A New Antiandrogen. 6α-Bromo-17β-hydroxy-17α-methyl-4-oxa-5α-androstan-3-one

An endocrinological investigation of 6-halo-4-oxa steroids has revealed highly stereospecific antiandrogenic activity in this series. Thus, of the 4 possible isomers of 6ξ-bromo-17β-hydroxy-17α-methyl-4-oxa-5ξ-androstan-3-one, only the 5α,6α-isomer (compound VI) has been found to exhibit significant antagonism towards exogenous testosterone.

The synthesis of the 4 isomeric oxasteroids IV, V, VI and VIII is outlined in Figure 1 and some of their physical properties are summarized in Table I.

Antiandrogenic activity was measured in immature Holtzman rats which had been castrated prior to use. Individual compounds were administered s.c. in 0.2 ml sesame oil once daily for 7 consecutive days. Testosterone was injected s.c. concurrently at a separate body site in the same volume and vehicle. Autopsies were performed on the day following the last treatment day. The results obtained with compound VI are shown in Table II. The data of Table II indicate that compound VI effectively inhibited testosterone stimulation of weight gain by the seminal vesicles and ventral prostates of castrated rats. They also show that the degree of antagonism was proportional to the dose of the oxasteroid.

The 4 isomers, IV, V, VI and VIII, were tested simultaneously to determine their comparative antiandrogenic activities. Each compound was administered at a dosage which was 100 times by weight the dose of testosterone used. This dosage ratio was at least 2 to 3 times the minimum effective level required to demonstrate antiandrogenic effects with compound VI, as established in

Table I. Physical constants of compounds IV, V, VI and VIII

Compound	mp (°C)	$[\alpha]_D^{25}$	Chemical shift [δCDCl$_3$] of protons[a]		
			C_{19}	C_5	C_6
IV	163–164°	— 9.6° (CH_3OH)	1.23 (s)	4.08 (d)	4.55 (m)
V	192.5–194.5°	—91.1° (THF)	1.05 (s)	4.20 (s, broad)	4.27 (m)
VI	226–226.5°	+ 93.2° (THF)	0.94 (s)	3.94 (s, broad)	3.95 (m)
VIII	189–192°	—41.5° (THF)	1.35 (s)	4.34 (s, broad)	4.34 (s, broad)

[a] Determined on a 100 MHz instrument.

Table II. Effects of compound VI on the androgenic activity of testosterone propionate (TP) in the castrated rat[a]

Dose (μg/day, s.c.) VI	TP	No. of animals	Mean ± standard error	
			Seminal vesicles (mg)	Ventral prostate (mg)
0	0	10	7.4 ± 0.6	8.6 ± 0.6
0	20	9	41.2 ± 3.1	40.4 ± 1.7
1000	20	10	22.4 ± 1.2	24.7 ± 1.4
2000	20	10	18.8 ± 1.1	23.1 ± 1.5
4000	20	5	13.5 ± 1.1	19.3 ± 1.6
8000	20	8	12.0 ± 1.0	16.4 ± 2.5

[a] 40–50 g rats castrated 1 day prior to use.

Table III. Effects of isomers of compound VI on the androgenic activity of testosterone (T) in the castrated rat[a]

Treatment[b]	No. of animals	Mean ± standard error	
		Seminal vesicles (mg)	Ventral prostate (mg)
T	9	28.2 ± 1.7	20.5 ± 1.0
T and IV	6	25.9 ± 1.5	19.0 ± 1.0
T and V	6	28.8 ± 3.1	21.8 ± 1.3
T and VI	7	18.5 ± 1.6	13.5 ± 0.9
T and VIII	8	27.0 ± 1.7	18.6 ± 1.0

[a] 40–50 g rats castrated 6 days prior to use. [b] IV, V, VI and VIII administered s.c. at a dose of 1500 μg/day. Testosterone injected s.c. at a dose of 15 μg/day.

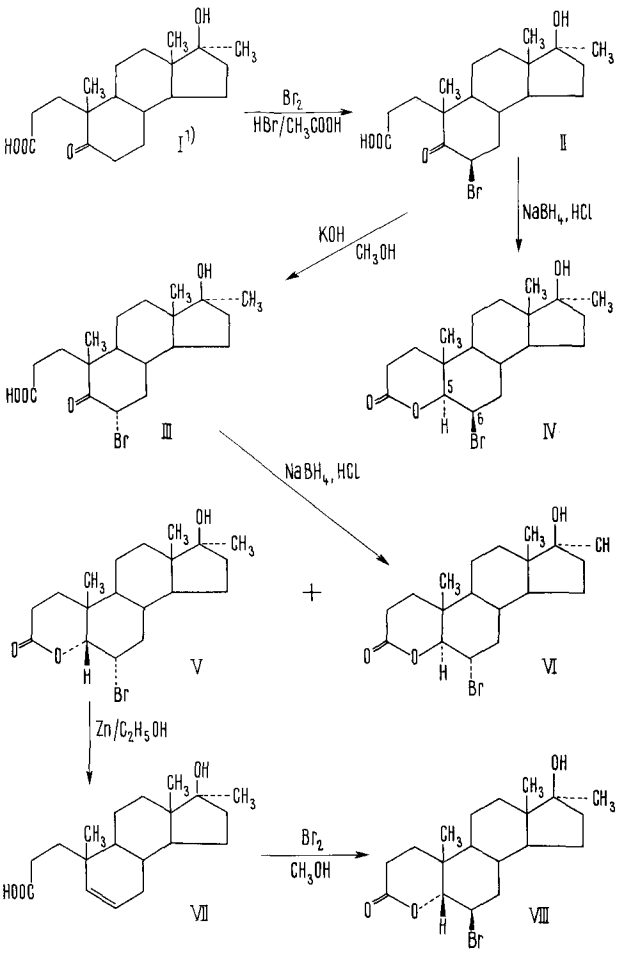

Fig. 1.

[1] M. Gut and M. Uskoković, J. org. Chem. *26*, 1943 (1961).

other studies. The data obtained with compounds IV, V, VI and VIII are shown in Table III. These results indicate that only the 5α, 6α-isomer VI manifested significant antiandrogenic effects.

The introduction of unsaturation at position 1 (compound IX, Figure 2) resulted in a reduction of antiandrogenic activity of about 50%. Although 17,17-dimethyl-Δ^{13}-steroids have been reported to have significant antiandrogenic activity[2], the 17,17-dimethyl-Δ^{13}-analogue (compound X) was completely devoid of the ability to antagonize testosterone.

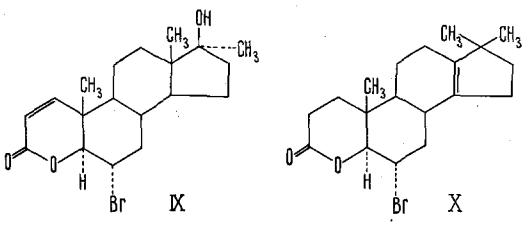

Fig. 2.

Zusammenfassung. Es wird gezeigt, dass 6α-Brom-17β-hydroxy-17α-methyl-4-oxa-5α-androstan-3-one beträchtliche antiandrogene Wirkung besitzt. Isomere dieser Verbindung mit verschiedener Konfiguration an C-5 und C-6 wurden als inaktiv befunden.

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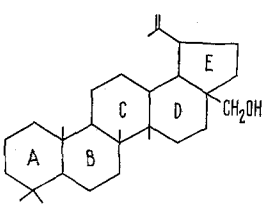
[2] A. SEGALOFF and R. B. GABBARD, Steroids *4*, 433 (1964).

Chemical Investigation of *Jasminum auriculatum* (VAHL) Leaves. VII. Structure of Jasminol – a New Triterpene

An unidentified triterpene, isolated from the leaves of *J. auriculatum* (Vahl) together with lupeol[1], appears to be new and has been provisionally named Jasminol. Jasminol, mp 208–210° (analyzed for $C_{30}H_{50}O$: C, 84.50; H, 11.74%; found: C, 84.43; H, 11.50%), $[\alpha]_D = +41.50°$ (chloroform), M^+ 426 (mass spectrum), responded to all the tests for triterpenes, depressed the melting point of lupeol and formed an acetate (mono), mp 170°. Its UV-spectrum, λ_{max}^{EtOH} 203 (log ε) 3.422, indicates the presence of a substituted double bond; the IR-spectrum shows a band at 3330 cm^{-1} (OH) with a supporting peak at 1050 cm^{-1}, indicating the presence of a primary hydroxyl group (CH_2OH). The peaks at 1390 cm^{-1} and 1370 cm^{-1} are due to gem-dimethyl function, this becomes more evident from the analysis of the NMR-spectrum of the substance. The signals at 9.15, 9.18, 9.05, 8.96, 8.98 τ account for angular methyls[2], at 8.33 and at 5.40 τ (doublet, J = 7.0 cps) are assigned to a vinylic methyl and to a vinylidine group (IR 1655 cm^{-1} and 885 cm^{-1}) respectively. Jasminol appears, therefore, to possess the Lup-20-ene type skeleton[3]. However, the presence of only 5 angular methyl protons and the presence of primary hydroxyl protons, 6.85 τ (2H), led us to assume that C-17 might have a primary hydroxyl function instead of the angular methyl. This idea was further supported by the fragmentation pattern of Jasminol in the mass spectrum. Lupeol and moretenol, in their mass spectrum, give a peak at m/e 139, indicating the presence of OH group in ring A[3]. As this peak is absent in Jasminol, no hydroxyl function is attached to ring A. The signals observed at 8.96 τ and at 9.05, 8.98 τ (C-8, C-10, C-14, Me), rule out its attachment to rings B or C. Hence the CH_2OH group is thought to be present either on ring D or E. But the splitting of ring C with rings D and E intact, would give rise to peaks at m/e 220 and m/e 249, when CH_2OH group is attached on C-17. Since these peaks are present in this compound's spectrum, and further the peak at m/e 395 formed due to elimination of water is being observed, it is inferred that the possible site of attachment of the CH_2OH group is at C-17, as in betulin[4]. Therefore it is proposed that Jasminol is Lup-20-ene-28β-Ol.



Zusammenfassung. Ein neues Triterpen, Jasminol, wurde aus Blättern von *Jasminum auriculatum* (Vahl) isoliert und als Struktur diejenige des Lup-20-ene-28β-ols wahrscheinlich gemacht.

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