the chick comb in animals not treated with androgen were significnatly reduced by administration of this compound. A-norprogesterone is not androgenic, estrogenic, anti-estrogenic, progestational or anti-progestational under the experimental conditions described.

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Biological Activities of Some 6-Methylated Progesterones.* (25449)

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Biological studies with a growing list of synthetic steroids have revealed marked increases in progestational potency that accompanied introduction of a 6α-methyl group into the molecule(1,2,3,4,5,6). Recent reports have indicated that adrenal depression is encountered in rats treated with some of these agents(7,8) and an earlier report from this laboratory showed that a relationship existed between progestational and estrogen-antagonistic potencies of relatives of 19-nortestosterone(9). The present report compares the progestational, estrogen - antagonistic and adrenal depressant properties of a series of 6-methylated derivatives of progesterone.

Materials and methods. Progestational activity was determined using our modification of uterine carbonic anhydrase assay(6) and the intrauterine assay of McGinty(10). Where possible, potency estimates for uterine carbonic anhydrase test were obtained from dose-response curves by comparing doses of compounds that produced approximately 50-60 enzyme units/100 mg tissue. Progesterone, administered subcutaneously in daily dose of 0.1 mg, produced this response and was used as the standard of comparison for compounds administered by either buccal or parenteral routes. Antagonism of estrone-induced uterine growth was determined in intact immature mice according to previously described methods(9). Briefly, estrone at 0.3 μg, which produced uterine weights averaging about 35 mg in controls, was mixed with test compounds. Estrogen antagonistic potency was determined from the dose of antagonist estimated to produce a 50% block of growth increment (oil controls averaged about 10 mg). Adrenal depressant activity was determined in spayed female rats. The animals were spayed at 30 days of age and received the test compound for 14 days, beginning 10 days after spaying (8).

Results. The metrotropic effects of various steroids are summarized in Table I. Introduction of 6α-methyl group into progesterone or 17α-acetoxyprogesterone was generally accompanied by increases in potency in each of the metrotropic assays. 6α-Methylprogesterone, which showed a slight decrease in potency in the estrogen antagonism test, was an

* Synthetic steroids used were prepared by Drs. P. B. Sollman, C. G. Bergstrom and W. M. Hoehn of the Division of Chemical Research, G. D. Searle and Co. and Dr. B. Löken, formerly of Root Chemical Inc., Roosevelt, Puerto Rico.

TABLE I. Progestational and Estrogen-Antagonistic Activity of Various 6-Methylated Steroids.

Compound	Progestational potency: Uterine carbonic anhydrase, Subcut. N*	Subcut. Rel. pot.	Buccal N*	Buccal Rel. pot.	Intrauterine assay N*	Intrauterine assay Rel. pot.	Estrone-antagonist assay N*	Estrone-antagonist assay Rel. pot.
Progesterone	96(56)	1	96(56)	1	45(22)	1	13 (4)	1
6α-CH_3-Progesterone	8 (3)	5	4 (2)	.2	12 (6)	5	8 (2)	.7
6-CH_3-6-Dehydroprogesterone	6 (2)	2			3 (2)	.5	14 (3)	.7
17α-OAc-Progesterone	8 (3)	10	5 (2)	.2	5 (3)	1	7 (2)	1.2
6α-CH_3-17-OAc-Progesterone	12 (4)	30	17 (6)	5	14 (6)	25	9 (2)	2.9
6β-CH_3- "	8 (2)	20	7 (3)	2	9 (3)	5	10 (2)	1
6-CH_3-6-Dehydro-17-OAc-Prog.	9 (3)	25	8 (2)	17	8 (2)	10	5 (1)	.6
6α-CH_3-21-F-17-OAc-Prog.	17 (4)	40-50	14 (5)	17	23 (7)	50	4 (1)	6.3
6-CH_3-6-Dehydro-21-F-17-OAc-Prog.	20 (6)	40	10 (3)	20	18 (5)	50	3 (1)	2.4

* Under N the parenthetical number indicates No. of tests in which compound was evaluated; number in front of parenthesis indicates total No. of groups of animals employed (4 rabbits/group; 8 to 10 mice/group).

exception. Fluorine substitution at C-21 further augmented activity of 6α-methyl-17-acetoxyprogesterone; this material was 40-50 times more potent than progesterone on subcutaneous administration, 17 times buccally, 50 times on intrautreine application and 6.3 times more potent than the standard in the estrogen antagonism test.

One compound was available in which the methyl group at carbon 6 had the β-configuration, *i.e.*, 6β-methyl-17α-acetoxyprogesterone. In each assay this compound appeared to be less potent than its 6α-methylated isomere, although it was more active than its parent compound.

Three compounds were tested in which the configuration of the 6-methyl group was planar: 6-methyl-6-dehydroprogesterone, 6-methyl-6-dehydro-17-acetoxyprogesterone and 6-methyl-6-dehydro - 17-acetoxy-21-fluoroprogesterone. In general the potencies of these agents were the same as or slightly reduced from those of corresponding 6α-methyl isomers. A notable exception to this was 6-methyl-6-dehydro-17-acetoxyprogesterone which had an oral potency 3 times that of the 6α-methyl isomere; on parenteral administration its potency was decreased in the intrauterine and estrogen antagonism tests.

Discussion. On the basis of these studies there seems to be a general correlation between results of parenteral and buccal administration of these materials in the carbonic anhydrase test. However, 3 materials in the 17-acetoxyprogesterone series, 6-methyl-6-dehydro, the 21 fuoro-6-methyl, and 6-methyl-6-dehydro-21-fluoro-derivatives are much more potent buccally than one would predict from their parenteral potencies. The intrauterine test appeared to be qualitatively correlated with uterine carbonic anhydrase assay. As we pointed out previously, estrogen antagonistic and progestational activities show some relationship(9). A similar correlation is suggested in these studies, although one material, 6α - methyl - 17α - acetoxy-21-fluoroprogesterone, was more potent as an antagonist than would have been predicted on the basis of its potency in the carbonic anhydrase test.

A number of compounds caused atrophy of the adrenal glands in treated rats. In certain experiments progesterone has shown this activity to a limited extent, although replicate experiments have not been consistent. In this study progesterone and 17-acetoxyprogesterone were inactive in this respect (Table II). All 6α-methylated derivatives of 17-acetoxyprogesterone tested were active. Introduction of a methyl group in the α position of carbon 6 in the progesterone molecule resulted in adrenal depressant effects, but this compound did not appear to be more potent than the 6α-methyl derivatives of 17α-acetoxyprogesterone. 6-Methyl - 6 - dehydroprogesterone appeared to be inactive; it seems strange that introduction of the double bond in this com-

TABLE II. Adrenal Depressant Activity of 6-Methylated Steroids in Rats.

Compound	Test	Dose (mg)	N	Adrenal wt (mg)
Oil	1	—	8	50.
	2	—	6	59.1
Progesterone	1	1	8	53.8
6α-CH_3-Progesterone	2	1	5	33.4*
6-CH_3-6-Dehydroprogesterone	2	1	6	53.5
17-Acetoxyprogesterone	1	1	8	57.4
6α-CH_3-17-OAc-Progesterone	1	.3	9	34.8*
	1	1	8	23.2*
6-CH_3-6-Dehydro-17-OAc-prog.	1	1	8	23.2*
6-CH_3-6-Dehydro-17-OAc-21-fluoroprog.	1	1	9	20.6*

* Mean differs significantly from mean of simultaneous oil-treated controls ($P < .01$; Wilcoxon Rank Sum Test).

pound reduced activity while having no effect on activity of the 17-acetoxyprogesterone form. Since several active progestins lack adrenal depressant activity it appears that the 2 activities are not directly related.

Summary. Progestational, estrogen-antagonistic and adrenal depressant activities of a series of 6-methylated steroids was determined. Generally, introduction of a 6α-methyl group increased potency over the parent compound; 6β-methylation of 17-acetoxyprogesterone increased potency to a lesser extent. When the configuration of the 6-methyl group was neither α nor β, potencies generally were about the same as or slightly less than the 6α-methylated form. Exception to this was 6 - methyl - 6-dehydro-17-acetoxyprogesterone which had high oral potency. Adrenal depression was noted following 6-methylation.

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Serum Levels After Single Oral Doses of 6-(α-Phenoxypropionamido) Penicillanate and Penicillin V.* (25450)

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Isolation of 6-aminopenicillanic acid by Bachelor *et al.*(1) has made possible the preparation of new penicillins and related compounds, not easily accessible in other ways. One such new synthetic penicillin is 6 - (α-phenoxypropionamido) penicillanate.†

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† Also designated α-phenoxyethyl penicillin (Syncillin, Maxipen); both the powder and the tablets consisted of a mixture of the d- and l- isomers.