# Some Radical Exchange Reactions during Nitrite Ester Photolysis[1]

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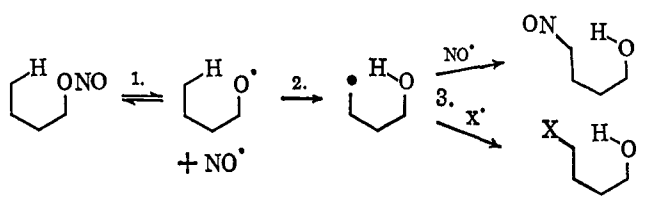
*Contribution from the Research Institute for Medicine and Chemistry, Cambridge, Massachusetts.* *Received July 6, 1965*

*The photolysis of nitrite esters in the presence of suitable radical sources (X·, Scheme I) affords products where, instead of NO being introduced at the δ-carbon, there is substitution by X. In this way iodine, bromine, and deuterium have been introduced into the 18 or 19 position of steroids. A new mechanism for the formation of 6β,19-ethers in steroids has been demonstrated and discussed.*

The photochemical reactions of nitrite esters have been extensively studied in recent years.[2] The mechanism whereby the photolysis of suitably constituted nitrite esters leads to intramolecular exchange of NO of the nitrite residue with a hydrogen atom attached to the δ-carbon atom has been elucidated.[3] By use of $N^{15}$ labeling it was shown that a "noncage," free-radical mechanism operates. During the photolysis of a nitrite ester, discrete nitric oxide molecules and rearranging alkoxy radicals are present. It was considered that competition for the resulting carbon radical between the nitric oxide and an alternative added radical source (X·, Scheme I) might be possible. A prelim-

**Scheme I**




inary account of the results obtained has already been presented.[4] In the sequel we give a fuller account of this and subsequent work.

Some instances of radical exchange reactions have been recorded in the literature.[5] For example, when the silver salt of 1-apocamphanecarboxylic acid was treated with bromine in carbon tetrachloride, two major products formed, the 1-bromo- and 1-chloroapocamphanes. The latter had been produced by competition between the bromine and solvent for the intermediate bridgehead radical.[6]

For Scheme I to operate, a radical source that can effectively compete with nitric oxide must be used. Initially iodine, a good radical scavenger,[5] was chosen.

Photolysis of 3β-acetoxy-cholestan-6β-yl nitrite (I)[7] in benzene containing iodine gave, as the major product after working up, the 6β,19-ether (II).[8] It was considered that the latter product was produced *via* intermediate formation of an iodohydrin followed by intramolecular elimination to furnish the tetrahydrofuran derivative II. Such iodohydrins have also been postulated as intermediates from the action of lead tetraacetate and iodine on alcohols.[9] The photolysis reaction was next applied to some steroidal 11β-ols containing the ring A dienone function. The derived 11β-alkoxy radicals are known to undergo intramolecular hydrogen abstraction preferentially at the C-18 methyl group.[10] Prednisolone 11β-nitrite 21-acetate (IVa, R = NO)[11] upon photolysis with iodine in benzene, followed by careful removal of excess iodine and solvent, furnished not the 18-oxime but 18-iodoprednisolone 21-acetate (IVa; R = H, X = I). Oxidation with chromic acid–acetone[12] yielded 18-iodoprednisone 21-acetate (Va, X = I). Attempted chromatography on alumina of the total photolysis product of IVa (R = NO) and iodine gave not the iodohydrin but 11β,18-epoxyprednisolone 21-acetate (VIIIa).

Dexamethasone 11β-nitrite 21-acetate (IVb; R = NO, X = H)[11] also gave, upon photolysis with iodine, a crystalline iodohydrin (IVb; R = H, X = I), which was converted into the 11-ketone (Vb, X = I) by oxidation with chromic acid–acetone. Similarly 17α,-20;20,21 - bismethylenedioxyprednisolone - 11β - nitrite (IVc; R = NO, X = H)[11] yielded the iodohydrin IVc (R = H, X = I). Treatment of the latter with methanolic potassium hydroxide eliminated hydrogen iodide with formation of the 11β,18-ether (VIIIc). Removal of the protecting bismethylenedioxy group was accomplished with aqueous formic acid to give 11β,18-epoxyprednisolone (VIII). Acetylation gave the 21-acetate identical with the material obtained by the more direct route from prednisolone acetate described above. When the iodohydrin IVc (R = H, X = I) was oxidized with chromic acid–acetone, an iodo ketone (Vc, X = I) formed. Treatment with methanolic potassium hydroxide produced the anticipated 12β,18-cycloprednisone derivative (VIc). Confirmation of the structure of VIc came from the observed shift, in the infrared spectrum, of the C-11 carbonyl absorption to a longer wave length, characteristic of conjugation to a cyclopropyl group.[13] The action of hydrogen iodide on the cyclopropyl ketone regenerated the iodo ketone

(1) This paper is Communication No. 34 from the Research Institute for Medicine and Chemistry. For Communication No. 33 see R. H. Hesse and M. M. Pechet, *J. Org. Chem.*, 30, 1723 (1965).
(2) For a recent review see A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, 17, 35 (1962); see also ref. 10.
(3) M. Akhtar and M. M. Pechet, *J. Am. Chem. Soc.*, **86**, 265 (1964).
(4) M. Akhtar, D. H. R. Barton, and P. G. Sammes, *ibid.*, **86**, 3394, (1964).
(5) For a recent case see T. E. Stevens and W. D. Emmons, *ibid.*, **80**, 338 (1958).
(6) P. Wilder and A. Winston, *ibid.*, **75**, 5370 (1953).
(7) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *ibid.*, **83**, 4076 (1961).
(8) M. Akhtar and D. H. R. Barton, *ibid.*, **86**, 1528 (1964).
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(10) M. Akhtar in "Advances in Photochemistry," Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1964, pp. 263–303.
(11) M. Akhtar, D. H. R. Barton, J. M. Beaton, and A. H. Hortmann, *J. Am. Chem. Soc.*, **85**, 1512 (1963).
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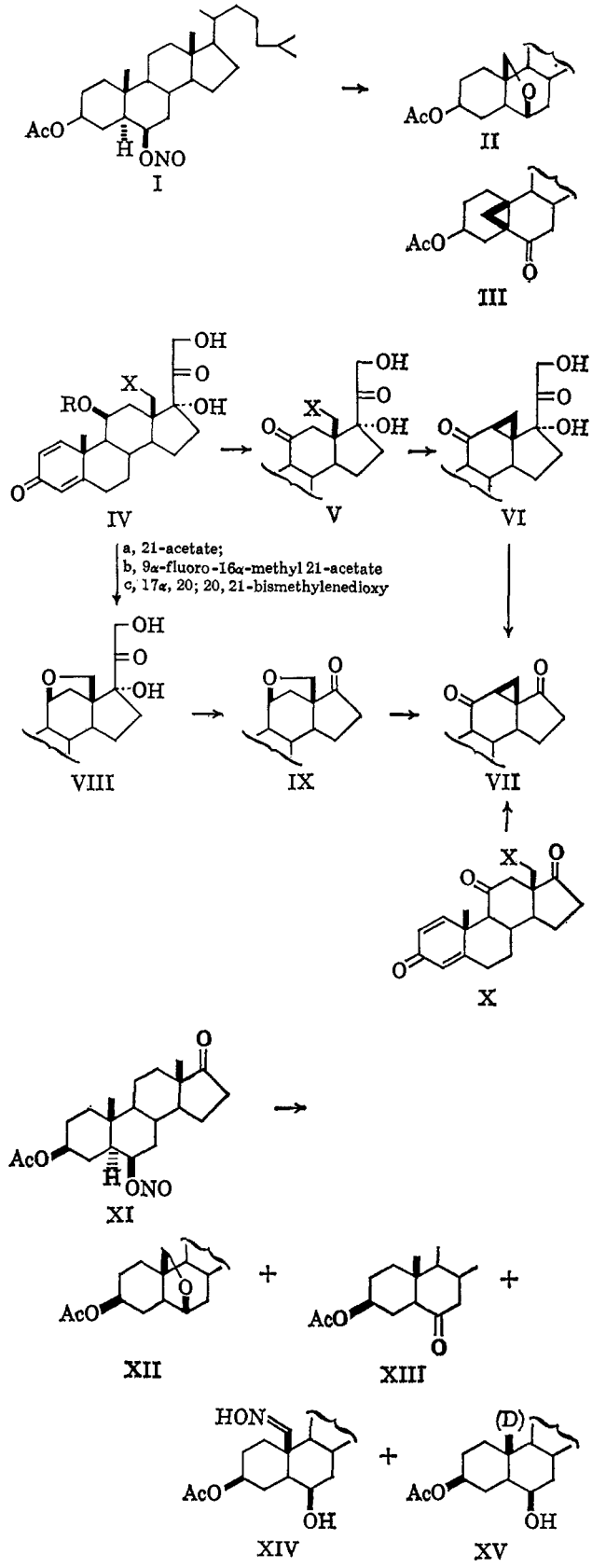



(Vc, X = I). Removal of the bismethylenedioxy protecting group from the cyclopropyl ketone proved difficult since the presence of a strong acid catalyst tended to give complex mixtures and very mildly acidic conditions proved ineffective. Use of small amounts of *p*-toluenesulfonic acid in formic acid performed the desired hydrolysis to give 12β,18-cycloprednisone (VI), readily converted into the 21-acetate (VIa).

The photolysis reaction was next applied to the nitrite ester of androsta-1,4-diene-3,17-dion-11β-ol. Upon photolysis, without any competing radicals present, this compound is known to give a D-homo-18-nor product.[14] The formation of this compound requires rearrangement of the initially formed C-18 radical. It was of interest to see whether competing iodine could "freeze" the reaction before rearrangement of the C-18 radical had a chance to occur. The initial product, after irradiation in the presence of iodine, was unstable, hydrogen iodide and iodine forming, so the initial photolysis product was oxidized with chromic acid–acetone directly. The iodo ketone (X, X = I) was obtained, no rearrangement having taken place. Treatment with mild base gave the cyclopropyl ketone (VII) which was also obtained by oxidative cleavage, with sodium bismuthate, of the side chain from 12β,18-cycloprednisone (VI). Similarly, the sodium bismuthate oxidation of 11β,18-epoxyprednisolone (VIII) yielded the androstane derivative (IX), identical with that obtained by mild base treatment of the initial photolysis product from androsta-1,4-dien-3,17-dion-11β-yl nitrite and iodine.

Attention was next directed to studies of bromine exchange. Bromotrichloromethane proved a suitable source.[15] With the nitrite ester of the cholestane derivative (I), irradiation in the presence of excess bromotrichloromethane gave a pale blue solution. The blue color of the reaction mixture was ascribed to the monomeric trichloronitrosomethane.[16] On removal of the solvent by distillation the blue compound codistilled. The main product, after treatment with mild base, was the 6β,19-ether (II) together with small amounts of the 6β-alcohol and 6-ketone. As with iodine, formation of the oxide may be explained by intermediate formation of the bromohydrin. The existence of the bromohydrin was demonstrated by oxidation of the crude photolysis product and chromatography to give 3β-acetoxy-5β,19-cyclocholestan-6-one,[8] presumably formed by elimination of hydrogen bromide from the expected 19-bromo 6-ketone.

Bromotrichloromethane can readily add across double bonds in radical reactions.[17] However, the nitrite ester of prednisolone acetate (IVa; R = NO, X = H) in benzene upon photolysis in the presence of the reagent, followed by chromic acid–acetone oxidation, gave 18-bromoprednisone acetate (Va, X = Br). Similarly, androsta-1,4-diene-3,17-dion-11β-yl nitrite furnished 18-bromo-androsta-1,4-diene-3,11,17-trione (X, X = Br). Finally, the prednisolone derivative (IVc; R = NO, X = H) with bromotrichloromethane, followed by treatment with methanolic potassium hydroxide, gave the 11β,18-ether (VIIIc).

These radical exchange reactions were also applied to systems involving alicyclic ring cleavage instead of hydrogen abstraction. An oxygen radical adjacent to a cyclopentyl ring is known to react preferentially by formation of a carbonyl group with carbon–carbon

(14) H. Reimann, A. S. Capomaggi, T. Strauss, E. P. Oliveto, and D. H. R. Barton, *J. Am. Chem. Soc.*, **83**, 4481 (1961).
(15) *Cf.* J. C. D. Brand and I. D. R. Stevens, *J. Chem. Soc.*, 629 (1958).
(16) W. Prandtl and K. Sennewald, *Ber.*, **62**, 1754 (1929).
(17) See C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, Table 6.4, p. 249.

Table I[a]

| Expt. | Mole equiv. of thiophenol[b] | Photolysis time, min. | % Ether[c] (XII) | % Ketone (XIII) | % Alcohol (XV) | % Oxime (XIV) |
|---|---|---|---|---|---|---|
| 1 | 0 | 75 | 2 | 12 | 19 | 60 |
| 2[d] | 0 | 210 | 23 | 11 | 21 | 26 |
| 3 | 1 | 45 | 22 | 18 | 47 | <10 |
| 4 | 2 | 50 | 19 | 12 | 68 | <10 |
| 5 | 4 | 45 | 6 | 14 | 77 | <5 |

[a] See Experimental Section for method. [b] Added as a 1 *N* solution in benzene. [c] Products as per cent theoretical yield. [d] Under dilute conditions, 120 mg. of nitrite in 250 ml. of benzene.

bond fission.[18] Cyclopentyl nitrite upon photolysis gives glutaraldehyde monoxime.[19] Photolysis of this nitrite in the presence of iodine gave δ-iodovaleraldehyde, identified as its 2,4-dinitrophenylhydrazone.[8] When bromotrichloromethane was used the δ-bromo compound was produced. Treatment of a tertiary nitrite, 1-methylcyclopentyl nitrite, with the same reagent gave 1-bromohexan-5-one, again isolated as its 2,4-dinitrophenylhydrazone.

In Scheme I, X· can, in principle, be a hydrogen atom source. With such hydrogen quenching two reaction centers exist, the initially produced oxygen radical (step 1) or the derived carbon radical (step 2). A simple test of which radical is quenched was made using deuterium labeling, the amount of deuterium at the δ-carbon atom being determined by mass spectrometry.

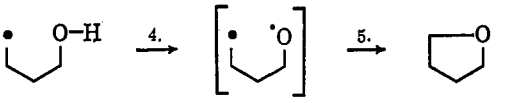
3β-Acetoxyandrostan-17-on-6β-ol, conveniently prepared by debromination of the 5α-bromo derivative[20] with the chromous acetate–thiol reagent,[21] was converted to its nitrite in the usual way. The photolysis of this nitrite in the presence of varying amounts of thiophenol was investigated, the results obtained being summarized in Table I. As expected the yield of 6β-ol increased with increasing thiophenol concentration. Unexpectedly the 6β,19-ether (XII) was also produced in the presence of thiophenol. In the absence of thiophenol little (*ca.* 2%) of the ether was formed, but the yield was increased substantially on photolysis in dilute solution (Table I, run 2).

When the photolysis was repeated in the presence of 1 equiv. of deuterated thiophenol (93% PhSD) the alcohol isolated showed, in its mass spectrum, the incorporation of 19.7% atom excess of deuterium at C-19; use of 2 equiv. of deuterated thiophenol raised this incorporation to 36% atom excess. These results indicate that it is substantially the carbon radical that is quenched and not the oxygen atom.[22]

When 1-methylcyclopentyl nitrite ester was photolyzed with 2 equiv. of deuterated thiophenol (90% PhSD), hexan-2-one was isolated as its 2,4-dinitrophenylhydrazone showing 58% atom excess deuterium in its C-6 methyl group.

These results show that step 2 of Scheme I follows rapidly upon step 1. They also show that the 6β,19-ether function (as in XII) can be formed other than by intramolecular elimination from a halohydrin. Experiment 2 of Table I suggests that alkoxyl, or equivalent derived radicals, can abstract hydrogen from the 6β-ol of the C-19 radical to furnish the ether. This can involve either radical displacement on hydrogen with concerted formation of the 6β,19-ether bond, or it can involve the transient formation of the 6β,19-diradical (see Scheme II) and hence the ether. The

**Scheme II**




dilution of the solution possibly facilitates the sweeping out of nitric oxide by the nitrogen stream relative to the rates of the competing "bimolecular" radical reactions. Alternately, the nitric oxide may be selectively removed by (photochemical) reaction with the solvent.

The effect of thiophenol in increasing the yield of ether is then most simply explained by the hypothesis that it reacts with, and hence removes, nitric oxide from the system. The radical-induced removal of hydrogen from the 6β-ol is thus favored.

## Experimental Section

Microanalyses were performed by Dr. Alfred Bernhardt, Max Planck Institute, Mulheim (Ruhr), Germany. Infrared spectra were recorded on an Infracord 137 spectrophotometer. Unless otherwise stated, ultraviolet spectra were determined in methanol and optical rotations in chloroform. Melting points were taken on a Kofler-type hot stage. N.m.r. spectra, where reported, were taken on a Varian Associates A-60 spectrometer in deuteriochloroform. Merck acid-washed alumina was used for chromatography unless stated to the contrary.

*Photolysis of 3β-Acetoxycholestan-6β-yl Nitrite (I) and Iodine.* A solution of 3β-acetoxycholestan-6β-yl nitrite (I, 742 mg.) and iodine (238 mg.) in anhydrous benzene (150 ml.) was photolyzed for 1.25 hr. under nitrogen at room temperature using a 550-w., high-pressure mercury lamp, as detailed previously.[3] The reaction mixture was washed successively with 10% aqueous sodium thiosulfate solution and water, dried ($Na_2SO_4$), and evaporated to dryness. The oil was refluxed for 15 min. with 5% methanolic potassium acetate (50 ml.), water was added, and the mixture was extracted with methylene chloride and worked up as usual. Crystallization from methanol afforded the ether II (346 mg.), m.p. 105–110°, and a second crop of 6-ketone (294 mg.).

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(19) P. Kabasakalian and E. R. Townley, *ibid.*, **27**, 2918 (1962).
(20) V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 4105 (1957).
(21) D. H. R. Barton and N. K. Basu, *Tetrahedron Letters*, 3151 (1964).
(22) R. A. Sneen and N. P. Matheny, *J. Am. Chem. Soc.*, **86**, 5503 (1964).

*Photolysis of 11β-Nitrites and Iodine.* The following example is illustrative. Freshly prepared 11β-nitrite of prednisolone acetate (IVa; R = NO, X = H; 4.1 g.) and iodine (0.85 g.) were photolyzed in benzene (175 ml.), under the usual conditions, for 2.25 hr. Some material, which had precipitated out during this time, was dissolved in methylene chloride (100 ml.) and added to the solution. The latter was worked up, as above, and the solvent was removed *in vacuo*. The residual gum was dissolved in methylene chloride (10 ml.) when crystallization commenced to give the iodohydrin (IVa; R = H, X = I; 0.623 g.), m.p. 129–133° dec. Repeated recrystallizations from methylene chloride gave colorless prisms: m.p. 131–134° dec.; $[\alpha]^{25}D$ +93.2° (*c* 0.86); $\lambda_{max}$ 243 mμ (ε 18,000); $\nu_{max}^{Nujol}$ 3600–3250 (m, broad), 1750 (s), 1660 (s), 1610 (m), and 1600 (m) cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{29}IO_6$: C, 52.35; H, 5.59; I, 24.04; O, 18.17. Found: C, 52.14; H, 5.50; I, 24.07; O, 18.21.

18-Iododexamethasone 21-acetate (IVb, R = H, X = I; 37%), was prepared in a similar manner: m.p. (from chloroform) 140–143° dec.; $[\alpha]^{26}D$ +89° (*c* 0.83); $\lambda_{max}$ EtOH 236 mμ (ε 12,600); $\nu_{max}^{Nujol}$ 3600 (s), 3500 (m, broad), 1760 (s), 1720 (s), 1670 (s), 1620 (m), and 1610 (m) cm.$^{-1}$.

*Anal.* Calcd. for $C_{24}H_{30}FIO_6$: C, 51.50; H, 5.40; I, 22.60. Found: C, 51.40; H, 5.23; I, 22.52.

17α,20;20,21-Bismethylenedioxy-18-iodoprednisolone (IVc; R = H, X = I; 47%) had m.p. (from methylene chloride–ether) 129–133° dec.; $[\alpha]^{23}D$ +2.1° (*c* 0.94); $\lambda_{max}$ 243 mμ (ε 16,200); $\nu_{max}^{Nujol}$ 3600 (s), 3400 (s), 1655 (s), 1615 (m), and 1600 (m) cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{29}IO_6$: C, 52.25; H, 5.53; I, 24.02; O, 18.17. Found: C, 52.36; H, 5.60; I, 23.95; O, 18.02.

*Oxidation of Iodohydrins.* The following example is illustrative. Crude iodohydrin (IVc; R = H, X = I; 1.1 g.), from the corresponding nitrite ester (2.0 g.), was dissolved in acetone (100 ml.) and treated with an excess of chromic acid–acetone at +5 to +10° for 5 min. The excess of the oxidant was decomposed with methanol, ice–water was added, and the reaction mixture was extracted with methylene chloride and worked up as usual. The residue, after several recrystallizations from acetone–hexane, gave 18-iodo-17α,20;20,21-bismethylenedioxyprednisone (Vc, X = I, 300 mg.): m.p. 186–189°; $[\alpha]^{25}D$ +5° (*c* 0.88); $\lambda_{max}$ 237 mμ (ε 16,800); $\nu_{max}^{KBr}$ 1710 (s), 1665 (s), 1620 (m), and 1600 (m) cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{27}IO_6 \cdot C_3H_6O$: C, 53.43; H, 5.69; I, 21.72; O, 19.16. Found: C, 53.41; H, 5.30; I, 22.01; O, 19.51.

18-Iodoprednisone acetate (Va, X = I, 12%) was prepared by the same procedure: m.p. (from acetone–hexane) 170–171.5°; $[\alpha]^{23}D$ +144° (*c* 1.0); $\lambda_{max}$ 238 mμ (ε 16,050); $\nu_{max}^{KBr}$ 3700 (s), 1740 (s), 1665 (s), 1620 (m), and 1610 (m) cm.$^{-1}$. The n.m.r. spectrum showed a singlet at τ 8.56 (C-19 methyl), a singlet at 7.82 (acetate, methyl), unresolved multiplet at 7.05 (C-18 methylene), and a quartet at 5.58, 5.26, 4.75, and 4.46 (C-21 methylene).

*Anal.* Calcd. for $C_{23}H_{27}IO_6$: C, 52.48; H, 5.17; I, 24.11; O, 18.24. Found: C, 52.58; H, 5.04; I, 24.13; O, 18.13.

11-Dehydro-18-iododexamethasone 21-acetate (Vb; X = I; 54%; calculated from pure iodohydrin) had m.p. (from methylene chloride–ether) 145–150° dec.; $[\alpha]^{29}D$ +125° (*c* 0.82); $\lambda_{max}^{EtOH}$ 233 mμ (ε 14,980); $\nu_{max}^{Nujol}$ 3500 (s), 1760 (s), 1740 (s), 1665 (s), 1620 (m), and 1600 (m) cm.$^{-1}$. Its n.m.r. spectrum showed a doublet at τ 8.96 and 9.08 (16α-methyl), singlet 8.50 (C-19 methyl), singlet 7.82 (acetate, methyl), quartet 5.57, 5.30, 4.80, and 4.52 (C-21 methylene).

*Anal.* Calcd. for $C_{24}H_{28}FIO_6$: C, 51.63; H, 5.30; I, 22.94. Found: C, 51.70; H, 5.06; I, 22.74.

*Preparation of 17α,20;20,21-Bismethylenedioxy-12β,-18-cycloprednisone (VIc).* A solution of the iodo ketone (Vc, X = I, 580 mg.) in methanolic potassium hydroxide (100 ml., 5%) was refluxed under nitrogen for 1 hr. After partial evaporation of solvent, under reduced pressure, the reaction mixture was worked up as usual. Crystallization of the residue from acetone–hexane gave the cyclopropyl ketone (VIc, 315 mg.): m.p. 288.5–289.5°; $[\alpha]^{21}D$ −20.8° (*c* 1.08); $\lambda_{max}$ 240 mμ (ε 16,350); $\nu_{max}^{KBr}$ 1660 (s), 1625 (m), and 1600 (m) cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 1680 (s), 1660 (s), 1625 (m), and 1610 (m) cm.$^{-1}$. The n.m.r. spectrum had a singlet at τ 8.75 (C-19 methyl), doublet 6.04, 6.08 (C-21 methylene), doublet 5.06, 5.04 and narrow multiplet centered at 4.96 (bismethylenedioxy groups).

*Anal.* Calcd. for $C_{23}H_{26}O_6$: C, 69.32; H, 6.58; O, 24.09. Found: C, 69.20; H, 6.59; O, 23.89.

The latter compound could also be obtained in 25% over-all yield from the nitrite (IVc; R = NO, X = H) when the photolysis mixture was directly oxidized, followed by base treatment and chromatography (using methanolic methylene chloride as eluent).

*Treatment of the Cyclopropyl Ketone VIc with Hydrogen Iodide.* A mixture of the 12β,18-cyclo derivative (VIc, 50 mg.), acetic acid (3 ml.), acetic anhydride (5 ml.), and aqueous hydriodic acid (0.1 ml., 47%) was stirred under nitrogen for 30 min. The reaction mixture was then poured into aqueous sodium thiosulfate (100 ml., 2%) and extracted with methylene chloride. Crystallization from acetone–hexane gave the iodo ketone (Vc, X = I, 27 mg., 41%) identical in all respects with the authentic specimen.

*Preparation of 12β,18-Cycloandrosta-1,4-diene-3,11,17-trione (VII).* Iodo ketone (X, X = I, 101.4 mg.) in ethanolic potassium acetate solution (5 ml., saturated) was heated to a gentle reflux for 20 hr. The mixture was poured into water (30 ml.) and extracted with methylene chloride. Working up in the usual manner and crystallizing from ether gave the ketone (VII, 54.2 mg.): m.p. 194–195°; $[\alpha]D$ +243° (*c* 0.93); $\lambda_{max}$ 244 mμ (ε 16,600); $\nu_{max}^{Nujol}$ 1730 (s), 1660 (shoulder), 1650 (s), 1615 (m), and 1605 (w) cm.$^{-1}$.

*Anal.* Calcd. for $C_{19}H_{20}O_3$: C, 77.05; H, 6.80; O, 16.15. Found: C, 77.04; H, 6.87; O, 15.97.

*Preparation of 12β,18-Cycloprednisone Acetate (VIa).* 17α,20;20,21-Bismethylenedioxy-12β,18-cycloprednisone (VIc, 3.0 g.) was dissolved in hot, aqueous formic acid (180 ml., 45% acid) in the presence of *p*-toluenesulfonic acid (250 mg.) and heated to reflux for 1 hr. under nitrogen. The cooled solution was poured into saturated sodium chloride solution (250 ml.) and extracted with methylene chloride. The crude product from the extraction was chromatographed through

silica gel (200 g.). The fraction eluted with 5% methanolic methylene chloride was crystallized from methanol to give needles of 12β,18-cycloprednisone (VI, 0.695 g.). An analytical sample (from aqueous ethanol) had m.p. 206–208°; $[\alpha]^{23}D$ +69.4° (*c* 1.0); $\lambda_{max}$ 244 mμ (ε 15,300); $\nu_{max}^{Nujol}$ 3500 (shoulder), 3400 (vs), 1705 (s), 1665 (shoulder), 1655 (s), 1610 (m), and 1600 (w) cm.$^{-1}$.

*Anal.* Calcd. for $C_{21}H_{22}O_5$: C, 71.18; H, 6.26; O, 22.56. Found: C, 71.04; H, 6.51; O, 22.71.

The 12β,18-cycloprednisone (VI, 690 mg.) was acetylated by dissolving in pyridine (10 ml.) and acetic anhydride (2 ml.) at room temperature and left stirring overnight. Working up afforded colorless needles of the acetate (VIa, 548 mg.): m.p. (from acetone–hexane) 224–227°; $[\alpha]^{24}D$ +52° (*c* 0.95); $\lambda_{max}$ 243 mμ (ε 15,000); $\nu_{max}^{KBr}$ 3400 (s), 1750 (s), 1730 (s), 1680 (s), 1660 (s), 1630 (m), and 1600 (m) cm.$^{-1}$. The n.m.r. spectrum showed a singlet at τ 8.73 (C-19 methyl), singlet 7.94 (acetate, methyl), and doublet 5.64, 5.68 (C-21 methylene).

*Anal.* Calcd. for $C_{23}H_{26}O_6$: C, 69.33; H, 6.58; O, 24.09. Found: C, 69.00; H, 6.49; O, 24.46.

*Side-Chain Cleavage from Cycloprednisone.* A sample of the diol (VI, 14.0 mg.) was dissolved in aqueous acetic acid (1:1, 1 ml.) and stirred at room temperature overnight with sodium bismuthate (52 mg.). The mixture was filtered through Hyflo-supercel, washing with glacial acetic acid (0.5 ml.) and methylene chloride (5 ml.). The liquor was washed with water (two 3-ml. portions) and then neutralized with aqueous ammonia solution. The organic layer was further washed with water (1 ml.). On working up, a colorless gum (8.4 mg.) was obtained which crystallized as needles after standing for 3 days under hexane. The product (4.5 mg.) had m.p. 193–195° and infrared spectrum identical with the cyclopropyl ketone (VII) obtained above.

*Preparation of 11β,18-Oxidoprednisolone 21-Acetate (VIIIa). i. From 17α,20;20,21-Bismethylenedioxyprednisolone 11β-Nitrite (IVc; R = NO, X = H).* The nitrite (1.25 g.) and iodine (0.7 g.) were photolyzed as described above, and the crude iodohydrin obtained was dissolved directly in methanolic potassium hydroxide solution (120 ml., 5%) and heated to reflux under nitrogen for 30 min. Water was added, and the solution was extracted with methylene chloride. After removal of solvents the residue was chromatographed, eluting with methanolic methylene chloride. The more polar fractions afforded recovered 17α,20;20,21-bismethylenedioxyprednisolone (IVc; R, X = H; 155 mg.). The less polar fractions gave 11β,18-oxido - 17α,20;20,21 - bismethylenedioxyprednisolone (VIIIc, 375 mg.): m.p. (from acetone–hexane) 255–260°; $[\alpha]^{23}D$ +5° (*c* 0.99); $\lambda_{max}$ 242 mμ (ε 16,160); $\nu_{max}^{KBr}$ 1660 (s), 1625 (m), and 1605 cm.$^{-1}$. The n.m.r. spectrum showed a singlet at τ 8.72 (C-19 methyl), doublet at 6.32, 6.30 (C-21 methylene), quartet at 6.39, 6.25, and 6.12, 5.97 (C-18 methylene), doublet at 5.55, 5.31 (11α-methine), and multiplet centered at 4.9 (bismethylenedioxy groups).

*Anal.* Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.04; O, 23.97. Found: C, 68.88; H, 6.92; O, 23.85.

The preceding derivative (VIIIc, 300 mg.) was added to a boiling mixture of aqueous formic acid (15 ml., 40%) and ethylene glycol (0.9 ml.) while a slow stream of nitrogen was passed through the reaction mixture. After heating to reflux for 3 hr. the latter was poured into ice water, and methylene chloride was extracted. Chromatography, using methanolic methylene chloride as eluent, gave, initially, starting material (50 mg.) and then, in the more polar fractions, 11β,18-oxidoprednisolone (VIII, 75 mg.). Crystallization from acetone–hexane gave m.p. 221–228°; $[\alpha]^{21}D$ +7.1° (*c* 0.71, dioxane); $\lambda_{max}$ 243 mμ (ε 15,800); $\nu_{max}^{KBr}$ 3680 (s), 1710 (s), 1660 (s), 1620 (m), and 1605 (m) cm.$^{-1}$.

*Anal.* Calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31; O, 22.32. Found: C, 70.18; H, 7.16; O, 22.50.

A solution of 11β,18-oxidoprednisolone (60 mg.) in pyridine (5 ml.) and acetic anhydride (1 ml.) was left overnight at room temperature. The product, isolated in the normal manner, was chromatographed on Florisil to yield, from acetone–hexane, 11β,18-oxidoprednisolone 21-acetate (VIIIa, 35 mg.): m.p. 199–206°; $[\alpha]^{21}D$ +102° (*c* 0.82); $\lambda_{max}$ 243 mμ (ε 13,500); $\nu_{max}^{KBr}$ 3500 (s), 1750 (s), 1710 (s) 1660 (s), 1620 (m), and 1600 (m) cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{28}O_5$: C, 68.97; H, 7.05. Found: C, 68.49; H, 6.79.

*ii. From Prednisolone 11β-Nitrite 21-Acetate (IVa; R = NO, X = H).* The crude iodohydrin from the photolysis of nitrite (3.2 g.) and iodine (2.3 g.), as described above, was chromatographed to give, with methanolic methylene chloride, two compounds. The less polar material proved to be the oxide (VIIIa, 330 mg.): m.p. 198–208°, $[\alpha]^{23}D$ +109° (*c* 1.07), identical in all respects with the material described above. The more polar compound (150 mg.) crystallized from acetone–hexane, proved to be identical with prednisolone 21-acetate.

*11β,18-Oxidoandrosta-1,4-diene-3,17-dione (IX). i. From Androsta-1,4-diene-3,17-dion-11β-yl Nitrite.* Photolysis of the nitrite (900 mg.) with iodine (1.6 g.) under the usual conditions afforded an oily residue on working up. The residue immediately was dissolved in a methanolic potassium acetate solution (100 ml., 5%) and refluxed for 1 hr. Water was added and the mixture was extracted with methylene chloride. Chromatography using methanolic methylene chloride as eluent, gave, after recrystallization from acetone–hexane, the oxide (IX, 190 mg.): m.p. 168–171°; $[\alpha]^{21}D$ +196° (*c* 1.1); $\lambda_{max}$ 242 mμ (ε 15,000); $\lambda_{max}^{KBr}$ 1740 (s), 1660 (s), 1625 (m), and 1600 (w) cm.$^{-1}$. The n.m.r. spectrum showed a singlet at τ 8.68 (C-19 methyl), quartet 6.60, 6.48, 5.97, and 5.84 (C-18 methylene), and a doublet 5.30 and 5.20 (C-11 methine).

*Anal.* Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43; O, 16.09. Found: C, 76.46; H, 7.19; O, 16.15.

*ii. From 11β,18-Oxidoprednisolone.* The oxide (VIII, 76.2 mg.) was oxidized with sodium bismuthate (200 mg.) in the manner described previously. Working up gave 11β,18-oxidoandrosta-1,4-diene-3,17-dione (IX, 42.9 mg.), m.p. (from acetone–hexane) 168–171°, identical with the material obtained from the above photolysis.

*Photolysis of Nitrite Esters with Bromotrichloromethane.* The following example is illustrative. 3β-Acetoxycholestan-6β-yl nitrite (I, 475 mg.) and bromo-

trichloromethane (10 g.) in benzene (80 ml.) were photolyzed in the usual apparatus using a 220-w. lamp, a Pyrex filter, and external cooling of the system with cold water. After 45 min., the pale green solution was washed with water, dried ($Na_2SO_4$), and evaporated to dryness under reduced pressure. The blue compound codistilled with the benzene at this stage to leave a pale yellow residue. The latter was heated with methanolic potassium acetate (5%) for 4 hr. before adding water and extracting with methylene chloride. The residue, after working up, was chromatographed eluting with benzene–methylene chloride mixtures to give, successively, 3β-acetoxy-6β,19-oxidocholestane (II, 35%), 3β-acetoxycholestan-6-one (5%), and 3β-acetoxycholestan-6β-ol (20%). The compounds were identified by comparison to authentic samples.

Similarly, 17α,20;20,21-bismethylenedioxyprednisolone 11β-nitrite (IVc; R = NO, X = H) and the reagent (24 equiv.) afforded the *11β,18-oxide* (VIIIc, 11%) and recovered 11β-alcohol (13%).

Finally, androsta-1,4-diene-3,17-dion-11β-yl nitrite, upon similar treatment with the reagent (24 equiv.), afforded the *11β,18-oxide* (IX, 23%), 11-ketone (X, X = H, 5%), and 11β-ol (39%).

*Preparation of 3β-Acetoxy-5β,19-cyclocholestan-6-one (III).* The nitrite (I, 0.50 g.) and $CCl_3Br$ (20 g.) were dissolved in anhydrous benzene (80 ml.) at room temperature and irradiated under the usual conditions with a 200-w. lamp until the nitrite had all reacted (followed by thin layer chromatography). The solvent was removed *in vacuo* and the residue was dissolved in acetone (50 ml.) and treated with excess chromic acid–acetone. After 5 min. the reaction product was isolated and chromatographed, using benzene–methylene chloride eluents, to give successively, 6β,19-oxide (II, 4%), 6-ketone (60%), and 5β,19-cyclo 6-ketone (III, 0.115 g., 24.5%). A repeat run gave, respectively, 9, 48, and 28% yields. The cyclopropyl ketone was identified by its infrared spectrum, melting point (124–125°), and mixture melting point with authentic material (undepressed).

*Preparation of 18-Bromoandrosta-1,4-diene-3,11,17-trione (X, X = Br).* Androsta-1,4-diene-3,17-dion-11β-yl nitrite (365 mg.) was irradiated with bromotrichloromethane (6.0 g.) by the method described above. The product solution was reduced to small bulk *in vacuo*, dissolved in acetone (15 ml.), and oxidized with excess chromic acid–acetone for 6 min. at room temperature. Methanol was added, followed by water, and the product was extracted with methylene chloride. Chromatography of the extract, using 0.1% methanolic methylene chloride as eluent afforded, after recrystallization from ethyl acetate, prisms of 18-bromoandrosta-1,4-diene-3,11,17-trione (X, X = Br, 78 mg.): m.p. 183–186° dec.; $[\alpha]^{25}D$ +212° (*c* 1.0); $\lambda_{max}$ 239 mμ (ε 17,200); $\nu_{max}^{Nujol}$ 1750 (s), 1715 (s), 1670 (s), 1630 (m), and 1610 (w) cm.$^{-1}$.

*Anal.* Calcd. for $C_{19}H_{21}BrO_3$: C, 60.55; H, 5.61; O, 12.72. Found: C, 60.72; H, 5.57; O, 12.54.

*Preparation of 18-Bromoprednisone Acetate (Va, X = Br).* Prednisolone 11β-nitrite 21-acetate (3.0 g.) and $CCl_3Br$ (26 g.) were photolyzed under the previously described conditions, and the crude product was immediately dissolved in acetone (60 ml.) and acidified with excess chromic acid–acetone at room temperature for 6 min. before working up as usual. On chromatography the fractions eluted with 0.75% methanolic methylene chloride were combined, re-evaporated to dryness, and dissolved in hot ethyl acetate (10 ml.). On cooling prisms of prednisone acetate (0.687 g.) formed. The mother liquors were combined, re-evaporated to dryness, and dissolved in methylene chloride–*n*-hexane (1:1, 10 ml.). On standing, the solution deposited needles, which after several recrystallizations from the same solvents, afforded pure 18-bromoprednisone acetate (Va, X = Br, 0.358 g.): m.p. 172–175° dec.; $[\alpha]^{25}D$ +179° (*c* 1.0); $\lambda_{max}$ 239 mμ (ε 16,300); $\nu_{max}^{Nujol}$ 3600 (s), 3400 (shoulder), 1750 (s), 1720 (m), 1670 (s), 1620 (m), and 1600 (w) cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{27}BrO_6$: C, 57.62; H, 5.67; O, 20.02. Found: C, 57.83; H, 5.75; O, 20.10.

*Cleavage of Cyclic Nitrite Esters with Radical Exchange.* The following example is illustrative. Cyclopentyl nitrite (1.15 g.) and iodine (1.39 g.) were dissolved in anhydrous benzene (120 ml.) and irradiated under the usual conditions with a 200-w. lamp for 3 hr. After extraction of the resulting solution with portions of aqueous sodium thiosulfate, the organic phase was sampled (10%) and the sample was added to Brady's reagent (from 0.2 g. of 2,4-dinitrophenylhydrazine) and methanol (25 ml.). The solution was allowed to stand for several hours before pouring into water and extracting with methylene chloride. The extract was filtered through a column of alumina (20 g.), washing with methylene chloride before evaporating to dryness and crystallizing from methanol. Yellow needles of the hydrazone formed (0.295 g., 75%), m.p. 127–128°, identical in its infrared spectrum with authentic material.

5-Bromopentanal 2,4-dinitrophenylhydrazone (9%, after distillation of the crude aldehyde) was similarly prepared but using bromotrichloromethane (20 equiv.) as the reagent: m.p. (from ethanol) 108–115°; $\nu_{max}^{Nujol}$ 3350 (m), 3100 (w), 1620 (s), and 1600 (m) cm.$^{-1}$.

*Anal.* Calcd. for $C_{11}H_{13}BrN_4O_4$: Br, 23.16. Found: Br, 23.14.

1-Bromohexan-5-one 2,4-dinitrophenylhydrazone (45%) was prepared as above, m.p. (from ethanol) 82–83°.

*Anal.* Calcd. for $C_{12}H_{15}BrN_4O_4$: Br, 21.98. Found: Br, 21.90.

*Preparation of 3β-Acetoxyandrostan-17-on-6β-yl Nitrite (XI).* 3β-Acetoxy-5α-bromo-6β-hydroxyandrostan-17-one[20] (4.07 g.) was added to a solution of chromous acetate (5.3 g., 5 equiv.) in dimethyl sulfoxide (redistilled, 75 ml.) under oxygen-free nitrogen in the presence of *n*-butyl mercaptan (1.60 ml., 8 equiv.). The deep purple mixture was stirred at 28° for 2 hr. before pouring into water (200 ml.) and then extracting with methylene chloride. After working up the extract in the usual manner, the product was chromatographed through alumina (grade III), eluting with methanolic methylene chloride. The main fractions yielded, as a colorless solid, the alcohol XV: m.p. (from acetone–petroleum ether (b.p. 60–80°)) 182–184°; $[\alpha]^{24}D$ +42.7° (*c* 0.63); $\nu_{max}^{Nujol}$ 3500 (m), 1730 (s), 1725 (s), and 1245 (s) cm.$^{-1}$; n.m.r. bands at τ 9.11 and 8.9 (C-18 and C-19 methyls) and 7.96 (acetate).

*Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.43; H, 9.25. Found: C, 72.52; H, 8.88.

The alcohol, on treatment at −20° with nitrosyl chloride in pyridine, afforded the nitrite ester (XI): m.p. 169–171.5°; $[\alpha]D$ +16.0°; $\nu_{max}^{Nujol}$ 1730 (s), 1720 (s), and 1638 (s) cm.$^{-1}$.

*Anal.* Calcd. for $C_{21}H_{31}NO_5$: N, 3.71. Found: N, 3.78.

*Photolyses of 3β-Acetoxy-androstan-17-on-6β-yl Nitrite with Thiophenol.* The following illustrates the general method used. To a solution of the nitrite (XI, 150 mg.) in anhydrous benzene (25 ml.) was added the appropriate amount of thiophenol as a 1 *N* solution in benzene. A stream of oxygen-free nitrogen gas was bubbled through the solution while photolyzing with a 125-w., high-pressure mercury lamp using a Pyrex filter. The course of the reaction was followed by thin layer chromatography. After disappearance of the nitrite ester, the reaction mixture was evaporated to dryness under reduced pressure and then the residue was chromatographed through alumina (grade III, 20 g.) using benzene–methylene chloride and finally methylene chloride–methanol mixtures to elute. The products were eluted in the order ether, ketone, alcohol, and finally from the most polar fractions "oxime" (containing some nitroso dimer).

Dark reactions with thiophenol showed only a very slow decomposition of the nitrite ester.

The ether, 3β-acetoxy-6β,19-oxidoandrostan-17-one (XII) showed m.p. (from ether–petroleum ether) 154–155°; $[\alpha]^{22}D$ +37.9° (*c* 1.04); $\nu_{max}^{Nujol}$ 1730 (s) and 1500 (w) cm.$^{-1}$; n.m.r. bands at τ 9.08, singlet (C-18 methyl), singlet at 7.98 (acetate), a partially resolved band at 6.20 (C-19 methylene), and multiplets centered at 5.96 and 5.35 (3α- and 6α-methines).

*Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 73.07; H, 8.72. Found: C, 72.89; H, 8.79.

The ketone XIII had m.p. 186–189°, unchanged on mixture melting with authentic material. The oxime, 3β-acetoxy-6β-hydroxy-19-oximinoandrostan-17-one (XIV), had m.p. (from ethyl acetate) 204–206°; $[\alpha]^{26}D$ +31.6° (*c* 1.0); $\nu_{max}^{Nujol}$ 3240, 3150 (s), 1730 (s), and 1260 (s) cm.$^{-1}$.

*Anal.* Calcd. for $C_{21}H_{31}NO_5$: C, 66.85; H, 8.28; N, 3.71. Found: C, 66.67; H, 8.27; N, 3.70.

*Preparation of Deuterated Thiophenol.* Essentially the method of Plant, Tarbell, and Whiteman[23] was used. The product showed the presence of some PhSH in its infrared spectrum so it (*ca.* 2 g.) was allowed to stand over portions of $D_2O$ (four 0.5-ml. portions) for periods of 2 to 3 days. The product was dried (anhydrous sodium sulfate) before use. The purity was determined by examination of its n.m.r. spectrum and observing the intensity of the band at τ 6.4, due to PhSH.

(23) D. Plant, D. S. Tarbell, and C. Whiteman, *J. Am. Chem. Soc.*, 77, 1572 (1955).

*Photolysis with Deuteriothiophenol.* The method was as described for thiophenol except that the deuteriothiophenol (93% as PhSD) was added neat.

With the nitrite ester (XI), photolyses using 1.17 and 2.2 equiv. of deuteriothiophenol, respectively, were performed. The alcohols XV isolated by chromatography (45 and 51%, respectively) were subjected to mass spectrometry and showed peaks at *m/e* 348, 349, and 350 of relative intensities 67:32:6 and 64:51:10 corresponding to 19.7 and 36% atom excess of deuterium, respectively. The spectra also showed peaks at *m/e* 273, 274, corresponding to the loss of acetic acid and a methyl group, of the same relative intensities, showing that the deuterium is incorporated into the C-19 positions.

*Photolysis of 1-Methylcyclopentyl Nitrite with Deuteriothiophenol.* Freshly prepared 1-methylcyclopentyl nitrite (distilled at 45–46° at 15 mm., 0.65 g.) and deuteriothiophenol (1.10 g., 2 equiv., 90%) were dissolved in anhydrous benzene (140 ml.) and photolyzed as described above. The solution was made up to 160 ml. volume before separating into four equal portions. To two of these were added portions of phenyl isocyanate (0.59 g., 5 equiv.). The clear solutions were left to stand at room temperature overnight before evaporation to small bulk. The residues were separately chromatographed eluting with benzene. Rechromatography of the initial fractions, using hexane–benzene mixtures, afforded the phenylurethan of 1-methylcyclopentanol[24] (24.9 mg., 9%), m.p. 85–87° and (21 mg., 7.5%) m.p. 84–88° from the two runs. A "blank" run in the absence of thiophenol gave trace amounts of urethan only (<2%).

The remaining two portions from the photolysis were each treated with 2,4-dinitrophenylhydrazine (250 mg.) in methanol (30 ml.) and concentrated hydrochloric acid (0.2 ml.). After leaving the mixtures at room temperature overnight, the products were worked up in the usual manner followed by chromatography through alumina, eluting with 1:4 methylene chloride–benzene to give the 2,4-dinitrophenylhydrazone of hexan-2-one (181.4 mg., 51% and 196 mg., 55%, respectively) showing m.p. 106–107 and 107–108°. The mass spectrum of the hydrazone showed peaks at *m/e* 280, 281, and 282 of relative intensities 11:17:3 corresponding to 58.2% atom excess of deuterium. The n.m.r. spectrum showed weakening of the triplet due to the terminal methyl group at τ 9.05.

*Acknowledgments.* We wish to thank Dr. M. M. Pechet for his interest and encouragement during this work. It is a pleasure to acknowledge the skillful technical assistance provided by Mrs. C. B. Pantuck, Mrs. Anita Scott-Read, and Miss Gail Berlinghieri. We thank Dr. E. S. Waight and his colleagues at Imperial College for the mass spectrometric results.

(24) E. G. E. Hawkins, *J. Chem. Soc.*, 2801 (1950).