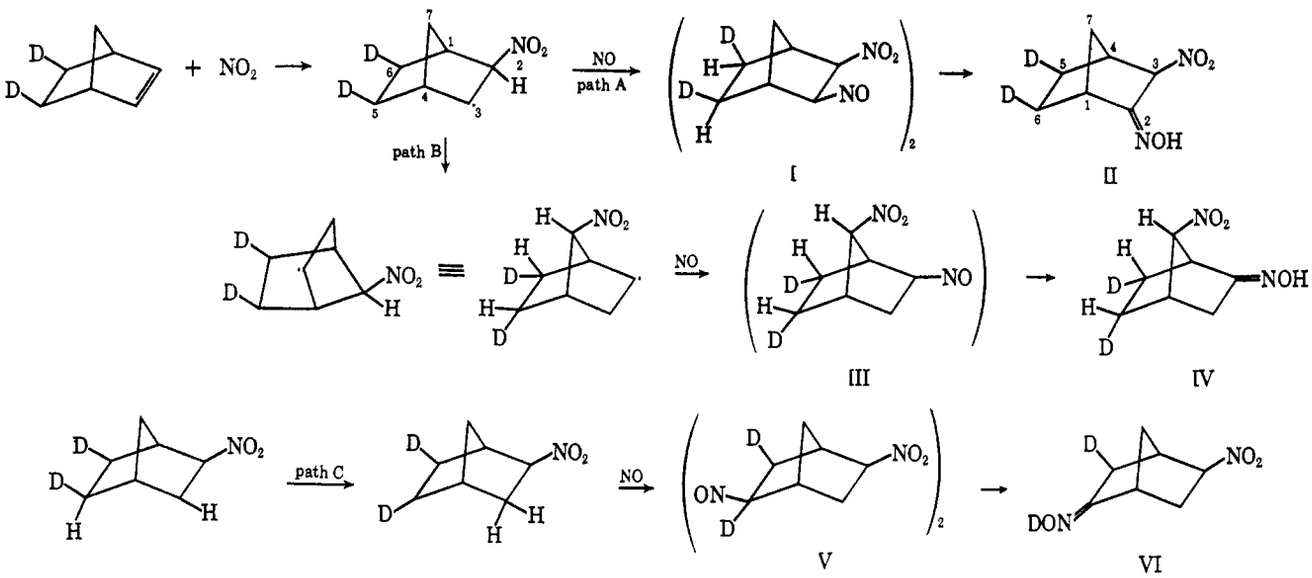
SCHEME I



The crystalline product is separated by filtration, washed with ether, air dried, and recrystallized from methylene chloride–pentane. A 60% yield of white crystals, mp 135°, is obtained.

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.42; H, 5.92; N, 16.47; O, 28.21. Found: C, 49.42; H, 6.13; N, 16.21; O, 28.07.

Norbornene Nitroxime.—A solution of norbornene pseudonitrosite in dioxane is refluxed under nitrogen until the green color of the nitroso monomer has completely disappeared (1–2 hr). The dioxane is evaporated leaving crude solid residue. Recrystallization from methylene chloride–pentane affords pure (75% yield) nitroxime, mp 167°.

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.42; H, 5.95; N, 16.47; O, 28.21. Found: C, 49.42; H, 5.90; N, 16.14; O, 28.54.

2,3-Diaminonorborane.—Treatment of 17 g (0.1 mol) of norbornene nitroxime in absolute ethanol with 1 g of Raney nickel at 75° and 1500 psi hydrogen for 2–3 days followed by filtration of the catalyst, evaporation of the solvent, and vacuum distillation of the crude oil affords 10 g of colorless, liquid distillate, bp 100–135° (0.2 mm). Gc studies reveal that a mixture of products is present. Treatment of an ethereal solution of the crude diamine with dry hydrogen chloride affords a salt which after recrystallization from ethanol fails to melt below 300°. *Anal.* Calcd for $C_7H_{14}N_2Cl_2$: C, 42.44; H, 8.13; N, 14.15; Cl, 35.79. Found: C, 42.02; H, 8.03; N, 13.87; Cl, 35.83. The nmr spectrum in D_2O reveals absorption patterns of area 6 at δ 1.7, area 2 at 2.7 (bridgehead protons), one-proton signals at 3.3 (quartet) and 3.7 ppm (triplet) as well as exchangeable proton absorption.

The infrared and nmr spectra of the dihydrochloride and retention time of the free diamine on a Carbowax 20M–KOH column at 150° are identical with the substance prepared according to the procedure of Inglessis.[6]

***exo,exo*-5,6-Dideuterionorbornene.**—The deuterated olefin is prepared according to the procedure of Baird, Franzus, and Surridge.[7] Reaction with nitrogen oxides and subsequent conversion into nitroxime are carried out in the manner described above.

Registry No.—Dinitrogen trioxide, 16529-92-3; norbornene, 498-66-8; norbornene pseudonitrosite, 16526-91-3; norbornene nitroxime, 16526-92-4; 2,3-diaminonorbornane dihydrochloride, 16526-93-5.

Acknowledgments.—The author gratefully acknowledges discussions with Dr. Boris Franzus and is indebted to Mr. J. J. Porcelli for experimental assistance.

Nuclear Magnetic Resonance Chemical Shifts of Cyclopropane HCH in Unsubstituted Bicyclo[*x*.1.0]alkanes as a Function of Ring Size[1]

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Received February 2, 1968

In connection with product identifications in another study,[2] we required samples of several bicyclo[*x*.1.0]-alkanes (Figure 1). These compounds were prepared by methyleneation of the appropriate cycloalkene with methylene iodide and zinc–copper couple.[2-4] When we examined the nuclear magnetic resonance (nmr) spectra of these bicycloalkanes, we were impressed with the continuing upfield shift of the signal from one of the cyclopropane CH_2 protons as the size of the larger ring increased from five to ten members (Table I). The signal associated with the proton geminal to the first apparently is shifted downfield by the same change that brings about the upfield shift of the first proton in the cyclopropane CH_2 group. We cannot be certain about the regularity of the shift, however, be-

(1) (a) Presented in part at the Southeast–Southwest Regional Meeting of the American Chemical Society, Memphis, Tenn., Dec 1965, paper no. 97, and at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, Abstracts, p S125. (b) We gratefully acknowledge partial support of this research by grants from the Petroleum Research Fund administered by the American Chemical Society (Grant No. 1817-A4) and the National Science Foundation (Grant No. GP 5749). (c) Based in part on a portion of the Ph.D. Dissertation of J. S. D., Louisiana State University, 1966. The financial assistance from the Charles E. Coates Memorial Fund, donated by George H. Coates, for preparation of the Ph.D. Dissertation of J. S. D. is gratefully acknowledged.

(2) J. G. Traynham and J. S. Dehn, *J. Amer. Chem. Soc.*, **89**, 2139 (1967).

(3) H. E. Simmons, E. P. Blanchard, and R. D. Smith, *ibid.*, **86**, 1347 (1964).

(4) A commercial mixture of *cis*- and *trans*-cyclododecene was used for the preparation of bicyclo[10.1.0]tridecane. The sample of bicyclotridecane used in this study was shown by gas chromatographic analysis to be approximately 50% *cis*, 50% *trans*; only one of the isomers (presumably *cis*) gave the upfield nmr signal reported.

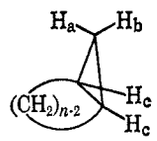

Figure 1.—*cis*-Bicyclo[*x*.1.0]alkanes: n = 5–12; x = 3–10.

cause the signal for the downfield proton in that geminal pair is obscured by the strong signals for other protons in several of the bicycloalkanes.

TABLE I

CHEMICAL SHIFTS OF CYCLOPROPANE CH_2 PROTONS IN *cis*-BICYCLO[*x*.1.0]ALKANES

Bicycloalkane	Registry no.	Chemical shift,[a] H_a	Chemical shift,[a] H_b
[2.1.0][b]		−0.4	−0.7
[3.1.0][c]		−0.02	−0.21
[4.1.0][c]		0.04	−0.47
[5.1.0]	16526-90-2	−0.02	(−0.7)
[6.1.0]	13757-43-2	0.30	(−0.4)
[7.1.0]	13758-98-0	0.42	(−0.4)
[8.1.0][d]	13757-44-3	0.48	−0.51
[10.1.0][e]		0.35	(−0.4)

[a] Center of signal, in parts per million, relative to internal tetramethylsilane; minus sign indicates downfield and parentheses indicate maximum upfield position. [b] Reference 12. [c] This compound also described by D. L. Muck and E. R. Wilson, *J. Org. Chem.*, **33**, 419 (1968). [d] The nmr spectrum of *trans*-bicyclo[8.1.0]undecane includes signals at −0.25 (cyclopropane CH_2, 2H) and −0.45 ppm (bridgehead H, 2). [e] See Reference 4.

Although there was uncertainty a few years ago about the relative magnitude of *cis* and *trans* vicinal coupling constants in cyclopropane derivatives,[5] the order $J_{cis} > J_{trans}$ seems to be firmly established and unchallenged now.[6] When both J_{ac} and J_{bc} can be discerned from the nmr spectrum, the assignment of the most upfield signal can be made with confidence.[7] When the signal for either H_a or H_b is completely obscured by the strong signals for other protons in the bicyclic hydrocarbon, however, the assignment is less clear. There has been disagreement on the shielding effects of alkyl groups on vicinal protons in cyclopropane derivatives,[6c,d,8] and the possibility of transannular end-on interactions (deshielding)[6d,9] in the medium-ring derivatives described here adds difficulty to the assignment. Whereas we were persuaded initially that the most upfield signal is associated with H_a rather than with H_b,[1c] the different viewpoints recorded in the literature since that time led us to confirm our first assignment with nuclear Overhauser effect (NOE) data.[10] Low intensity irradiation of a $DCCl_3$ solution of bicyclo[3.1.0]hexane at a frequency corresponding to the absorbance of the larger ring protons proximal to H_a but not spin–spin coupled to it led to the NOE. The shapes of the nmr signals due to H_a and H_b were essentially unchanged, but the integrated intensity of the (more upfield) H_a signal increased significantly (23%). Irradiation at other frequencies, both upfield and downfield, failed to produce the NOE. This result clearly identifies the more upfield signal with H_a. Likewise, similar irradiation produced a similar increase (25%) in the integrated intensity of the most upfield signal in the spectrum of bicyclo[8.1.0]undecane, again identifying that signal with H_a rather than H_b.

The upfield position of nmr signals for cyclopropane hydrogens (relative to other methylene hydrogens) is, of course, well known, but few chemical shifts of cyclopropane hydrogens as far upfield as some included in Table I have been reported before. The shielding of H_a reaches a maximum with the ten-membered ring, and in that system the chemical shift of H_a is nearly the same as that of the *syn* proton, shielded by the aromatic ring current, in homotropylium cation (0.6 ppm,)[11] and higher than that of the *syn* protons in unsaturated systems such as bicyclo[3.1.0]hex-2-ene,[12] bicyclo[2.1.0]-but-2-ene,[12] and bicyclo[6.1.0]nona-2,4,6-triene.[13] The signal from *cis*-bicyclo[10.1.0]tridecane is not so far upfield as that from *cis*-bicyclo[8.1.0]undecane. This result is reminiscent of other manifestations of medium ring effects.[14] Identification of the upfield signal with H_a for both common and medium ring derivatives, however, indicates that transannular, end-on interactions (which are presumably responsible for many medium ring effects[14b]) are insufficient in these bicycloalkanes to alter the relative positions of the H_a and H_b signals. The differences in shielding of H_a must be associated with a continuous change in C–C bond anisotropy effects rather than with a change in kind of interactions among these compounds. Models do not reveal any striking differences among these bicycloalkanes in proximity of H_a and the flanking methylenes, certainly not enough to provide a ready explanation of the upfield shift of the H_a signal as a function of ring size. Apparently the anisotropy effects in these saturated hydrocarbons are surprisingly sensitive to small changes in geometry.

Experimental Section

Nmr data were obtained with Varian Associates HA-60, A-60A and HA-100 instruments, with the assistance of Mr. W. Wegner. All chemical shift data are relative to internal tetramethylsilane reference and are for benzene or chloroform-*d* solutions. NOE data were obtained by a frequency sweep method with the HA-100 instrument and 40 mV irradiation; benzene was used as a reference line for field–frequency lock.[10a]

Most of the bicycloalkanes used have been described previously.[15] *trans*-Bicyclo[8.1.0]undecane was prepared in 80% yield by methyleneation[3] of *trans*-cyclodecene;[16] it distilled at

(5) (a) G. L. Closs and L. E. Closs, *ibid.*, **82**, 5723 (1960); (b) U. Schöllkopf and G. J. Lehmann, *Tetrahedron Lett.*, 165 (1962).

(6) (a) G. L. Closs, R. A. Moss, and J. J. Coyle, *J. Amer. Chem. Soc.*, **84**, 4985 (1962); (b) U. Schöllkopf, A. Lerch, and J. Paust, *Chem. Ber.*, **96**, 2266 (1963); (c) W. G. Dauben and W. T. Wipke, *Pure Appl. Chem.*, **9**, 539 (1964); (d) W. G. Dauben and W. T. Wipke, *J. Org. Chem.*, **32**, 2976 (1967).

(7) On the basis of all data presently available on J_{vic} for 7-H of 7-substituted norcaranes, the more upfield signal is invariably associated with the *syn* proton (H_a in Figure 1). See also ref 6d.

(8) (a) D. E. Minnikin, *Chem. Ind.* (London), 2167 (1966); (b) D. T. Longone and A. H. Miller, *Chem. Commun.*, 447 (1967); (c) T. Ando, F. Namigata, H. Yamanake, and W. Funasaka, *J. Amer. Chem. Soc.*, **89**, 5719 (1967).

(9) (a) S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *ibid.*, **87**, 5247 (1965); (b) M. A. Battiste and M. E. Brennan, *Tetrahedron Lett.*, 5857 (1966).

(10) (a) F. A. L. Anet and A. J. Bourn, *J. Amer. Chem. Soc.*, **87**, 5250 (1965); (b) J. G. Colson, P. T. Lansbury, and F. D. Saeva, *ibid.*, **89**, 4987 (1967); (c) M. C. Woods, H. C. Chiang, Y. Nakadaira, and K. Nakanishi, *ibid.*, **90**, 522 (1968).

(11) C. E. Keller and R. Pettit, *ibid.*, **88**, 606 (1966).

(12) J. I. Brauman, L. E. Ellis, and E. E. van Tamelen, *ibid.*, **88**, 846 (1966).

(13) T. J. Katz and P. J. Garratt, *ibid.*, **86**, 5194 (1964).

(14) (a) V. Prelog, *J. Chem. Soc.*, **420** (1950); (b) J. Sicher in "Progress in Stereochemistry," Vol. 3, P. B. D. de la Mare and W. Klyne, Ed., Butterworth and Co. Ltd., London, 1962, Chapter 6.

(15) Reference 2 and references cited there.

(16) J. G. Traynham, D. B. Stone, and J. L. Couvillion, *J. Org. Chem.*, **32**, 510 (1967).

76–78° (8 mm) and its nmr spectrum included signals at −0.25 (cyclopropane CH_2, 2 H) and at −0.45 ppm (bridgehead H, 2 H).

Anal.[17] Calcd for $C_{11}H_{20}$: C, 86.8; H, 13.2. Found: C, 86.4; H, 13.1.

Registry No.—*trans*-Bicyclo[8.1.0]undecane, 15840-80-9.

(17) By R. Seab in these laboratories.

N^6,3′-O-Disubstituted Deoxyadenosine[1]

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Deoxyadenosine derivatives possessing alkali or hydrazine labile protecting groups at the N^6 and 3′-O positions are attractive intermediates for use in synthesizing oligonucleotides by the phosphotriester method.[1,2] A route to such compounds is to block the reactive 5′ oxygen of N^6-acyl- or benzoyldeoxyadenosine, introduce the desired substituent on the 3′ oxygen, and then remove selectively the protecting group on the 5′ oxygen. Since N^6-benzoyldeoxyadenosine derivatives readily undergo depurination in acidic media,[3,4] the protecting group on the 5′-oxygen atom should be one that can be removed without resort to acidic conditions. At the same time, strong alkaline conditions for removal of this group are precluded if an acyl group is to be retained on the 3′ oxygen.

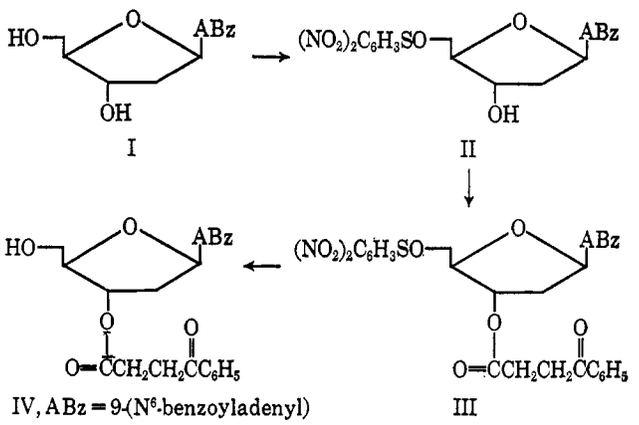
The 2,4-dinitrobenzenesulfenyl group, which protects oxygen of hydroxyl groups during acylation reactions and can be removed readily by the action of thiophenol in pyridine,[5] appeared to have the requisite properties for protecting the 5′-oxygen of deoxyadenosine derivatives. As a test of this approach we explored the synthesis of 3′-O-(β-benzoylpropionyl)-N^6-benzoyldeoxyadenosine *via* 5′-O-(2,4-dinitrobenzenesulfenyl)-N^6-benzoyldeoxyadenosine.

Preliminary experiments were conducted with thymidine to see if the 5′ oxygen of a nucleoside with free 3′- and 5′-hydroxyl groups could be preferentially sulfenylated. At room temperature the degree of selectivity was low. However, when the reaction was carried out with slightly less than 1 equiv of 2,4-dinitrobenzenesulfenyl chloride at 0°, a 37% yield of 5′-O-(2,4-dinitrobenzenesulfenyl)thymidine was obtained along with small amounts of the 3′-O-dinitrobenzenesulfenyl isomer (10%) and a higher sulfenylated product (~8%). The 3′ isomer has been prepared previously from 5′-O-tritylthymidine.[5]

N^6-Benzoyldeoxyadenosine underwent reaction with 2,4-dinitrobenzenesulfenyl chloride considerably more slowly than did thymidine. A suitable method for formation of the 5′-oxygen derivative was found to be treatment of N^6-benzoyldeoxyadenosine with 1.5 equiv of 2,4-dinitrobenzenesulfenyl chloride in pyridine at 20° for 1.5 hr. Under these conditions a 45% yield of 5′-O-(2,4-dinitrobenzenesulfenyl)-N^6-benzoyldeoxyadenosine, a 12% yield of the corresponding 3′-O isomer, and a 13% yield of a disulfenylated derivative were obtained.

A flowsheet depicting the formation of 5′-O-(2,4-dinitrobenzenesulfenyl)-N^6-benzoyldeoxyadenosine (II), introduction of a β-benzoylpropionyl group at the 3′ oxygen to give III, and cleavage of the dinitrobenzenesulfenyl group to yield 3′-O-(β-benzoylpropionyl)-N^6-benzoyldeoxyadenosine (IV) is shown in Chart I.

CHART I



Compound III was obtained in 54% yield by reaction of II with excess β-benzoylpropionic acid and dicyclohexylcarbodiimide. The dinitrobenzenesulfenyl group could be cleaved from the 5′ oxygen cleanly with thiophenol in pyridine, as in the case of the thymidine derivatives.[5] We used hydrogen sulfide in pyridine in the preparative experiment for this purpose, however, since it was found that hydrogen sulfide effects the cleavage and the reaction mixture can be worked up more conveniently than one containing excess thiophenol.

In the case of the mono(dinitrobenzenesulfenyl) derivatives of thymidine the assignment of structure is clear as the higher melting isomer is known from independent synthesis[5] to be the 3′-oxygen derivative. Two lines of evidence point to the fact that the lower melting isomer of mono(dinitrobenzenesulfenyl)-N^6-deoxyadenosine is the 5′-oxygen derivative: (1) The lower melting isomer was obtained in preponderate amount, in accord with the observation that the 5′-oxygen of nucleoside derivatives is in general attacked more readily than the 3′-oxygen. (2) The R_f value of the lower melting isomer (in ethyl acetate on silica slides) is less than that for the higher melting isomer, in agreement with the observation that the R_f values for 5′-oxygen derivatives of nucleosides are less than the R_f values of the corresponding 3′-oxygen derivatives (*e.g.*, for the 2,4-dinitrobenzenesulfenyl, the *p*-monomethoxytrityl, and the isobutyloxycarbonyl derivatives[6] of thymidine). Proof that the β-benzoylpropionyl group in IV is joined at the 3′-oxygen, and therefore that the 2,4-dinitroben-

(1) Part XI in series on Nucleotide Chemistry. Part X: R. L. Letsinger, M. H. Caruthers, P. S. Miller, and K. K. Ogilvie, *J. Amer. Chem. Soc.*, **89**, 7146 (1967). This research was supported by the Division of General Medical Sciences, National Institutes of Health (GM-10265).

(2) R. L. Letsinger and K. K. Ogilvie, *ibid.*, **89**, 4801 (1967).

(3) H. Schaller, G. Weimann, B. Lerch, and H. G. Khorana, *ibid.*, **85**, 3821 (1963).

(4) W. Moon, S. Nishimura, and H. G. Khorana, *Biochemistry*, **5**, 937 (1966).

(5) R. L. Letsinger, J. Fontaine, V. Mahadevan, D A. Schexnayder, and R. E. Leone, *J. Org. Chem.*, **29**, 2615 (1964).

(6) K. K. Ogilvie and R. L. Letsinger, *ibid.*, **32**, 2365 (1967).