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

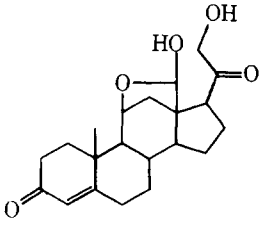
Robert W. Freerksen, W. Edward Pabst, Michael L. Raggio, Steven A. Sherman, Randall R. Wroble, and David S. Watt*

Contribution from the Department of Chemistry, University of Colorado, Boulder, Colorado 80309. *Received August 25, 1976*

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



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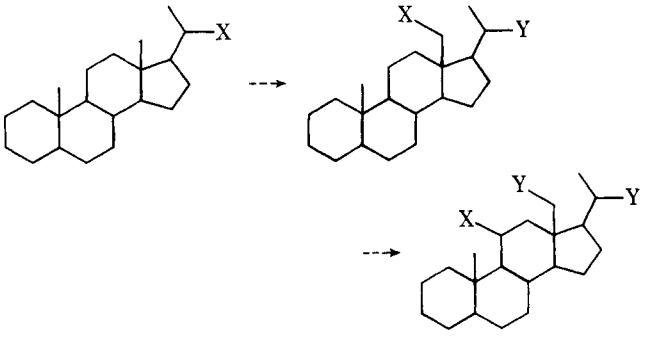
total synthesis[3] of **1**, a particular limitation in the partial synthesis of **1** was the limited availability of naturally occurring steroids bearing oxygen functionality at C-11 and C-18.

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

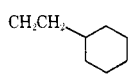
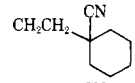
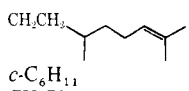
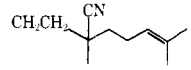
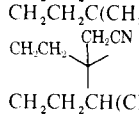
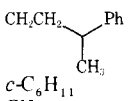
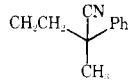
Recently, we reported[1] that the photolysis of α-peracetoxynitriles **3** derived from secondary nitriles **2** provided δ-ketonitriles **4** (Table I). This new photochemical reaction possessed the reiterative feature crucial to the success of the scheme outlined above. For example, the α-peracetoxynitrile

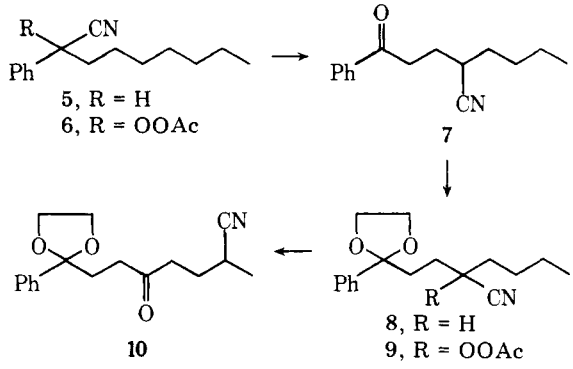


6 obtained from 2-phenylnonanenitrile (**5**) was photolyzed to provide the δ-ketonitrile **7**. To confirm the regioselectivity of this process, **7** was independently synthesized by alkylating hexanenitrile with β-bromopropiophenone ethylene ketal and hydrolyzing the ethylene ketal. A second peracetoxy 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	CH_3	$CH_2(CH_2)_4CH_3$	65		
b	CH_3	$CH_2CH_2CH(CH_3)_2$	64	$CH_2CH_2C(CH_3)_2CN$	50
c	CH_3		63		47
d	CH_3		67		28
e	CH_3	$c\text{-}C_6H_{11}$	53		
f	CH_3	CH_2Ph	89		
g	CH_3		60		18
h	CH_2Ph	$c\text{-}C_5H_9$	57		
i	CH_2Ph	CH_2Ph	90		
j	CH_2Ph	$CH_2(CH_2)_2CH_3$	69		
k		$-(CH_2)_5-$	72		
l	Ph	CH_3	69		
m	Ph	CH_2CH_3	49		
n	Ph	$CH_2CH_2CH_3$	57	$CH_2CH_2CH_2CN$	15
o	Ph	$CH(CH_3)_2$	81		
p	Ph	$CH_2(CH_2)_2CH_3$	72	$CH_2CH_2CH(CH_3)CN$	22
q	Ph	$CH_2CH_2CH(CH_3)_2$	63	$CH_2CH_2C(CH_3)_2CN$	52
r	Ph	$CH_2CH_2C(CH_3)_3$	73		10
s	Ph	$CH_2CH_2CH_2Ph$	77	$CH_2CH_2CH(CN)Ph$	10
t	Ph		72		9
u	Ph	$c\text{-}C_6H_{11}$	74		
v	Ph	$p\text{-}FC_6H_4$	65		
w	Ph	$p\text{-}ClC_6H_4$	56		
x	Ph	Ph	85		

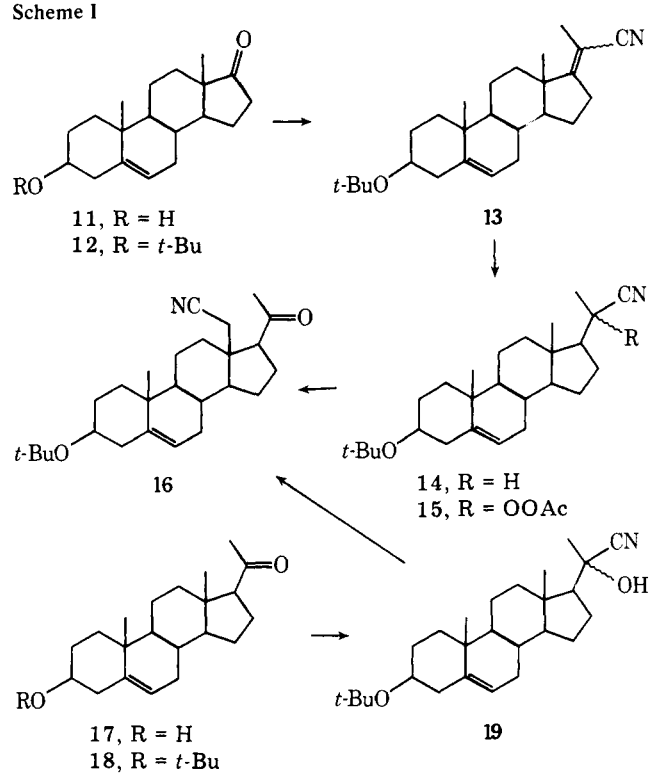


alize the C-18 angular methyl group. To evaluate the merits of this approach, we have contrasted the peracetoxynitrile–ketonitrile reaction with the cyanohydrin–ketonitrile reaction developed by Kalvoda.[1]

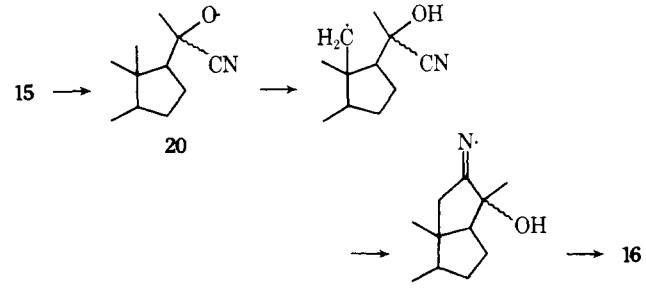
With aldosterone (**1**) as the ultimate goal, we selected steroid precursors possessing a C-3 oxygen substituent which could be transformed to the enone synthon in **1**. As shown in Scheme I, dehydroepiandrosterone (**11**) was protected as the 3β-*tert*-butyl ether[5] **12** in 73% yield and condensed 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

Scheme I



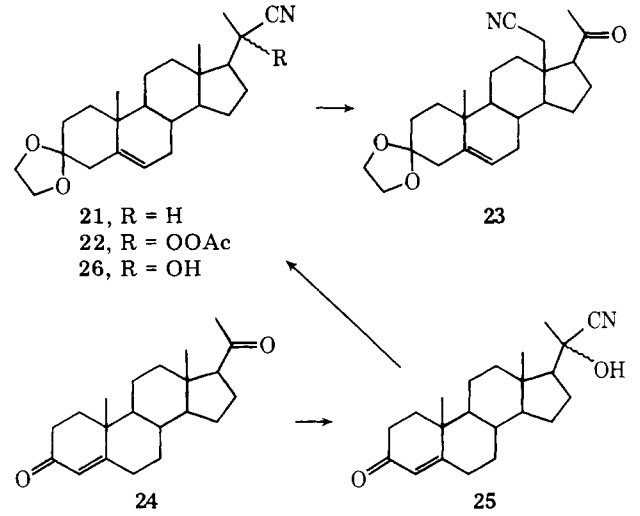
Hanovia lamp effected the desired functionalization of the C-18 angular methyl group in providing the 18-cyano-20-ketosteroid **16** in 46% yield. The balance of the reaction mixture consisted principally of the ketone **18** and a small amount of unreacted **15**. The 18-cyano-20-ketosteroid **16** 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.

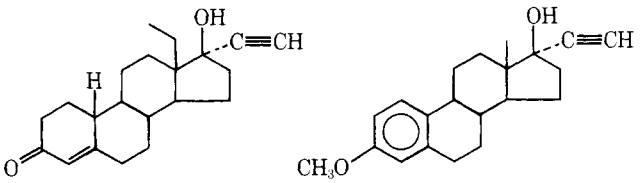
The comparison of the two routes was expanded to include functionality at C-3 more labile than *tert*-butyl ethers. As shown in Scheme II, the ketal nitrile[6] **21** was converted to the

Scheme II



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.

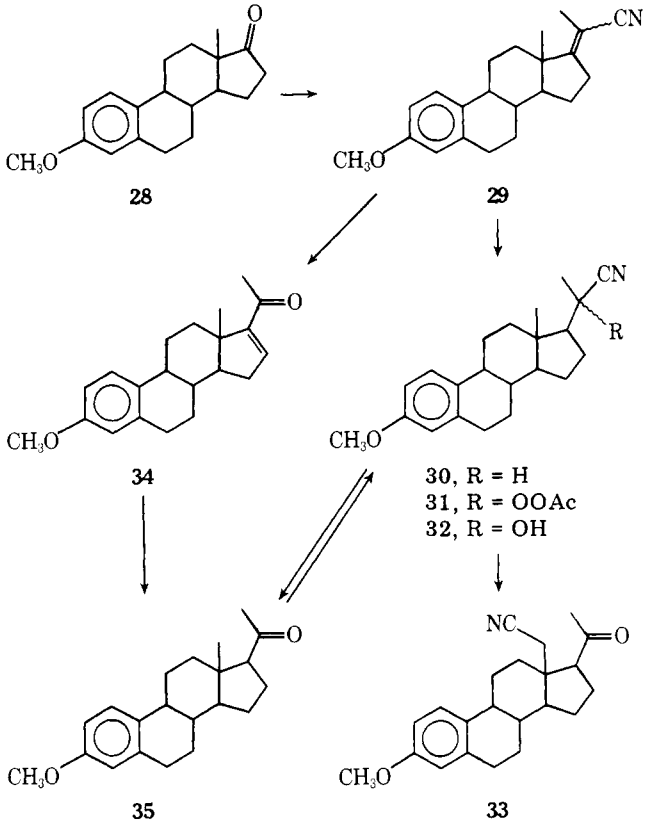
Apart from our interest in aldosterone (**1**), we also wanted to synthesize 18-substituted analogues of the contraceptive agent, norgestrel (**27**).[10] One approach to such compounds involved the synthesis of the 18-cyano-20-ketone **33**. As shown in Scheme III, application of the reaction sequence 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.



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



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 I.

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 (CCl_4) δ 0.60–1.05 (m, 3, $(CH_2)_6CH_3$), 1.05–2.10 (m, 12, $(CH_2)_6CH_3$), 3.61 (t, J = 7.5 Hz, 1, PhC*H*), and 7.32 (s, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 215 (7) and 117 (100). Anal. ($C_{15}H_{21}N$) 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 (CCl_4) δ 0.65–1.05 (m, 3, CH_2CH_3), 1.05–2.3 (m, 12, CH_2), 1.90 (s, 3, $COCH_3$), 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. ($C_{17}H_{23}NO_3$) 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 (CCl_4) δ 0.65–1.15 (m, 3, CH_2CH_3), 1.15–2.2 (m, 8, CH_2), 2.35–2.85 (m, 1, CHCN), 3.13 (t, J = 7 Hz, 2, $COCH_2$), 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. ($C_{15}H_{19}NO$) 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 ($CDCl_3$) δ 0.7–1.1 (m, 3, CH_2CH_3), 1.1–2.35 (m, 10, CH_2), 2.35–2.8 (m, 1, CHCN), 3.6–4.25 (m, 4, OCH_2CH_2O), 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 ($CDCl_3$) δ 0.7–1.05 (m, 3, CH_2CH_3), 1.05–2.2 (m, 10, CH_2), 2.05 (s, 3, $COCH_3$), 3.6–4.2 (m, 4, OCH_2CH_2O), 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. ($C_{19}H_{25}NO_5$) 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 ($CDCl_3$) δ 1.31 (d, J = 7 Hz, 3, $CHCH_3$), 1.5–3.0 (m, 9, $CHCH_3$ and CH_2), 3.6–4.2 (m, 4, OCH_2CH_2O), 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. ($C_{17}H_{21}NO_3$) 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 (CCl_4) δ 0.7–2.2 (m, 13, $(CH_2)_5CH_3$), 1.63 (s, 3, $CH_3C(CN)(OOAc)CH_2$), and 2.11 (s, 3, $COCH_3$); 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 (CCl_4) δ 0.95 (d, J = 5.5 Hz, 6, $CH(CH_3)_2$), 1.1–2.0 (m, 5, CH_2 and $CH(CH_3)_2$), 1.63 (s, 3, $CH_3C(CN)(OOAc)CH_2$), and 2.12 (s, 3, $COCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 139 (1), 124 (2), 114 (1), 111 (1), 110 (1), and 99 (3). Anal. ($C_{10}H_{17}NO_3$) C, H.

3c: R_f 0.57 in 1:1 ether–hexane; IR (TF) 4.50 (C≡N), 5.57 μ (C=O); NMR (CCl_4) δ 0.7–2.1 (m, 15, CH and CH_2), 1.61 (s, 3, $CH_3C(CN)(OOAc)CH_2$), and 2.10 (s, 3, $COCH_3$); 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 (CCl_4) δ 0.94 (broad d, J = 5 Hz, 3, $CHCH_3$), 1.0–2.2 (m, 15, $CHCH_3$, CH_2 and vinyl CH_3), 1.64 (s, 3, $CH_3C(CN)(OOAc)CH_2$), 2.10 (s, 3, $COCH_3$), and 5.06 (m, 1, vinyl H); a small signal at δ 4.66 suggested that an isomer of **3d** bearing a $C(CH_3)=CH_2$ 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 (CCl_4) 0.8–2.3 (m, 11, CH_2 and CH_3), 1.59 (s, 3, $CH_3C(CN)(OOAc)CH$), and 2.12 (s, 3, $COCH_3$); 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 ($CDCl_3$) δ 1.58 (s, 3, CH_3), 2.13 (s, 3, $COCH_3$), 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. ($C_{12}H_{13}NO_3$) C, H.

3g: R_f 0.37 in 1:2 ether–hexane; IR (TF) 5.57 (C=O) and 6.25 μ (aromatic); NMR (CCl_4) δ 2.01 (s, 6, CH_3 and $COCH_3$), 2.62 (s, 3, aromatic CH_3), 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. ($C_{12}H_{13}NO_3$) 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 (CCl_4) δ 1.4–2.2 (m, 9, CH and CH_2), 2.10 (s, 3, $COCH_3$), 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 (CCl_4) δ 1.92 (s, 3, $COCH_3$), 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 (CCl_4) δ 0.7–1.05 (m, 3, CH_2CH_3), 1.05–1.9 (m, 6, $(CH_2)_3CH_3$), 2.06 (s, 3, $COCH_3$), 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 ($CHCl_3$) 5.58 and 5.62 μ sh (C=O); NMR (CCl_4) δ 1.3–2.4 (m, 10, CH_2), and 2.10 (s, 3, $COCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 152 (2), 151 (16), 110 (9), 109 (100). Anal. ($C_9H_{13}NO_3$) C, H.

3l: R_f 0.28 in 1:3 ether–hexane; IR (TF) 5.57 μ (C=O); NMR (CCl_4) δ 1.98 (s, 6, $COCH_3$ 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 (CCl_4) δ 1.07 (t, J = 7 Hz, 3, CH_2CH_3), 1.90 (s, 3, $COCH_3$), 1.9–2.4 (m, 2, CH_2CH_3), 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. ($C_{12}H_{13}NO_3$) C, H.

3n: R_f 0.41 in 1:3 ether–hexane; IR (TF) 5.57 μ (C=O); NMR (CCl_4) δ 0.8–1.1 (m, 3, CH_2CH_3), 1.1–2.3 (m, 4, CH_2), 1.88 (s, 3, $COCH_3$), 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. ($C_{13}H_{15}NO_3$) 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 (CCl_4) δ 0.88 and 1.28 (two d, J = 7 Hz, 6, $CH(CH_3)_2$), 1.86 (s, 3, $COCH_3$), 1.85–2.65 (m, 1, $CH(CH_3)_2$), 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. ($C_{13}H_{15}NO_3$) C, H.

3p: R_f 0.32 in 1:3 ether–hexane; IR (TF) 5.57 μ (C=O); NMR (CCl_4) δ 0.7–2.5 (m, 9, $(CH_2)_3CH_3$), 1.88 (s, 3, $COCH_3$), and 7.3–7.8 (m, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 189 (1), 174 (2), 173 (13), 172 (11), 145 (7), 132 (5), 131 (11), 130 (6), 120 (31), and 105 (100). Anal. ($C_{14}H_{17}NO_3$) C, H.

3q: R_f 0.36 in 1:3 ether–hexane; IR (TF) 5.56 μ (C=O); NMR (CCl_4) δ 0.88 and 0.91 (two d, J = 6 Hz, $CH(CH_3)_2$), 1.0–2.4 (m, 5, CH and CH_2), 1.90 (s, 3, $COCH_3$), 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. ($C_{15}H_{19}NO_3$) 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_2Ph), 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 (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, $CH_2C(CN)$), 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. ($C_8H_{13}NO$) 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_2CN), 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. ($C_{10}H_9NO$) 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, $COCH_2CH_2$), 2.25-2.65 (m, 2, CH_2CN), 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, $COCH_2CH_2$), 2.4-2.9 (m, 1, CHCN), 3.14 (t, 2, $COCH_2CH_2$), 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, $COCH_2CH_2$), 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, $COCH_2CH_2$), 2.25 (s, 2, CH_2CN), 2.75-3.15 (m, 2, $COCH_2CH_2$), 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, $COCH_2CH_2$), 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, $COCH_2CH_2$), 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), $J \approx 7$ 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 ($CDCl_3$) δ 0.96 and 1.02 (two s, 6, C-18 and C-19 angular CH_3), 1.20 (s, 9, $C(CH_3)_3$), 1.75 (s, 3, C-21 CH_3), 2.13 (s, 3, CH_3CO), 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. ($C_{28}H_{43}NO_4$) 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 ($CDCl_3$) δ 1.01 (s, 3, C-19 angular CH_3), 1.20 (s, 9, $C(CH_3)_3$), 2.30 (s, 3, CH_3CO), 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. ($C_{26}H_{39}NO_2$) 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 ($CDCl_3$) δ 0.82 (s, 3, C-18 angular CH_3), 1.01 (s, 3, C-19 angular CH_3), 1.20 (s, 9, $C(CH_3)_3$), 2.13 (s, 3, $COCH_3$), 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. ($C_{25}H_{40}O_2$) 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 ($CDCl_3$ + Me_2SO-d_6) δ 0.97 and 0.99 (two s, 6, C-18 and C-19 angular CH_3), 1.17 (s, 9, $C(CH_3)_3$), 1.55 (s, 3, C-21 CH_3), 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. ($C_{26}H_{41}NO_2$) 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 ($CHCl_3$) 5.59 μ (C=O); NMR ($CDCl_3$) δ 0.97 and 1.05 (two s, 6, C-18 and C-19 angular CH_3), 1.74 (s, 3, C-21 CH_3), 2.13 (s, 3, $COCH_3$), 3.96 (s, 4, OCH_2CH_2O), 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 ($7.04 \text{ g} \times 10^{-2}$ 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 ($CDCl_3$) δ 0.96 (s, 3, C-18 angular CH_3), 1.86 (broad s, 3, C-21 vinyl CH_3), 3.78 (s, 3, OCH_3), 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. ($C_{22}H_{27}NO$) 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 ($CDCl_3$) δ 0.76 (s, 3, C-18 angular CH_3), 1.30 and 1.36 (two d, 3, J = 7 Hz for each diastereomer, C-21 CH_3), 3.75 (s, 3, OCH_3), 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.

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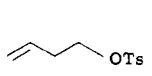
Homoallylic Participation in Cyclohexen-4-yl Tosylate

Joseph B. Lambert*[1a] and Sidney I. Featherman[1b]

Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois 60201. *Received June 14, 1976*

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**), cyclohexen-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



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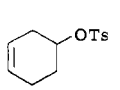
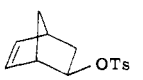


2-OTs



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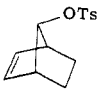

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