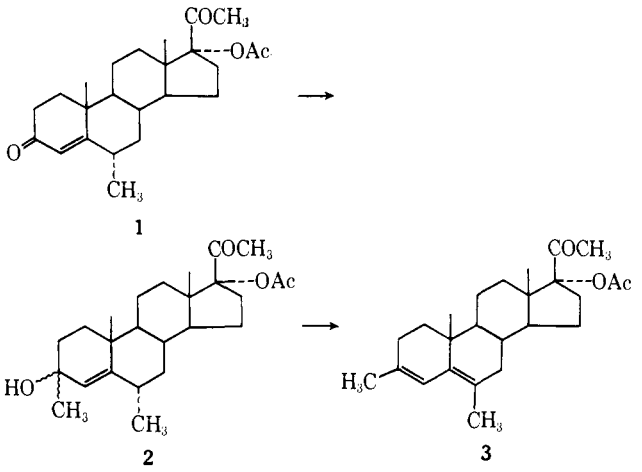

pure **2** was treated with dilute methanolic HCl, **3** was obtained in quantitative yields.

Biological Data.—The progestational activity of **2** and **3** was determined by the Clauberg test[5] and the endometrial response was scored according to the index of McPhail.[6] Compound **2** at dose levels of 0.5 and 1.0 mg/kg exhibited a McPhail index of 1.9 and 2.8, respectively, whereas the corresponding diene **3** showed a McPhail index score of 1.0 at 0.5 mg/kg.

Experimental Section[7]

3ξ,17α-Dihydroxy-3ξ,6α-dimethylpregn-4-en-20-one 17-Acetate (2).—A solution containing 3.0 g of 17α-acetoxy-6α-methylprogesterone (**1**) in 50 ml of dry THF was added dropwise to a cooled solution of 15 ml of MeMgBr (Arapahoe Chemicals) in 15 ml of dry THF. The mixture was stirred at 20–25° for 0.5 hr and the excess Grignard reagent was decomposed with 100 ml of cold H_2O. The mixture was extracted with 100 ml of ether and the etheral solution was washed several times (H_2O), dried (Na_2SO_4), and evaporated to dryness. Repeated recrystallization of the residue from ether gave 900 mg (29%) of **2**: mp 195–197°; $[\alpha]D$ +48.2°; λ_{max}^{KBr} 2.84, 5.76, and 5.85 μ; no uv absorption between 200–300 mμ. *Anal.* ($C_{25}H_{38}O_4$) C, H.

17α-Acetoxy-3,6-dimethylpregn-3,5-dien-20-one (3).—Compound **2** (700 mg) was treated with 5.0 ml of dilute methanolic HCl at room temperature for 24–36 hr. The mixture was then poured into a large amount of ice and water and the solid material thus separated was filtered off. Recrystallization from MeOH gave **3** in quantitative yield, mp 153–154°, $[\alpha]D$ −44.5°, λ_{max}^{KBr} 5.77 and 5.84 μ, λ_{max}^{EtOH} 243 mμ. *Anal.* ($C_{25}H_{36}O_3$) C, H.

Acknowledgment.—I wish to thank Dr. R. P. Blye for biological evaluations.

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Anabolic Cyclic Esters of 19-Nortestosterone

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Esterification of steroid hormones has frequently resulted in the intensification and prolongation of the hormonal response. Several reviews have been published on steroid esters and their pharmacology.[1] A recent study from these laboratories has indicated the utility of the highly symmetrical cagelike adamantane molecule in the form of adamantoic acid in the ester portion of anabolic steroid derivatives.[2]

The utility of cycloalkyl or bicycloalkyl as alkyl substituents has been studied in several pharmacological areas.[3] We wish to report the preparation and evaluation of several cycloalkyl esters of the anabolic steroid, 19-nortestosterone, in a duration myotrophic assay.

The nortestosterone 17β-esters were prepared *via* the acid chlorides as previously described.[2] The cycloheptane- and cycloundecanecarboxylic and cyclooctaneacetic acids are now available commercially, while the homoadamantoic and adamantaneacetic acids were prepared from adamantoic acid by the procedure described by Stetter and Rauscher.[4] The *exo*-2-norbornene-5-carboxylic acid was obtained by purification of a commercial sample utilizing the procedure of VerNooy and Rondestvedt.[5]

Treatment of the above acids with thionyl chloride produced the respective acid chlorides. The α-chloro-substituted acid chlorides were prepared by prolonged treatment with aged thionyl chloride.[6]

Evaluation of potency and duration of effect was established by the myotrophic–androgenic assay method of Hershberger, Shipley, and Meyer[7] in immature castrate male rats. The data are reported in Table I.

The cyclic esters I[8]–III show an early strong androgenic response as measured by the seminal vesicles while the cycloundecanecarboxylate ester V does not, and this response begins to diminish after the third week. Significantly increasing levator ani responses are shown also by the *c*-$C_{7,8}$-carboxylate esters. While ester I begins to diminish in myotrophic activity about the sixth week, it is noteworthy that the cyclooctanecarboxylate ester (III) continues to be active to the eighth week. This potency and duration of activity is also seen in the adamantoate ester.[2]

While ester VIII shows a good ratio of myotrophic activity *vs.* androgenic activity at the four- and six-week levels, the over-all potency is lower compared to the other esters. Similarly, the cyclooctaneacetate ester VI has good separation of activity but the anabolic potency is only half that of the cyclooctane ester III. Both of the α-chloro-substituted esters IV and VII were of weaker activity.

Two variations on the adamantane molecule were

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TABLE I
19-NORTESTOSTERONE 17β-ESTERS

No.	Ester	Mp, °C	Formula	Analyses	Duration of myotrophic-androgenic response[a] 2 weeks SV	2 weeks LA	3 weeks SV	3 weeks LA	4 weeks SV	4 weeks LA	6 weeks SV	6 weeks LA	8 weeks SV	8 weeks LA
I	Cyclohexanecarboxylate	90–91	$C_{25}H_{36}O_3$		131.9	62.1			19.2	83.4	50.0	11.3		
II	Cycloheptanecarboxylate	104–106	$C_{26}H_{38}O_3$	H; C[b]	86.1	30.9	76.8	50.1	69.6	75.3	18.9	36.5	19.3	107.7
III	Cyclooctanecarboxylate	108–111	$C_{27}H_{40}O_3$	C, H	83.3	30.5	105.8	76.7	51.6	75.1	15.2	72.5	55.5	130.6
IV	α-Chlorocycloundecanecarboxylate	111–116	$C_{30}H_{51}ClO_3$	C, H, Cl	3.1	15.1	3.1	16.8	2.1	11.5				
V	Cycloundecanecarboxylate	88–89	$C_{30}H_{48}O_3$	C, H	7.8	32.8			1.8	38.5	3.9	30.7		
VI	Cyclooctaneacetate	66–68	$C_{28}H_{42}O_3$	C, H	27.1	54.1			17.8	36.8	21.8	36.0	1.8	29.7
VII	α-Chlorocyclooctaneacetate	159–160	$C_{28}H_{41}ClO_3$	C, H, Cl	(−0.90	15.5			(−1.1)	(−1.3)	(−6.7)	10.0	11.0	5.6
VIII	2-*exo*-Norbornene-5-carboxylate	Oil	$C_{25}H_{34}O_3$	H; C[c]	6.1	3.6			7.8	35.5	1.9	26.2		
IX	Adamantaneacetate	148–153	$C_{30}H_{42}O_3$	C, H	22.6	15.6			8.1	30.8	(−0.2)	19.9		
X	Homoadamantoate	194–196	$C_{30}H_{42}O_3$	C, H	0.7	27.2			6.5	14.1	19.7	45.5	0.8	21.1

[a] The dose employed was a single subcutaneous injection of 8 mg except for esters V, IX, and X in which it was 7.5 mg. SV = seminal vesicle, LA = levator ani. Values are given as milligrams increase over control. [b] C: calcd, 78.35; found, 78.81. [c] C: calcd, 79.15; found, 78.48.

studied. While the degree of separation of myotrophic and androgenic activities in IX and X is very good, and the androgenic response is quite low at the fourth and sixth week, the anabolic potency is less than that reported for the adamantoate ester.

Experimental Section[9]

Acids.—The cycloheptane- and cycloundecanecarboxylic, and cyclooctaneacetic acids are available from Aldrich Chemical Co. Homoadamantoic and adamantaneacetic acids were prepared from adamantoic acid by the procedure of Stetter and Rauscher.[11] The *exo*-2-norbornene-5-carboxylic acid was obtained by the iodolactonization purification procedure.[5] Cyclooctanecarboxylic acid was prepared by carbonation of the cyclooctyl bromide, albeit in low yield.[10]

Acid Chloride.—The above carboxylic acids were converted to their respective acid chlorides by means of purified $SOCl_2$.[6] A more convenient procedure which gave the cyclooctanecarbonyl chloride directly utilizing peroxide-catalyzed carboxylation with oxalyl chloride[12] in the presence of cyclooctane is described below.

Cyclooctanecarbonyl Chloride.—A solution of 100 g of cyclooctane (1.14 moles), 94 ml of redistilled oxalyl chloride (0.52 mole), and 6.6 g of recrystallized benzoyl peroxide (0.027 mole) was heated under reflux for 24 hr. Fractionation of the solution yielded 23.75 g of cyclooctanecarbonyl chloride, bp 105–115° (9 mm), yield 12.5%. The remainder of material recovered by distillation consisted of oxalyl chloride (66 ml) and cyclooctane (77 g). The yield based on recovered hydrocarbon was 67%.

α-Chlorocyclooctaneacetyl Chloride.—To 500 mg of cyclooctaneacetic acid was added 7.5 ml of aged undistilled $SOCl_2$. The solution was refluxed on the steam bath for 7 hr and then allowed to remain at room temperature overnight. Excess $SOCl_2$ was evaporated under vacuum, leaving a lightly colored residue. *Anal.* Calcd for $C_{10}H_{16}Cl_2O$: Cl, 31.77. Found: Cl, 30.65.

Steroid 17β-Cyclic Esters.—The preparation of the 17β-esters essentially followed the previously published procedure.[2] The physical constants for these compounds appear in Table I. The crystalline esters were isolated directly from the reaction mixture and in some cases were purified by chromatography.

19-Nortestosterone 17β-(α-Chlorocyclooctaneacetate).—Chromatography over Florisil of the reaction residue resulting from reaction of 7.6 g of nortestosterone and 5 g of α-chlorocyclooctaneacetyl chloride in benzene and pyridine furnished 5.2 g of ester. Recrystallization from ether gave two forms of crystalline products, mp 159–160° and 123–125°. The lower melting form had the proper analysis and the identical optical rotation and X-ray pattern as the higher melting form. Nmr data reveal 54 (18-H, s), 283 (17-H, s), 351 (4-H, s), and 248.5 (–CHCO–, d, J = 7 cps) cps.

(9) All melting points are uncorrected. The microanalyses were performed by Messrs. W. L. Brown, H. L. Hunter, and D. L. Cline. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

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Synthesis of 6-Hydroxy-5,8-dioxo-7-(9-hydroxy-9′-*n*-pentyltetradecyl)carbostyril[1]

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Proceeding from the weak activity shown by hydrolapachol (Ia) against *Plasmodium lophurae* in ducks, Fieser and colleagues (during the period 1942–1945) systematically and very effectively prepared a number of related napthoquinones with improved antimalarial properties.[2a] Of these, the carefully designed lapinone (Ib) offered most promise of not being easily transformed to an inactive metabolic product and inhibiting parasite respiration. Shortly after World War II, a brief clinical trial of lapinone against *Plasmodium vivax* gave encouraging results.[2b] The present and increasing need for an effective chemotherapeutic treatment of *Plasmodium falciparum* infestations in man led us to explore further the interesting lead provided by lapinone. As the important metabolic products of certain quinoline-type antimalarials appear to be quinoline-quinones and carbostyrils,[3] synthesis and antimalarial evaluation of carbostyril VIII seemed an important objective.

The ready oxidation of cyclohexyl ketone II with molecular oxygen in dimethyl sulfoxide containing potassium *t*-butoxide to hydroxyquinone III as reported[4] earlier was selected as the starting point for the synthesis of quinone VIII. Pyridone II was easily obtained by a two-step reaction sequence from 1,3-dioxocyclohexane. Accordingly, the preparation of

(1) This study received support from the U. S. Army Medical R and D Command under Contract DA-49-193-MD-3010 and the present manuscript is Contribution No. 349 from the Army Research Program on Malaria.

(2) (a) A most interesting review of this subject has been prepared by L. F. Fieser, "The Scientific Method," Reinhold Publishing Corp., New York, N. Y., 1964, p 163; see also, L. F. Fieser, J. P. Schirmer, S. Archer, R. R. Lorenz, and P. I. Pfaffenbach, *J. Med. Chem.*, **10**, 513 (1967); (b) G. Fawaz and L. F. Fieser, *J. Am. Chem. Soc.*, **72**, 996 (1950).

(3) Therapeutic activity of the important 6-methoxy-8-aminoquinoline antimalarials has been attributed to their *in vivo* conversion to quinoline-quinones and rabbit liver was found to convert quinine into the corresponding carbostyril derivative. References pertinent to this subject and a summary of experiments concerned with preparation of 5,6-dioxocarbostyrils will be obtained by referring to: R. R. Holmes, J. Conrady, J. Guthrie, and R. McKay, *ibid.*, **76**, 2400 (1954).

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