Anabolic 19-Nortestosterone Bicyclo[2.2.2]octane- and -octenecarboxylates[1a]

R. M. SCRIBNER,

Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

R. I. DORFMAN, AND W. H. ROOKS, II

Institute of Hormone Biology, Syntex Research, Palo Alto, California

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Esters of 19-nortestosterone with 4'-substituted and 4'-unsubstituted bicyclo[2.2.2]octane- and -oct-2'-enecarboxylic acids have been prepared and tested as anabolic agents. Several of these esters having either no 4' substituents or relatively small 4' substituents show exceptionally long-acting myotrophic activity and very low androgenic activity. Extremely bulky esters are inactive. An aid to comparing injectable anabolic candidates having prolonged activity has been devised; called the *integrated myogenic margin*, it is a function of both separation of myogenic activity from androgenic activity and duration of activity.

Anabolic steroids may be defined from the therapeutic point of view as steroids which stimulate the synthesis of cellular protein.[1] Experimentally the anabolic effect is best indicated by increased nitrogen retention.[2,3]

The ideal anabolic agent would, first of all, be free of androgenic properties, but despite much research in this area, no effective anabolic agent free of masculinizing side effects is yet available to the physician.[4] Secondly, a case can be made that the ideal anabolic agent should have characteristics which permit establishment of a steady concentration of drug within the patient over a long period of time, thus mimicking the steady secretion of the natural anabolic agent testosterone.[1b] Brown and Samuels[5] have shown that a prolonged, relatively low level of testosterone propionate, administered intramuscularly, far more effectively causes nitrogen retention than does a brief intravenous infusion of a high concentration of testosterone.

Edgren[6] found with a modified Hershberger[7] test that compounds related to 19-nortestosterone consistently produced significant myotrophic (anabolic) effects at dose levels below the threshold of androgenic response as measured by the rat ventral prostate. The effect seemed associated with the absence of the C-19 angular methyl group since a series of testosterone derivatives showed no such separation of activities. Overbeek, *et al.*,[8] have shown that when 19-nortestosterone is esterified with acids of increasing chain lengths, both duration of action and ratio of anabolic to androgenic activity increase. Numerous esters of 19-nortestosterone with long-chain or bulky carboxylic acids have been prepared and evaluated[9,10] in recent years, and several such esters have been used in the clinic as injectable, long-acting, anabolic agents. Insight into the action of some of these esters *in vivo* has been gained recently by a study of van der Vies.[11] For the phenylpropionate, decanoate, and oleate esters of 19-nortestosterone the ratio of anabolic to androgenic activity in the rat depends on the rate at which the esters are released from the intramuscular depot. Though long-acting in their anabolic–androgenic effects, these esters are rapidly hydrolyzed once in the blood and free 19-nortestosterone is the ultimate stimulator of the target organs.[12] The rate and concentration at which 19-nortestosterone reaches target receptors are fully determined by the rate of release of ester from the depot.

Though slow release can be an advantageous consequence of esterification with bulky carboxylic acids, it is reasonable to expect that the best anabolic activity would reside in esters in which lipophilicity and resistance toward hydrolysis[13] are at an optimum level rather than maximum level. For example, an ester with very high lipophilic character could be released too slowly from its depot to have significant activity, or once released would be irreversably adsorbed in the first lipophilic area with which it came in contact.[14] making it unavailable to the appropriate esterases or other sites of action. Similarly, a very hindered ester might be entirely resistant to hydrolysis and being inactive *per se* would have no androgenic or anabolic activity.

Recent availability[15–19] of a number of new 4-sub-

(1) (a) This paper is Contribution No. 1528 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, Del. 19898. (b) H. L. Kruskemper, "Anabolic Steroids," Academic Press, New York, N. Y., 1968.

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(4) "New Drugs Evaluated by the A.M.A. Council on Drugs," American Medical Association, Chicago, Ill., 1967, Chapter 42.

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(8) G. A. Overbeek, J. van der Vies, and J. de Visser, *Protein Metab. Influence Growth Horm. Anabolic Steroids, Nutr. Health Dis. Int. Symp. 1962*, 185 (1962); G. A. Overbeek, J. de Visser, *Acta Endocrinol.*, **35**, 59 (1960).

(9) See for example G. A. Overbeek and J. de Visser, *ibid.*, **24**, 209 (1957); *ibid.*, **38**, 285 (1961); J. de Visser and G. A. Overbeek, *ibid.*, **35**, 405 (1960); E. Diczfalusy, *ibid.*, **35**, 59 (1960); U. Saglid, *Acta. Med. Scand.*, **173**, 367 (1963).

(10) R. T. Rapala, R. J. Kraag, and K. Gerzon, *J. Med. Chem.*, **8**, 580 (1965).

(11) J. van der Vies, *Acta Endocrinol.*, **49**, 271 (1965).

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(15) J. G. Whitney, W. A. Gregory, J. C. Kauer, J. A. Snyder, R. E. Benson, and E. C. Hermann, *J. Med. Chem.*, **13**, 254 (1970), and ref therein.

(16) J. C. Kauer, Netherlands Patent Application 657979, Dec 23, 1965. *Chem. Abstr.*, **64**, 15772b (1966); F. W. Baker and L. M. Stock, *J. Org. Chem.*, **32**, 3344 (1967).

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(18) H. D. Holtz and L. M. Stock, *J. Amer. Chem. Soc.*, **86**, 5188 (1964); F. W. Baker, and R. C. Parish, and L. M. Stock, *ibid.*, **89**, 5677 (1967).

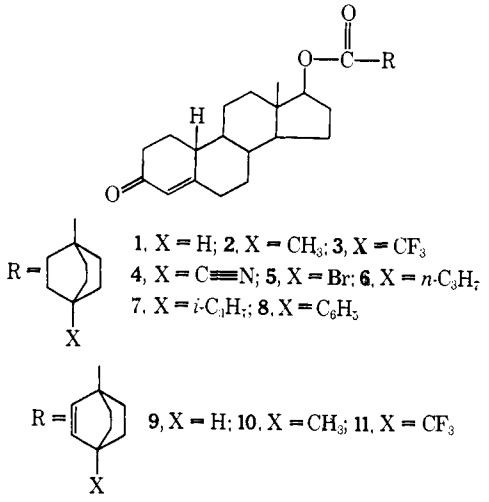
(19) J. D. Roberts, W. T. Moreland, Jr., and W. Frazer, *ibid.*, **75**, 637 (1953).

Table I
Characterization of the 19-Nortestosterone Bicyclo[4.4.4]octane- and -oct-2-enecarboxylates[a]

No.	19-Nortestosterone-	Mp, °C[b]	[α]D, deg[c]	Formula	Analyses[d]	Method of preparing acid[e]
1	Bicyclo[2.2.2]octane-1'-carboxylate	149–150	+56	$C_{27}H_{38}O_3$	C, H	*f*
2	4'-Methylbicyclo[2.2.2]octane-1'-carboxylate	196–201		$C_{28}H_{40}O_3$	C, H	*f*
3	4'-Trifluoromethylbicyclo[2.2.2]octane-1'-carboxylate	199–204	+44	$C_{28}H_{37}F_3O_3$	C, H, F	*g*
4	4'-Cyanobicyclo[2.2.2]octane-1'-carboxylate	193–200	+57	$C_{28}H_{37}NO_3$	C, H, N	*h*
5	4'-Bromobicyclo[2.2.2]octane-1'-carboxylate	215–219	+58	$C_{27}H_{37}BrO_3$	C, H, Br	*h*
6	4'-*n*-Propylbicyclo[2.2.2]octane-1'-carboxylate	191–194	+64	$C_{30}H_{44}O_3$	C, H	*f*
7	4'-Isopropylbicyclo[2.2.2]octane-1'-carboxylate	204–207	+57	$C_{30}H_{44}O_3$	C, H	*f*
8	4'-Phenylbicyclo[2.2.2]octane-1'-carboxylate	205–212	+64	$C_{33}H_{42}O_3$	C, H	*g*
9	Bicyclo[2.2.2]oct-2'-ene-1'-carboxylate	143–147		$C_{27}H_{36}O_3$	C, H	*f*
10	4'-Methylbicyclo[2.2.2]oct-2'-ene-1'-carboxylate	179–183	+66	$C_{28}H_{38}O_3$	C, H	*f*
11	4'-Trifluorobicyclo[2.2.2]oct-2'-ene-1'-carboxylate	178–179	+49	$C_{28}H_{35}F_3O_3$	C, H, F	*g*
13	Bis(19-nortestosterone) bicyclo[2.2.2]octane-1',4'-dicarboxylate	200–210[j]	+85	$C_{46}H_{62}O_6$	C, H	*i*

[a] Ir, uv, and pmr spectra were consistent with assigned structures. [b] Melting points are uncorrected. They were taken with a Kofler hot stage microscope on samples that had been purified by chromatography on neutral, activity III alumina and recrystallized from Me_2CO–hexane. [c] Measured in $CHCl_3$ at *c* 1.0–1.2%. [d] Analyses are indicated only by symbols of the elements. Analytical results obtained for these elements were within ±0.3% of the theoretical values. [e] We are indebted to Drs. J. C. Kauer, J. G. Whitney, and W. A. Gregory of the Du Pont Central Research and Industrial and Biochemicals Departments for supplying many of these bicyclo-[2.2.2]octane- and -oct-2-enecarboxylic acids. [f] See Ref 16. [g] Ref 15. [h] Ref 17 and 19. [i] Ref 17. [j] Crystallized from Me_2CO.

stituted bicyclo[2.2.2]octane- and -oct-2-enecarboxylic acids made it possible to synthesize a number of esters of these acids with 19-nortestosterone and to evaluate them as potential anabolic agents. Most of these esters are represented by structures **1** through **11** and are characterized in Table I. The rationale behind this study was that it might be possible to *optimize*



lipophilicity and esterase susceptibility of esters **1–11** by varying the electronic,[18] steric, and hydrophobic[14] character of the substituents X.

Chemistry.—The bicyclo[2.2.2]octane- and -oct-2-ene-1-carboxylic acids used to prepare esters **1–11** were prepared according to published procedures involving either high pressure addition of ethylene to alkyl α-pyrone-3-carboxylates[15,16] or by conventional reactions using 4-ethoxycarbonyl bicyclooctane-1-carboxylic acid as the progenitor.[17,19] The bicyclooctane carboxylic acids thus obtained were converted into the corresponding acid chlorides by $SOCl_2$ in C_6H_6 containing a catalytic amount of DMF.

19-Nortestosterone esters **1–11** were prepared by reaction of 1 equiv of the appropriate acid chloride with the steroid alcohol, either in pyridine solvent at room temperature for several days or in refluxing C_6H_6[20] with a small excess of pyridine for 20–40 hr. The latter procedure gave better yields of ester, but even after several crystallizations the product contained several per cent of an impurity detected by tlc on silica gel as a component less polar than the major component. From crude ester **10** this impurity was isolated by column chromatography and identified as the dienol diester **12** on the basis of nmr and uv spectra [λ_{max} 234 mμ (ε 18,800)]. Ester **12** could be prepared in good yield by treatment of 19-nortestosterone with excess 4-methylbicyclo[2.2.2]oct-2-ene-1-carbonyl chloride in boiling toluene for 72 hr in the presence of pyridine.

Under forcing conditions analogous to those used to prepare **12**, diester **13** was prepared from 19-nortestosterone and bicyclo[2.2.2]octane-1,4-bis(carbonyl chloride).[17,21] Ester **13** represents an extremely bulky bridgehead carboxylic acid ester. In a sense the steroid itself contributes to the bulk of the carboxylic moiety. It is interesting to note in the context of the previous discussion that this very bulky ester shows little or no androgenic or anabolic activity when administered to rats by subcutaneous injection.

Anabolic–Androgenic Activity. A. 14-Day Hershberger Assay[22a] (Daily Treatment.)—Preliminary evaluation of anabolic and androgenic potencies of five esters (**1**, **2**, **7**, **9**, **10**) was carried out using a Hershberger assay.[7] Male rats[22b] were castrated at 21 days of age and, beginning on the day of surgery, received the test compound dissolved in sesame oil subcutaneously once daily for 14 days. On the day after the last injection, the animals were sacrificed and the levator ani (LA), ventral prostate (VP), and seminal vesicles (SV) were removed and weighed. The end-point used was the tissue:body wt ratio (mg of tissue/g of body wt .

(20) A. Kukis and J. M. R. Beveridge, *J. Org. Chem.*, **25**, 1219 (1960); see also ref 10.

(21) Enol esters probably were formed under the forcing conditions used to prepare **13**, but being polymeric they were readily removed by column chromatography.

(22) (a) Tests carried out at the Endocrine Laboratories of Madison, Wis., under the direction of Dr. E. G. Shipley; (b) Holtzman Co. Madison, Wis.; (c) Simonsen Laboratories, Gilroy, Calif.; (d) Badger Rat Co., Madison, Wis.

Each compound was tested at 3 dose levels, using 5 rats per dose. Testosterone propionate (TP) was tested concurrently at 4 dose levels and served as the standard for comparison of the test materials. Standard statistical procedures[23] for determining the potencies of the materials relative to TP were used. Myogenic: androgenic ratios were calculated by dividing the anabolic potency (LA) by the androgenic potency (average of SV and VP). Table II compares the activities of the 5 esters.

TABLE II
FOURTEEN-DAY MYOGENIC-ANDROGENIC ASSAY

Compd	Dose levels (mg/day)	Relative potency, TP = 1: Androgenic[a]	Relative potency, TP = 1: Myogenic	M:A ratio
Testosterone	0.1, 0.25, 0.5	0.08	0.13	1.6
19-Nortestosterone[b]	0.05, 0.1, 0.25	<0.02	0.07	>3.5
Ester 1[b]	0.05, 0.1, 0.25	<0.02	0.14	>7
Ester 2	0.25, 0.5, 1.0	0.02	~0.4	~20
Ester 7	0.1, 0.25, 0.5	<0.02	0.17	>9
Ester 9	0.25, 0.5, 1.0	0.04	≥0.7	≥17
Ester 10	0.25, 0.5, 1.0	0.03	~0.5	~17

[a] Average of values for SV and VP. [b] Run simultaneously with testosterone. Potency converted and expressed relative to TP.

B. Long-Term Anabolic–Androgenic Assays (Single Treatment). (1) 4-Week Studies.—Esters **3** through **8** and **10** through **12** were tested for prolonged androgenic and anabolic activity. A single subcutaneous injection of the test compound was administered on day 1 to castrate immature male rats[22c] in a vehicle consisting of 90% sesame oil and 10% benzyl alcohol. The rats were sacrificed on day 29. Table III lists data

TABLE III
FOUR-WEEK STUDY. THE PROLONGED MYOGENIC–ANDROGENIC ACTIVITIES OF A SERIES OF BICYCLOOCTANE ESTERS OF 19-NORTESTOSTERONE

Material administered	Total dose (mg)	No. of rats	% increase of mean tissue ratio[a] over control after 28 days: Ventral prostate	Seminal vesicles	Levator ani
TP[b]	3.4	7	467	360	18
3	4.8	7	200	80	127
4	4.4	7	200	200	86
6	4.5	7	33	40	59
TP	3.4	7	160	171	10
7	2.5	7	60	43	71
TP	3.4	7	225	320	0
5	4.9	7	50	20	44
8	4.9	7	0	0	0
11	4.8	7	75	60	66
TP	3.4	7	380	475	0
10	4.2	7	60	150	77
TP	3.4	7	100	180	7
12	5.7	7	20	20	14

[a] Milligrams of tissue weight per gram of body weight. [b] Testosterone propionate.

from 5 separate experiments in which one or more of these esters were studied at equimolar doses.

The low activity of dienol diester **12** (Table III) was confirmed in additional tests in which the compound

TABLE IV
LONG-TERM ANABOLIC–ANDROGENIC ASSAY

Treatment	1 wk: VP	1 wk: SV	1 wk: LA	2 wk: VP	2 wk: SV	2 wk: LA	3 wk: VP	3 wk: SV	3 wk: LA	4 wk: VP	4 wk: SV	4 wk: LA	6 wk: VP	6 wk: SV	6 wk: LA	8 wk: VP	8 wk: SV	8 wk: LA	12 wk: VP	12 wk: SV	12 wk: LA
Sesame oil only[a]	13.8	11.0	23.7	11.8	10.6	42.8	10.6	10.8	34.8	13.2	12.7	75.3	11.0	10.2	91.5	11.1	10.2	100.1	9.2	10.1	101.9
Testosterone propionate (2.0 mg)[b]	113.4	76.4	51.7	80.7	63.4	57.5	46.0	47.7	39.4	35.7	45.0	71.0	23.7	38.5	87.8	22.5	40.9	103.3	15.8	34.8	107.9
19-Nortestosterone phenylpropionate (7.5 mg)[b]	115.0	82.2	72.8	98.8	93.5	111.0	118.9	113.8	132.2	102.6	96.1	161.7	33.7	60.8	161.0	24.2	45.9	150.4	24.6	48.8	164.6
1 (7.2 mg)[b]	39.0	30.4	55.3	25.2	27.1	97.5	21.9	27.6	110.7	26.1	27.4	144.4	15.8	32.7	170.8	13.7	29.0	212.7	15.3	29.1	250.3
9 (7.2 mg)[b]	55.4	44.1	64.5	44.4	41.0	109.3	27.5	36.4	123.0	28.8	39.4	145.7	37.6	57.8	196.0	18.0	37.2	213.4	15.2	43.3	301.9
2 (7.8 mg)[b]	16.3	12.6	36.4	40.0	39.1	101.6	20.5	27.6	118.2	29.9	40.2	146.3	21.6	36.2	183.6	19.4	32.9	196.5	16.7	38.7	250.2

[a] Ten rats per week. [b] Six rats per week.

(23) D. J. Finney, "Statistical Methods in Biological Assay," Hafner Publishing Co., New York, N. Y., 1964.

was administered daily in an aqueous vehicle to immature castrate male rats subcutaneously for 7 days using a total dose of 10 mg, or orally by gavage for 10 days using a total dose of 20 mg.

(2) **12-Week Studies.**[22a]—Esters **1**, **2**, **9**, and **13** were tested in assays modeled after one used by Rapala, *et al.*[10] Each ester was administered subcutaneously in sesame oil on the day of surgery only to castrate 21-day-old male rats.[22d] Organ weights were determined using groups of 6 rats at weekly or biweekly intervals following the injection, with the last autopsy at the beginning of the 12th week. The results, except for those of ester **13** which showed little or no activity, are summarized in Table IV. Note from Table IV that the levator ani in the untreated castrate controls continued to grow in the absence of testicular hormone and reached maximum weight in approximately 8 weeks. To facilitate comparison, the data for similarly tested testosterone propionate and 19-nortestosterone phenylpropionate are also shown in Table IV.

For each of these 5 esters, tissue weights of the treated animals were plotted as mg increase over the weights of the corresponding tissues of the untreated castrate controls. To assist in the comparison of esters we devised a relationship termed the integrated myogenic margin (IMM) expressed in mg-weeks. The values for IMM were calculated by integrating the area lying under the LA curve and subtracting from this the area lying under the corresponding SV curve. This was easily done gravimetrically. IMM values (Table V)

Table V
Integrated Myogenic Margins (IMM) from Long-Term Myogenic-Androgenic Assay (Calculated from Table IV)

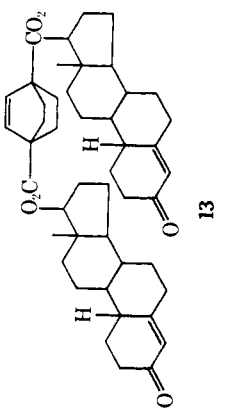
Test material	Dose, mg	—IMM at week indicated— 8	12
Testosterone propionate	2.0	−270	−380
19-Nortestosterone phenylpropionate	7.5	+23	+110
1	7.2	+350	+740
2	7.8	+350	+730
9	7.2	+360	+880

thus reflect not only separation of myotrophic (anabolic) from androgenic activity but also duration of the myotrophic response. A high positive value for IMM is thus desirable for an anabolic candidate. Note that testosterone propionate has a negative IMM value because the area under the curve for the androgen indicator (SV) is greater than the area under the curve for the myogenic indicator (LA). In assessing the significance of the IMM values, it should be recognized that for a given compound IMM will be dose dependent unless the dose–response curves for SV and LA happen to be parallel. The 19-nortestosterone esters in this set of assays were tested using equimolar dose levels.

(3) **18-Week Studies.**—Eighteen-week studies similar to the 12-week studies were performed using a different vehicle (90% sesame oil, 10% $PhCH_2OH$), rats from a different supplier,[22c] and lower equimolar doses of esters **1**, **9**, and **10** with an equimolar dose of testosterone propionate. Usually 6 rats per group were sacrificed at each time period. The test data are summarized in Table VI and the corresponding IMM values calculated at the end of each period are given in Table VII.

Table VI
Long-Term Anabolic–Androgenic Assay

Treatment	Dose, mg	Average organ weights, mg at weeks indicated: 3 VP	3 SV	3 LA	6 VP	6 SV	6 LA	8 VP	8 SV	8 LA	10 VP	10 SV	10 LA	15 VP	15 SV	15 LA	18 VP	18 SV	18 LA
Control	0	12.5	10.8	25.9	8.9	10.4	44.9	15.0	14.4	40.3	7.9	14.0	48.7	13.9	15.5	50.7	8.2	9.5	48.3
T.P.	5.4	55.1	57.5	40.5	14.8	28.9	43.7	19.4	28.4	62.8	17.8	31.0	49.9	17.8	33.3	37.3	13.2	27.3	42.1
1	4.1	41.0	23.9	44.5	16.5	23.1	78.7	11.5	17.9	77.2	12.0	21.7	52.9	15.2	22.7	68.1	10.7	19.7	52.5
9	4.1	48.8	37.0	40.7	17.1	27.1	73.9	13.6	23.9	61.6	18.1	26.2	51.5	17.4	28.1	72.5	8.9	16.5	72.6
10	4.2	38.8	24.9	49.2	13.2	19.6	75.5	14.4	21.7	62.6	15.1	34.9	70.1	14.4	21.0	67.5	11.9	20.4	55.8



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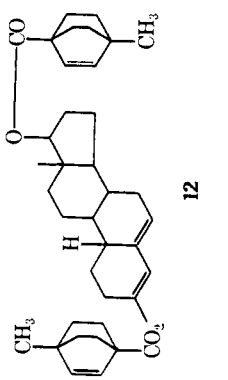

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TABLE VII
INTEGRATED MYOGENIC MARGINS FROM LONG-TERM MYOGENIC–ANDROGENIC ASSAY

Test material	Dose (mg)	IMM at week indicated						
		1	3	6	8	10	15	18
Testosterone propionate	3.4	−16	−112	−160	−159	−166	−253	−306
1	4.1	+2	+37	+114	+167	+197	+214	+220
9	4.1	−5	+16	+85	+110	+112	+112	+162
10	4.2	+7	+60	+155	+193	+209	+239	+250

Conclusions

Several of the bicyclo[2.2.2]octane- and -oct-2'-ene-carboxylic acid esters of 19-nortestosterone described here have unusually long-lasting myogenic (anabolic) activity and low androgenicity compared to 19-nortestosterone phenylpropionate (Tables IV and V). IMM values conveniently summarize separation of myogenic from androgenic activity and duration of activity, but absolute IMM values and even the relative order of IMM values for a series of compounds depend on the dose levels studied (Tables V and VII).

Differences in biological activity between the bicyclo[2.2.2]octane esters and the corresponding bicyclo[2.2.2]oct-2'-ene esters studied appear to be small and within the probable range of experimental error. Compare esters **1** and **9** [Tables II, V, and VII), **2** and **10** (Table II), and **3** and **11** (Table III). Likewise the 4'-unsubstituted and 4'-Me substituted esters have comparable activities, which can be seen by comparing esters **1** and **2** (Tables II and V) and **9** and **10** (Tables II and VII). No direct comparison can be made for the small electronegative substituents 4'-CF_3 and 4'-C≡N (in **3**, **4**, and **11**), however it appears that in the saturated bicyclooctane series the substituted esters do not have activity which is meaningfully different from the unsubstituted ester (**1**), whereas the substituted unsaturated bicyclooctene ester **11** is less active than the unsubstituted ester **9**. The 4'-bromo substituent (**5**) and the moderately large 4'-*n*-propyl (**6**) and 4'-isopropyl (**7**) groups decrease ester activity, whereas the larger 4'-phenyl-substituted ester 8 is inactive (Table III).

More detailed studies on ester **10** will be described in forthcoming publications.

Experimental Section[24]

Acid Chlorides.—This procedure typifies preparation of the acid chlorides used to prepare esters 1–12. A mixture of 25 g of 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, 35 ml of $SOCl_2$, and 1 drop of DMF in 50 ml of C_6H_6 was heated at reflux for 2 hr. Fractional distn of the reaction mixture gave 18.2 g of 4-methylbicyclo[2.2.2]oct-2-ene-1-carbonyl chloride: bp 58° (1.3 mm); λ_{max} ($CHCl_3$) 5.60, 6.21, 7.25 μ; nmr ($CDCl_3$) AB quartet (2) centered at 6.26 ppm, 1.40 (s, 3) ppm. Similarly, 4-methylbicyclo[2.2.2]octane-1-carbonyl chloride, bp 56° (0.9 mm), bicyclo[2.2.2]oct-2-ene-1-carbonyl chloride bp 48–49° (0.9 mm), and bicyclo[2.2.2]octane-1-carbonyl chloride, bp 78° (3.5 mm) were prepared. The acid chlorides used to prepare esters **3**, **8**, and **11** were isolated by evaporation of the C_6H_6 *in vacuo* and were not distilled prior to use. Bicyclo[2.2.2]octane-1,4-bis(carbonyl chloride) was prepared by a published procedure.[17]

19-Nortestosterone Esters. Method A. 19-Nortestosterone 4'-Methylbicyclo[2.2.2]oct-2'-ene-1'-carboxylate (10).—This procedure typifies preparation of esters 1–11 and 13 (Table I). A solution of 4.0 ml of 4-methylbicyclo[2.2.2]oct-2-ene-1-carbonyl chloride, 5.0 g of 19-nortestosterone, and 4.0 ml of C_5H_5N in 125 ml of dry C_6H_6 was heated at reflux temp for 8 hr. The mixture was cooled, diluted with Et_2O, and washed twice with cold 5% aq NaOH, once with H_2O, and then with satd NaCl solution. Evaporation of solvent gave 9.3 g of crude ester, which was applied as a solution in C_6H_6 to a column of 200 g of neutral, activity grade III alumina and eluted with C_6H_6. Crystallization from Me_2CO–hexane gave 4.2 g of 19-nortestosterone 4'-methyloct-2'-ene-1'-carboxylate (Table I): λ_{max} ($CHCl_3$) 5.83, 6.03, 6.20, 8.00 μ, λ_{max} (EtOH) 238 mμ (ε 17,900). Tlc of a portion of this ester on silica gel using 1:1 $CHCl_3$–Et_2O eluant showed the presence of a major minor component R_f 0.87 in addition to the major component at R_f 0.68. Isolation of the mobile impurity as a glass was accomplished by column chromatography by elution from neutral, activity grade III alumina with 5% C_6H_6 in petr ether. The impurity was identified as **12** on the basis of uv (λ_{max} 233 mμ), nmr, and ir spectra, and identity with authentic **12**, prepared as described below.

Traces of diester **12** were removed from **10** by heating at reflux a solution of crude **10** in MeOH containing about 0.4% (by wt) of Na_2CO_3 and 0.7% of H_2O.[25] The strong, characteristic odor of methyl 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylate apparent after this reaction was completed suggests that under these conditions transesterification rather than simple hydrolysis predominates.

Method B. 19-Nortestosterone Bicyclo[2.2.2]octane-1'-carboxylate (1).—This method, though generally inferior to method A, was used as an alternate route to ester 1 and several other esters. A solution of 2.7 g of 19-nortestosterone and 2.2 g of bicyclo[2.2.2]octane-1-carbonyl chloride in 15 ml of C_5H_5N was stirred for 4 days at room temp and then poured into H_2O. Extraction with Et_2O and chromatography on 150 g of neutral, activity grade III alumina gave in the C_6H_6–petr ether (1:1) eluate, after crystn from Me_2CO–hexane, 1.62 g of 19-nortestosterone bicyclo[2.2.2]octane-1'-carboxylate, mp 148.5–150°, identical with that prepared by method A.

Estra-3,5-diene-3,17β-diol Bis(4'-methylbicyclo[2.2.2]oct-2-ene-1-carboxylate) (12).—A solution of 5.48 g (20 mmoles) of 19-nortestosterone, 14.4 g (80 mmoles) of 4-methylbicyclo[2.2.2]-oct-2-ene-1-carbonyl chloride, and 12.4 ml of C_5H_5N in 200 ml of PhMe was heated at reflux for 72 hr. The reaction mixture was cooled, diluted with C_6H_6, and washed with H_2O and twice with satd $NaHCO_3$ solution. Evaporation of solvent gave a mushy solid which after washing with petr ether weighed 8.5 g. Two crystallizations from Me_2CO gave 6.3 g of crystalline **12**. Further purification by chromatography on neutral III alumina and elution with petr ether–C_6H_6 gave, after crystallization from CH_2Cl_2–Me_2CO, 2.9 g of **12** as white needles: mp 205–216° (Kofler); homogeneous by tlc and identical with **12** accompanying ester **10**; $[\alpha]^{24}D$ −68° (c 1.0 $CHCl_3$); λ_{max} (EtOH) 234 mμ (ε 18,800); λ_{max} ($CHCl_3$) 3.30, 3.39, 3.48, 5.79, 5.99 (w), 6.10 (w), 6.16 (w); nmr ($CDCl_3$), AB quartet (4) centered at 6.2 ppm, 5.78 ppm (1, C-4 vinyl); 5.47 (broad) ppm (1, C-6 vinyl). *Anal.* $C_{38}H_{50}O_4$: C, H.

(24) Boiling points and melting points are uncorrected.

(25) We are indebted to Dr. F. Alvarez of the Syntex Institute of Organic Chemistry for the suggestion on which this procedure is based.