normal implantation of the fertilized egg in the mouse. It is possible that endogenous relaxin production might synergize with P toward the end of the period. The fact that estrogen depresses decidual reaction after traumatization in the mouse suggests that early pregnancy is a period when estrogen is undesirable. The secretion of estrogen at this time might interfere with normal implantation.

In a study of the hormonal requirements for mammary gland growth in ovariectomized mice, it was shown that 1 μg EB plus 3 mg P administered for 19 days induced the greatest lobule-alveolar development as measured by DNA. However, the level of DNA attained experimentally by this treatment was only 57.6% of the DNA observed in normal mice pregnant 18 days(6). The present observations suggest that EB during the first 9 or 10 days might be a depressing factor in lobule-alveolar growth just as it depresses the placentomata reaction. In contrast, in the rat, daily administration of 1 μg EB plus 2 or 3 mg P for 19 days resulted in mammary gland growth as measured by DNA comparable to that of rats pregnant 18-20 days(7). These differences in the mouse and rat in regard to the role of estrogen in placentomata production and mammary gland growth suggest that mice secrete little or no estrogen during the first half of pregnancy.

Summary. Mature mice, ovariectomized for 7 to 10 days, were administered 0.1 μg EB for 3 days as a pretreatment followed by graded levels of P alone for 9 days. On day 5, the right uterine horn was traumatized by a sharp needle throughout its length. On day 4 post-trauma, the right and left horns were separated and compared in weight. The placentomata reaction increased as P was increased to 1.0 mg/day, then decreased with levels of 2 to 10 mg/day. Relaxin alone as a substitute for P had no effect. During pretreatment on reduced levels of EB, relaxin showed a slight response and during the post-trauma period with P a marked response was observed. When EB was administered with P during post-trauma period, the reaction was reduced. This observation suggests that mice secrete little or no estrogen during the first half of pregnancy.

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Anti-Androgenic Activity of a Series of 17-Iminosteroids. (28449)

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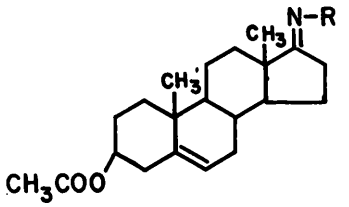
In recent years there has been considerable interest in compounds which inhibit the action of testosterone. Dorfman and Nes(1) reported that dihydroisosteviol inhibited the action of testosterone on the chick comb but not on the seminal vesicles or prostate of the rat. Dorfman and Stevens(2) also reported that a perhydrophenanthrene derivative inhibited the action of testosterone on both the chick comb and the accessory glands of the castrate rat. This latter compound was not estrogenic but was slightly androgenic and produced inhibition of pituitary gonadotrophin secretion in parabiotic rats. Byrnes *et al.*(3) reported that 11α-hydroxy-progesterone partially inhibited the stimulatory ef-



COMPOUND	R GROUP
I	$CH_2CH_2CH_2-N$
II	CH_2CH_2OH
III	$CH_2CH_2CH_2-N$ O
IV	$CH_2CH_2CH_2-N$ $N-CH_3$
V	$CH_2CH_2CH_2-N(C_2H_5)(C_2H_5)$

FIG. 1. Structural formulae of some 17-iminosteroids.

fect of testosterone propionate on the seminal vesicles and ventral prostate glands and the levator ani muscle in castrated rats. This compound also produced inhibition of the accessories in intact male rats along with gonadal inhibition. Lerner *et al.*(4) also observed a testosterone-antagonistic effect in castrated rats using A-norprogesterone. These anti-androgenic effects in castrated rats were noted only when the dose of the inhibiting compound was 20 to 50 times that of the androgen administered. A potent compound which would inhibit the prostatic response to androgens without inhibiting secretion of pituitary gonadotrophin would be of special interest in treatment of prostatic hypertrophy. We have recently noted appreciable anti-androgenic activity in castrated rats with a series of 17-iminosteroids.

Materials. The structural formulae of the compounds used are shown in Fig. 1.

Methods and results. Androgen antagonism. The test procedure was as follows: Male rats 23 days of age were castrated. Starting 18 days later they were treated intramuscularly daily for 7 days with a total dose of 0.5 mg testosterone propionate, with or without 2 or 5 mg of the 17-iminosteroid. The daily doses of each compound were combined in a single injection in 0.1 ml of corn oil. On the day after the last injection the seminal vesicles were dissected free of the coagulating glands, drained of fluid, and weighed to the nearest 0.1 mg on a torsion balance. The ventral prostate glands and levator ani muscles were also dissected out and weighed.

Two assays were run on each compound and the data are combined in Table I. At the 5 mg dose all of the iminosteroids reduced the response of the seminal vesicles and ventral prostate glands to 0.5 mg of testosterone propionate. However, the androgenic effect of testosterone propionate was not completely obliterated by any of the compounds. There was a tendency toward an inhibitory effect of the iminosteroids on the levator ani muscle weights but this decrease was less marked and in some cases was not statistically significant. There was no significant effect on body weight gain. Thus these iminosteroids inhibited more specifically the androgenic effects of testosterone propionate.

Several of these compounds (I, II, V) have been tested for androgenic activity in immature castrated rats, using the method previously described(5), and were found to be slightly active but not over 1% as potent as testosterone propionate. In intact immature mice, all were found to produce minimal uterine growth in 3 days at a total dose of 0.3 to 1 mg per mouse.

Pituitary gonadotrophin inhibition. Preliminary results are available on the possible effects of 2 of these compounds on pituitary gonadotrophin secretion. Adult female rats were ovariectomized and treated for 30 days with a dose of 5 mg of the compound in corn oil, per rat, per day. The pituitaries were removed, homogenized in saline and injected into immature rats, twice daily for 3 days. Each recipient received a total of ½ donor pituitary.

The number of rats used, the resultant

TABLE I. Inhibitory Effect of Certain Iminosteroids on Response to Testosterone Propionate in Castrated Male Rats.

Compound*	Total dose (mg/rat)	No. of rats	Seminal vesicles (mg)†	Ventral prostate (mg)†	Gain in body wt (g)†	Levator ani (mg)†
I	5	16	37.6 ± 2.1	43.1 ± 1.7	29.6 ± 1.6	81.1 ± 2.1
	2	8	59.0 ± 3.7	65.8 ± 3.3	32.8 ± 2.1	89.5 ± 5.2
	none	16	76.0 ± 2.3	80.8 ± 3.5	30.8 ± 1.3	107.9 ± 3.7
II	5	16	47.8 ± 3.2	55.6 ± 3.7	28.4 ± 1.4	91.2 ± 4.9
	2	8	71.5 ± 2.1	75.6 ± 3.9	34.9 ± 1.3	91.1 ± 8.0
	none	16	78.9 ± 1.6	82.4 ± 3.1	33.9 ± 1.8	98.5 ± 3.6
III	5	15	43.2 ± 2.0	46.9 ± 2.5	32.2 ± 1.8	88.6 ± 2.1
	2	8	60.9 ± 2.9	55.9 ± 3.4	30.5 ± 1.2	94.0 ± 4.8
	none	16	80.2 ± 4.1	78.4 ± 3.4	35.2 ± 1.1	109.8 ± 2.9
IV	5	16	52.6 ± 1.7	54.8 ± 2.0	32.9 ± 1.3	87.0 ± 2.5
	2	8	56.2 ± 1.5	58.8 ± 2.9	33.2 ± 2.1	94.1 ± 3.5
	none	16	80.2 ± 4.1	78.4 ± 3.4	35.2 ± 1.1	109.8 ± 2.9
V	5	14	39.4 ± 2.2	40.3 ± 2.3	35.3 ± 1.8	84.6 ± 2.8
	2	8	64.9 ± 2.9	59.2 ± 2.8	31.9 ± 1.7	99.6 ± 2.6
	none	16	66.6 ± 1.6	64.9 ± 1.7	35.9 ± .8	99.9 ± 3.1

* See Fig. 1.

† Mean ± standard error.

mean ovarian weights and standard errors were:

Castrate Controls	(249)	53.9 ± 1.1 mg
Compound I	(8)	60.8 ± 4.9
" II	(8)	62.0 ± 7.9

Thus neither of these compounds reduced the extent of accumulation of gonadotrophin in the pituitary gland following ovariectomy.

In intact young adult male rats a daily dose of 5 mg failed to reduce significantly either testis weight or the weights of the accessory glands, in a period of 14 days (Table II). The lack of effect on testis weight is further indication that pituitary gonadotrophin secretion is not affected. It is surprising, however, that no decreases in weights of seminal vesicles and ventral prostates were observed in these intact animals. Further study of the effect of these 17-iminosteroids on the action of endogenous androgen will be required.

TABLE II. Effect of Certain 17-Iminosteroids on Growth and Organ Weights in Intact Male Rats. All rats received daily injections of 5 mg for a period of 14 days.

Compound*	Final body wt (g)†	Testes (g)†	Seminal vesicles (mg)†	Ventral prostate (mg)†
I	318	3.15	367	398
II	293	3.39	481(a)	492(a)
III	297	3.17	309	440
IV	287	3.30	355	300
V	314	3.32	293(b)	326

* See Fig. 1.

† Mean values for groups of 5 rats. Values marked (a) are significantly higher ($P<.01$) and those marked (b) are significantly lower ($P<.01$) than simultaneously run controls. No other values were significantly different than controls ($P<.05$).

Summary. A series of five 17-iminosteroids was tested in combination with testosterone propionate in castrated male rats. All of these compounds inhibited the response to testosterone propionate in the seminal vesicles and ventral prostate glands. There was no indication of inhibition of pituitary gonadotrophin secretion in spayed female rats treated with several of these compounds. While inhibition of the action of exogenous testosterone propionate was obtained, no effect on endogenous androgen was observed in intact males at the dose used.

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