Application of Electron Spin Resonance Spectroscopy to Problems of Structure and Conformation. IX. Semidiones Derived from Cyclopentanones. Assignment of Structure to Steroidal D-Ring Ketones[1]

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The oxidation of cyclopentanone, monosubstituted cyclopentanones, and bicyclic and steroidal derivatives of cyclopentanone by air in basic dimethyl sulfoxide solution has been studied. Although this method gives the expected radical anions (semidiones) in many cases, the preferred method for generation of the semidiones is the reaction of the corresponding α-bromo, α-hydroxy, or α-acetoxy ketones with potassium *t*-butoxide in dimethyl sulfoxide. With 17-keto steroids having a *trans*-C/D ring fusion, dimeric radical anions are first formed if direct oxidation of the ketone is attempted. However, the α-bromo or α-hydroxy ketones do not suffer from this drawback in the presence of excess base and yielded the monomeric semidiones. The oxidation of D-ring steroidal ketones is highly selective and provides a rapid and convenient method for distinguishing between position isomers (17- and 16-keto steroids or 17- and 15-keto steroids) and stereo isomers (13α- and 13β-17-keto steroids or 14α- and 14β-17-keto steroids). Some vinylogs of 1,2-semidiones have also been prepared.

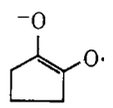
A study of the oxidation of a variety of ketones to radical anions (semidiones), detected by electron spin

$$-\mathrm{COCH_2}- \xrightarrow[O_2]{B^-} -\mathrm{C(O\cdot)=C(O^-)}-$$

resonance (esr) spectroscopy, has enabled us to study the conformational preferences of monocyclic semidiones,[2,3] to locate the position of the carbonyl group and assign configurations to ring junctures in decalones and their steroidal derivatives,[3,4-7] to detect changes in configuration at more distant centers in the steroids,[3,6] and to determine the preferred conformations of several *cis*-decalones.[6] We have now examined from a similar standpoint the oxidation of cyclopentanone, monosubstituted cyclopentanones, and fused-ring systems derived from cyclopentanone, including steroids.

Results

Cyclopentanone.—In contrast to cyclohexanone, which readily affords a high concentration of cyclohexane-1,2-semidione by exposure to air of a solution in dimethyl sulfoxide (DMSO) containing potassium *t*-butoxide,[3] cyclopentanone yields only a low concentration of the semidione **1** which decays within a few minutes. Treatment of pure 2-bromocyclopentanone



a^H = 13.12 (4) gauss

1

with potassium *t*-butoxide in DMSO[8] fails to generate **1**, even in low concentration. However, a high concentration of **1** can be readily attained by the spontaneous disproportionation[8] of 2-hydroxycyclopentanone or 2-acetoxycyclopentanone in DMSO containing potassium *t*-butoxide, and the radical can be detected for hours. Its esr spectrum at 25° (Figure 1) consists of five lines with intensities in the ratio 1:4:6:4:1 and indicates hyperfine splitting (hfs) by four equivalent α-hydrogen atoms (a^H = 13.12 gauss). Hyperfine splitting by the β-hydrogen atoms has not been resolved and must be less than 0.05 gauss. The equivalence of the four α-hydrogen atoms is consonant with either a planar structure for **1** or a rapid time averaging between two nonplanar but equally populated conformations of **1**, such as envelope conformations. Of these two possibilities, the latter appears more likely since a puckering of the ring would minimize eclipsing strain between the hydrogen atoms at C-4 and those on adjacent carbon atoms. In d_6-DMSO the semidione gives a^D = 1.99 (4) gauss, a^H/a^D = 6.60. At high-signal amplification the undeuterated semidione yields a doublet splitting a few per cent as intense as the main peaks and assigned to the natural abundance of C^{14} at the carbonyl carbon atoms, a^C = 5.6 gauss. Since in cyclohexane-1,2-semidione $a_{CO}{}^C$ is 4.9 gauss,[9] it appears that there is a higher spin density on the carbonyl carbons in **1** than in its cyclohexane analog. Spin densities in the two systems can be evaluated from the equation[2]

$$a^H = B\rho_C \cos^2\theta$$

where θ is the dihedral angle between C_π–C_α–H and p_z-orbital–C_α planes. If we assume **1** to be planar with sp^3 hybridization at the α-carbon atom (θ = 30°) we find $B\rho_C$ = 17.3. Solving the two simultaneous equations for cyclohexane with $a_{axial}{}^H$ = 13.2 and $a_{equatorial}{}^H$ = 6.59 gauss yields $B\rho_C$ = 13.8 (θ_{axial} = 13°); ρ_C(cyclopentane)/ρ_C(cyclohexane) = 1.25. Using a more realistic value of θ for cyclopentene derivatives of 27°[10] yields a $B\rho_C$ for **1** of 16.7. Since the preferred value of B is 40 gauss for a radical anion,[11] values of ρ_C in the range of 0.4 to 0.3 are indicated for **1** and its cyclohexane analog.

Monosubstituted Cyclopentanones.—Puckered conformations should be favored for substituted cyclo-

(1) Reactions of Resonance Stabilized Anions. XXVI. For part XXV, see G. A. Russell and E. A. Janzen, *J. Am. Chem. Soc.*, **89**, 300 (1967). This work was supported by grants from the National Science Foundation and the National Institute of General Medical Sciences.

(2) G. A. Russell and E. T. Strom, *ibid.*, **86**, 744 (1964).

(3) E. R. Talaty and G. A. Russell, *ibid.*, **87**, 4867 (1965).

(4) G. A. Russell and E. R. Talaty, *ibid.*, **86**, 5345 (1964).

(5) G. A. Russell and E. R. Talaty, *Science*, **148**, 1217 (1965).

(6) E. R. Talaty and G. A. Russell, *J. Org. Chem.*, **31**, 3455 (1966).

(7) G. A. Russell, E. T. Strom, E. R. Talaty, K.-Y. Chang, R. D. Stephens, and M. C. Young, *Rec. Chem. Progr.* (Kresge-Hooker Sci. Lib.), **27**, 3 (1966).

(8) G. A. Russell, R. D. Stephens, and E. R. Talaty, *Tetrahedron Letters*, 1139 (1965).

(9) E. T. Strom and G. A. Russell, *J. Chem. Phys.*, **41**, 1514 (1964).

(10) G. V. Smith and H. Kriloff, *J. Am. Chem. Soc.*, **85**, 2016 (1963).

(11) G. A. Russell, E. T. Strom, E. R. Talaty, and S. A. Weiner, *ibid.*, **88**, 1998 (1966).

TABLE I

INITIAL PROPORTIONS AND HYPERFINE SPLITTING CONSTANTS OF SEMIDIONES DERIVED FROM MONOSUBSTITUTED CYCLOPENTANONES

R	Initial ratio of 2:3	Hfsc of 2, gauss		Hfsc of 3, gauss	
		a_α^H	a_β^H	a_α^H	a_β^H
CH_3	30:70	14.46, 14.01, 11.62	*a*	14.36, 14.36, 12.48, 12.48	0.38 (d)
$CH(CH_3)_2$	64:36	14.43, 13.94, 12.62	0.2 (d)	15.63, 15.63, 11.07, 11.07	0.52 (d)
$C(CH_3)_3$	>89:<11	14.40, 13.96, 12.38	0.33 (d)[b]	15.68, 15.68, 11.30, 11.30	0.50 (d)
C_6H_5	<10:>90	14.2, 14.2, 12.0[c]		14.55, 14.55, 11.85, 11.85	0.35 (d)

[a] Not resolved, but peaks are broad. Occasionally, a separation of 0.6 gauss into doublets (d) is seen. [b] Tendency to split by another β hydrogen of the order of 0.08 gauss. [c] Hfsc are only approximate owing to low concentration of this semidione.

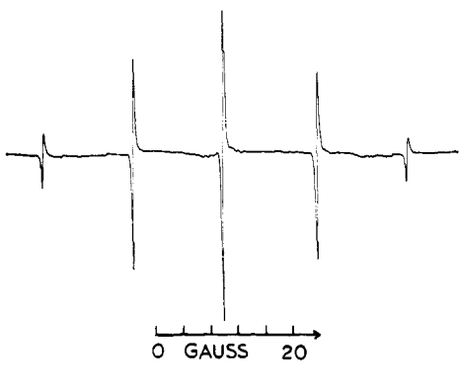
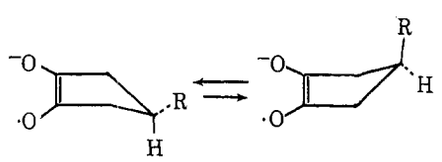


Figure 1.—First-derivative esr spectrum of cyclopentane-1,2-semidione obtained by treatment of 2-hydroxycyclopentanone with potassium *t*-butoxide in dimethyl sulfoxide at 25°.

pentanesemidiones. The two conformations for the monosubstituted derivatives are not expected to be equally populated (the one having the substituent in an equatorial position at the tip of the envelope being preferred), although rapid time averaging will occur, as was found to be the case with monosubstituted cyclo-



hexanesemidiones.[3] Consequently, there will be a difference in the hyperfine splitting constants (hfsc) of the α-hydrogen atoms of the monosubstituted semidiones, the difference being greater with a bulky group such as *t*-butyl. These expectations have been partially realized in a study of the oxidation products of 3-methyl-, 3-isopropyl-, 3-*t*-butyl-, and 3-phenylcyclopentanone. Each of these ketones gives rise to two semidiones (**2** and **3**). The proportions of the two

2 **3**

a, R = CH_3
b, R = $CH(CH_3)_2$
c, R = $C(CH_3)_3$
d, R = C_6H_5

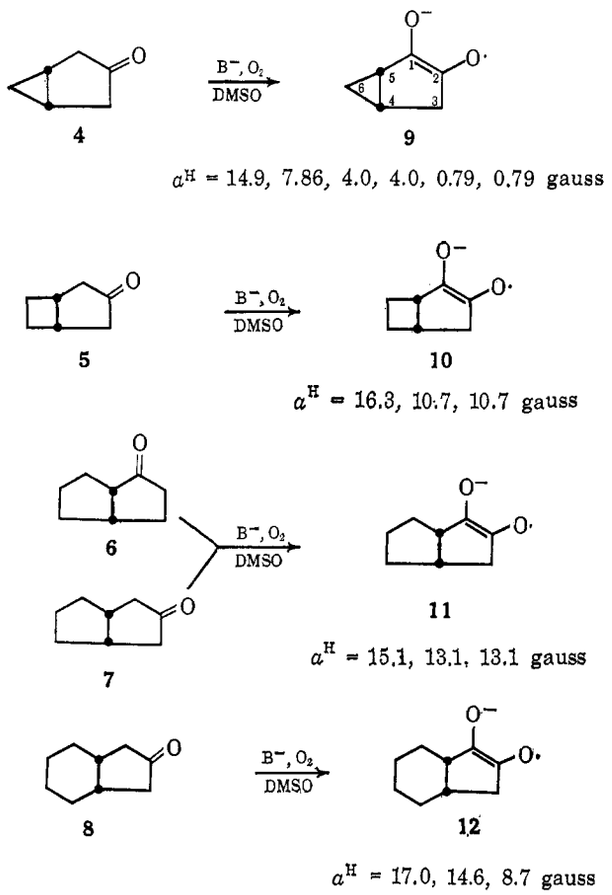
radicals depend greatly on the nature of the substituent. The hyperfine splitting constants of these semidiones and their initial proportions are given in Table I.

In a puckered, envelope-like conformation, the α-hydrogen atoms would be located in two different configurations similar to the quasi-axial and quasi-equatorial configurations in the half-chair form of cyclohexene, the quasi-axial hydrogen having the larger hfsc.[2,3] However, the maximum difference in the hfsc of "quasi-axial" and "quasi-equatorial" hydrogen atoms of **3** is not so large as in the corresponding cyclohexanesemidiones,[3] indicating only a small difference in the values of θ for these two types of hydrogen in the $\cos^2\theta$ equation. The data of Table I indicate a greater conformational preference in **3** for R = isopropyl or *t*-butyl than for R = methyl (R = CH_3, Δa^H = 1.88 gauss; R = $(CH_3)_3C$, Δa^H = 4.78 gauss). Surprisingly, less conformational preference is seen when R = phenyl than when R = isopropyl. The sum of $a_{\text{"axial"}}{}^H + a_{\text{"equatorial"}}{}^H$ for **3** varies from 26.3 to 27.0 gauss *vs.* 26.2 gauss for the parent ring system, suggesting that the degree of puckering of the ring may also vary with substituent along with the variation in the populations of the stable molecular arrangements.

Although the 3-substituted cyclopentanones furnish a higher concentration of semidiones than the unsubstituted ketone, the relative stabilities of the semidiones depend markedly on the nature of the substituent, the most stable ones being those bearing a *t*-butyl substituent. Radical anion **2** which has a tertiary hydrogen atom in the α position decays faster than the corresponding radical anion (**3**), a situation similar to that encountered with the six-membered semidiones.[3,6] For example, although **2c** is almost exclusively present in the initial oxidate from 3-*t*-butylcyclopentanone, the proportion of this radical anion decreases to 58% after 80 min and to 39% after 220 min. 2-*t*-Butylcyclopentanone furnishes only a single radical anion (**2c**), although in low yield. However, 2-methyl- and 2-phenylcyclopentanone fail to yield detectable quantities of **2a** and **2d**. 3-Methylcyclopentane-1,2-dione is not converted into **2a** when treated with potassium *t*-butoxide in DMSO in the absence of air, and, in fact, only low yields of **1** can be obtained from cyclopentane-1,2-dione under these conditions. This behavior contrasts strongly with the corresponding cyclohexane derivatives[3] and appears to be due to the higher enol content of the cyclopentane-1,2-diones (3-methylcyclopentane-1,2-dione is exclusively in the enolic form).

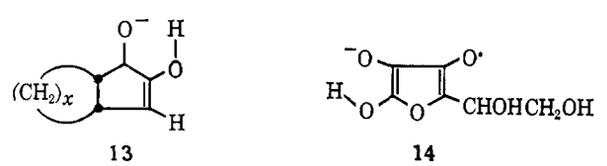
Bicyclic Derivatives of Cyclopentane-1,2-semidione Having a 1,2 Ring Fusion.—The conversions of **4–8** into **9–12** have been examined. These conversions are shown in Scheme I, and the spectrum of **9** is shown in Figure 2. All six hydrogen atoms can be detected and one, strong, long-range interaction must occur. By analogy with other bicyclic systems displaying long-range interactions it can be expected that the *anti* hydrogen at C-6, which is in a W-plan arrangement

SCHEME I



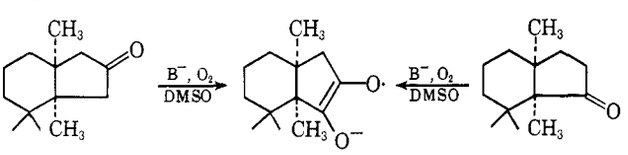
with the p_z orbital at C-1, is involved in this long-range interaction.[12] However, we will postpone a full discussion on this subject at this time.

The bicyclic system dictates that **10** and **11** must exist in a *cis* configuration while the ring junction is most likely *cis* in **12**.[13] Because of the tendency of cyclopentane-1,2-dione derivatives to exist in the enolic structure, we were concerned that the structures of **9–12** might actually be **13**. For example, it appears



13 **14**

that the radical anion from ascorbic acid exists in the enolic structure **14**.[7] However, the enolic structure for **12**, and hence for **10** and **11** as well, would seem to be excluded by the observation that **15** and **16**[14] oxidize to give a semidione with hfs by two hydrogen atoms.



15 **17** **16**

a^H = 14.1, 8.6 gauss

$a_{CH_3}{}^H \simeq 1$ gauss

(12) G. A. Russell and K.-Y. Chang, *J. Am. Chem. Soc.*, **87**, 4381 (1965); G. A. Russell, K.-Y. Chang, and C. W. Jefford, *ibid.*, **87**, 4383 (1965).

(13) See E. L. Eliel and C. Pillar, *ibid.*, **77**, 3600 (1955).

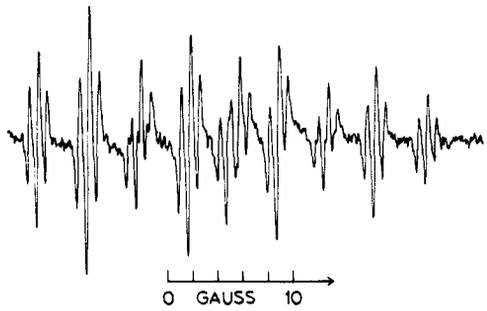


Figure 2.—First-derivative esr spectrum of radical anion formed by oxidation of bicyclo[3.1.0]hexan-3-one in basic dimethyl sulfoxide solution at 25°. The decrease in the intensities of the lines on the high-field side of the spectrum is caused by a rapid decay of the radical anion.

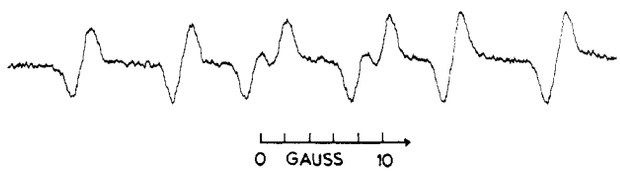
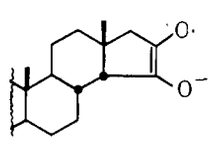


Figure 3.—First-derivative esr spectrum of semidione formed by exposure of a solution of 5α-androstan-3β-ol-16-one in dimethyl sulfoxide containing potassium *t*-butoxide to air at 25°.

By analogy with **17**, it appears that in **10–12** the hydrogen atoms of the α-methylene group are not equivalent. The α-methine hydrogen atoms probably have hfsc of 4.0, 10.7, 13.1, and 17.0 in **9–12**, respectively. Additional long-range interactions may be present in **10–12** since the observed spectra had rather broad lines. However, no additional hyperfine splitting was noticed. In any event hfsc for such interactions would have to be <1 gauss.

Steroidal Derivatives of Cyclopentanone.—Oxidation of 5α-androstan-3β-ol-16-one (**19**) and 5α,14β-androstan-15-one (**19**) gives identical semidiones with hfs by three nonequivalent α-hydrogen atoms (Figure 3) to which we assign partial structure **20**. By analogy with



20

a^H = 16.29, 14.25, 8.35 gauss

12 and **17** it is presumed that the largest hfsc is for the methine hydrogen atom and that the C/D ring junction has assumed the more stable *cis* fusion (epimerization at C-14) in accordance with recognized stabilities of Δ^{15} steroids.[15] Under higher resolution the spectrum of Figure 3 shows further splitting of each of the eight lines into sextets with an average separation of 0.4–0.5 gauss. This fine structure presumably involves the methyl group at C-13 and other hydrogen atoms β or γ to the dicarbonyl system. Oxidation of samandaron (**21**),[16] 3-methoxyestra-1,3,5(10)-trien-16-

(14) H. Erdtman and T. Norin, *Chem. Ind.* (London), 622 (1960); T. Norin, *Acta Chem. Scand.*, **17**, 738 (1963).

(15) D. K. Banerjee, S. Chatterjee, C. N. Pillai, and M. V. Bhatt, *J. Am. Chem. Soc.*, **78**, 3769 (1956).

(16) G. Habermehl, *Ber.*, **96**, 840 (1963).

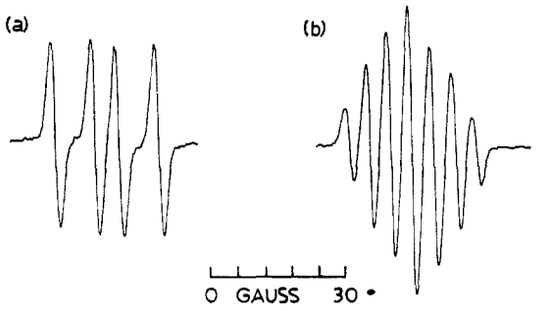
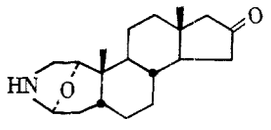


Figure 4.—First-derivative esr spectra of radical anions formed immediately after exposure to air of basic solutions of 17-keto steroids in dimethyl sulfoxide at 25°: (a) 3β-hydroxy-13α,14α-androst-5-en-17-one; (b) 5α-androstan-17-one.

one (**22a**), and 3-methoxy-14β-estra-1,3,5(10)-trien-16-one (**22b**) affords semidiones which are identical with



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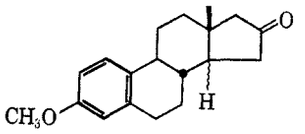
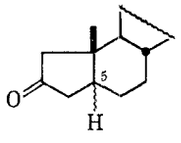


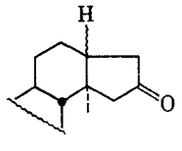
22a, 14α
b, 14β

20 as far as the hfsc of the α-hydrogen atoms is concerned (fine structure was not resolved). Hence, modification of ring A has no effect on the position of enolization and oxidation in 16-ketoandrostanes nor on the main hfsc of the resulting semidione. One must therefore conclude that "conformational transmission"[17] from ring A to ring D does not play any major role in the steroidal ketones examined.

A related class of steroidal ketones comprises the A-nor-2-keto steroids. In fact, these compounds can be looked upon as enantiomers of 18-nor-14α-methyl-16-keto steroids as far as partial structures are concerned (for example, compare partial structures **23** and **25**). Exposure to air of solutions of A-nor-5α-

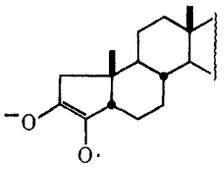


23, 5α
24, 5β



25, 13β
26, 13α

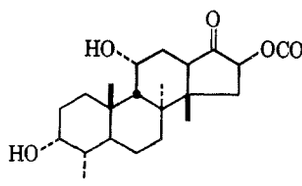
pregnane-2,20-dione (**23a**), A-nor-5α-cholestan-2-one (**23b**), A-nor-5β-androstan-17β-ol-2-one (**24a**), A-nor-5β-pregnane-2,20-dione (**24b**), and A-nor-5β-cholestan-2-one (**24c**) in DMSO containing potassium *t*-butoxide give identical semidiones which are characterized by esr spectra consisting of eight lines. Therefore, partial structure **27** is assigned to these semidiones. The



27, a^H = 16.17, 14.29, 8.30 gauss

similarity of the hfsc of **20** and **27** suggests that these radical anions have similar conformations. Furthermore, since both **23** and **24** as well as **22a** and **22b** oxidize toward the least substituted ring juncture, one would predict that a similar position of enolization and oxidation will occur in the enantiomeric ketones **25** and **26**.

Although we have no examples of ketones of type **25** or **26**, we have examined a related α-acetoxy ketone (**28**). Treatment of this compound with potassium *t*-butoxide in DMSO in the absence of air generates a semidione (**29**),[18] the esr spectrum of which has eight



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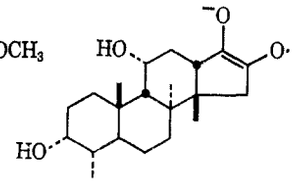
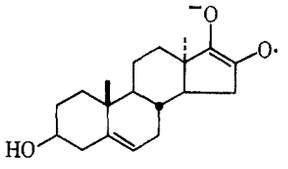


29, a^H = 11.72, 10.00, 5.78 gauss

lines as expected. A further splitting of each line into quintets (average separation = 0.35 gauss) can be noticed under high resolution. This semidione may be regarded as a substituted derivative of **27**. However, the hfsc of the two semidiones are quite different, indicating a considerable difference in their conformations.

17-Ketoandrostanes without a methyl group at C-14 give distinctly different esr spectra from the oxidation products of 16-oxoandrostanes or A-nor-2-keto steroids described above. Oxidation of 3β-hydroxy-13α,14α-androst-5-en-17-one (**30**) affords a semidione (**31**) in



31, a^H = 14.23, 8.80 gauss

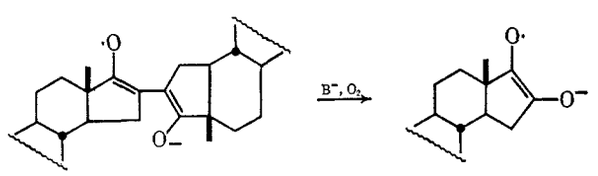
which there is hfs by two nonequivalent hydrogen atoms (those at C-15) (Figure 4a). No further splitting has been observed. On the other hand, oxidation of a 17-keto steroid with a *trans*-C/D ring juncture yields an oxidate having an entirely different esr spectrum. Treatment of 5α-androstan-17-one (**32a**), 5α-androstan-3α-ol-17-one (**32b**), 3β,12β-dihydroxy-5α-androstan-17-one (**32c**), 3-methoxyestra-1,3,5(10)-trien-17-one (**32d**), 6-aza-3-methoxyestra-1,3,5(10)-trien-17-one (**32e**), and 3-methoxyestra-1,3,5(10),6,8(9)-pentaen-17-one (**32f**) with potassium *t*-butoxide and air in DMSO solution under the usual conditions of our experiments (0.05 *M* ketone, 0.1 *M* base) yields a paramagnetic product (**33**) having an esr pattern of seven lines in the intensity ratio 1:2:3:4:3:2:1 (a^H = 9.34, 9.34, 4.67, 4.67 gauss) (Figure 4b). Under high resolution, each of these lines shows a tendency to split into a heptet (average separation ≅ 0.55 gauss). The relative intensities of the seven principal lines, however, change slowly when the solution is allowed to stand, and a new pattern of four lines of equal intensity (semidione **34**)

(17) D. H. R. Barton, A. J. Head, and P. J. May, *J. Chem. Soc.*, 935 (1957); D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *ibid.*, 1297 (1960).

(18) Initially, a transient radical of about one-eighth the concentration of **29** is also formed. This radical may be the 13α epimer of **29**.

begins to emerge after a few hours. If more air is admitted at this stage, again a clean, seven-line pattern is observed immediately, which decays to form a four-line pattern which is initially superimposed on the seven-line pattern. If this process of exposure to controlled amounts of air is repeated, eventually the radical with the seven-line pattern is no longer produced and only **34**, a^H = 12.67, 7.18 gauss, is detected (experiments performed with ketones **32a–c**). Even under moderate resolution, each of the four lines of **34** is split further into what may appear to be a 1:3:3:1 quartet; however, a careful inspection of the spectrum under higher resolution reveals this further splitting to be really a doublet ($a^H \cong 0.9$ gauss) of 1:3:3:1 quartets ($a^H \cong 0.5$ gauss).

In order to elucidate the nature of the semidiones **33** and **34**, we have studied the reactions of some derivatives of **32**. Reaction of a solution of 3-hydroxyestra-1,3,5(10)-triene-16,17-dione (**35**) in DMSO with potassium *t*-butoxide does not spontaneously generate appreciable amounts of a semidione.[3] However, **35** can be reduced to a semidione having an esr spectrum of four lines indistinguishable from **34** by treatment with the anion of propiophenone in DMSO solution[3] in the absence of air. On the other hand, when a mixture of the 16,17-dione (**35**) and 17-keto-5α-androstane (**32a**) is treated with a degassed solution of potassium *t*-butoxide in DMSO (concentrations in the mixture = 0.032, 0.15, and 0.20 *M*, respectively), the radical **33** (characterized by the seven-line pattern) is produced spontaneously. The foregoing results suggest that **33** is a dimeric semidione while **34** is a monomeric (Δ^{16}) species. This is verified by the finding



33 **34**

that a variety of 16-bromo or 16-hydroxy 17-ketones spontaneously form only semidiones similar to **34** when treated with 2 to 3 equiv of potassium *t*-butoxide in DMSO. Table II summarizes the hfsc observed for these semidiones.

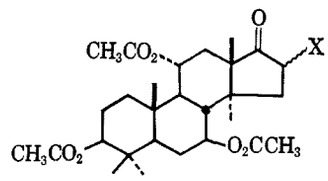
TABLE II

HYPERFINE SPLITTING CONSTANTS OF 13β-METHYL-14α-16,17-SEMIDIONES (GAUSS)

α-Bromo or hydroxy ketone	Major doublet splittings[a]	Other hfs $a_{CH_3}^H$	Other hfs a^H [b]
16α-Bromo-5α-androstan-17-one (**36**)	12.7, 7.2	0.89	0.45
3β,17β-Dihydroxyandrost-5-en-16-one (**37**)	12.7, 7.2	0.89	0.45
3-Methoxy-16α-bromoestra-1,3,5(10)-trien-17-one (**38**)	12.7, 7.2	0.91	0.82
3α-17β-Dihydroxy-5β-androstane-11,16-dione (**39**)	12.7, 7.2	0.87	0.46

[a] Exchanged for deuterium in d_6-DMSO. [b] Additional fine structure differing from compound to compound is seen in all cases.

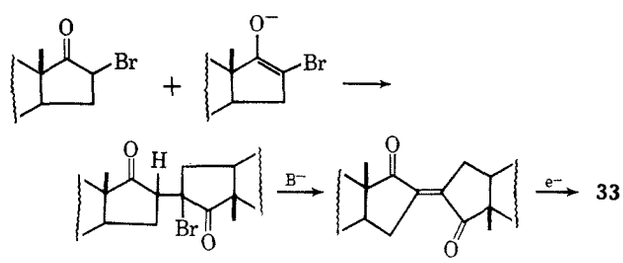
To rule out possible complications owing to enolic structures, a 14α-methyl-17-ketoandrostane (**40**) was prepared. Oxidation of **40a** with 400% excess of



40a, X = H
b, X = Br

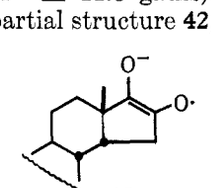
potassium *t*-butoxide initially gives a four-line pattern, similar to **34**, but shortly thereafter a mixture of radical anions is detected. Continued oxidation, as described for **32a–c**, regenerates the four-line pattern. The α-bromo derivative **40b** generates only a single semidione stable for hours in DMSO containing excess potassium *t*-butoxide. The major hfsc of the semidiones from **40a** and **40b** are a^H = 13.08, 7.07 gauss, indicating that in **34** the major doublet splittings arise from the methylene hydrogen atoms and that enolic structures can be discounted.

It actually is possible to form the dimeric semidione (**33**) from α-bromo ketone **36** but not from α-hydroxy ketones **37** and **39**. By using solutions 0.03 *M* in **36** and 0.015 *M* in potassium *t*-butoxide, semidione **33** is the only paramagnetic product detected. Undoubtedly its formation involves the reactions shown.



Continued oxidations of such solutions in presence of an excess of base will convert **33** into **34**.

The facile distinction between the C-13 epimeric 17-keto steroids described above led us to examine whether a similar distinction is possible for the corresponding C-14 epimers. The only examples of 13β,14β-17-keto steroids that we have studied are the 6-aza derivatives. However, the presence of a piperidine ring (ring B) should not affect our results since the 6-aza-13β,14α-17-keto steroid (**32e**) behaved like other 13β,14α-17-keto steroids. Oxidation of 6-aza-3-methoxy-14β-estra-1,3,5(10)-trien-17-one (**41a**) furnishes initially only a single semidione, albeit in low concentration, exhibiting hyperfine splitting by two equivalent hydrogen atoms ($a^H \cong 11.3$ gauss). This semidione probably has the partial structure **42**, since the average



42

of the hfsc for the 13α,14α-16,17-semidione (**31**) is approximately the same, namely, 11.5 gauss. On further oxidation, the triplet pattern is quickly replaced by a complex esr spectrum, which may be interpreted as mainly a triplet of triplets (a^H = 10.97, 10.97, 6.26, 6.26 gauss) superimposed on a spectrum consisting of at least 19 lines. The triplet of triplets

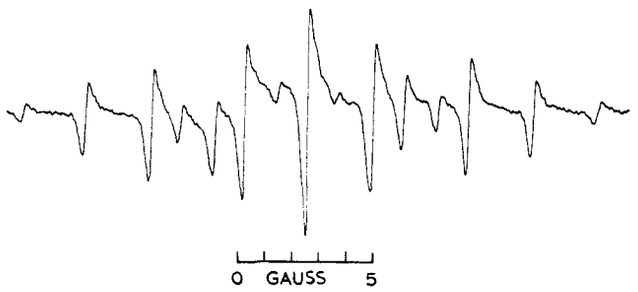
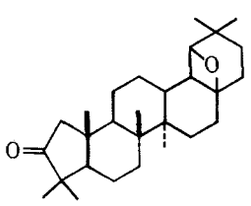


Figure 5.—First-derivative esr spectrum of radical anion obtained by treatment of cyclohexane-1,4-dione with potassium *t*-butoxide in dimethyl sulfoxide at 25°.

probably arises from a dimeric semidione analogous to **33** (the C-14 epimer of **33**), but the origin of the more complex pattern is obscure. Treatment of a solution of 6-aza-3-methoxy-14β-estra-1,3,5(10),6,8(9)-pentaen-17-one (**41b**) in DMSO with potassium *t*-butoxide and air gives a spectrum exhibiting a major quintet splitting of which the second and fourth peaks are quite broad and show a tendency to split into doublets. Under favorable conditions, the central peak can be resolved into three lines. The relative intensities of the peaks do not change with time or temperature (5 to 60°). The spectrum is consistent with hfs by two pairs of hydrogen atoms, a^H = 9.77, 9.77, 8.32, 8.32 gauss, and is assigned to the dimeric semidione similar to that obtained from **41a**.

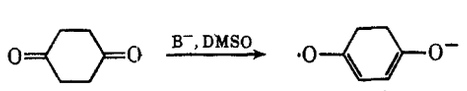
Some A-nor-1-keto steroids have also been examined. A-nor-5α-cholestan-1-one (**43**) gives only a single semidione (four-line esr spectrum) irrespective of reaction conditions. This is obviously the monomeric species related to (but not enantiomeric with) **34**, with a^H = 12.46, 7.40, ~0.5 and $a_{CH_3}{}^H \cong 0.95$ gauss. Oxidation of **44** yields slowly a semidione that shows



44

no large hfs and only a small tendency to split into a sextet having an average separation of 0.95 gauss.

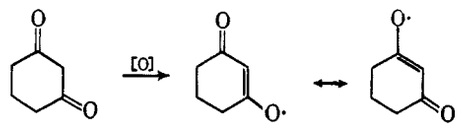
Conjugated Semidiones.—In the course of this work we have prepared some radical anions which may be regarded as vinylogs of the 1,2-semidiones (**33** being one example already encountered). Treatment of cyclohexane-1,4-dione with potassium *t*-butoxide in DMSO solution produces the unsaturated radical anion **45** (Figure 5). Upon treatment with oxygen **45**



45

a^H = 5.79 (2), 2.35 (4) gauss

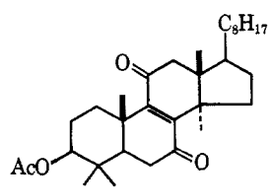
is destroyed to give a new radical anion displaying a 1:4:6:4:1 quintet splitting, a^H = 2.43 gauss, undoubtedly due to *p*-benzosemiquinone. Cyclohexane-1,3-dione fails to give a radical anion under these conditions. Moreover, attempts to prepare the potentially stable neutral radical (**46**) by various oxidations of cyclohexane-1,3-dione have been unsuccessful.



46

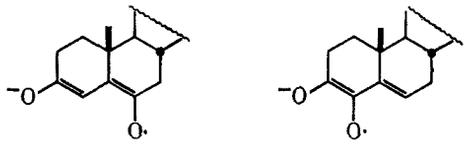
Attempts were also made to prepare the five-membered analogs of **45** or **46** from cyclopentane-1,3-dione. However, treatment of this dione with potassium *t*-butoxide in DMSO gives rise to only a weak but complex esr signal. Similar treatment of 2-acetylcyclopentane-1,3-dione, which could presumably generate cyclopentane-1,3-dione under the strongly basic conditions, fails to yield the desired radicals. Instead, a spectrum of at least 31 lines, arising from some condensation product, is observed.

Treatment of **47**, or its saturated derivative, with potassium *t*-butoxide in DMSO solution yields the $\Delta^{8,9}$-



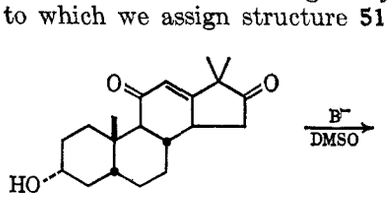
47

7,11-semidione (a^H = 5.44, 4.72, 1.38, 1.38 gauss). A more complicated esr spectrum is produced upon treatment of 5α-cholestane-3,6-dione or its $\Delta^{4,5}$ derivative with potassium *t*-butoxide in DMSO solution. The lines of the esr spectrum are broad and only tentative values of the hfsc of **48** are obtainable, $a^H \cong$ 9.3, 5.4, 5.4, 2.5, and 1.6 gauss. Oxidation of cholest-4-en-3-one or pregn-4-ene-3,20-dione in basic solution also yields the spectrum assigned to **48** although up to 20% of another radical anion is also observed, presumably **49** and/or the isomeric $\Delta^{4,5}$-2,3-semidione.



48 **49**

Treatment of 17,17-dimethyl-3α-hydroxy-18-nor-5β-androst-12-ene-11,16-dione (**50**) with potassium *t*-butoxide in DMSO leads to the spontaneous formation of a radical anion exhibiting hfs by four hydrogen atoms to which we assign structure **51**. The hydrogens in-



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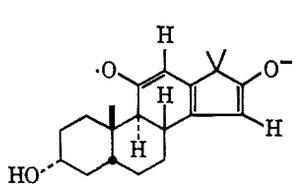
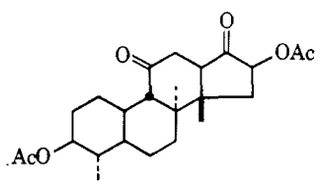


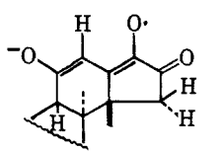
51, a^H = 7.66, 4.83, 4.23, 2.54 gauss

volved in hfs are undoubtedly those at C-15, C-12, C-9, and C-8. When the same reaction is performed in d_6-DMSO, two hydrogen atoms are exchanged immediately with deuterium atoms, one hydrogen atom (a^H = 2.54 gauss) is exchanged slowly (90 min for complete exchange), and the fourth hydrogen atom (a^H = 7.66 gauss) is not exchanged (at least over a period of 4 hr). The hydrogen atoms that are exchanged rapidly most likely are those at C-15 and C-9 because they are α to the carbonyl groups. The hydrogen atom that is exchanged slowly is probably the one at C-8 since it is allylic in **51**. The hydrogen atom at C-12 is not exchanged because it is vinylic in both **50** and **51**.

Reaction of 3β,16β-diacetoxy-4α,8α,14β-trimethyl-18-nor-5α,9β,13α-androstane-11,17-dione (**52**) with potassium *t*-butoxide in DMSO in the absence of air yields a mixture of radical anions of which one decays rapidly. After about 1 hr, only a single radical anion with hfs by four hydrogen atoms is detected. The longer lived radical anion possibly has the partial structure **53**,

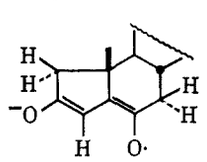


52



53, a^H = 10.90, 6.30, 4.50, 4.50 gauss

an example of a vinylog of a semitrione.[7] The radical anion that decays faster is probably the 11-keto-16,17-semidione, which could be a precursor of **53**. By oxidation of A-norcholest-3-en-2-one (**54**), a 20-line esr spectrum is obtained. However, this spectrum cannot be analyzed in terms of a single radical anion. Sixteen of the lines appear to arise from a single radical anion involving hfs by five hydrogen atoms (a^H = 7.11, 7.11, 7.11, 4.74, 1.24 gauss). A possible structure consistent with the hfs pattern is **55**. The remaining four lines of approximately equal intensity are possibly due to **56** (a^H = 6.98, 1.07 gauss) in which hfs by only the hydrogens indicated is involved.



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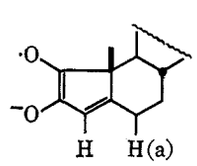
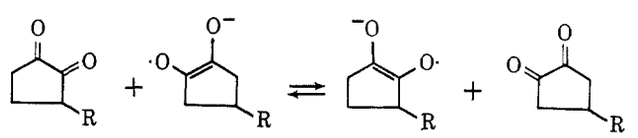


56

Discussion

13β-Methyl 14α-17-ketones and 13α-methyl 14α-17-ketones are readily distinguished by oxidation in DMSO solutions containing potassium *t*-butoxide and detection of the semidiones by esr spectroscopy. With limited amounts of oxygen the ketone with the *trans*-C/D ring fusion yields the seven-line spectrum of **33** (Figure 4b) which is clearly distinguishable from the four-line spectrum from the ketone having the *cis*-C/D ring fusion (13α,14α) (Figure 4a). In addition, the 13α-methyl 14α-17-ketones can also be distinguished from the 13β-methyl 14β-17-ketones, since only the former class of steroids gives a four-line spectrum when oxidized with limited amounts of air. The 16- and 15-ketones all oxidize to yield an entirely different semidione (**20**) with major hfs by three hydrogen atoms (Figure 3). The driving force for preferred oxidation at C-15 rather than C-17 in a *trans* 16-ketone is undoubtedly thermodynamic[19] while the $\Delta^{15(16)}$-semidione is undoubtedly further stabilized by epimerization at C-14.[15]

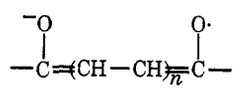
Oxidation of 3-methylcyclopentanone leads to predominant attack away from the alkyl group as judged from the ratio of semidiones detected (**2** and **3** formed in the ratio of 30:70). Bromination of this ketone in *t*-butyl alcohol followed by reaction of the crude α-bromo ketones in DMSO solution with potassium *t*-butoxide leads to the same ratio of semidiones.[8] Either both processes are measuring the relative stabilities (rate of formation or equilibrium concentrations) of the two enolates or both processes are measuring the position of the equilibrium between the semidiones and their respective diketones. The latter process, however, cannot be involved with all substituents since



3 **2**

bromination and oxidation of 3-*t*-butylcyclopentanone yield diametrically opposite results, bromination yielding almost exclusively **3**[8] and oxidation yielding almost exclusively **2**. The preferred oxygenation at C-2 probably arises from a preferred enolization toward C-2 because of a relief in eclipsing strain, which should be considerable even in a puckered conformation of the ketone. Apparently, oxygen traps the enolate anions with little kinetic discrimination. Bromination, on the other hand, appears to give kinetic discrimination with the bromine being directed as far from the bulky *t*-butyl group as possible because of steric reasons. On this basis the oxidation of 3-isopropylcyclopentanone to yield a ratio of semidiones (**2**:**3** = 64:36) intermediate between that from the 3-methyl- and 3-*t*-butylcyclopentanones is to be expected. However, the reason for the almost exclusive oxygenation at C-5 in 3-phenylcyclopentanone is not immediately obvious. Apparently the phenyl ring either stabilizes the $\Delta^{1(2)}$ enolate anion against oxidation or somehow stabilizes the $\Delta^{1(5)}$ enolate so that C-5 is the preferred point of oxidation.

The present results indicate that a wide variety of unsaturated conjugated semidiones (**57**) are potentially



57

available. 1,4-Diketones spontaneously react with potassium *t*-butoxide in DMSO solution to form **57**,

(19) L. J. Chinn, *J. Org. Chem.*, **29**, 3304 (1964). Chinn calls attention to the need for a satisfactory technique to differentiate 13β,14α- and 13α,14α-17-keto steroids. With steroidal samples of 5–10 mg we have never encountered any ambiguities in such assignments by the esr–oxidation method.

$n = 1$. Under these conditions, the $\Delta^{2,3}$-1,4-diones also spontaneously form **57**. Such semidiones are apparently the major oxidation products to be expected from the oxidation in basic solution of α,β-unsaturated ketones containing a γ-methylene group. Examples of **57** in which the oxygen atoms are located in a 1,6, 1,8, 1,10, etc., arrangement ($n = 2, 3, 4$, etc.) can be readily imagined. Semidione **51** appears to represent such a 1,6-conjugated semidione.

Experimental Section[20]

The details given in a previous paper[3] under the headings of Materials and Formation and Detection of Radical Anions pertain also to the present paper. However, the basic dimethyl sulfoxide solutions of the cyclopentanones generally required much shorter times of exposure to air (3–5 sec) for generation of semidiones.

Bicyclo[3.1.0]hexan-3-one (**4**).—This ketone was prepared from Δ^3-cyclopentenol essentially as was described in the literature.[21]

cis-**Bicyclo[3.2.0]heptan-3-one** (**5**).—*cis*-1,2-Bis(carbethoxymethyl)cyclobutane[22] was cyclized by a procedure similar to that of Bloomfield and Fennessey.[23] To a solution of 6.12 g (0.027 mole) of the diester in 50 ml of DMSO was added under nitrogen 0.625 g (0.015 mole) of sodium hydride and 13 ml of of DMSO over a period of 30 min. The reaction mixture was heated to 90–96° for 15 min, poured into about 250 ml of ice–water, and extracted twice with ether. The aqueous phase was neutralized, 10 ml of concentrated sulfuric acid was added (diluted to about 50%), and the mixture was refluxed for 2 hr. Steam distillation followed by extraction with ether and evaporation of the ether furnished the desired ketone. It was purified by conversion into the semicarbazone and hydrolysis of the semicarbazone, mp 195–198° dec (lit.[24] mp 197–200° dec), after recrystallization from ethanol and water.

cis-**Hexahydroindan-2-one** (**8**).—*cis*-1,2-Bis(hydroxymethyl)-cyclohexane ditosylate[25] was cyclized to the corresponding enamino nitrile, mp 117–118°, by a known procedure (the period of heating with sodium hydride being 5 hr).[23] In a helium atmosphere, 8.8 g of the enamino nitrile was refluxed with a mixture of 38.7 ml of concentrated sulfuric acid, 313 ml of water, and 159 ml of glacial acetic acid for 1–2 hr. The reaction mixture was diluted with water and the desired ketone was isolated by steam distillation. The mass spectrum of its semicarbazone (mp 200–201°) showed a parent peak at m/e 195.

2-Bromocyclopentanone and **2-acetoxycyclopentanone** were prepared as described previosly.[6]

2-Hydroxycyclopentanone,[26] **16α-bromo-5α-androstan-17-one**,[27] **cyclopentane-1,3-dione**,[28] and **2-acetylcyclopentane-1,3-dione**[28] were obtained by known procedures.

7,11-Diketodihydrolanosteryl Acetate (**47**).—Commercial "lanosterol"[6] was acetylated with pyridine and acetic anhydride at 100° (2 hr), and the lanosteryl acetate was hydrogenated as described by Marker, *et al.*,[29] except that the hydrogenation proceeded smoothly at room temperature (absorption of hydrogen ceased within 30 min at an initial pressure of 32 psi) even though all of the starting material was not in solution. Oxidation of dihydrolanosteryl acetate to **47** was effected essentially as described in the literature.[30]

3β,7β,11α-Triacetoxy-4,4,14α-trimethyl-5α-androstan-17-one (**40a**).—7,11-Diketodihydrolanosteryl acetate (**47**) was reduced by zinc dust and glacial acetic acid[30] to the 8,9-dihydro derivative (7,11-diketolanostanyl acetate), mp 222.0–223.5°. Contrary to the literature,[30] which claims the formation of the same compound (mp 222–224°) by catalytic (platinum) reduction of **47** at 70°, followed by filtration of a solution of the reaction product in petroleum ether through alumina, we have found that catalytic reduction of **47** in glacial acetic acid (amounts as in the literature[30]) at room temperature with hydrogen at an initial pressure of 34 psi gives a different product, mp 207.0–208.2° (crystallized from methanol–chloroform), unchanged after filtration of a pentane–benzene solution through neutral alumina.

The 7,11-diketolanostanyl acetate (mp 222.0–223.5°) was reduced by sodium in 1-propanol to 3β,7β,11α-trihydroxylanostane, hemihydrate (from aqueous ethanol) mp 206.0–207.0°[31] (lit.[32] mp 207–208°). Acetylation with acetic anhydride and pyridine yielded the triacetate, mp 136.0–137.2° (from methanol) (lit.[32] mp 156°),[33] no hydroxyl group by infrared. The triacetoxylanostane was oxidized with chromic acid; **40a** was isolated as described by Barton, *et al.*[32] The mass spectrum of the product, mp 193.0–194.5° (lit.[32] 190–191°), exhibited a parent peak (M) at m/e 490. Principal peaks also occurred at m/e 430 (M − CH_3CO_2H), 370 (M − $2CH_3CO_2H$), 310 (M − $3CH_3CO_2H$), and 295 (M − $3CH_3CO_2H$ − CH_3).

16-Bromo-3β,7β,11α-triacetoxy-4,4,14α-trimethyl-5α-androstan-17-one (**40b**).—Compound **40a** (4.9 mg, 0.01 mmole) was dissolved in the minimum amount of a mixture of glacial acetic acid and ether (5:2, respectively, v/v) and allowed to react with 1.7 mg (1.05 molar proportion) of bromine and a trace of hydrogen bromide for 15 hr at room temperature in a stoppered test tube. The solution, which was still yellow, was evaporated to dryness under reduced pressure, and the residue was washed with cold pentane and dried. The mass spectrum of the crude bromo derivative thus obtained, mp 213–218°, had parent peaks of about equal intensity at m/e 570 and 568. The presence of a peak at m/e 490 indicated that the bromo compound was contaminated with its parent ketone (**40a**). The crude bromo derivative, however, was suitable for our esr experiments since only the bromo compound would give rise to radical anions upon treatment with an excess of potassium *t*-butoxide in DMSO in the absence of air.[8]

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(20) All melting points (capillary) are uncorrected.

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(31) Treatment of the compound (mp 207.0–208.2°) obtained by catalytic reduction of **47** with sodium and 1-propanol under the same conditions yielded a different product melting at 165.0–166.5° (from aqueous propanol).

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(33) The literature[32] melting point appears to be in error, particularly because no discrepancy was noted in the subsequent step.