57. The Crystal and Molecular Structures of an Unusual Estra-Steroid and of its Dihydroproduct

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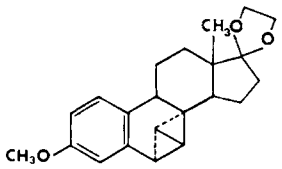
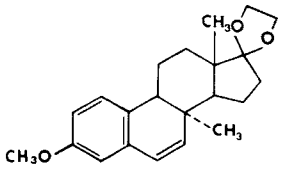
Summary. The crystal and molecular structures of 17-ethylenedioxy-3-methoxy-6,7,8-methylidyne-1,3,5(10)-estratriene (**1**) and of 17β-bromo-acetoxy-3-methoxy-8α-methyl-1,3,5(10),6-estratetraene (**3**) have been determined by X-ray analysis. A short discussion of the structures is given, and a new picture of the structure-activity relation of estrogenics is proposed.

The geminal hydrogenolysis of the steroidal bicyclobutane **1** leading to the 8α-methylsteroid **2** has been described in an earlier communication [1]. The X-ray analysis of **1** and **3**, the 17-bromoacetyl derivative obtained from **2**, now confirms the predictions [1] concerning the structures of **1** and **2** and supports the proposed reaction mechanism.



1



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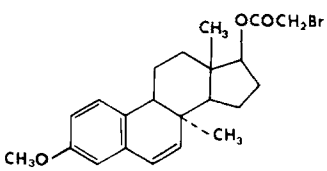

3

Structural data on bicyclobutanes are of interest because of the increasing accessibility and synthetic potential (see, *e.g.* [2]) of this class of highly strained compounds (for a review, see [3]). The only relevant crystal structure analysis hitherto available is for *Masamune*'s tricyclo[2.1.0.$0^{2,5}$]pentane system [4]. From the results of this analysis it was not certain if the C–C bond of length 1.44(5) Å across the four-membered ring was significantly shorter than the other four bonds averaging 1.53(3) Å.

Structures of 8α-estra-derivatives are of interest in connection with estrogenic activity. Indeed, a number of 8α-estra-derivatives show activities comparable to that of estradiol itself [5] in spite of the considerable difference in molecular shape between the 8α- and the natural 8β-steroids. A structural correlation of **3** with estradiol and 8β-methyl-estradiol suggests a general specification of the geometrical requirements for estrogenic activity.

Structure analysis of 17-ethylenedioxy-3-methoxy-6,7,8-methylidyne-1,3,5(10)-estratriene (1). – The compound crystallizes from 2-propanol in the form of diamond-shaped translucent platelets. Cell dimensions and space group were determined from precession photographs; intensity measurements were made with a linear diffractometer [6] using graphite-monochromatized Mo$K\alpha$ radiation. Crystallographic

data and intensity statistics are summarized in Table 1. Absorption corrections were not applied.

Table 1. *Crystallographic Data and Intensity Statistics for 17-ethylenedioxy-3-methoxy-6,7,8-methylidyne-1,3,5(10)-estratriene* (**1**)

Formula $C_{22}H_{26}O_3$; molecular weight 338.447. Space group $P2_12_12_1$.		
Cell dimensions $a = 29.58(7)$ Å; $b = 6.50(1)$; $c = 9.16(1)$; $V = 1760$ Å^3.		
Observed density $d_o = 1.26(2)$ g/cm^3; calculated density $d_c = 1.28$.		
Nb. of molecules/cell $Z = 4$.		
Total no. of reflexions ($\sin\theta/\lambda \leqslant .56$ Å^{-1}) 1577; no. of significant reflexions[a]) 1054.		
$\bar{B}$ (overall)	4.2 Å^2	
$\langle \lvert E \rvert \rangle$	0.844	(0.886)[b])
$\langle \lvert E^2-1 \rvert \rangle$	0.831	(0.736)
$\langle E^2 \rangle$	1.002	(1.000)

[a]) Intensity I is significant if $I > 3\sqrt{(P+B)} + 0.02\,I$, where P = peak counts, B = background counts, $I = (P-B)$.

[b]) Values in round brackets are theoretical values [8].

Structural analysis. The structure was solved by a method similar to the multisolution method described by *Germain, Main & Woolfson* [7]. In the first calculated *E-Fourier*-map with 379 E-values ($\lvert E \rvert \geqslant 1.2$) a chemically reasonable arrangement of peaks could be recognized; the model, however, could not be refined below $R = 0.35$. Essentially the same *E-Fourier*-map was obtained with different starting-sets of phases, but in one map all peaks were shifted by a small amount in the x-direction ($\Delta x = 0.025$ (ca. 0.7 Å)). For this structure block-diagonal least-squares refinement proceeded without difficulties to $R = 0.074$. Hydrogen atoms were located from a difference-*Fourier*-map and their positions and isotropic temperature factors refined. All significant structure factors were included in the calculations. A list of structure factors will be sent to interested parties upon request (*HPW*). Atomic parameters are given in Table 2, bond lengths, bond angles, and torsion angles are summarized in Fig. 1 and 2.

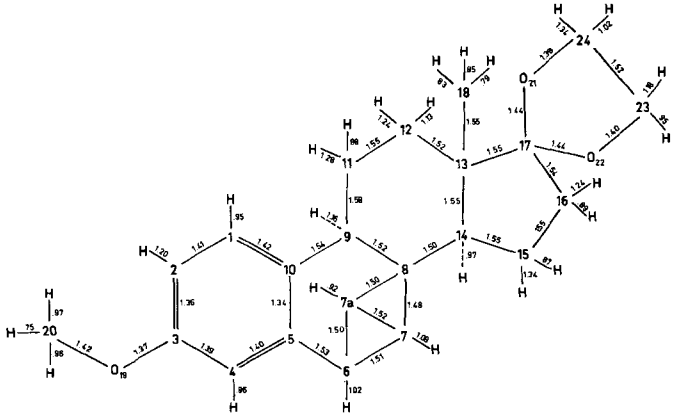

Fig. 1. *Bond lengths in compound* **1**

The average e.s.d. for C—C and C—O bonds is 0.013 Å, for C—H bonds 0.10 Å

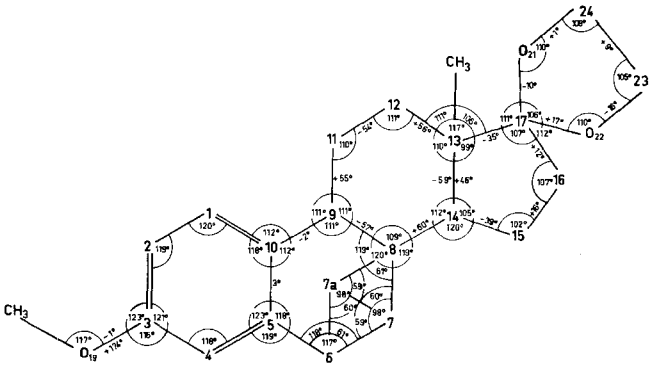

Fig. 2. *Bond angles and torsion angles of compound* **1**
The average e.s.d. for bond angles is 0.8°, for torsion angles 1.4°

Table 2. *Fractional coordinates and anisotropic thermal parameters for* **1**

Atom	x	y	z	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
C1	0.2805	0.5115	-0.0286	8	267	135	3	-2	53
C2	0.3280	0.4862	-0.0336	9	377	117	4	4	34
C3	0.3468	0.3132	0.0237	10	453	83	22	-11	-7
C4	0.3200	0.1539	0.0763	11	284	102	8	-12	13
C5	0.2733	0.1850	0.0831	10	246	64	11	-8	-7
C6	0.2434	0.0143	0.1443	14	192	129	8	-15	9
C7	0.2019	0.0815	0.2276	11	261	135	-13	-11	52
C7A	0.1977	-0.0141	0.0777	11	231	144	14	-10	-60
C8	0.1790	0.1962	0.1094	9	223	75	5	1	19
C9	0.2014	0.3839	0.0428	7	238	82	3	0	48
C10	0.2530	0.3545	0.0327	8	341	65	7	1	2
C11	0.1806	0.4351	-0.1120	9	423	88	14	3	93
C12	0.1285	0.4602	-0.1012	8	320	113	16	1	20
C13	0.1071	0.2716	-0.0311	7	317	76	8	5	22
C14	0.1288	0.2316	0.1191	8	253	84	-7	2	46
C15	0.0980	0.0665	0.1907	12	329	163	0	-3	9
C16	0.0503	0.1391	0.1428	14	403	169	-8	1	56
C17	0.0571	0.2913	0.0160	10	387	104	-2	0	-23
C18	0.1096	0.0816	-0.1327	13	319	107	21	-6	-53
C19	0.3922	0.2760	0.0234	7	562	149	18	-2	63
C20	0.4202	0.4274	-0.0419	9	803	245	28	-2	111
C21	0.0473	0.4950	0.0697	10	407	145	5	3	-67
O22	0.0252	0.2562	-0.0994	10	466	148	-10	-10	-43
O23	0.0064	0.4431	-0.1443	21	380	213	5	-24	50
O24	0.0174	0.5925	-0.0231	19	308	287	21	1	-43

Atom	x	y	z	Atom	x	y	z
H.C1	0.268	0.640	-0.059	H2.C15	0.109	-0.056	0.188
H.C2	0.345	0.639	-0.081	H1.C16	0.033	0.264	0.228
H.C4	0.332	0.026	0.108	H2.C16	0.042	0.016	0.109
H.C6	0.258	-0.113	0.189	H1.C18	0.136	0.058	-0.128
H.C7	0.192	-0.025	0.313	H2.C18	0.096	-0.016	-0.091
H.C7A	0.183	-0.132	0.048	H3.C18	0.103	0.133	-0.212
H.C9	0.195	0.484	0.139	H1.C20	0.419	0.441	-0.147
H1.C11	0.190	0.281	-0.193	H2.C20	0.440	0.403	0.006
H2.C11	0.189	0.535	-0.171	H3.C20	0.411	0.542	0.017
H1.C12	0.121	0.527	-0.224	H1.C23	0.030	0.416	-0.246
H2.C12	0.123	0.585	-0.018	H2.C23	-0.018	0.491	-0.201
H.C14	0.126	0.355	0.178	H1.C24	-0.008	0.598	0.052
H1.C15	0.101	0.192	0.305	H2.C24	0.033	0.751	-0.101

The expression used for the anisotropic thermal vibration is

$$T = \exp[-(h^2b_{11} + k^2b_{22} + l^2b_{33} + 2\,hkb_{12} + 2\,hlb_{13} + 2\,klb_{23})].$$

The b_{ij}-values in the table have to be multiplied by 10^{-4}. The hydrogen atoms have been given a fixed isotropic thermal parameter of $B = 2.0$ Å^2.

Analysis of the molecular packing reveals no unusually short intermolecular distances, the shortest H...H distances being 2.2 Å and the shortest C...C distances 3.26 Å.

Structure analysis of 17β-bromoacetoxy-3-methoxy-8α-methyl-1,3,5(10),6-estratetraene (3). – The compound crystallizes from 2-propanol as prismatic needles. Cell dimensions, space group, and intensity data (Table 3) were obtained in the same way as described for compound **1**. Absorption corrections were not applied.

Table 3. *Crystallographic Data and Intensity Statistics for 17β-bromoacetoxy-3-methoxy-1,3,5(10),6-estratetraene* (**3**)

Formula $C_{22}H_{27}O_3Br$; molecular weight 419.367. Space group $P2_12_12_1$.		
Cell dimensions $a = 22.83(3)$ Å; $b = 10.47(2)$; $c = 8.35(1)$; $V = 1996$ Å^3.		
Observed density $d_o = 1.37(2)$ g/cm^3; calculated density $d_c = 1.39$.		
No. of molecules/cell $Z = 4$.		
Total no. of reflexions ($\sin\theta/\lambda \leqslant .56$ Å^{-1}) 1656; no. of significant reflexions[a]) 767.		
B (overall)	5.4 Å^2	
$\langle\|E\|\rangle$	0.835	(0.886)[b])
$\langle\|E^2-1\|\rangle$	0.795	(0.736)
$\langle E^2\rangle$	1.000	(1.000)

[a]) and [b]) see footnotes Table 1.

Structural analysis. From the 3-dimensional *Patterson*-function the bromine atom was located at $x = 0.20$, $y = 0$, $z = 0$. The resulting arrangement of bromine atoms belongs to the space group *Cmcm* and the bromine-phased F_0-*Fourier*-map would then also correspond to this space group. In order to avoid this troublesome spurious sym-

metry, direct methods were applied to solve the structure. Starting with three origin-defining phases and some 25 phases of strong E-values with large bromide contributions (accepting the phase of the bromine contribution as the phase of the structure factor), the phases of 391 reflexions with $|E| \geqslant 1.20$ were calculated by application of the tangent-formula [8]. The resulting *E-Fourier*-map revealed clearly the positions of all non-hydrogen atoms. These positions were refined by least-squares analysis, first introducing isotropic, then anisotropic temperature factors for all 26 atoms. The final R-value was 0.096, based on all significant reflexions. A final difference-*Fourier*-map showed a large number of peaks, some of which could be attributed to hydrogen atoms. Further refinement was not attempted, however. A list of structure factors will be sent to interested parties upon request (*HPW*). Atomic

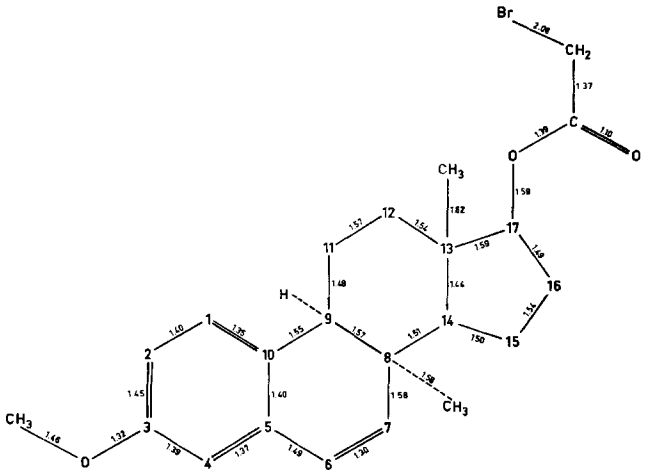

Fig. 3. *Bond lengths in compound* **3**
The average e.s.d. of C—C and C—O bonds is 0.035 Å, of C—Br 0.018 Å

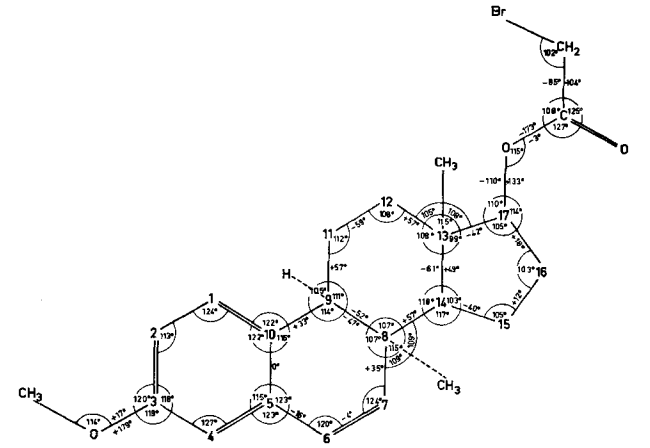

Fig. 4. *Bond angles and torsion angles in compound* **3**
The average e.s.d. for bond angles is 2.8°, for torsion angles 3.2°

Table 4. *Atomic parameter of* **3**

Atom	x	y	z	B(Å^2)
C1	0.5437	0.6810	-0.4268	3.4
C2	0.5916	0.7270	-0.5193	3.7
C3	0.6290	0.8087	0.4316	3.0
C4	0.6122	0.8557	0.2840	4.0
C5	0.5661	0.8144	-0.1981	1.6
C6	0.5549	0.8609	-0.0368	3.2
C7	0.5164	0.8005	0.0545	2.5
C8	0.4828	0.6774	-0.0030	3.2
C9	0.4732	0.6876	-0.1882	3.2
C10	0.5277	0.7353	-0.2777	4.4
C11	0.4287	0.7870	-0.2285	3.7
C12	0.3682	0.7555	-0.1428	3.9
C13	0.3782	0.7543	0.0356	4.2
C14	0.4234	0.6556	0.0705	2.0
C15	0.4217	0.6427	0.2491	5.1
C16	0.3551	0.6466	0.2945	3.3
C17	0.3273	0.6856	0.1402	5.1
O18	0.6752	0.8675	-0.5034	5.9
C19	0.6878	0.8084	-0.6615	5.4
C20	0.5229	0.5581	0.0408	1.8
C21	0.3852	0.9026	0.0945	2.5
O22	0.2765	0.7899	0.1687	3.4
C23	0.2241	0.7679	0.0854	4.4
O24	0.2166	0.6864	0.0096	6.5
C25	0.1851	0.8638	0.1373	5.0
Br	0.2029	1.0168	-0.0147	5.4

The B-values given in this table correspond to an isotropic thermal motion with a mean-square displacement $\langle r^2 \rangle$ equal to that of the anisotropic thermal motion refined in the least-squares calculations.

parameters are given in Table 4; bond lengths, bond angles, and torsion angles are summarized in Figures 3 and 4.

Analysis of the molecular packing reveals no unusually short intermolecular contacts or hydrogen bonds.

Discussion. – A perspective view of **1** is given in Fig. 5. Rings A and B, together with the methoxy group, form a planar system with the two apex-atoms of the bicyclobutyl system, C7 and C7a, symmetrically above and below the plane by 0.76(1) Å. The bicyclobutyl moiety has approximate C_{2v} (mm) symmetry with an angle of 122° between the planes of the two three-membered rings. The five C–C bonds in the system are equal in length within experimental error, with an average of 1.504(6) Å, which is slightly shorter than the normal C–C single bond (1.54 Å); this general shortening is typical for cyclopropyl compounds (*e.g.* cyclopropyl chloride, C–C average 1.51 Å [9]).

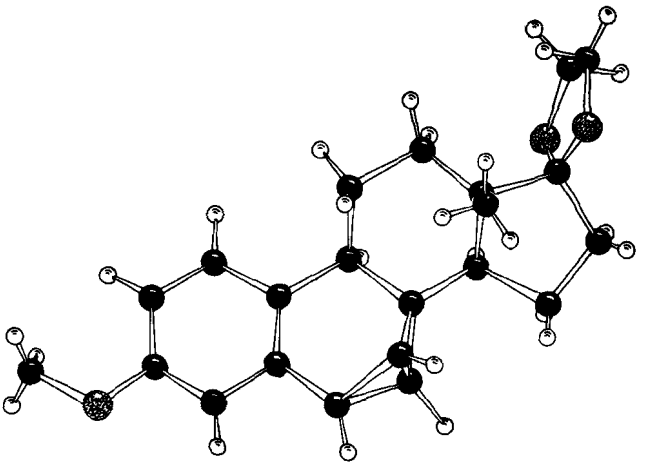

Fig. 5. *Perspective view of compound* **1**
The projection makes an angle of about 10° with the normal of the plane of rings A and B.
● = carbon, ◉ = oxygen, ○ = hydrogen

In *Masamune*'s special tricyclo[2.1.0.0^{2,5}]pentane system [4], the bond common to the two three-membered rings was thought to be shorter than the other four bonds by about 0.09 Å, which contrasts with our results.

The C-ring is in a nearly undistorted chair conformation (see torsion angles, Fig. 2). Ring D has almost the same conformation (approximate C_2-symmetry) as found in many other steroids, *e.g.* androsterone [10]. The five-membered acetal ring is slightly non-planar; as seen from the torsion angles (Fig. 2) it occurs as a rather flattened 'envelope' conformation (approximate C_s-symmetry) with O2 as the flap.

There is a close intramolecular contact of 3.2 Å between the 13β-methyl and C7, the bicyclobutyl apex-atom on the β-side. This may explain why exclusively α-attack (*i.e.* attack on the unhindered C7a apex-atom) is observed in the hydrogenolysis of this system [1].

A perspective view of **3** is given in Fig. 6. The characteristic feature of the 8-*iso*-steroid skeleton is the *cis*-fusion of rings B and C, which brings the mean plane through

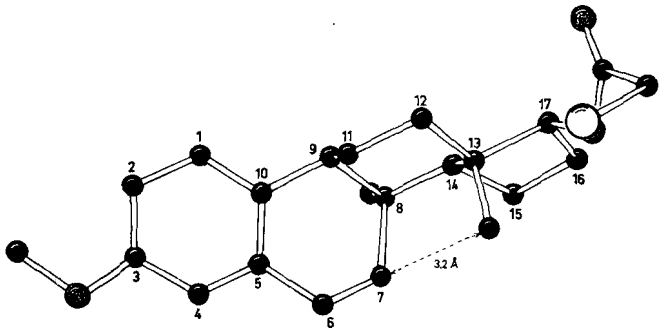

Fig. 6a. *Perspective view of the steroidal skeleton of compound* **3**
Projection is perpendicular to the mean plane through the A-ring.
● = carbon, ◉ = oxygen, ○ = bromine

rings A and B almost perpendicular to the mean plane through rings C and D. As a consequence the 13β-methyl group comes into close contact with C7, the interatomic distance being 3.2 Å. The Δ^6-double bond should then be considerably hindered from both the α- and the β-sides by the 8α- and 13β-methyl groups respectively, which might explain the very slow [1] catalytic hydrogenation of **2**. The O-methyl group is in the plane of the aromatic A-ring. The conformation of ring B has approximate C_2-symmetry (2-fold axis through the middle of bonds C5–C6 and C8–C9), and the torsion angles (Fig. 4) are in reasonable agreement with those derived from a microwave investigation of 1,3-cyclohexadiene [11]. The conformations of rings C and D are again very similar to those observed in **1** and other steroids [10] in spite of the B/C *cis*-fusion.

A geometrical parameter thought to be of importance for estrogenic activity, the O3–O17β distance, has the value 11.00 $\pm$ 0.05 Å in natural estradiol [12]. Presumably the steroid is attached by hydrogen bonding to the receptor through these two oxygens [13], and it has been noted that their separation corresponds quite closely to two turns of the protein α-helix (separation: 10.76 Å). The very high activity observed with compounds of the unnatural 8α-skeleton [5], invites further speculation on the steroid-receptor complex. We find that the O3–O17β distance in **3** is 10.31(1) Å. It is possible that this represents the lower bound of an acceptable range of O...O separations, of which the upper bound is given by the 11.0 Å separation in estradiol.

8β-methyl-estradiol has no estrogenic activity [14], although the O–O separation is about 10.8 Å; *i.e.* well within the acceptable range mentioned above, and the structural difference in the steroid backbone of 8β-methyl-estradiol and of estradiol is minimal compared with the difference between 8α- and 8β-steroids. This difference in activity leads us to reconsider the role of the backbone in the structure-activity relationship.

For both 8β- and 8α-estra-derivatives it is possible to construct planes passing through O3 and O17β, such that the steroidal backbone is entirely on one side of that plane[1]). Fig. 7 shows estradiol, 8β-methyl-estradiol, and compound **3** projected parallel to these planes. It appears to us that for estrogenic activity the shaded area above the plane should be free of projecting groups, such as the 8β-methyl group in Fig. 7b. It further appears that the supporting backbone is only important to maintain the appropriate O...O distance (10.7 $\pm$ 0.3 Å). The backbone itself may be considerably modified; it should not, however, project above the defined plane into the shaded area.

We may now visualize the following picture of the estrogenic receptor-substrate interaction: The substrate is attached to the receptor by hydrogen bonding through the two oxygens, the hydrogen bonds being more or less perpendicular to, and above, the plane indicated in Fig. 7. Any groups or parts of the backbone considerably above the plane would prevent the substrate from approaching closely enough to the receptor surface. An interesting exception is the 13β-CH_3 group; it is known that this group represents an optimum, in that both the 13β-H and the 13β-C_2H_5 analogs show significantly reduced estrogenic activities [15]. There has to be a niche in the receptor surface into which the 13β-CH_3 group can fit while the larger 13β-C_2H_5 can not.

[1]) Models for the active drugs [5] 8α-methyl-estradiol, 8α,14β-estra-1,3,5(10)-triene-3,17α-diol, estrone and 8α-estrone show that the construction of similar planes is possible.

Additionally, we have to assume that the 13β-CH_3 (but not the 13β-H) group, on penetrating the niche, induces a conformational change in the protein that facilitates optimum alignment with the substrate molecule.

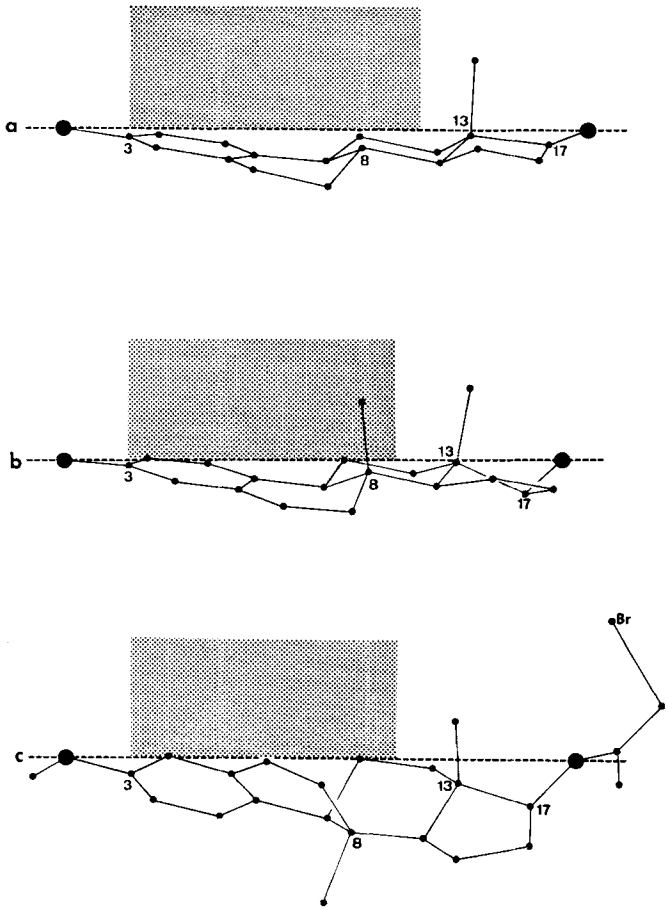

Fig. 7. *Projections of a) estradiol, b) 8β-methyl-estradiol, and c) compound* **3**

The direction of projection has been chosen in a way that all steroidal backbone atoms lie on one side of the projecting plane through atoms O3 and O17β

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58. 1-Substituierte Cycloheptatrienverbindungen

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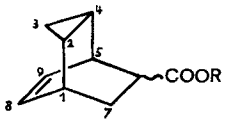
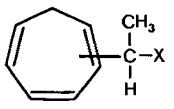
Summary. Cycloheptatriene reacts with acrylic esters, in the presence of catalytic amounts of tricarbonyl-triphenylphosphine-nickel, to yield a mixture of α-cycloheptatrienyl-propionic acid esters (**2a**) substituted in various positions. Methacrylic acid ester yields likewise α-cycloheptatrienyl-isobutyric acid ester (**3a**). Both types of ester mixtures undergo thermal isomerizations by 1,5-hydrogen shifts to give mixtures which contain predominantly the (C-1)-substituted cycloheptatrienyl-carboxylic acid esters (**2a**, **3a**). Pure α-(1-cycloheptatrienyl) derivatives can be prepared from **2a** and **3a**. A detailed NMR. study of the ester mixtures before and after thermal isomerization shows the proportions of the various isomers in the mixture. The mechanism of the formation of **2a** and **3a** is explained in terms of a catalysed ene-reaction of the primary formed 7-substituted cycloheptatriene derivatives with subsequent consecutive 1,5-hydrogen shifts.

Einleitung. – Die thermische, unkatalysierte Reaktion von Cycloheptatrien mit Acrylestern führt mit oder ohne Lösungsmittel im Bereich von 130–200° in einer [2 + 2 + 2]-Cycloaddition zu einem Gemisch von *exo*- und *endo*-Tricyclo[3.2.2.$0^{2,4}$]-non-8-en-6-carbonsäureestern (**1**) neben geringen Mengen von *endo*-Bicyclo[4.2.1]-nona-2,4-dien-carbonsäureestern [1].

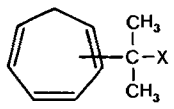
Die thermische, durch Aluminiumchlorid katalysierte Reaktion von Cycloheptatrien mit Acrylestern in Methylenchlorid liefert hingegen in 95-proz. Reinheit die Ester der Tricyclo[3.2.2.$0^{2,4}$]non-8-en-6-*endo*-carbonsäure [1].



1



2a,b



3a

a: X = $-COOC_4H_9$

b: X = $-COOC_2H_4-O-C_2H_5$