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Synthesis of Physiologically Active Steroid Esters and Spirolactones*

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Some steroid hemimalonates, alkylhemimalonates and acetoacetates have been easily prepared in high yields by the reaction of hydroxysteroids with Meldrum acid, its alkyl- and acylderivatives, respectively. Decarboxylation of the hemimalonates and alkylhemimalonates allowed the synthesis of several hydroxysteroid esters, some of them being widely used in medical practice.

17α-hydroxyprogesterone hemimalonate and its acetoacetate, in the presence of bases, undergo cyclodehydration giving rise to spirolactones which are potential aldosterone antagonists.

INTRODUCTION

Esterification of some natural and modified steroids is of great importance in the preparation of highly active compounds with prolonged action. Testosterone capronate and enanthate, as well as the same esters of 17α-hydroxyprogesterone, are widely used in clinical practice[1]. Several 17α-hydroxyprogesterone esters have found use as oral gestogens in the therapy of some disorders during pregnancy[2]. Some hydrocortisone esters (at 17α- and 21-OH groups) exhibit a high antiinflammatory potency, higher than that of betamethasone valerate[3]. Steroid esters have found application as tools for the isolation of steroid-specific receptors in affinity chromatography[4], as haptens in immunological research[5] and as substrates (or inhibitors) for studying the enzyme action mechanisms[6].

It is known that preparation of steroid esters is often complicated by side reactions, especially when the compounds have labile or sterically hindered hydroxygroups. This report describes a rather new and simple method for the preparation of steroid esters, in which these difficulties are avoided.

EXPERIMENTAL

Synthesis of Hemimalonates (III, VIII, XV)

To 30 ml of a benzene solution of 1 mmol of hydroxysteroid, 1.1 mmol of Meldrum acid (I, R = H)[7] was added and the mixture was refluxed until the reaction was over (monitoring with TLC; reaction time and solvent systems for TLC are shown in Table I). Benzene was evaporated in vacuo to 10 ml volume

* Dedicated to Professor Mihailo Lj. Mihailović on the occasion of his 60th birthday.

and the mixture was kept in the refrigerator to crystallize. The product was filtered off and crystallized from hexane-acetone. Yields and melting points of the compounds so obtained are summarized in Table I and the mass-spectroscopical data in Table II.

TABLE I

Hemimalonates

Starting compound	Time hrs	Hemi-malonate	Yield %	M. point (decomp.) (acetone-hexane)	Solvents for elution (TLC)
Testosterone	8	(III)	93	170—173	$CHCl_3$ — ether, 3 : 1
Desoxycortico-sterone	5	(VIII)	80	172—175	hexane — ethylacetate, 1 : 1
Estrone	6	(X)	85	174—178	$CHCl_3$ — ether, 5 : 1
17α-hydroxy-progesterone	5	(XV)	95	168—171	$CHCl_3$ — ether, 2 : 1
17α-hydroxy-progesterone	10	(XVI) +(XX)	72 10	168—170	hexane — ethyl acetate, 2 : 1
17α-hydroxy-progesterone	8	(XVII) +(XXI)	80 5	168—172	hexane — ethyl acetate, 2 : 1
17α-hydroxy-progesterone	10	(XVIII) +(XXII)	75 7	168—170	hexane — ethyl acetate, 1 : 1

Decarboxylation of Hemimalonates

The hemimalonates (III, VIII, XV—XVIII) are cautiously heated at 160—170 °C up to melting and the end of CO_2 evolution. After cooling the product was crystallized from hexane-acetone. Yields and melting points are given in Table III.

Synthesis of 17α-Hydroxyprogesterone Hemimalonates (XV—XVIII)

To 20 ml of a dioxane solution of 1 mmol of 17α-hydroxyprogesterone (XIV), 1.9 mmol of an alkylderivative of Meldrum acid [8] was added and the mixture was refluxed 8—10 hours. The solvent was evaporated in vacuo, the residue was taken in chloroform and washed with 8% solution of $NaHCO_3$. After evaporation of the solvent and chromatography on silicagel (in the system hexane — ethyl acetate, 2 : 1), 17α-hydroxyprogesterone butyrate (valerate or capronate) was isolated. The water layer was acidified with 10% solution of hydrochloric acid and extracted by chloroform. By routine procedure hemimalonates (XV—XVIII) were obtained. Yields and physico-chemical data of all compounds are given in Tables I and II.

Synthesis of Hydroxysteroid Acylacetates (V—VII, XI, XII)

To 20 ml of a benzene solution of 1 mmol of the hydroxysteroid, 1,8 mmol of 5-acyl-2,2-dimethyl-1,3-dioxane-4,6-dione (II)[9] was added and the mixture was refluxed until the reaction was over (monitoring with TLC). The solvent was removed and the residue was chromatographed on a column with silicagel. The product was eluted with chloroform-ether, 5 : 1, and purified by crystallisation. The reaction conditions, yields and physico-chemical data are given in the Tables II and IV.

Compound	IR-spectra (ν, cm^{-1}) in nuyol	Mass-spectra m/z (relative intensity, %)	NMR-spectra δ in $CDCl_3$
(III)	1605, 1630, 1725, 1730, 2500—3300	374 (M^+, 3), 330 (M^+—CO_2, 62), 315 (M^+—CO_2—CH_3, 6), 312 (M^+—CO_2—H_2O, 3), 302 (M^+—CO_2—CO, 4), 288 (M^+—CO_2—$COCH_3$ +H, 100)	
(VIII)	1605, 1660, 1710, 1740, 1765, 2550—3400	M^+ absent, 372 (M^+—CO_2, 100), 357 (M^+—CO_2—CH_3, 19), 354 (M^+—CO_2—H_2O, 24), 345 (5), 340 (14), 331 (57)	
(X)	1490, 1600, 1710, 1745, 1760, 2600—3350	M^+ absent, 341 (2), 340 M^+—OH, 1), 313 (M^+—CO_2 + H, 16), 270 (M^+—CO_2—$COCH_3$ + H, 100)	
(XV)	1605, 1660, 1710, 1730, 2650—3300	416 (M^+, 1), 398 (M^+—H_2O, 1), 380 (M^+—$2H_2O$, 1), 372 (M^+—CO_2, 80), 354 (M^+—H_2O—CO_2 100), 344 (3), 339 (4), 329 (M^+—CO_2—$COCH_3$, 90)	0,69 (s, 3H, 18-CH_3), 1,19 (s, 3H, 19-CH_3), 2,1 (s, 3H, 21-CH_3), 3,46 (s, 2H, CO—CH_2—COOH), 5,81 (s, 1H, 4-H), 8,5 (broad signal s, 1H, COOH)
(XVI)	1630, 1670, 1715, 1730, 2550—3000	443 (M^+—1,1), 441 (2), 426 (M^+—H_2O, 2), 400 (M^+—CO_2, 26), 385 (M^+—CO_2—CH_3, 3), 382, (M^+—CO_2—H_3O, 6), 372 (M^+—CO_2—CO, 8), 357 (M^+—CO_2—$COCH_3$, 100)	0,69 (s, 3H, 18-CH_3), 1,03 (t, 3H, CH_3), CH_2, 1,19 (s, 3H, 19-CH_3), 2,08 (s, 3H, 21-CH_3), 2,95 (dq, 2H, CH_3CH_2CH), 3,35 (dd, 1H, CH_3CH_2CH), 5,78 (s, 1H, 4-H), 9,7 (broad signal s, 1H, COOH)
(XVII)	1613, 1625, 1716, 1742, 2500—3300	M^+ absent, 414 (M^+—CO_2, 46), 399 (M^+—CO_2—CH_3, 3), 396 (M^+—CO_2—H_2O, 5), 386 (M^+—CO_2—CO, 27), 371 (M^+—CO_2—$COCH_3$, 50), 329 (M^+—COCH (C_3H_7)COOH, 100)	0,75 (s, 3H, 18-CH_3), 1,03 (t, 3H, CH_3CH_2), 1,25 (s, 3H, 19-CH_3), 2,18 (s, 3H, 21-CH_3), 3,08 (dt, 2H, C_2H_5 CH_2CH) 3,56 (dd, 1H, C_3H_7CH), 5,87 (s, 1H, 4-H) 8,55 (broad signal s, 1H, COOH)

Table II to be continued

Table II (continued)

(XVIII)	1600, 1643, 1720, 1742, 2570—3450	M^+ absent, 428 (M^+—CO_2, 18), 413 (M^+—CO_2—CH_3, 9), 410 (M^+—CO_2—H_2O, 27), 400 (M^+—CO_2—CO, 4), 385 (M^+—CO_2—$COCH_3$, 87), 329 (M^+—COCH (C_4H_9)COOH, 100)	
(V)	1210, 1620, 1680, 1710, 1740	400 (M^+, 39), 387 (M^+—CH_3, 12), 360 (M^+—$COCH_2$, 55), 345 (M^+—CH_2CO—CH_3, 10), 329 (M^+-iso C_3H_7CO, 12), 287 (M^+-side chain, 100)	
(VI)	1250, 1610, 1670, 1700, 1740	444 (M^+, 24), 429 (M^+—CH_3, 5), 402 (M^+—$COCH_2$, 61), 413 (M^+—OCH_3, 38), 387 (M^+—$COCH_2$—CH_3, 17), 385 (M^+—$COOCH_3$, 56), 329 (M^+—$COCH_2CH_2COOCH_3$, 18), 287 (M^+-side chain, 100)	
(VII)	1240, 1620, 1680, 1701, 1740	414 (M^+, 45), 399 (M^+—CH_3, 17), 372 (M^+—$COCH_2$, 60), 357 (M^+—$COCH_2$—CH_3, 5), 329 (M^+-iso C_4H_9CO, 10), 287 (M^+-side chain, 100)	0,82 (s, 3H, 18-CH_3), 0,92 (d, 6H, J 9Hz, $(CH_3)_2CH$), 1,19 (s, 3H, 19-CH_3), 2,42 (m, 2H, $COCH_2CH <$), 3,43 (s, 2H, $COCH_2CO$), 4,68 (m, 1H, 17 α-H), 5,75 (s, 1H, 4-H)
(XI)	1210, 1680, 1750, 1790	400 (M^+, 20), 385 (M^+—CH_3, 9) 358 (M^+—CH_2CO, 12), 343 (M^+—CH_2CO—CH_3, 8), 315 (M^+-iso C_4H_9CO, 21), 273 (H^+-side chain, 100)	
(XII)	1270, 1640, 1710, 1730, 1750	M^+ absent, 483 (M^+—$COOCH_3$, 8), 468 (M^+—$COOCH_3$—CH_3, 15), 441 (M^+—$COCH_2CH_2COOCH_3$, 80), 385 (100), 371 (25)	
(XXIV)	1620, 1660, 1680, 1710, 1720	396 (M^+, 100), 381 (M^+—H_2O, 7), 368 (M^+—CO, 2), 363 (M^+—CH_3—H_2O, 7), 342 (M^+—CH_2CO, 3), 341 (M^+—CH_3CO, 2), 319 (M^+—CH_3—H_2O—CO_2, 3), 229 (M^+-ring system D/E, 42), 166 (30)	1,00 (s, 3H, 18-CH_3), 1,19 (s, 3H, 19-CH_3), 2,42 (s, 3H, 21-CH_3), 2,56 (s, 3H, 24-CH_3), 5,76 (s, 1H, 4-H)

Table II to be continued

Table II (continued)

(XXV)	1260, 1602, 1670, 1685, 1750	438 (M^+, 100), 423 (M^+—CH_3, 19), 420 (M^+—H_2O, 16), 405 (M^+—CH_3—H_2O, 16), 396 (M^+—CH_2CO, 5), 395 (M^+—CH_3CO, 3), 351 (M^+—CH_3—H_2O—CO_2, 13), 229 (M^+-ring system D/, 55), 209 (30)	0,95 (d, 3H, J6, 5Hz, 26-CH_3), 0,96 (d, 3H, J6, 5Hz, 27-CH_3), 1,00 (s, 3H, 18-CH_3), 1,19 (s, 3H, 19-CH_3), 2,39 (s, 3H, 21-CH_3), 2,84 (m, 2H, 24-CH_2), 5,76 (s, 1H, 4-H)
(XXVI)	1250, 1610, 1650, 1710, 1725	468 (M^+, 3), 453 (M^+—CH_3, 1), 439 (M^+—CO, 4), 435 (M^+—CH_3—H_2O, 2), 409 (M^+—$COOCH_3$, 1), 395 (M^+—CH_2COOCH_3, 63), 381 (M^+—$CH_2CH_2COOCH_3$, 68), 353 (48), 329 (78), 311 (67), 229 (100)	
(XXVII)	1605, 1630, 1645, 1710 1770, 2600—3200	398 (M^+, 6), 380 (M^+—H_2O, 2), 355 (9), 354 (M^+—CO_2, 100), 339 (M^+—CO_2—CH_3, 32), 326 (M^+—CO_2—CO, 12), 321 (M^+—CO_2—CO—H_2O, 10), 229 (82).	1,05 (s, 3H, 18-CH_3), 1,20 (s, 3H, 19-CH_3), 2,61 (s, 3H, 21-CH_3), 5,76 (s, 1H, 4-H), 11,4 (broad signal s, 1H, COOH)
(XXVIII)	965, 1620, 1630, 1665 1740	354 (M^+, 100), 339 (M^+—CH_3, 38), 336 (M^+—H_2O, 3), 321 (M^+—CH_3—H_2O, 3), 320 (8), 293 (6), 229 (81)	0,98 (s, 3H, 18-CH_3), 1,19 (s, 3H, 19-CH_3), 2,15 (d, 3H, J 1,2Hz, 21-CH_3), 5,74 (s, 1H, 4-H), 5,83 (d, 1H, J 1,2Hz, 22-H)

TABLE III

Hydroxysteroid Esters

Starting hemimalonate	Ester	Yield %	M. point/°C (hexane-acetone)	Reference
(III)	(IV)	85	136—137	[12]
(VIII)	(IX)	92	156—158	[13]
(X)	Estrone acetate	50	142—143	[14]
(XV)	(XIX) + (XXVIII)	91 5	243—245	[11]
(XVI)	(XX)	89	130—132	[15]
(XVII)	(XXI)	93	136—138	[15]
(XVIII)	(XXII)	95	119—121	[15]

TABLE IV

Hydroxysteroid Acylacetates and Acylspirolactones

Starting compound	Reaction product	Reaction time, hrs	Yield	M. point/°C (hexane-acetone)
Testosterone	(V)	2.5	42	87— 88.5
Testosterone	(VI)	2.5	93	76— 77
Testosterone	(VII)	2.5	38	83— 84
19-Nortestosterone	(XI)	1.5	40	94— 95
Cholesterol	(XII)	1.5	71	68— 69
17α-Hydroxyprogesterone	(XXIV)	6	76	229—230
17α-Hydroxyprogesterone	(XXV)	0.75	70	222—224
17α-Hydroxyprogesterone	(XXVI)	2	80	215—216

Synthesis of Acylspirolactones (XXIV—XXVI)

To 30 ml of a benzene solution of 1 mmol 17α-hydroxyprogesterone (XIV), 1.7 mmol of compound II and 1.7 mmol of triethylamine were added and the mixture was refluxed until the reaction was completed (4—6 hours; monitoring with TLC). After removal of the solvent in vacuo and chromatography of the residue on silicagel (elution with chloroform-ether, 5 : 1) the acylspirolactones (XXIV—XXVI) were isolated. Yields and physico-chemical data are summarized in Tables II and IV.

Synthesis of Spirolactone (XXVIII)

a) To 4 ml of a pyridine solution of 140 mg (0.34 mmol) of the hemimalonate (XV) a drop of pyperidine was added and the mixture was heated for 4 hours at 50—60 °C. After cooling and diluting with chloroform, the mixture was washed with 10% solution of hydrochloric acid and water. The organic layer was dried, evaporated in vacuo and the residue was chromatographed on silicagel. Elution with hexane-ethylacetate 1 : 1 gave 85 mg (70%) of the spirolactone (XXVIII), m. p. 226—228 °C (hexane-acetone)[10] and 20 mg (15%) 17α-hydroxyprogesterone acetate (XIX), m. p. 243—245 °C (acetone).[11]

b) Decarboxylation of 100 mg of (XXVII) according to the method described above) and crystallisation of the product from hexane afforded 85 mg (96%) of the spirolactone (XXVIII) identical in every respect to the compound obtained above. Spectral data are given in Table II.

Synthesis of Carboxyspirolactone (XXVII)

a) To 5 ml of a methylene chloride solution of 140 mg of the hemimalonate (XV), 1 ml of pyridine and a drop of pyperidine were added and the mixture was refluxed for 4 hours. After cooling, washing with 10% solution of hydrochloric acid and water, with subsequent crystallisation from acetone, 120 mg (90%) of the carboxyspirolactone(XXVII) m. p. 175—177° (decomp) were obtained.

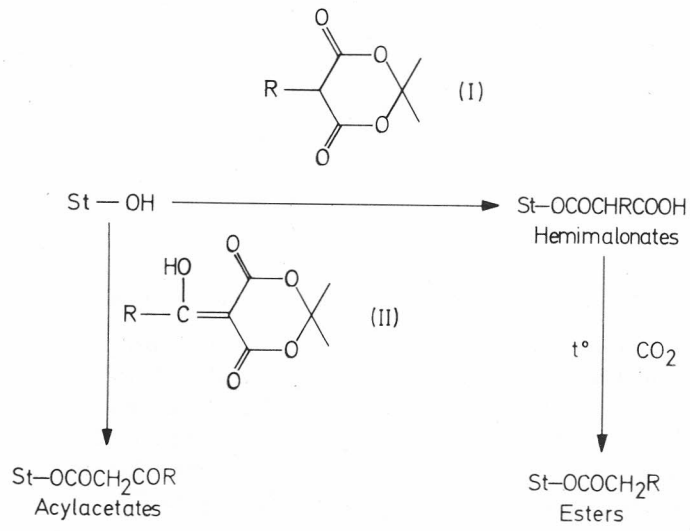
b) To 5 ml of a benzene solution of 50 mg (XV), 10 mg of ammonium acetate and two drops of acetic acid were added and the mixture was refluxed for 8 hours. After the usual treatment and crystallisation from acetone, 45 mg (95%) of (XXVII) were obtained. Spectral data are given in Table II.

RESULTS AND DISCUSSION

Synthesis of Hemimalonates and Their Decarboxylation

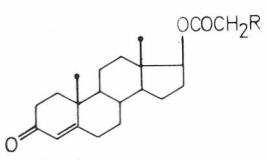
It is very convenient to use Meldrum acid (I, R =H) and its 5-alkylderivatives as acylating agents for the synthesis of hemimalonates. The reaction results mostly in a high yield when components are boiled in benzene or dioxane solution according to the following scheme:

Scheme I

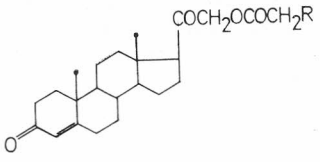


St—residue of steroid molecule
R —H or Alkyl

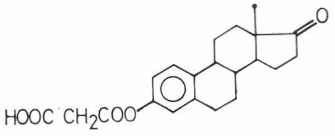
Scheme II



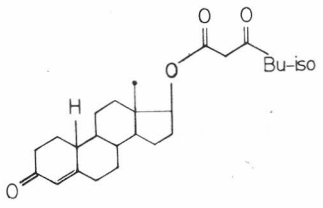
(III) R = COOH
(IV) R = H
(V) R = COC_3H_7-iso
(VI) R = $COCH_2CH_2COOCH_3$
(VII) R = COC_4H_9-iso



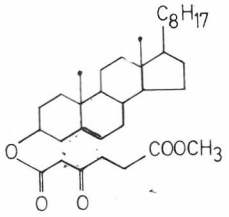
(VIII) R = COOH
(XI) R = H



(X)



(XI)



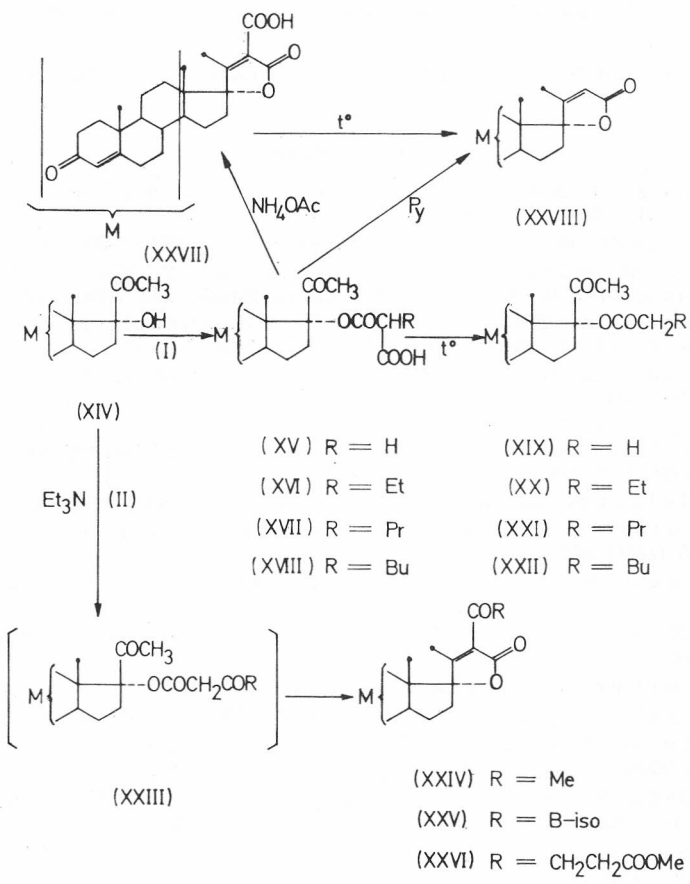
(XIII)

The structures of the compounds obtained are shown in Schemes I and II.

The hemimalonates (III, VIII, X, XV—XVIII) easily undergo decarboxylation on heating to the melting point (usually at 160—170 °C) with the formation of the corresponding esters (IV, IX, XIX—XXII). Some of them (XIX, XXII) are used as gestogens of prolonged action. It should be noted that decarboxylation of the 17α-hydroxyprogesterone hemimalonate (XV) is accompanied with formation of small quantities (up to 5%) of the spirolactone (XXVIII) (see below).

The reaction leading to hemimalonates (XVI—XVIII) is usually accompanied with further decarboxylation to esters (XX—XXII), the yield of which does not exceed 10%.

Scheme III



Synthesis of Steroid Acetoacetates (V—VII, XI, XII) and Spirolactones (XXIV—XXVIII)

Heating of hydroxysteroids (testosterone, 19-nor-testosterone, cholesterol) with 5-acylderivatives (II) of Meldrum acid in inert solvents leads to the formation of acylacetates (V—VII, XI, XII)[16] in good yields. Strange as it may see, but in the case of desoxycorticosterone this reaction gave a mixture of products from which it was impossible to isolate the desired compound.

17α-hydroxyprogesterone (XIV) reacts with 5-acylderivatives of Meldrum acid rather easily (in benzene solution in the presence of triethylamine) giving rise to the corresponding acylacetates, which undergo cyclodehydration with the formation of acylspirolactones (XXIV—XXVI). An analogous transformation was found in the case of 17α-hydroxyprogesterone hemimalonate (XV). Its heating with ammonium acetate in benzene or with pyridine and pyperidine in methylene chloride afforded the carboxyspirolactone (XXVII). The heating of XV in pyridine with some pyperidine leads to cyclodehydration

with the subsequent decarboxylation and formation of the spirolactone (XXVIII), which can also be obtained by simple thermal decomposition of XXVII.

The spirolactones so obtained are of interest as potential aldosterone antagonists[17].

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SAŽETAK

Sinteza i fiziološka aktivnost steroidnih estara i spiro-laktona

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Dejstvom Meldrum-ove kiseline, odnosno njenih alkil- i acil-derivata na hidroksi-steroide, lako postaju odgovarajući hemimalonati, alkil-hemimalonati i aceto-acetati u visokom prinosu. Dekarboksilacijom hemimalonata i alkil-hemimalonata dobiven je veći broj estara steroidnih alkohola, od kojih se neki primenjuju i u medicinskoj praksi.

Kada se hemimalonat i aceto-acetat 17α-hidroksi-progesterona izloži dejstvu baza vrši se ciklodehidratacija, pri čemu se grade spiro-laktoni koji su potencijalni aldosteron-antagonisti.