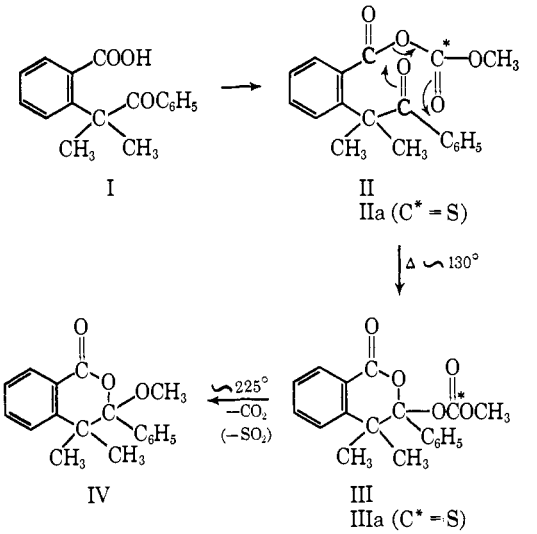
New Reactions Predicted by a [3.3.1]Bicyclic Mechanism[1]

Sir:

Because certain reactions had been postulated to take place by a novel [3.2.1]bicyclic mechanism,[2] we were led to explore the possibility that other bicyclic paths might be discovered. Herein are described several new reactions. These reactions were discovered by predicting that they would take place by a [3.3.1]bicyclic mechanism.

On treatment of *o*-(α,α-dimethylphenacyl)benzoic acid[3] (I) with methyl chlorocarbonate and Dabco,[4] a high yield of the mixed anhydride,[5] II, mp 85–88°, was obtained. The same compound was also prepared in high yield by treatment of the sodium salt of I with methyl chlorocarbonate. On heating II for a short time at 130–135° resolidification occurred. The solid isolated, mp 219° dec, was the rearranged lactonic ester,[5] III. On heating above the melting point III lost carbon dioxide to give the pseudo ester,[3] IV, mp 172–174°, in high yield. When methyl chlorosulfite[6] was substituted for methyl chlorocarbonate in the above reactions, we were unable to isolate compounds IIa and IIIa analogous to II and III, but they were undoubtedly present. However, on heating of the crude reaction mixture sulfur dioxide was readily lost and high yields of pseudo ester IV were obtained.

We believe that the facile rearrangement of II to III occurs by a [3.3.1]bicyclic mechanism as indicated by the arrows in formula II. The two indicated carbonyl carbons of I are the bridgehead carbons which define the [3.3.1]bicyclic system. This rearrangement takes place with about the same ease as that of the comparable intermediate prepared from *o*-benzoylbenzoic acid and methyl chlorocarbonate,[2b] a reaction that involves a [3.2.1]bicyclic path.[2] A similar path is undoubtedly involved for the sulfur-containing intermediates IIa and IIIa.



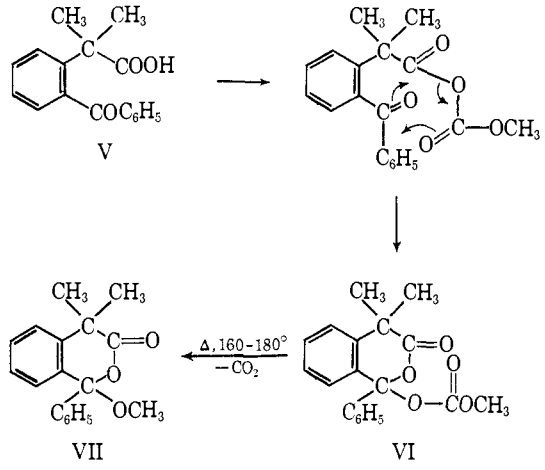
When *o*-benzoyl-α,α-dimethylphenylacetic acid[7] (V) was treated with methyl chlorocarbonate in the presence of Dabco in ether at 0–5° a compound, mp 131–132°, was obtained in 89% yield to which the lactonic ester structure VI[5] is assigned. The same compound was obtained in 82% yield when the sodium salt of V was allowed to react with methyl chlorocarbonate at room temperature. Undoubtedly an acyclic compound analogous to II was formed initially in both cases as shown in the illustration, but this rearranged to VI even though the temperature during work-up never exceeded 30°. Support for the argument that the initially formed compound has the acyclic mixed anhydride structure may be derived from the fact that the ultraviolet spectra of V and its sodium salt are nearly the same as that of the normal methyl ester of V ($\lambda_{max}^{CHCl_3}$ 250 mμ (ϵ 13,720)) and quite different from that of the pseudo methyl ester of V ($\lambda_{max}^{CHCl_3}$ 262 mμ (ϵ 533)). As in the case of the pyrolysis of III to IV, pyrolysis of VI at 160–180° resulted in loss of carbon dioxide and formation of VII, mp 119–120°, the pseudo methyl ester[7] of V, in almost quantitative yield. The rearrangement of the initially formed mixed anhydride (analogous to II) to the lactonic ester VI undoubtedly occurs by a [3.3.1]bicyclic path which, in this case, must provide such a favorable route that rearrangement occurs rapidly at room temperature.

When the intermediate formed by reaction of the sodium salt of V with methyl chlorosulfite was heated in benzene, sulfur dioxide was evolved and a high yield of VII was obtained. Because of the instability of the intermediates involved they were not isolated. However, we believe a [3.3.1]bicyclic reaction path similar to that involving the carbonate is involved.

If there is any generality to the [3.3.1]bicyclic path there are many new reactions, such as the ones above

(1) This research was supported by a grant from the U. S. Army Research Office, Durham, N. C.
(2) (a) M. S. Newman and C. Courduvelis, *J. Am. Chem. Soc.*, **86**, 2942 (1964); (b) *ibid.*, **88**, 781 (1966).
(3) M. Renson and L. Christiaens, *Bull. Soc. Chim. Belges*, **71**, 405 (1962).
(4) 1,4-Diaza[2.2.2]bicyclooctane. We thank the Houdry Process Co., Marcus Hook, Pa., for a generous supply of Dabco.
(5) All new compounds gave acceptable carbon and hydrogen analyses and had infrared, ultraviolet, and nmr spectra consistent with the assigned structures.
(6) M. S. Newman and W. S. Fones, *J. Am. Chem. Soc.*, **69**, 1046 (1947).
(7) M. Renson and L. Christiaens, *Bull. Soc. Chim. Belges*, **71**, 379 (1962).

described, which may be predicted by changing the atoms involved in the bicyclic path. Some of these are under study in these laboratories.



V VII VI

Melvin S. Newman, Slobodan Mladenovic
Evans Chemistry Laboratory of the Ohio State University
Columbus, Ohio 43210
Received May 23, 1966

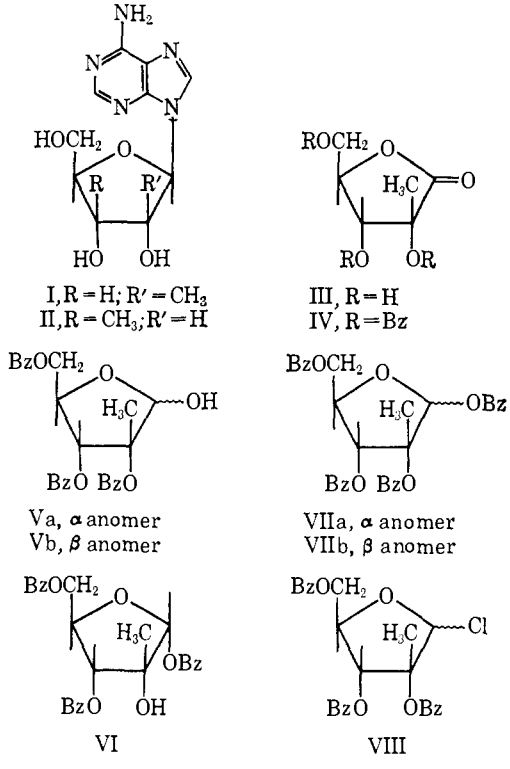
Branched-Chain Sugar Nucleosides. A New Type of Biologically Active Nucleoside

Sir:

It has been proposed[1] that the therapeutic value of a number of biologically active adenosine analogs is limited by their facile conversion into the less active inosines through the action of adenosine deaminase. Hence, adenosine analogs resistant to the action of adenosine deaminase are of interest. We wish to report two new adenine nucleosides, 2′-C-methyladenosine (I) and 3′-C-methyladenosine (II),[2] which have biological activity as measured by their ability to inhibit the growth of KB cells in culture and at the same time show a marked resistance to the action of adenosine deaminase. These compounds are the first examples of nucleosides containing branched-chain sugars.

The cytotoxicity of the 2′- and 3′-C-methyladenosine against KB cells in culture was determined by the method of Gitterman and co-workers.[3] As measured by protein determination, the inhibitory effect of both 2′-C-methyladenosine and 3′-C-methyladenosine was between 65 and 80% at a concentration of 10 μg/ml. The activity of calf intestine adenosine deaminase with I and II was compared with that observed with adenosine. Deamination was determined spectrophotometrically by the change in absorption at 265 mμ. 3′-C-Methyladenosine was not measurably deaminated over a period of 10 min under conditions where adenosine was completely deaminated in 2.5 min. The rate of deamination of 2′-C-methyladenosine was $^1/_{25}$ that observed when adenosine was the substrate.

For the synthesis of 2′-C-methyladenosine (I), a suitable derivative of the hitherto undescribed 2-C-methyl-D-ribofuranose was required. 2-C-Methyl-D-ribono-γ-lactone (α-D-glucosaccharinic acid lactone, III)[4] was a convenient starting material. The lactone III, after conversion into its 2,3,5-tri-O-benzoyl derivative (IV) [mp 140–141°; λ_{max}^{Nujol} 5.56 μ (lactone), 5.70, 5.79 (ester); $[\alpha]D$ −79° (*c* 1, $CHCl_3$)], was reduced with bis(3-methyl-2-butyl)borane (disiamylborane)[5] to produce an anomeric mixture of 2,3,5-tri-O-benzoyl-2-C-methyl-D-ribofuranose (V) as the main product. The mixture of Va and Vb was not separated. When their separation was attempted by chromatography on acid-washed alumina, a complete rearrangement to 1,3,5-tri-O-benzoyl-2-C-methyl-α-D-ribofuranose (VI) ([α]D +92° (*c* 1, $CHCl_3$)) resulted. The same rearrangement occurred, but only to a slight extent, during chromatography of the reduction products on silica gel. Benzoylation of the mixed anomers of V with benzoyl chloride in pyridine produced 1,2,3,5-tetra-O-benzoyl-2-C-methyl-α(β)-D-ribofuranose. Following chromatography, one of the anomers (presumably β),



I, R = H; R′ = CH_3
II, R = CH_3; R′ = H
III, R = H
IV, R = Bz
Va, α anomer
Vb, β anomer
VIIa, α anomer
VIIb, β anomer
VI
VIII

VIIa, was isolated as a crystalline solid [mp 159–160°; λ_{max}^{Nujol} 5.72 and 5.80 μ (ester); $[\alpha]D$ + 68° (*c* 1, $CHCl_3$); τ^{CDCl_3} 2.90 (singlet, H-1) and 4.02 ppm (doublet, H-3) ($J_{3,4}$ = 7.3 cps)]; the other (presumably α) was obtained as a pure syrup [λ_{max}^{neat} 5.76 μ (ester); $[\alpha]D$ +68° (*c* 1, $CHCl_3$); τ^{CDCl_3} 3.12 (singlet, H-1) and 4.30 ppm (broad singlet, H-3, half-width 4–5 cps)]. The tentative anomeric configurational assignments of VIIa and VIIb are based on the observation that VIIa (β) was much more easily converted, in ethereal hydrogen chloride, into the chloro sugar VIII than was VIIb (α). The more rapid conversion of the β anomer into the chloro sugar is to be expected because of the predicable anchimeric effect

(1) G. A. LePage and I. G. Junga, *Cancer Res.*, **25**, 46 (1965).
(2) For a description of the synthesis of II see E. Walton, F. W. Holly, and R. F. Nutt, Winter Meeting of the American Chemical Society, Phoenix, Ariz., Jan 1966, Abstract 37C.
(3) C. O. Gitterman, R. W. Burg, G. E. Boxer, D. Meltz, and J. Hitt, *J. Med. Chem.*, **8**, 664 (1965).
(4) E. Peligot, *Compt. Rend.*, **89**, 918 (1879).
(5) The reduction of several nonbranched, acylated hexono-γ-lactones has been described by P. Kohn, R. H. Samaritano, and L. M. Lerner, *J. Am. Chem. Soc.*, **86**, 1457 (1964).