Tetrahedron Letters No.52, pp. 6495-6501, 1966. Pergamon Press Ltd.
Printed in Great Britain.

TOTAL SYNTHESIS OF STEROIDS I.

THE PREPARATION OF 17β-HYDROXY-DES-A-ANDROST-9-EN-5-ONE

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(Received 14 October 1966)

In an earlier communication (1), Uskoković *et al.* described the conversion of normal steroids to retrosteroids (i.e. 9β,10α-steroids) via BCD tricyclic intermediates. Therefore, it became important to plan the total synthesis of such a compound, i.e., (-)8.

The starting material, 2-methylcyclopentane-1,3-dione was prepared in a 44% overall yield by modifications of the original Panouse procedure (2), in which it was obtained in a 20.6% overall yield.

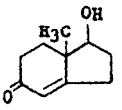
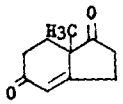
Michael addition of methyl vinyl ketone to 2-methylcyclopentane-1,3-dione followed by dehydration, without isolation of the ketol intermediate, gave the known racemic 7,7a-dihydro-7a-methyl-1,5(6H)-indanedione (±)2 in 73% yield (3). The 1-keto group of the dione had previously been selectively and stereospecifically reduced with sodium borohydride to give the unsaturated keto alcohol (±)1 as an oil (4). In the present work, reduction with lithium aluminum tri-tertiary butoxy hydride gave (±)1 as a crystalline solid, m.p. 66.5-67.5°. It was also

possible to obtain crystalline (±)1 by the original method (4) although in somewhat lower yield. The 1β-equatorial configuration of the hydroxyl group is in agreement with the product development control principle, as applied by L. J. Chinn to the reduction of the unhindered 17-keto group of steroids (5).

The 3,5-dinitrobenzoate of (±)1 was then prepared in good yield, and had a mp of 149-150°. It was characterized by ultraviolet, infrared and nmr spectroscopy, and also by microanalysis (C, H, N). Boyce and Whitehurst (4) reported the compound with a mp of 90-91°, but gave no physical chemical or microanalytical data. Refluxing the ester with ethyl alcohol and a little acid resulted in transesterification; the alcohol (±)1 and ethyl 3,5-dinitrobenzoate mp 91-92°, were isolated. Since Boyce and Whitehurst used ethyl alcohol to recrystallize their compound, they most probably isolated ethyl 3,5-dinitrobenzoate.

The optically active bicyclic hydroxy ketone (+)1 was prepared in a high overall yield (75%) by resolving the corresponding racemic alcohol (±)1 via the hydrogen phthalate-brucine salt; (+)1 had previously been prepared from the racemic diketone (±)2 by microbiological means (6). The chemical resolution method, besides giving a high yield of the desired product, did not require any chromatography. In our hands, the microbiological method gave less satisfactory yields, and purification by chromatography was necessary.

TABLE I

Compound	Properties
 (+)1	m.p. 67-68.5° (Et_2O-Peth) and 84-85.5° (i-Pr_2O)
CrO_3	ϵ_{240} 13,400 (EtOH)
	$[\alpha]_D^{25}$ + 90.4° (Bz.)
 (+)2	m.p. 66-66.5°
	ϵ_{238} 10,800 (EtOH)
	$[\alpha]_D^{25}$ + 360° (Bz.)

The crude dextrorotatory alcohol (+)1 showed a slightly higher optical rotation than the pure compound. This apparent anomaly is due to the presence of a small amount of the diketone (+)2 which has a very high specific rotation, and which could be separated by preparative thin-layer chromatography.

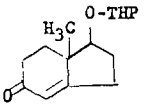
The hitherto unknown levorotatory unsaturated keto alcohol (-)1 was obtained in 52% overall yield by the chemical resolution method. The two enantiomeric alcohols [(+)1 and (-)1] had, as expected, identical melting points, uv, ir and nmr spectra, and identical but opposite rotations.

The dextrorotatory unsaturated keto alcohol (+)1 was chosen to prepare the levorotatory title compound (-)8, because the absolute configuration of (+)1 has previously been determined (7), and it corresponds

to the absolute configuration of testosterone at C-13 and C-17. Since (-)8 was first obtained by the degradation of testosterone acetate (8), it was expected that (+)1 could be converted to (-)8 by introducing the new centers of asymmetry at C-8 and C-14 in a stereospecific fashion. It should be mentioned that the scheme was first carried out with racemic (±)1, and gave (±)8 with the desired relative configuration.

Alkylation of the tetrahydropyranyl ether 3 of the optically active alcohol (+)1 gave the desired C-alkylation product 4 in 58% yield and the O-alkylation product 5 in 31% yield. O-alkylation products of weakly acidic ketones have recently been reported in the literature (9).

Catalytic hydrogenation, equilibration of the side chain, and ring closure gave the desired levorotatory BCD tricyclic intermediate (-)8 in a 39% yield based on the C-alkylation product 4. The compound was identical in every respect with an authentic sample obtained from Roussel-Uclaf, prepared by an independent total synthesis (10a, b).

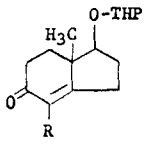


3

1. NaH/DMSO;

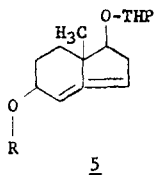
2. R-Br

R = $CH_3CH_2CCH_2CH_2$-



4

+



5

λ_{max} 248.5 mμ (MeOH); 246.5 mμ (Et_2O)

ε 12,500; 15,600

$\nu_{max}^{CHCl_3}$ 1658 cm^{-1} 1639 (s.) and 1600 (m.) cm^{-1}

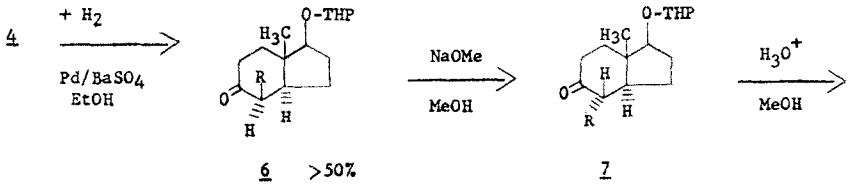
5 $\xrightarrow[H_3O^+]{CHCl_3}$ 3 (major) + 5 (minor) $\xrightarrow[20°]{1\ hr.}$ (+)1 (major) + 3 (minor)

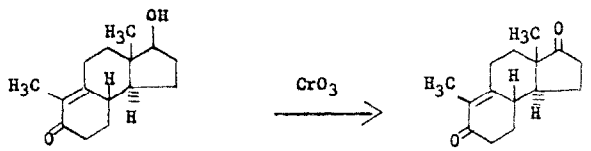
2 min., 20°

Based on the 39% overall yield in the conversion of 4 to (-)8, the catalytic hydrogenation* of 4 must have given a reasonable amount (at least 50%) of the C/D trans isomer 6. On the other hand, it had been

* Velluz et al. (cf. ref. 10 a and b) have shown that with a propionic acid side chain at C-8 a fair amount of the desired C/D trans isomer can be obtained.

reported previously (4) that the racemic bicyclic unsaturated keto alcohol (±)1 gave under a variety of hydrogenation conditions only the thermodynamically more stable C/D cis isomer.





[C-13 Me 54.5 cps] [C-13 Me 62.0 cps ($\Delta\nu$ 7.5 cps)]

Oxidation with the Jones reagent gave the dextrorotatory tricyclic diketone (+)9. The difference between the chemical shifts of the C-13 methyls (steroidal numbering) of (-)8 and (+)9 is in agreement with the difference observed with the C-13 methyl signals of 14α,17β-hydroxy and 17-keto steroids. The nmr data thus support the assigned stereochemistry.

Acknowledgment. The authors express their thanks to Mr. F. Bizzarro and Mr. C. Parios for their technical assistance in this investigation. Thanks also are due to Drs. F. Vane and T. Williams for the nmr, to Dr. V. Toome for the uv and to Dr. S. Traiman for the ir spectroscopic data, and to Dr. A. Steyermark for the microanalyses.

References

1. M. Uskoković, J. Iacobelli, R. Philion and T. Williams, J.Amer.Chem.Soc 88, 4538 (1966).
2. J. J. Panouse and C. Sannie, Bull.Soc.Chim. France, 1955, 1036.
3. C. B. C. Boyce and J. S. Whitehurst, J.Chem.Soc., 2022 (1959).
4. C. B. C. Boyce and J. S. Whitehurst, J.Chem.Soc., 4547 (1960).
5. L. J. Chinn, J. Org. Chem., 27, 54 (1962).
6. W. Acklin, V. Prelog and A. P. Prieto, Helv.Chim.Acta, 41, 1416 (1958).
7. W. Acklin and V. Prelog, Helv.Chim.Acta, 42, 1239 (1959).
8. M. P. Hartshorn and E. R. H. Jones, J.Chem.Soc., 1312 (1962).
9. G. J. Heiszwolf and H. Kloosterziel, Chem.Comm., 1966, 51.
10. a) L. Velluz, G. Nominé, G. Amiard, V. Torelli and J. Cérède, Compt. rend., 257, 3086 (1963); b) Fr.Pat. 1,359,675 (1.14.63) by Roussel-Uclaf.