Tetrahedron, Supplement No. 7, pp. 391 to 395. Pergamon Press Ltd. Printed in Northern Ireland

STEROID HORMONES—XVII[1]

FURTHER A-HOMOSTEROID HORMONES

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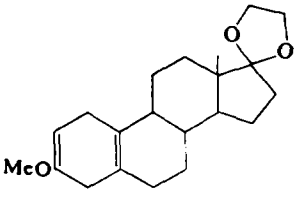
(*Received* 7 *March* 1966)

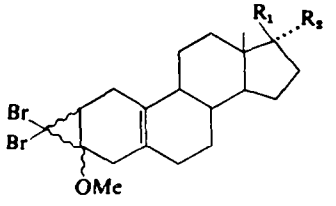
Abstract—Addition of dibromocarbene to the dihydrooestrone derivative (I) gives different mixtures of stereoisomeric products (II) according to conditions. One series is readily converted directly into tropones by the action of silver salts, the other indirectly by initial reaction with pyridine. The bis-adduct (III) has been converted into A-homotestosterone (VIII).

PREPARATIONS of steroid tropones and of angular methylated steroids have been previously described,[2,3] based on initial addition of dibromocarbene to dihydrooestrone derivatives. In order to improve and to extend the process, it has been further investigated.

Addition of bromoform to a mixture of I and potassium t-butoxide in benzene and t-butanol gave as the only isolated product, after complete deketalization, a 40%



I



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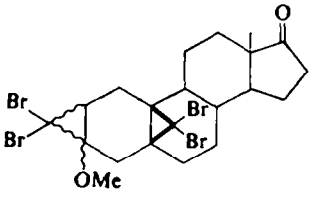

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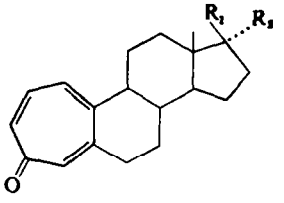

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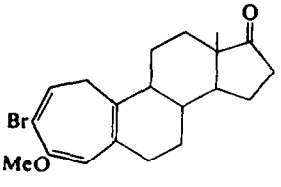

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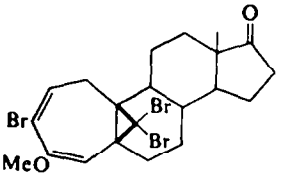
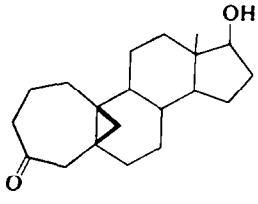
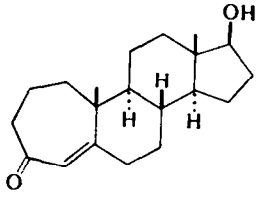


VI

[1] A. J. Birch, D. T. Connor, P. E. Cross and G. S. R. Subba Rao, *J. Chem. Soc.* (C) 54, (1966).
[2] A. J. Birch, J. M. H. Graves and J. B. Siddall, *J. Chem. Soc.* 4234 (1963).
[3] A. J. Birch, J. M. Brown and G. S. R. Subba Rao, *J. Chem. Soc.* 3309 (1964).



VII



VIII

yield of isomer-A of II (R_1, R_2 = O), m.p. 154–155°, identical with the adduct reported.[3] By contrast, reaction at −30° using pure potassium t-butoxide in ether gave in a combined yield of 75%, a mixture of isomer-A of II (R_1, R_2 = O), m.p. 154–155°, isomer-B of II (R_1, R_2 = OCH_2CH_2O), m.p. 161–162° and III, m.p. 195–196°. Hydrolysis of the ketal, m.p. 161–162° gave isomer-B of II (R_1, R_2 = O), m.p. 180–182°, which was distinct from isomer-A, m.p. 154–155°. The difference is presumably stereochemical and based on direction of addition of the carbene to form the cyclopropane ring. The isomers showed greatly different reactivities towards silver nitrate or silver perchlorate in aqueous acetone. Isomer-A gave smoothly, as already noted,[2] the tropone (IV; R_1, R_2 = O) after about 30 min reflux. Isomer-B lost bromide ion very slowly and gave only a small amount of tropone after 72 hr. However, isomer-B readily reacted with boiling pyridine[4] to give V, m.p. 158–162°, the structure of which was supported by spectra. Although V did not give the tropone on hydrolysis with 2N HCl, it readily did so with silver perchlorate in aqueous acetone, or by reaction with boron trifluoride etherate in formic acid at 0°. Using the isomer-A of II (R_1, R_2 = O) 17-substituted derivatives II (R_1 = OH, R_2 = C≡CH) and II (R_1 = OH, R_2 = Me) were prepared by standard methods. Refluxing these adducts with silver perchlorate in aqueous acetone gave the tropone derivatives IV (R_1 = OH, R_2 = C≡CH) and IV (R_1 = OH, R_2 = Me).

Attempts to rearrange III (R_1, R_2 = O), the β-configuration of the 5,10-bridge of which is known,[3] with silver salts under various conditions gave unfavourable results. However, refluxing in pyridine gave VI, $C_{21}H_{25}Br_3O_2$, m.p. 210–212°, the structure of which was supported by spectra: λ_{max} 270 mμ (ε 4500); ν_{max} 1730 and 1630 cm^{-1}, τ 3·28 (t, H-2), τ 4·45 (S, H-4a), τ 6·35 (OMe), τ 9·15 (18-Me). Reduction of VI with lithium in liquid ammonia gave a bromine-free gum containing an enol-ether group (ν_{max} 1665 cm^{-1}), which on acid hydrolysis gave VII, m.p. 138–140°. This on reaction with hydrogen chloride in chloroform gave a gum which slowly crystallized and which produced a crystalline 2,4-dinitrophenylhydrazone. It showed spectra to be expected of A-homotestosterone (VIII): λ_{max} 235 mμ (ε 16,500), ν_{max} 3350, 1695, 1660 (sh) and 1620 cm^{-1}, τ 4·45 (=CH), 6·3 (OH), 9·00 (19-Me) and 9·2 (18-Me). The preparation of an A-homotestosterone with an αβ-unsaturated carbonyl seems, surprisingly, not to have been reported. The isomeric 3-ketones[5] exist as the stable βγ-unsaturated isomers.

EXPERIMENTAL

Addition of dibromocarbene to 1,4-dihydrooestrone-3-methyl ether-17-ethylene ketal

(i) To a mixture of 1,4-dihydrooestrone 3-methyl ether-17-ethylene ketal (1 g) in benzene (20 ml) and potassium t-butoxide from K (0·25 g) in redistilled t-butanol (20 ml) was added under N_2, a

[4] A. B. Font, *Bull. Soc. Chim. Fr.* **5**, 906 (1964).

[5] W. S. Johnson, M. Neeman, S. P. Birkeland and N. A. Fedoruk, *J. Amer. Chem. Soc.* **84**, 989 (1962).

solution of bromoform (1·53 g) in benzene (15 ml) over a period of 30 min at 0° and the mixture stirred for about 1·5 hr. Water (30 ml) was then added, the organic layer separated, washed with water, dried and the solvent removed to give a crystalline product which showed ketone and ketal bands in the IR spectrum. This was deketalised with 1 N HCl in acetone and the monodibromocarbene adduct-A 17-ketone crystallized from acetone as prisms (0·3 g), m.p. 154–155°, identical in IR spectrum and m.p. with the mono-adduct ketone reported earlier.[8]

(ii) Potassium t-butoxide was prepared by dissolving K in t-butanol. Excess of the alcohol was removed by distillation finally under vacuum on a steam bath. The cake was powdered and directly used in the carbene additions.

A mixture of 1,4-dihydrooestrone-3-methyl ether-17-ethylene ketal (1 g) and powdered potassium t-butoxide (0·45 g) in dry ether (20 ml) was cooled to −30° and a solution of bromoform (1·5 g) in dry ether (10 ml) added dropwise under N_2 over 20 min with stirring, which was continued for another 2 hr. Addition of water, extraction with benzene (3 × 20 ml) and working up in the usual way gave a gum (1·25 g) which crystallized on trituration with ether. The crystals (0·35 g) were collected and twice recrystallized from acetone to give needles of the *monodibromocarbene adduct-17-ethylene ketal*-B, m.p. 160–162°, ν_{max} 1180, 1160, 1120, 1100, 1010 and 995 cm^{-1}. (Found: C, 52·8; H, 6·2. $C_{23}H_{30}Br_2O_3$ requires: C, 52·6; H, 6·01%.)

From the mother-liquor an additional quantity of crystalline material (0·75 g) separated which on crystallization from acetone gave prisms, m.p. 154–155° of the monoadduct ketone-A, identical with that reported above.

The adduct ketal-B, m.p. 160–162° was deketalized with methanolic 1 N HCl and the product crystallized twice from acetone to give prisms of the *monodibromocarbene adduct-17-ketone*-B, m.p. 182–184°, ν_{max} 1730 and 1025 cm^{-1}. (Found: C, 52·35; H, 5·6; Br, 34·6. $C_{20}H_{26}Br_2O_3$ requires: C, 52·4; H, 5·7; Br. 34·7%.)

This ketone-B depressed the m.p. of the monoadduct ketone-A, m.p. 154–155° and showed considerable differences in the IR and NMR spectra.

A small quantity of the bis adduct (52 mg), m.p. 194–195° was isolated from the mother-liquors.

Rearrangement of the adducts with silver perchlorate A-*homoestr*-1(10),2,4a-*triene*-4, 17-*dione*

The monoadduct ketone-A, m.p. 154–155° (250 mg) and silver perchlorate (300 mg) in aqueous acetone (1:4; 30 ml) were refluxed for 30 min; a copious precipitate of AgBr had separated in less than 10 min. The filtrate was concentrated under red. press., water (25 ml) was added, and the product extracted with benzene as a dark brown gum (92 mg).

This gum in benzene was chromatographed on neutral alumina (10 g). Elution with benzene–ether (4:1) gave the starting material (23 mg). Further elution with benzene ether (1:4) gave the tropone analogue of oestrone (IV; R_1, R_2 = O) (56 mg)[8] which crystallized from AcOEt as colourless prisms, m.p. 146–150°, λ_{max} 231, 234, 237 and 313 mμ (ε 26,600, 27,100, 27,800 and 10,200) ν_{max} 1730, 1628, 1588, 1558 and 1528 cm^{-1}.

The adduct ketone-B, m.p. 182–184° (300 mg) and silver perchlorate (300 mg) were refluxed in aqueous acetone (30 ml) as before. Although there was some precipitate of AgBr formed after 6 hr the reaction was not complete even after 72 hr. The mixture was filtered from the AgBr and worked up to give a dark brown gum (125 mg). This was chromatographed on neutral alumina. Elution with benzene–ether gave a pale yellow glass which resisted crystallization. This was fractionated with AcOEt–light petroleum to give a colourless precipitate, m.p. 95–128°, λ_{max} 232–237 and 310 mμ (ε 15,000 and 6000), ν_{max} 1730, 1625, 1585 and 1527 cm^{-1}.

The adduct ketal-B, m.p. 160–162° was refluxed with silver perchlorate in aqueous acetone for 71 hr. Working up as before gave the crude tropone-17-ketone (38 mg), m.p. 145–146° identical with the one reported above from isomer-A.

Rearrangement with pyridine. The monoadduct ketone-B, m.p. 180–182° in dry pyridine (analar, 20 ml) was refluxed for 2 hr. After cooling, the pyridine hydrobromide (105 mg, 1 mole) was filtered, and the pyridine removed under red. press. to give a gum which was taken up in ether, washed with water, ice cold 4N HCl, water, $NaHCO_3$aq, water and dried. The solvent was removed to give 3-*bromo-4-methoxy*-A-*homoestra*-2,4,5(10)-*trien*-17-*one* (215 mg) which was crystallized from ether, m.p. 158–162°, λ_{max} 281 mμ (ε 8000), ν_{max} 1740, 1610 and 1556 cm^{-1}, τ 3·25 (t H-2), 4·2 (s H-4a), 6·32 (OMe), 9·1 (18-CH_3). (Found: C, 63·6; H, 6·5. $C_{20}H_{23}BrO_2$ requires: C, 63·7; H, 6·6%.)

The above bromo-triene (200 mg) was dissolved in formic acid (10 ml), BF_3-etherate (2 ml) was

added, and the mixture kept at 0° and vigorously stirred for 2 hr. After evaporation under red. press., a brown mass (115 mg) was obtained. This was diluted with water (20 ml) and extracted with $CHCl_3$. The product (95 mg) was purified by filtration through neutral alumina and crystallized from AcOEt–light petroleum to give A-homooestr-1(10),2,4a(5)-trien-4, 17-dione, m.p. 143–146°, λ_{max} 232, 237 and 310 mμ (ε 25,000 and 10,450), ν_{max} 1740, 1635, 1590 and 1530 cm^{-1}. This was identical with the tropone reported previously.[8]

The bromo-triene, m.p. 158–162° (200 mg) and silver perchlorate (200 mg) were refluxed in aqueous acetone (1:4) for 30 min. The precipitated AgBr was filtered and the filtrate concentrated to give a dark brown residue (125 mg). This resisted crystallization but had the expected tropone and 17-carbonyl spectra: λ_{max} 232, 235, 237 and 312 mμ (ε 22,000, 23,400, 21,800 and 9800), ν_{max} 1735, 1634, 1585 and 1527 cm^{-1}.

Rearrangement of the bis-adduct and preparation of A-*homotestosterone* (VIII)

The adduct III (1·2 g) was refluxed in pyridine (20 ml) for 2 hr. Addition of water, ether extraction, washing with ice-cold 2N HCl and working up in the usual way gave crystalline 3-*bromo*-4-*methoxy*-5(10)-*dibromomethylene*-A-*homooestra*-2,4-*dien*-17-*one* (VI, 995 mg) crystallized from acetone, m.p. 210–212°, λ_{max} 270 mμ (ε 4500), ν_{max} 1730 and 1630 cm^{-1}, τ 3·28 (t H-2), 4·45 (s H-4a), 6·35 (O—CH_3), 9·15 (18-CH_3). (Found: C, 46·1; H, 4·7. $C_{21}H_{26}Br_2O_2$ requires: C, 45·9; H, 4·7%.)

The above VI in tetrahydrofuran (5 ml) was added to Li (250 mg) in liquid ammonia (50 ml). After 5 min, EtOH was added and the ammonia evaporated. Addition of water and ether extraction gave a gum (112 mg). The gum in aqueous acetone was reacted with 2N HCl. The 17β-*hydroxy*-5(10)-*methylene*-A-*homooestran*-4-*one* (VII) after chromatography on alumina crystallized from ether, m.p. 138–140°, ν_{max} 3420 and 1710 cm^{-1}. (Found: C, 79·4; H, 9·7. $C_{20}H_{30}O_2$ requires: C, 79·5; H, 9·9%.)

This product VII (80 mg) in $CHCl_3$ was saturated with dry HCl, left overnight and worked up as usual; no crystalline product could initially be obtained even after chromatography. However, the gum had the expected spectra and slowly crystallized to A-*homotestosterone*, m.p. 168–172°, λ_{max} 235 mμ (ε 16,500), ν_{max} 3350, 1695, 1660 (sh) and 1620 cm^{-1}, τ 4·45 (C=CH), 6·3 (OH), 9·00 (19-CH_3), 9·2 (18-CH_3). (Found: C, 78·5; H, 9·9. $C_{20}H_{30}O_2$ requires: C, 79·5; H, 9·9%.) The 2,4-*dinitrophenylhydrazone* was prepared in the usual way and had m.p. 148–150°, λ_{max} 381, mμ (ε16,630). (Found: C, 64·5; H, 7·5. $C_{36}H_{34}N_4O_5$ requires: C, 64·7; H, 7·1%.)

Preparation of the adduct (II; R_1 = OH, R_2 = —C≡CH). A solution of II (R_1, R_2 = O; 200 mg) in dry tetrahydrofuran (10 ml) was added to a suspension of lithium acetylide, prepared by passing pure acetylene through LAH (200 mg) in tetrahydrofuran. Left overnight at room temp the mixture was worked up by adding sat NH_4Claq and extracting with $CHCl_3$. Removal of the solvent from the dried extract gave a crystalline *product* (II; R_1 = OH, R_2 = —C≡CH) (138 mg), m.p. 132–134° ν_{max} 3380, 3270 and 765 cm^{-1}. (Found: C, 54·0; H, 6·0. $C_{22}H_{28}Br_2O_2$ requires: C, 54·5; H, 5·8%.

17-α-*Ethinyl*-17β-*hydroxy*-A-*homooestr*-1(10)-2,4a-*triene*-4-*one* (IV–R_1 = OH, R_2 = —C≡CH)

The adduct II (R_1 = OH, R_2 = —C≡CH; 100 mg) and silver perchlorate (100 mg; 4 moles) in aqueous acetone (1:4, 30 ml) were refluxed for 1 hr. Working up in the usual way gave the 17-α-*ethinyl*-17β-*hydroxy*-A-*homooestra*-1(10),2,4a-*triene*-4-*one* (IV; R_1 = OH, R_2 = —C≡CH) (25 mg) which crystallized from AcOEt–EtOH (1:1), m.p. 181–185°, λ_{max} 237 and 315 mμ (ε 26,300 and 10,120), ν_{max} 3270, 3380, 1628, 1550 and 1525 cm^{-1}. (Found: C, 82·0; H, 8·0. $C_{21}H_{24}O_2$ requires: C, 81·8; H, 7·8%.)

This compound IV (R_1 = OH, R_2 = —C≡CH) was alternately prepared from IV (R_1, R_2 = O; 50 mg) by adding lithium acetylide, prepared as above, preferentially to the 17-ketone. Working up in the usual way gave IV (R, = OH, R_2 = —C≡CH), m.p. 180–185° identical with the compound reported above.

Preparation of the adduct (II; R_1 = OH, R_2 = CH_3). An ethereal solution of II (R_1, R_2 = O; 400 mg) was added dropwise to a cooled mixture of MeMgBr (prepared from 0·5 g Mg) under N_2. It was vigorously stirred for 1 hr the mixture poured into a sat NH_4Claq and worked up to give the 17β-*hydroxy*-17α-*methyl-dibromocarbene adduct* (II; R_1 = OH, R_2 = CH_3; 350 mg), m.p. 176–180° ν_{max} 3380 and 765 cm^{-1}. (Found: C, 51·7; H, 6·5. $C_{21}H_{30}Br_2O_2$ requires: C, 53·2; H, 6·3%.)

17β-Hydroxy-17α-methyl-A-homooestr-1(10),2,4a-trien-4-one (IV; $R_1 = OH$, $R_2 = CH_3$)

The above adduct (200 mg) and silver perchlorate (200 mg) in aqueous acetone (1:4, 30 ml) were refluxed for 2 hr. The *17β-hydroxy-17α-methyl* A-*homooestr*-1(10),2,4a-*trien*-4-*one* (IV; $R_1 = OH$, $R_2 = CH_3$) was obtained as a crude solid m.p. 160–180°, having the characteristic absorption spectra, λ_{max} 232 and 367 mμ (ε 22,150 and 9925), ν_{max} 3360, 1630, 1550 and 1527 cm^{-1}.

A portion which was repeatedly crystallized from AcOEt had m.p. 198–200° (dec). (Found: C, 81·1; H, 8·5. $C_{20}H_{26}O_2$ requires: C, 80·5; H, 8·7%.)

Acknowledgement—Part of this work was carried out during the tenure of an I.C.I. Fellowship (G. S. R. S. R.). We are indebted also to Syntex S.A. for financial support and for a gift of material.