strengths of these two signals the equilibrium constant for *N*-benzylidene-*m*-nitroaniline is calculated to be 0.028 M^{-1} which is close to 0.023 M^{-1} at 25° obtained by uv spectrophotometry. These facts indicate the stoichiometry of the reaction described above.

Rate and Equilibrium Measurements. The reaction was carried out in methanol–acetonitrile (90:10 v/v) and followed in a cell compartment of a spectrophotometer. The reaction was started when methanolic potassium hydroxide (0.1 ml) was added to a thermostated solution of benzylideneanilines (2.9 ml) and the extinction (E) at an appropriate wavelength (320–340 nm) was followed. Because of the excess methanol the equilibrium constant (K_0) was calculated by the following equation

$$K_0 = \frac{E_0 - E_\infty}{E_\infty[\mathrm{MeOH}]}$$

where subscripts 0 and ∞ refer to time 0 and equilibrium state, respectively.

Plot of log ($E_t - E$) *vs.* time t gave a good straight line from which pseudo-first-order rate constant for a reversible reaction, k_{obsd}, was obtained. Using the values of [MeOH], K_0, and k_{obsd}, apparent forward second-order rate constant, k_f^{MeOH}, was calculated by means of the equations

$$k_{obsd} = \frac{2.303}{t} \log \frac{E_0 - E_\infty}{E_t - E_\infty}$$

and

$$k_f^{MeOH} = \frac{k_{obsd}K_0}{[\mathrm{MeOH}]K_0 + 1}$$

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Steroidal Nitrones

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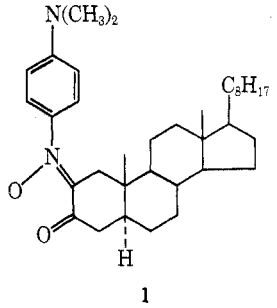
Steroidal 6- and 20-aldonitrones were prepared. 3-Ketonitrones were also prepared, and, in the case of Δ^4-3-ketonitrones, stereoisomers were separated and configurations assigned on the basis of uv and nmr spectroscopy.

Bambury, *et al.*, have published several reports on heterocyclic containing nitrones having antimicrobial activity.[1] Nitrone groups increase water solubility and the ability of a molecule to penetrate cell membranes.[2] For these reasons, we extended our work to the steroid field, and report here some of our findings on the preparation of 6-aldonitrones, 20-aldonitrones, and 3-ketonitrones.

Several steroidal nitrones are reported as intermediates in the Kröhnke reaction.[3] For example, the ketonitrones **1**[4] and **2**[5] were prepared and converted to the corresponding α-diketones. Similarly, the 21-aldonitrones **3**,[6] **4**,[6] and **5**[7] were prepared and converted to the 21-aldehydes. Other examples of steroid-like nitrones in which the nitrone is an integral part of the ring system, such as **6**,[8] **7**,[8] and **8**,[9] have also been reported. Subsequent to the completion of this work, Barton and coworkers[10] reported the conversion of 3-ketonitrones **9** *via* a Beckmann-type rearrangement to amides **10**, but no details for preparing **9** were given.

6-Aldonitrones. Steroidal 6-carboxaldehydes are readily available from Vilsmeier–Haack formylation of the corresponding 3-enol ethers **11** according to Burn, *et al.*[11] Experimentation showed that nitrone formation was best accomplished by heating a mixture of **12**, *N*-alkylhydroxylamine salt, and sodium bicarbonate in aqueous methanol containing pyridine. The resulting nitrones **13** are crystal-



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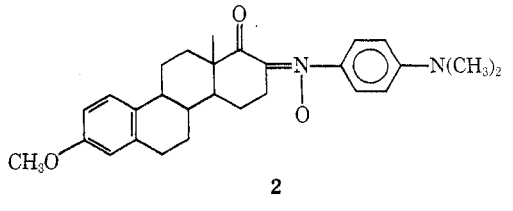

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Table I
Aldonitrones and Ketonitrones

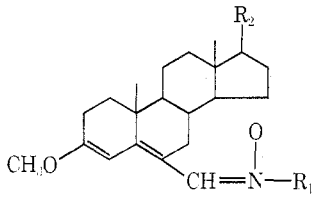
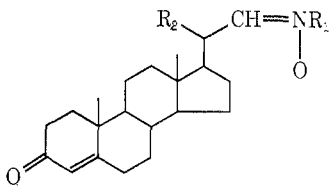
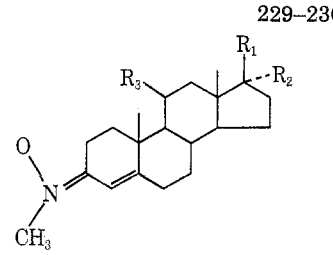
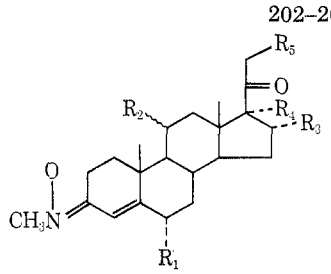
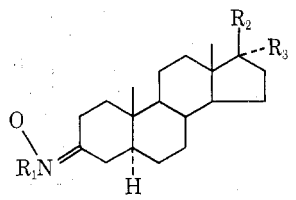
Compd	R_1	R_2	R_3	R_4	R_5	Misc	Mp, °C	Yield, %	Isomer	Formula[f]
										
14	CH_2CH_2OH						231–232 dec	67.6		$C_{23}H_{35}NO_4$
15	CH_3						244.5	68.0		$C_{22}H_{33}NO_3$[h]
16	CH_2CH_2OH						124–127	30.4		$C_{25}H_{37}NO_4 \cdot H_2O$
17	CH_3						247–249	55.8		$C_{24}H_{35}NO_3 \cdot {}^1/_4H_2O$
18	CH_2CH_2OH	O[a]					248–249	7.5		$C_{23}H_{31}NO_5 \cdot {}^1/_4H_2O$
19	CH_3	O[a]					242–244 dec	13.7		$C_{22}H_{29}NO_4$[g]
										
22	CH_2CH_2OH	CH_3					189–191	66.9		$C_{24}H_{37}NO_3$
23	CH_3	CH_3					178–180	35.6		$C_{23}H_{35}NO_2 \cdot {}^1/_2H_2O$
24	$CH(CH_2OH)CH_2CH_3$	CH_3					173–176	64.2		$C_{26}H_{41}NO_3$
25	CH_2CH_2OH	CH_3[b]					217–218	4.5		$C_{24}H_{35}NO_3 \cdot {}^1/_4H_2O$
26	CH_2CH_2OH	CH_3[b]					187, 210	10.4		
27	CH_3	CH_3[b]					182.5–185	19.3		$C_{23}H_{33}NO_2$[i]
28	CH_3	CH_3[c]					197–199 dec	22.0		$C_{24}H_{38}N_2O_2 \cdot H_2O$
29	CH_2CH_2OH	H[b,d]					214–215 dec	70.2		$C_{23}H_{31}NO_4$[j]
30	CH_3	H[b,d]					229–230 dec	68.4		$C_{22}H_{29}NO_3$
										
37	OH	H	H			${}^1/_4H_2O$	234–235 dec	18.5[e]	Syn	$C_{20}H_{31}NO_2 \cdot {}^1/_4H_2O$
38	OH	H	H			${}^1/_4H_2O$	170–171 dec	3.3	Anti	$C_{20}H_{31}NO_2 \cdot {}^1/_4H_2O$
39	OH	H	H			${}^1/_4H_2O$ NCH_2CH_2OH	180–182.5	42.2	Anti/syn 50:50	$C_{21}H_{33}NO_3 \cdot {}^1/_4H_2O$
40	OH	CH_3	H			${}^1/_4H_2O$	184–186	23.8	Syn	$C_{21}H_{33}NO_2 \cdot {}^1/_4H_2O$
41	OH	CH_3	H			${}^1/_2H_2O$	187–189	6.0	Anti	$C_{21}H_{33}NO_2 \cdot {}^1/_2H_2O$
42	OH	C≡CH	H				234–235 dec	26.3	Syn	$C_{22}H_{31}NO_2$
43	OAc	H	H			Δ^6	189–190 dec	23.8	Syn	$C_{22}H_{31}NO_3$
	OAc	H	H			Δ^6	187–188 dec		Anti	
44	OH	H	H			19-nor	217–218 dec	60.5	Syn	$C_{19}H_{29}NO_2$
45	O		H				202–203 dec	12.4	Syn	$C_{20}H_{29}NO_2$
										
46	H	H	H	H	H		152–154			$C_{22}H_{33}NO_2$
47	H	H	H	H	H		185–186 dec		Anti	$C_{22}H_{33}NO_2$
48	H	α-OAc	H	H	H		210–212 dec		Syn	$C_{24}H_{35}NO_4$
	H	α-OH	H	H	H		231–232 dec		Syn	$C_{22}H_{33}NO_3$[g]
49	H	H	H	OH	H		245–247 dec	67.2	Anti/syn 20:80 Anti	$C_{22}H_{33}NO_3$[g]

Table I (*Continued*)

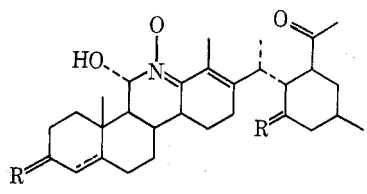
Compd	R_1	R_2	R_3	R_4	R_5	Misc	Mp, °C	Yield, %	Isomer	Formula[f]
50	H	H	H	OAc	H		197–198	31.8	Syn	$C_{24}H_{35}NO_4$
	H	H	H	OAc	H		195–197 dec	10.0	Anti	$C_{24}H_{35}NO_4$
51	H	H	H	H	OAc		162–165	8.0	Syn	$C_{24}H_{35}NO_4$
52	H	β-OH	H	OH	OH	$^1/_4H_2O$	259–260 dec	45.8	Anti/syn 50:50	$C_{22}H_{33}NO_5 \cdot {}^1/_4H_2O$
53	H	β-OH	H	OH	OH	NCH_2CH_2OH	220 dec	20.0	Syn	$C_{23}H_{35}NO_6$
54	CH_3	H	CH_3	H	H		185–187	24.4	Syn	$C_{24}H_{37}NO_2$
55	α-CH_3	H	H	OAc	H		209–212 dec		Syn	$C_{25}H_{37}NO_4$
56	α-CH_3	H	H	OAc	H		168–170 dec		Anti	$C_{25}H_{37}NO_4$
57	CH_3	H	H	OAc	H	Δ[6]	203 dec	32.2	Syn	$C_{25}H_{35}NO_4$
	CH_3	H	H	OAc	H	Δ[6]	197–201	12.1	Anti	$C_{25}H_{35}NO_4$



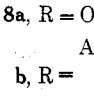
58	CH_3	O					150–152	65.0		$C_{20}H_{31}NO_2 \cdot {}^1/_2H_2O$[k]
59	CH_3	OH	H				196–198	43.3		$C_{20}H_{33}NO_2 \cdot {}^1/_2H_2O$
60	CH_2CH_2OH	OH	H				195–197	73.7		$C_{21}H_{33}NO_3 \cdot H_2O$
61	CH_3	OH	CH_3				210–213	39.1		$C_{21}H_{35}NO_2$
62	CH_2CH_2OH	OH	CH_3				115–117	44.8		$C_{22}H_{37}NO_3 \cdot 1^1/_2H_2O$[g,l]

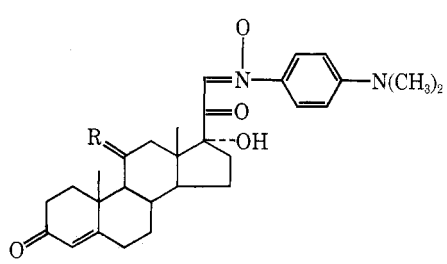
[a] 11-Oxo. [b] 17(20)-Ene. [c] 3-*N*-Methylnitrone. [d] 1-En-11β-ol. [e] Yield raised to 74.2% (0.1 *M* scale) in another run. [f] C, H, and N analyses were within 0.3% of calculated values. [g] C analysis was within 0.4% of calculated value. [h] Calcd: C, 73.50. Found: C, 72.97. [i] Calcd: C, 77.70. Found: C, 77.26. [j] Calcd: C, 71.66. Found: C, 71.22. [k] Calcd: C, 73.59. Found: C, 73.14. [l] Calcd: H, 10.33. Found: H, 9.96.

line solids with ultraviolet maxima at 238–240 (ε 9000–9600) and 333–334 nm (ε 14,700–17,600) and nuclear magnetic resonance (nmr) signals for the imino proton at δ 7.1–8.2. This compares with ultraviolet maxima at 219–221 (ε 10,000–12,000) and 319–323 nm (ε 14,000–16,000) and nmr signals for the aldehyde proton at δ 10.2 for the parent aldehydes. It is interesting that the 17β-acetoxy group was hydrolyzed under these conditions using a hydrochloride salt of the hydroxylamine. Table I lists the compounds prepared in this series.



8a, R = O Δ[4]

b, R =  5α



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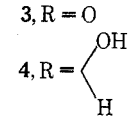
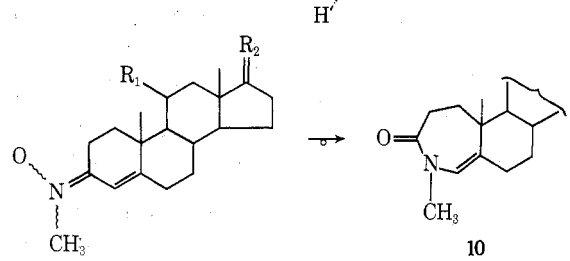
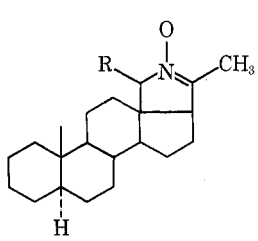
4, R = 

5, R = H_2



9 **10**



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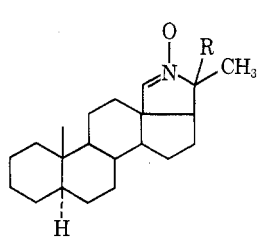

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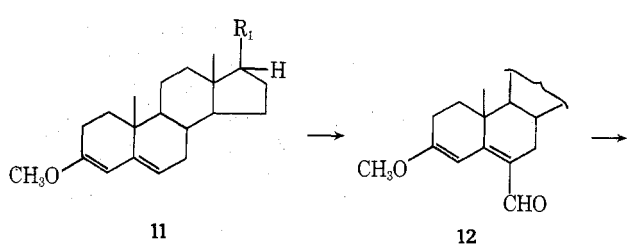
R = H, OH



11 **12**

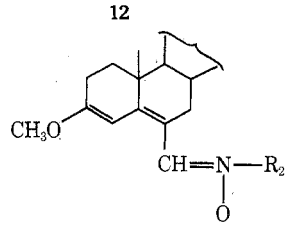


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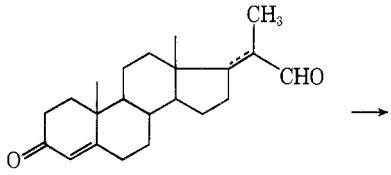
Table II

N-Oxide	Assigned structure	Uv max	Nmr, ppm: Proton adjacent oxide oxygen	Nmr, ppm: Proton away from oxide oxygen
Nonsteroids	Anti	211, 228, 304 (higher)		2.38
	Syn	205, 221.5, 228	2.16 (higher field)	
Δ^4 steroids	Anti	242–243, 293–296 (higher)		6.65–6.85
	Syn	288–292	6.00–6.38 (higher field)	

20-Aldonitrones. Several steroidal 20-carboxaldehydes are commercially available or available by a simple one-step oxidation. These aldehydes **20** were readily converted



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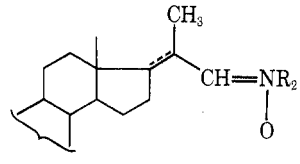

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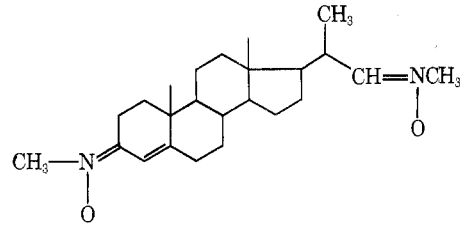


28

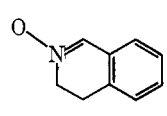
to the corresponding nitrones **21** by the methods described above. The nitrones are crystalline compounds readily purified by silica gel column chromatography.

Reaction of 3-oxopregn-4-ene-20-carboxaldehyde with an excess of *N*-methylhydroxylamine hydrochloride gave, in addition to the expected aldonitrone **23**, a second compound which had no carbonyl absorption bands in its infrared spectrum and had two NCH_3 signals in its nmr at 3.70 and 3.72 ppm. Elemental analyses corresponded to $C_{24}H_{38}N_2O_2 \cdot H_2O$, which confirmed the structure as dinitrone **28**. Table I lists the compounds prepared in this series.

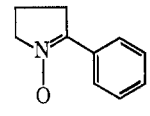
3-Ketonitrones. Reaction of aliphatic ketones with *N*-alkylhydroxylamines is reported to be sluggish and the resultant ketonitrones are hygroscopic, unstable species.[12] For example, the *N*-methyl nitrone of cyclopentanone is reported as very hygroscopic and is instantly hydrolyzed by water and decomposed by ethanol.[13] To the contrary, we have found the 3-ketonitrones to be readily formed, stable, and only slightly hygroscopic. The 3-ketonitrones were generally prepared by refluxing overnight a mixture of steroid, alkylhydroxylamine salt, and sodium bicarbonate in absolute ethanol in the dark. There seems to be some difference in which acid salt is used in the reaction. In the case of *N*-methylhydroxylamine, where both the hydrochloride and oxalate salts were available, the hydrochloride reacted more rapidly, giving a more stereochemically pure product. The reaction proved quite versatile for 3-keto steroids except dihydroprogesterone, which was inexplicably refractory.

Silica gel chromatography of the crude product separated, in several cases, stereoisomeric pairs of nitrones. Isomerism in nitrones has been previously reported,[12] and ultraviolet spectra have been used to determine syn and anti configurations. However, this method of analysis is still tenuous, since there is no confirmatory evidence for generalization.

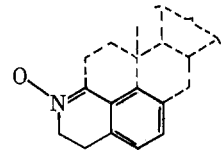
Nitrone **31** with the phenyl group and the oxygen atom fixed in the anti configuration absorbs at 211, 228, and 304 nm, while nitrone **32** absorbing at 205, 221.5, and 288 nm is rigidly held in the syn configuration. In other words, the higher absorbing isomer is anti and the lower absorbing isomer is syn. These two compounds are redrawn in **31a** and **32a**, respectively, with a partial steroid skeleton superimposed in dotted lines to show the relationship of these two compounds to the steroidal nitrones **33** and **34**. In our steroidal pairs, one isomer absorbed at 288–292 nm and the other at 242–243 and 293–296 nm. The 293–296 nm absorbing isomers were tentatively assigned the anti configuration (**33**) and the other isomer the syn configuration (**34**) assuming for the moment that assignments by ultraviolet maxima are valid.



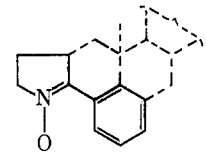
31
anti



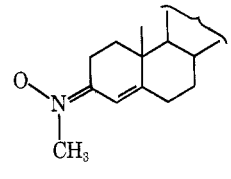
32
syn



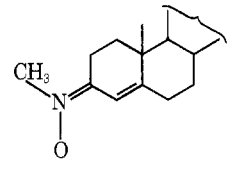
31a



32a

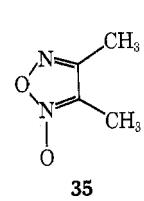


33

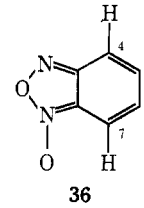


34

The proton nmr spectrum of dimethylfurazan oxide (**35**) consists of two peaks at 2.16 and 2.38 ppm, while that of dimethylfurazan consists of a single peak at 2.31 ppm.[14] The highfield peak at 2.16 ppm was associated with the methyl group adjacent to the *N*-oxide oxygen.[15] Similarly, in assigning chemical shifts of the 4 and 7 protons in benzofurazan oxide (**36**) the higher field peak was assigned to the proton adjacent to the *N*-oxide oxygen (7 proton).[16]



35



36

Thus, one would expect to find that C_4 vinyl proton of **34** at higher field than the corresponding proton of **33**. Also, one would expect the *N*-methyl group in **34** to be some-

what more deshielded than its counterpart in **33** and, therefore, at lower field. This is indeed the case. The steroids assigned to the anti configuration by uv maxima have C_4-proton peaks at 6.65–6.85 ppm, while the other isomer has peaks at 6.00–6.28 ppm. Further, the assigned anti isomers have *N*-methyl peaks at 3.67–3.70 ppm while the other isomer has peaks at 3.71–3.84 ppm. These data, summarized in Table II, confirm the stereochemical sssignments made for the isomers and corroborate the use of uv maxima for distinguishing between conjugated syn and anti nitrone pairs.

Table I lists the androstene, the pregnene nitrones, and the saturated 3-ketonitrones prepared. The latter compounds were homogeneous by tlc analysis and had no outstanding spectral characteristics. Thus, although these nitrones, too, must exist as stereoisomeric pairs, they were not detected. Biological testing of the nitrones found them less active than the parent ketones.

Experimental Section[17]

***N*-(2-Hydroxyethyl)-α-(17β-hydroxy-3-methoxyandrosta-3,5-dien-6-yl)nitrone (14). General Procedure for 6- and 20-Aldonitrones.** A mixture of 17-acetoxy-3-methoxyandrosta-3,5-diene-6-carboxaldehyde (30.1 g, 81 mmol), $NaHCO_3$ (40 g), and *N*-(2-hydroxyethyl)hydroxylamine oxalate (25 g, 0.116 mol) in MeOH (1 l.)–H_2O (50 ml)–pyridine (15 ml) was stirred under reflux in the dark for 22 hr. The hot reaction mixture was filtered and the filtrate was concentrated to a yellow paste. The resulting solid (43 g) was crystallized from aqueous MeOH to give **14** (23.5 g).

17α-Methyl-3-methyliminoandrost-4-en-17β-ol *anti*- and *syn*-*N*-Oxide (40 and 41). General Method for 3-Ketonitrones. A mixture of methyltestosterone (30.6 g, 0.1 mol), $NaHCO_3$ (35 g), and *N*-methylhydroxylamine oxalate (18.9 g, 0.1 mol) in absolute EtOH (75 ml) was stirred overnight in the dark under reflux. The reaction mixture was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel (350 g), collecting 250-ml fractions and eluting with Me_2CO (1 l.), Me_2CO–5% MeOH (1 l.), and Me_2CO–10% MeOH (7 l.). Fractions 11–16 were combined and concentrated and the residue was crystallized from acetone–ether–hexane to give **40** (8.0 g). Fractions 28–33 were combined and concentrated and the residue was triturated with ether to give **41** (2.0 g).

Acknowledgment. The authors wish to thank Dr. Vladimir Petrow for suggesting this problem and to his helpful discussions throughout the course of this work.

Registry No.—**12** (R_2 = OH), 50276-51-2; **12** (R_2 = OAc), 5490-78-8; **14**, 50324-69-1; **15**, 50324-70-4; **16**, 50324-71-5; **17**, 50324-72-6; **18**, 50324-73-7; **19**, 50324-74-8; **19** 6-carboxaldehyde derivative, 50323-68-7; **20** (R_2 = CH_3), 24254-01-1; **22**, 50324-77-1; **23**, 50324-78-2; **24**, 50324-79-3; **25**, 50324-80-6; **25** 20-carboxaldehyde derivative, 50323-70-1; **27**, 50324-81-7; **28**, 50324-82-8; **29**, 50324-83-9; **29** 20-oxo derivative, 50324-76-0; **30**, 50324-84-0; **37**, 50324-85-1; **37** 3-oxo derivative, 58-22-0; **38**, 50324-87-3; *syn*-**39**, 50324-88-4; *anti*-**39**, 50324-89-5; **40**, 50324-90-8; **40** 3-oxo derivative, 58-18-4; **41**, 50324-92-0; **42**, 50324-93-1; **42** 3-oxo derivative, 434-03-7; *syn*-**43**, 50324-95-3; *anti*-**43**, 50324-96-4; **43** 3-oxo derivative, 2352-19-4; **44**, 50324-98-6; **44** 3-oxo derivative, 434-22-0; **45**, 50325-00-3; **45** 3-oxo derivative, 63-05-8; *syn*-**46**, 50325-01-4; **46** 3-oxo derivative, 57-83-0; **47**, 50325-02-5; **48** (R_2 = α-OAc), 50325-03-6; **48** (R_2 = α-OAc) 3-oxo derivative, 2268-98-6; **48** (R_2 = α-OH), 50325-05-8; **48** (R_2 = α-OH) 3-oxo derivative, 80-75-1; *syn*-**49**, 50276-50-1; *anti*-**49**, 50325-07-0; **49** 3-oxo derivative, 68-96-2; *syn*-**50**, 50276-49-8; *anti*-**50**, 50324-68-0; **50** 3-oxo derivative, 302-23-8; **51**, 50325-08-1; **51** 3-oxo derivative, 56-47-3; *syn*-**52**, 50325-10-5; *anti*-**52**, 50325-12-7; **52** 3-oxo derivative, 50-23-7; **53**, 50325-14-9; **54**, 50323-53-0; **54** 3-oxo derivative, 1816-78-0; **55**, 50323-55-2; **55** 3-oxo derivative, 71-58-9; **56**, 50323-57-4; *syn*-**57**, 50323-58-5; *anti*-**57**, 50278-60-9; **57** 3-oxo derivative, 595-33-5; **58**, 50323-60-9; **58** 3-oxo derivative, 846-46-8; **59**, 50323-62-1; **59** 3-oxo derivative, 521-18-6; **60**, 50323-64-3; **61**, 50323-65-4; **61** 3-oxo derivative, 521-11-9; **62**, 50323-67-6; *N*-(2-hydroxyethyl)hydroxylamine oxalate, 50323-86-9; *N*-methylhydroxylamine oxalate, 7665-00-1; *N*-methylhydroxylamine hydrochloride, 593-56-6; *N*-(2-hydroxyethyl)hydroxylamine hydrochloride, 24395-54-8.

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(17) All melting points were determined in open capillary tubes on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 521 grating spectrophotometer using KBr pellets. Ultraviolet spectra were recorded on a Perkin-Elmer 350 spectrophotometer in ethanol. Nmr spectra were run on a Varian A-60A with Me_4Si as an internal standard. The standard drying agent used was $MgSO_4$ and the solvents were removed under vacuum on a rotary evaporator.

Steroidal Alkaloids. CLXI.[1] Stereospecific Synthesis of (22*R*)- and (22*S*)-22-Aminocholesterol

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The stereospecific syntheses of the two epimeric 22-aminocholesterols from the two known epimeric 22-hydroxycholesterols *via* tosylate → azide → amine are described. These amines are also obtained by the reduction of 22-ketocholesterol oxime.

Recent reviews,[2,3] describing the biogenesis of pregnenolone from cholesterol, feature the importance of a C-22 hydroxylated species. Therefore it seemed interesting to synthesize 22-substituted derivatives of cholesterol in