ACTA CHEMICA SCANDINAVICA 17 (1963) 2536–2547

Long-acting *p*-Alkoxyhydrocinnamic Acid Esters of Steroid Hormones

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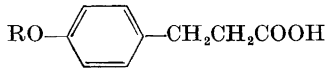
The preparation and some of the pharmacological properties of a series of *p*-alkoxyhydrocinnamic acid esters of various steroid hormones are described. Esterification with this type of acids results in a greatly enhanced intensity and duration of steroid hormone effect. Optimal prolongation of the effect of various steroid hormones was shown to depend on the length of the *p*-alkoxy group.

It is well established that esterification of steroid hormones prevents their rapid inactivation and results in a significant potentiation and prolongation of their biological effect.[1–3] Esters with great therapeutical value were prepared, *i.a.* with hydrocinnamic acid and cylopentylpropionic acid or with fatty acids with 5 to 10 carbon atoms. In order to increase the duration and intensity of steroid hormone effect, we have attempted to combine these two types of esters by preparing a series of *p*-alkoxyhydrocinnamic acid esters. It was found that optimal intensity and duration of action of such esters depends on the length of the *p*-alkoxy group and that it is different for various types of steroid hormones.

The various *p*-alkoxyhydrocinnamic acids and anhydrides prepared for the purposes of the present investigation are summarized in Table 1. They were synthesized according to known methods (see Experimental part). All anhydrides and 6 of the acids are new. The various steroid hormone esters prepared are compiled in Table 2. They were synthesized by conventional methods (see Experimental part). The assessment of their prolonged androgenic, anabolic, oestrogenic, or progestational effect was carried out as described previously.[4]

Fig. 1 shows the weight of the ventral prostate of castrated rats 42 days following a single intramuscular injection of *p*-alkoxyhydrocinnamic acid esters of testosterone. It appears from the data of Fig. 1 that maximal androgenic effect was obtained when the *p*-alkoxy group consisted of 6 to 7 carbon atoms. On the basis of this experiment the *p*-hexoxyhydrocinnamic acid ester was singled out for a detailed study of the intensity and duration of androge-

Table 1. Melting points (uncorrected) and equivalent weights of various *p*-alkoxyhydrocinnamic acids and their anhydrides.



R	Acids				Anhydrides		
	Method [a]	M.p. °C [b]	Equiv. wt		M.p. °C [c]	Equiv. wt	
			Calc.	Found		Calc.	Found
Methyl	A	102–3 [d]	180	181	60–2	171	171
Ethyl	A, B	103–4 [e]	194	196	69–70	185	187
Propyl	A, B	96–7 [f]	208	211	48–50	199	201
Isopropyl	B	74–5 [g]	208	209	oil	199	205
Butyl	A	86–7 [h]	222	225	73–4	213	214
Isobutyl	A, B	82–3 [i]	222	217	43–4	213	218
Pentyl	A	74–5	236	242	46–7	227	233
Isopentyl	A	77–8 [j]	236	233	69–70	227	233
Hexyl	A, B	73–4	250	254	49–50	241	240
Heptyl	B	72–3	264	268	50–1	255	252
Octyl	A, B	71–2	278	275	50–1	269	266
Decyl	B	80–1	306	306	56–7	297	299
Docecyl	A, B	84–5	334	335	59–60	325	327

a) See Experimental part.
b) After recrystallization from aqueous methanol.
c) After recrystallization from hexane.
d) Lit.[5] m.p. 101–2°.
e) Lit.[6] m.p. 106.5°.
f) Lit.[5] m.p. 95–6°.
g) Lit.[7] m.p. 72–3°.
h) Lit.[5] m.p. 85–6°.
i) Lit.[7] m.p. 77–8°.
j) Lit.[7] m.p. 74–5°.

nic effect, as shown in Fig. 2. The data of Fig. 2. indicate that the prolonged androgenic activity of testosterone propionate is significantly increased following the introduction of a phenyl group. However, the potency of the hydrocinnamate is increased most markedly as a result of the introduction of a hexoxy group in *p*-position. It is of interest that the effect of the *p*-hydroxyhydrocinnamic acid ester is superior to that of the hydrocinnamate, both with regard to the duration and intensity of effect.* In a previous investigation [4] the *p*-hexoxyhydrocinnamate of testosterone has been compared with some commercially available testosterone esters, including the enanthate. The intensity and duration of androgenic effect of the *p*-hexoxyhydrocinnamate greatly exceeded that of the other esters studied. These results together with the data of the present investigation (Fig. 2) clearly indicate that the introduction of a long-chain *p*-alkoxy group into the hydrocinnamate of testosterone will combine the pharmacological advantages of esterification with both types of acids. This has also been borne out in clinical steroid excretion studies with various testosterone esters.[8] The same relationship was found with regard to

* A study of the *p*-acetoxy- and *p*-chlorohydrocinnamic acid esters of testosterone revealed that the duration and intensity of the androgenic effect of these esters is definitely superior to that of the phenyl propionate.

Table 2. Melting points (uncorrected) and optical rotations ($c = 1.0$ in dioxane) of *p*-alkoxyhydrocinnamic acid esters of various steroids.

Alkyl part of the *p*-alkoxy group	Testosterone-17 esters [a]			19-Nortestosterone-17-esters [b,c]		Estradiol-3,17-diesters [a]			Estradiol-17-monoesters [b,d]		17*a*-Hydroxy progesterone-17-esters,[e,f]	
	Method [g]	M.p. °C	$[\alpha]_D$	M.p. °C	$[\alpha]_D$	Method [g]	M.p. °C	$[\alpha]_D$	M.p. °C	$[\alpha]_D$	M.p. °C	$[\alpha]_D$
Methyl	C,D	148—50	83	126—7	50	C,D	80—2	37	143—4	53	137—8	43
Ethyl	D	119—20	82	—	—	C	66—8	34	128—30	51	—	—
Propyl	C	110—1	79	43—4	52	C,D	72—3	36	126—8	48	—	—
Isopropyl	D	109—10	75	—	—	C,D	oil	34	117—9	47	—	—
Butyl	D	87—8	77	42—4	59	D	61—2	31	142—3	48	109—11	44
Isobutyl	D	109—10	74	—	—	C	95—6	33	131—2	46	—	—
Pentyl	D	84—5 [h]	76	56—7	45	D	61—2	29	113—5	47	91—3	37
Isopentyl	D	98—9	78	—	—	—	—	—	—	—	109—10	40
Hexyl	D	70—1 [h]	76	53—5	45	C,D	67—9	34	101—2	49	97—8	45
Heptyl	D	57—8	69	50—2	44	C	64—5	30	80—1	43	—	—
Octyl	D	48—50	67	—	—	C,D	67—8	29	75—6 [i]	41	42—5	38
Decyl	D	61—3	63	—	—	—	—	—	—	—	—	—
Docecyl	D	58—9	64	—	—	C,D	75—6	25	90—2 [i]	36	oil	29

a) After recrystallization from ethanol.
b) After recrystallization from aqueous methanol.
c) Prepared according to method D.
d) Prepared according to method E.
e) After recrystallization from isopropylether.
f) Prepared according to method F.
g) See Experimental part.
h) These compounds have also another crystal form with lower m.p. See Experimental part.
i) Prepared from the corresponding 3-acetate. See Experimental part.

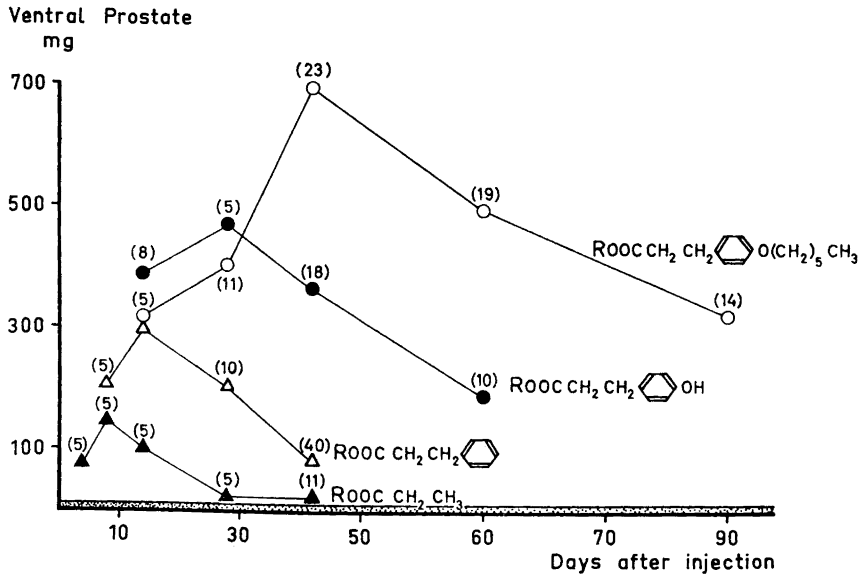


Fig. 1. Weight of the ventral prostate in castrated adult rats treated with various *p*-alkoxyhydrocinnamates of testosterone, as a function of the number of carbon atoms in the *p*-alkoxypart of the molecule. (Zero indicates a *p*-hydroxy group.) The animals were killed 42 days after a single intramuscular injection of the equivalent weight of 4.35 mg of testosterone in oil. Figures in parentheses indicate the number of animals used. Shaded area corresponds to the 95 % fiducial range of the ventral prostate weight in castrated rats.

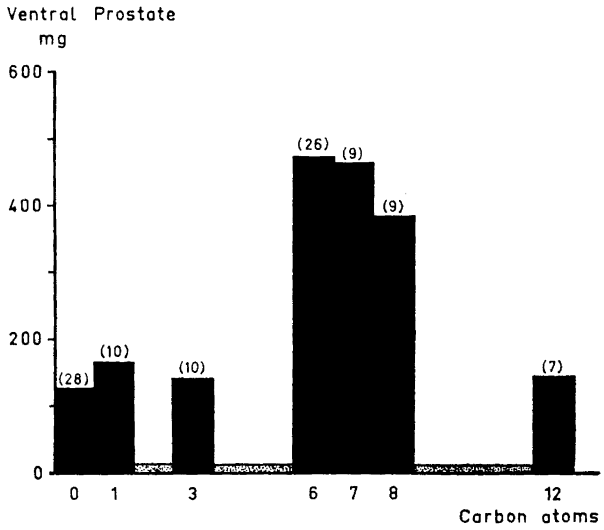


Fig. 2. Effect of a single intramuscular injection of various esters of testosterone (R) on the ventral prostate weight in castrated adult rats. Each animal was treated with the equivalent of 8.7 mg testosterone in oily solution. Figures in parentheses indicate the number of animals used. Shaded area corresponds to the 95 % fiducial range of the ventral prostate weight in castrated rats.

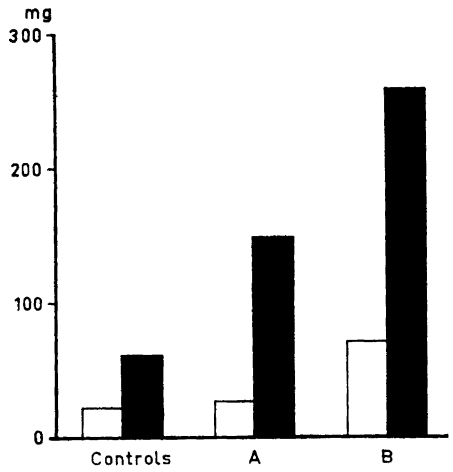


Fig. 3. Effect of *p*-propoxy-(A), and *p*-hexoxy-(B) hydrocinnamic acid esters of 19-nortestosterone on the weight of ventral prostate (open columns) and levator ani muscle (filled columns) of castrated rats 42 days following a single intramuscular injection of 4.35 mg 19-nortestosterone equivalent in oil. Each column represents the mean of 5 animals.

the prolongation of the anabolic effect of 19-nortestosterone, as shown in a previous communication [4] and in Fig. 3.

A study of the prolonged estrogenic effect of various 17-*p*-alkoxyhydrocinnamates of 17β-estradiol revealed that maximal prolongation was obtained with the *p*-propoxyhydrocinnamate, whereas the prolonged estrogenic activity

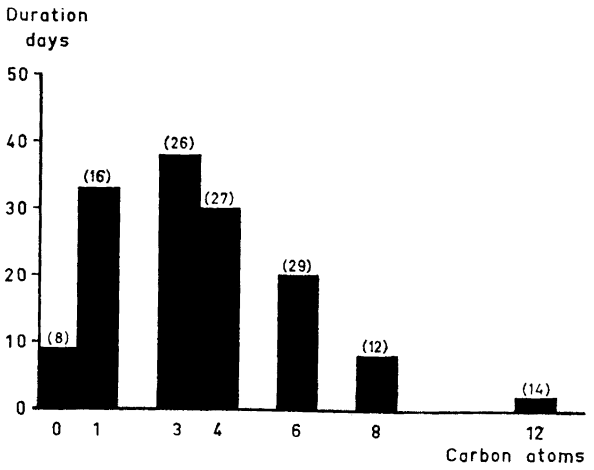


Fig. 4. Duration of vaginal smears in spayed mice treated with various 17-*p*-alkoxyhydrocinnamic acid esters of 17β-estradiol, as a function of the number of carbon atoms in the *p*-alkoxy-part of the moleculs. (Zero indicates a *p*-hydroxy group.) The animals were injected intramusculary with a single dose equivalent of 5 μg of 17β-estradiol in oil. The numbers in parentheses indicate the number of animals. Geometric mean values.

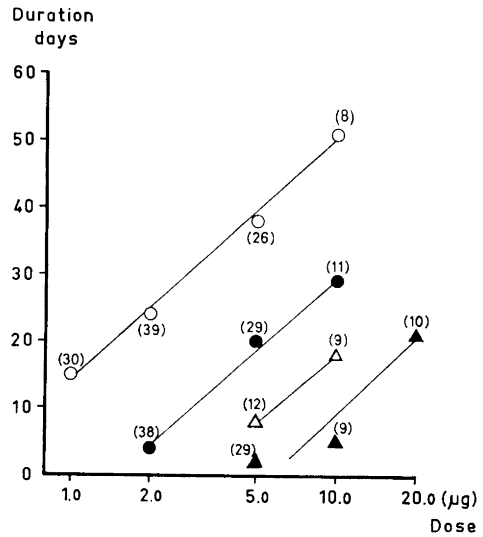


Fig. 5. Duration of cornified vaginal smears in spayed mice following a single intramuscular injection of various 17-*p*-alkoxyhydrocinnamic acid esters of 17*β*-estradiol. Numbers in parentheses indicate the number of animals used at the various dose levels *cf.* footnote below. Open circles: *p*-propoxy-, filled circles: *p*-hexoxy-, open triangles: *p*-octoxy- and filled triangles: *p*-dodeoxyhydrocinnamate. The scale of dose is logarithmic, and the individual symbols indicate geometric mean values.

of the *p*-hexoxyhydrocinnamate was significantly less, as indicated in Figs. 4 and 5. A similar difference in the length of the fatty acid required for optimal prolongation of 17*β*-estradiol and testosterone, respectively, was observed previously by other investigators.[2,3] The data of Fig. 5 indicate that there is a linear relationship between the logarithm of dose * and the duration of estrogenic effect of preparations with various numbers of carbon atoms in the *p*-alkoxy moiety. It is also apparent that the long-acting potency of these esters decreases with increasing length of the *p*-alkoxy group. This can be illustrated by plotting the dose required for a mean duration of effect of 15 days against the number of C-atoms in the alkoxy group. A linear relationship is shown in Fig. 6, where the logarithm of dose (in *μ*g) is plotted against the logarithm of C-atoms.

It is of interest to note that a minor branching in the alkoxy group does not seem to diminish the long-acting properties; *p*-isopropoxy- and *p*-isobutoxyhydrocinnamic acid esters show approximately the same duration of action as their corresponding esters with normal alkoxy group. When the 3,17-bis-*p*-propoxyhydrocinnamate of 17*β*-estradiol was investigated, 5 *μ*g (25 animals) gave only a mean duration of 4 days and 10 *μ*g (15 animals) only 9 days. This decrease in duration of effect is in agreement with that found with 3,17-diesters [2,3] of 17*β*-estradiol with fatty acids.

* All doses indicated throughout this paper are expressed in steroid equivalents.

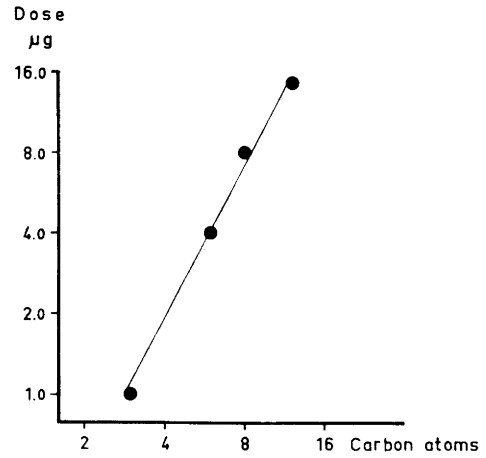


Fig. 6. Correlation between the number of carbon atoms in the *p*-alkoxy part of 17-*p*-alkoxyhydrocinnamic acid esters of 17β-estradiol and the dose (in µg 17β-estradiol equivalents) of each which results in a duration of 15 days of cornified vaginal smears in spayed mice. These doses were calculated from the data of Fig. 5. Both scales are logarithmic, but are graduated in true units.

In order to study the influence of the introduction of the *p*-alkoxy group into another type of a 17-ester of 17β-estradiol, the 17-*p*-hexoxybenzoate was prepared. The duration of estrogenic effect was poor: a mean duration of 3 days with 5 µg (14 animals) and 7 days with 10 µg (15 animals).

The poor duration of estrogenic effect of the 3,17-diester and that of the 17-*p*-hexoxybenzoic acid ester at the dose levels tested can not be taken as a general indication that such esters lack a prolonged estrogenic activity, when tested at higher dose levels.[2,3]

Finally an investigation of the various *p*-alkoxyhydrocinnamates of 17α-hydroxyprogesterone indicated that this type of esterification results in pro-

Table 3. Progestational proliferation of the endometrium of polyestradiol phosphate-primed immature rabbits 16 days following a single intramuscular injection of 12 mg of various *p*-alkoxyhydrocinnamic acid esters of 17α-hydroxyprogesterone.

Alkyl part in the *p*-alkoxy group	Number of animals	Progestational proliferation *a* Mean score
Butyl	14	2.5
Pentyl	4	1.6
Isopentyl	4	1.0
Hexyl	5	1.6
Octyl	4	1.6

a) Scored according to McPhail.[9]

gestational compounds with prolonged activity. The data shown in Table 3 seems to indicate that the *p*-butoxyhydrocinnamate exhibits the longest duration among the esters tested. The prolonged progestational activity of this compound is comparable to that of 17*α*-hydroxyprogesterone caproate.[4]

DISCUSSION

The method of assay of prolonged estrogenic effect used in this investigation was the same as described previously.[10] Using the duration of cornified smears in spayed mice as an index of response and using a 4-point design with 15 to 20 animals on each dose level, statistically valid bioassays could be obtained when the various *p*-alkoxyhydrocinnamic acid esters were compared. However, the mean precision of the assays (expressed as Gaddum's λ-criterion [11]) was much less ($\lambda = 0.34$) than that reported in previous investigations using various polyestradiol phosphate ($\lambda = 0.13$) preparations [10] or various polystilbestrol phosphate ($\lambda = 0.11$) preparations.[12] In view of the poor precision of the assays where oily solutions of various estradiol esters are compared, it is easy to see that by the use of this method it is not possible to establish minor differences in the long-acting potency of such preparations.

The poor precision of such assays was found to depend on an enormous variation in response to the same dose by individual animals; thus the duration of cornified smears within the same group often varied for instance between 10 and 60 days. A similar variability in response to polyestradiol phosphate or polystilbestrol phosphate preparations has never been observed.

The reason for this great variation is just as incompletely understood at present, as the exact mode of action of various steroid hormone esters. Thus, for instance, it is not known how much hormone is retained at the site of injection and how much of it is deposited in secondary depots such as body fat or the reticuloendothelial system. Thus whereas information is available on the over-all distribution of polyestradiol phosphate in the various tissues of rodents,[13] similar information on the distribution of various steroid hormone esters is scanty.

Furthermore it is not known whether steroid hormone esters can exert their biological effect as such or only after hydrolysis.[3] If such hydrolysis is a prerequisite for pharmacological action, it is conceivable that great differences exist with regard to the rate of hydrolysis of different types of esters in the organism. Moreover it remains to be learned how different types of esters will affect the intermediary metabolism of the steroid in question, its circulating form over-all distribution and excretion in the urine.

That significant differences exist in the urinary excretion of 17-ketosteroids following the administration of various testosterone esters was conclusively shown.[8,14] It is not known, however, how much steroid ester or metabolites thereof are retained in the body where and in which form at a time when pharmacological effect can no longer be demonstrated. Until some of these questions have been satisfactorily answered progress in this field will necessarily remain empirical.

EXPERIMENTAL

Melting points are uncorrected. Ultra-violet spectra were measured in ethanol with a Beckman DU spectrophotometer, infra-red spectra in potassium bromide disks with a Perkin-Elmer model 21 instrument and rotations ($c = 1.0$) in dioxane.

Esters of testosterone, 19-nortestosterone and 17α-hydroxyprogesterone were analyzed according to the method of Umberger.[15] The esters of estradiol were analyzed by estimating the acid part of the molecule. After hydrolysis in a 0.5 N alcoholic potassium hydroxide solution the amount of free acid was determined alkalimetrically *via* a cation exchange resin in the acid form. The values found were in good agreement with those calculated. All of the esters prepared were also controlled by their ultra-violet and infra-red spectra.

p-*Alkoxybenzaldehydes.* With the exception of the commercially available anisaldehyde these were prepared according to the experimental procedure described by Pierce *et al.*[5] They have all been described previously.[5,16-19] With *n*-alkylbromides the yields were 80—85 % (dodecyloxybenzaldehyde only 55 %). The isobutoxy- and isopentoxybenzaldehydes were prepared using the corresponding isoalkyliodides in 32 respectively 51 % yield.

p-*Alkoxycinnamic acids.* These were prepared from the *p*-alkoxybenzaldehydes by the Doebner reaction.[20] The aldehyde (0.1 mole), malonic acid (0.15 mole), pyridine (0.25 mole) and a few drops of piperidine were heated together on the steam bath for about 8 h, and then boiled gently for an additional 2 h. The solution was then poured into a mixture of conc. hydrochloric acid (25 ml) and crushed ice (50 g). The precipitate was collected, washed with water and then crystallized from aqueous ethanol after decolorizing with Norit. The yields of *p*-alkoxycinnamic acids were 70—90 %. Apart from the isopentoxycinnamic acid which is new (yield 75 %; m.p. 145—6°; equiv. wt. found 234, calc. 234) the acids exhibited melting points in agreement with those given in the literature.[5,18,19,21]

p-*Alkoxyhydrocinnamic acids.* (See Table 1). *Method A.*[22] Preparation from the corresponding alkoxycinnamic acids by reduction of the potassium salt in water with Raney nickel as catalyst. *p*-Hexoxycinnamic acid (40 g) was dissolved in a hot solution of potassium hydroxide (9.5 g) in water (300 ml). About 7 g of Raney nickel was added and the mixture was hydrogenated at a pressure of about 30 lb at room temperature overnight. Next day the catalyst was filtered off and the *p*-hexoxyhydrocinnamic acid was precipitated with hydrochloric acid, washed with water and dried. The yields of the various *p*-alkoxyhydrocinnamic acids were between 90—95 %.

Method B. Preparation from the methyl ester of phloretic acid and alkyl halogenide according to the experimental procedure described by Pierce *et al.*[23] for the preparation of *p*-alkoxybenzoic acids. With the exception of ethyliodide and isopropyliodide the alkylbromides were used. The yields were about 70 % with the exception of the two isoalkoxyhydrocinnamic acids in which case the yields were only about 35 %.

p-*Alkoxyhydrocinnamoyl chlorides.* The acid chlorides were prepared by refluxing a mixture of the acid (1 part) and thionyl chloride (2 parts) in chloroform for 2 h. After removing the chloroform and excess thionyl chloride by evaporation *in vacuo*, the acid chlorides were distilled *in vacuo* (at about 1 mm). The yields were between 80—90 % with the exception of the decyloxy- and docecyloxyhydrocinnamoyl chlorides. In these cases the yields were only 50 and 30 %, due to decomposition during distillation.

p-*Alkoxyhydrocinnamoyl anhydrides.* (See Table 1). The method of Gerrard and Thrush [24] was used. None of the anhydrides prepared have been described earlier. *p*-Hexoxyhydrocinnamic acid (25 g, 0.2 mole) was dissolved under anhydrous conditions in a mixture of dry benzene (75 ml) and dry pyridine (8.1 ml, 0.1 mole). After cooling to about 0° a solution of thionyl chloride (3.6 ml, 0.05 mole) in dry benzene (25 ml) was added with stirring during 15 min at this temperature. The reaction mixture was then left at room temperature for half an hour and thereafter poured into a separatory funnel containing a mixture of conc. hydrochloric acid (40 ml) and crushed ice (50 g). The benzene solution was immediately washed with water, with cold potassium bicarbonate solution and finally with cold water. After drying over anhydrous sodium sulfate, the benzene was removed *in vacuo*. The anhydride was obtained as an oil which could be used without any further purification. Crystallization from hexane gave 18.8 g (78 %) of *p*-hexoxyhydrocinnamoyl anhydride. The yields of crystallized products of the various anhydrides varied between 75—85 %.

p-*Alkoxyhydrocinnamic acid esters of various steroids.* (See Table 2). The esters were prepared by conventional procedures. Typical examples of the methods used are given below.

Method C. Estradiol-17β (10.1 g, 0.037 mole) was dissolved in dry pyridine (60 ml). At a temperature of about $-10°$ a solution of *p*-propoxyhydrocinnamoyl chloride (25 g, 0.11 mole) in dry chloroform (40 ml) was added with shaking under anhydrous conditions. After one hour at $-10°$ the reaction mixture was kept at room temperature overnight. Most of the chloroform was then removed *in vacuo* and the excess acid chloride destroyed by the addition of crushed ice. Ether-ethyl acetate (1:1, 200 ml) was then added and the resulting mixture washed with dilute hydrochloric acid, water, potassium bicarbonate solution and finally again with water. After drying over anhydrous sodium sulfate the solvent was removed *in vacuo*. The resulting oil was dissolved in ethanol (1500 ml) on a steam bath, water (200 ml) was added and the resulting solution decolorized with Norit. Cooling overnight gave 20 g (85 %) of estradiol-3,17-bis-*p*-propoxyhydrocinnamate.

Most of the diesters of estradiol were prepared in this way with yields between 70–85 %.

When testosterone esters were prepared by this method (using 1.5 mole acid chloride) the yields were about 75 %. However, it appeared more difficult to decolorize the esters than in method D, probably because of the presence of the Δ^4-3-keto function which may to some extent form an enol ester.

Method D. Testosterone (10.1 g, 0.035 mole) and *p*-hexoxyhydrocinnamoyl anhydride (21.7 g, 0.045 mole) were dissolved in dry pyridine (30 ml) under anhydrous conditions. The reaction mixture was kept at room temperature overnight. The excess anhydride was then destroyed by the addition of water (10 ml) and the product isolated in the same manner as described above using ether-ethyl acetate (1:1, 100 ml) for extraction. The resulting oil was dissolved in warm ethanol (250 ml) and when the ester began to crystallize on cooling, water (60 ml) was added in small portions. 15 g (83 %) of testosterone-17-*p*-hexoxy-hydrocinnamate were obtained.

Some of the estradiol-3,17-diesters (using 2.5 mole anhydride), most of the testosterone- and all of the 19-nortestosteroneesters were prepared in this way with yields between 60–90 %.

Method E. All the 17-monoesters of estradiol were prepared by selective alkaline hydrolysis of the corresponding 3,17-diesters.[25] A solution of potassium carbonate (3.2 g) in water (35 ml) was poured into methanol (2500 ml). To the resulting solution estradiol-3,17-bis-*p*-propoxyhydrocinnamate (10 g) in acetone (150 ml) was added with stirring and in an atmosphere of N_2. The reaction mixture was kept at room temperature for 3 h with continued stirring. After filtration, dilute hydrochloric acid was added to a pH of about 7.5, and the solution was cooled with ice-water. By adding water (300 ml) in small portions the 17-monoester started to crystallize. Recrystallization with decolorizing with Norit gave 7 g (85 %) of estradiol-17-*p*-hexoxyhydrocinnamate. The yields of the various 17-monoesters were between 80–90 %.

In preparing esters with a long alkoxy-group it was found preferable (depending on the low solubility of the corresponding diesters) to start with estradiol-3-acetate-17-*p*-alkoxyhydrocinnamate. These mixed diesters were prepared from estradiol-3-acetate according to method D. After recrystallization from methanol, estradiol-3-acetate-17-*p*-octoxyhydrocinnamate had m.p. 57–8°, $[\alpha]_D = +36$, and estradiol-3-acetate-17-*p*-dodeoxyhydrocinnamate m.p. 57–9°, $[\alpha]_D = +37$.

Method F. All the 17-esters of 17α-hydroxyprogesterone were prepared from 17α-hydroxyprogesterone with a slight modification of the method used by Batres *et al.*[26] 17α-Hydroxyprogesterone (10 g, 0.03 mole) and dried *p*-toluenesulfonic acid (6 g) were added to a solution of *p*-butoxyhydrocinnamoyl anhydride (32 g, 0.075 mole) in dry benzene (350 ml). The mixture was heated on the steam bath with shaking under anhydrous conditions. After about 10 min a clear solution was obtained, which was brought to room temperature and left at this temperature for 48 h. To effect hydrolysis of the excess anhydride it was found preferable to add a mixture of pyridine-water (10:1, 40 ml). Next day the reaction mixture was reduced *in vacuo* to a volume of about 250 ml and the product isolated in the same manner as described above using ether-ethyl acetate (1:1, 200 ml) for extraction. The resulting oil was dissolved in isopropylether (150 ml) and the 17α-hydroxyprogesterone-*p*-butoxyhydrocinnamate (12.3 g, 76 %) crystallized

on cooling. If only 2 or 4 g of *p*-toluenesulfonic acid was used the yield was about 30, respectively 50 %.

Other new steroid esters not described in Table 2 which were used in this investigation

Testosterone-17-p-*acetoxyhydrocinnamate* was prepared using *p*-acetoxyhydrocinnamoyl chloride according to method C. After recrystallization from aqueous methanol it had a m.p. of 144–5°. Yield 80 %.

Testosterone-17-p-*hydroxyhydrocinnamate* was prepared from the corresponding *p*-acetoxy-compound by hydrolysis according to method E. After recrystallization from benzene it had a m.p. of 198–200°. Yield 85 %.

Testosterone-17-p-*chlorohydrocinnamate*. From testosterone and *p*-chlorohydrocinnamoyl chloride according to method C. After recrystallization from aqueous methanol it had a m.p. 142–3°. Yield 75 %.

Estradiol-17-p-*hexoxybenzoate*. The corresponding 3-acetate was first prepared from estradiol-3-acetate according to method C, in 84 % yield, m.p. 82–3° (from ethanol). Then this diester was hydrolysed according to method E. The resulting estradiol-17-*p*-hexoxybenzoate had a m.p. 63–5° (from methanol) and was obtained in 90 % yield.

Estradiol-17-p-*hydroxyhydrocinnamate*. The estradiol-3,17-bis-*p*-carbometoxyhydrocinnamate was first prepared according to method C. It was obtained as an oil which after hydrolysis according to method E gave the estradiol-17-*p*-hydroxyhydrocinnamate in a total yield of 80 %, m.p. 172–3° (from aqueous methanol).

Dimorphism observed with some of the steroid esters. In the preparation of testosterone-*p*-hexoxyhydrocinnamate compounds with two different melting points were obtained. On further examination it was found that crystals with the lower m.p. after melting crystallize again at a temperature which is a few degrees higher than the previous m.p. and these new crystals have then the higher m.p. If the melted compound is undercooled to room temperature it crystallized in the form with the lower m.p. and so the two forms seems to be monotropic. Careful grinding of crystals with the lower m.p. will result in a higher m.p. although a slight movement in the ground mass can be observed when the temperature passes the lower m.p. Most of the esters prepared were re-investigated after grinding, however, a higher m.p. was found only with the corresponding *p*-pentoxy ester.

Testosterone-*p*-pentoxyhydrocinnamate: Metastable form (leaflets) m.p. 61–2°, stable form (needles) m.p. 84–5°.

Testosterone-*p*-hexoxyhydrocinnamate: Metastable form (prisms) m.p. 60–1°, stable from (needles) m.p. 70–1°.

When the IR-spectra of the dimorphous forms were compared they behaved identically in 1 % solutions in either carbon disulphide or chloroform but small differences were found, as expected,[27] when the material was investigated in potassium bromide disks.

Acknowledgement. The excellent technical assistance of Miss Leila Nilsson, Mr. K.-E. Lundvall and Mr. A. Olsson is gratefully acknowledged.

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Received July 1, 1963.