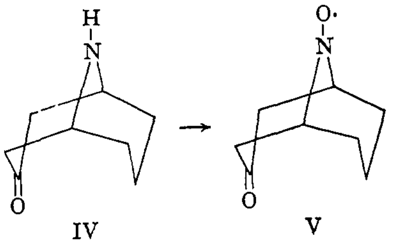
nitroxide free radical, in which any nitrone formation would be prohibited by Bredt's rule. Treatment[12] of 1.5 g of norpseudopelletierine (IV) in 15 ml of water


IV V

by 1.8 ml of 30% hydrogen peroxide in the presence of 10 mg of phosphotungstic acid gave, after ether extraction, chromatography on aluminum oxide, and recrystallization from ether, 308 mg (30% yield) of V, mp 120–121° (*Anal.* Found for $C_8H_{12}NO_2$: C, 62.12; H, 7.78; N, 9.28). The ultraviolet, infrared, and esr spectra are consistent with the nitroxide structure, showing the characteristic ultraviolet absorption[2,3,12] at 462 mμ (ϵ 8.5) in chloroform, blue shifted to 445 mμ (ϵ 6.4) in methanol, the carbonyl infrared absorption in CCl_4 at 1715 cm^{-1}, and the classical esr triplet, with a nitrogen splitting increasing with the solvent polarity,[3,12] going from 17.55 oersteds in benzene solution to 18.45 oersteds in water.[13]

This radical, although stable in the solid state and in benzene or water solution, is very reactive, much more than the related di-*t*-butyl nitroxide or 2,2,6,6-tetramethylpiperidine-N-oxyl; for instance, the ultraviolet or esr absorption disappears rapidly in acid or in basic solution.

The existence of V suggests that nitroxides are resistant to dimerization but that they are "stable" only when no double bond can be formed between the nitrogen and the adjacent carbon. Bis(trifluormethyl) nitroxide[14,15] may be another example of this rule.

(12) *Cf.* R. Brière, H. Lemaire, and A. Rassat, *Bull. Soc. Chim. France*, **11**, 3273 (1965).

(13) In deoxygenated benzene solution, each component of the triplet is divided into at least 17 lines separated by 0.66 oersted and attributed to different protons of the molecule.

(14) W. D. Blackley and R. R. Reinhard, *J. Am. Chem. Soc.*, **87**, 802 (1965).

(15) S. P. Makarov, A. I. Iakubovich, S. S. Dubov, and A. N. Medvedev, *Dokl. Akad. Nauk SSSR*, **160**, 1319 (1965).

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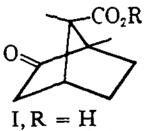
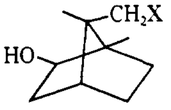
Received April 21, 1966

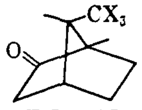
Deuterium and the Octant Rule

Sir:

D-(+)-Isoketopinic acid (I) has been prepared from D-(+)-camphor by α bromination, π bromination, α debromination, displacement of the π bromine by acetate, saponification, and oxidation.[1] The corresponding methyl ester II is converted to the 2,9-diol III by lithium aluminum hydride, and selective 9-*p*-toluenesulfonation followed by lithium aluminum hydride reduction and Sarrett oxidation affords D-(+)-camphor. The molecular amplitudes of the Cotton effects of starting camphor and product camphor are identical, +62.89 ± 0.31 and + 62.56 ± 0.54°, respectively,[2] showing that optical purity is retained throughout the synthetic sequence. When the two lithium aluminum hydride reductions are replaced by lithium aluminum deuteride reductions, D-(+)-camphor-9,9,9-d_3 (at least 97.9% d_3 by mass spectral analysis) is obtained. The molecular rotations of this product are smaller in magnitude than those of camphor at both the peak (312 mμ) and the trough (274 mμ) of the Cotton effect, which as a result has a molecular amplitude of only +60.92 ± 0.23°,[2] 3% less than that of the protio counterpart.


I, R = H
II, R = CH_3


III, X = OH
IV, X = $OSO_2C_7H_7$
V, X = H


VI, X = H
VII, X = D

The 9-methyl group of camphor lies in a positive octant,[3] but the atomic refractivity of deuterium is less than that of hydrogen (the polarizability of a C–D bond is less than that of a C–H bond).[4–6] Thus deuterium (like fluorine[3,7]) should be expected to produce a contribution to the Cotton effect of sign opposite that predicted by the general octant rule, as is observed. Streitwieser[8] recently showed that compounds whose sole optical activity results from the difference between hydrogen and deuterium have normal (plain) rotatory dispersion properties, and thus that "deuterium behaves as an ordinary substituent so far as optical activity is concerned." We feel that the present result suggests[9] that deuterium is also a normal substituent so far as the octant rule is concerned, so long as its atomic refractivity properties are not overlooked. The magnitude of our observed effect, however, seems remarkably large.[9,10]

Acknowledgment. We are grateful to the National Science Foundation for Grant GB-1606 which partially supported this work, to Dr. Joseph Wolinsky and Mr.

(1) E. J. Corey, S. W. Chow, and R. A. Scherrer, *J. Am. Chem. Soc.*, **79**, 5773 (1957); E. J. Corey, M. Ohno, S. W. Chow, and R. A. Scherrer, *ibid.*, **81**, 6305 (1959).

(2) Rotatory dispersion measurements were obtained at 24° with a Durrum-Jasco ORD/UV-5 recording spectropolarimeter. Methanol solutions (*ca.* 1 mg/ml) were prepared from two samples of each of three independently synthesized batches of camphor and camphor-d_3, and two ORD spectra were obtained from each solution. All measurements were made within a continuous 18-hr period, and the solutions were examined in random sequence.

(3) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

(4) R. P. Bell, *Trans. Faraday Soc.*, **38**, 422 (1942).

(5) W. Fickett, *J. Am. Chem. Soc.*, **74**, 4204 (1952).

(6) J. H. Brewster, *ibid.*, **81**, 5475 (1959); *Tetrahedron Letters*, No. 20, 23 (1959).

(7) C. S. Barnes and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1962 (1962).

(8) A. Streitwieser, Jr., L. Verbit, and S. Andreades, *J. Org. Chem.*, **30**, 2078 (1965).

(9) The deuteriomethyl group is smaller than a methyl group [*cf.* A. Horeau, A. Nouaille, and K. Mislow, *J. Am. Chem. Soc.*, **87**, 4957 (1965), and references therein]. Consequently when deuterium replaces hydrogen at C-9 there could be a decrease in nonbonded interactions between C-9 substituents and the remainder of the molecule, thereby producing a small conformational change in the ring system. That such a conformational distortion, rather than the atomic refractivity difference between D and H, is responsible for part or all of the osberved diminution of Cotton effect amplitude cannot be excluded as a possibility in the present example.

(10) C. Djerassi and B. Tursch, *J. Am. Chem. Soc.*, **83**, 4609 (1961), found no difference in the amplitudes of the Cotton effects of 3β-acetoxycholestan-7-one and 3β-acetoxy-6β-deuteriocholestan-7-one, and observed no (<42°) rotation at 322 mμ for 3-deuteriocyclopentanone, both of which results suggested that the effect of deuterium would be small if observable at all. In our camphor-d_3, of course, three deuterons have replaced protons in a positive octant, and in addition they are differently located in the octant (farther from the carbonyl, however) than those in the Djerassi compounds.

Don Dimmel of Purdue University for the mass spectral data, and to Mr. Richard N. McCarty for carrying out some of the initial synthetic experiments.

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[12] U. S. Government Grantee, 1960–1962, administered by the Institute of International Education.

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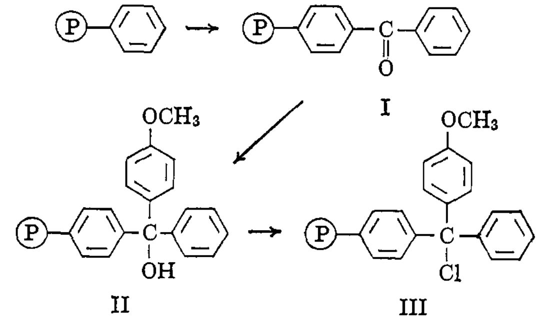
Deoxyribooligonucleotide Synthesis on a Polymer Support[1]

Sir:

The principle of carrying out reactions between reactants when one of these is provided in a readily separable form has been expressed in literature from time to time[2] and it has recently been developed with striking success by Merrifield for the synthesis of polypeptides.[3] In the Merrifield procedure, a polypeptide chain is built up in a stepwise manner from one end while it is linked by a covalent bond at the other end to an *insoluble* polymeric support. Polypeptide synthesis on a polymer support has been developed more recently in an alternative form by Shemyakin and coworkers[4] in which the polymer, polystyrene, supporting the growing peptide chain is actually soluble in the medium of reaction, and therefore the repetitive condensations are performed in completely homogeneous phase. The concept of polymer support synthesis could in principle lend itself to work in the polynucleotide field, and one synthetic approach embodying this principle has already been outlined by Letsinger and Mahadevan.[5] We have also been investigating for some time various means of carrying out deoxyribopolynucleotide synthesis on a polymer support and herein describe an approach which is among those that we have investigated.

Preparation of Polymer. In concept, the approach is akin to that used previously by Shemyakin, *et al.*, in the peptide field. The starting material in our work was polystyrene of average molecular weight 270,000[6] and the steps used in preparation of the appropriate derivative are shown in Chart I. The polystyrene (10 g) was subjected to a Friedel-Crafts reaction with benzoyl chloride (51 mmoles) and aluminum chloride (51 mmoles) in carbon disulfide. The product (I; 13.2 g, λ_{max} 257 mμ in dioxane) was isolated as a yellowish resinous powder. I (2 g) was allowed to react in benzene with *p*-methoxyphenylmagnesium bromide (4 mmoles of an ethereal solution) to give the substituted trityl alcohol (II; 2 g) which gave coloration characteristic of *p*-methoxytrityl cation on addition of perchloric acid.[7] Treatment of II (1.2 g) with acetyl chloride in cyclohexane gave the monomethoxytrityl chloride (III; 1.1 g) which was isolated as a fluffy white powder. Determination of chloride ions released on treatment with methanol and pyridine showed the reactive halogen content to be 0.4 mmole/g of the derivatized polymer.

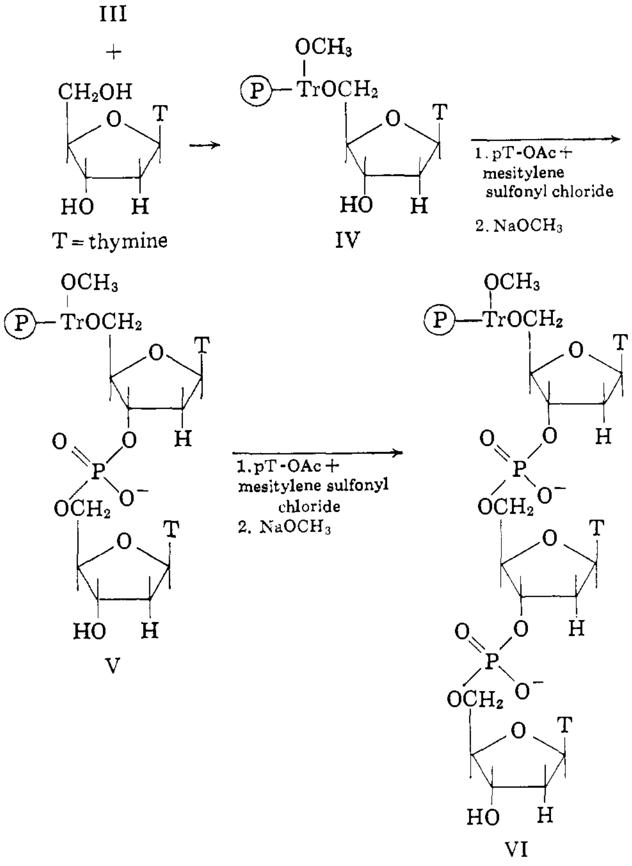
Chart I. Preparation of Polystyrene-Supported *p*-Methoxytrityl Chloride



Ⓟ = polystyrene backbone

Deoxyribooligonucleotide Synthesis. The typical steps used are illustrated in Chart II. Thus trityl chloride (III), 500 mg, was allowed to react with thymidine (70 mg) in pyridine (6 ml) first at room temperature for 12 hr and then at 65–75° for 30 min. Methanol (1 ml) was then added and, after 30 min at 75°, pyridine (5 ml) was added and the reaction mixture was poured

Chart II. Deoxyribooligonucleotide Synthesis Using Polystyrene-Supported Methoxytrityl Chloride (III)



$\text{VI} \xrightarrow{\text{TFA in CHCl}_3}$ thymidylyl-(3′→5′)-thymidylyl-(3′→5′)-thymidine

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[1] This work has been supported by grants from the National Science Foundation (Grant No. GB-3342), the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service (Grant No. CA-05178), and the Life Insurance Medical Research Fund (Grant No. G-62-54).

[2] See, for example, J. J. Cebra, D. Givol, H. I. Silman, and E. Katchalski, *J. Biol. Chem.*, **236**, 1720 (1961).

[3] R. B. Merrifield, *Science*, **150**, 178 (1965).

[4] M. M. Shemyakin, Y. A. Ovchinnikov, A. A. Kinyushkin, and I. V. Kozhevnikova, *Tetrahedron Letters*, 27, 2323 (1965).

[5] R. L. Letsinger and V. Mahadevan, *J. Am. Chem. Soc.*, **87**, 3526 (1965).

[6] This preparation (Lot No. 683) and several others with different average molecular weights were kindly supplied by Dr. E. T. Dumitru of Dow Chemical Co., Midland, Mich.

[7] H. Schaller, G. Weimann, B. Lerch, and H. G. Khorana, *J. Am. Chem. Soc.*, **85**, 3821 (1963).