(1972).
(60) J. W. McIver, Jr., Acc. Chem. Res., 7, 72 (1974); M. J. S. Dewar and S. Kirschner, J. Am. Chem. Soc., 96, 6809 (1974); H. Metiu, J. Ross, and R. Silbey, J. Chem. Phys., 61, 3200 (1974).
(61) R. C. Bingham, M. J. S. Dewar, and D. H. Lo, J. Am. Chem. Soc., 97, 1285

(1975); 97, 1294 (1975).
(62) N. L. Allinger and J. T. Sprague, J. Am. Chem. Soc., 94, 5734 (1972).
(63) "Organic Syntheses", Collect. Vol. 2, 250 (1943).
(64) In our preliminary report[13] the temperature was incorrectly given as 52.0°C.

Photolysis of α-Peracetoxynitriles. 2.[1] A Comparison of Two Synthetic Approaches to 18-Cyano-20-ketosteroids

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Abstract: A new photochemical reaction was utilized to functionalize unactivated carbon–hydrogen bonds in the C-18 angular methyl group in steroids. The photolysis of 20-peracetoxy-20-cyanosteroids derived from 17-ketosteroids furnished 18-cyano-20-ketosteroids. For example, the following sequence of reactions was applied to 3β-hydroxyandrost-5-en-17-one (11): (1) protection of the hydroxyl group in 11 using isobutylene–sulfuric acid to furnish 3β-tert-butoxyandrost-5-en-17-one (12), 73% yield; (2) condensation of 12 with the anion of 2-(diethylphosphono)propionitrile to afford 3β-tert-butoxy-20-carbonitrilepregna-5,17(20)-diene (13), 74% yield; (3) magnesium in methanol reduction of 13 to provide 3β-tert-butoxy-20-carbonitrilepregn-5-ene (14), 85% yield; (4) sequential treatment of 14 with lithium diisopropylamide, oxygen gas, and acetyl chloride to obtain 3β-tert-butoxy-20-carbonitrile-20-peracetoxypregn-5-ene (15), 62% yield; and (5) the photolysis of 15 to furnish 3β-tert-butoxy-18-carbonitrilepregn-5-en-20-one (16), 46% yield. In the same manner, 20-carbonitrile-20-peracetoxypregn-5-en-3-one ethylene ketal (22) afforded 18-carbonitrilepregn-5-ene-3.20-dione 3-ethylene ketal (23) in 21% yield, and 20-carbonitrile-3-methoxy-20-peracetoxy-19-norpregna-1,3,5(10)-triene (31) furnished 18-carbonitrile-3-methoxy-19-norpregna-1,3,5(10)-trien-20-one (33) in 39% yield. Finally, the new photochemical approach to 18-cyano-20-ketosteroids was contrasted with the cyanohydrin–ketonitrile reaction developed by Kalvoda.

Introduction

In recent years, a variety of ingenious synthetic methods have been developed to functionalize unactivated carbon–hydrogen bonds in steroids.[2] The impetus for such investigations was provided, in part, by the occurrence of the relatively rare mineralcorticosteroid, aldosterone (1). Apart from the


1
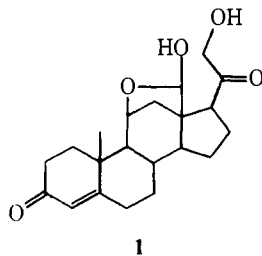
total synthesis[3] of 1, a particular limitation in the partial synthesis of 1 was the limited availability of naturally occurring steroids bearing oxygen functionality at C-11 and C-18.

An examination of the functionality in aldosterone (1) revealed the 1,4 relationship of the oxygen substituents at C-11, C-18, and C-20. We were attracted to the possibility of introducing this functionality in a sequential fashion starting with a steroid functionalized only at C-20. To achieve this objective, we required a reiterative reaction in which a parent functional group (X) would migrate down the backbone of the steroid nucleus regioselectively and leave behind a daughter functional group (Y). A schematic representation of this process is shown below.

Results and Discussion

Recently, we reported[1] that the photolysis of α-peracetoxynitriles **3** derived from secondary nitriles **2** provided δ-ke-
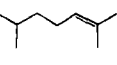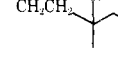
tonitriles **4** (Table I). This new photochemical reaction possessed the reiterative feature crucial to the success of the scheme outlined above. For example, the α-peracetoxynitrile
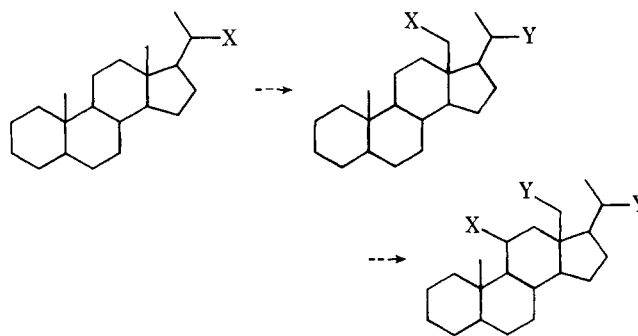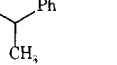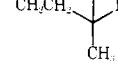
6 obtained from 2-phenylnonanenitrile (5) was photolyzed to provide the δ-ketonitrile 7. To confirm the regioselectivity of this process, 7 was independently synthesized by alkylating hexanenitrile with β-bromopropiophenone ethylene ketal and hydrolyzing the ethylene ketal. A second peracetoxy group was introduced in the ketal nitrile 8 and the α-peracetoxynitrile 9 was photolyzed to obtain the δ-ketonitrile 10 in which the cyano group of 5 had clearly undergone two successive δ migrations. The only variation in this regioselectivity was observed in the photolysis of δ-peracetoxynitrile 3r which afford the ε-ketonitrile 4r.

Having developed a reaction which incorporated a reiterative feature as well as a high degree of regioselectivity, we returned to the objective of functionalizing unactivated carbon–hydrogen bonds in steroid systems. We now wish to report the first phase of our application of this reaction to function-

Table I. Synthesis of α-Peracetoxynitriles 3 RR'CH(OOAc)CN and δ-Ketonitriles 4 RCOR"

	R	R'	Isolated yield of 3, %	R"	Isolated yield of 4, %
a	CH₃	CH₂(CH₂)₄CH₃	65		
b	CH₃	CH₂CH₂CH(CH₃)₂	64	CH₂CH₂C(CH₃)₂CN	50
c	CH₃	CH₂CH₂—(cyclohexyl)	63	CH₂CH₂—(cyclohexyl, CN)	47
d	CH₃	CH₂CH₂—(prenyl)	67	CH₂CH₂—(CN)	28
e	CH₃	c-C₆H₁₁	53		
f	CH₃	CH₂Ph	89		
g	CH₃	(o-tolyl-CH₃)	60	(o-aryl-CH₂CN)	18
h	CH₂Ph	c-C₅H₉	57		
i	CH₂Ph	CH₂Ph	90		
j	CH₂Ph	CH₂(CH₂)₂CH₃	69		
k		—(CH₂)₅—	72		
l	Ph	CH₃	69		
m	Ph	CH₂CH₃	49		
n	Ph	CH₂CH₂CH₃	57	CH₂CH₂CH₂CN	15
o	Ph	CH(CH₃)₂	81		
p	Ph	CH₂(CH₂)₂CH₃	72	CH₂CH₂CH(CH₃)CN	22
q	Ph	CH₂CH₂CH(CH₃)₂	63	CH₂CH₂C(CH₃)₂CN	52
r	Ph	CH₂CH₂C(CH₃)₃	73	CH₂CH₂—(CH₂CN)	10
s	Ph	CH₂CH₂CH₂Ph	77	CH₂CH₂CH(CN)Ph	10
t	Ph	CH₂CH₂—(Ph, CH₃)	72	CH₂CH₂—(CN, Ph, CH₃)	9
u	Ph	c-C₆H₁₁	74		
v	p-FC₆H₄	CH₃	65		
w	p-ClC₆H₄	CH₃	56		
x	Ph	Ph	85		

Scheme 1

11, R = H
12, R = t-Bu → 13

NC· ... → 16 ← 14, R = H; 15, R = OOAc (t-BuO)

17, R = H
18, R = t-Bu → 19 (t-BuO)

15 → 20 → ... → 16

alize the C-18 angular methyl group. To evaluate the merits of this approach, we have contrasted the peracetoxynitrile–ketonitrile reaction with the cyanohydrin–ketonitrile reaction developed by Kalvoda.[1]

With aldosterone (1) as the ultimate goal, we selected steroid precursors possessing a C-3 oxygen substituent which could be transformed to the enone synthon in 1. As shown in Scheme I, dehydroepiandrosterone (11) was protected as the 3β-tert-butyl ether[5] 12 in 73% yield and condensed with the anion of 2-(diethylphosphono)propionitrile[6] to furnish the α,β-unsaturated nitrile 13 in 74% yield. The magnesium in methanol reduction of 13 provided the saturated nitrile 14 in 85% yield. The sequential treatment of 14 with lithium diisopropylamide, oxygen, and acetyl chloride afforded the 20-peracetoxy-20-nitrile[8] 15 in 62% yield.

The photolysis of 15 in benzene using a 450-W high-pressure

5, R = H
6, R = OOAc

7

8, R = H
9, R = OOAc

10
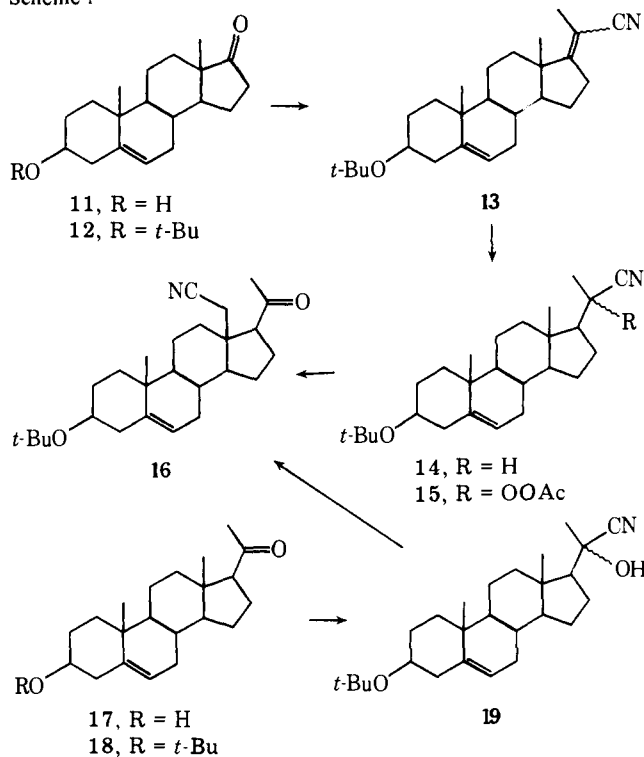
Hanovia lamp effected the desired functionalization of the C-18 angular methyl group in providing the 18-cyano-20-ketosteroid 16 in 46% yield. The balance of the reaction mix-

15 → 20 → ... → 16
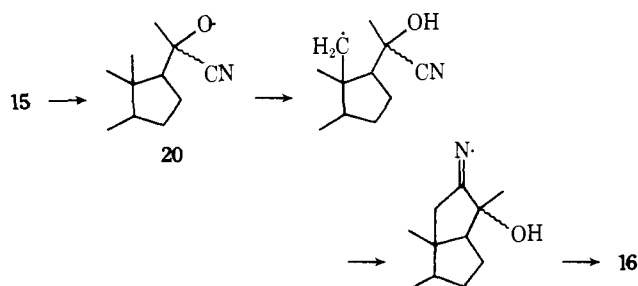
ture consisted principally of the ketone 18 and a small amount of unreacted 15. The 18-cyano-20-ketosteroid 16 was readily identified by the NMR spectrum which displayed the C-21 methyl signal at δ 2.30 but no high-field C-18 angular methyl signal. A mechanism consistent with the formation of 16 involves the generation of the radical 20 which abstracts a hydrogen atom from the C-18 angular methyl group. The subsequent migration of the cyano group provides the 18-cyano-20-ketosteroid[9] 16.

Kalvoda[4] has devised an alternate synthesis of 18-cyano-20-ketosteroids which involves the intermediacy of the same radical 20. To apply Kalvoda's reaction in this system, pregnenolone (17) was protected as the 3β-tert-butyl ether 18 in 59% yield and converted to the cyanohydrin 19 in 38% yield. The photolysis of 19 in the presence of lead tetraacetate, iodine, and calcium carbonate afforded the 18-cyano-20-ketone 16 in 37% yield. In comparing the two routes for the preparation of 16, the cyanohydrin route offers the distinct advantage of requiring fewer steps than the α-peracetoxynitrile route. On the other hand, the photolysis step of the α-peracetoxynitrile route is experimentally simpler than the cyanohydrin route. In this example, the overall yield of 16 from 17 and 11 are 8 and 13%, respectively, and we would conclude that the two routes are comparable.

The comparison of the two routes was expanded to include functionality at C-3 more labile than tert-butyl ethers. As shown in Scheme II, the ketal nitrile[6] 21 was converted to the

Scheme II

CN
R

21, R = H
22, R = OOAc
26, R = OH

23
NC

O

24

25
CN
OH
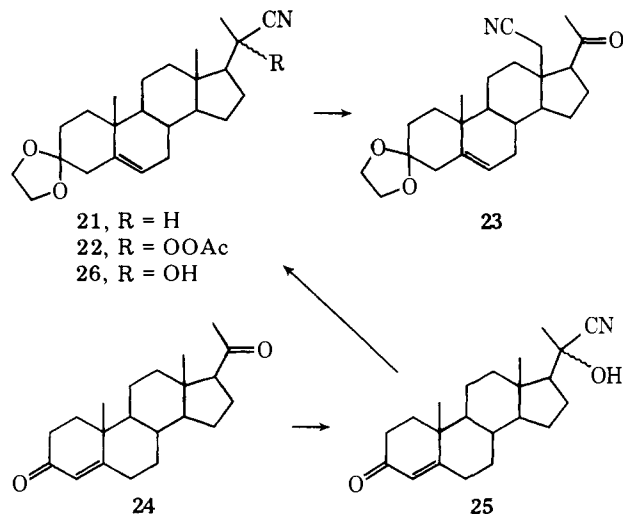
20-peracetoxy-20-nitrile **22** and subsequently photolyzed to provide the 18-cyano-20-ketosteroid **23**. Kalvoda[4b] has achieved the synthesis of **23** from progesterone (**24**) via the cyanohydrin **26**. Although the yields of the key photochemical reactions (**22 → 23**, 21% vs. **26 → 23**, 30%) are comparable, the Kalvoda route again entails fewer synthetic operations than the α-peracetoxynitrile route.

Apart from our interest in aldosterone (**1**), we also wanted to synthesize 18-substituted analogues of the contraceptive agent, norgestrel (**27**).[10] One approach to such compounds involved the synthesis of the 18-cyano-20-ketone **33**. As shown in Scheme III, application of the reaction sequence discussed earlier to estrone 3-methyl ether (**28**) provided the 20-peracetoxy-20-nitrile **31** in 34% overall yield from **28**. The photolysis of **31** secured the 18-cyano-20-ketone **33** in 39% yield.

OH
C≡CH
H
O

27

OH
C≡CH
CH₃O

36
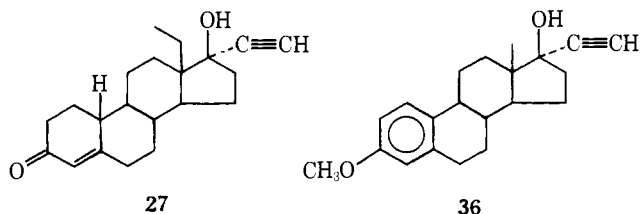
To employ Kalvoda's cyanohydrin route in the preparation of **33** first required the synthesis of the ketone **35**. Djerassi[11] has reported an efficient four-step synthesis of **35** from mestranol (**36**). In addition, we devised two alternate routes to **35** which involve either (1) the oxidative decyanation[8] of **30** to **35** or (2) the oxidative decyanation of **29** to the α,β-unsaturated ketone **34** followed by catalytic hydrogenation[13] of **34** to provide **35**. However, efforts to secure the cyanohydrin **32** derived from **35** using hydrogen cyanide in acetic acid or acetone cyanohydrin–triethylamine failed entirely. In an effort to assess the applicability of the Kalvoda reaction in estrane systems related to **32**, we subjected the cyanohydrin[17] of 3-acetoxy-19-norpregna-1,3,5(10)-trien-20-one to the Kalvoda reaction and obtained an intractable mixture of products from which we were unable to isolate any of the desired 18-cyano-20-ketosteroid. This failure was not totally unexpected given the propensity of lead tetraacetate to oxidize other sites in the cyanohydrin such as the benzylic carbons[18] at C-6 and C-9.

In summary, we have developed methodology for the introduction of a C-18 cyano group in steroids. This new procedure for the synthesis of 18-cyano-20-ketosteroids from 20-peracetoxy-20-cyanosteroids is comparable or, in one case, superior to the Kalvoda procedure[4] for the synthesis of 18-cyano-20-ketosteroids from 20-hydroxy-20-cyanosteroids. We are presently investigating the application of this reaction to functionalize other positions in a steroid nucleus.

Scheme III

O
CH₃O

28

CN
CH₃O

29

O
CH₃O

34

CN
R
CH₃O

30, R = H
31, R = OOAc
32, R = OH

O
CH₃O

35

NC
O
CH₃O

33
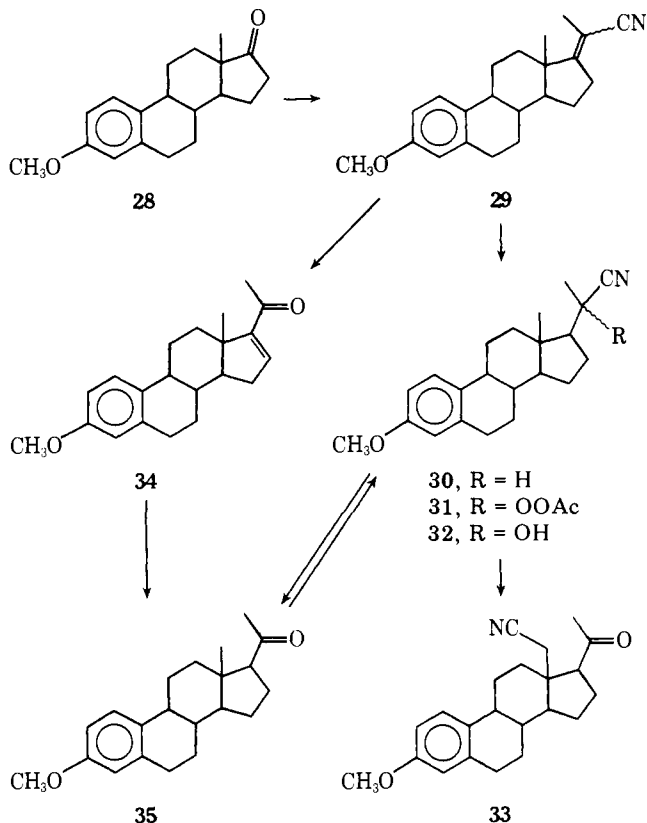
Experimental Section

Infrared spectra were determined on a Perkin-Elmer Model 337 spectrophotometer. NMR spectra were determined on a Varian A-60A or EM390 spectrometer. Mass spectra were determined on a Varian MAT CH5 mass spectrometer. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Ga. Unless otherwise specified, preparative layer chromatography was performed on 2 mm thick 20 × 20 cm Merck silica gel F254 plates.

The following experimental procedures starting with 2-phenylnonanenitrile (**5**) are typical of the synthesis and photolysis of the α-peracetoxynitriles 3 in Table 1.

2-Phenylnonanenitrile (5). The procedure of Watt[14] was repeated using 11.7 g (0.1 mol) of phenylacetonitrile and 18.8 g (0.105 mol) of n-heptyl bromide to afford 13.2 g (62%) of **5**: bp 117.5–120.5 °C (0.35 mm); IR (TF) 4.48 (C≡N) and 6.36 μ (aromatic); NMR (CCl₄) δ 0.60–1.05 (m, 3, (CH₂)₆CH₃), 1.05–2.10 (m, 12, (CH₂)₆CH₃), 3.61 (t, J = 7.5 Hz, 1, PhCH), and 7.32 (s, 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 215 (7) and 117 (100). Anal. (C₁₅H₂₁N) C, H.

α-Peracetoxynitrile 6. To 111 mg (1.1 mmol) of diisopropylamine in 2.6 ml of anhydrous THF under a nitrogen atmosphere at −78 °C was added 0.41 ml of 2.71 M (1.1 mmol) n-butyllithium in hexane. The solution was stirred for 10 min, and 215 mg (1.0 mmol) of **5** in 1.0 ml of THF was introduced. The yellow solution was stirred for 10 min, and oxygen was bubbled into the solution at −78 °C for 30 min. The reaction was quenched with 0.29 ml of acetyl chloride and was stirred for 1 h at −78 °C and 1 h at 0 °C. The product was diluted with 50 ml of ether and 10 g of ice, washed with two 20-ml portions of water and 20 ml of saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated, and the product was chromatographed on three silica gel plates in 1:3 ether-hexane.

A band (R_f 0.46) was eluted to afford 216.3 mg (75%) of **6**: IR (TF) 5.56 μ (C=O); NMR (CCl₄) δ 0.65–1.05 (m, 3, CH₂CH₃), 1.05–2.3 (m, 12, CH₂), 1.90 (s, 3, COCH₃), and 7.2–7.8 (m, 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 216 (1), 215 (5), 214 (7), 204 (17), 133 (11), 131 (11), 121 (8), 120 (72), and 105 (100). Anal. (C₁₇H₂₃NO₃) C, H.

δ-Ketonitrile 7. A solution of 289 mg (1.0 mmol) of **6** in 4.0 ml of anhydrous, degassed benzene in a quartz test tube was irradiated for

1 h with a 450-W high-pressure Hanovia lamp housed in a quartz immersion well. The solvent was evaporated, and the product was chromatographed on a silica gel plate in 1:9 ether-hexane.

A band (R_f 0.18) was eluted to afford 44.7 mg (20%) of **7**: IR (TF) 4.49 (C≡N), 5.94 (C=O), 6.27 and 6.33 μ (aromatic); NMR (CCl₄) δ 0.65-1.15 (m, 3, CH₂CH_3), 1.15-2.2 (m, 8, CH₂), 2.35-2.85 (m, 1, CHCN), 3.13 (t, J = 7 Hz, 2, COCH₂), and 7.1-8.2 (m, 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 229 (1), 178 (1), 134 (1), 133 (4), 121 (3), 120 (32), 106 (9), and 105 (100).

An analytical sample was prepared by evaporative distillation at 180-185 °C (0.4 mm). Anal. (C₁₅H₁₉NO) C, H.

Alternate Synthesis of δ-Ketonitrile 7 from Hexanenitrile. The procedure of Watt[14] was repeated to effect the alkylation of 97 mg (1.0 mmol) of hexanenitrile with 308 mg (1.2 mmol) of β-bromopropiophenone ethylene ketal to afford, after chromatography on a silica gel plate in 1:3 ether-hexane, a band (R_f 0.40) furnishing 164 mg (60%) of ketal nitrile **8**.

A solution of 206 mg (7.55 × 10⁻¹ mmol) of the ketal nitrile **8** in 7.5 ml of 1:2:3 1 M hydrochloric acid-acetic acid-THF was stirred for 24 h at 25 °C. The reaction was diluted with 50 ml of ether. washed with two 25-ml portions of water, two 25-ml portions of saturated sodium bicarbonate solution, and 25 ml of saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvents were evaporated to afford after chromatography on a silica gel plate in 1:3 ether-hexane a band (R_f 0.30) 167 mg (97%) of δ-ketonitrile **7** identical with the product isolated in the photolysis of **6**.

Ketal Nitrile 8. A mixture of 179 mg (0.782 mmol) of **7**, 97 mg (1.56 mmol, 2 equiv) of distilled ethylene glycol, and ca. 10 mg of p-toluenesulfonic acid monohydrate in 25 ml of benzene was refluxed under a Dean-Stark trap for 24 h. The product was diluted with 50 ml of ether. washed with 25 ml of saturated sodium bicarbonate solution, two 25-ml portions of water, and 25 ml of saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated to afford 197 mg (92%) of ketal nitrile **8**: IR (TF) 4.49 μ (C≡N); NMR (CDCl₃) δ 0.7-1.1 (m, 3, CH₂CH_3), 1.1-2.35 (m, 10, CH₂), 2.35-2.8 (m, 1, CHCN), 3.6-4.25 (m, 4, OCH₂CH₂O), and 7.2-7.65 (m, 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 197 (1), 196 (4), 152 (1), 151 (1), 150 (11), 149 (100), and 105 (37).

Ketal α-Peracetoxynitrile 9. The procedure described in the preparation of **6** was repeated to afford, after chromatography on silica gel in 1:1 ether-hexane, a band (R_f 0.45) furnishing 2.25 mg (65%) of **9**: IR (TF) 5.56 μ (C=O); NMR (CDCl₃) δ 0.7-1.05 (m, 3, CH₂CH_3), 1.05-2.2 (m, 10, CH₂), 2.05 (s, 3, COCH₃), 3.6-4.2 (m, 4, OCH₂CH₂O), and 7.2-7.65 (m, 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 210 (1), 205 (2), 185 (2), 161 (1), 159 (1), 151 (2), 150 (10), 149 (100), and 105 (28). Anal. (C₁₉H₂₅NO₅) C, H.

Ketal δ-Ketonitrile 10. The procedure described for the preparation of **7** was repeated using 555 mg (1.60 mmol) of α-peracetoxynitrile **9** to afford, after chromatography on silica gel in 1:1 ether-hexane, a band (R_f 0.23) furnishing 120 mg (26%) of **10**: IR (TF) 4.49 (C≡N) and 5.83 μ (C=O); NMR (CDCl₃) δ 1.31 (d, J = 7 Hz, 3, CHCH_3), 1.5-3.0 (m, 9, CHCH_3 and CH₂), 3.6-4.2 (m, 4, OCH₂CH₂O), and 7.2-7.7 (m, 5, aromatic H); mass spectrum (70 eV at 60 °C) m/e (rel intensity) 210 (4), 205 (2), 177 (1), 176 (1), 161 (2), 151 (1), 150 (10), 149 (100), and 105 (40). Anal. (C₁₇H₂₁NO₃) C, H.

Spectral Data for α-Peracetoxynitriles 3 in Table I. 3a: R_f 0.44 in 1:3 ether-hexane; IR (TF) 4.50 (C≡N) and 5.56 μ (C=O), NMR (CCl₄) δ 0.7-2.2 (m, 13, (CH₂)₅CH₃), 1.63 (s, 3, CH_3C(CN)(OOAc)CH₂), and 2.11 (s, 3, COCH₃); mass spectrum (70 eV) m/e (rel intensity) 139 (5), 128 (8), 111 (6), 107 (7), 99 (6), 85 (13), 73 (26), 71 (29), and 58 (100).

3b: R_f 0.48 in 1:3 ether-hexane; IR (TF) 4.48 (weak C≡N), 5.5 μ (C=O); NMR (CCl₄) δ 0.95 (d, J = 5.5 Hz, 6, CH(CH_3)₂), 1.1-2.0 (m, 5, CH₂ and CH(CH₃)₂), 1.63 (s, 3, CH_3C(CN)(OOAc)CH₂), and 2.12 (s, 3, COCH₃); mass spectrum (70 eV) m/e (rel intensity) 139 (1), 124 (2), 114 (1), 111 (1), 110 (1), and 99 (3). Anal. (C₁₀H₁₇NO₃) C, H.

3c: R_f 0.57 in 1:1 ether-hexane; IR (TF) 4.50 (C≡N), 5.57 μ (C=O); NMR (CCl₄) δ 0.7-2.1 (m, 15, CH and CH₂), 1.61 (s, 3, CH_3C(CN)(OOAc)CH₂), and 2.10 (s, 3, COCH₃); mass spectrum (70 eV) m/e (rel intensity) 179 (2), 165 (2), 164 (9), 152 (13), 151 (9), 150 (6), 137 (12), 136 (26), 135 (35), and 134 (13).

3d: R_f 0.52 in 1:2 ether-hexane; IR (TF) 5.65 μ (C=O); NMR (CCl₄) δ 0.94 (broad d, J = 5 Hz, 3, CHCH_3), 1.0-2.2 (m. 15, CHCH₃, CH₂ and vinyl CH₃), 1.64 (s, 3, CH_3C(CN)(OOAc)CH₂), 2.10 (s, 3, COCH₃), and 5.06 (m, 1, vinyl H); a small signal at δ 4.66 suggested that an isomer of **3d** bearing a C(CH₃)=CH_2 group was present; mass spectrum (70 eV) m/e (rel intensity) 192 (3), 190 (2), 182 (3), 179 (5), 164 (7), 151 (7), 150 (6), 149 (6), 137 (10), 136 (10), 135 (6), 134 (5), and 125 (11).

3e: R_f 0.37 in 1:3 ether-hexane; IR (TF) 5.57 μ (C=O); NMR (CCl₄) 0.8-2.3 (m, 11, CH₂ and CH₃), 1.59 (s, 3, CH_3C(CN)-(OOAc)CH), and 2.12 (s, 3, COCH₃); mass spectrum (70 eV) m/e (rel intensity) 137 (22), 126 (13), 111 (6), 105 (10), 83 (55), 71 (25), and 55 (100).

3f: R_f 0.20 in 1:3 ether-hexane; bp 145-150 °C (0.35 mm); IR (TF) 5.60 μ (C=O); NMR (CDCl₃) δ 1.58 (s, 3, CH₃), 2.13 (s, 3, COCH₃), 3.23 (s, 2, CH_2Ph), and 7.36 (s, 5, aromatic H): mass spectrum (70 eV) m/e (rel intensity) 183 (1), 182 (6), 168 (1), 157 (2), 150 (3), 141 (1), 135 (1), 134 (3), 133 (2), 131 (1), 129 (1), 125 (1) and 91 (100). Anal. (C₁₂H₁₃NO₃) C, H.

3g: R_f 0.37 in 1:2 ether-hexane; IR (TF) 5.57 (C=O) and 6.25 μ (aromatic); NMR (CCl₄) δ 2.01 (s, 6, CH₃ and COCH₃), 2.62 (s, 3, aromatic CH₃), and 7.1-7.7 (m, 4, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 191 (1), 176 (1), 175 (1), 161 (1), 160 (1), 149 (4), 148 (1), 147 (1), 146 (5), 145 (44), 144 (26), 134 (6), 132 (31), 131 (13), and 130 (100). Anal. (C₁₂H₁₃NO₃) C, H.

3h:[15] R_f 0.34 in 1:3 ether-hexane; IR (TF) 5.57 (C=O) and 6.25 μ (aromatic); NMR (CCl₄) δ 1.4-2.2 (m, 9, CH and CH₂), 2.10 (s. 3, COCH₃), 3.10 and 3.43 (AB quartet, J = 14.5 Hz, 2, CH_2Ph), and 7.32 (s, 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 199 (5), 105 (5), 97 (11), 92 (11), and 91 (100).

3i:[15] R_f 0.41 in 1:1 ether-hexane; IR (TF) 5.57 (C=O), 6.09, 6.22, and 6.31 μ (aromatic); NMR (CCl₄) δ 1.92 (s, 3, COCH₃), 3.10 (s. 4, CH_2Ph), and 7.30 (s, 10, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 165 (15), 163 (56), 154 (10), 153 (67), 152 (77). 151 (27), 150 (6), 142 (19), 141 (10), 136 (9), 134 (5), and 59 (100).

3j:[15] R_f 0.39 in 1:3 ether-hexane; IR (TF) 5.57 (C=O) and 6.25 μ (aromatic); NMR (CCl₄) δ 0.7-1.05 (m, 3, CH₂CH_3), 1.05-1.9 (m. 6, (CH_2)₃CH₃), 2.06 (s, 3, COCH₃), 3.20 (s, 2, CH_2Ph), and 7.32 (s, 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 187 (7), 92 (14), and 91 (100).

3k: R_f 0.33 in 1:2 ether-hexane; mp 46.5-48 °C (from hexane): IR (CHCl₃) 5.58 and 5.62 μ sh (C=O); NMR (CCl₄) δ 1.3-2.4 (m, 10, CH₂). and 2.10 (s. 3, COCH₃): mass spectrum (70 eV) m/e (rel intensity) 152 (2), 151 (16), 110 (9), 109 (100). Anal. (C₉H₁₃NO₃) C, H.

3l: R_f 0.28 in 1:3 ether-hexane: IR (TF) 5.57 μ (C=O); NMR (CCl₄) δ 1.98 (s, 6, COCH₃ and CH_3C(CN)(OOAc)Ph) and 7.3-7.8 (m, 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 131 (6), 120 (28), and 105 (100).

3m: R_f 0.30 in 1:3 ether-hexane; bp 150-160 °C (0.25 nm): IR (TF) 5.57 μ (C=O); NMR (CCl₄) δ 1.07 (t, J = 7 Hz, 3, CH₂CH_3), 1.90 (s, 3, COCH₃), 1.9-2.4 (m, 2, CH_2CH₃), and 7.2-7.7 (m. 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 219 (2), 188 (1), 187 (9), 146 (10), 145 (89), 144 (83), 134 (8), 132 (19), 131 (18), 130 (18). and 105 (100). Anal. (C₁₂H₁₃NO₃) C, H.

3n: R_f 0.41 in 1:3 ether-hexane; IR (TF) 5.57 μ (C=O); NMR (CCl₄) δ 0.8-1.1 (m. 3, CH₂CH_3), 1.1-2.3 (m. 4, CH₂), 1.88 (s. 3, COCH₃), and 7.2-7.8 (m. 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 173 (1), 148 (3), 147 (1), 146 (1), 133 (1), 132 (3), 131 (36), 106 (9). and 105 (100). Anal. (C₁₃H₁₅NO₃) C, H.

3o: R_f 0.36 in 1:3 ether-hexane: bp 160-165 °C (0.2 mm): IR (TF) 5.57 μ (C=O): NMR (CCl₄) δ 0.88 and 1.28 (two d, J = 7 Hz, 6, CH(CH_3)₂), 1.86 (s, 3, COCH₃), 1.85-2.65 (m, 1, CH(CH₃)₂), and 7.2-7.7 (m. 5, aromatic H): mass spectrum (70 eV) m/e (rel intensity) 163 (2), 160 (1), 159 (7). 158 (9). 157 (13). 156 (6), 148 (4), 142 (11), 132 (5), 131 (33), and 105 (100). Anal. (C₁₃H₁₅NO₃) C, H.

3p: R_f 0.32 in 1:3 ether-hexane: IR (TF) 5.57 μ (C=O): NMR (CCl₄) δ 0.7-2.5 (m, 9, (CH_2)₃CH₃), 1.88 (s. 3, COCH₃), and 7.3-7.8 (m. 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 189 (1), 174 (2), 173 (13), 172 (7), 145 (7). 132 (5). 131 (11). 130 (6), 120 (31), and 105 (100). Anal. (C₁₄H₁₇NO₃) C, H.

3q: R_f 0.36 in 1:3 ether-hexane; IR (TF) 5.56 μ (C=O): NMR (CCl₄) δ 0.88 and 0.91 (two d, J = 6 Hz, CH(CH_3)₂), 1.0-2.4 (m. 5, CH and CH₂), 1.90 (s, 3, COCH₃), and 7.3-7.8 (m. 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 220 (1), 205 (2), 204 (5), 187 (11), 186 (9), 176 (6), 148 (7), 147 (5), 133 (6), 131 (8), 130 (8). 121 (6), 120 (52), and 105 (100). Anal. (C₁₅H₁₉NO₃) C, H.

3r: R_f 0.46 in 1:3 ether-hexane; IR (TF) 5.57 μ (C=O); NMR (CCl$_4$) δ 0.88 (s, 9, C(CH$_3$)$_3$), 1.0-2.3 (m, 4, CH$_2$), 1.90 (s, 3, COCH$_3$), and 7.25-7.75 (m, 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 201 (2), 200 (2), 191 (1), 190 (6), 134 (5), 133 (20), 131 (7), 120 (7), and 105 (100). Anal. (C$_{16}$H$_{21}$NO$_3$) C, H.

3s: R_f 0.32 in 1:3 ether-hexane; IR (TF) 5.57 (C=O) and 6.24 μ (aromatic); NMR (CCl$_4$) δ 1.85 (s, 3, COCH$_3$), 1.7-2.3 (m, 4, CH$_2$), 2.45-2.85 (m, 2, CH$_2$Ph), and 6.9-7.7 (m, 10, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 249 (1), 236 (2), 235 (12), 234 (6), 224 (19), 156 (7), 143 (13), 131 (13), 129 (22), 121 (13), 120 (100), and 105 (80). Anal. (C$_{19}$H$_{19}$NO$_3$) C, H.

3t: R_f 0.29 in 1:3 ether-hexane; IR (TF) 5.57 (C=O) and 6.36 μ (aromatic); NMR (CCl$_4$) 1.16 and 1.18 (two d, J = 7 Hz, 3, CHCH$_3$) 1.77 (s, 3, COCH$_3$), 1.6-2.3 (m, 4, CH$_2$), 2.5-3.0 (m, 1, CHPh), and 6.9-7.7 (m, 10, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 250 (1), 249 (3), 248 (5), 239 (2), 238 (10), 133 (6), 131 (12), 121 (8), 120 (86), and 105 (100). Anal. (C$_{20}$H$_{21}$NO$_3$) C, H.

3u: R_f 0.39 in 1:3 ether-hexane; IR (TF) 5.57 μ (C=O); NMR (CCl$_4$) δ 0.9-2.4 (m, 11, CH and CH$_2$), 1.87 (s, 3, COCH$_3$), and 7.2-7.7 (m, 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 207 (1), 200 (1), 199 (7), 198 (5), 168 (9), 133 (9), 132 (4), 131 (15), and 105 (100). Anal. (C$_{16}$H$_{19}$NO$_3$) C, H.

3v: R_f 0.26 in 1:3 ether-hexane; IR (TF) 5.57 μ (C=O) and 6.22 μ (aromatic); NMR (CCl$_4$) δ 1.95 and 1.98 (two s, 6, CH$_3$ and COCH$_3$) and 7.0-7.8 (m, 4, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 191 (2), 165 (1), 164 (1), 150 (5), 149 (24), 148 (25), 140 (13), 138 (19), 124 (8) and 123 (100). Anal. (C$_{11}$H$_{10}$FNO$_3$) C, H.

3w: R_f 0.26 in 1:3 ether-hexane; IR (TF) 5.57 (C=O) and 6.26 μ (aromatic); NMR (CCl$_4$) δ 1.93 and 1.98 (two s, 6, CH$_3$ and COCH$_3$) and 7.35-7.8 (m, 4, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 207 (8), 167 (19), 166 (31), 165 (57), 164 (67), 156 (7), 154 (23), 141 (32), 140 (9), 139 (100), 138 (6), 137 (10), and 128 (11). Anal. (C$_{11}$H$_{10}$ClNO$_3$) C, H.

3x: R_f 0.29 in 1:3 ether-hexane; mp 92-94 °C from 1:6 CHCl$_3$-ether); IR (CHCl$_3$) 5.58 (C=O) and 6.28 μ (aromatic); NMR (10% CDCl$_3$ in CCl$_4$) δ 1.97 (s, 3, COCH$_3$) and 7.25-7.7 (m, 10, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 267 (1), 235 (1), 210 (1), 209 (4), 208 (8), 194 (8), 193 (56), 192 (99), 191 (5), 190 (8), 183 (8), 182 (53), 181 (9), 166 (8), 165 (34), 154 (6), 153 (6), 152 (6), and 105 (100). Anal. (C$_{16}$H$_{13}$NO$_3$) C, H.

Spectral Data for δ-Ketonitriles 4 in Table I. 4b: R_f 0.23 in 1:1 ether-hexane; IR (TF) 4.49 (C≡N) and 5.82 μ (C=O); NMR (CCl$_4$) δ 1.34 (s, 6, C(CH$_3$)$_2$), 1.55-1.95 (m, 2, CH$_2$C(CN)), 2.17 (s, 3, COCH$_3$), and 2.45-2.8 (m, 2, COCH$_2$); mass spectrum (70 eV) m/e (rel intensity) 139 (6), 124 (7), 99 (10), 97 (8), 96 (10), 83 (8), 82 (10), 71 (6), 69 (45), 68 (11), and 42 (100). Anal. (C$_8$H$_{13}$NO) C, H.

4c: R_f 0.33 in 1:1 ether-hexane; IR (TF) 4.50 (C≡N) and 5.82 μ (C=O); NMR (CCl$_4$) δ 0.8-2.3 (m, 12, CH$_2$), 2.15 (s, 3, COCH$_3$), and 2.4-2.8 (m, 2, COCH$_2$); mass spectrum (70 eV) m/e (rel intensity) 179 (9), 165 (1), 164 (6), 152 (7), 137 (7), 136 (20), 135 (29), 134 (7), 131 (5), 122 (14), 121 (14), 120 (6), 119 (9), 110 (11), 109 (97), 108 (16), and 42 (100). Anal. (C$_{11}$H$_{17}$NO) C, H.

4d: R_f 0.35 in 1:1 ether-hexane; IR (TF) 4.50 (C≡N) and 5.82 μ (C=O); NMR (CCl$_4$) δ 0.8-2.4 (m, 6, CH$_2$), 1.29 (s, 3, C(CN)CH$_3$). 1.67 (broad s, 6, vinyl CH$_3$), 2.16 (s, 3, COCH$_3$), 2.4-2.8 (m, 2, COCH$_2$), and 5.12 (m, 1, vinyl H); mass spectrum (70 eV) m/e (rel intensity) 207 (5), 193 (1), 192 (1), 190 (1), 189 (1), 180 (1), 179 (4), 178 (2), 174 (1), 165 (1), 164 (2), 163 (1), 162 (1), 150 (5), 137 (10), 136 (10), 125 (16), 122 (28), and 58 (100).

4g: R_f 0.30 in 1:1 ether-hexane; IR (TF) 4.48 (C≡N), 5.95 (C=O), 6.25 and 6.37 μ (aromatic); NMR (CCl$_4$) δ 2.57 (s, 3, COCH$_3$), 4.08 (s, 2, CH$_2$CN), and 7.1-8.0 (m, 4, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 158 (12), 145 (6), 144 (51), 133 (11), and 132 (100). Anal. (C$_{10}$H$_9$NO) C, H.

4n: R_f 0.48 in 1:9 ether-benzene; IR (TF) 4.57 (C≡N), 5.95 (C=O), 6.26 and 6.32 μ (aromatic); NMR (CCl$_4$) δ 1.85-2.25 (m, 2, COCH$_2$CH$_2$), 2.25-2.65 (m, 2, CH$_2$CN), 3.13 (t, 2, COCH$_2$), and 7.2-8.2 (m, 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 173 (8), 106 (8), 105 (100), 77 (48), and 73 (12). Anal. (C$_{11}$H$_{11}$NO) C, H. A 2,4-dinitrophenylhydrazone derivative had mp 182.5-183.5 °C (from methanol-chloroform).

4p: R_f 0.15 in 1:3 ether-hexane; mp 45.5-47.5 °C (from 1:5 ether-hexane); IR (TF) 4.49 (C≡N), 5.95 (C=O), 6.27 and 6.33 μ (aromatic); NMR (CCl$_4$) δ 1.34 (d, J = 7 Hz, 3, CHCH$_3$), 1.65-2.15 (m, 2, COCH$_2$CH$_2$), 2.4-2.9 (m, 1, CHCN), 3.14 (t, 2,

COCH$_2$CH$_2$), and 7.2-8.1 (m, 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 187 (2), 133 (2), 121 (2), 120 (24), 106 (8), and 105 (100). Anal. (C$_{12}$H$_{13}$NO) C, H. A 2,4-dinitrophenylhydrazone derivative had mp 147-149 °C (from methanol-chloroform).

4q: R_f 0.20 in 1:3 ether-hexane; mp 53.5-55.5 °C (from 1:5 ether-hexane); IR (CHCl$_3$) 4.49 (C≡N), 5.95 (C=O), 6.28 and 6.34 μ (aromatic); NMR (CDCl$_3$) δ 1.40 (s, 6, C(CH$_3$)$_2$), 1.8-2.25 (m, 2, COCH$_2$CH$_2$), 3.0-3.4 (m, 2, COCH$_2$), and 7.3-8.2 (m, 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 201 (2), 133 (2), 106 (11), 105 (100), and 77 (32). Anal. (C$_{13}$H$_{15}$NO) C, H.

4r: R_f 0.12 in 1:3 ether-hexane; mp 54.5-55.5 °C (from 1:2 ether-hexane); IR (CHCl$_3$) 4.47 (C≡N), 5.94 (C=O), 6.28 and 6.33 μ (aromatic); NMR (CCl$_4$) δ 1.10 (s, 6, C(CH$_3$)$_2$), 1.6-1.95 (m, 2, COCH$_2$CH$_2$), 2.25 (s, 2, CH$_2$CN), 2.75-3.15 (m, 2, COCH$_2$CH$_2$), and 7.2-8.1 (m, 5, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 215 (2), 201 (1), 200 (4), 187 (1), 175 (4), 157 (2), 156 (1), 133 (5), 106 (9), and 105 (100). Anal. (C$_{14}$H$_{17}$NO) C, H.

4s: R_f 0.20 in 1:3 ether-hexane; IR (TF) 4.49 (C≡N), 5.95 (C=O), 6.28 and 6.34 μ (aromatic); NMR (CCl$_4$) δ 1.95-2.45 (m, 2, COCH$_2$CH$_2$), 3.0-3.4 (m, 2, COCH$_2$), 4.00 (d of d, J = 6.5, 8.5 Hz, 1, CHCN), and 7.0-8.2 (m, 10, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 249 (3), 224 (1), 219 (1), 208 (1), 207 (1), 196 (1), 165 (1), 162 (1), 160 (1), 153 (2), 152 (1), 151 (5), 149 (1), 147 (3), 146 (7), 136 (9), 134 (15), 132 (9), 121 (9), 120 (84), 117 (5), 116 (6), and 105 (81). Anal. (C$_{17}$H$_{15}$NO) C, H.

4t: R_f 0.20 in 1:3 ether-hexane; IR (TF) 4.49 (C≡N), 5.95 (C=O), 6.28 and 6.33 μ (aromatic); NMR (CDCl$_3$) δ 1.78 (s, 3, CH$_3$), 2.2-3.3 (m, 4, COCH$_2$CH$_2$), and 7.2-8.2 (m, 10, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 263 (3), 159 (2), 149 (1), 134 (2), 133 (8), 120 (10), 106 (10), and 105 (100). Anal. (C$_{18}$H$_{17}$NO) C, H.

3β-tert-Butoxyandrost-5-en-17-one (12). The procedure of Beyerman and Heiszwolf[5] was repeated using 25 g of dehydroepiandrosterone (11), 100 ml of isobutylene, 59 ml of dichloromethane, and 2 ml of concentrated sulfuric acid to afford after recrystallization from ether-dichloromethane, 21.8 g (73%) of **12**: mp 168.5-171 °C (with gas evolution) (lit.[5a] mp 174-179 °C; lit.[5b] mp 165-178 °C); IR (KBr) 5.78 μ (C=O); NMR (CDCl$_3$) δ 0.89 and 1.03 (two s, 6, C-18 and C-19 angular CH$_3$), 1.20 (s, 9, C(CH$_3$)$_3$), and 5.36 (m, 1, C-6 vinyl H); mass spectrum (70 eV) m/e (rel intensity) 344 (11), 288 (12), 255 (17), and 57 (100).

3β-tert-Butoxy-20-carbonitrilepregna-5,17(20)-diene (13). To 126 mg of 57% sodium hydride (washed with three 1-ml portions of anhydrous hexane to remove mineral oil) in 3 ml of anhydrous THF under a nitrogen atmosphere was added 573 mg (3.0 mmol, 3.0 equiv) of 2-(diethylphosphono)propionitrile in 1.0 ml of anhydrous THF. The addition of the phosphonate was accompanied by copious hydrogen gas evolution and the formation of a white precipitate. To the phosphonate salt was added 344 mg (1.0 mmol) of **12** in 5 ml of THF and 1.0 ml of HMPA. The solution (precipitate dissolves rapidly following the addition of HMPA) was refluxed for 48 h. The reaction was poured into 50 ml of cold water and extracted with 100 ml of dichloromethane. The organic layer was washed successively with two 50-ml portions of water and 50 ml of brine and dried over anhydrous magnesium sulfate. The product was chromatographed on two silica gel plates in dichloromethane to afford 282 mg (74%) of **13** as a mixture of E and Z isomers: R_f 0.41; IR (KBr) 4.54 (C≡N) and 6.11 μ (conjugated C=C); NMR (CDCl$_3$) δ 0.94 and 1.02 (two s, 6, C-18 and C-19 angular CH$_3$), 1.20 (s, 9, C(CH$_3$)$_3$), 1.82 (broad s, 3, C-21 vinyl CH$_3$ of E and Z isomers), and 5.34 (m, 1, C-6 vinyl H); mass spectrum (70 eV) m/e (rel intensity) 381 (100), 326 (10), 325 (42), 308 (20), 307 (45), 292 (31), 268 (63), 213 (26), and 57 (82).

An analytical sample was prepared by three recrystallizations from anhydrous ether, mp 170-178 °C. Anal. (C$_{26}$H$_{39}$NO) C. H.

3β-tert-Butoxy-20-carbonitrilepregn-5-ene (14). The procedure of Profitt, Watt, and Corey[7] was repeated using 381 mg (1.0 mmol) of **13** and 960 mg (40 equiv) of magnesium in 20 ml of absolute methanol to afford, after chromatography on two silica gel plates in 1:50 ethyl acetate-dichloromethane, 326 mg (85%) of **14**: R_f 0.42; IR (KBr) 4.50 μ (C≡N); NMR (CDCl$_3$) δ 0.75 (s, 3, C-18 angular CH$_3$), 1.00 (s, 3, C-19 angular CH$_3$), 1.20 (s, 9, C(CH$_3$)$_3$), 1.25-1.45 (two d (not well resolved), J = 7 Hz, 3, C-21 CH$_3$), and 5.31 (m, 1, vinyl H); mass spectrum (70 eV) m/e (rel intensity) 383 (8), 327 (9), 309 (10), 294 (9), 271 (11), 270 (16), 161 (5), 121 (11), 113 (16), and 57 (100).

An analytical sample was prepared by two recrystallizations from ether-dichloromethane, mp 218-221 °C. Anal. (C$_{26}$H$_{41}$NO) C,

H.

3β-tert-Butoxy-20-carbonitrile-20-peracetoxypregn-5-ene (15). To a solution of 1.3 mmol of lithium diisopropylamide in 2.0 ml of anhydrous THF-hexane under a nitrogen atmosphere at −78 °C was added 383 mg (1.0 mmol) of **14** in 3 ml of 33% HMPA-THF. Dry oxygen gas was bubbled (250 ml/min) through the solution at −78 °C for 30 min. The reaction was quenched with 0.30 ml of acetyl chloride, stirred for 60 min at −78 °C and 30 min at 0 °C, diluted with 50 ml of ether, washed successively with two 20-ml portions of water and 25 ml of brine, and dried over anhydrous magnesium sulfate. The product was chromatographed on two silica gel plates in 1:75 ethyl acetate-dichloromethane (two developments) to afford 285 mg (62%) of **15**: R_f 0.48; IR (KBr) 5.59 μ (C=O); NMR (CDCl₃) δ 0.96 and 1.02 (two s, 6, C-18 and C-19 angular CH₃), 1.20 (s, 9, C(CH₃)₃), 1.75 (s, 3, C-21 CH₃), 2.13 (s, 3, CH₃CO), and 5.33 (m, 1, C-6 vinyl H); mass spectrum (70 eV) m/e (rel intensity) 286 (15), 285 (24), 119 (10), and 57 (100).

An analytical sample was prepared by three recrystallizations from anhydrous ether, mp 134–35 °C (bubbles). Anal. (C₂₈H₄₃NO₄) C, H.

3β-tert-Butoxy-18-carbonitrilepregn-5-en-20-one (16). A solution of 457 mg (1.0 mmol) of **15** in 4.0 ml of anhydrous, degassed benzene in a quartz test tube was irradiated with a high-pressure 450-W Hanovia lamp for 2 h. The product was chromatographed on two silica gel plates in 1:20 ethyl acetate-dichloromethane to afford 182.8 mg (46%) of **16**: R_f 0.39. Analysis of this material indicated that it was slightly (<3%) contaminated with **18**. This impurity was removed by two recrystallizations from ether-dichloromethane to afford 66.8 mg (17%) of **16**: mp 172–176 °C; IR (KBr) 4.49 (C≡N) and 5.88 μ (C=O); NMR (CDCl₃) δ 1.01 (s, 3, C-19 angular CH₃), 1.20 (s, 9, C(CH₃)₃), 2.30 (s, 3, CH₃CO), and 5.31 (m, 1, C-6 vinyl H); mass spectrum (70 eV) m/e (rel intensity) 397 (5), 341 (11), 285 (23), 285 (36), 283 (12), and 57 (100).

An analytical sample was prepared by four recrystallizations from ether-dichloromethane, mp 172–175 °C. Anal. (C₂₆H₃₉NO₂) C, H.

The procedure of Kalvoda[4] was repeated by irradiating 399 mg (1.0 mmol) of **19**, 2.4 g of lead tetraacetate, 800 mg of calcium carbonate, and 254 mg of iodine in 50 ml of cyclohexane at 80 °C for 1 h to afford, after chromatography and recrystallization as described above, 148 mg (37%) of **16** having IR, NMR, and mass spectra identical with **16** prepared from **15**.

3β-tert-Butoxypregn-5-en-20-one (18). To 15 g of pregnenolone (**17**), 90 ml of isobutylene (20 equiv), and 50 ml of dichloromethane in a 50-ml Parr bottle cooled in dry ice was added slowly 1 ml of concentrated sulfuric acid. The bottle was shaken on a Parr apparatus for 22 h to obtain a homogeneous solution. The isobutylene was allowed to evaporate. The product was diluted with 250 ml of dichloromethane, and the acid was neutralized with 10 ml of 1 M sodium hydroxide solution. The product was stirred with 100 ml of water (lower dichloromethane layer is a gelatinous white suspension at this stage) which was subsequently withdrawn via a water aspirator. The gelatinous dichloromethane layer was transferred to a 1 l. Erlenmeyer flask and stirred with 100 g of anhydrous calcium chloride (4 mesh). The dichloromethane solution was decanted and filtered through a 3-cm pad of Celite 545 to afford a clear pale-yellow solution. The solvent was evaporated to afford 14.2 g of a pale-yellow solid which is ca. 90% pure **18** by TLC analysis. The crude product was purified by column (5 cm) chromatography on 450 g of Merck silica gel 60 using 1:20 ethyl acetate-dichloromethane as eluent to afford 12.0 g of solid and finally by recrystallization from anhydrous ether to afford 10.5 g (59%) of white **18**: mp 154–157 °C; IR (KBr) 5.89 μ (C=O); NMR (CDCl₃) δ 0.82 (s, 3, C-18 angular CH₃), 1.01 (s, 3, C-19 angular CH₃), 1.20 (s, 9, C(CH₃)₃), 2.13 (s, 3, COCH₃), and 5.34 (m, 1, C-6 vinyl H); mass spectrum (70 eV) m/e (rel intensity) 372 (58), 316 (39), 298 (37), 260 (30), and 57 (100).

An analytical sample was prepared by preparative layer chromatography followed by recrystallization from anhydrous ether: mp 156–158.5 °C. Anal. (C₂₅H₄₀O₂) C, H.

3β-tert-Butoxy-20-carbonitrilepregn-5-en-20-ol (19). To 5.35 g (14.4 mmol) of **18** dissolved in the minimum volume of hot acetone cyanohydrin (20 ml) was added 0.5 ml of triethylamine. As the solution cooled, a heavy yellow precipitate appeared which was collected and dried under high vacuum. The product was dissolved in 300 ml of hot dichloromethane, filtered through a 3-cm pad of Celite 545 under vacuum (to remove suspended solid), and reduced in volume

to 100 ml on the steam bath to afford 2.16 g (38%) of **19** as white plates: mp 210–215 °C; IR (KBr) 2.85 (OH) and 4.52 μ (C≡N, weak); NMR (CDCl₃ + Me₂SO-d₆) δ 0.97 and 0.99 (two s, 6, C-18 and C-19 angular CH₃), 1.17 (s, 9, C(CH₃)₃), 1.55 (s, 3, C-21 CH₃), and 5.26 (m, 1, C-6 vinyl H); mass spectrum (70 eV) m/e (rel intensity) 399 (4), 373 (24), 372 (84), 316 (47), 315 (25), 298 (42), 283 (35), 260 (56), 213 (31), and 57 (100). Anal. (C₂₆H₄₁NO₂) C, H.

20-Carbonitrile-20-peracetoxypregn-5-en-3-one Ethylene Ketal (22). The procedure described in the preparation of **15** was repeated using 369 mg (1.0 mmol) of **21** to afford, after chromatography on two silica gel plates in ether, 262 mg (59%) of **22**: R_f 0.65; IR (CHCl₃) 5.59 μ (C=O); NMR (CDCl₃) δ 0.97 and 1.05 (two s, 6, C-18 and C-19 angular CH₃), 1.74 (s, 3, C-21 CH₃), 2.13 (s, 3, COCH₃), 3.96 (s, 4, OCH₂CH₂O), and 5.31 (m, 1, C-6 vinyl H); mass spectrum (70 eV) m/e (rel intensity) 443 (2), 399 (7), 383 (11), 369 (9), 369 (14), 316 (6), 157 (6), 145 (7), 131 (9), 119 (17), 107 (13), 105 (21), and 99 (100). All attempts to induce **22** to crystallize were unsuccessful.

18-Carbonitrilepregn-5-ene-3,20-dione 3-Ethylene Ketal (23). The procedure described in the preparation of **16** was repeated using 443 mg of **22** (2 h irradiation time) to afford, after chromatography on two silica gel plates in ether, 81 mg (21%) of **23** having mp 199–202 °C (lit.[4b] mp 192–96 °C) and spectral data in accord with literature values.[4b]

20-Carbonitrile-20-hydroxypregn-4-en-3-one (25). The procedure of Ercoli and Ruggieri[16] was modified by adding 0.2 ml of distilled triethylamine to a warm, mechanically stirred solution of 25 g (0.08 mol) of progesterone (**24**) in 50 ml (0.55 mol) of acetone cyanohydrin. The solution was stirred for 2 h while slowly cooling to 25 °C. A heavy white precipitate was collected, washed with ca. 100 ml of anhydrous ether, and dried under high vacuum to afford 24.1 g (89%) of **25** as an amorphous white solid: mp 193–200 °C dec (lit.[16] mp 190 °C dec); IR (KBr) 3.01 (OH), 6.10 (conjugated C=O), and 6.21 μ (C=C). The IR showed a very weak absorption at 5.89 μ characteristic of the C-20 ketone in **24**. Recrystallization of the crude **25** from ethanol or dichloromethane served only to increase the **24** contaminant as evidenced by the IR spectrum and depressed melting point. The crude **25** was suitably pure for direct use in the preparation of **26**.

20-Carbonitrile-20-hydroxypregn-5-en-3-one Ethylene Ketal (26). The procedure of Ercoli and Ruggieri[16] was repeated using 14.8 g of **25** to afford 15.9 g (96%) of **26**: mp 176–191 °C dec (lit.[16] mp 195 °C dec); IR and UV spectrum disclosed that approximately 30% unreacted **25** was present. Modifications in the experimental procedure and recrystallization of crude product from various solvents failed to improve this situation.

20-Carbonitrile-3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraene (29). The procedure described in the preparation of **13** was repeated using 10 g (3.52 × 10⁻² mol) of estrone 3-methyl ether (**28**), 2.97 g (7.04 g × 10⁻² mol, 2 equiv) of 57% sodium hydride, and 13.4 g (7.04 × 10⁻² mol, 2 equiv) of 2-(diethylphosphono)propionitrile in 225 ml of THF at reflux for 36 h to afford, after column (5 cm diameter) chromatography on 400 g of Merck silica gel 60 using dichloromethane as eluent, 7.00 g (62%) of **29**. This product was recrystallized from dichloromethane to afford 6.43 g (57%) of **29**: mp 183–196 °C; IR (KBr) 4.55 (C≡N), 6.11 (conjugated C=C), and 6.22 μ (aromatic); NMR (CDCl₃) δ 0.96 (s, 3, C-18 angular CH₃), 1.86 (broad s, 3, C-21 vinyl CH₃), 3.78 (s, 3, OCH₃), and 6.6–7.4 (m, 3, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 321 (100), 306 (6), 293 (8), 292 (18), 227 (40), 214 (37), 199 (21), 173 (41), 160 (41), 159 (44), 147 (24), and 115 (27).

An analytical sample was prepared by three recrystallizations from ether-dichloromethane, mp 184–186 °C. Anal. (C₂₂H₂₇NO) C, H.

20-Carbonitrile-3-methoxy-19-norpregna-1,3,5(10)-triene (30). The procedure of Profitt, Watt, and Corey[7] was repeated using 321 mg (1.0 mmol) of **29** and 2.4 g (100 mmol, 100 equiv) of magnesium in 40 ml of absolute methanol to afford a 77:23 mixture of **30** and **29** according to the NMR integration of the C-18 angular methyl signals (δ 0.76 for **30** and δ 1.12 for **29**). The crude product was subjected to a second reduction using an additional 2.4 g of magnesium to afford 296 mg (92%) of **30**: IR (KBr) 4.49 (C≡N), 5.21 and 6.37 μ (aromatic); NMR (CDCl₃) δ 0.76 (s, 3, C-18 angular CH₃), 1.30 and 1.36 (two d, 3, J = 7 Hz for each diastereomer, C-21 CH₃), 3.75 (s, 3, OCH₃), and 6.5–7.3 (m, 3, aromatic H); mass spectrum (70 eV) 323 (100), 296 (21), 199 (26), 173 (25), 160 (15), 159 (12), and 147 (26).

An analytical sample was prepared by three recrystallizations from dichloromethane–ether, mp 184–186 °C. Anal. ($C_{22}H_{29}NO$) C, H.

20-Carbonitrile-3-methoxy-20-peracetoxy-19-norpregna-1,3,5-(10)-triene (31). The procedure described for the preparation of **15** was repeated using 323 mg of **30** to afford, after chromatography on two silica gel plates in 1:3 hexane–dichloromethane, 235 mg (60%) of **31**: R_f 0.51; IR (KBr) 5.59 (C=O) and 6.22 μ (aromatic); NMR ($CDCl_3$) δ 0.98 (s, 3, C-18 angular CH_3), 1.78 (s, 3, C-21 CH_3), 2.04 (s, 3, $COCH_3$), 3.78 (s, 3, OCH_3), and 6.55–7.35 (m, 3, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 397 (13), 354 (17), 337 (36), 323 (20), 312 (39), 271 (100) 227 (21), 199 (22), 186 (15), 173 (58), 160 (28), and 147 (37).

An analytical sample was prepared by three recrystallizations from ether–dichloromethane, mp 146–148 °C. Anal. ($C_{24}H_{31}NO_4$) C, H.

18-Carbonitrile-3-methoxy-19-norpregna-1,3,5(10)trien-20-one (33). A solution of 161 mg (0.41 mmol) of **31** in 1.6 ml of dry degassed benzene in a quartz test tube was irradiated for 2 h. The solvent was evaporated, and the product was chromatographed on a silica gel plate in 1:20 ethyl acetate–dichloromethane to afford 53 mg (39%) of **33**: R_f 0.60; IR (KBr) 4.48 (C≡N), 5.88 (C=O), and 6.22 μ (aromatic); NMR ($CDCl_3$) 2.33 (s, 3, $COCH_3$), 3.78 (s, 3, OCH_3), and 6.50–7.35 (m, 3, aromatic H); mass spectrum (70 eV) m/e (rel intensity) 337 (61), 312 (23), 252 (27), 173 (20), 147 (14), 91 (14), and 84 (100).

An analytical sample was prepared by two recrystallizations from ether–dichloromethane, mp 215–217 °C. Anal. ($C_{22}H_{27}NO_2$) C, H.

References and Notes

(1) Part I: D. S. Watt, *J. Am. Chem. Soc.*, **98**, 271 (1976).
(2) For recent reviews, see (a) W. Carruthers, "Some Modern Methods of Organic Synthesis", Cambridge University Press, London, 1971, Chapter 4; (b) K. Heusler and J. Kalvoda, *Angew. Chem., Int. Ed. Engl.*, **3**, 525 (1964); (c) J. Kalvoda and K. Heusler, *Synthesis*, 501 (1971); (d) D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms", Elsevier, New York, N.Y., 1968, Chapter 10; and (e) J. Fried and J. A. Edwards, Ed., "Organic Reactions in Steroid Chemistry", Vol. II, Van Nostrand-Reinhold, New York, N.Y., 1972, Chapter 12.
(3) For a historical account, see L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, N.Y., 1959, pp 713–720.
(4) (a) Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **17**, 475 (1961); (b) J. Kalvoda, Ch. Meystre, and G. Anner, *Helv. Chim. Acta*, **49**, 424 (1965); (c) J. Kalvoda, *Ibid.*, **51**, 267 (1968); (d) A. Kasal and V. Cerney, *Collect. Czech. Chem. Commun.*, **31**, 2759 (1966); (e) K. van Moorselaar and S. J. Halkes, *Recl. Trav. Chim. Pays-Bas*, **88**, 737 (1969).
(5) (a) H. C. Beyerman and G. J. Heiszwolf, *J. Chem. Soc.*, 755 (1963); and (b) H. C. Beyerman and G. J. Heiszwolf, *Recl. Trav. Chim. Pays-Bas*, **84**, 203 (1965).
(6) M. L. Raggio and D. S. Watt, *J. Org. Chem.*, **41**, 1873 (1976).
(7) J. A. Profitt, D. S. Watt, and E. J. Corey, *J. Org. Chem.*, **40**, 127 (1975).
(8) S. J. Selikson and D. S. Watt, *J. Org. Chem.*, **40**, 267 (1975).
(9) Kalvoda (ref 4c) has established that the mechanism of the cyanohydrin-ketonitrile reaction involves an intramolecular migration of the nitrile group. Since the results of the α-peracetoxynitrile–ketonitrile reaction are consistent with the intermediacy of the radical **20**, we have depicted an intramolecular nitrile migration for this reaction also.
(10) (a) D. Lednicer, "Contraception: The Chemical Control of Fertility", Marcel Dekker, New York, N.Y., 1969; and (b) D. J. Richards, Ed., "Aspects of the Chemistry, Pharmacology and Clinical Use of a New Progestagen: Norgestrel", Blackwell Scientific Publications, Oxford, 1968.
(11) J. S. Mills, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6113 (1958).
(12) R. R. Wroble and D. S. Watt, *J. Org. Chem.*, **41**, 2939 (1976).
(13) L. Velluz and G. Muller, *Bull. Soc. Chim. Fr.*, 166 (1950).
(14) D. S. Watt, *Tetrahedron Lett.*, 707 (1974).
(15) α-Peracetoxynitrile proved too unstable to obtain a satisfactory elemental analysis.
(16) A Ercoli and P. de Ruggieri, *Gazz. Chim. Ital.*, **84**, 312 (1954).
(17) C. J. Sih, K. C. Wang, and H. H. Tai, *Biochemistry*, **7**, 796 (1968).
(18) K. Wiberg, "Oxidation in Organic Chemistry", Academic Press, New York, N.Y., 1965, pp 278–366.

Homoallylic Participation in Cyclohexen-4-yl Tosylate

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Abstract: In hydroxylic solvents (HOS) the major substitution solvolysis product of cyclohexen-4-yl tosylate (**2-OTs**) has the same structure as the starting material, with tosylate replaced by –OS. The stereochemistry of this pathway can be determined by stereospecifically replacing one of the protons at the 5-position with deuterium and following the stereochemical relationship between the 4-proton and the remaining 5-proton by NMR. Inversion at the 5-position is taken to indicate solvent displacement, and retention to indicate some form of homoallylic assistance. Mixed stereochemistry can indicate either multiple pathways or a free carbonium ion mechanism. In this manner we have learned that aqueous 1,4-dioxane reacts with complete inversion, acetic acid with 17% retention, formic acid with 40% retention, and hexafluoro-2-propanol with complete retention. Thus the highly nucleophilic aqueous medium reacts entirely by solvent displacement. In acetic acid the homoallylic process has only just begun to compete observably with solvent displacement, in formic acid it has not quite reached the point of equal importance, and in the highly ionizing HFP it has become the sole mechanism.

Homoallylic participation may be defined as the assistance of a nonconjugated, unsymmetrically disposed double bond in the departure of a leaving group.[2] The fundamental acyclic, monocyclic, and bicyclic systems for observation of this phenomenon are, respectively, allylcarbinyl (**1**), cyclo-

hexen-4-yl (**2**), and *exo*-2-norbornenyl (**3**). The process should be distinguished from that in the fully symmetrical case with equivalent 1,3- and 1,4-overlap, as in the bishomocyclopropenyl ion produced from *anti*-7-norbornenyl tosylate (**4**). The ion