weight at 105°C. There are, however, a number of problems to be considered. Perhaps the only effect on these agents is to speed the metabolites of the sulfhydryl group out of the tissue or to prevent the production of these sulfhydryl groups. This assumes a rather high rate of metabolism of sulfhydryl by the skin. The possibility that there is a binding of these agents with sulfhydryl groups must also be considered.

Summary. An amperometric titration method for determining sulfhydryl groups was applied to mouse skin. The total sulfhydryl, the protein sulfhydryl and by subtraction, the soluble sulfhydryl contents were determined after painting with anthracene, DBA, DMBA, or a combination of the 2 carcinogens. The anthracene and the solvent, acetone, had no effect on the sulfhydryl levels. In general the shape of the curve of the total sulfhydryl content of the epidermis and dermis was the same, although the dermis contained approximately half that of the epidermis. For the most part, the effect on the protein sulfhydryl paralleled the corresponding total sulfhydryl curve. Most of the change in the soluble sulfhydryl level is presumed to occur in the epidermis. No cause and effect relationship to carcinogenesis or anticarcinogenesis is supported by these observations on the sulfhydryl groups of the skin.

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Received July 18, 1957. P.S.E.B.M., 1957, v96.

Antifibromatogenic and Antihysterotrophic Activities of Synthetic Androgens (19-nor-methyltestosterone, 19-nor-testosterone phenlypropionate, Δ^1-testosterone and Δ^1-androstenedione).* (23448)

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Both the progestational and antiestrogenic (antifibromatogenic, antihysterotrophic, antiluteinizing) activities of 19-nor-progesterone are greatly superior to those of progesterone (1,2,3). The same is true for 19-nor-ethinyltestosterone(4,5,6,7). The progestational activity of 19-nor-methyltestosterone in women is considerable(8); it is active by oral administration(9). Various activities of 19-nor-testosterone and of its esters also are remarkable (10). Results with the antifibromatogenic and antihysterotrophic activities of 19-nor-methyltestosterone (nMT) and of 19-nor-testosterone phenylpropionate (nTpp) are given in the present paper. Results obtained with Δ^1 derivatives of androstene also have been included. The glucocorticoid activity of Δ^1-hydrocortisone is several times that of

* Cordial thanks are due to Dr. G. A. Overbeek, Department of Pharmacological Research, N. V. Organon, Oss, Holland, for a generous supply of the 4 synthetic androgens.

TABLE I. Antifibromatogenic and Antihysterotrophic Activities of 19-nor-Testosterone Phenylpropionate (nTpp) and 19-nor-Methyltestosterone (nMT) Compared to Those of Testosterone Propionate (Tp) and Methyltestosterone (MT); of Δ^1-Testosterone (Δ^1-T) and Δ^1-Androstenedione (Δ^1-A) Compared to Those of Testosterone (T) and Androstenedione (A); in 149 Castrated Female Guinea Pigs with Subcutaneously Implanted Pellets of Estradiol (Absorption: 46 to 65 μg/day). Duration of experiments: 3 mo. For classification of results see(12,13).

Steroid tested						
Compound	μg/day	No. of animals	Fibrous tumoral effect†	Q_{2-3}‡	Uterine wt	No. of pellets; conc. (%)
Tp*	215 (162–267)	18	1.8 ± .46	.6	2.7 (3.1– 4.2)	1; 100
nTpp	8 (7– 11)	5	6.1 ± 1.40	1.4§ 2.5	3.9 (3.1– 4.7)	1; 20
nTpp	19 (14– 26)	15	2.7 ± .66	.5	3.6 (1.6– 5.5)	1; 40 & 2; 20
nTpp	38 (32– 51)	8	1.1 ± .20	0	2.9 (1.8– 5.1)	3; 20
MT	11 (2– 28)	13	6.2 ± 1.03	1.8	5.4 (2.2– 9.9)	1; 20 & 40
MT	255 (231–276)	7	.7 ± .18	4.0 0	4.1 (3.0– 6.4)	1; 80
nMT	15 (2– 28)	20	1.7 ± .40	.1	3.1 (1.0–12.2)	1-3; 20
T	51 (47– 53)	5	3.8 ± 1.52	1.0	3.6 (2.5– 4.7)	2; 40
T	300 (118–484)	14	2.8 ± .51	.6	3.2 (1.7– 4.9)	1-2; 80
Δ^1-T	65 (40– 93)	10	3.7 ± .72	2.7 .9	2.2 (1.6– 3.3)	1-2; 40
Δ^1-T	375 (244–534)	16	5.1 ± .72	1.6	3.6 (2.0– 6.7)	1-2; 80
A	422 (273–572)	8	3.3 ± .63	2.3 .7	3.5 (2.4– 5.1)	1-2; 80
Δ^1-A	396 (266–536)	10	6.3 ± 1.14	2.0	4.5 (2.5–10.7)	1-2; 80

* See(12), p. 152, Table 14. With corrections.
† Arbitrary values for No. and size of tumors, ranging from 0 to 12; see(12).
‡ Arbitrary values for large tumors only; see(13).
§ Significant difference.

hydrocortisone(11). Thus clinical interest is attached to the question of the antifibromatogenic activity both of Δ^1-testosterone (Δ^1-T) and Δ^1-androstenedione (Δ^1-A) and of the mentioned 19-nor-compounds.

Methods were the same as in our former paper(6).

Results obtained with nTpp and nMT are given in Table I to be compared with those obtained with testosterone propionate (Tp) and methyltestosterone (MT). Fig. 1 and 2

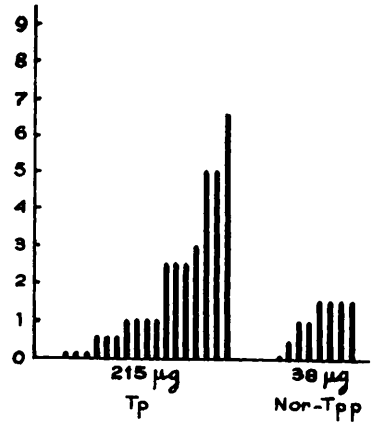

FIG. 1. Height of columns—F.T.E. of individual animals. Antifibromatogenic activity of 38 μg/day of 19-nor-testosterone phenylpropionate is equal and probably even superior to that of 215 μg/day of testosterone propionate.

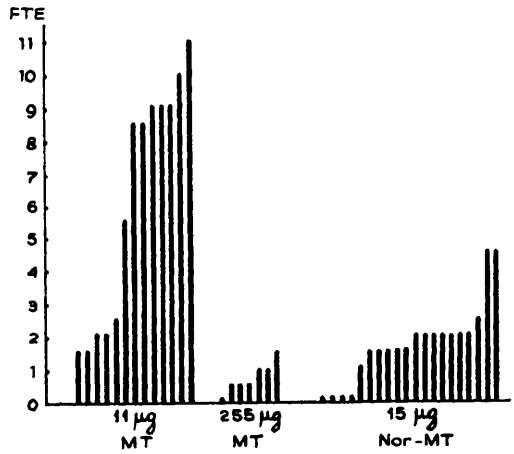

FIG. 2. Height of columns—F.T.E. of individual animals. With 15 μg/day of 19-nor-methyltestosterone almost the same result is obtained as with 255 μg/day of methyltestosterone; difference between 15 μg/day of the nor-cpd. and 11 μg/day of methyltestosterone is very striking.

give the individual results obtained in each comparative group. With an average of 19 μg/day of nTpp the antifibromatogenic action approaches that of 215 μg/day of Tp; with 38 μg/day of nTpp a more definite result is obtained than with the 6-fold of TP (Fig. 1). Thus the antifibromatogenic activity of nTpp is about 6 times that of Tp.

No less clearcut were the comparative re-

sults with MT and nMT. The antifibromatogenic activity of 15 μg/day of nMT approaches that of 255 μg/day of MT (Fig. 2). With 11 μg/day of MT no antifibromatogenic action was obtained; 15 μg/day of nMT were sufficient to produce a very pronounced action, with a significant difference of 4.0 compared to 11 μg/day of MT. The antihysterotrophic activity of nMT, compared to that of MT, is even more remarkable; the small quantities of nMT used were more effective than the large quantity of MT. The antifibromatogenic activity of nMT is about 10 times that of MT.

Table I summarizes also the comparative results with the two Δ^1-cpds. The antifibromatogenic activity of the 2 cpds. decreases considerably in comparison to T and A (significant difference between Δ^1-T and T: 2.7). A decrease of the antihysterotrophic activity also is very probable.

Summary. The antifibromatogenic and antihysterotrophic activities of 19-nor-testosterone phenylpropionate and 19-nor-methyltestosterone are 6 to 10 times greater than those of testosterone propionate and methyltestosterone respectively. The activity of testosterone is decreased by Δ^1. No activity is obtained even with very considerable quantities of Δ^1-testosterone or Δ^1-androstenedione.

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Received July 23, 1957. P.S.E.B.M., 1957, v96.

Determination and Physiologic Disposition of Meprobamate.* (23449)

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Although the use of the tranquilizing agent 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate (meprobamate) has become widespread, relatively little is known about its physiologic disposition and metabolic fate. This report includes a specific method for determination of meprobamate in urine and the results of metabolic studies *in vivo* and *in vitro*.

Methods. Estimation of Meprobamate. Meprobamate is isolated from biological material by extraction into ether at an alkaline pH. After evaporation of the ether the amount of drug is determined spectrophotometrically at 450 mμ, at which wavelength the drug exhibits a pronounced peak when heated with sulfuric acid (Fig. 1). *Procedure.* To 3 ml of urine in a 15 ml glass-stoppered centrifuge tube are added 0.2 ml 1 N sodium hydroxide and 5 ml of ether.† Shake 5 minutes and centrifuge the tube. Two ml of the ether phase are evaporated to dryness under a stream of air in a heavy-walled test tube, and

* A preliminary report was presented at Am. Chem. Soc., Miami, April, 1957.

† Ether was Mallinckrodt anhydrous analytical reagent.