Addition of Nitryl Iodide to Olefins[1]

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The reaction of silver nitrite with iodine in the presence of olefins was studied and was found to lead to nitro-iodo adducts. The reaction has the characteristics of a nitryl iodide addition and appears to proceed by a free-radical attack of an NO_2 species on the double bond. Stereochemical and regiochemical considerations are discussed. The method provides a selective synthesis of β-iodonitro-, vinylnitro-, and nitroalkanes under mild reaction conditions.

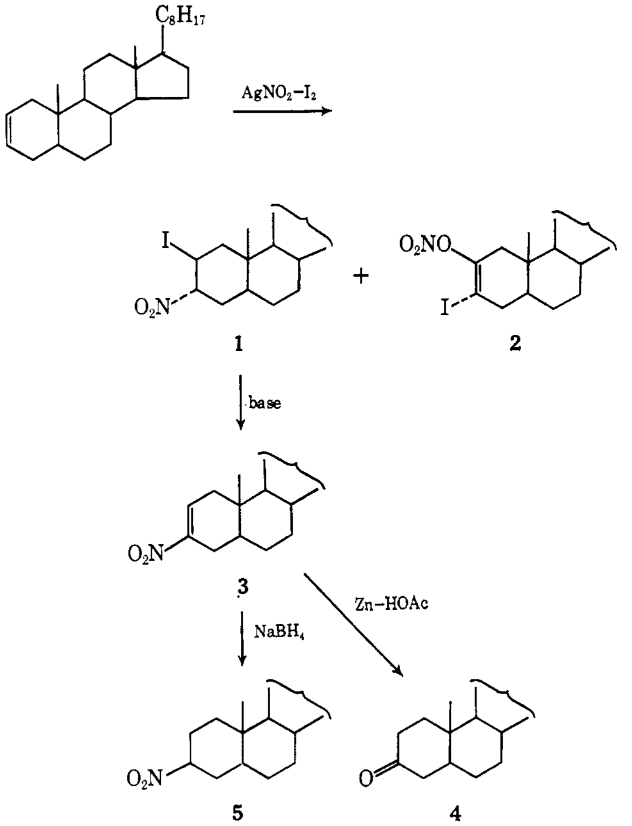
Addition reactions of pseudohalogens to olefins have recently gained in importance through their synthetic and mechanistic applications.[3] In extending pseudohalogen chemistry, this paper describes the reaction of nitryl iodide with olefins and illustrates the reaction pathway, stereochemistry, regiochemistry,[4] and products.

The reaction of silver nitrite and iodine in the presence of cyclohexene was first reported by Birchenbach to give dinitro- and iodo-nitro adducts.[5] This reaction was disregarded until 1964 when its synthetic utility and mild conditions were initially described.[1a] More recently, the mild reaction conditions of the nitryl iodide reaction have been emphasized by its use in the nitration of sugars.[6] An alternate means to synthesize nitro iodides *via* the strong oxidizing agent, dinitrogen tetroxide, has been described by Stevens and Emmons.[7]

In analogy with other pseudohalogens,[3] the reaction of silver nitrite with iodine is expected to lead to INO_2. This reagent is theoretically capable of dual heterolysis to NO_2^+ and I^- or to I^+ and NO_2^- as well as to homolysis into free radicals; hence it can function as nitryl iodide or as iodine nitrite and either ionically or free radically.

To gain information on the stereochemistry and regiochemistry of the addition of NO_2I to olefins, the reaction of silver nitrite and iodine was studied in ether in the presence of 2-cholestene. The major product (51%) was 2β-iodo-3α-nitrocholestane (**1**) together with 26% unreacted 2-cholestene and 5% 3α-iodo-2β-cholestanyl nitrate (**2**) (Scheme I). The position of the NO_2 function in **1** was proven by elimination to 3-nitrocholest-2-ene (**3**), and subsequent reduction to the known 3-cholestanone (**4**). Sodium borohydride reduction of the vinyl nitro compound (**3**) led to the known 3β-nitrocholestane (**5**).[8]

Scheme I



Attempted conversion of **1** to a steroidal aziridine was unsuccessful; treatment with zinc or with $LiAlH_4$ led to 2-cholestene by diaxial elimination of INO_2, whereas ferrous sulfate and HCl led to recovery of starting material.

The nmr spectrum of the nitro iodide **1** indicates secondary protons at τ 4.79 and 5.16 geminal to a nitro and an iodine function, respectively. Both signals have half-widths of 8 Hz indicative of equatorial protons[9] and hence of *trans* diaxially oriented NO_2 and I groups. The nmr of the nitro iodide **1** also indicates a C-19 methyl signal at τ 8.83, a shift of 0.40 ppm from the signal in cholestane. Although this is a large shift, it is not surprising since most of the 2-axial groups cause a significant shift of the C-19 methyl group.[3b,10,11] Of the many functionalities considered, iodine has been reported to have a particularly strong anistropic effect increasing in the order chloride > bromide > iodide.[12] This progression fits the observed chemical shifts for the 2-axial halides noted in Table I.

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[1] (a) Presented in part before the Symposium on Electrophilic Additions to Olefins, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964. (b) A. Hassner in L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 757. (c) Stereochemistry. XLIII. For paper XLII, see A. Hassner, R. J. Isbister, and A. Friederang, *Tetrahedron Lett.*, in press.

[2] (a) The work described was taken from the thesis submitted by J. E. Kropp in partial fulfillment of the requirements for the Ph.D. degree from the University of Colorado (1965). (b) Participant, NSF Summer Research Program for College Teachers.

[3] For instance (a) A. Hassner and F. W. Fowler, *J. Amer. Chem. Soc.*, **90**, 2869 (1968); (b) A. Hassner, M. E. Lorber, and C. Heathcock, *J. Org. Chem.*, **32**, 540 (1967), and references cited therein.

[4] Regio is used to describe directional effects in bond making or breaking: A. Hassner, *ibid.*, **33**, 2684 (1968).

[5] L. Birchenbach, J. Goubeau, and E. Berniger, *Ber.*, **65**, 1339 (1932).

[6] W. A. Szarek, D. G. Lance, and R. L. Beach, *Chem. Commun.*, 356 (1968).

[7] T. E. Stevens and W. D. Emmons, *J. Amer. Chem. Soc.*, **80**, 338 (1958).

[8] J. R. Bull, E. R. H. Jones, and G. D. Meakins, *J. Chem. Soc.*, 2601 (1965). We are greatful to Dr. Meakins for a sample of **5**.

[9] A. Hassner and C. H. Heathcock, *J. Org. Chem.* **30**, 1748 (1965).

[10] K. Tori and T. Komeno, *Tetrahedron*, **21**, No. 2, 309 (1965).

[11] A. Hassner and F. Boerwinkle, *J. Amer. Chem. Soc.*, **90**, 216 (1968).

[12] G. S. Reddy and J. H. Goldstein, *J. Chem. Phys.*, **38**, 2736 (1936).

TABLE I

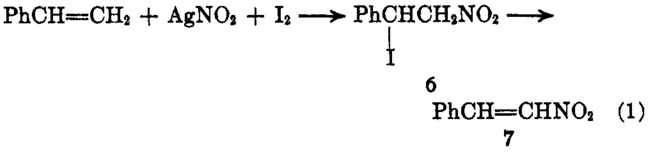
NMR SHIFTS OF STEROIDAL C-19 PROTONS

2 substituent	3 substituent	C-19 methyl, τ	Shift, ppm, from cholestane
H	H	9.23	0.00
2β-I	3α-NO_2	8.83	−0.40
2β-Br	3α-Br	8.86	−0.37
2β-Br	3α-N_3	8.91	−0.32[a]
2β-Cl	3α-I	8.89	−0.34[a]
2β-NO_2	H	9.32	+0.12[b]
H	3β-NO_2	9.13	−0.10
2β-OH	3α-SH	9.00	−0.23[c]
2β-OH	H	8.98	−0.25[c]
H	3α-SH	9.22	−0.01[c]
2β-SH or SCOMe	H	8.95	−0.28[c]
2α-SH	H	9.17	−0.06[c]
2β-N_3	3α-Br	9.01	−0.22[a]
2β-N_3	3α-I	9.02	−0.21[d]
2β-NCO	3α-I	8.98	−0.25[e]
2β-ONO_2	3α-I	9.10	−0.13

[a] See ref 11. [b] A. Hassner, J. M. Larkin, and J. E. Dowd, *J. Org. Chem.*, **33**, 1733 (1968). [c] See ref 10. [d] See ref 3a. [e] See ref 3b.

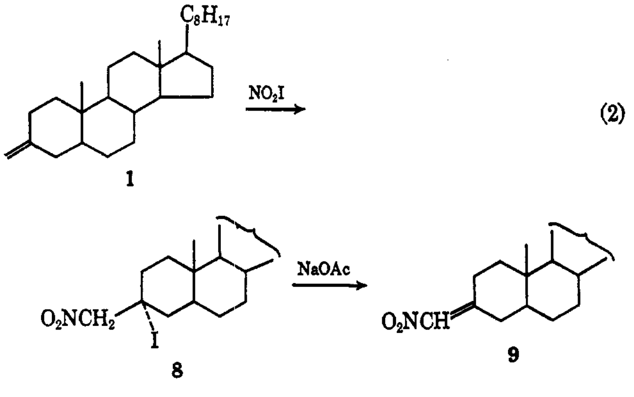
It is clear from the shifts of the C-19 protons in Table I that 2β-hydroxy-3α-cholestanethiol (0.18 ppm) and 2β-hydroxycholestane (0.20 ppm) show almost the same shift of the C-19 methyl signal; hence the 3α substituent has only a slight effect upon the C-19 absorption. Analogously the large shift of the C-19 protons in 2β-iodo-3α-nitrocholestane (**1**) would appear to be due mainly to the 2β-iodo group with only slight influence by the 3α-nitro function.

The fact that the nitro group in **1** occupies the 3α position suggested that the pseudohalogen was not reacting as iodonium nitrite (INO_2) through a three-membered iodonium ion intermediate,[3b] but instead had behaved as nitryl iodide (NO_2I). This conclusion was confirmed by the regiochemistry of the reaction of silver nitrite and iodine in the presence of styrene. The unstable nitro iodide **6** on treatment with pyridine produced the known β-nitrostyrene (**7**) (eq 1).

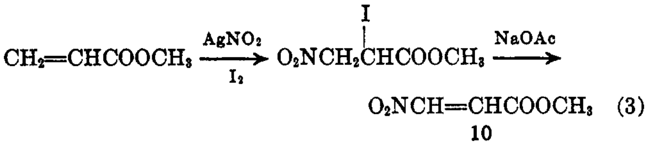


$$PhCH{=}CH_2 + AgNO_2 + I_2 \longrightarrow \underset{\mathbf{6}}{PhC\underset{I}{H}CH_2NO_2} \longrightarrow \underset{\mathbf{7}}{PhCH{=}CHNO_2} \quad (1)$$

The regioselectivity of NO_2I additions was further demonstrated by the formation of 3-iodo-3-(nitromethyl)cholestane (**8**) from the addition to 3-methylenecholestane (eq 2). The structure of **8** was apparent from HI elimination with sodium acetate to 3-(nitromethylene)cholestane (**9**).



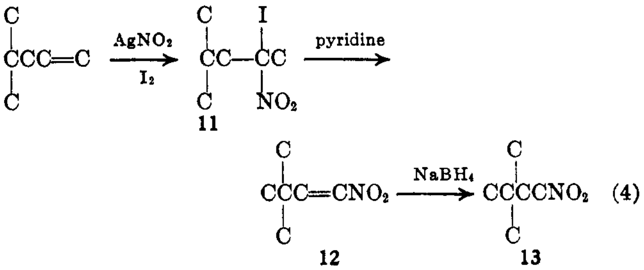
The above results do not differentiate between attack by NO_2^+ or $NO_2\cdot$ on the terminal carbon of the olefin. Substantiation for the free-radical pathway was obtained by studying the NO_2I addition to an unsaturated ester substrate, since the creation of a positive charge, but not of a free radical, next to a carbonyl group is very unfavorable.[13,14] The product from reaction of methyl acrylate with nitryl iodide and subsequent elimination with sodium acetate was methyl 3-nitroacrylate (**10**) (eq 3), identical with **10** obtained by Shechter, *et al.*,[15]



$$CH_2{=}CHCOOCH_3 \xrightarrow[I_2]{AgNO_2} O_2NCH_2\overset{I}{C}HCOOCH_3 \xrightarrow{NaOAc} \underset{\mathbf{10}}{O_2NCH{=}CHCOOCH_3} \quad (3)$$

in the free-radical addition of nitryl chloride (NO_2Cl) to methyl acrylate. A free-radical addition is also consistent with the fact that the formation of **1** is greatly inhibited in the presence of oxygen.

In studying the effect of bulky groups upon the addition reaction of bromine in methanol, Newman, *et al.*,[16] found that the direction of addition allowed a differentiation between a free carbonium ion pathway and one involving a cyclic intermediate. When *t*-butylethylene was treated with silver nitrite and iodine, the crude adduct **11** was obtained which on elimination of HI with pyridine led to vinylnitro compound **12**. The nmr spectrum of this compound shows doublets at τ 2.87 (J = 13.5 Hz) and 3.28 (J = 13.5 Hz) indicative of a *trans* olefin and ruling out the possibility of a terminal $C{=}CH_2$. Reduction of **12** by sodium borohydride gave the saturated nitro compound **13** (eq 4) that showed a classical A_2X_2 absorption in the nmr spectrum.



$$C\underset{C}{\overset{C}{C}}C{=}C \xrightarrow[I_2]{AgNO_2} \underset{\mathbf{11}}{C\underset{C}{\overset{C}{C}}{-}\underset{NO_2}{\overset{I}{C}}C} \xrightarrow{pyridine} \underset{\mathbf{12}}{C\underset{C}{\overset{C}{C}}C{=}CNO_2} \xrightarrow{NaBH_4} \underset{\mathbf{13}}{C\underset{C}{\overset{C}{C}}CCNO_2} \quad (4)$$

Since the nitro group is the attacking species and it becomes bonded to the terminal carbon, the intermediate radical or ion was probably not bridged; otherwise opening by INO_2 should have led to the opposite regioisomer.

The diaxial iodo–nitro adduct **1** provides a good testing ground to show whether participation by a neighboring NO_2 group is possible in solvolysis reactions. Though Jeffery, *et al.*,[17] found no assistance by an NO_2 group in the solvolysis of benzyl halides, neighboring-group participation was reported for *o*-

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(13) A. M. Mattocks and W. H. Hartung, *J. Biol. Chem.*, **165**, 501 (1946).

(14) H. Shechter and F. Conrad, *J. Amer. Chem. Soc.*, **75**, 5610 (1953).

(15) H. Shechter, F. Conrad, A. L. Daulton, and R. E. Kaplin, *ibid.*, **74**, 3052 (1952).

(16) W. H. Puterbaugh and M. S. Newman, *ibid.*, **79**, 3469 (1957).

(17) E. A. Jeffery, L. J. Andrews, and R. M. Keefer, *J. Org. Chem.*, **29**, 3365 (1964).

nitrobenzyl tosylates.[18] When **1** was refluxed with silver sulfate, nitrate, or perchlorate in alcohol it was recovered essentially unchanged; a small amount of nitro olefin was formed but no methyl ethers were detectable by nmr. On the refluxing of **1** in absolute methanol in the presence of silver oxide, 3-nitro-2-cholestene (**3**) was obtained in 99% yield.

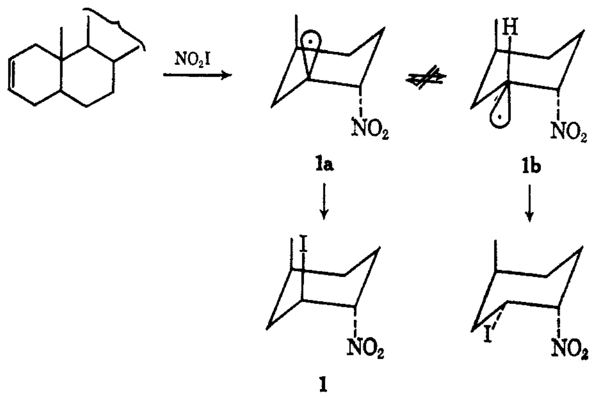
The reaction of $AgNO_2$ and I_2 with olefins does not involve the initial formation of diiodide followed by reaction with silver nitrite since no nitro compounds were obtained upon treating an equilibrated solution of 2-cholestene and its diiodide (obtained from 2-cholestene and iodine) with $AgNO_2$. Further evidence for the formation of an NO_2I species[19] was obtained by filtering the solids from the reaction mixture of silver nitrite and iodine before the addition of the olefin. Upon addition of 2-cholestene the nitro iodide **1** was produced, albeit in very poor yield.

The nitro iodide **1** was also obtained in good yield by slow addition of dinitrogen tetroxide to a solution of 2-cholestene and iodine in nonpolar solvents. This reaction also proceeds through attack of NO_2 on the double bond followed by quenching of the radical with iodine.

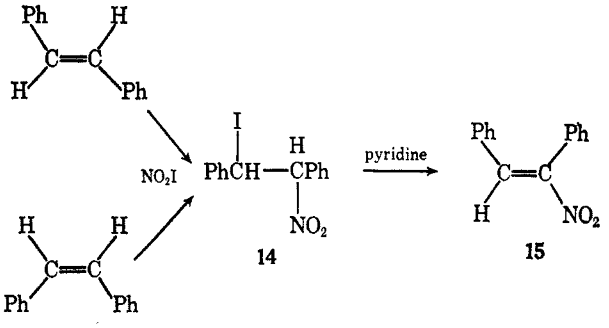
The *trans* stereochemistry in adduct **1** suggests that either a stable pyramidal radical is produced or the quenching reaction is more rapid than inversion of the radical formed. Since Brand and Stevens[20] have shown that 2-nitrocyclohexyl radicals lead to a great deal of epimerization, the *trans* diaxial NO_2I addition to 2-cholestene warrants an explanation. Approach from the α side in steroids occurs for steric reasons. In the *trans* fused decalin system stereoelectronic factors are responsible for the preferred axial attack by the NO_2 radical with simultaneous development of an axial radical. The resulting adduct radical will prefer to have a chair rather than a twist–boat conformation thus giving rise to **1a**. Using the propositions of Brand and Stevens, radical **1a** must be short lived and not allow for the epimerization that takes place in the case of nitryl chloride, dinitrogen tetroxide, or dinitrogen pentoxide additions to cyclohexene. Instead the intermediate nitroalkyl radical (**1a**) is apparently trapped very rapidly and efficiently by iodine before it can invert to **1b** (Scheme II). In this fashion the product is kinetically controlled giving rise to the sterically unfavored 1,3-diaxial arrangement of iodine and C-19 methyl. Other examples of stereoselective radical addition to a cyclohexene system such as the thiol addition to *t*-butylcyclohexene[21] or diaxial radical additions to steroid 5-enes can be similarly explained.[22]

When nitryl iodide was added to *cis*- and *trans*-stilbene, the resulting product appeared to be a diastereoisomeric mixture (**14**) with an nmr doublet at τ 3.43 (1 H) and two doublets at 3.74 ($^1/_2$ H) and 3.86 ($^1/_2$ H). This mixture was dehydrohalogenated to give the same *cis*-1,2-diphenyl-1-nitrostilbene (**15**) (Scheme III) as that obtained by Stevens and Emmons.[7]

Scheme II

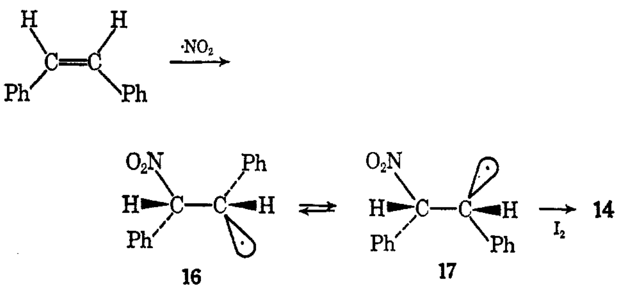


Scheme III



After treating an excess of *cis*-stilbene with nitryl iodide, the nmr of the crude product indicated the unreacted stilbene to be solely the *cis* isomer, suggesting that the formation of the nitro radical is nonreversible. Since no *cis–trans*-stilbene isomerization had occurred, yet a diastereoisomeric mixture of products was obtained, a long-lived pyramidal structure (**16**) must not be formed. Instead, the phenyl stabilized radical **16** is interconverted to **17** before it is quenched by iodine (Scheme IV).

Scheme IV



Unlike nitryl fluoroborate, NO_2I does not serve as an efficient source of positive nitrylium ions as evidenced by its failure to nitrate toluene or methyl benzoate. With phenol, *o*- and *p*-nitrophenols as well as iodophenols were obtained.

Experimental Section

Preparation of 2β-Iodo-3α-nitrocholestane (1). A. General Procedure. Reaction with $AgNO_2$–I_2 in Ether.—Silver nitrite, 1.16 g (7.55 mmol), and iodine, 3.85 g (15.1 mmol), were stirred in 75 ml of ether for 30 min and 2-cholestene, 2.79 g (7.55 mmol), was added while the headspace of the reaction flask was flushed with dry nitrogen (if the headspace was not flushed with nitrogen

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[18] W. B. Dickinson, *J. Amer. Chem. Soc.*, **86**, 3580 (1964).

[19] NO_2I is easily oxidized in polar solvents to INO_3. The addition of this species to olefins will be discussed in a subsequent publication.

[20] J. C. D. Brand and I. D. R. Stevens, *J. Chem. Soc.*, 629 (1958); *Chem. Ind.* (London), 1742 (1955).

[21] (a) E. S. Huyser and J. R. Jeffrey, *Tetrahedron*, **21**, 3083 (1965); (b) F. G. Bordwell, P. S. Landis, and G. S. Whitney, *J. Org. Chem.*, **30**, 3764 (1965).

[22] C. W. Shoppee and R. Lack, *J. Chem. Soc.*, 4864 (1960).

during the reaction, the yield of the isolated nitro compound dropped to less than 30%). The mixture was stirred for 4 hr and filtered and the solids were washed with ether. The ether was washed with a solution of $NaHSO_3$ and 100 ml of saturated sodium chloride solution and dried ($MgSO_4$). The ethereal solution was then evaporated under a stream of nitrogen until the orange-brown residue was dry.

A portion (0.1013 g) of the crude material was dissolved in 4.9868 g of Spectro Grade chloroform. Infrared spectral analysis, using calibrations by means of the hill and valley technique for the transmittance at 1630 cm^{-1} for **2**, indicated the presence of 5% 3α-iodo-2β-cholestanyl nitrate (**2**).

The orange-brown solids were triturated with 5 ml of hexane and cooled in an ice chest. The solids were filtered off and washed with a small amount of cold hexane. After the mixture was dried, 2.033 g (51%), mp 127-135°, of a white solid was obtained. Several recrystallizations from ethyl acetate gave an analytical sample of **1**: mp 141-143°; ir (KBr) 1548, 1367, and 870 cm^{-1} (nitrate); nmr peaks at τ 4.79 (m, 1, $W_{1/2}$ = 8 Hz), 5.16 (m, 1, $W_{1/2}$ = 8 Hz), and 8.83 (s, 3). The hexane mother liquor was chromatographed on alumina to give 0.732 g (26%) of 2-cholestene, mp 70-72°.

Anal. Calcd for $C_{27}H_{46}NO_2I$: C, 59.65; H, 8.53; N, 2.58. Found: C, 59.54; H, 8.59; N, 2.47.

B. Reaction with N_2O_4-I_2.—A solution of 1.5 g (4.06 mmol) of 2-cholestene and 2.05 g (8.12 mmol) of iodine were stirred in 75 ml of dry ether and approximately 0.46 g (5.0 mmol) of dinitrogen tetroxide in 5 ml of hexane was added dropwise over a period of 0.5 hr. This solution was stirred for an additional 2 hr and then worked up as usual. Upon evaporation, 1.272 g of a tan product was obtained. The crude infrared spectrum showed nitro absorption at 1545 cm^{-1}, and no absorption characteristic of nitrate or of 2-cholestene. This crude product was recrystallized once from ethyl acetate to give **1**, melting at 138-140°, and identical by infrared spectra with material obtained under procedure A.

Preparation of 3-Nitro-2-cholestene (3).—A mixture of 0.250 g (0.46 mmol) of 2β-iodo-3α-nitrocholestane (**1**) and 0.109 g (0.92 mmol) of silver oxide (dried in a vacuum oven) was refluxed for 4 hr in 100 ml of methanol. The solution was cooled to room temperature, filtered through a sintered-glass funnel, and evaporated to give 0.188 g (99%) of white solid: mp 90-100°; ir 1509 and 1339 cm^{-1} (NO_2); nmr τ 2.90 (br, 1, C=H). This material was recrystallized from ether-methanol to give **3**, mp 122-124°.

Anal. Calcd for $C_{27}H_{45}NO_2$: C, 78.02; H, 10.91; N, 3.37. Found: C, 77.34; H, 10.78; N, 3.67.

Zinc Reduction of 3-Nitro-2-cholestene (3).—Zinc dust (800 mg) was added in portions during 1 hr to a stirred warm (40°) suspension of 250 mg of 3-nitro-2-cholestene (**3**) in 15 ml of acetic acid and 0.5 ml of water. After 4 hr of reflux, the mixture was filtered hot and the zinc was washed well with hot HOAc. Addition of water and extraction with ether gave 116 mg of product which on crystallization from methanol (86 mg) melted at 124-127° and was identical by ir, mixture melting point, and 2,4-dinitrophenylhydrazone formation with 3-cholestanone.

3β-Nitrocholestane (5).—A mixture of 400 mg (0.965 mmol) of nitro olefin **3**, 14 ml of ethanol, and 70 mg (2 mmol) of $NaBH_4$ was stirred at room temperature for 3 hr and allowed to stand for an additional 14 hr. Work-up with water and 0.1 *N* HCl and ether extraction yielded 343 mg of **5**, mp 90-98°; recrystallization from methanol gave a product of mp 94-96.5°, identical with an authentic sample.[8]

Preparation of β-Nitrostyrene (7).—The general procedure was used incorporating 2.96 g (19.2 mmol) of silver nitrite, 9.75 g (38.4 mmol) of iodine, and 2.00 g (19.2 mmol) of styrene in 75 ml of dry ether. Upon evaporation the oil was taken up in 10 ml of ether and 10 ml of pyridine was added. This mixture was stirred for 2 hr at room temperature and then extracted with a large volume of pentane and water. The pentane was repeatedly washed with water, then dried ($MgSO_4$), and distilled at 0.5-mm pressure. Material boiling 80-120° was collected and recrystallized from methanol to give two crops: 0.618 g, mp 54-55°; and 0.770 g, mp 35-42°. The total yield was 49%. The infrared spectra of these products were identical with those of a known sample of β-nitrostyrene (lit.[23] mp 54°).

3-Methylenecholestane was obtained as described[24] by heating 5.0 (13.0 mmol) of cholestan-3-one in 30 ml of tetrahydrofuran with triphenylphosphinemethylene prepared from 6.62 g (16.4 mmol) of triphenylmethylphosphonium iodide and 17.7 mmol of NaH in dimethyl sulfoxide at 55° for 20 hr. Chromatography on alumina gave 3.925 g (78%) of 3-methylenecholestane. Recrystallization from ether-methanol gave a product of mp 62-64° (lit.[24] mp 64-65°); ir 3045, 1751, 1641, and 881 cm^{-1}.

3-Iodo-3-(nitromethyl)cholestane (8). A. Using Silver Nitrite and Iodine.—The general procedure was used incorporating 0.832 g of silver nitrite (5.42 mmol), 2.76 g of iodine (10.84 mmol), and 2.00 g of 3-methylenecholestane (5.25 mmol). After evaporation with nitrogen and trituration with hexane, two crops of a light brown solid were obtained: 0.875 g, mp 131-136°; and 0.100 g, mp 125-131°. The total yield was 34%. This material was recrystallized from acetone to give an analytical sample, mp 142-144°. The unstable nitroiodocholestane **8** turned brown and lost iodine upon standing, even in the dark. Infrared showed peaks at 1548, 1368, and 646 cm^{-1}; nmr showed τ 5.05 (s, 1). The hexane mother liquor was chromatographed to give 0.440 g (53%) of starting olefin.

Anal. Calcd for $C_{28}H_{48}NO_2I$: C, 60.31; H, 8.68; N, 2.51. Found: C, 61.01; H, 9.14; N, 2.12.

B. Using Dinitrogen Tetroxide and Iodine.—A solution of 5.0 g (17.6 mmol) of 3-methylenecholestane and 2.4 g (18.0 mmol) of iodine were stirred together at room temperature in 150 ml of dry ether and 1.4 g (36.0 mmol) of dinitrogen tetroxide in 5 ml of hexane was added dropwise over a period of 1 hr. This solution was stirred for an additional 2 hr and worked up as usual to give 7.485 g (77% yield), mp 123-134°. The product was recrystallized from acetone to give **8**, an unstable white solid, mp 142-143°, which was identical with **8** obtained by method A. Upon standing at room temperature and in the dark for 2 days this material turned a light brown.

3-(Nitromethylene)cholestane (9).—A solution of 2.5 g of 3-iodo-3-(nitromethyl)cholestane **8** was dissolved in 150 ml of dry ether and 2.50 g of freshly fused sodium acetate was added. This mixture was refluxed for 17 hr and allowed to cool to room temperature. After the solids were filtered, the filtrate was evaporated to give 1.927 g of crude product in 99% yield. The infrared spectrum of the crude product showed only a trace of saturated nitro compounds with absorption at 1548 cm^{-1}. Recrystallization of this product from ether-methanol gave an analytical sample of **9**: mp 97-98°; ir 3160, 1630, 1511, 822, and 761 cm^{-1}; nmr signals at τ 3.30 (s, 1) and 9.09 (s).

Methyl 3-Nitroacrylate (10).—A mixture of 2.0 g (23.2 mmol) of freshly distilled methyl acrylate, 3.58 g (23.2 mmol) of silver nitrite, and 11.7 g (46.4 mmol) of iodine in 100 ml of ether was allowed to react as in the general procedure to give a brown oil. This oil was stirred with 2.0 g (27.8 mmol) of anhydrous sodium acetate for 3 hr at room temperature. Vacuum distillation gave 0.240 g of methyl 3-nitroacrylate (higher yields of elimination products are achieved if freshly fused sodium acetate is refluxed with the product for 17 hr[15]): mp 36-37° (lit.[16] mp 38°); infrared absorption at 1720, 1522 cm^{-1}; nmr peaks at τ 2.35 (1 H, J = 13 Hz) and 2.99 (1 H, J = 13 Hz).

3,3-Dimethyl-1-nitro-1-butene (12).—The general procedure was used incorporating 5.5 g (35.7 mmol) of silver nitrite, 18.0 g (71.4 mmol) of iodine, 3.00 g (35.7 mmol) of 3,3-dimethylbutene, and 200 ml of dry ether to give 4.29 g (45%) of an inseparable mixture of 3,3-dimethyl-2-iodo-1-nitrobutane and 3,3-dimethyl-2-iodobutyl nitrate upon evaporation: infrared absorption at 1638, 1558, 1371, and 1279 cm^{-1}; nmr peaks at τ 4.80 (t, 1), 4.56 (d, 2), and minor signals at 4.72 (d) and 4.22 (t).

The crude product mixture of 5.4 g of 3,3-dimethyl-2-iodo-1-nitrobutane and 3,3-dimethyl-2-iodobutyl nitrate was dissolved in 10 ml of ether and treated with 10 ml of pyridine. After 15 min a solid precipitated out. The mixture was stirred for an additional 4 hr, poured into ice water, and extracted with pentane. The pentane was dried over anhydrous magnesium sulfate and evaporated to give 2.83 g (98%) of a yellow oil. This material was distilled on a spinning-band column to give an analytical sample: bp 30° (1 mm); $n^{24}D$ 1.4546; infrared absorption at 3123, 1641, 1529, 1349, 967, 842, and 719 cm^{-1}; nmr peaks at τ 2.87 (d, 1, J = 13.5 Hz), 3.28 (d, 1, J = 13.5 Hz).

Anal. Calcd for $C_6H_{11}NO_2$: C, 55.79; H, 8.59; N, 10.85. Found: C, 55.80; H, 8.59; N, 10.89.

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3,3-Dimethyl-1-nitrobutane (13).—3,3-Dimethyl-1-nitrobut-1-ene (2.83 g) was dissolved in 50 ml of methanol and 1.00 g of sodium borohydride was added. This mixture was stirred for 24 hr at room temperature, poured into water, made acidic with dilute hydrochloric acid, and extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and evaporated to give 0.483 g (17%) of 3,3-dimethyl-1-nitrobutane: nmr peaks at τ 5.54 (t, 2), 8.04 (t, 2).

A. Reaction of *trans*-Stilbene with Silver Nitrite and Iodine.—The general procedure was used incorporating 5.85 g (32.5 mmol) of *trans*-stilbene, 2.50 g (16.3 mmol) of silver nitrite, and 8.25 g (32.5 mmol) of iodine in 75 ml of ether. After reaction the mixture was filtered and the solids were washed free of iodine color with ether. The solids were heated on a steam bath with 150 ml of benzene and filtered while hot. The combined filtrates were worked up as usual. Recrystallization from benzene gave 4.232 g of product **14**: mp 167–169°; infrared absorption at 1540, 1352, and 723 cm^{-1}; nmr peaks at τ 3.43 (d, 1, J = 12 Hz), 3.74 (d, $W_{1/2}$ = 12 Hz), and 3.86 (d, $W_{1/2}$ = 12 Hz). The analytical sample melted at 172–173°.

Anal. Calcd for $C_{14}H_{12}NO_2I$: C, 47.61; H, 3.43; I, 35.94. Found: C, 47.81; H, 3.67; I, 36.24.

The mother liquor gave 4.087 g of unreacted olefin which was found to be only *trans*-stilbene by nmr with a signal at τ 2.9.

B. Reaction of *cis*-Stilbene with Silver Nitrite and Iodine.—The previous reaction was repeated incorporating 2.56 g of silver nitrite, 16.5 g of iodine, and 3.0 g of *cis*-stilbene. After work-up 2.40 g of crude **14**, mp 167–169°, was obtained. The infrared and nmr spectra were identical with those of the analyzed sample. The nmr of the mother liquor indicated that the recovered olefin consisted solely of *cis*-stilbene with a signal at τ 3.45.

***cis*-α-Nitrostilbene (15).**—A solution of 1.50 g of 1,2-diphenyl-1-iodo-2-nitroethane (**14**) was dissolved in 10 ml of ether and 10 ml of pyridine and allowed to stand at room temperature for 2 hr. This mixture was extracted with pentane–water and the pentane was repeatedly washed with water. After drying ($MgSO_4$) and evaporation 1.132 g of a dark brown solid was obtained. Chromatography on silica gel gave 0.812 g of **15** as a bright yellow solid, mp 72–73° (89%) (lit.[7] mp 74–75°).

Registry No.—Nitryl iodide, 15465-40-4; **1,** 20429-43-0; **3,** 13643-70-4; **8,** 20429-45-2; **9,** 20429-46-3; **12,** 20429-42-9; **14,** 20429-47-4.

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Nucleosides. LX.[1a] Fluorocarbohydrates. XXII.[1b] Synthesis of 2-Deoxy-2-fluoro-D-arabinose and 9-(2-Deoxy-2-fluoro-α- and -β-D-arabinofuranosyl)adenines[2]

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Nucleophilic attack of KHF_2 on methyl 2,3-anhydro-5-*O*-benzyl-α-D-riboside is shown to occur largely at the 2 position (in contrast to the β-D anomer) and leads to methyl 5-*O*-benzyl-2-deoxy-2-fluoro-α-D-arabinoside (**4b**), thus achieving the first *direct* synthesis of a 2-fluoropentose derivative. From **4b**, 2-deoxy-2-fluoro-D-arabinose (**6**) is obtained. Fusion of 1,3-di-*O*-acetyl-5-*O*-benzyl-2-deoxy-2-fluoro-D-arabinose with 2,6-dichloropurine affords a readily resolved α–β mixture of 9-glycosylpurine nucleosides, which are converted into 9-(2-deoxy-2-fluoro-α- and -β-D-arabinofuranosyl)adenines (**14** and **15**). Confirmation of the anomeric configuration of these nucleosides is obtained by conversion into their 5′-tosylates (**16** and **17**) and by cyclization of the β anomer to its 3,5′-cyclo nucleoside (**18**).

9-β-D-Arabinofuranosyladenine[3] (Ara-A) is an effective inhibitor of the growth of several mouse tumors.[4,5] However, the efficacy of this drug is reduced by the conversion of Ara-A *in vivo* into the inactive inosine analog by adenosine deaminase.[5] These results suggest that an analog of Ara-A which would maintain its chemotherapeutic effect without undergoing enzymatic degradation would be desirable. Toward this end, the synthesis of the 2′-fluoro analog of Ara-A was undertaken. Such a nucleoside may also be regarded as a 2′-fluoro analog of 2′-deoxyadenosine occurring in DNA.

In previous studies we reported the synthesis of 2′-deoxy-2′-fluoro analogs of uridine,[6a] 5-fluorouridine,[6a] ribothymidine,[6a] and cytidine[6b] by treatment of 2,2′-anhydro nucleosides with hydrogen fluoride. By glycosyl cleavage of the 5,6-dihydro derivative of 2′-deoxy-2′-fluorouridine, 2-deoxy-2-fluoro-D-ribose[6c] was obtained. We now report the first synthesis of a 2-fluoropentose from a pentoside precursor and its conversion into 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine (**10b**).

It was demonstrated[7] that treatment of the β-epoxide (**1**) with KHF_2 in ethylene glycol gave the 3-fluoro xyloside (**2**) as the only isolable product (Scheme I). That the 3-fluoro isomer was the predominant product from this reaction may be due to steric factors related to the methoxy group in the β configuration. It may be expected, particularly in view of previous results with

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[1] For previous papers in these series see (a) Nucleosides. LIX: K. A. Watanabe, M. P. Kotick and J. J. Fox, *Chem. Pharm. Bull.*, **17**, 416 (1969). (b) Fluorocarbohydrates. XXI: R. C. Young, R. A. Dwek, and P. W. Kent, *Carbohyd. Res.*, in press.

[2] This work was supported in part by funds from British Scientific Research Council (J. A. W.), the British Medical Research Council (N. F. T.) and the National Cancer Institute, National Institutes of Health, U. S. Public Health Service Grant 08748 (J. J. F. and J. A. W.).

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