ANTI-ANDROGENIC ACTIVITY OF 7,8,9,10-TETRA-HYDRO-7-OXO-BENZO (C) PHENANTHRIDINE (A₁₁-IV) ON IMMATURE, CASTRATED, MALE RATS

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Summary. One of the aza-analogues, 7,8,9,10-tetrahydro-7-oxo-benzo (c) phenanthridine exhibited an anti-androgenic activity on immature, castrated, male rats. The compound had an interesting anti-androgenic activity as the effect of testosterone-induced gain in weight of the ventral prostate was significantly inhibited by the compound. This compound did not, however, inhibit the androgen-induced weight increase of the seminal vesicle.

Azasteroids, in which the nitrogen replaces the carbon atom of a perhydro-1,2-cyclopentanophenanthrene system, have been found to exhibit some androgenic, oestrogenic and progestational activity. Suzuki (1964) has shown anti-androgenic activity in four alkylamine derivatives of testosterone and nortestosterone. This subject has recently been reviewed by Alauddin & Martin-Smith (1962) and Martin-Smith & Sugrue (1964). In view of this interest, the aza-analogue 7,8,9,10-tetrahydro-7-oxo-benzo (c) phenanthridine was tested for androgenic, anti-androgenic and anabolic activity on immature, castrated, male rats and adult, male rats.

The anti-androgenicity of the test compound was assessed by the method described by Hershberger, Shipley & Meyer (1953) as modified by Potts, Beyler & Burnham (1960) on castrated, immature, male rats. The castrated male rats were divided into four groups of ten rats each 1 week after the operation and treated as follows:

- Group-1 control animals were given 6% ethanol orally for 7 days. (Ethanol was the solvent used.)
- Group-2 animals were given the test compound at a dose of 10.0 mg/kg orally.
- Group-3 animals were given testosterone propionate, 10.0 mg/kg intramuscularly.
- Group-4 animals were given the test compound, 10.0 mg/kg orally together with testosterone propionate 10.0 mg/kg intramuscularly.

The test compound and testosterone propionate were given for 7 days. Twenty-four hours after the last medication, the animals were killed and the ventral

prostate, seminal vesicle and levator ani muscle were excised, blotted on a filter paper and weighed on a torsion balance. In another series of experiments, the test compound was given to adult male rats for 21 days. At the end of that period, the animals were killed and the ventral prostate and testes dissected out, weighed and compared with the weight of the same organs in similar groups of rats which had been given ethanol daily instead of the drug.

Table 1 shows the results obtained in a group of ten rats which had received the compound. The compound reduced by 43.87% the increase in weight of the ventral prostate gland caused by testosterone propionate. While the mean

TABLE 1

THE WEIGHT OF THE VENTRAL PROSTATE, SEMINAL VESICLE AND LEVATOR ANI IN IMMATURE, CASTRATED, MALE RATS AFTER ADMINISTRATION OF TESTOSTERONE AND COMPOUND

Sr. No.	Groups	No. of rats used	Mean weight $\pm$ S.D.		
			Ventral prostate (mg/100 g)	Seminal vesicle (mg/100 g)	Levator ani (mg/100 g)
1	Control (a)	10	7.98 $\pm$ 2.82	10.45 $\pm$ 4.43	27.61 $\pm$ 7.80
2	Test compound (b)	10	Not found	10.40 $\pm$ 0.34	44.74 $\pm$ 6.17
3	Testosterone propionate (c)	10	104.50 $\pm$ 38.70	144.40 $\pm$ 30.2	74.38 $\pm$ 11.06
4	Test compound + testosterone propionate (d)	10	59.18 $\pm$ 6.08	172.77 $\pm$ 4.57	102.34 $\pm$ 10.14
P value			a and b < 0.01 c and d < 0.01	a and b > 0.05 c and d > 0.01	a and b < 0.01 c and d < 0.01

TABLE 2

EFFECT OF COMPOUND ON THE VENTRAL PROSTATE AND TESTES OF ADULT MALE RATS WHEN ADMINISTERED FOR 21 DAYS AT A DOSE OF 10 MG/KG

Group	No. of rats	Mean weight of ventral prostate (mg/100 g)	Mean weight of testes (mg/100 g)
Control	10	135.3 $\pm$ 3.93	835.0 $\pm$ 23.0
Compound	10	105.63 $\pm$ 2.79	668.0 $\pm$ 34.3
Difference in weight		30.33	167.0
P value		< 0.01	< 0.01

weight of ventral prostate in rats which received testosterone was 104.50 $\pm$ 38.70 mg/100 g, it was only 59.18 $\pm$ 6.08 mg/100 g in animals to which the compound had been given simultaneously with testosterone at a dose of 10.0 mg/kg. The differences were significant ($P < 0.01$). When the weight of the seminal vesicle was studied, it was observed that the animals injected with testosterone had a mean weight of 144.40 $\pm$ 30.2 mg/100 g compared with the mean control weight of 10.45 $\pm$ 4.43 mg/100 g in the control, immature rats. In the rats to which the compound was given at the same time as testosterone propionate, the mean seminal vesicle weight was 172.77 $\pm$ 4.57 mg/100 g. This increase in weight

over those animals which received testosterone alone was not significant ($P > 0.01$). The results indicated that the compound inhibited the increase in weight of the ventral prostate but not the increase in the weight of the seminal vesicle in immature, castrated rats after administration of testosterone. Data in which the levator ani muscle weight was compared indicated that the compound possessed significant anabolic activity as shown by the increase in weight of this muscle ($P < 0.01$). When given with testosterone propionate, the compound significantly enhanced the anabolic activity of the former ($P < 0.01$). When the compound was given to adult, male rats the results indicated that the compound decreased the weight of the ventral prostate and the testes to a significant degree ($P < 0.01$) as shown in Table 2. The compound is interesting in that it prevents the androgen-induced weight gain of the ventral prostate but not of the seminal vesicle in castrated, immature, male rats. This dissociation of the effects of the compound on the prostate and the seminal vesicle suggests that the compound is acting, not at the pituitary level, but preferentially at the level of the target organ, i.e. the ventral prostate.

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