270. Steroid Total Synthesis, Part III[1]. 9β, 10α-Testosterone[2]

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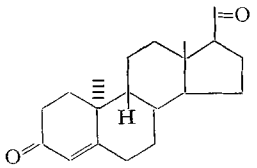
(13. IX. 71)

Summary. The total synthesis of 9β,10α-testosterone *via* a BCD-tricyclic intermediate is described. The latter compound – 17β-hydroxy-des-A-androst-9-en-5-one – was obtained in optically active form by our previously reported scheme, using an efficient resolution step early in the synthesis. New results regarding the asymmetric induction step are also discussed.

9β,10α-Steroids (retro-steroids) are important unnatural steroids which have been found to exhibit interesting endocrinological properties [2]. The partial synthesis [3] of 9β,10α-progesterone (**1**) from progesterone and the total synthesis [4] of the same compound from (–)-17β-hydroxy-des-A-androst-9-en-5-one (**2a**) have been reported previously. This paper describes the total synthesis of 9β,10α-testosterone **3** [5] as well as new results obtained in the course of our work [1] on the synthesis of the intermediate **2a**.



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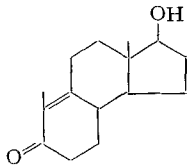
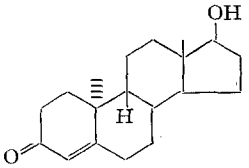


2a



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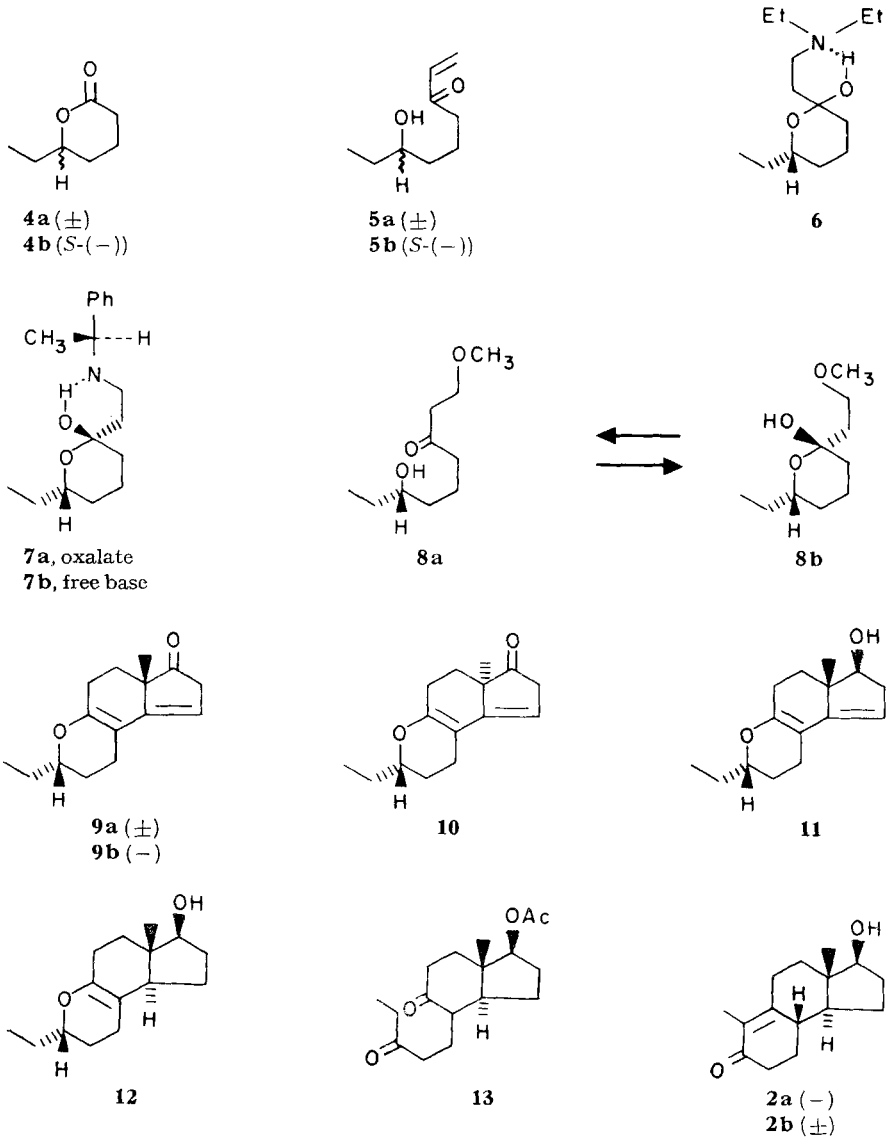
Total Synthesis of (–)-17β-Hydroxy-des-A-androst-9-en-5-one (**2a**). We reported [1] the synthesis of **2a** from (*S*)-(–)-5-hydroxydecanoic acid lactone **4b**, involving a novel asymmetric induction for the key step **5b** → **9b** (see scheme I). An alternate approach, here described, is based on the optical resolution of the base **7b** and its transformation to the optically active key intermediate **9b** and thence to the desired product **2a**. Our hope for a successful resolution of a base such as **7b** was based on the finding that the *Mannich* adduct **6**, which was readily obtained from the vinyl ketone **5b**, does mainly exist as the internal hemiacetal and probably assumes a relatively rigid spiroheterocyclic structure, due to the hydrogen bond between the hydroxyl group and the nitrogen atom. We were gratified to find that the mixture of diastereo-isomers formed upon adding (–)-α-methylbenzylamine to the racemic vinyl ketone **5a** could readily be resolved *via* the oxalates and crystallization from acetone. Thus, the oxalate **7a** ($[\alpha]_D^{25} = -37°$) was obtained in good yield and, by treatment with sodium carbonate solution, gave the base **7b**, $[\alpha]_D^{25} = -14.7°$. The latter, when dissolved in chloroform, was found to contain about 25% of the 'open form' (IR.

[1] Part II; see [1].

[2] Presented at the Third International IUPAC Congress on the Chemistry of Natural Products (Steroids and Terpenes), Mexico City, Mexico, D.F., April 21–25, 1969; Program 14-A.

Scheme I



and NMR. analysis)[3]). Although both **7a** and **7b** were found to react with 2-methylcyclopentane-1,3-dione to give the diene **9b**, we chose to first convert the base **7b** to the methanol adduct **8a, b**, which is afforded in 90% yield by heating **7b** in methanol containing sodium hydrogencarbonate and benzaldehyde. In addition to **8a, b**, one obtains the *Schiff*-base derived from (−)-α-methylbenzylamine and benzaldehyde. According to IR. and NMR. analysis, the methanol adduct is a mixture

[3]) See Experimental.

of the 'open' hydroxyketo form **8a** and its cyclic hemiacetal form **8b**, the ratio being approximately 1:1.

Upon reacting **8a**, **b** with 2-methylcyclopentane-1,3-dione in boiling toluene/acetic acid [1], we obtained in 80.5% yield after chromatography, a mixture ($[\alpha]_D^{25} = -166°$) of the two dienes **9b** and **10**. By combination of chromatography and crystallization, we were able to isolate the *'trans'* product **9b** in what we believe to be optically pure form ($[\alpha]_D^{25} = -195°$). In addition, we obtained a crystalline product which had $[\alpha]_D^{25} = -125°$. By TLC., UV. and IR. analysis these two products were indistinguishable, and there was but a very slight and inconclusive difference in the NMR. spectra. However, the CD. spectra (see Fig. 1) were significantly different: the first product ($[\alpha]_D^{25} = -195°$) gave rise to two opposite *Cotton* effects at 244 nm ($\Theta = 39{,}000$) and 272 nm ($\Theta = 16{,}000$) which are due to the diene and carbonyl chromophors, respectively, thus providing a proof [1] for the absolute stereochemistry of the two chiral centers present in **9b**. In contrast, the CD. spectrum (see Fig. 2) of the second product ($[\alpha]_D^{25} = -125°$) was practically devoid of the carbonyl *Cotton*

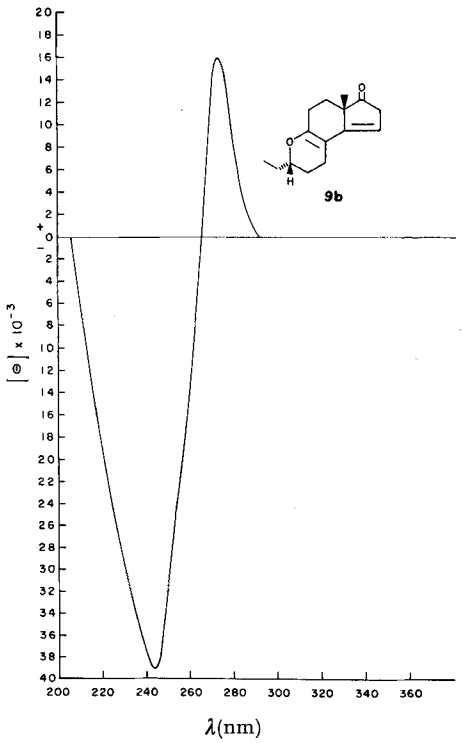


Fig. 1. *CD. Spectrum of* **9b** *in Dioxane*

effect, but showed again a negative *Cotton* effect at 250 nm ($\Theta = 29{,}200$) due to the diene chromophor. The absence of the carbonyl *Cotton* effect is best explained by the postulate that the product isolated is a 1:1 mixture consisting of **9b** and its 13α-methyl isomer **10**. As expected on the basis of this CD. analysis, the first product led

to the optically pure BCD-tricyclic compound **2a** by the sequence described [1] previously (**9b** → **11** → **12** → **13** → **2a**). On the other hand, the second product afforded completely racemic **2b**, thus supporting our postulate.

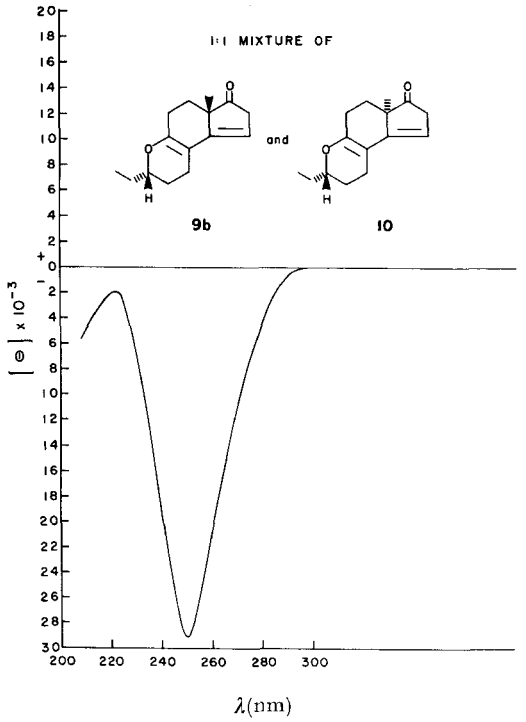


Fig. 2. *CD. Spectrum of* **9b** *and* **10b** (*1 : 1*) *in Dioxane*

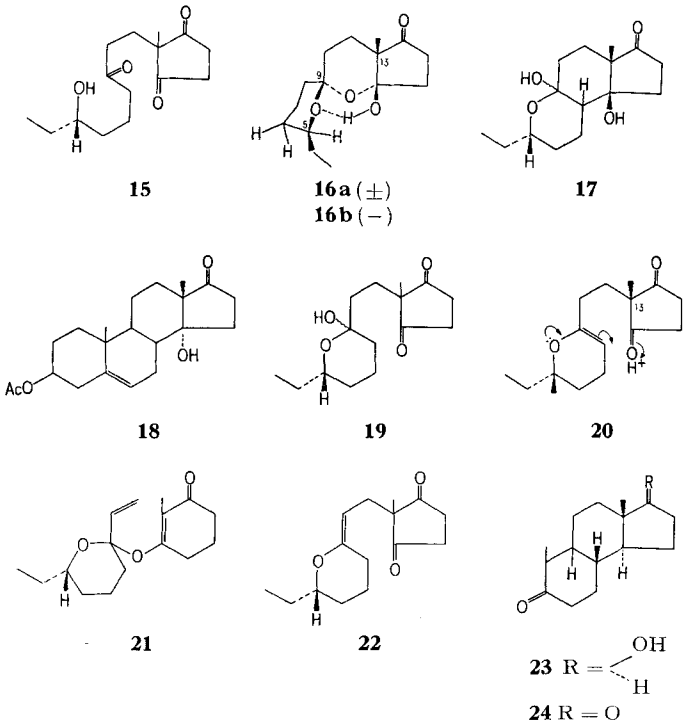
The degree of asymmetric induction in the formation of the new chiral center (C-13) of the diene **9b** can be estimated on the basis of a) the rotation[4]) observed for the mixture **9b** and **10**, and b) the yield obtained for pure **9b** and the 1:1 mixture **9b** and **10**. We estimate that the 13α/13β ratio is in the order of 1:4, thus favoring the '*trans*'-isomer **9b**.

Our attempts to optimize the degree of asymmetric induction in the formation of the diene **9b** from the optically active precursor **5b** (common intermediate derivable from **6** [1], **7b** and **8a**) led to the following interesting findings: Quaternization of the amine **7b** with methyl iodide followed by reaction with 2-methylcyclopentane-1,3-dione in boiling *t*-butanol gave, after chromatography, some diene (**9b** and **10**; ~ 6%), and a new intermediate in 30% yield, best represented as **16b** (Scheme II). The new intermediate **16b**, a crystalline compound (m.p. 91.5–96°; $[\alpha]_D^{25} = +93°$), appears to be uniform and one of several possible hemiacetal forms derived from the

4) The calculation is based on the following figures: $[\alpha]_D^{25} = -195°$ and $-55°$ for **9b** (see above) and **10**, respectively. The latter figure is derived from the fact that the 1:1 mixture of **9b** and **10** was found to have $[\alpha]_D^{25} = -125°$. The calculation disregards possible interactions between the two isomers, and is, therefore, at best an approximation.

Michael adduct **15**. The IR. spectrum of **16b** in chloroform shows 1 carbonyl band at 1745 cm^{-1} and a band for a bonded hydroxyl group at 3550 cm^{-1}, which did not change upon dilution. The NMR. spectrum of **16b** (see Exper.) is in agreement with the proposed structure.

Scheme II



The CD. spectrum (dioxane) of **16b** exhibits a weak positive *Cotton* effect with 2 maxima at 293 and 302 nm, $\Theta = +2007$ and $+2227$, respectively. In contrast the 14α-hydroxy-17-oxo-steroid **18** is known [6] to have a stronger, positive *Cotton* effect, $\Theta = +5700$. Application of the octant rule [7] to the 2 systems (*Dreiding* models) suggests that a 13β-methyl-14β-hydroxy-17-oxo moiety should have a weaker *Cotton* effect than its 14α-isomer. It can be seen from a *Dreiding* model that structure **16b** is a very favorable arrangement. Both tetrahydropyran rings as well as the third ring, which contains 3 oxygen atoms and is held together by the hydrogen bond, assume the chair conformation, the ethyl group at C-5 being in the equatorial position. The axial position of the proton at C-5 is evident from the NMR. spectrum. Furthermore, the C–O bonds are both in the favored axial orientation (anomeric effect; see [8]).

A racemic compound (**16a**; m.p. 98.5–103°), exhibiting IR. and NMR. data identical with those of **16b**, had been obtained earlier from the vinyl ketone **5a** upon reaction with 2-methylcyclopentane-1,3-dione in *t*-butanol and water at 50°[3]. In addition, we had found that **16a** reacts smoothly with *p*-toluenesulfonic acid in benzene at room temperature, giving rise to racemic **9a** in excellent yield[3]. This seemed to indicate a very high degree of asymmetric induction. Indeed, when these

conditions were applied to the (+)-enantiomer **16b** (reaction time: 2 h), the two dienes **9b** and **10** were obtained in a ratio[4]) of about 20:1, in a total yield of 90% ($[\alpha]_D^{25}$ of the chromatographed mixture = −189°). A significantly inferior degree of asymmetric induction was observed on treating **16b** with acetic acid in boiling toluene or with hydrobromic acid and acetic acid in hexane-toluene at 0°, since the rotations found for the chromatographed mixture **9b** and **10** were −176° and −174° respectively, indicating a ratio[4]) **9b**:**10** of about 5:1. Reducing to 10 min the reaction time of **16b** with *p*-toluenesulfonic acid in benzene at room temperature cleanly gave **17** as the only intermediate in about 74% yield, in addition to about 15% of the diene mixture **9b** and **10**. The new intermediate **17**, an oil, had 1 carbonyl band at 1740 cm^{-1} and two hydroxyl bands at 3595 and 3510 cm^{-1}. The NMR. spectrum (see Exper.) appears to support the proposed structure **17**. The CD. spectrum (dioxane) of **17** again exhibits a weak positive *Cotton* effect (maxima at 295 and 304 nm, Θ = +754 and +807, respectively), thus indicating the presence of a 13β-methyl-14β-hydroxy-17-keto grouping. Treatment of **17** with *p*-toluenesulfonic acid in benzene at room temperature gave an excellent yield of the *'trans'*-compound **9b**, containing only about 10% of the isomeric *'cis'*-compound **10**, as calculated[4]) from the optical rotation ($[\alpha]_D^{25}$ = −189°).

As regards the *mechanism of formation* of the diene **9b** from **5b** (or derived adducts such as **6**, **7b** and **8a**), we think that the first step consists of a *Michael* addition leading to the adduct **15** (Scheme II). Our finding[3]) that methyl vinyl ketone also undergoes *Michael* addition (without ensuing ring closure!) when reacted with 2-methylcyclopentane-1,3-dione in boiling acetic acid–xylene lends support to our idea, although we cannot rule out other possibilities, such as the one involving a sigmatropic rearrangement of the hypothetical system **21**, which would afford the interesting enol ether **22**. As pointed out above, the cyclic hemiacetal **16b** is derived from the hydroxy-ketone **15** which is very likely in equilibrium with several hemiacetal forms, such as **19**, **16b**, and stereoisomers thereof. Obviously, the equilibrium favors the isomer **16b**, since this compound can be isolated in crystalline form and gives spectral data (IR. and NMR.) consistent with a uniform compound. As regards the crucial 'cyclization' step, we suggest the enol ether **20** as a hypothetical intermediate, and bond formation taking place as indicated. The reaction [9] of the carbonyl group with an enol ether moiety would seem to be rather facile in our case, due to the proximity of the two reactive centers. Formation of **20** from **15** *via* **19** in an acid-catalysed reaction can easily be visualized. We further believe that the observed asymmetric induction takes place at this stage, *viz.* in the conversion of **20**, which has a prochiral center at C-13, to **17**, as shown. A clear cut preference of the reaction depicted in **20** over the alternative with the methyl group in the α position is not evident from model inspections. On the other hand, it is very tempting to speculate that the asymmetric induction may be a result of the preferred formation of the hemiacetal **16b**, in the sense that the chirality of C-13 may be preserved in the process leading to the diene **9b**.

As reported in [1], the condensation product **9b** needs not be separated from its 13α-isomer **10** for the transformation to the tricyclic compound **2a**, since crystallization of optically impure **2a** readily yields optically pure material. The reduction of the mixture **9b** and **10** ($[\alpha]_D^{25}$ = −166°; obtained from the ketone **8a**, **b**) was performed

with Dibal-H or sodium borohydride rather than with lithium aluminum hydride. The further transformations (**11** → **12** → **13** → **2a**) were readily achieved as reported [1] previously, simple crystallization of the desired product **2a** being the only purification step. A sample of **11** ($[\alpha]_D^{25} = -195°$), which is believed to be optically pure, was obtained by reduction of the pure ketone **9b**. The surprisingly small difference of the $[\alpha]_D$ values of **9b** and **11** is probably the result of two opposite effects.

In order to prepare *9β,10α-testosterone* (**3**), the BCD-tricyclic compound **2a** was first converted to the BC-*cis* intermediate **23**, using the published procedure [10] (preparation of the 17-O-acetyl-**2a**, hydrogenation with rhodium on alumina in HCl-ethanol, followed by hydrolysis; 70% overall yield). The final transformation of **23** to retro-testosterone (**3**) was achieved by annelation [3] with methyl vinyl ketone (MVK)[5]). The condensation conditions were carefully investigated in order to optimize the yield. The best procedure consists in reacting **23** with 0.75 equivalent of MVK in *t*-butanol at 50° in the presence of catalytic amounts of sodium hydroxide. The product is separated by chromatography on alumina, affording 20–23% of **3** and 55–60% of recovered starting material **23**, so the conversion yield amounts to about 54%. Secondary reaction of **3** with MVK is the major limiting factor, whereas the undesirable alkylation at C-6 does not appear to cause much trouble. The annelation procedure described by *Yanagita et al.* [11] (4-dimethylamino-2-butanone and catalytic amounts of sodium) gave inferior results. Interestingly, the diketone **24** reacted fairly selectively with MVK under our best conditions, affording 15% of retro-androst-4-ene-3,17-dione and 40% of recovered **24**.

Retro-testosterone (**3**), the final product of this total synthesis, was compared with an authentic sample [5] and found to be identical in all respects.

Experimental

General. – M.p.'s were taken on a *Thomas Hoover* apparatus and are uncorrected. IR. spectra were recorded on a *Beckman* Model IR-9 instrument. UV. spectra were recorded on a *Cary* Model 14 spectrophotometer. NMR. spectra were measured on a *Varian* HA-100 or A-60 A spectrometer, using tetramethylsilane as an internal standard. ORD. and CD. spectra were measured on a *Jasco* Model ORD. UV-5 instrument. Optical rotations were recorded on a *Perkin-Elmer* Model 141 polarimeter. All reactions and chromatograms were routinely monitored by thin-layer chromatography (TLC.). (*Brinkman* silica gel GF 254 plates, benzene-ethyl acetate 1:1.) The spots were developed by spraying with 50% aqueous *p*-toluenesulfonic acid followed by heating to 150°. *Woelm* neutral aluminium oxide grade III and silica gel 0.2–0.5 mm were used for column chromatography. Usual working up means 3 extractions with benzene, washing with brine, saturated $NaHCO_3$ solution and brine, drying over Na_2SO_4, filtration, and evaporation at 40° in vacuo.

1. **(–)-3(5)-Ethyl-6a(*S*)-methyl-1,2,3,5,6,6a-hexahydro-cyclopenta[*f*]chromen-7(8*H*)-one (9b) from *rac.*-lactone 4a *via* 7,8.** – *2*(S)-[*2*-((S)-α-*Phenylethyl-amino*)-*ethyl*]-*6*(S)-*ethyl-tetrahydropyran-2-ol oxalate* (**7a**). A solution of lactone **4a** (51.2 g, 0.4 mole) in tetrahydrofuran (THF) (525 ml) under nitrogen was cooled to –75° in a dry ice-acetone bath. A solution of 3.0 M vinylmagnesium chloride in THF (215 ml, 0.64 mole) was added within 10 min at a temperature of –60°. The mixture was stirred for an additional 10 min at –60°. After cooling to –75°, methanol (40 ml) was added carefully to the reaction mixture at –60°. For complete hydrolysis, the mixture was poured into a 10% ammonium chloride solution (350 ml). The resulting emulsion was treated with a few drops of glacial acetic acid until two clear layers resulted. The aqueous layer was separated and extracted with THF (2 × 500 ml and 2 × 200 ml). The combined THF

[5]) Experiments performed by *R. Walter*.

extract (crude *vinyl ketone* **5a**) was washed with brine and then treated with (−)-α-methylbenzylamine (48.4 g, 0.4 mole). The solution was left at room temperature for 2 h and was then evaporated to dryness. The residue was diluted with hexane (250 ml), placed in a separatory funnel and treated with 800 ml of a 1:1 mixture of acetone and 1.5 N sulfuric acid. The aqueous layer was separated and extracted with more hexane (250 ml). The hexane extract was washed with 100 ml of a 1:1 mixture of acetone and 1.5 N sulfuric acid. The two combined aqueous layers were cooled in an ice-bath, made pH 11 (with 20% Na_2CO_3 solution) and then extracted with ether (2 × 500 ml and 2 × 200 ml). The combined extract was washed with brine, dried ($MgSO_4$) and the solvent removed to give 92.4 g of yellow oil. This material was dissolved in acetone (175 ml) and added to a solution of oxalic acid (36 g) in acetone (170 ml). The solution was left at room temperature for 5 h and in the refrigerator (0°) for 15 h. The crystals were filtered off and washed with cold acetone and cold isopropyl ether. After drying over P_2O_5 in a high vacuum, 36.5 g of crude **7a** were obtained; m.p. 121–122°, $[\alpha]_D^{25} = -28.8°$ (MeOH). Recrystallization from acetonitrile (1090 ml; some insoluble material was filtered off) at room temperature (5 h) and finally at 0° (20 h) gave pure **7a** (29.4 g; 20.1% from **4a**); colorless crystals, m.p. 123–124°, $[\alpha]_D^{25} = -38.8°$ (MeOH). A sample was crystallized again from acetonitrile for analysis: colorless crystals, m.p. 123–124°, $[\alpha]_D^{25} = -37.2°$ (MeOH).

$C_{17}H_{27}NO_2 \cdot (CO_2H)_2$	Calc.	C 62.10	H 7.96 N 3.81%
(367.4)	Found	,, 62.46	,, 8.10 ,, 4.08%

Free base **7b**. A mixture of the oxalate **7a** (1.84 g) and water (90 ml) was heated to 50° until all the material dissolved. The resulting solution was cooled and treated with a 20% Na_2CO_3 solution until pH 10 was reached. The usual working up gave **7b** (1.39 g) as an oil. A sample was chromatographed on alumina. Elution with hexane-ether-(2:1) and -(1:2) afforded the analytical sample; colorless oil, $[\alpha]_D^{25} = -14.7°$ (*c* = 1.04, benzene). IR. ($CHCl_3$): 3440–3200, 1710 cm^{-1}. NMR. ($CDCl_3$): δ 0.93 (*t*, 0.75 H, *J* = 7 Hz, 0.25 CH_3CH_2), 0.96 (*t*, 2.25 H, *J* = 7 Hz, 0.75 CH_3CH_2), 7.18 (*s*, 5 H, phenyl).

$C_{17}H_{27}NO_2$ (277,42) Calc. C 73.60 H 9.81 N 5.05% Found C 73.44 H 9.95 N 5.24%

2(S)-(2-Methoxethyl)-6(S)-ethyl-tetrahydropyran-2-ol (**8a,b**). A mixture of '*Mannich* base' **7b** (1.0 g, 3.62 mmoles), methanol (20 ml), sodium hydrogencarbonate (100 mg) and benzaldehyde (540 mg, 5.1 mmoles) was refluxed for 17 h. The reaction mixture was concentrated to a volume of 5 ml, diluted with brine and extracted with ether. The ether extract was washed with brine, dried (Na_2SO_4) and evaporated to give crude **8a,b** (1.6 g) as a colorless oil which was chromatographed on silica gel (40 g). Elution with benzene and benzene-ether-(19:1) gave the *Schiff* base derived from (−)-α-methyl-benzylamine and benzaldehyde as a colorless oil (625 mg). Further elution with benzene-ether-(4:1), -(2:1), -(1:2) and pure ether yielded the methanol adduct **8a,b** (612 mg); colorless oil. IR. ($CHCl_3$): 3460, 1717 cm^{-1}. NMR. ($CDCl_3$): δ 0.93 (*t*, 3 H, *J* = 7.5 Hz, CH_3CH_2), 3.28 (*s*, 1.5 H, 0.5 CH_3O), 3.31 (*s*, 1.5 H, 0.5 CH_3O). Mass Spectrum (*m/e*): 188 (M^+), 141, 129, 105 (base peak) and 87.

3(S)-Ethyl-6aβ(S)-methyl-1,2,3,5,6,6a-hexahydro-cyclopenta[f]chromen-7(8H)-one (**9b**) *and 1:1 mixture of* **9b** *and* **10**. A mixture of **8a,b** (997 mg, 5.3 mmoles), toluene (19 ml), 2-methylcyclopentane-1,3-dione (770 mg, 6.87 mmoles) and acetic acid (9 ml) was carefully degassed, placed under nitrogen and heated at 110° for 16 h, using a *Dean Stark* trap. (At this temperature there was slight reflux but not enough for water to distill over.) The temperature was then raised to 130° for 1 h. The usual working up gave 1.14 g of crude product which was chromatographed on alumina (50 g). Elution with hexane, hexane-ether-(9:1) and -(4:1) afforded the mixture **9b** and **10** (991 mg) as orange colored crystals; $[\alpha]_D^{25} = -165.6°$ (*c* = 1.43, $CHCl_3$). This product, when crystallized from 2-propanol (6 ml) at room temperature, produced the *1:1 mixture of* **9b** *and* **10** (285 mg): colorless crystals, m.p. 99–103°, $[\alpha]_D^{25} = -125.5°$ (*c* = 1.09, $CHCl_3$). Further recrystallizations from 2-propanol gave the analytical sample: colorless crystals, m.p. 99.5–102°, $[\alpha]_D^{25} = -125.26°$ (*c* = 1.15, $CHCl_3$). IR. ($CHCl_3$): 1747, 1648 cm^{-1}. UV.$_{max}$ (EtOH) at 253 nm (ε = 17,400). NMR. ($CDCl_3$): δ 0.97 (*t*, 3 H, *J* = 7 Hz, CH_3CH_2), 1.12 (*s*, 3 H, CH_3), 3.71 (*m*, 1 H, H(3)), 5.39 (*t*, 1 H, *J* = 2.5 Hz, H(9)). ORD. (*c* = 0.2584, dioxane, 23°) $[\Phi]_{700}$ −187°, $[\Phi]_{589}$ −252°, $[\Phi]_{255}$ −10,400°, $[\Phi]_{232}$ 0°, $[\Phi]_{206\,(last)}$ +7000°. CD. (*c* = 0.0028 M, dioxane, 23°) $[\Theta]_{298}$ 0, $[\Theta]_{250}$ −29,200, $[\Theta]_{222}$ −1890, $[\Theta]_{208\,(last)}$ −5660.

$C_{15}H_{20}O_2$ (232.30) Calc. C 77.55 H 8.68% Found C 77.55 H 8.79%

The mother liquor was evaporated and the residue (650 mg) chromatographed on alumina (20 g). Elution with hexane gave **9b** (313 mg) as colorless crystals; m.p. 70–75.5°, $[\alpha]_D^{25} = -190.7°$ ($CHCl_3$). Recrystallization from hexane at −15° afforded the analytical sample: colorless crystals, m.p. 73–75°, $[\alpha]_D^{25} = -194.86°$ ($c = 1.11$, $CHCl_3$). IR. ($CHCl_3$): 1745, 1647 cm^{-1}. UV.$_{max}$ (EtOH) at 253 nm ($\varepsilon = 18{,}400$). NMR. ($CDCl_3$): δ 0.96 (*t*, 3 H, $J = 7$ Hz, CH_3CH_2), 1.11 (*s*, 3 H, CH_3), 3.68 (*m*, 1 H, H(3)), 5.39 (*t*, 1 H, $J = 2.5$ Hz, H(9)). ORD. ($c = 0.2584$, dioxane, 23°) $[\Phi]_{700} -323°$, $[\Phi]_{589} -446°$, $[\Phi]_{315} -17{,}700°$, $[\Phi]_{293}$ 0°, $[\Phi]_{285} +1080°$, $[\Phi]_{258} -22{,}700°$, $[\Phi]_{234}$ 0°, $[\Phi]_{207} +19{,}400°$. CD. ($c = 0.0028$ M, dioxane, 23°) $[\Theta]_{292}$ 0, $[\Theta]_{272} +16{,}000$, $[\Theta]_{265}$ 0, $[\Theta]_{244} -39{,}100$, $[\Theta]_{206\,(last)}$ 0.

$C_{15}H_{20}O_2$ (232.30) Calc. C 77.55 H 8.68% Found C 77.24 H 8.64%

2. **(−)-17β-Hydroxy-des-A-androst-9-en-5-one (2a) from diene 9b.** – *3(S)-Ethyl-6a(S)-methyl-1,2,3,5,6,6a,7,8-octahydro-cyclopenta*[f]*chromen-7β-ol* (**11**). A mixture of sodium borohydride (170 mg, 4.5 mmoles), water (3 ml) and ethanol (12 ml) was treated with a solution of **9b** (1.2 g, 5.17 mmoles) in benzene (4.8 ml) at 0°. The reaction mixture was stirred at 0° for 1 h. The usual working up gave crude **11** (1.17 g) as an oil which was chromatographed on silica gel (50 g). Elution with benzene-ether-(9:1), -(4:1) and -(2:1) afforded 892 mg of semi-crystalline material. Further chromatography on alumina (25 g), elution with hexane-ether-(9:1), -(4:1) and -(2:1) gave pure **11**; slightly tan crystals, m.p. 63–73°, $[\alpha]_D^{25} = -194.4°$ ($CHCl_3$). IR. ($CHCl_3$): 3630, 1647 cm^{-1}. UV.$_{max}$ (EtOH) at 252 nm ($\varepsilon = 18{,}000$). NMR. ($CDCl_3$): δ 0.96 (*t*, 3 H, $J = 7$ Hz, CH_3CH_2), 0.96 (*s*, 3 H, CH_3), 3.65 (*m*, 1 H, H(3)), 5.0 (*m*, 1 H, H(9)).

$C_{15}H_{22}O_2$ (234.32) Calc. C 76.88 H 9.46% Found C 76.90 H 9.62%

Hydrogenation of **11**. A solution of crude **11** (27.2 g) in toluene (540 ml) and triethylamine (1.3 ml) was hydrogenated at room temperature using a 5% palladium on carbon catalyst (4.0 g). The uptake of hydrogen (2.95 l) stopped after 3 h. The catalyst was filtered off, washed with benzene, and the combined filtrate evaporated to give *crude* **12** (27.9 g) as an oil.

Diketone **13** *from* **12**. – *Acetylation*. A solution of crude **12** (27.9 g) in pyridine (270 ml) was treated with acetic anhydride (80 ml) at 0° with stirring. The resulting mixture was stirred at room temperature for 15 h and then evaporated to dryness. The residue was worked up as usual and afforded 31 g of crude *O-acetyl-***12** as an oil.

Hydration and oxidation. A mixture of crude O-acetyl-**12** (31 g), acetone (600 ml) and 1 N H_2SO_4 (180 ml) was left at room temperature for $1^1/_2$ h, then cooled to −5° and treated with 65 ml of freshly prepared *Jones* reagent. The mixture was then stirred at room temperature for $3^1/_2$ h and after diluting with benzene (600 ml) followed by the usual working up, *crude* **13** was obtained as an oil (32.0 g).

Cyclization. A mixture of crude **13** (32.0 g), benzene (320 ml) and *p*-toluenesulfonic acid monohydrate (3.2 g) was refluxed (*Dean Stark* trap) for $2^1/_2$ h with stirring. The usual working up gave 28.4 g of crude *O-acetyl-***2a**.

Hydrolysis to (−)-17β-Hydroxy-des-A-androst-9-en-5-one (**2a**). A mixture of the crude cyclization product (28.4 g), methanol (150 ml) and 2 N NaOH (56 ml) was stirred at room temperature for 15 h and then poured into a mixture of hexane (280 ml) and water (170 ml). The aqueous phase was separated and extracted with hexane (100 ml) followed by benzene (5 × 250 ml). The combined benzene extracts were washed with brine, dried (Na_2SO_4) and evaporated to give crude **2a** (16.6 g; brown, crystalline). This was dissolved in benzene (60 ml) and by addition of hexane (110 ml) over a period of 1 h, gave crystals which were filtered and washed with a mixture of hexane-benzene-(3:1). Thus, 10.58 g of pure **2a** were obtained; colorless crystals, m.p. 163–168°, $[\alpha]_D^{25} = -38.3°$ ($c = 1.02$, $CHCl_3$), cf. [1].

(±)17β-Hydroxy-des-A-androst-9-en-5-one (**2b**) *from the 1:1 mixture of* (**9b**) *and* (**10**). The transformation was carried out as described above. Starting with 13 g of the 1:1 mixture of **9b** and **10**, 11.2 g of crude hydrolysis product were obtained. This was chromatographed on alumina (440 g). Elution with benzene, benzene-ethylacetate-(19:1), -(9:1), -(4:1) and -(2:1) afforded **2b** (7.1 g) as colorless crystals; m.p. 127–135°, $[\alpha]_D^{25} = 0°$ ($CHCl_3$). Recrystallization from ether-hexane and benzene-hexane gave the analytical sample **2b**: colorless crystals, m.p. 133–136°, $[\alpha]_D^{25} = 0°$ ($CHCl_3$), cf. [1].

3. **Alternative mode of formation of the dienes 9 and 10 from the vinylketone 5 *via* 16 and 17.** – *Cyclic hemiacetal* **16b**. A mixture of '*Mannich* base' **7b** (2.77 g), acetone (30 ml), methyl iodide

(5 ml) and anhydrous potassium carbonate (5.5 g) was stirred at room temperature for 20 h, the precipitate filtered off and washed with acetone. The residue obtained after evaporation of the filtrate was mixed with *t*-butyl alcohol (60 ml), water (30 ml) and 2-methylcyclopentane-1,3-dione (2.24 g) and refluxed for 24 h. The mixture was concentrated, diluted with methylene chloride, and extracted with saturated oxalic acid solution, saturated $NaHCO_3$ solution and brine. The aqueous layers were re-extracted with methylene chloride and the combined organic layers were dried (Na_2SO_4) and evaporated to give crude **16b** (2.5 g) as an oil which was chromatographed on silica gel (125 g). Elution with benzene-ether-(9:1) yielded 150.2 mg of **9b** and **10**. Further elution with benzene-ether-(4:1), -(2:1) and -(1:1) gave **16b** (1.96 g), which was recrystallized from 2-propanol at −15° to afford pure **16b** (815 mg): colorless crystals, m.p. 82–90°, $[\alpha]_D^{25} = +92.3°$ ($c = 1.0$, $CHCl_3$). A sample was recrystallized from 2-propanol at 0° to give the analytical sample: colorless crystals, m.p. 91.5–96°, $[\alpha]_D^{25} = +93.2°$ ($c = 0.955$, $CHCl_3$). IR. ($CHCl_3$): 3550, 1745 cm^{-1}. NMR. ($CDCl_3$): δ 0.92 (*t*, 3 H, $J = 8$ Hz, CH_3CH_2), 0.97 (*s*, 3 H, 13-CH_3), 3.74 (*s*, 1 H, OH; exchanged by D_2O addition), 3.90 (*d* of *d* of *t*, 1 H, $J_{aa} = 10.5$, $J_{ae} = 2.5$, $J_{vic} = 6$ Hz, H(5). ORD. ($c = 0.328$, dioxane, 23°) $[\Phi]_{700}$ +21.6°, $[\Phi]_{589}$ +35°, $[\Phi]_{321}$ +1059°, $[\Phi]_{312-309}$ +660° (shoulder), $[\Phi]_{302}$ 0°, $[\Phi]_{282}$ −831°, $[\Phi]_{238}$ 0°, $[\Phi]_{208\,(last)}$ +457°. CD. ($c = 0.012$ M, dioxane, 23°) $[\Theta]_{328}$ 0, $[\Theta]_{310}$ +1430 (inflection), $[\Theta]_{302}$ +2227, $[\Theta]_{296}$ +1980, $[\Theta]_{293}$ +2007, $[\Theta]_{256}$ 0, $[\Theta]_{245}$ −55, $[\Theta]_{232}$ 0, $[\Theta]_{208\,(last)}$ +385. $C_{15}H_{24}O_4$ (268.35) Calc. C 67.13 H 9.01% Found C 67.07 H 9.20%

Racemic cyclic hemiacetal **16a**. A mixture of crude vinyl ketone **5a** (2.0 g), *t*-butyl alcohol (40 ml), water (10 ml) and 2-methylcyclopentane-1,3-dione (3.0 g) was heated to 70° for 20 h. The residue obtained after evaporation of the reaction mixture was worked up as usual to give 5.0 g of an oily product, which was chromatographed on alumina (75 g). Elution with hexane-benzene-(9:1), -(2:1), -(1:1), -(1:2), pure benzene, and benzene-ethyl acetate-(9:1) yielded 2.04 g of **16a** as a semi-crystalline material. Recrystallization from pentane at −15° gave pure **16a** (692 mg); colorless crystals, m.p. 90–97°. A sample was recrystallized from 2-propanol for analysis: colorless crystals, m.p. 98.5–103°. IR. ($CHCl_3$): 3550, 1745 cm^{-1}. NMR. ($CDCl_3$): δ 0.93 (*t*, 3 H, $J = 8$ Hz, CH_3CH_2), 0.98 (*s*, 3 H, 13-CH_3), 3.75 (*s*, 1 H, OH), 3.90 (*d* of *d* of *t*, 1 H, $J_{aa} = 10.5$, $J_{ae} = 2.5$, $J_{vic} = 6$ Hz, H(5).

$C_{15}H_{24}O_4$ (268.35) Calc. C 67.13 H 9.01% Found C 67.10 H 9.25%

Diene **9a** *from* **16a**. A mixture of **16a** (190 mg), benzene (8 ml) and *p*-toluenesulfonic acid monohydrate (36 mg) was stirred at room temperature for $1^1/_2$ h. The usual working up gave crude **9a** which was chromatographed on alumina. Elution with pure hexane, hexane-benzene-(19:1), -(9:1) and -(4:1) afforded pure **9a** (142.5 mg); colorless crystals, m.p. 103–106°. This material was identical with the earlier reported product [12].

Dienes **9b** *and* **10** *from* **16b**. – a) A mixture of **16b** (100 mg), benzene (3 ml) and *p*-toluenesulfonic acid monohydrate (pTS) (10 mg) was stirred at room temperature for 50 min. After adding another 10 mg of pTS, the mixture was stirred for another 2 h. The usual working up gave 87.4 mg of crude product, which was chromatographed on silica gel (10 g). Elution with benzene-ether-(9:1) and -(4:1) afforded the mixture **9b** and **10** (78.2 mg); colorless crystals, $[\alpha]_D^{25} = -188.6°$ ($c = 1.047$, $CHCl_3$).

b) A mixture of **16b** (80.0 mg), toluene (3.0 ml) and glacial acetic acid (1.0 ml) was refluxed for 1 h. The usual working up gave 70.4 mg of crude product, which was chromatographed as described above to give the mixture of **9b** and **10** (60.9 mg); colorless crystals, $[\alpha]_D^{25} = -176.1°$ ($c = 1.025$, $CHCl_3$).

c) A solution of **16b** (100 mg) in hexane (2.5 ml) and toluene (0.5 ml) was cooled to 0° and treated with a 30% solution of hydrobromic acid in acetic acid (0.03 ml). The reaction mixture was left at 0° for 1 h and then treated with another 0.03 ml of the same acid solution. After $1^1/_2$ h at 0°, another 0.03 ml of the acid solution was added. After a total reaction time of $3^1/_2$ h at 0° the mixture was worked up as usual to give 83.2 mg of a crude product. This was chromatographed as described above and gave the mixture of **9b** and **10** (76.4 mg); colorless crystals, $[\alpha]_D^{25} = -174.0°$ ($c = 1.123$, $CHCl_3$).

Intermediate **17**. A mixture of **16b** (200 mg), benzene (6 ml) and *p*-toluenesulfonic acid (20 mg) was stirred at room temperature for 10 min and then worked up as usual to afford 181 mg of crude product. This was chromatographed on silica gel (18 g). Elution with benzene-ether-(9:1) gave

25.4 mg of diene mixture **9b** and **10**. Further elution with benzene-ether-(4:1), -(2:1) and -(1:1) afforded pure **17** (148 mg); colorless oil. IR. ($CHCl_3$): 3595, 3510, 1740 cm^{-1}. NMR. ($CDCl_3$): δ 0.85 (*t*, 3 H, J = 7 Hz, CH_3CH_2), 0.99 (*s*, 3 H, 13-CH_3), 2.78 (*d*, 1 H, OH; exchanged by D_2O addition), 3.64 (*s*, 1 H, *OH*; exchanged by D_2O addition), 3.79 (*m*, 1 H, H(5)). ORD. (c = 0.4504, dioxane, 23°) $[\Phi]_{700}$ +21°, $[\Phi]_{589}$ +35°, $[\Phi]_{321}$ +2034°, $[\Phi]_{313-310}$ +1244° (shoulder), $[\Phi]_{304}$ 0°, $[\Phi]_{279}$ −2105° $[\Phi]_{261}$ −1842°, $[\Phi]_{237}$ −2572°, $[\Phi]_{228}$ −2452°, $[\Phi]_{215}$ −2871°, $[\Phi]_{208\,(last)}$ −1974°. CD. (c = 0.0836 M, dioxane, 23°) $[\Theta]_{330}$ 0, $[\Theta]_{314}$ +260 (inflection), $[\Theta]_{304}$ +402, $[\Theta]_{300-296}$ +363 (shoulder), $[\Theta]_{254}$ 0, $[\Theta]_{208\,(last)}$ −868.

Dienes **9b** *and* **10** *from* **17**. A mixture of **17** (82.6 mg), benzene (3 ml) and *p*-toluenesulfonic acid (16 mg) was stirred at room temperature for 2 h. The usual working up afforded 70.0 mg of crude product, which was chromatographed on silica gel (5.0 g). Elution with benzene-ether-(9:1) and -(4:1) gave the mixture **9b** and **10** (63.6 mg); colorless crystals, $[\alpha]_D^{25} = -189.6°$ (c = 0.955, $CHCl_3$).

4. **Condensation of methyl vinyl ketone with 2-methylcyclopentane-1,3-dione.** – A mixture of 2-methylcyclopentane-1,3-dione (5.6 g), xylene (110 ml) and acetic acid (55 ml) was refluxed for 5 min and then treated with a solution of freshly distilled methyl vinyl ketone (7.0 g) in xylene (55 ml). The mixture was refluxed for 45 min and worked up as usual to give 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione (3.14 g). The structure of the product was assured by comparison (TLC., IR., NMR.) with an authentic sample[6]).

5. **9β,10α-Testosterone (3)** [5]. – 4.73 g of **23** [10] were dissolved in *t*-butyl alcohol (100 ml) at 35°. After flushing the reaction flask with nitrogen, sodium hydroxide (50 mg) was added and the mixture was stirred at 50° until all sodium hydroxide dissolved. At this point, a solution of freshly distilled methyl vinyl ketone (1.05 g) in benzene (10 ml) was added (stirring, 50°) over a period of 30 min. The mixture was stirred an additional 30 min at 50°, and after cooling, treated with glacial acetic acid (0.3 ml) and evaporated to dryness. The residue (5.2 g) was dissolved in ether (50 ml) and filtered through alumina (25 g). Elution with more ether (500 ml) afforded 4.9 g of a mixture consisting mostly of **3** and starting material (**23**); $UV._{max}$ (EtOH) at 242 nm (ε = 6650). This product was chromatographed on alumina (500 g). Fractions (500 ml each) were taken as follows, 1–5: benzene, 6–10: benzene-ether-(19:1), 11–16: benzene-ether-(9:1), and 17–20: ether. Fractions 6–9 were evaporated to give pure starting material **23** (2.758 g). Fractions 11–16 were evaporated and the residue (1.686 g) crystallized from ether to give pure **3** (1.079 g): colorless crystals, m.p. 154–156°, $[\alpha]_D^{25} = -140.8°$ (c = 0.50, dioxane); cf. [5]. The mother liquor of the above crystallization plus fractions 5, 10 and 17–19 were combined and re-chromatographed as described above to give additional amounts of **23** (88 mg) and **3** (180 mg). Thus, a total of 1.26 g of pure **3** and a total of 2.84 g of starting material (**23**) was obtained. Direct yield 21.8%; conversion yield 54%.

6. **9β,10α-Androst-4-ene-3,17-dione.** 1.0 g of diketone **24** was dissolved in *t*-butyl alcohol (30 ml) at 35°. The reaction flask was then flushed with nitrogen and sodium hydroxide (20 mg) was added. The mixture was stirred at 50° until all NaOH was dissolved. Next, it was treated with a solution of freshly distilled methyl vinyl ketone (0.3 g) in benzene (5 ml) during 30 min. After the mixture had been stirred for an additional 30 min at 50° it was cooled, treated with glacial acetic acid (0.1 ml) and evaporated to dryness. The residue was dissolved in ether and filtered through an alumina column (10 g). Elution with ether afforded a crude product (0.97 g). This material was combined with a second crude (0.48 g), prepared the same way from 0.50 g of **24**, and chromatographed on alumina (150 g). Elution with benzene gave 580 mg of starting material **24**. Further elution with benzene-ether-(9:1) afforded 507 mg of oil which was crystallized from acetone/isopropyl ether at 0° to give pure retro-androst-4-ene-3,17-dione (273 mg); colorless crystals, m.p. 153–154°; cf. [5]. This product was found to be identical with authentic material obtained from **3** by oxidation.

We would like to express our gratitude to the staff of our Physical Chemistry Department for the numerous spectral and micro-analytical determinations required in this work. We are particularly grateful to Dr. *V. Toome* for the interpretation of the CD. spectra.

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[6]) We would like to thank Dr. *Z. Hajos* for this sample; cf. [13].

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271. Solvolysis and Isomerization of *cis*- and *trans*-1-Bromo-1-(*p*-anisyl)-propene (α-Bromoanethole)

Mesomeric Vinyl Cations, Part V

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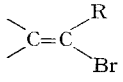
(6. X. 71)

Summary. The influence of a β-methyl group on the reactivity of two stereoisomeric vinyl bromides has been studied. In 80% ethanol *cis*-(**8**) and *trans*-α-bromoanethole (**9**) undergo first order reactions leading to *p*-methoxypropiophenone (**15**), 1-ethoxy-1-(*p*-anisyl)-propene (**16**) and *p*-anisylpropyne (**12**). Solvolysis of the *cis* isomer **8** is accompanied by isomerization to the more stable *trans* isomer **9** which is approx. eight times less reactive than **8**. *Cis-trans* isomerization is also observed in nitrobenzene at 150°.

These results are in agreement with the unimolecular substitution-elimination (S_N1-$E1$) mechanism which competes with *cis-trans* isomerization at the ion pair stage.

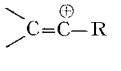
The solvolysis rate of **9** is slightly lower and that of **8** somewhat higher than the rate of α-bromo-*p*-methoxystyrene (**3c**). In the absence of other effects a β-methyl group therefore slightly depresses the ionization rate, presumably by steric hindrance of solvation. These results confirm the negligible polar influence of a β-methyl substituent on the stability of vinyl cations.

In previous papers it was shown that vinyl bromides **1** containing activating α-substituents, such as aryl (**1a**) or alkenyl (**1b**), possess considerable solvolytic

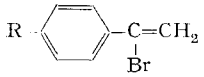


1

a) R = aryl
b) R = alkenyl

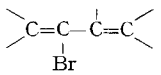


2



3

a) R = H
b) R = NH_2
c) R = OCH_3



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