Chem. Pharm. Bull. 17(11)2319—2329(1969)

UDC 547.92.07.04

Studies on the Synthesis of the Steroids having an Arylcyclopropane Ring at Position 2 and 3. I

Sadao Hayashi and Taichiro Komeno

Shionogi Research Laboratory, Shionogi & Co., Ltd.[1]

(Received June 11, 1969)

Wolff–Kishner reduction under Huang Minlon's condition of 2-arylmethylene-3-oxo-steroids were investigated, and following results were obtained. 1. Reaction of 2-benzylidene-5α-androstan-3-one (I) gave 2α,3α-phenylmethylene-5α-androstane (II) and 5α-androstano[3,2-*c*]pyrazole (IV). 2. Reaction of 2-benzylideneandrost-4-en-3-one (XXII) gave 2α,3α-phenylmethyleneandrost-4-ene (XXIII), 5β-androstano[3,2-*c*]pyrazole (XXIV), IV and androst-4-eno[3,2-*c*]pyrazole (XXV). 3. Reaction of 2-benzylideneandrost-4,6-dien-3-one (XXVI) gave 2α,3α-phenylmethyleneandrost-4,6-diene (XXVII) and XXV. Stereochemistry of products and reasonable explanation for the reaction process were presented.

In recent years a number of detailed investigations dealing with the steroidal cyclopropanes have been reported. In one of the latest investigations,[2] synthesis of 2α,3α-phenylmethylene-5α-androstan-17β-ol acetate (IIb) was described by Evans, *et al.* This prompted us to report our continuing work in this field. The present paper includes comments on the synthesis of 5α-androstan (II), androst-4-en (XXIII) and androst-4,6-dien-17β-ol (XXVII) having arylcyclopropane ring at C-2 and C-3, and also on the minor products of the corresponding pyrazole derivatives IV, XXIV and XXV. Wolff-Kishner reduction of 2-benzylidene-17β-hydroxy-5α-androstan-3-one (I)[3] under Huang Minlon's condition gave the compound II,the endocyclic α,β-unsaturated ketone III and the 5α-androstano[3,2-*c*]pyrazole derivative IV.

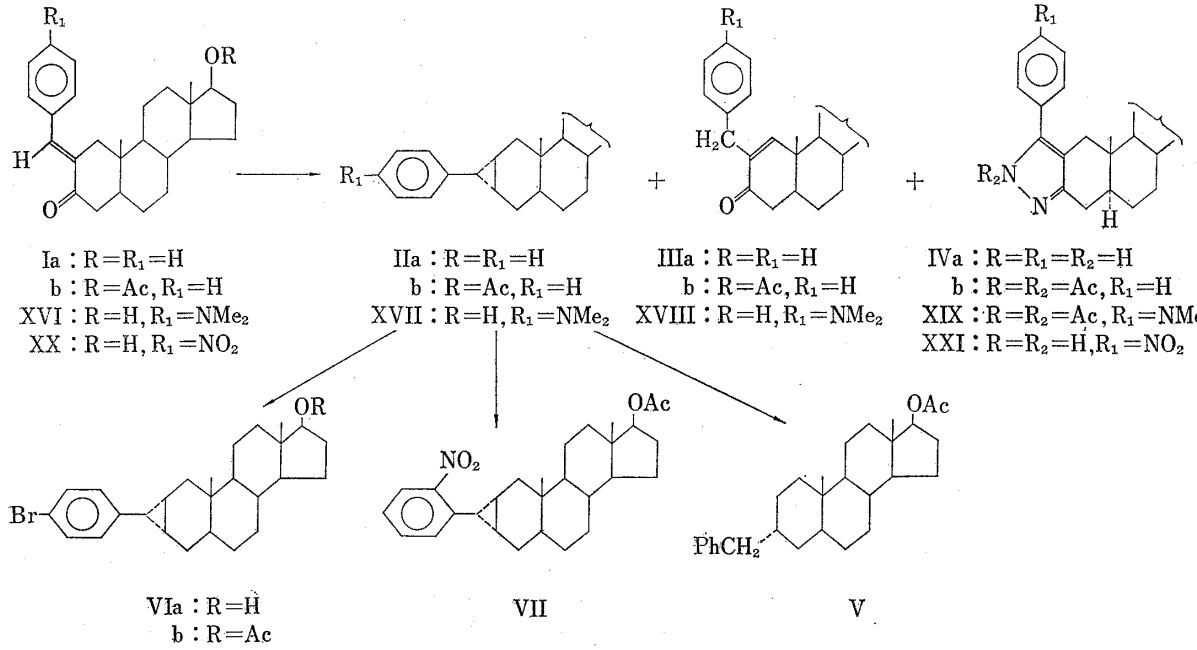


Chart 1

1) Location: *Fukushima-ku, Osaka.*
2) D.E. Evans, G.S. Lewis, P.J. Palmer and D.J. Weyell, *J. Chem. Soc.* (*C*), **1968**, 1197.
3) D.H.R. Barton, F. McCapra, P.J. May and F. Thudium, *J. Chem. Soc.*, **1960**, 1297; v.W. Fritsch, G. Seidl and H. Rushing, *Ann. Chem.*, **677**, 139 (1964).

The presence of a cyclopropane ring in the compound II was shown by the following evidences: (1) absence of olefinic proton signals in its nuclear magnetic resonance (NMR) spectrum, (2) similar ultraviolet (UV) spectrum with that of phenyl cyclopropane (Table II), (3) uptake of one molar equivalent of hydrogen in catalytic hydrogenation over palladized charcoal to give the benzyl derivative (V) which shows similar UV absorption with that of toluene, (4) smooth bromination and nitration to give *p*-bromophenyl- (VI) and *o*-nitrophenyl- (VII) compound respectively.

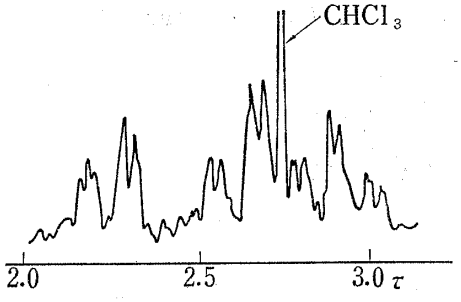


Fig. 1. NMR Spectrum of VII in $CDCl_3$ (TMS)

The NMR spectrum of VI shows A_2B_2 type signals due to para substituted aromatic protons, while that of VII shows a more complete pattern due to the ortho nitro group as shown in Fig. 1. In a recent paper[4] predominant ortho-nitration was described on phenylcyclopropane.

In this paper the stereochemistry of II could be deduced in a different way from that which Evans, *et al.*[2] reported. In order to assign the configuration of the cyclopropane ring, four isomers of benzyl derivatives at C-2 and C-3, one of which must be identical with the reduction product (V), were synthesized through following processes. Catalytic reduction of I over palladized charcoal gave the 2α-benzyl-3-ketone (VIII), a small amount of 2β-benzyl-5α-androstan-17β-ol (IX), and 2ξ-benzyl-5α-androstan-3ξ,17β-diol (X). Wolff–Kishner reduction of VIII, followed by acetylation, afforded 2α-benzyl-5α-androstan-17β-ol acetate (XI).

Hydrogenolysis of IIIb gave the 2β-benzyl compound (IX), VIII and 2ξ-benzyl-17β-acetoxy-5α-androstan-3ξ-ol (XII) the diacetate of which was not identical with the X-diacetate.

Both isomers IX and XI were also obtained by hydrogenation of 2-benzyl-5α-androst-2-en-17β-ol acetate (XIII) which was prepared from VIII in several steps.

Both IX and XI were not identical with the product V obtained by hydrogenation of IIb.

Similar catalytic reduction of 3-benzyl-5α-androst-2-en-17β-ol (XIV), which was prepared from 17β-hydroxy-5α-androstan-3-one by Grignard reaction with benzylmagnesium bromide followed by dehydration, afforded two stereoisomers (XV and V) of benzyl group at C-3 in a ratio about 13:1. The ratio was given by comparison of integrals of the 19-CH_3, 18-CH_3 and benzyl methylene protons of the reaction mixture.

Minor component of the two isomers was identical with the reduction product V. Since in hydrogenation of Δ^2-double bond with the substituent at C-3, it is known that hydrogen attacks predominantly from α side of the molecule, the major compound XV was deduced to have β-benzyl group and hence the compound V must have α-benzyl group.

The optical rotatory dispersion (ORD) plain curves of these four stereoisomers (Fig. 2) show that the isomers with axial (R) benzyl group at C-2 (IX) and C-3 (V) are more dextrorotatory than their stereoisomers (XI and XV) respectively in a region from 230 to 400 mμ, as indicated in $[\alpha]_D$ values. In the case of the stereoisomers at C-2, the isomer XI is levorotatory contrary to the dextrorotatory isomer IX.

Similar relationship is shown in their NMR spectra(TableIII). Both methylene protons of axial benzyl group of IX and V are shifted to a lower field than those of equatorial benzyl group of XI and XV. The chemical shift of 19-CH_3 protons of IX are deshielded by 11.5 cps compared to that of XI showing 1,3-diaxial relation between 19-CH_3 and benzyl methylene.

These physical data well account for their stereoisomers. Therefore α-configuration was assigned to the benzyl group of the compound V and consequently to the cyclopropane ring of the compound II.

4) R.H. Hahn, T.F. Corbin and H. Shechter, *J. Am. Chem. Soc.*, **90**, 3404 (1968).

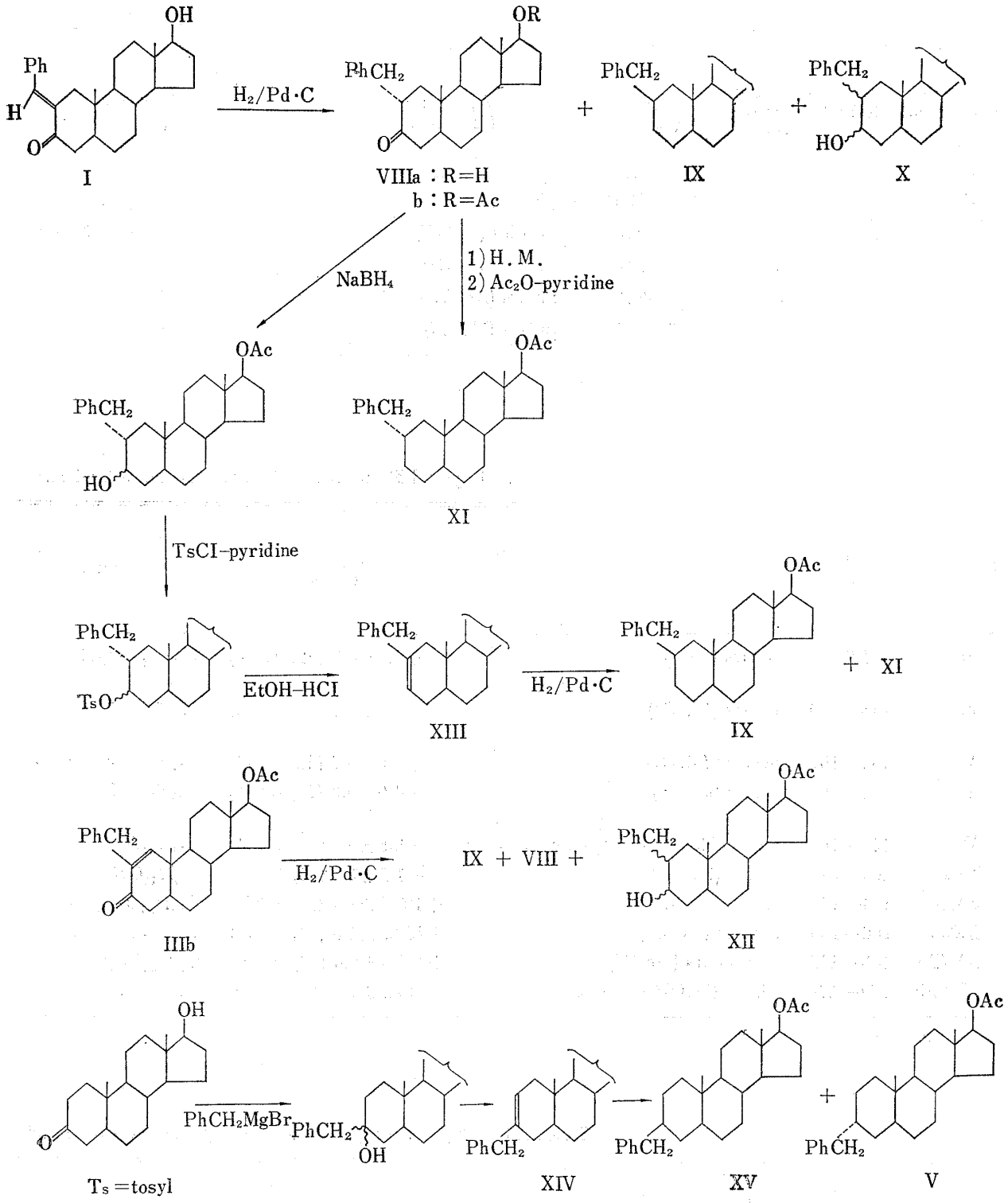


Chart 2

The configuration of the phenyl group could be assigned as β because it was more stable than the α-configuration. Verbit, *et al.*[5] reported that the negative sign of the 222 mμ Cotton effect is characteristic of a phenyl ring attached to a carbon of the R-configuration of a disubstituted cyclopropane derivatives, on the other hand Brewster, *et al.*[6] said that the negative

5) L. Verbit and Y. Inouye, *J. Am. Chem. Soc.*, **89**, 5717 (1967).
6) J.H. Brewster and J.G. Buta, *J. Am. Chem. Soc.*, **88**, 2233 (1966); P. Crabbé, and W. Klyne, *Tetrahedron*, **23**, 3449 (1967); H.E. Smith, M.E. Warren, Jr. and L.I. Katzin, *ibid.*, **24**, 1327 (1968).

Table I. Physical Properties and Analytical

Compound	Method	Reaction time (hr)	mp (°C)	Appearance (recryst. sol.)	$[\alpha]_D$ $CHCl_3$ (°C, *c*)
Ib	A		224—226	plates (MeOH)	−157.8±4.1 (23, 0.488)
XVI	B	6.5	213—215	needles (MeOH)	−373.1±8.3 (25, 0.495)
XX	A	21	193—194	needles (MeOH)	−111.1±1.5 (22, 1.005)
XXIIb	B	48	200—201	pillars (AcOEt–cyclohexane)	− 27.0±0.7 (22, 0.982)
XXVI	B	4.5	197—198	pillars (MeOH)	− 83.1±2.8 (21, 0.443)

a) in MeOH

Table II. Physical Properties and Analytical Data for 2α,3α-

Compound	mp (°C)	Appearance (recryst. solvent)	$[\alpha]_D$ $CHCl_3$ (°C, *c*)	Formula
IIa	178	pillars (MeOH)	+4.0±0.3 (22, 1.140)	$C_{26}H_{36}O\cdot\frac{1}{2}H_2O$
IIb	148—149	pillars (MeOH)	+2.9±0.3 (22, 1.086)	$C_{28}H_{38}O_2$
VIa	166—167	needles (MeOH)	+0.9±0.7 (23, 0.571)	$C_{26}H_{35}OBr\cdot\frac{1}{4}H_2O$
VIb	188—190	plates (*n*-hex.)	−4.0±0.3 (22, 0.958)	$C_{28}H_{37}O_2Br$
VII	157—160	light yellow plates (*n*-hex. acetone)	+8.8±0.5 (22, 0.741)	$C_{28}H_{37}O_4N$
XVII	203—205	plates (MeOH)	−1.2±1.2 (25, 0.259)	$C_{28}H_{41}ON$
XXIIIa	144—146	pillars (MeOH)	+123.8±1.7 (23, 0.955)	$C_{26}H_{34}O\cdot\frac{1}{2}H_2O$
XXIIIb	166—169	needles (MeOH)	+133.5±2.0 (24, 0.857)	$C_{28}H_{36}O_2$
XXVIIa	153—155	fine pillars (MeOH)	+123.4±4.0 (23, 0.406)	$C_{26}H_{32}O\frac{1}{2}H_2O$
XXVIIb	177—178	plates (MeOH–acetone)	+ 87.8±1.3 (24, 0.959)	$C_{28}H_{34}O_2$

a) in MeOH

Table III. Physical Properties and Analytical Data for Four

	Position and configuration of benzyl group	mp (°C)	Appearance (recryst. solvent)	$[\alpha]_D CHCl_3$ (°C, *c*)
IX	2β	152—154	needles (MeOH)	+13.1±1.1 (22, 0.464)
XI	2α	148—149	pillars (MeOH)	−33.9±0.8 (22, 0.998)
XV	3β	95—96	plates (MeOH)	+ 2.6±0.4 (23, 0.973)
V	3α	122	needles (MeOH)	+ 5.7±1.0 (23, 0.470)

a) 1 peak

Data for 2-Benzylidene Steroids

UV λ_{max}^{EtOH} mμ (log ε)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	NMR (τ) Ar–H (doublet, J cps)
224 (3.85), 231 (sh 3.76), 294 (4.20)	$C_{28}H_{36}O_3$	79.96	8.63		80.18	8.86		2.44 (2.5)
253 (3.98), 328 (sh 3.86), 388 (4.33)	$C_{28}H_{39}O_2N$	79.76	9.32	3.32	79.80	9.36	3.18	2.42 (2.6)
213 (sh 3.59), 311 (4.21)	$C_{26}H_{33}O_4N$	73.73	7.85	3.31	73.49	8.01	3.02	2.50 (2.1)
234 (4.05), 266 (4.08), 306 (4.14)	$C_{28}H_{34}O_3$	80.34	8.19		80.35	8.27		2.41 (2.5)
231 (4.18), 318 (4.38)[a]	$C_{26}H_{30}O_2$	83.38	8.07		83.41	8.09		2.27 (2.6)

Arylmethylene-5α-androstanes (II, VI, VII, XVII, XXIII and XXVII)

Analysis (%) Calcd. C	H	N	Br	Found C	H	N	Br	UV λ_{max}^{EtOH} mμ (log ε)	NMR (cps) δ in $CDCl_3$ 19-H
83.64	9.92			83.72	9.87			225.5 (4.11), 255.5 (sh 2.59), 262.5 (2.73), 269 (2.81), 276 (2.71)	49.8
82.71	9.42			82.79	9.30			225 (4.13), 257.5 (sh 2.68), 264 (2.79), 271 (2.84), 278 (2.73)	50.4
69.71	7.87		17.84	69.87	7.83		18.15		
69.12	7.88		16.45	68.93	7.67		16.63	234 (4.28), 270.3 (2.91), 278 (2.92), 286.6 (2.72)	49.8
74.47	8.26	3.10		74.84	8.35	2.78		220 (4.12), 258 (sh 3.51), 311 (3.27)	49.2
82.50	10.14	3.44		82.70	10.05	3.49		254 (4.31), 302 (3.27)[a]	49.8
83.98	9.42			83.85	9.39				
83.12	8.97			82.82	8.94			235(4.11), 270.5 (3.04), 278 (2.85)	65.5
84.51	9.00			84.54	8.96				
83.54	8.51			83.29	8.53			255 (4.54)	64.6

Stereoisomers of Benzyl-5α-androstanes (IX, XI, XV and V)

Formula	Analysis (%) Calcd. C	H	Found C	H	NMR (cps) δ 18-H	19-H	$CDCl_3$ Ph CH_2 (J cps)
$C_{28}H_{40}O_2$	82.30	9.87	82.10	9.75	46.8	57.0	160 (7.5)
$C_{28}H_{40}O_2$	82.30	9.87	82.09	9.79	45.5[a]	45.5[a]	146 (6.0)
$C_{28}H_{40}O_2$	82.30	9.87	82.44	9.83	46.0[a]	46.0[a]	149 (6.0)
$C_{28}H_{30}O_2$	82.30	9.87	82.61	9.61	47.5	48.0	162 (7.5)

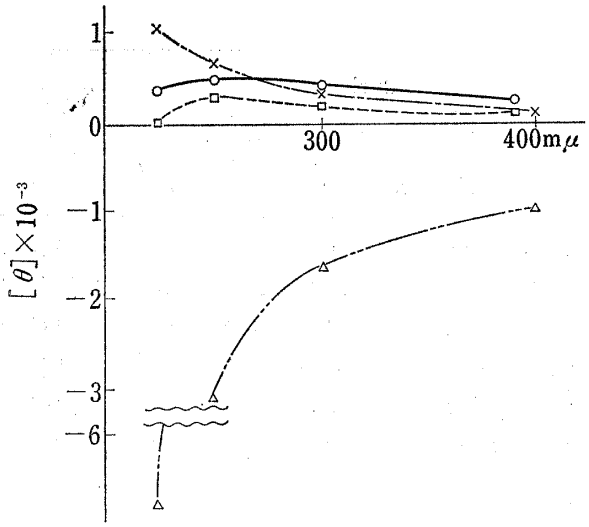


Fig. 2. ORD Spectra of IX, XI, XV and V

×———×: 2β-benzyl-5α-androstan-17β-ol acetate (IX)
△———△: 2α-benzyl-5α-androstan-17β-ol acetate (XI)
□--------□: 3β-benzyl-5α-androstan-17β-ol acetate (XV)
○———○: 3α-benzyl-5α-androstan-17β-ol acetate (V)

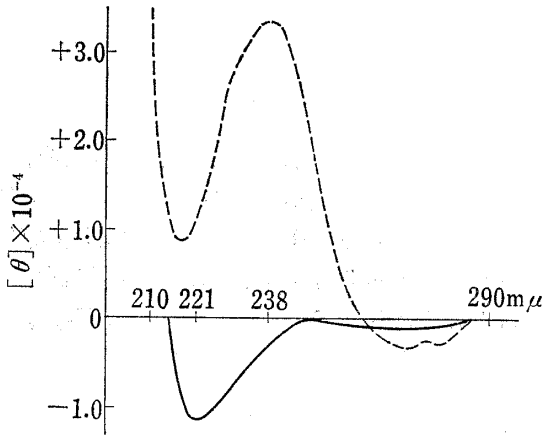


Fig. 3. CD Spectra of IIb and XXIIIb

——: 2α,3α-phenylmethylene-5α-androstan-17β-ol acetate (IIb)
------: 2α,3α-phenylmethylene androstan-4-en-17β-ol acetate (XXIIIb)

sign of the 260—270 mμ Cotton effect is characteristic of a phenyl ring attached to a carbon of the R-configuration. The compound IIb shows negative Cotton effects in the two regions as shown in Fig. 3, therefore β-configuration assigned to phenyl group accounts well for these Cotton effects in any case.

The compound III was characterized as the endoenone by its UV spectrum: λ_{max}^{EtOH} 247.5 mμ (log ε 4.13), 330 mμ (log ε 2.15), by its IR spectrum: 1631 (ν conj C=O), 1598 cm^{-1} (ν conj C=C) and by its NMR spectrum: vinyl proton at 3.53 τ.

The compound IV was assigned by its UV spectrum: λ_{max}^{EtOH} 256 mμ (log ε 4.16) which value is compatible with that of 3-methyl-5-phenylpyrazole: λ_{max}^{EtOH} 251 mμ (log ε 4.29).[7]

Wolff-Kisher reduction of *p*-dimethylaminophenylmethylene derivative (XVI) proceeds in a similar manner, affording the cyclopropane derivative (XVII), the endo-enone (XVIII) and the pyrazole derivative (XIX), however the reaction of *p*-nitrophenylmethylene derivative (XX) did not give these corresponding products because of high sensitivity of the nitro group to alkaline reagent.

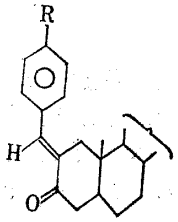
In general the intermediate of Wolff–Kishner reduction is 1- and/or 2-pyrazoline. Attempts to isolate the intermediate in these reactions were fruitless. In the reactions of I, XVI and XX with or without acidic catalyst in ethanol, pyrazole derivatives IV, XIX and XXI were isolated in a low yield and no pyrazoline derivative was detected. In the reaction at 130—140° (using KOH) under Huang–Minlon's condition also the pyrazoline could not be isolated but pyrazole derivative (IV) and a little amount of cyclopropane derivative (II) was isolated in the case of I (Table IV).

This fact suggests that pyrazoline A is the intermediate of the reaction as well known. However the very easy tendency of pyrazoline to aromatise to pyrazole derivative indicates that in the cyclopropane formation there is another process *via* intermediate B which is immediately denitrogenated before the cyclisation to pyrazoline. Very high yields of cyclopropanosteroid in the reaction at 210° compared with the low yield of pyrazole derivative when treated in acidic or alkaline media at low temperature accounts for this intermediate B (Chart 3).

Similar reaction of 2-benzylidene-17β-hydroxy-androst-4-en-3-one (XXII) was carried out under the same condition to give the cyclopropano derivatives (XXIII), androst-4-eno[3,2-*c*]pyrazole(XXV), 5α-androstano[3,2-*c*]pyrazole(IV) and 5β-androstano[3,2-*c*]pyrazole(XXIV).

7) I.I. Grandberg and A.N. Kost, *Z. Obshch. Khim.*, **29**, 650 (1959).

TABLE IV. Reaction of 2-Benzylidene-17β-hydroxy-5α-androstan-3-one with $NH_2NH_2H_2O$



	Starting material R[a)]	Catalyst	Reaction temperature (°C)	Reaction time (hr)	Products (%) Cyclopropane	Endoenone	Pyrazole
I	H	KOH	130—140	2	2.5 (II)	23 (III)	19 (IV)
I	H	KOH	210	3	61 (II)	21 (III)	5.4 (IV)
XVI	NMe_2	KOH	210	3	34 (XVII)	6.7 (XVIII)	4.2 (XIX)

a) *para* substituent of phenyl group in I and XVI

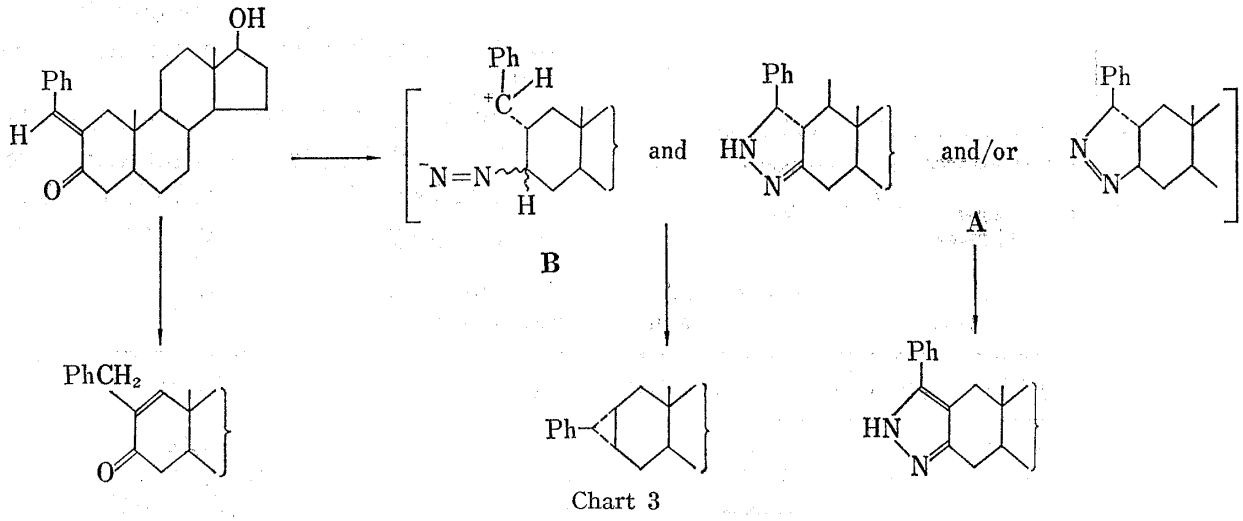
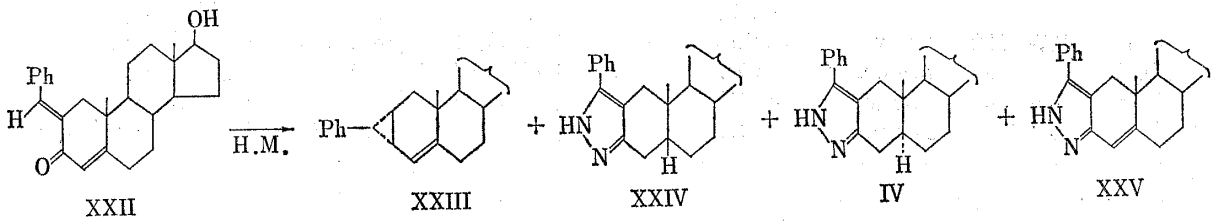
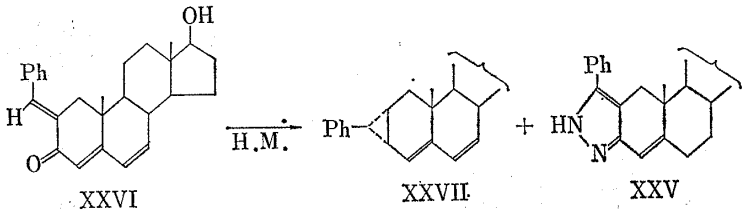


Chart 3





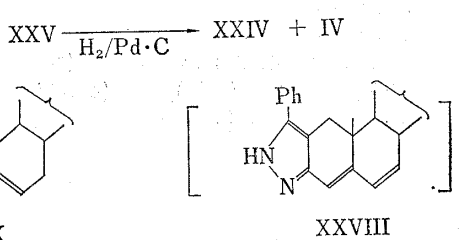


Chart 4

H.M.=Huang Minlon's condition

The 2-benzylideneandrost-4,6-dien-3-one (XXVI) was also treated under the same condition to give the corresponding cyclopropane 4,6-diene (XXVII) and XXV.

Reduction of XXV over palladized charcoal gave two androstano[3,2-*c*]pyrazole derivatives, 5α (IV) and 5β (XXIV) in a ratio about 2:7. The compound XXIV shows the same experimental formula and UV maximum as the compound IV, but has the 19-CH_3 resonance showing 22.8 cps downfield shift relative to the isomer IV. The CD spectra of the isomers IV and XXIV have opposite signs at the maxima 211 mμ and 214 mμ respectively as shown in Fig. 4. Prefered β-side attack of hydrogen was also observed in the Kishner reaction of XXII in which case 5β-isomer (XXIV) was favored over the 5α-isomer (IV) by about 4:1. These preferences for 5β-isomer formation is probably due to an appropriate combination of structural features and reaction conditions.[8]

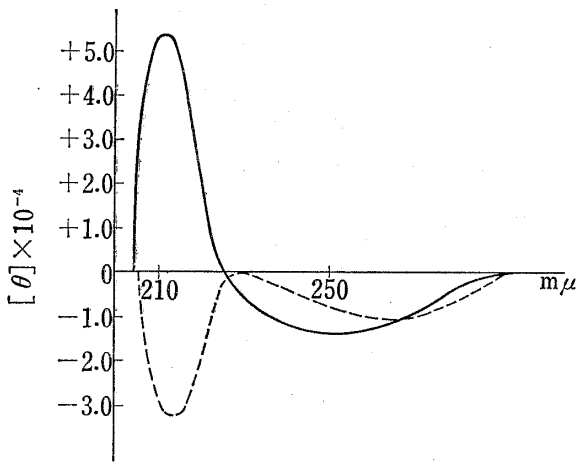


Fig. 4. CD Spectra of IV and XXIV

—— : 5′-phenyl-17β-hydroxy-5α-androstano [3,2-C] pyrazole (IV)
------ : 5′-phenyl-17β-hydroxy-5β-androstano [3,2-C] pyrazole (XXIV)

The physical data summarized in Table II and V are in agreement with these formulations. The measured UV maxima of phenylcyclopropano derivatives (II,

Table V. Physical Properties and Analytical Data for Androstano[3,2-*c*]pyrazoles (IV, XXIV, XIX, XXI) and Androsteno[3,2-*c*]pyrazole (XXV)

Compound	mp (°C)	Appearance	Recryst. solvent	$[\alpha]_D$ $CHCl_3$ (°C, *c*)	Formula
IV	169—170	rocks	MeOH	+ 49.3±1.9 (20, 0.481)	$C_{26}H_{34}ON_2$
IVb	132—134	pillars	MeOH	+ 57.1±0.5 (20, 0.897)	$C_{30}H_{38}O_3N_2$
XXIV	161—162	pillars	CH_2Cl_2	−121.9±3.9 (22, 0.415)	$C_{26}H_{34}ON_2 \cdot \frac{1}{4}H_2O$
XXIVb	197—198	needles	MeOH	− 66.1±1.7 (22, 0.610)	$C_{30}H_{38}O_3N_2$
XXV	157—159	fine rocks	cyclo-hex. acetone	+127.9±12.8 (24, 0.129)	$C_{26}H_{32}ON_2 \cdot \frac{1}{2}C_6H_{12}$
XXVb	132—133	needles	MeOH	+118.4±1.9 (24, 0.821)	$C_{30}H_{36}O_3N_2$
XIXb	143—145	fine rocks	MeOH	+ 27.9±1.3 (23, 0.513)	$C_{32}H_{43}O_3N_3$
XXI	>290	fine pillars	MeOH	+ 3.9±1.6 (23, 0.279)	$C_{26}H_{33}O_3N_3 \cdot \frac{1}{2}H_2O$

Compound	Analysis (%) Calcd. C	H	N	Found C	H	N	UV λ_{max}^{EtOH} mμ (log ε)	NMR (cps) δ $CDCl_3$ 19-H
IV	79.95	8.78	7.17	79.49	8.90	7.36	256 (4.16)	45.3
IVb	75.91	8.07	5.90	75.89	8.06	5.96	274.5 (4.27)	
XXIV	78.99	8.73	7.09	78.92	8.56	7.24	256 (4.17)	68.1
XXIVb	75.91	8.07	5.90	76.09	8.02	6.01	275 (4.27)	
XXV	80.97	8.80	6.51	80.91	8.78	6.28	258 (4.37)	59.8
XXVb	76.24	7.68	5.93	76.25	7.61	6.05	222 (4.23), 262 (sh 4.09), 270 (4.10), 282 (sh 4.04), 315 (3.94), 330 (sh 3.83)	
XIXb	74.24	8.37	8.12	74.20	8.57	8.33	230 (4.13), 255 (4.13), 310 (4.16)[a]	48.0
XXI	70.27	7.65	9.46	70.23	7.58	9.54	228 (4.06), 326 (4.14)	45.1

b: diacetate a) in MeOH

8) M.G. Combe, H.B. Henbest and W.R. Jackson, *J. Chem. Soc.* (*C*), **1967**, 2467.

XXIII and XXVII) corresponding to the primary benzene band, classified ^1L_a in the Platt notation, are in good accordance with extending conjugation of the double bond with phenyl-cyclopropyl orbital.

In the reaction of XXII, auto-oxidation occurred to give XXV in one part and double bond rearrangement to give IV and XXIV in another part at the same time. In the reaction of XXVI double bond rearrangement to give XXV occurred mainly and no dieno[3,2-*c*]pyrazole (XXVIII) was produced, however a very little amount of XXIV and androst-5-eno[3,2-*c*]-pyrazole (XXIX) could be obtained in the case of longer heating at 140° before heating at 210°. The compound XXIX was characterized by its UV spectrum: λ_{max}^{EtOH} 225 mμ (log ε 4.10), 262 mμ (log ε 2.76) and by the presence of vinyl proton at 5.31 τ (doublet, J=5.7 cps) in its NMR spectrum. These compounds (XXIX and XXIV) were probably produced by reduction of XXVIII and XXV by hydrazine reagent respectively.

Reasonable explanation for migration of double bond to form the pyrazole nucleus is shown in Chart 5.

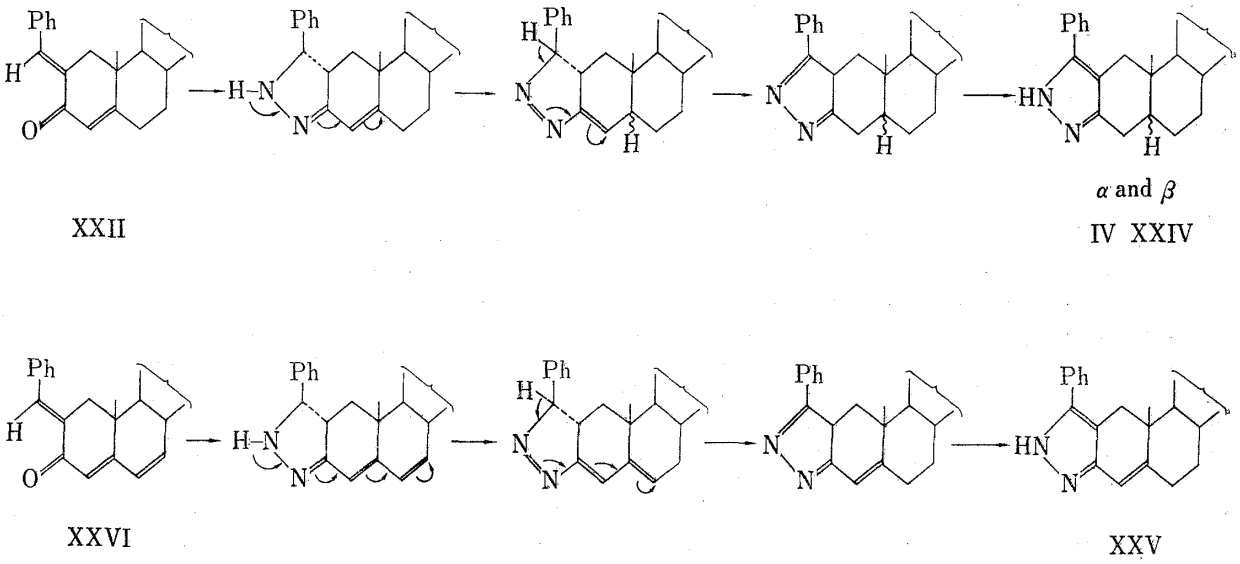


Chart 5

Experimental[9]

General Method for the Preparation of 2-Arylmethylene-Steroids——Method A: To a solution of Na metal (2 mmoles) in MeOH (20 ml) at room temperature was added appropriate benzaldehyde (3.8 mmoles) and 17β-hydroxy-5α-androstan-3-one (3.45 mmoles). The reaction mixture was stirred at room temperature for 21 hr. The precipitate was filtered and crystallized from MeOH.

Method B: A stirred mixture, as method A, was heated under reflux for appropriate hr. After evaporation of the solvent the residue was solved in CH_2Cl_2, washed with water until neutral, and the solvent was evaporated. Purification of the product was effected by chromatography over alumina followed by preparative thin-layer chromatography (TLC) on silica gel GF (Merk) and by recrystallization from suitable solvent.

General Method for Wolff-Kishner Reduction of 2-Arylmethylene-Steroids——A mixture of appropriate 2-arylmethylenesteroid (1.32 mmoles), KOH (1 g), 90% $NH_2NH_2H_2O$ (5 ml) and triethyleneglycol (TEG) (20 ml) was gradually heated to 180° during 1 hr, then the temperature of the reaction mixture raised to 210° by distilling off the excess of $NH_2NH_2H_2O$ and water. After a further 3 hr at this temperature, the reaction mixture was cooled, poured into ice-water, and the products were extracted with CH_2Cl_2, washed with water until neutral, dried over Na_2SO_4, and the solvent was removed in a reduced pressure. The products were isolated and purified by chromatography over alumina (Merk neutral with 3% water, 50 g) eluting with benzene–CH_2Cl_2, CH_2Cl_2 and 1% MeOH in CH_2Cl_2 successively, followed by preparative TLC on silica

9) All melting points were uncorrected. The NMR spectra were measured with Varian A-60 spectrometer using tetramethylsilane as internal standard.

gel GF (Merk) developing with a 1:1 mixture of AcOEt–cyclohexane and by recrystallization from a suitable solvent. Yield of products a) from I and XVI. See Table IV. IIIa: mp 182—184°. *Anal.* Calcd. for $C_{26}H_{34}O \cdot 1/4H_2O$: C, 81.20; H, 9.50. Found: C, 81.00; H, 9.00. IIIb: mp 213—215°. $[\alpha]_D^{22.5}$ +71.0 (c=9.51, $CHCl_3$). *Anal.* Calcd. for $C_{28}H_{36}O_3$: C, 79.96; H, 8.63. Found: C, 80.08; H, 8.76. XVIII: mp 249—251°. $[\alpha]_D^{23}$ +74.6 (c=0.850, $CHCl_3$). *Anal.* Calcd. for $C_{28}H_{39}O_2N$: C, 79.76; H, 9.32; N, 3.32. Found: C, 79.95; H, 9.18; N, 3.02. NMR (in $CDCl_3$) τ: 3.70 (1H, C–1H). b) From XX. Attempts to isolate the products were fruitless. c) From XXII. XXIII: 61%, XXIV: 11%, IV: 3.3%, XXV: 8.3%. The products IV and XXV are in a same band on preparative TLC, the yields are calculated from a comparison of the integrals of 18-CH_3 at 9.24 (IV) and 9.21 (XXV), 19-CH_3 at 9.24 (IV) and 9.01 (XXV) and C-4 H at 3.86 τ (XXV). d) From XXVI. XXVII: 30.5%, XXV: 36%.

2α-Benzyl-5α-androstan-17β-ol Acetate (V)——The acetate IIb (100 mg) in EtOH (50 ml) was hydrogenated over 10% Pd–C at room temperature. One equivalent of H_2 (5.9 ml) was absorbed. The catalyst was removed and the filtrate was concentrated in a reduced pressure. The residue was recrystallized from MeOH to give 92 mg (92%) of V. UV λ_{max}^{EtOH} mμ (log ε): 206 (3.94), 209 (3.95), 214 (sh 3.84), 218 (3.68), 243 (sh 1.93), 249 (2.13), 254 (2.27), 259.5 (2.36), 262 (2.36), 265(2.24), 268.7 (2.27).

2α,3α-(*p*-Bromophenylmethylene)-5α-androstan-17β-ol Acetate (VIb)——To a solution of IIb (94 mg) in $CHCl_3$ (5 ml) with a small amount of iron–filings was added bromine (0.020 ml) dropwise under stirring in 1 hr at 5—10°, the stirring was continued at 15—20° for another 3 hr. The resulting solution was added into ice–water, extracted with CH_2Cl_2, washed with 10% Na_2CO_3 and water until neutral, dried over Na_2SO_4. After evaporation of the solvent the residue was recrystallized from *n*-hexane to give 102 mg (91%) of VI.

2α,3α-(*o*-Nitrophenylmethylene)-5α-androstan-17β-ol Acetate (VII)——To a stirred solution of Ac_2O (4 ml) and nitric acid (d 1.5, 0.1 ml) was added IIb in small portions at −5°. The temperature was raised up gradually to 15°, and maintained for 1 hr at this temperature. The reaction mixture was poured into ice–water, neutralized with Na_2CO_3, extracted with CH_2Cl_2, and the extract was washed with water, dried over Na_2SO_4, and concentrated. The product was purified by preparative TLC on silica gel G (Merk) developing with a 4:1 mixture of cyclohexane–AcOEt to give 91 mg (82%) of VII. The other product such as para isomer did not be isolated although the NMR spectrum of the reaction mixture shows A_2B_2 type signals of para-substituted aromatic protons.

Reduction of 2-Benzylidene-17β-hydroxy-5α-androstan-3-one (I)——A mixture of I (1.0 g), 10% Pd–C (500 mg) and EtOH (85 ml) was shaken at room temperature and atmospheric pressure until 77 ml (1.2 molar equivalent) of H_2 has been absorbed (at 21°). After the catalyst was filtered, the mixture was concentrated in a reduced pressure. The preparative TLC of the residue on silica gel GF developing with a 2:1 mixture of cyclohexane–AcOEt afforded 2β-benzyl-5α-androstan-17β-ol (7 mg, 0.7%) which acetate (IX) was identical with authentic sample obtained from III, 2α-benzyl-17β-hydroxy-5α-androstan-3-one (VIIIa: 832 mg, 83%) and 2ξ-benzyl-5α-androstan-3ξ, 17β-diol (X: 157 mg, 16%). VIIIa: mp 138—141°, fine needles (from cyclohexane–acetone). $[\alpha]_D^{23}$ −70.7 (c=0.389, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{36}O_2 \cdot 3/4H_2O$: C, 79.28; H, 9.53. Found: C, 78.94; H, 9.47. VIIIb (acetate): mp 144—146°, needles (from *n*-hexane–ether). $[\alpha]_D^{20}$ −66.4 (c=0.976, $CHCl_3$). *Anal.* Calcd. for $C_{28}H_{38}O_3$: C, 79.62; H, 9.00. Found: C, 79.31; H, 9.02. X: mp 196—197°, needles (from acetone). *Anal.* Calcd. for $C_{26}H_{38}O_2$: C, 81.62; H, 10.01. Found: C, 81.46; H, 10.00. X-Diacetate: mp 148—149°, plates (from MeOH). $[\alpha]_D^{24}$ +31.0 (c=0.754, $CHCl_3$). *Anal.* Calcd. for $C_{30}H_{42}O_4 \cdot 1/4H_2O$: C, 76.51; H, 9.03. Found: C, 76.63; H, 8.99.

2α-Benzyl-5α-androstan-17β-ol Acetate (XI)——A mixture of VIII (100 mg), 90% $NH_2NH_2H_2O$ (1.5 ml) and KOH (0.3 g) in TEG (5 ml) was heated to 180° during 1 hr, then the temperature of the reaction mixture raised to 210° for 3 hr. The reaction mixture was cooled, poured into ice–water, and the product was ex tracted with CH_2Cl_2. The extract was acetylated with pyridine (2 ml) and Ac_2O (1 ml) at room temperature overnight. The work-up in usual manner afforded XI, mp 147—148°. The mixture melting point of V and the derived sample shows depression.

Reduction of 2-Benzyl-17β-acetoxy-5α-androst-1-en-3-one (IIIb)——The acetate IIIb(110 mg) in EtOH (30 ml) was hydrogenated over 20% Pd–C at room temperature and atmospheric pressure until practically 3 molar equivalent of H_2 (18.9 ml at 21°) had been absorbed. After the catalyst was filtered, the mixture was concentrated in a reduced pressure, and the products were isolated by preparative TLC on Silica Gel G developing with a 4:1 mixture of cyclohexane–AcOEt. 2β-Benyzl-5α-androstan-17β-ol acetate (IX): 30 mg (28%), mp 152—154°. The mixture melting point of V and XI shows depression. XI: 18 mg (17%). XI and 9 mg of IX were calculated from the signals of NMR spectrum of the mixture obtained from the mother liquid of recrystallization of IX. 2ξ-Benzyl-17β-acetoxy-5α-androstan-3ξ-ol (XII): 23 mg (21%), mp 200—202°, needles (from acetone). *Anal.* Calcd. for $C_{28}H_{40}O_3 \cdot 3/4H_2O$: C, 76.75; H, 9.54. Found: C, 76.90; H, 9.12. XII-Diacetate: mp 163—165°, needles (from MeOH). $[\alpha]_D^{24}$ +36.2 (c=0.944, $CHCl_3$). *Anal.* Calcd. for $C_{30}H_{42}O_4$: C, 77.21; H, 9.07. Found: C, 76.85; H, 9.24. VIIIb: 3 mg.

Reduction of 2-Benzyl-5α-androst-2-en-17β-ol Acetate (XIII)——The acetate VIIIb was reduced with $NaBH_4$ (10.8 mg) in MeOH (10 ml) with stirring at room temperature. (The reaction mixture was added into water, extracted with CH_2Cl_2, washed successively with water, 5% HCl, 10% Na_2CO_3 and water again until neutral, and dried over Na_2SO_4). The work-up in usual manner afforded the 3ξ-hydroxy compound

(79 mg) which was treated with tosylchloride (100 mg) and pyridine (3 ml). The tosylate (100 mg) was heated with collidine (3 ml) and xylene (3 ml) under reflux for 10 hr. The work-up in usual manner gave XIII (45 mg, 58%). IR cm^{-1}: $\nu_{C=O}^{OR}$ 1738, 1242; δ_{C-H} (aromatic) 761, 701. NMR (in $CDCl_3$) τ: 9.31 (3H, 18-CH_3), 9.24 (3H, 19-CH_3), 7.99 (3H, CH_3CO–), 6.77 (2H, $PhCH_2$–), 4.59 (1H, C–3H), 2.80 (5H, C_6H_5). The acetate XIII (39 mg) was hydrogenated over 10% Pd–C to give the mixture (32 mg, 82%) of IX and XI in a ratio about 1:1 by comparison of the integrals of the NMR spectra.

3-Benzyl-5α-androst-2-en-17β-ol (XIV)——To a solution of $C_6H_5CH_2MgBr$ prepared from $C_6H_5CH_2Br$ (43 ml) and Mg-filings (730 mg) in dry ether (50 ml) was added dropwise a solution of 17β-hydroxy-5α-androstan-3-one (1.74 g) in dry tetrahydrofuran (30 ml) with stirring, and the reaction mixture was heated under reflux for 1 hr and the stirring was continued overnight at room temperature. The reaction mixture was added into ice–water, acidified with 10% HCl, and extracted with CH_2Cl_2. The extract was washed with water, 10% Na_2CO_3 and water again until neutral, dried over Na_2SO_4 and evaporated. The residue was chromatographed over alumina (Merk neutral contained 3% water, 65 g) eluting with a 3:7 mixture of benzene–CH_2Cl_2 to give 1.364 g (64%) of 3ξ-benzyl-5α-androstan-3ξ,17β-diol which was characterized as monoacetate, mp 152—153°, needles (from *n*-hexane). *Anal.* Calcd. for $C_{28}H_{40}O_3$: C, 79.20; H, 9.50. Found: C, 79.45; H, 9.46. A solution of the 3ξ-benzyl-3ξ-hydroxy compound (200 mg) in EtOH (20 ml) with conc. HCl (1 ml) was heated under reflux for 5 hr. After working up in usual way as described above, the product was purified by preparative TLC on gilica gel G (Merk) developing with a 1:1 mixture of cyclohexane–AcOEt to give 136 mg (71% from the 3ξ-hydroxy compound) of XIV, mp 128—130°, fine pillars (from *n*-hexane-acetone). $[\alpha]_D^{23}$ +57.7 (c=0.766, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{36}O$: C, 85.66; H, 9.95. Found: C, 85.81; H, 10.03. NMR δ (cps): 42.5 (3H, 18-CH_3), 43.8 (3H, 19-CH_3), 193.5 (2H, $PhCH_2$), 322.5 (1H, C-17H).

Reduction of 3-Benzyl-5α-androst-2-en-17β-ol (XIV)——XIV (95 mg) was hydrogenated over 10% Pd–C (300 mg) in EtOH (25 ml). One molar equivalent of H_2 was absorbed. The catalyst was removed, the filtrate was concentrated in a reduced pressure. Acetylation of the residue with Ac_2O (2 ml) in pyridine (3 ml) gave the mixture of XV and V. Recrystallization of the mixture from MeOH gave 81 mg of XV and repeated recrystallizations from mother liquid gave 3 mg of V which was identical with the reduction product from II by mixture melting point determination and comparison of their IR spectra. Yields of XV and V were 89% and 6.5% respectively by comparison of the integrals of the NMR spectrum of the mixture.

Reduction of 5′-Phenyl-17β-hydroxyandrost-4-eno[3,2-*c*]pyrazole (XXV)——The compound XXV (50 mg) in MeOH (25 ml) was hydrogenated over 10% Pd–C to yield, after isolation by preparative TLC in usual manner, 15 mg (30%) of XXIV and 4 mg (8%) of IV. The yield of IV was calculated from its NMR spectrum of the integrals of the mixture of IV and XXV which are in same band on TLC.

Attempts of Isolation of Intermediate——1) From 2-Benzylidene-17β-hydroxy-5α-androstan-3-one (I): a. A mixture of I (500 mg), 90% $NH_2NH_2H_2O$ (1 ml), conc. HCl (2 ml) and MeOH (40 ml) was heated under reflux for 3 hr, evaporated and extracted with CH_2Cl_2. The extract was washed with water until neutral, dried over Na_2SO_4 and evaporated. Upon separation by chromatography over alumina (Merk neutral contained with 3% water) eluting with benzene–CH_2Cl_2 and 1% MeOH in CH_2Cl_2, there were obtained 115 mg (22%) of IV which was characterized as diacetate, mp 132—134°.

b. A mixture of I (500 mg), 90% $NH_2NH_2H_2O$ (1 ml) and MeOH (40 ml) was hated under reflux for 4 hr to give 121 mg (23%) of IV after separation by preparative TLC on silica gel GF (Merk) developing with a 1:1 mixture of cyclohexane–AcOEt.

c. A mixture of I (200 mg), 80% $NH_2NH_2H_2O$ (2.5 ml), KOH (0.4 g) and TEG (12 ml) was heated at 130—140° for 2 hr, added into ice-water and extracted with CH_2Cl_2. The result is shown in Table IV.

2) From 2-(*p*-Dimethylaminobenzylidene)-17β-hydroxy-5α-androstan-3-one (XVI): A mixture of XVI (500 mg), 80% $NH_2NH_2H_2O$ (2 ml) and MeOH (35 ml) was heated under reflux for 5.5 hr. The work-up was carried out in usual way as described above to give 221 mg (36%) of XIX which was characterized as diacetate, mp 143—145°.

3) From 2-(*p*-Nitrophenylmethylene)-17β-hydroxy-5α-androstan-3-one (XX): A mixture of XX (200 mg), 90% $NH_2NH_2H_2O$ (0.5 ml) and MeOH (20 ml) was heated under reflux for 2 hr. The work-up was carried out in usual way as described above to give 37 mg (18%) of XXI, mp>290°. Other products show carbonyl band in their IR spectra and could not be led to crystalline substances.

4) From 2-Benzylidene-Δ^6-testosterone (XXVI): A mixture of XXVI (1.182 g), 90% $NH_2NH_2H_2O$ (11 ml), KOH (2.2 g) and TEG (40 ml) was heated at 140° for 40 min, and the temperature was raised to 180° and maintained at this temperature for 20 min, then at 210° for 3 hr. The work-up was carried out in usual way as described above to give 307 mg (27%) of XXVII, 648 mg (53%) of XXV, 53 mg (2.6%) of XXIX and 8 mg (0.53%) of XXIV. XXIX: mp 193—195° needles (from MeOH). $[\alpha]_D^{23}$ −247.5 (c=0.915, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{34}ON_2$: C, 79.95; H, 8.78; N, 7.17. Found: C, 79.85; H, 8.83; N, 7.65. IR cm^{-1}: ν_{N-H} 3374; $\nu_{C=N}$ 1604 (Nujol).

Acknowledgement The authors wish to thank Dr. K. Takeda, Director of this Laboratory, for many helpful discussions and suggestions throughout the course of this work.