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STEROIDS CONTAINING RING A AROMATIC - IV

MECHANISM OF THE DIENONE-PHENOL REARRANGEMENT[1]

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The dienone-phenol rearrangement has attracted considerable attention in recent years[3]. It was suggested that in steroids the formation of 3-hydroxy-1-methyl product proceeds via a simple 1,2 shift of the 19-methyl group from C-10 to C-1. This implies that C-4 of the 1,4-dien-3-one remains at its initial position in the phenol. However, the possibility of a second mechanism cannot be ruled out a priori. Formally, the formation of a 3-hydroxy-1-methyl phenol can be rationalized as proceeding via initial migration of the C-19 methyl group from C-10 to C-5, analogous to the Westphalen rearrangement. This would then be followed by formation of spiro intermediate Ib centered at C-10, and subsequent migration of the C-6-10 bond to C-1. In such a case C-4 of the 1,4-dien-3-one would be located at C-2 of the phenol. The suggested spiro intermediate Ib in the alternative mechanism is somewhat similar to Ia postulated for the formation of 1-hydroxy-4-methyl products[3]. In this communication we provide conclusive proof that the formation of 3-hydroxy-1-methyl steroidal phenols proceeds exclusively by a 1,2 shift of the 19-methyl group to C-1.

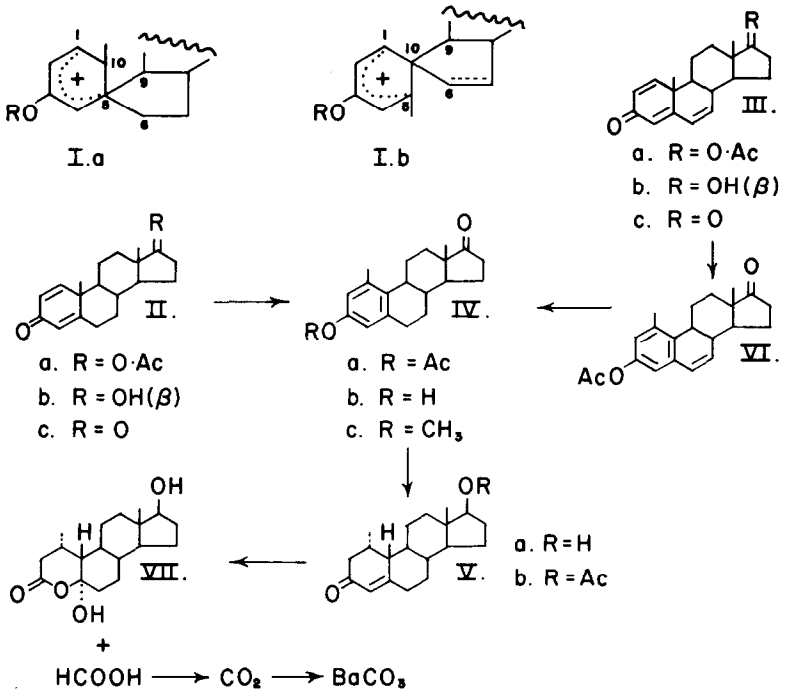
The investigations were carried out on 4-C^{14}-testosterone. Since the 3-hydroxy-1-methyl-phenol, IV, can be obtained either from the 1,4-dien-3-one IIc or the 1,4,6-trien-3-one IIIc, the mechanism of the rearrangement was studied for both cases.

The 4-C^{14}-17β-acetoxyandrosta-1,4-dien-3-one (IIa) was prepared by treat-

ment of 4-C^{14}-testosterone acetate with 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ)[4]. The 4-C^{14}-17β-acetoxyandrosta-1,4,6-trien-3-one (IIIa) was prepared in two steps as described earlier[5,6]. The acetates IIa and IIIa were hydrolyzed to the alcohols IIb and IIIb, then oxidized with chromium trioxide in pyridine to the corresponding[6] 17-ketones IIc and IIIc. The 1,4-diene-dione IIc was rearranged with aqueous acetic acid-hydrochloric acid giving a mixture of the para and meta phenols[7]. The phenols were then leached with hot 2N sodium hydroxide solution[7], and the base insoluble 1-hydroxy-4-methyl product was collected by filtration. Acidification of the filtrate provided the 3-hydroxy-1-methyl compound IVb, which was converted to 3-methoxy-1-methylestra-1,3,5(10)-trien-17-one (IVc) by treatment with dimethyl sulfate and aqueous sodium hydroxide[6]. Reduction of the ether IVc with lithium in liquid ammonia[8] gave 17β-hydroxy-1α-methyl-19-norandrost-4-en-3-one (Va), which was acetylated to the 17β-acetate Vb.

The triene-dione IIIc was rearranged to the acetate (VI), by treatment with acetic anhydride and p-toluene sulphonic acid[9]. Hydrogenation of the phenol acetate VI over palladium-charcoal resulted in IVa. The obtained phenol acetate IVa was then treated as described above to give Vb.

The products (Vb) from the two experiments were ozonized in ethyl acetate[10] at -70°. The ozonides were decomposed with water. The formic acid derived from C-4 was separated by distillation and oxidized with mercuric acetate to carbon dioxide which was collected as barium carbonate[11]. From the non-volatile residue 4-oxa-17β,5α-dihydroxy-1α-methyl-19-norandrostane-3-one (VII) m.p. 152-153°, was obtained. The lactol gave correct analytical values for compound VII (Found: C, 70.18; H, 9.00; $C_{18}H_{28}O_4$ requires C, 70.10; H, 9.15), and its structure was assigned on the basis of previous observations[12]. The distribution of radioactivity[13] in the products obtained is compiled in Table 1. It is evident that in both cases C-4 contained all the radioactivity initially present in 17β-acetoxy-



1α-methyl-19-norandrost-4-en-3-one (Vb), hence also in the phenol (IV). No radioactivity was detected in the 4-nor-lactol VII. Thus it can be concluded with certainty that the rearrangement of both the 1,4-dien-3-one and the 1,4,6-trien-3-one to the 3-hydroxy-1-methyl phenol IV proceeds by the same route. The mechanism involves scission of the C-10(19) bond and migration of the angular methyl[9] to C-1. This excludes alternate mechanisms. Work on the mechanism of formation of 1-hydroxy-4-methyl phenols is in progress.

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Table I

Distribution of C^{14} in Products Derived from
3-Methoxy-1-methylestra-1,3,5(10)-triene-17-one (IVc)

Substance Analyzed	Specific Activity c/min/mmole x 10^3	
	Compound	Rearranged
	IIc	IIIc
V	42	50
C_4 - $BaCO_3$	39	48.5
VII	none	none

REFERENCES

1. This work was supported by a grant from the U. S. Public Health Service CA-04663-04 End. Paper (V) of this series "Steroids" in press.
2. Post doctoral fellow 1960 .
3. For leading references see: B. R. Davis and T. G. Halsall, J. Chem. Soc. 1833, (1962). R. B. Woodward in Perspectives in Organic Chemistry, A. Todd editor, Interscience N. Y. 1956, p. 178.
4. D. Burn, D. N. Kirk and V. Petrow, Proceedings Chem. Soc. 14, (1960).
5. H. J. Ringold and A. Turner, Chemistry and Industry 211, 1962.
6. E. Caspi, E. Cullen and P. K. Grover, J. Chem. Soc. in press 1963.
7. A. S. Dreiding, W. J. Pummer and A. J. Tomaszewski, J. Amer. Chem. Soc. 75, 3159, (1953).

8. H. J. Ringold, G. Rosenkranz and F. Sondheimer, J. Amer. Chem. Soc. 78, 2477, (1956).

9. C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki and St. Kaufman, J. Amer. Chem. Soc. 72, 4540, (1950).

10. E. Caspi, B. T. Khan and W. Schmid, J. Org. Chem. 26, 3894, (1961).

11. E. Caspi, W. Schmid and B. T. Khan, J. Org. Chem. 26, 3898, (1961).

12. E. Caspi, W. Schmid and B. T. Khan, Tetrahedron 18, 767 (1962).
E. Caspi, B. T. Khan and S. N. Balasubrahmanyam, Tetrahedron 18, 1013 (1962).

13. The counting procedure is described in E. Caspi, R. I. Dorfman, B. T. Khan, G. Rosenfeld and W. Schmid, J. Biol. Chem. 237, 2085, (1962).