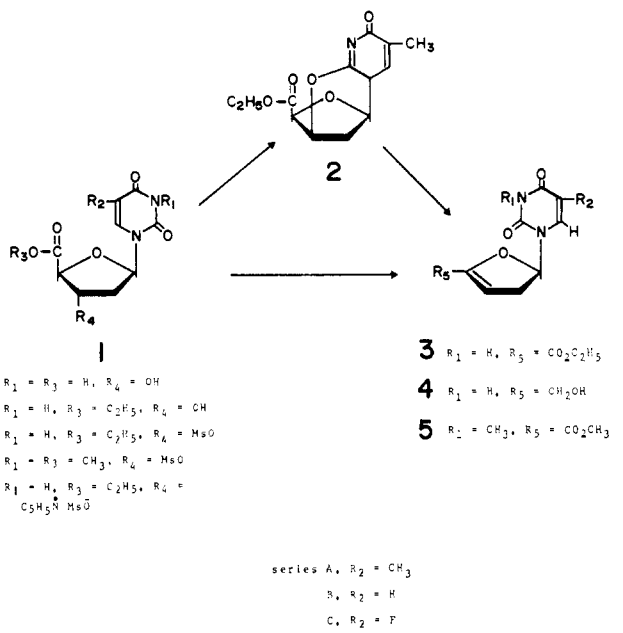
## Nucleosides. XII. A Synthesis of 3′,4′-Unsaturated Pyrimidine Nucleosides

*Sir:*

Reports from this laboratory and others[1] have described the direct introduction of 2′,3′ unsaturation into the carbohydrate moiety of a relatively wide spectrum of nucleosides *via* the base-catalyzed (E2) decyclization of the ether linkage in both 2,3′- and 3′,5′-anhydronucleosides. We wish now to report a practical synthetic approach to the previously inaccessible pyrimidine 2′-deoxy-3′,4′-unsaturated nucleosides (**4**)[2] together with evidence that favors an E1cB mechanism for these reactions and the unique spectral characteristics of these modified nucleosides.

The synthesis of **4** (series A)[3] commenced with the esterification of the readily available 1-(2-deoxy-β-D-*erythro*-pentofuranosyluronic acid)thymine[4] (thymidine-5′-carboxylic acid, **1a**) in ethanol–triethyl orthoformate–HCl to give **1b** [86% yield; mp 244–245°; ir (KBr) 1743 $cm^{-1}$ (CO ester)], which on treatment with methylsulfonyl chloride in pyridine at −20° afforded ethyl 3′-O-(methylsulfonyl)thymidine-5′-carboxylate [**1c**; 87% yield; mp 130–133°; uv max (EtOH) 264 nm (ε 13,100), min 235 nm (ε 5100); ir (KBr) 1754 (CO ester), 1178 $cm^{-1}$ (sulfonate)]. The interaction of **1c** and either excess triethylamine or sodium benzoate in DMF at 100° gave ethyl 3′-deoxy-3′-thymidinene-5′-carboxylate[5] (**3**, 80% yield): mp 229–231°; $[\alpha]^{24}D$ −115.8° (*c* 0.5, $CHCl_3$); uv max (EtOH) 256 nm (ε 6500), min 230 nm (ε 3200) [ORD (1st extremum) 269 nm (φ −12,000)]; ir (KBr) 1724 $cm^{-1}$ (CO, conjugated ester); nmr ($CDCl_3$)[6] 6.94 (*d* 1, CH-6). Selective reduction of **3** to 2′-deoxy-3′-thymidinene (**4**)[5,7] was effected with sodium bis(methoxyethoxy)aluminum hydride: mp 160–165°; with a prior change of state at 105–110°; $[\alpha]^{23}D$ −134.6° (*c* 0.5, dioxane); uv max (95% EtOH) 267 nm (ε 7500), min 234 nm (ε 2200); nmr (acetone-$d_6$) 7.29 (*d* 1, CH-6). The same series of reactions applied to 2′-deoxyuridine-5′-carboxylic acid[8] (**1a**, series B, $R_2$ = H) and 5-fluoro-2′-deoxyuridine-5′-carboxylic acid[9] (**1a**, series C, $R_2$ = F) gave the corresponding 2′,3′-dideoxy-3′-uridinene (**4**) in reasonably good overall yield.




The intervention of a 2,3′-anhydronucleoside (**2**) in the reaction path leading (from **1c**) to **3** was presumed[1a,c] but could not be detected. However, a sample of **2** [mp 227–229°; $[\alpha]^{23}D$ −64.2° (*c* 0.5, $H_2O$); uv max (EtOH) 244 nm (ε 6200), min 219 nm (ε 3700)], which was readily obtained (67% yield) on refluxing **1c** in aqueous $BaCO_3$,[10] was only partially converted to **3** on treatment with $Et_3N$ in DMF at 100° after 2 hr. In fact, the same transformation in $Et_3N$–DMSO-$d_6$ at 100° showed a $t_{1/2} \sim 120$ min as deduced from the rate of appearance of the CH-6 proton in the nmr spectrum of **3**. By contrast, the conversion of **1c** to **3** in the same base–solvent system, but at 50°, showed a $t_{1/2} \sim 28$ min.

The formation of **2** as an intermediate is also contraindicated by the following evidence: (a) methyl 3-methyl-3′-O-(methylsulfonyl)thymidine-5′-carboxylate (**1d**) [mp 106–108°; $[\alpha]^{23}D$ +30.2° (*c* 0.5, $CHCl_3$); uv max (EtOH) 264 nm (ε 7500), min 235 nm (ε 2500)], prepared (25% overall yield) by sequential treatment of **1a** with dimethylformamide dimethylacetal[11] and methylsulfonyl chloride in pyridine, was readily converted ($Et_3N$–DMF, 100°) to the corresponding 3′,4′-unsaturated ester [**5**, 76% yield; mp 138–139°; $[\alpha]^{22}D$ −105° (*c* 0.5, $CHCl_3$); uv max (EtOH) 254 nm (ε 6800), min 230 nm (ε 3900); nmr 6.96 (s 1, CH-6), 6.82 (m 1, CH-1′), 6.03 (t 1, CH-3′)]; (b) the pyridinium salt [**1e**; series A); mp 283–286°, $[\alpha]^{23}D$ −49.6° (*c* 0.5, $H_2O$)], derived on refluxing **1c** in dry pyridine for

(1) (a) J. P. Horwitz, J. Chua, I. L. Klundt, M. A. Da Rooge, and M. Noel, *J. Amer. Chem. Soc.*, **86**, 1896 (1964); (b) J. P. Horwitz, J. Chua, M. A. Da Rooge, and M. Noel, *Tetrahedron Lett.*, 2725 (1964); (c) J. P. Horwitz, J. Chua, M. A. Da Rooge, M. Noel, and I. L. Klundt, *J. Org. Chem.*, **31**, 205 (1966); (d) J. P. Horwitz, J. Chua, and M. Noel, *Tetrahedron Lett.*, 1343 (1966); (e) J. P. Horwitz, J. Chua, M. Noel, and J. T. Donatti, *J. Org. Chem.*, **32**, 817 (1967); (f) P. Reichard, *J. Biol. Chem.*, **237**, 3513 (1962); (g) N. Otake, S. Takeuchi, T. Endo, and H. Yonehara, *Tetrahedron Lett.*, 1411 (1965); (h) J. R. McCarthy, Jr., R. K. Robins, and M. J. Robins, *J. Amer. Chem. Soc.*, **90**, 4993 (1968); **88**, 1549 (1966); (i) J. P. H. Verheyden and J. G. Moffatt, *ibid.*, **88**, 5684 (1966); (j) J. R. McCarthy, Jr., M. J. Robins, and R. K. Robins, *Chem. Commun.*, 536 (1967); (k) T. A. Khwaja and C. Heidelberger, *J. Med. Chem.*, **10**, 1066 (1967); (l) G. Kowollik, K. Gaertner, G. Etzold, and P. Langen, *Carbohyd. Res.*, **12**, 301 (1970).

(2) In the course of the present study, G. H. Jones and J. G. Moffatt, (a) Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, No. CARB-15; (b) U. S. Patent 3,457,255 (1969), *Chem. Abstr.*, 72, 3727 (1970), reported a synthesis of related 3′,4′-unsaturated ribonucleosides, *e.g.*, 3′-deoxyuridin-3′-en-5′-aldehyde, by a base-catalyzed elimination of 2′,3′-O-benzylidene ribonucleoside-5′-aldehydes.

(3) Analytical values for all compounds described in this work were consistent with the indicated structures.

(4) G. P. Moss, C. B. Reese, K. Schofield, R. Shapiro, and A. R. Todd, *J. Chem. Soc.*, 1149 (1963).

(5) See ref 1c for the basis of this nomenclature.

(6) Nmr spectra were measured in deuteriochloroform at 60 MHz (unless otherwise indicated) and were in agreement with the assigned structure. Chemical shifts are quoted in parts per million downfield from internal tetramethylsilane standard and coupling constants in hertz to the nearest 0.5 Hz.

(7) Application of systematic nomenclature to 4 leads to the name (−)-(*R*)-2,3-dihydro-2-(thymin-1-yl)-5-hydroxymethylfuran.

(8) K. Imai and M. Honjo, *Chem. Pharm. Bull. (Tokyo)*, **13**, 7 (1965).

(9) K. C. Tsou, N. J. Santora, and E. E. Miller, *J. Med. Chem.*, **12**, 173 (1969).

(10) G. Etzold, R. Hintsche, and P. Langen, German Patent 65794 (1969); *Chem. Abstr.*, **71**, 91828 (1969).

(11) J. Žemlička, *Collect. Czech. Chem. Commun.*, **28**, 1060 (1963); *ibid.*, in press; H. Brechbühler, H. Büchi, E. Hatz, J. Schreiber, and A. Eschenmoser, *Angew. Chem.*, **75**, 296 (1963); H. Brechbühler, H. Büchi, E. Hatz, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, 48, 1746 (1965); H. Vorbrüggen, *Angew. Chem.*, **75**, 297 (1963).

10 hr, gave **3** in 71% yield on treatment with sodium benzoate in DMF at 100°.

On the basis of these findings, it is concluded that the principal route to **3** occurs by way of preliminary proton abstraction at C-4′ of **1c** to give its anionic conjugate base followed by unimolecular loss of mesylate anion from the conjugate base. This, then, is the E1cB mechanism[12] which is standard for the formation of α,β-unsaturated carbonyl compounds.[13] The same mechanistic interpretation may be applicable to the formation of **3** from **2** with the observed differences in the rate of formation of product from the corresponding anionic intermediate a consequence of the relatively poorer leaving group character of the thyminyloxy residue (in **2**) *vis-à-vis* mesylate anion.

The introduction of 3′,4′ unsaturation into **3** is accompanied by a hypsochromic shift of *ca.* 10 nm in the ultraviolet absorption $\lambda_{max}$, which reverts to the value(s) characteristic of pyrimidine nucleosides, including the 2′,3′-unsaturated derivatives, on (selective) reduction of the carboethoxy function to **4**. Moreover, the 3′,4′-unsaturated nucleosides show a negative Cotton effect from which it may be concluded that these derivatives, like the 2′,3′-olefinic nucleosides,[14] but unlike the normal pyrimidine β-nucleosides, have the *syn* conformation in aqueous solution. Molecular models indicate the possibility of an effective overlap of π orbitals comprising the 2-carbonyl of the aglycon and the conjugated unsaturation of the sugar where **3** is in a *syn* conformation. As a consequence of orbital overlap, an anhydronucleoside-like structure would be approximated in an excited state and thereby account for the observed hypsochromic shift in **3**. This same interaction, though obviously less important in **4**, may also serve to explain the diamagnetic shift of H-6 (70–100 Hz) observed in the nmr spectra of **3**, **4**, and **5** relative to the parent structure.

On the other hand, there is little to suggest a steric barrier in the 3′,4′-unsaturated nucleosides that would restrict rotation about the glycosyl–nitrogen bond. Consequently, it is possible that in the ground state these structures exist in the opposite conformation. Moreover, molecular models indicate that in the *anti* conformation H-6 lies directly above the plane of the 3′,4′ double bond which would account for the observed shielding effect. By contrast, a corresponding anisotropic effect in the pyrimidine 2′,3′-unsaturated nucleosides is not indicated and apparently explains the normal chemical shift of H-6.

The possibility that the rotameric composition of a nucleoside, such as **3**, can differ in two low-lying energy states, which is suggested by the spectral data and which hetetofore has not been considered, has significant biochemical and biophysical implications.

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(12) D. V. Banthorpe in "Reaction Mechanisms in Organic Chemistry," E. D. Hughes, Ed., Elsevier, Amsterdam, 1962, Chapter 4.

(13) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1969, p 649.

(14) T. R. Emerson, R. J. Swan, and T. L. V. Ulbricht, *Biochemistry*, **6**, 843 (1967).

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## Steric Control in the Reaction of Diphenylcarbene with Olefins. Thoughts on the Structure of Diphenylcarbene in Solution[1]

*Sir:*

The development of the chemistry of triplet carbenes dates from the report of Etter, Skovronek, and Skell[2] that diphenylcarbene (**1**) added nonstereospecifically to olefins. These authors suggested a structure for **1** in which a central, sp-hybridized carbon atom was flanked by two perpendicular phenyl rings. Closs and Closs[3,4] later showed that addition was largely stereospecific and that the olefinic products of an abstraction–recombination process were the major compounds produced in the reaction. Nevertheless, the properties of diphenylcarbene have been generally regarded as both well known and archetypal of triplet carbenes. Neither is the case. Reports on the chemistry of **1** are rare and fragmentary, and the hydrogen abstraction–recombination process is not the path generally followed by triplets.[5–7]

The problem of the strangeness of **1** is accentuated by a comparison of properties with those of the related fluorenylidene (**2**) which reacts with olefins to give mainly cyclopropanes.[6] Abstraction–recombination is

1 2

always a minor process. Esr spectroscopy on **1** and **2** initially indicated that a quite similar geometry was attained by both, at least at low temperature in rigid medium. In particular, both were bent, and **1** was thought to possess a structure in which the rings were more coplanar than perpendicular.[8] The question of why two such structurally similar molecules should react so differenlty was puzzling indeed.[9]

(1) This work was generously supported by the National Science Foundation through Grants GP-7819 and GP-12759.

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(3) G. L. Closs and L. E. Closs, *Angew. Chem.*, 74, 431 (1962).

(4) G. L. Closs, *Top. Stereochem.*, **3**, 193 (1968).

(5) T. W. Eder and R. W. Carr, *J. Phys. Chem.*, **73**, 2074 (1969), and references therein.

(6) M. Jones, Jr., and K. R. Rettig, *J. Amer. Chem. Soc.*, **87**, 4013 (1965), and unpublished work.

(7) M. Jones, Jr., W. Ando, and A. Kulczycki, Jr., *Tetrahedron Lett.*, 1391 (1967).

(8) R. W. Brandon, G. L. Closs, C. E. Davoust, C. A. Hutchison, Jr., B. E. Kohler, and R. Silbey, *J. Chem. Phys.*, **43**, 2006 (1965), and references therein.

(9) It has been pointed out[4] that **1** and **2** differ in their electronic structures, **1** being odd, alternant and **2** not.