Preparation of Some 7,7-Dimethyl-19-nor Steroids by Total Synthesis. Structure Determination by X-Ray Diffraction

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Application of the Torgov–Smith scheme for steroid total synthesis to 6-methoxy-3,3-dimethyl-1-tetralone, whose preparation is described, afforded 7,7-dimethylestradiol 3-methyl ether. This was converted to the 19-nortestosterone analog. X-Ray crystallographic analysis of the latter as the 17-(*p*-bromo)benzoate revealed the compound to have the 8α,14β configuration. An explanation is advanced to rationalize this finding.

In search for hormonal agents with increased potency, fewer side effects, and possible splits in activity, steroid analogs methylated in virtually every accessible position have been prepared.[1] Some such modifications, for example, the compounds methylated in the 6β[2] and 7α[3] positions, have in fact led to biologically interesting agents.

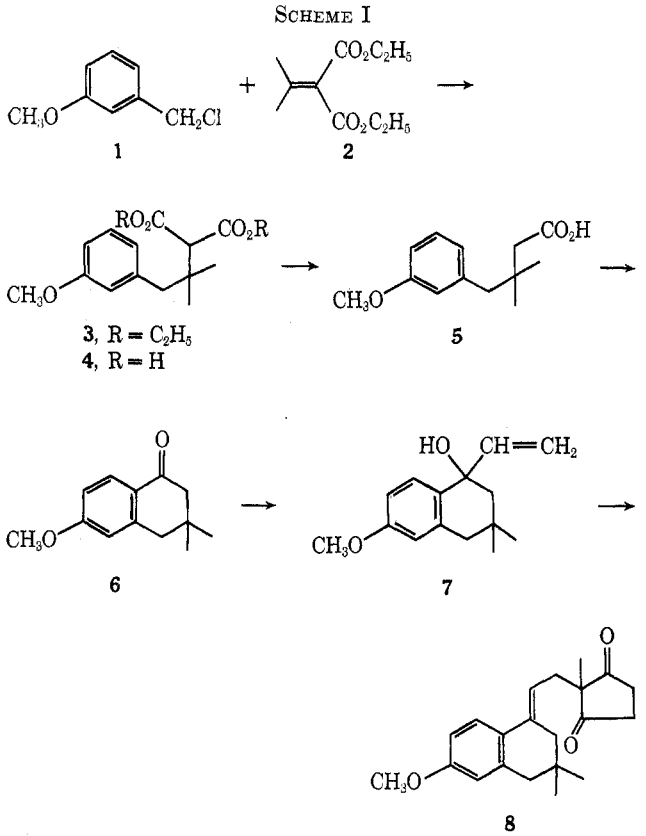
Due in part to difficulties in accessibility, many fewer geminally dimethylated compounds have been examined. The 4,4-dimethyl steroids, prepared by exhaustive methylation of conjugated 3-en-4-ones,[4] and the 7,7-dimethyl compounds prepared by the ingenious scheme of Julia[5] are the best studied examples in this series.

Since the 7α-methyl-19-nor steroids are some of the most potent known agents,[3] we wished to ascertain the effect of adding an additional methyl group in the 7β position of such a molecule. The previously employed scheme for the preparation of the corresponding 19-methyl counterpart[5] proceeds through the 3,5-cyclo steroids; since these are but difficulty accessible in the 19-nor series, we chose to approach our goal by total synthesis. In particular, we chose the versatile and relatively short Torgov–Smith synthesis.[6,7]

The key intermediate, tetralone (**6**), was obtained as shown in Scheme I. Conjugate addition of *m*-methoxybenzylmagnesium chloride to diethyl isopropylidenemalonate proceeded in an average yield of 55%. Neither inverse addition nor the presence of copper salt had any great influence on this yield. Saponification afforded the corresponding dicarboxylic acid. This last was decarboxylated and the oily product cyclized (phosphorus pentachloride–stannic chloride) without prior purification to give the desired bicyclic intermediate.

Reaction of **6** with the vinyl Grignard reagent gave the corresponding alcohol as an oil; attempts to purify this chromatographically led to extensive decomposition. Reaction of the crude alcohol with 2-methylcyclopentane-1,3-dione in the presence of a trace of base[8] completed the buildup of the carbon skeleton to afford **8**.

SCHEME I



Initial attempts at cyclization with *p*-toluenesulfonic acid in benzene gave only isomerization of the styrene double bond, **9**. It was necessary to resort to ethanolic hydrogen chloride to effect the ring closure. The exposure time to acid in this reaction proved critical; in our hands 10 min proved optimum. We further were not able to scale up this reaction beyond 5–10 g. It is of note, too, that the structure of the product represents a deviation from the Torgov scheme; whereas in the previous work there is present an extended conjugated system (**11**), in the dimethyl series, **10**, one double bond is conjugated with the aromatic ring while the other has moved into conjugation with the 17 ketone. This, as we will see, has some important stereochemical consequences.

Catalytic reduction followed by treatment of the product with sodium borohydride led cleanly to the 17 alcohol **13**. Attempted Birch reduction in the absence of added alcohol failed to go in this case, again in con-

(1) E. Tororomanoff, *Bull. Soc. Chim. Fr.*, 888 (1960); P. D. Klimstra and F. B. Colton in "Contraception: The Chemical Control of Fertility," D. Lednicer, Ed., Marcel Dekker, New York, N. Y., 1969.

(2) H. J. Ringold, E. Batres, and G. Rosencrantz, *J. Org. Chem.*, **22**, 99 (1957); G. Cooley, B. Ellis, D. N. Kirk, and V. Petrow, *J. Chem. Soc.*, 4112 (1957); J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes, and W. E. Dulin, *J. Amer. Chem. Soc.*, **80**, 2964 (1958).

(3) J. A. Campbell, S. C. Lyster, G. W. Duncan, and J. C. Babcock, *Steroids*, **1**, 317 (1963).

(4) See, for example, F. Gautschi and K. Bloch, *J. Biol. Chem.*, **233**, 1343 (1958).

(5) S. Julia, C. Neuville, and M. Davis, *Bull. Soc. Chim. Fr.*, 297 (1960).

(6) S. N. Ananchenko and I. V. Torgov, *Dokl. Akad. Nauk. SSSR*, **127**, 533 (1959).

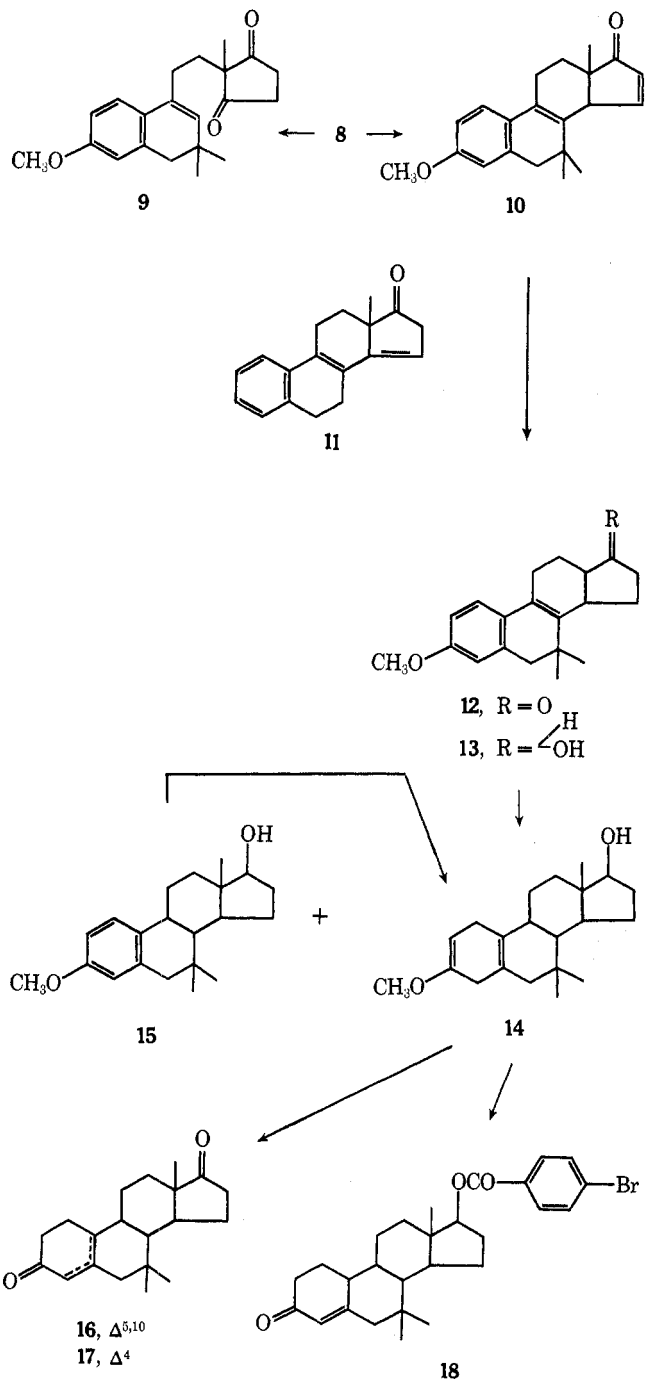
(7) G. A. Hughes and H. Smith, *Chem. Ind. (London)*, 1022 (1960).

(8) For an interesting discussion of the mechanism of this reaction, see C. H. Kuo, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **33**, 3126 (1968).

trast to previous work. Reaction in the presence of *tert*-butyl alcohol invariably produced mixtures of the aromatic compound **15** and the product of overreduction **14**. The former could be converted cleanly to the enol ether by reexposure to the conditions of the Birch reduction.

Hydrolysis of the enol ether proved very slow. Thus, exposure to mineral acid for 18 hr still gave a mixture of the conjugated and unconjugated enones. Since this mixture proved essentially inseparable, it was oxidized with Jones reagent to the diones. This could now be separated to afford **16** and **17** (Scheme II).

SCHEME II



The observed spontaneous shift of the double bond during cyclization casts some doubt on the stereochemistry at the 14 position. Though it is well known that

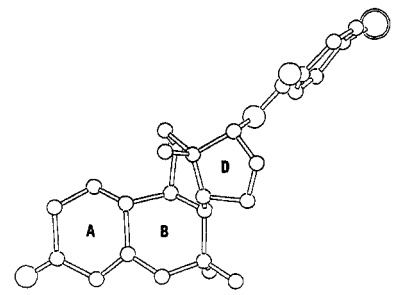


Figure 1.—Drawing, from X-ray results, of one of the symmetry independent molecules of **18**. Drawing is in projection down the *b* axis of the crystal.

perhydroindanes prefer the cis ring junction, molecular models of **10** suggest that the additional methyl groups at 7 may introduce new factors. We turned first to the nmr spectra of these compounds in an effort to clarify the stereochemistry. We had hoped to be able to assign the methyl resonance peaks to individual methyl groups and thus learn something of their environments. As Table I shows, however, these peaks fail to show the type of behavior, in going from compound to compound, to allow an *a priori* assignment.

TABLE I
NMR CHEMICAL SHIFTS OF METHYL GROUPS

Compd	Methyl group resonance, Hz		
8	56	56	70
9	58	58	68
10	63	70	70
12	58	58	67
13	51	55	62
14	53	62	62
15	57	59	59

Since these compounds are, further, too far removed from natural steroids for proof of structure by interconversion to a known compound, we resorted to X-ray diffraction for determination of stereochemistry. To this end, the enol ether **14** was first treated with 1 equiv of butyllithium. This was then followed by *p*-bromobenzoyl bromide and the product subjected to hydrolysis. Preparative tlc afforded a sample of **18** which on careful crystallization gave a single crystal suitable for the structural work.

X-Ray Diffraction Study.—A three-dimensional X-ray diffraction analysis was carried out using the heavy atom method to obtain a trial structure. Figure 1 shows the conformation and configuration of one of the two symmetry-independent molecules; the other molecule is identical in configuration and very similar in conformation. The configuration at both B–C and C–D ring fusions is cis; these are anti to each other, giving rise to a folding of the molecule at C ring fusions, as shown in Figure 1. The degree of folding may be estimated by calculating angles between the "best" planes through each of the rings in the steroid portion of the molecule. These calculations indicate that the C ring makes angles of about 60, 76, and 45° with A, B, and D rings, respectively. In contrast, the A–B, A–D, and B–D angles are about 16, 18, and 33° (Table II).

The B and C rings have chair conformation and the D ring has four atoms approximately planar and the fifth atom, carbon 17, about 0.5 Å out of this plane. In the A ring, constrained by the double bonds, five of

TABLE II
BOND ANGLES (IN DEGREES) AND STANDARD DEVIATIONS (IN PARENTHESES)

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
C(2)	C(1)	C(10)	108 (3)	C(2′)	C(1′)	C(10′)	112 (3)
C(1)	C(2)	C(3)	113 (4)	C(1′)	C(2′)	C(3′)	111 (3)
C(2)	C(3)	O(1)	117 (5)	C(2′)	C(3′)	O(1′)	128 (5)
C(2)	C(3)	C(4)	117 (4)	C(2′)	C(3′)	C(4′)	122 (4)
O(1)	C(3)	C(4)	125 (5)	O(1′)	C(3′)	C(4′)	108 (4)
C(3)	C(4)	C(5)	118 (4)	C(3′)	C(4′)	C(5′)	114 (4)
C(4)	C(5)	C(6)	114 (4)	C(4′)	C(5′)	C(6′)	125 (4)
C(4)	C(5)	C(10)	123 (4)	C(4′)	C(5′)	C(10′)	129 (4)
C(6)	C(5)	C(10)	122 (3)	C(6′)	C(5′)	C(10′)	107 (3)
C(5)	C(6)	C(7)	111 (3)	C(5′)	C(6′)	C(7′)	116 (3)
C(6)	C(7)	C(8)	108 (3)	C(6′)	C(7′)	C(8′)	112 (3)
C(6)	C(7)	C(19)	107 (3)	C(6′)	C(7′)	C(19′)	103 (3)
C(6)	C(7)	C(20)	111 (3)	C(6′)	C(7′)	C(20′)	111 (3)
C(8)	C(7)	C(19)	112 (3)	C(8′)	C(7′)	C(19′)	114 (3)
C(8)	C(7)	C(20)	108 (3)	C(8′)	C(7′)	C(20′)	111 (3)
C(19)	C(7)	C(20)	110 (3)	C(19′)	C(7′)	C(20′)	107 (3)
C(7)	C(8)	C(9)	107 (3)	C(7′)	C(8′)	C(9′)	105 (2)
C(7)	C(8)	C(14)	112 (3)	C(7′)	C(8′)	C(14′)	113 (3)
C(9)	C(8)	C(14)	114 (3)	C(9′)	C(8′)	C(14′)	116 (3)
C(8)	C(9)	C(10)	114 (3)	C(8′)	C(9′)	C(10′)	114 (2)
C(8)	C(9)	C(11)	105 (3)	C(8′)	C(9′)	C(11′)	107 (2)
C(10)	C(9)	C(11)	106 (3)	C(10′)	C(9′)	C(11′)	112 (3)
C(1)	C(10)	C(5)	113 (3)	C(1′)	C(10′)	C(5′)	106 (3)
C(1)	C(10)	C(9)	109 (3)	C(1′)	C(10′)	C(9′)	111 (3)
C(5)	C(10)	C(9)	100 (3)	C(5′)	C(10′)	C(9′)	114 (3)
C(9)	C(11)	C(12)	112 (3)	C(9′)	C(11′)	C(12′)	110 (2)
C(11)	C(12)	C(13)	110 (3)	C(11′)	C(12′)	C(13′)	105 (3)
C(12)	C(13)	C(14)	118 (3)	C(12′)	C(13′)	C(14′)	122 (3)
C(12)	C(13)	C(17)	117 (3)	C(12′)	C(13′)	C(17′)	116 (3)
C(12)	C(13)	C(18)	105 (3)	C(12′)	C(13′)	C(18′)	99 (3)
C(14)	C(13)	C(17)	108 (3)	C(14′)	C(13′)	C(17′)	106 (3)
C(14)	C(13)	C(18)	109 (3)	C(14′)	C(13′)	C(18′)	111 (3)
C(17)	C(13)	C(18)	99 (3)	C(17′)	C(13′)	C(18′)	101 (3)
C(8)	C(14)	C(13)	116 (3)	C(8′)	C(14′)	C(13′)	112 (3)
C(8)	C(14)	C(15)	112 (3)	C(8′)	C(14′)	C(15′)	111 (3)
C(13)	C(14)	C(15)	103 (3)	C(13′)	C(14′)	C(15′)	100 (3)
C(14)	C(15)	C(16)	110 (3)	C(14′)	C(15′)	C(16′)	112 (3)
C(15)	C(16)	C(17)	106 (3)	C(15′)	C(16′)	C(17′)	101 (3)
C(13)	C(17)	C(16)	104 (3)	C(13′)	C(17′)	C(16′)	109 (3)
C(13)	C(17)	O(2)	101 (3)	C(13′)	C(17′)	O(2′)	102 (3)
C(16)	C(17)	O(2)	113 (3)	C(16′)	C(17′)	O(2′)	109 (3)
C(17)	O(2)	C(21)	109 (3)	C(17′)	O(2′)	C(21′)	112 (3)
O(2)	C(21)	O(3)	124 (4)	O(2′)	C(21′)	O(3′)	125 (4)
O(2)	C(21)	C(22)	107 (3)	O(2′)	C(21′)	C(22′)	108 (3)
O(3)	C(21)	C(22)	128 (4)	O(3′)	C(21′)	C(22′)	127 (4)
C(21)	C(22)	C(23)	109 (3)	C(21′)	C(22′)	C(23′)	104 (3)
C(21)	C(22)	C(27)	128 (3)	C(21′)	C(22′)	C(27′)	127 (3)
C(23)	C(22)	C(27)	123 (3)	C(23′)	C(22′)	C(27′)	130 (3)
C(22)	C(23)	C(24)	115 (3)	C(22′)	C(23′)	C(24′)	103 (3)
C(23)	C(24)	C(25)	119 (3)	C(23′)	C(24′)	C(25′)	126 (3)
Br(1)	C(25)	C(24)	114 (3)	Br(2)	C(25′)	C(24′)	116 (3)
Br(1)	C(25)	C(26)	122 (3)	Br(2)	C(25′)	C(26′)	123 (3)
C(24)	C(25)	C(26)	121 (3)	C(24′)	C(25′)	C(26′)	121 (4)
C(25)	C(26)	C(27)	121 (3)	C(25′)	C(26′)	C(27′)	118 (3)
C(22)	C(27)	C(26)	119 (3)	C(22′)	C(27′)	C(26′)	121 (3)

the ring atoms are roughly in a plane and carbon 1 is about 0.7 Å out of this plane.

Even considering the rather high standard deviations in this structure determination, there is little doubt that O(1) is a carbonyl oxygen and that there is also a double bond between C(4) and C(5). Bond lengths (Table III) were observed to be 1.22 and 1.24 Å between C(3) and O(1) in the two molecules and 1.39 and 1.40 Å between C(4) and C(5). In addition, plane calculations (Table IV) show that within experimental error the appropriate area is planar in each molecule.

Discussion

In its many applications to date, the Torgov–Smith scheme for the total synthesis of steroids has been notable for the degree of stereochemical control; products with unnatural configuration, if present, are usually by-products.[9] The present deviation from that stereochemistry thus deserves some comment.

In the usual course of events, the product of cyclization of ring C gives a conjugated diene **11**, in which

(9) T. B. Windholz, R. D. Brown, and A. A. Patchett, *Steroids*, **6**, 409 (1965).

TABLE III
BOND LENGTHS (Å) AND STANDARD DEVIATIONS (IN PARENTHESES)

Atom	Atom	Distance	Atom	Atom	Distance
Br(2)	C(25′)	1.89 (0.04)	Br(1)	C(25)	1.85 (0.03)
C(1′)	C(2′)	1.54 (0.05)	C(1)	C(2)	1.49 (0.06)
C(1′)	C(10′)	1.56 (0.05)	C(1)	C(10)	1.55 (0.06)
C(2′)	C(3′)	1.49 (0.06)	C(2)	C(3)	1.68 (0.07)
C(3′)	O(1′)	1.22 (0.05)	C(3)	O(1)	1.21 (0.06)
C(3′)	C(4′)	1.47 (0.07)	C(3)	C(4)	1.52 (0.07)
C(4′)	C(5′)	1.39 (0.05)	C(4)	C(5)	1.40 (0.05)
C(5′)	C(6′)	1.72 (0.05)	C(5)	C(6)	1.48 (0.05)
C(5′)	C(10′)	1.63 (0.05)	C(5)	C(10)	1.66 (0.05)
C(6′)	C(7′)	1.52 (0.05)	C(6)	C(7)	1.54 (0.05)
C(7′)	C(8′)	1.53 (0.04)	C(7)	C(8)	1.66 (0.04)
C(7′)	C(19′)	1.55 (0.05)	C(7)	C(19)	1.48 (0.05)
C(7′)	C(20′)	1.72 (0.05)	C(7)	C(20)	1.58 (0.05)
C(8′)	C(9′)	1.57 (0.04)	C(8)	C(9)	1.51 (0.05)
C(8′)	C(14′)	1.49 (0.04)	C(8)	C(14)	1.62 (0.04)
C(9′)	C(10′)	1.54 (0.05)	C(9)	C(10)	1.60 (0.05)
C(9′)	C(11′)	1.55 (0.04)	C(9)	C(11)	1.53 (0.04)
C(11′)	C(12′)	1.71 (0.04)	C(11)	C(12)	1.57 (0.04)
C(12′)	C(13′)	1.64 (0.05)	C(12)	C(13)	1.64 (0.05)
C(13′)	C(14′)	1.64 (0.05)	C(13)	C(14)	1.44 (0.05)
C(13′)	C(17′)	1.56 (0.05)	C(13)	C(17)	1.63 (0.05)
C(13′)	C(18′)	1.59 (0.05)	C(13)	C(18)	1.68 (0.05)
C(14′)	C(15′)	1.52 (0.05)	C(14)	C(15)	1.62 (0.05)
C(15′)	C(16′)	1.63 (0.05)	C(15)	C(16)	1.46 (0.04)
C(16′)	C(17′)	1.43 (0.05)	C(16)	C(17)	1.46 (0.05)
C(17′)	O(2′)	1.53 (0.04)	C(17)	O(2)	1.61 (0.04)
O(2′)	C(21′)	1.43 (0.04)	O(2)	C(21)	1.39 (0.04)
C(21′)	O(3′)	1.17 (0.04)	C(21)	O(3)	1.12 (0.05)
C(21′)	C(22′)	1.60 (0.05)	C(21)	C(22)	1.54 (0.05)
C(22′)	C(23′)	1.51 (0.05)	C(22)	C(23)	1.49 (0.05)
C(22′)	C(27′)	1.41 (0.05)	C(22)	C(27)	1.38 (0.05)
C(23′)	C(24′)	1.44 (0.05)	C(23)	C(24)	1.48 (0.05)
C(24′)	C(25′)	1.51 (0.05)	C(24)	C(25)	1.39 (0.05)
C(25′)	C(26′)	1.34 (0.05)	C(25)	C(26)	1.43 (0.05)
C(26′)	C(27′)	1.33 (0.05)	C(26)	C(27)	1.38 (0.05)

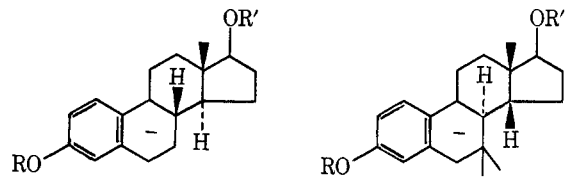
TABLE IV
DEVIATIONS (Å) FROM LEAST-SQUARES PLANES THROUGH THE CONJUGATED DOUBLE BONDS PORTION OF THE MOLECULE[a]

	Molecule 1		Molecule 2	
	C(2)	0.10	C(2′)	0.10
	C(3)	−0.03	C(3′)	−0.09
	O(1)	0.03	O(1′)	0.04
	C(4)	−0.11	C(4′)	−0.05
	C(5)	−0.06	C(5′)	−0.02
	C(6)	0.13	C(6′)	0.08
	C(10)	−0.07	C(10′)	−0.07
cos (*a*)	0.200		0.222	
cos (*b*)	0.927		−0.929	
cos (*c*)	−0.317		0.295	
d_{origin}	1.83 Å		4.17 Å	

[a] Direction cosines are with respect to the real cell axes.

C-14 is trigonal. Molecular models reveal that in the present series such a structure involves considerable interaction between the geminal dimethyl groups at 7 and the proton at C-15. The shift of the double bond to 15 relieves this strain by introducing a "fold" at the C–D ring junction. Since both double bonds of the new system 10 are conjugated, little of the delocalizing energy present in **11** is lost. It is apparent too that the normal preference for cis five–six ring fusions asserts itself. It is not, however, at present clear why the borohydride reduction of the 17 ketone goes so cleanly to the α alcohol.

The stereochemistry of the Birch reduction of enones has been clearly delineated.[10] Though considerable work has been carried out on the steric course of the reduction of styrenoid systems,[11] this reaction is not nearly as well understood. Precedent suggests, however, that the predominant product will be that derived from entry of the first proton trans to that present at the proximate saturated carbon atom. In the normal course of events this affords an intermediate such as i. In the present series this proton will add instead from the α side to give the intermediate ii; this accounts for the observed configuration at C-8, in our final product.



i ii

It was proposed some time ago that the direction of addition of the second proton is controlled by kinetic rather than thermodynamic factors.[12] That is, the proton will add from the less hindered side. In the case of intermediate i, this leads to the observed 9α product, an interesting case where the kinetic and thermodynamic predictions coincide. In the 7,7-dimethyl series, however, the less hindered side of the molecule is also the α side; in this case, however, the product of kinetic addition will be the less stable cis B–C ring fusion. Again, this accords with the observed stereochemistry.

In sum then, the fact that C-14 assumed the β configuration at an early stage in the synthesis caused three additional chiral centers to go awry. This finding points up the key importance of the circumstance that the Torgov–Smith scheme leads initially to a trigonal center at C-14; the subsequent catalytic reduction allows the introduction of a proton at 14α, which in turn leads to the natural configuration for the remaining centers.

Experimental Section[13]

Synthesis. Diethyl (*m*-Methoxy-α,α-dimethylphenethyl)malonate (3).—A solution of 13.3 g (0.085 mol) of *m*-methoxybenzyl chloride in 100 ml of ether was added dropwise for 1.5 hr to 2.10 g (0.088 g-atom) of magnesium. The mixture was cooled in ice and treated with 12.0 g of diethyl isopropylidenemalonate[14] in 100 ml of ether. Following 16 hr standing at room temperature, the mixture was cooled in ice and treated with 50 ml of 2.5 *N* hydrochloric acid. The organic layer was washed with water and brine and taken to dryness. The residual oil was distilled at 0.55 mm to give, after some forerun, 14.35 g (52.5%) of the ester, bp 154–163°, largely 161–163°.

(*m*-Methoxy-α,α-dimethylphenethyl)malonic Acid (4).—A solution of 14.14 g (0.044 mol) of the ester and 30 ml of 50% sodium hydroxide in 170 ml of methanol was heated at reflux overnight. The bulk of the solvent was removed *in vacuo* and the residue dissolved in water. The solution was washed with ether and

(10) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **86**, 1761 (1964).

(11) See, for example, P. W. Rabideau and R. G. Harvey, *J. Org. Chem.*, **35**, 25 (1970); U. R. Ghatak, N. R. Chatterjee, A. K. Banerjee, J. Chakravarty, and R. E. Moore, *J. Org. Chem.*, **34**, 3739 (1969), and references therein.

(12) H. E. Zimmerman, *J. Amer. Chem. Soc.*, **78**, 1168 (1956).

(13) All melting points are uncorrected and reported as obtained on a Thomas-Hoover capillary melting point apparatus. Nmr spectra obtained in deuteriochloroform on a Varian A-60A spectrometer. The authors are indebted to the Department of Physical and Analytical Chemistry of The Upjohn Co. for elemental and spectral determinations.

(14) A. C. Cope and E. M. Hancock, *J. Amer. Chem. Soc.*, **60**, 2644 (1930).

then acidified. The precipitated oil was extracted with ether, and this solution washed with brine and taken to dryness. The residue was recrystallized from ether–carbon tetrachloride to afford 7.70 g (66%) of acid, mp 127–132°.

The analytical sample from an earlier run melted at 132–135°; nmr complex aromatic region (4 H) and 2 exchangeable H, singlets at δ 3.8 (3 H), 3.3 (1 H), 2.9 (2 H), 1.15 (6 H). *Anal.* Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81; neut equiv, 266, 133. Found: C, 62.97; H, 6.87; neut equiv, 278, 139.

3,4-Dihydro-6-methoxy-3,3-dimethyl-1(2*H*)-naphthalenone (6).—The malonic acid (9.22 g, 0.034 mol) was heated in a flask immersed in an oil bath at 175–180° until effervescence had completely stopped (40 min). The monoacid was obtained as 7.46 g of viscous oil: nmr complex region δ 6.6–7.4 (4 H), singlets at δ 3.8 (3 H), 2.68 (2 H), 2.25 (2 H), 1.08 (6 H).

Phosphorus pentachloride (7.05 g, 0.034 mol) was added to a solution of the decarboxylation product in 100 ml of benzene. The mixture was heated at reflux for 1 hr and then cooled in ice. Stannic chloride (8.75 g, 0.034-mol) was added and the dark solution stirred under reflux for 1.5 hr. The mixture was cooled in ice and treated with 50 ml of 2.5 *N* hydrochloric acid. The organic layer was separated, washed with water and brine, and taken to dryness. The residue was chromatographed over 700 ml of Florisil[15] (elution with 2% acetone, Skellysolve B).[16] The crystalline fractions were combined and recrystallized from Skellysolve B to give 4.96 g (71.5%) of solid, mp 40–42°. *Anal.* Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.39; H, 7.98.

1,2,3,4-Tetrahydro-6-methoxy-3,3-dimethyl-1-vinyl-1-naphthol (7).—A solution of 12.89 g (0.064 mol) of the tetralone in 120 ml of THF was added to the Grignard reagent prepared from 24 ml of vinyl bromide and 6.3 g of magnesium in 160 ml of THF. Following 16 hr standing at room temperature the reaction mixture was treated with 100 ml of saturared ammonium chloride and the product isolated in the usual way. The resulting oil still showed a sizable CO band (1680 cm^{-1}) in the ir. The oil was again treated with the same quantity of vinyl magnesium bromide as above. The crude carbinol was obtained as a viscous oil.

3-Methoxy-7,7-dimethyl-8,14-secoestra-1,3,5(10),9(11)-tetraene-14,17-dione (8).—A mixture of 18.39 g (0.079 mol) of the crude vinylcarbinol, 7.05 g (0.063 mol) of 2-methylcyclopentane-1,3-dione, and 0.6 g of potassium hydroxide in 250 ml of methanol was heated at reflux for 4 hr. The bulk of the solvent was removed *in vacuo* and the residue dissolved in ether and 100 ml of 1 *N* sodium hydroxide. The organic layer was washed in turn with two further portions of 100 ml of 1 *N* sodium hydroxide, water, and brine. The solid which was obtained when the solution was taken to dryness was chromatographed over 2 l. of Florisil (elution with 3% acetone in Skellysolve B). There was obtained 15.12 g (59%) of the diketone, mp 79–82.5°.

The analytical sample (obtained from petroleum ether, bp 30–60°) melted at 83–86°. The nmr is in good agreement with the structure. *Anal.* Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.02; H, 8.06.

***dl*-3-Methoxy-7-7-dimethyl-8,14-secoestra-1,3,5(10),8-tetraene-14,17-dione (9).**—A solution of 0.50 g (1.5 mmol) of the diketone **8** and 10 mg of *p*-toluenesulfonic acid in 50 ml of benzene was heated at reflux for 6 hr. The solution was allowed to cool, diluted with ether, and washed with sodium bicarbonate and brine. The solid which remained when the solution was taken to dryness was recrystallized several times from petroleum ether to give crystals: mp 76–79°; mmp (with starting material) 69–80°; nmr broad singlet at δ 5.36, complex A_2B_2 centered at δ 2. *Anal.* Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.47; H, 8.28.

***dl*-3-Methoxy-7,7-dimethyl-14β-estra-1,3,5(10),8,15-pentaen-17-one (10).**—The powdered dione (2.50 g, 7.7 mmol) was quickly added to 50 ml of well-stirred ice-cold 8.5 *N* hydrogen chloride in ethanol. At the end of 10 min the dark solution was poured into saturated sodium bicarbonate. The precipitate was taken up in ether, washed with water and brine, and taken to dryness. The residual slightly gummy solid was recrystallized from Skellysolve B to afford 1.54 g (65%) of the tetracyclic ketone, mp 144–147°. Further recrystallization gave a sample of the steroid: mp 146–148°; nmr complex aromatic region (3 H) doublet of doublets at δ 7.6 and 6.1 (2 H), singlet at 3.8 (3 H), broad band centered at 3.45 (1 H), singlet at 3.2 (2 H), broad multiplet 2.6–1.5 (4 H), singlet at 1.25 (6 H), singlet at 1.10 (3 H). *Anal.* Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.61; H, 8.07.

***dl*-3-Methoxy-7,7-dimethyl-14β-estra-1,3,5(10),8-tetraen-17-one (12).**—A mixture of 1.65 g (5.4 mmol) of the pentaene and 0.20 g of 10% palladium on charcoal in 200 ml of benzene was shaken under an atmosphere of hydrogen until the uptake of gas stopped (35 min). The catalyst was collected on a filter and the solution taken to dryness. The residual solid was recrystallized from aqueous methanol to give 1.40 g (85%) of product, mp 98–105°.

The analytical sample from an earlier run melted at 104–106°. *Anal.* Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 80.85; H, 8.47.

***dl*-3-Methoxy-7,7-dimethyl-14β-estra-1,3,5(10),8-tetraen-17α-ol (13).**—To a solution of 1.40 g (4.5 mmol) of the ketone in 60 ml of methanol there was added 0.40 g of sodium borohydride. The mixture was stirred at room temperature for 4 hr and the bulk of the solvent removed *in vacuo*. The residue was dissolved in ether and water and the organic layer washed with water and brine. The solid which remained when the solution was taken to dryness was recrystallized from Skellysolve B to afford 1.33 g (95%) of crystals, mp 126.5–128.5°. *Anal.* Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.59; H, 9.21.

***dl*-3-Methoxy-7,7-dimethyl-8α,14β-estra-1,3,5(10)-trien-17α-ol (15). and *dl*-3-Methoxy-7,7-dimethyl-8α,14β-estra-2,5(10)-dien-17α-ol (14).**—Liquid ammonia (60 ml) was distilled from over sodium into a well-stirred solution of 0.50 g (1.6 mmol) of the tetraene in 1 ml of *tert*-butyl alcohol in 30 ml of THF. Approximately one-third of a 50-mg (7.4 mmol) portion of lithium was then added. The remaining metal was added as soon as the color had faded. At the end of 30 min, 1 g of ammonium chloride was added to the mixture. The solvent was evaporated under a stream of nitrogen and the residue dissolved in ether and water. The organic layer was washed with water and brine and taken to dryness. The residual gum was carefully chromatographed on 50 ml of silica gel (elution with 10% acetone in Skellysolve B) to afford first the enol ether as crystals followed by the triene as a series of gums which crystallized on trituration with cyclohexane.

The former (125 mg, 24.8%) was recrystallized from aqueous methanol to mp 117–118°. *Anal.* Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.05; H, 10.11.

The second fraction was recrystallized from cyclohexane to give 0.25 g (49%) of the triene as its cyclohexane solvate (confirmed by nmr), mp 75–85°. *Anal.* Calcd for $C_{21}H_{30}O_2 \cdot C_6H_{12}$: C, 81.35; H, 10.65. Found: C, 81.26; H, 10.73.)

Reduction of 14 to 15.—Proceeding exactly as above a solution of 5.30 g (0.017 mol) of the triene and 10 ml of *tert*-butyl alcohol in 300 ml of THF and 600 ml of liquid ammonia was treated with 0.77 g (0.11 g-atom) of lithium. Following 1.5 hr of stirring the product was worked up as previously. The crude product was chromatographed (silica gel, 5% acetone in Skellysolve B) and then recrystallized to afford 2.67 g (50%) of enol ether, mp 118–120°, identical with that obtained above.

***dl*-7,7-Dimethyl-8α,14β-estr-4-ene-3,17-dione (17) and *dl*-7,7-Dimethyl-8α,14β-estr-5(10)-ene-3,17-dione (16).**—A solution of 2.10 g of the enol ether and 20 ml of 2.5 *N* hydrochloric acid in 60 ml of methanol was allowed to stand at room temperature overnight. The mixture was worked up in the usual way to afford the testosterones as a gum. An ice-cooled, well-stirred solution of the gum in 80 ml of acetone was treated dropwise with 4.2 ml of Jones reagent. The mixture was concentrated on the rotary evaporator and the residue dissolved in ether and water. The organic layer was washed with water and brine and taken to dryness. The residual gum was carefully chromatographed on 200 ml of silica gel (elution with 10% acetone in Skellysolve B) to give first 0.23 g (11%) of crystalline unconjugated ketone followed by 1.13 g (57%) of the conjugated enone. The former was recrystallized from petroleum ether (cooling in freezer) to mp 87.5–89.5°, ν_{max} 1745, 1710 cm^{-1}. *Anal.* Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.95; H, 9.46.

The second fraction was recrystallized from ether–Skellysolve B to give 0.93 g of crystals: mp 145–148°; ν_{max} 1745, 1660, 1610 cm^{-1}; λ_{max} 242 nm (ε 17,340). *Anal.* Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.37; H, 9.47.

17α-Hydroxy-7,7-dimethyl-8α,14β-estr-4-en-3-one *p*-Bromobenzoate (18).—Butyllithium in pentane (1.1 ml of 1.55 *N*) was added to 500 mg (1.6 mmol) of the steroid alcohol in 10 ml

(15) A synthetic magnesia–silica gel absorbent manufactured by the Floridin Co., Warren, Pa.

(16) A petroleum fraction, bp 60–70°, sold by the Skelly Oil Co.

TABLE V

FINAL POSITIONAL AND THERMAL PARAMETERS AND THEIR STANDARD DEVIATIONS (IN PARENTHESES)[a]

Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Br(1)	−10320 (16)	−7607 (58)	50000 (0)	264 (9)	3146 (110)	499 (18)	−316 (63)	33 (29)	46 (98)
Br(2)	−19938 (16)	64874 (58)	57163 (34)	311 (10)	3136 (111)	580 (21)	308 (68)	−240 (29)	176 (105)

Atom	x	y	z	B	Atom	x	y	z	B
O(1)	3487 (10)	2063 (36)	2293 (15)	10.84 (0.94)	O(1′)	2367 (11)	3700 (38)	8337 (14)	9.72 (0.89)
O(2)	579 (9)	5289 (30)	4094 (12)	7.04 (0.71)	O(2′)	−536 (9)	139 (28)	6772 (12)	6.50 (0.68)
O(3)	−53 (9)	6930 (36)	4252 (14)	8.82 (0.78)	O(3′)	−1249 (8)	−1328 (33)	6758 (13)	7.31 (0.72)
C(1)	2192 (15)	2349 (55)	2518 (22)	8.59 (1.26)	C(1′)	1074 (12)	3340 (43)	8191 (17)	4.88 (0.91)
C(2)	2629 (16)	2683 (52)	2153 (22)	8.77 (1.29)	C(2′)	1535 (13)	3093 (41)	8562 (18)	5.32 (0.98)
C(3)	3131 (19)	2510 (59)	2563 (26)	10.90 (1.45)	C(3′)	1962 (18)	3377 (60)	8172 (26)	9.70 (1.30)
C(4)	3113 (14)	3055 (49)	3227 (22)	7.22 (1.14)	C(4′)	1986 (15)	2780 (48)	7536 (21)	6.95 (1.14)
C(5)	2682 (14)	3675 (47)	3452 (20)	5.94 (1.02)	C(5′)	1560 (15)	2162 (47)	7308 (20)	6.99 (1.16)
C(6)	2715 (11)	4493 (43)	4060 (19)	4.47 (0.89)	C(6′)	1488 (13)	1327 (45)	6586 (19)	6.61 (1.06)
C(7)	2321 (12)	3829 (42)	4488 (19)	4.47 (0.92)	C(7′)	1035 (13)	1821 (43)	6255 (19)	6.04 (0.99)
C(8)	1806 (11)	4063 (43)	4133 (18)	5.35 (0.95)	C(8′)	593 (10)	1385 (40)	6628 (15)	3.53 (0.82)
C(9)	1823 (11)	2979 (40)	3564 (17)	4.40 (0.96)	C(9′)	627 (10)	2541 (35)	7214 (16)	2.92 (0.78)
C(10)	2183 (12)	3656 (47)	3052 (18)	5.38 (0.98)	C(10′)	1045 (14)	2088 (44)	7640 (18)	5.76 (0.99)
C(11)	1325 (12)	3112 (45)	3289 (18)	5.63 (1.03)	C(11′)	144 (12)	2429 (44)	7548 (16)	5.38 (1.02)
C(12)	1222 (11)	4946 (44)	3033 (17)	5.09 (1.03)	C(12′)	74 (11)	430 (40)	7853 (17)	3.97 (0.84)
C(13)	1309 (12)	6382 (47)	3569 (18)	5.15 (0.96)	C(13′)	156 (12)	−903 (47)	7283 (20)	6.69 (1.04)
C(14)	1674 (11)	6056 (45)	4014 (18)	5.83 (1.01)	C(14′)	537 (11)	−491 (42)	6735 (18)	4.81 (0.93)
C(15)	1469 (12)	6989 (39)	4618 (16)	4.63 (0.95)	C(15′)	292 (13)	−1363 (51)	6201 (20)	7.93 (1.15)
C(16)	1034 (13)	7918 (42)	4466 (17)	5.85 (0.98)	C(16′)	−169 (13)	−2463 (44)	6419 (19)	6.38 (1.09)
C(17)	839 (12)	7059 (50)	3933 (18)	7.57 (1.22)	C(17′)	−301 (13)	−1545 (50)	6959 (21)	7.79 (1.13)
C(18)	1440 (12)	8188 (43)	3189 (17)	5.63 (1.00)	C(18′)	305 (14)	−2565 (50)	7657 (20)	7.61 (1.17)
C(19)	2344 (11)	4859 (39)	5054 (21)	5.74 (0.97)	C(19′)	1075 (12)	802 (42)	5651 (18)	6.63 (0.99)
C(20)	2390 (13)	1869 (48)	4639 (18)	7.03 (1.17)	C(20′)	1040 (16)	3957 (60)	6063 (22)	12.75 (1.54)
C(21)	109 (15)	5621 (57)	4243 (21)	7.50 (1.12)	C(21′)	−1037 (15)	−59 (51)	6681 (19)	6.50 (1.07)
C(22)	−120 (13)	3899 (47)	4416 (17)	4.76 (0.92)	C(22′)	−1242 (13)	1746 (52)	6466 (18)	5.49 (1.00)
C(23)	−624 (15)	4200 (51)	4590 (19)	7.69 (1.18)	C(23′)	−1770 (12)	1437 (51)	6407 (18)	6.17 (1.02)
C(24)	−887 (13)	2642 (55)	4779 (18)	7.45 (1.21)	C(24′)	−1950 (13)	3095 (50)	6234 (18)	6.41 (1.07)
C(25)	−672 (13)	1046 (46)	4716 (16)	5.21 (1.01)	C(25′)	−1657 (15)	4639 (52)	6063 (20)	7.66 (1.20)
C(26)	−171 (13)	904 (46)	4609 (17)	5.79 (1.03)	C(26′)	−1189 (12)	4681 (46)	6165 (17)	4.60 (0.97)
C(27)	95 (12)	2310 (51)	4452 (18)	5.80 (1.05)	C(27′)	−976 (12)	3238 (51)	6341 (18)	5.45 (0.94)

[a] Coordinates and anisotropic temperature factors of Br atoms are multiplied by 10^5. Coordinates of C and O atoms are multiplied by 10^4. The z coordinate of Br(1) was held fixed because of the polar space group.

of benzene, followed by 370 mg of *p*-bromobenzoyl chloride. After 48 hr the mixture was poured into ether and aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, and taken to dryness. The residue was chromatographed on two 25-g silica gel plates (development with methylene chloride). The less polar zone was scraped off and eluted to give 0.43 g of crude acylated enol ether. A solution of that gum and 3.3 ml of 2.5 *N* hydrochloric acid in 10 ml of THF was allowed to stand for 2 days. The solvent was removed *in vacuo* and the residue taken up in ether. This last solution was washed with water and brine and taken to dryness. The residue was chromatogaphed on two preparative silica gel plates (20% acetone in Skellysolve B). The major zone was collected as above. The resulting solid was recrystallized twice from ether–Skellysolve B to yield 200 mg (26%) of product, mp 118.5–120°. *Anal.* Calcd for $C_{27}H_{33}BrO_3$: C, 66.80; H, 6.85; mol wt, 484. Found: C, 66.68; H, 7.17; mol wt, 484, 486.

X-Ray Analyis of 18. A. Crystal data: orthorhombic; space group $Pna2_1$; $a = 28.28 \pm 0.04$, $b = 7.84 \pm 0.02$, $c = 22.00 \pm 0.03$ Å, $Z = 8$, $V = 4880 \pm 14$ Å^3, $\rho_{calcd} = 1.319$ g/cc. The crystals are small, clear plates. Weissenberg and precession photographs showed that the crystals are orthorhombic, with systematic absences in the $0kl$ plane for $k + l = 2n + 1$, and in the $h0l$ plane for h odd. Possible space groups were therefore limited to $Pna2_1$, which is acentric, with a multiplicity of 4, and (with axes permuted), $Pnma$, which is centric and has a multiplicity of 8. Unit cell volume and molecular weight indicated 8 molecules in the unit cell.

Three-dimensional intensity data were gathered on the UPACS computerized diffractometer system (a General Electric diffractometer with an Electronics and Alloys full-circle orienter, Datex automated, controlled by an IBM 1800 computer). The crystal orientation was determined by the computer before the data collection. Nickel-filtered Cu K radiation was used. The θ–2θ scan technique was employed with 3.6° scans at 2°/min and with 30-sec background observations at each end of the scan. Four reflections were monitored periodically during the data collection. By the end of the data collection, check reflections had lost 25% of their original intensity. A correction for decay was made by using check intensities to fit a deterioration scale scale factor as a polynomial function of time.

For weighting purposes, $\sigma(I)$ for each reflection was approximated by

$$\sigma(I) = [\sigma^2(I)_{\substack{\text{counting}\\\text{statistics}}} + (dI)^2]^{1/2}$$

where d (= 0.0288) was estimated by the data reduction program from check reflection variation (after deterioration correction). The usual adjustments were made on the data: Lorentz and polarization corrections; absorption correction[17] (transmissions ranged from 68 to 91%); and Wilson scaling to place the data on an approximate absolute scale. Standard propagation of error methods were used to carry standard deviations through all these calculations.

Crystal quality was not good enough to obtain data at high 2θ values. Intensities of almost all reflections with a 2θ angle greater than 90° were less than three times their standard deviations; accordingly, 90° was used as a cut-off point for the data. The data were edited by deletion of all reflections with intensities less than twice their standard deviations. The final data set contained only 1176 reflections.

B. Trial Solution.—A trial solution for the bromine position was found by Patterson analysis, postulating space group $Pna2_1$ with 2 symmetry-independent molecules in the unit cell. Most of one molecule was obvious in the first electron density map when reflections were phased according to contributions from the two bromines only. Two more structure-factor and electron-density calculations were needed to get starting coordinates for all the atoms.

C. Refinement.—Coordinates were refined using multiple-matrix least squares; the function minimized was $\Sigma w[|F_o|^2 - |F_c|^2]^2$.

The weighting function used at first was the Hughes $1/F_o$ type.

(17) W. R. Busing and H. A. Levy, *Acta Crystallogr.*, **10**, 180 (1957).

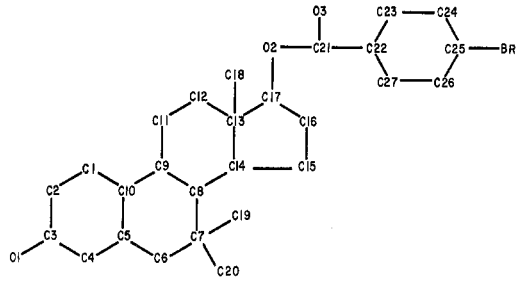


Figure 2.—Numbering.

After several cycles of refinement, w was set equal to the reciprocal of $\sigma^2(F_0^2)$ which was estimated during data reduction.

Because of the size (62 symmetry-independent atoms), the 259 refinable parameters were split into several matrices. All temperature factors were in one matrix together with the scale factor for F_0. Since a strong pseudosymmetric relation between the two molecules was noted, the coordinate matrix scheme was designed to put like parts of the molecules together in three different matrices. Anisotropic temperature factors for the bromine atoms were refined, but the data were judged not suitable for determination of anisotropic temperature factors on carbon and oxygen atoms or for determination of hydrogen atom coordinates. The addition of these parameters would have brought the total number of refinable parameters to 638, too many to determine with only 1176 observations. Refinement was terminated when all shifts were less than $^1/_4$ of corresponding standard deviations. The final value of the R index ($R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$) was 0.111; the standard deviation of fit, $[(\Sigma w[|F_o|^2 - |F_c|^2]^2)]^{1/2}/(m - s)^{1/2}$, was 2.29

Final parameters are given in Table V for both symmetry independent molecules.[18] The numbering scheme is shown in Figure 2. Numbering follows the convention for steroids as far as possible; C(1) through C(18) have conventional numbering. The remainder of the atoms are numbered C(19)–C(27) and O(1)–O(3). Bond distances and angles are given in Tables II and III.

All calculations were carried out on IBM 360/30 and IBM 360/50 computers using the programs of the CRYM crystallographic system developed by one of the authors (D. J. D.). Atomic form factors are from "International Tables for X-Ray Crystallography."[19]

Registry No.—**3,** 25380-93-2; **4,** 25380-94-3; **5,** 25380-95-4; **6,** 25380-96-5; **7,** 25380-97-6; **8,** 25380-98-7; **9,** 31020-45-8; **10,** 31025-03-3; **12,** 31025-04-4; **13,** 31025-05-5; **14,** 31025-06-6; **15,** 31025-07-7; **16,** 31025-08-8; **17,** 31025-09-9; **18,** 31025-10-2.

(18) Listings of observed and calculated structure factors will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(19) "International Tables for X-Ray Crystallography," Vol. III, Kynoch Press, Birmingham, England, (1962), pp 202–205.

Synthesis of Racemic Muscone and Cyclopentadecanone (Exaltone) from 1,9-Cyclohexadecadiene

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Muscone (**11**) and exaltone (**19**) have been synthesized from 1,9-cyclohexadecadiene (**1**). Unsaturated monoepoxide **2** upon treatment with butyllithium was converted into an α,β-unsaturated alcohol **3** and oxidized with chromic acid into the corresponding ketone **5**. This, upon treatment with methylmagnesium bromide in the presence of cuprous chloride, was converted into β-methylcyclohexadecenone (**6**) and then hydrogenated to β-methylcyclohexadecanone (**7**). The dibromide of **7** underwent a Favorski rearrangement to produce a mixture of 3-methyl and 15-methyl cyclopentadecene-1-carboxylate (7:3) which on treatment with hydrazoic acid was converted into muscone (**11**) and 2-methylcyclopentadecanone (**12**), respectively. In a similar way, 1-carboxymethyl-1-cyclopentadecene (**18**) obtained from dibromocyclohexadecanone was converted into exaltone (**19**). In another experiment, saturated epoxide **13** was rearranged to the allylic alcohol **15** and oxidized to the unsaturated ketone **16** which was then converted to **7**.

Muscone (**11**) [(−)-3-methylcyclopentadecanone] is the principal odorous constituent of musk pod obtained from the male deer *Moschus Moschiferus*. Owing to its rare occurrence in nature and its exotic and useful odor, many routes[1] have been developed for the synthesis of muscone. This paper reports a synthesis of (±)-muscone (**11**) and exaltone (**19**) from 1,9-cyclohexadecadiene (**1**).[2]

Addition of 1 mol of peracetic acid to diene **1** (three isomers, cis,cis, trans,trans, and cis,trans) yielded 69% of unsaturated monoepoxide **2** (four isomers, cis,cis, trans,trans, cis,trans, and trans,cis). All these isomers were separable on an analytical glc column. It should be noted that these unsaturated monoepoxides **2** and the corresponding saturated epoxides **13** possess weak musk odor.

Treatment of **2** with 1 mol of butyllithium[3,4] afforded a mixture of α,β-unsaturated secondary alcohol **3** (50%) and cyclohexadecenone **4**. Attempts to convert **2** to **3** with other reagents, *viz.*, alumina[5] and aluminum isopropoxide,[6] were not successful. The allylic alcohol **3** thus formed was isolated by column chromatography and then oxidized to the corre-

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