XII. Hydrazones and Symmetrical Dihydrazones of 2α-Methyltestosterone, 2α, 17α-Dimethyltestosterone, and 17α-Ethyl-2α-Methyltestosterone

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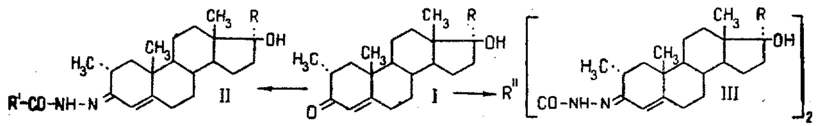
The present communication is a continuation of investigations [1, 2] on the synthesis of derivatives of the androstane series in order to obtain substances with an increased anabolic and a low androgenic activity.

It is known that a C=N bond at C_3 enhances the anabolic properties of androstane hydroxyketones [3], and that at the present time 2α-methyldihydrotestosterone and its derivatives [4] and testosterone and its ethers can be used as effective anabolic preparations in the treatment of cancer of the breast. Consequently, we have synthesized a group of hydrazones and symmetrical dihydrazones of 2α-methyltestosterone and its 17α-methyl and 17α-ethyl derivatives; these compounds contain a 2α-methyl group, which decreases their androgenic properties and enhances their anabolic properties, as well as a C=N bond at C_3 conjugated with the double bond present in the testosterone molecule:



R=H, CH_3, C_2H_5; R' and R'' — radicals of monobasic and dibasic acids

Table 1

Hydrazones of 2α-Methyltestosterone

Initial acid hydrazide	Method of purification	Color	Yield, %	Mp, °C	Formula	N, % found	N, % calculated
Formic (I)		white	99.9	212—214	$C_{21}H_{32}O_2N_2$	8.18	8.15
Acetic (II)		yellow	84.5	247—249	$C_{22}H_{34}O_2N_2$	7.80	7.82
Propionic (III)		white	99.8	237—240	$C_{23}H_{36}O_2N_2$	7.51	7.53
Butyric (IV)	c	•	99.6	147—150	$C_{24}H_{38}O_2N_2$	7.20	7.26
Caproic (V)		yellow	98.4	141—143	$C_{26}H_{42}O_2N_2$	6.70	6.77
Enanthic (VI)			70.5	143—145	$C_{27}H_{44}O_2N_2$	6.47	6.55
Stearic (VII)	b		20.8	199—201	$C_{38}H_{66}O_2N_2$	4.85	4.81
Benzoic (VIII)	a		50.3	203—205	$C_{27}H_{36}O_2N_2$	6.65	6.67
Phenylacetic (IX)	b	white	83.8	193—195	$C_{28}H_{38}O_2N_2$	6.41	6.47
Phenylpropionic (X)	c		67.2	147—149	$C_{29}H_{40}O_2N_2$	6.32	6.26
Cinnamic (XI)	a		47.4	219—221	$C_{29}H_{38}O_2N_2$	6.27	6.30
α-Methylcinnamic (XII)			66.0	167—169	$C_{30}H_{40}O_2N_2$	6.13	6.08
α-Methydihydro-cinnamic (XIII)	c	yellow	99.7	74—76	$C_{30}H_{42}O_2N_2$	6.14	6.06
Anisic (XIV)	a	white	60.3	177—180	$C_{28}H_{38}O_3N_2$	6.26	6.22
Phenoxyacetic (XV)		orange	46.8	206—208	$C_{28}H_{38}O_3N_2$	6.21	
p-Chlorophenoxy-acetic (XVI)	b		25.0	212—214	$C_{28}H_{37}O_3ClN_2$	5.75	6.22
Phenylethyl-acetic (XVII)	c		65.5	140—142	$C_{30}H_{42}O_2N_2$	6.01	5.78 6.06
Salicylic (XVIII)			27.6	244—247	$C_{27}H_{36}O_3N_2$	6.40	6.40
Anthranilic (XIX)			41.7	253—256	$C_{27}H_{37}O_2N_3$	9.69	9.66
p-Aminobenzoic (XX)			69.5	214—216	$C_{27}H_{37}O_2N_3$	9.64	9.66
p-Aminosali-cylic (XXI)			67.2	210—212	$C_{27}H_{37}O_3N_3$	9.34	9.33
3α-Hydroxycholanic (XXII)			31.5	290—292	$C_{44}H_{70}O_3N_2$	4.13	4.15
3α, 6α-Dihydroxy-cholanic (XXIII)	a	white	65.7	227—229	$C_{44}H_{70}O_4N_2$	4.10	4.07
3α, 12α-Dihydroxy-cholanic (XXIV)			87.3	305—308	$C_{44}H_{70}O_4N_2$	4.07	4.07
3α, 7α, 12α-Tri-hydroxycholanic (XXV)			85.5	227—229	$C_{44}H_{70}O_4N_2$	4.00	3.96
3α-Hydroxy-12α-meth-oxychol-9(11)-enic (XXVI)			42.0	169—171	$C_{44}H_{70}O_4N_2$	3.92	3.99
3β-Hydroxychol-5-enic (XXVII)			67.3	173—175	$C_{44}H_{68}O_3N_2$	4.20	4.17
3β-Hydroxyetiochol-5-enic (XXVIII)	b		58.8	160—163	$C_{40}H_{60}O_3N_2$	4.60	4.55
Nicotinic (XXIX)			28.7	184—186	$C_{26}H_{35}O_2N_3$	10.23	10.25
Isonicotinic (XXX)			50.3	234—236	$O_{26}H_{35}O_2N_3$	10.25	10.25

Table 2

Hydrazones of 2α, 17α-Dimethyltestosterone

Initial acid hydrazide	Method of purification	Color	Yield, %	Mp, °C	Formula	N, %	
						found	calculated
(I)			61.6	227–230	$C_{22}H_{34}O_2N_2$	7.84	7.82
(II)			59.7	222–224	$C_{23}H_{36}O_2N_2$	7.56	7.53
(III)	b	white	73.4	212–214	$C_{24}H_{38}O_2N_2$	7.25	7.26
(IV)			70.8	176–178	$C_{25}H_{40}O_2N_2$	6.96	7.00
(V)			51.7	206–209	$C_{27}H_{44}O_2N_2$	6.58	6.55
(VI)			50.0	222–224	$C_{28}H_{46}O_2N_2$	6.32	6.34
(VII)			37.2	165–167	$C_{39}H_{68}O_2N_2$	4.61	4.69
(VIII)	a		99.7	208–210	$C_{28}H_{38}O_2N_2$	6.40	6.46
(IX)			8[illegible].5	196–198	$C_{29}H_{40}O_2N_2$	6.30	6.26
(X)	b		99.8	158–160	$C_{30}H_{42}O_2N_2$	6.01	6.06
(XI)	a		41.2	166–169	$C_{30}H_{40}O_2N_2$	6.10	6.08
(XII)			98.4	149–151	$C_{31}H_{42}O_2N_2$	5.98	5.92
(XIII)	c	yellow	99.8	138–141	$C_{31}H_{44}O_2N_2$	5.81	5.89
(XIV)			99.8	284–286	$C_{29}H_{40}O_3N_2$	6.04	6.04
(XV)			34.0	183–185	$C_{29}H_{40}O_3N_2$	6.01	6.04
(XVI)			82.3	144–146	$C_{29}H_{39}O_3N_2Cl$	5.68	5.64
(XVII)			33.0	210–212	$C_{31}H_{44}O_2N_2$	5.91	5.89
(XVIII)			99.8	220–222	$C_{28}H_{38}O_3N_2$	6.25	6.22
(XIX)			70.3	235–238	$C_{28}H_{39}O_2N_3$	9.35	9.37
(XX)		brown	91.5	202–204	$C_{28}H_{89}O_2N_3$	9.38	9.37
(XXI)	a		42.3	248–250	$C_{28}H_{39}O_3N_3$	9.03	9.03
(XXII)		yellow	99.8	207–209	$C_{45}H_{72}O_3N_2$	4.15	4.08
(XXIII)			99.9	234–236	$C_{45}H_{72}O_4N_2$	4.00	3.97
(XXIV)			89.7	258–260	$C_{45}H_{72}O_4N_2$	3.97	3.97
(XXV)		white	99.9	252–254	$C_{45}H_{72}O_5N_2$	3.95	3.89
(XXVI)			98.7	225–227	$C_{46}H_{72}O_4N_2$	3.96	3.92
(XXVII)			99.9	238–240	$C_{45}H_{70}O_4N_2$	4.13	4.08
(XXVIII)	c		90.4	122–124	$C_{41}H_{62}O_3N_2$	4.38	4.45
(XXIX)	a	yellow	99.8	181–183	$C_{27}H_{37}O_2N_3$	9.60	9.65
(XXX)			98.8	208–210	$C_{27}H_{37}O_2N_3$	9.63	9.65

Table 3

Hydrazones of 17α-Ethyl-2α-Methyltestosterone

Initial acid hydrazide	Method of purification	Color	Yield, %	Mp, °C	Formula	N, %	
						found	calculated
(I)	c		99.9	230–236	$C_{23}H_{36}O_2N_2$	7.61	7.53
(II)	b	white	51.3	194–198	$C_{24}H_{38}O_2N_2$	7.22	7.26
(III)	c		82.7	216–218	$C_{25}H_{40}O_2N_2$	7.05	7.00
(IV)			79.5	198–200	$C_{26}H_{42}O_2N_2$	6.84	6.77
(V)	b	green	59.7	187–190	$C_{28}H_{46}O_2N_2$	6.39	6.34
(VI)			21.8	168–170	$C_{29}H_{48}O_2N_2$	6.08	6.14
(VIII)	a	yellow	36.8	160–163	$C_{29}H_{40}O_2N_2$	6.21	6.26
(IX)		white	35.8	212–214	$C_{30}H_{42}O_2N_2$	6.06	6.06
(X)		yellow	27.8	153–155	$C_{31}H_{44}O_2N_2$	5.92	5.88
(XII)		white	33.7	138–140	$C_{32}H_{44}O_2N_2$	5.79	5.73
(XIII)	b	yellow	47.3	135–138	$C_{32}H_{46}O_2N_2$	5.75	5.71
(XIV)			48.3	173–176	$C_{30}H_{42}O_3N_2$	5.84	5.87
(XV)			20.7	127–130	$C_{30}H_{42}O_3N_2$	5.85	5.87
(XVI)	c	white	64.5	114–116	$C_{30}H_{41}O_3ClN_2$	5.40	5.47
(XVII)			67.5	158–160	$C_{32}H_{46}O_2N_2$	5.78	5.71
(XVIII)		yellow	71.2	172–175	$C_{29}H_{40}O_3N_2$	6.13	6.13
(XIX)		brown	35.6	250–252	$C_{29}H_{41}O_2N_3$	9.09	9.07
(XX)		yellow	34.8	261–264	$C_{29}H_{41}O_2N_3$	9.06	9.07
(XXI)		brown	69.2	270–273	$C_{29}H_{41}O_3N_3$	8.74	8.76
(XXII)			70.3	230–232	$C_{46}H_{74}O_3N_2$	4.02	3.99
(XXIII)	a		92.0	246–249	$C_{46}H_{74}O_4N_2$	3.91	3.90
(XXIV)		white	36.8	178–180	$C_{46}H_{74}O_4N_2$	3.96	3.90
(XXV)			89.7	235–238	$C_{46}H_{74}O_5N_2$	3.82	3.82
(XXVI)		yellow	67.5	226–229	$C_{47}H_{74}O_4N_2$	3.88	3.84
(XXVII)		white	94.0	236–238	$C_{46}H_{72}O_3N_2$	4.00	4.00
(XXIX)		yellow	36.7	175–178	$C_{28}H_{39}O_3N_3$	9.38	9.35
(XXX)			26.8	178–180	$C_{28}H_{39}O_2N_3$	9.34	9.35

The initial 2α-methyltestosterone, 2α, 17α-dimethyltestosterone, and 17α-ethyl-2α-methyltestosterone were synthesized from the corresponding hydroxymethyl compounds [2] by hydrogenating them in methanolic solution over palladized carbon in a similar manner to the synthesis of 2α-methyldihydrotestosterone [1]. The compounds isolated corresponded to the 2α-methyltestosterone and its 17α-methyl and 17α-ethyl derivatives described by Ringold [5].

The hydrazones and symmetrical dihydrazones of the steroid hydroxyketones mentioned were prepared with high yields by heating them with the corresponding acid hydrazides in alcoholic solution.

Table 4

Symmetrical Dihydrazones of 2α-Methyltestosterone

Initial acid hydrazide	Method of purification	Color	Yield, %	Mp, °C	Formula	N, %	
						found	calculated
Oxalic (XXXI)			90.1	262—264	$C_{42}H_{62}O_4N_4$	8.18	8.17
Malonic (XXXII)			86.3	275—279	$C_{43}H_{64}O_4N_4$	8.00	8.00
Succinic (XXXIII)			84.7	206—208	$C_{44}H_{66}O_4N_4$	7.89	7.86
Glutaric (XXXIV)			99.7	242—244	$C_{45}H_{68}O_4N_4$	7.78	7.72
Adipic (XXXV)			99.9	234—237	$C_{46}H_{70}O_4N_4$	7.61	7.56
Sebacic (XXXVI)	a	white	76.4	190—192	$C_{50}H_{78}O_4N_4$	7.06	7.02
Tartaric (XXXVII)			81.0	228—231	$C_{44}H_{66}O_6N_4$	7.54	7.51
Malic (XXXVIII)			57.9	249—251	$C_{44}H_{66}O_5N_4$	7.67	7.66
Fumaric (XXXIX)			34.1	230—232	$C_{44}H_{64}O_4N_4$	7.92	7.87
Phthalic (XL)			79.3	358—361	$C_{48}H_{66}O_4N_4$	7.34	7.34

The hydrazones isolated consisted of solid poorly crystalline substances. (Only the hydrazones of 17α-methyl-2α-methyltestosterone substituted by stearic, cinnamic, and 3β-hydroxyetiochol-5-enic acids could not be isolated in the solid state.) They were readily soluble in alcohols, ether, and ethyl acetate, sparingly soluble in hexane and petroleum ether, and insoluble in water. Hydrazones containing an amino group in a benzene ring were insoluble in alcohols and, in addition to these, the hydrazones of salicylic and steroid acids were insoluble in ether.

On comparing the properties of the hydrazones of 2α-methyltestosterone and its 17α-methyl and 17α-ethyl derivatives with the analogous compounds of testosterone, dihydrotestosterone, 2α-methyldihydrotestosterone, and their 17α-methyl and 17α-ethyl derivatives [2] the following conclusions can be drawn:

a) the yield of hydrazones for all four groups (testosterone, 2α-methyltestosterone, dihydrotestosterone, and 2α-methyldihydrotestosterone) does not basically depend on the presence of a double bond at C_4 and a 2α-methyl group;

b) their solubility in alcohols increases from dihydrotestosterone to 2α-methyldihydrotestosterone, testosterone, and 2α-methyltestosterone;

c) the hydrazones of dihyrotestosterone are insoluble in ether; the solubilities of derivatives of 2α-methyldihydrotestosterone and testosterone are greater and approximately the same, and the hydrazones of 2α-methyltestosterone are mainly soluble in ether.

Table 5

Symmetrical Dihydrazones of 2α, 17α-Dimethyltestosterone

Initial acid hydrazide	Method of purification	Color	Yield, %	Mp, °C	Formula	N, %	
						found	calculated
(XXXI)			88.5	228—231	$C_{44}H_{66}O_4N_4$	7.85	7.86
(XXXII)			99.9	240—243	$C_{45}H_{68}O_4N_4$	7.70	7.72
(XXXIII)			99.6	207—210	$C_{46}H_{70}O_4N_4$	7.60	7.56
(XXXIV)			97.8	227—230	$C_{47}H_{72}O_4N_4$	7.42	7.42
(XXXV)	a	yellow	99.3	257—260	$C_{48}H_{74}O_4N_4$	7.27	7.27
(XXXVI)			99.8	237—240	$C_{52}H_{82}O_4N_4$	6.93	6.87
(XXXVII)			99.5	220—223	$C_{46}H_{70}O_6N_4$	7.22	7.26
(XXXVIII)			58.5	222—224	$C_{46}H_{70}O_5N_4$	7.37	7.40
(XXXIX)			99.9	264—267	$C_{46}H_{68}O_4N_4$	7.58	7.57
(XL)			55.0	302—304	$C_{50}H_{70}O_4N_4$	7.12	7.12

The same regularities are observed not only for derivatives of testosterone but also for their 17α-methyl and 17α-ethyl homologs.

All that has been said above does not relate to the hydrazones of steroid acids. For the latter the yield was quantitative in the majority of cases for all groups, apart from the hydrazones of 2α-methyldihydrotestosterone and 17α-ethyl-

2α-methyltestosterone, where the yields were much lower. They are all insoluble in ether. The solubility of the hydrogenated compounds in alcohol is low and does not depend on the presence of the 2α-methyl group; for the compounds of the testosterone series it increases markedly, and the steroid hydrazones of 2α-methyltestosterone are readily soluble in alcohols.

The symmetrical dihydrazones of 2α-methyltestosterone and its 17α-methyl and 17α-ethyl homologs are solid poorly crystalline substances. The yields of these compounds are almost quantitative for 2α, 17α-dimethyltestosterone, slightly less for 2α-methyltestosterone, and considerably less for the 17α-ethyl derivative. They are all sparingly soluble in alcohols and ethyl acetate and insoluble in ether, hexane, petroleum ether, and water.

Table 6

Symmetrical Dihydrazones of 17α-ethyl-2α-methyltestosterone

Initial acid hydrazide	Method of purification	Color	Yield, %	Mp, °C	Formula	N, %	
						found	calculated
(XXXI)	b	white	44.6	227–230	$C_{46}H_{70}O_4N_4$	7.51	7.53
(XXXII)	a		43.4	236–238	$C_{47}H_{72}O_4N_4$	7.41	7.42
(XXXIII)			84.5	228–231	$C_{48}H_{74}O_4N_4$	7.29	7.27
(XXXIV)			42.0	242–244	$C_{49}H_{76}O_4N_4$	7.16	7.16
(XXXV)			82.7	250–253	$C_{50}H_{78}O_4N_4$	7.01	7.02
(XXXVI)			77.3	248–250	$C_{51}H_{86}O_4N_4$	6.60	6.55
(XXXVII)			41.3	198–200	$C_{48}H_{74}O_6N_4$	6.95	6.98
(XXXVIII)			58.7	220–223	$C_{48}H_{74}O_5N_4$	7.16	7.13
(XXXIX)			17.3	292–295	$C_{48}H_{72}O_4N_4$	7.28	7.29
(XL)		yellow	56.5	328–330	$C_{52}H_{74}O_4N_4$	6.83	6.83

On making an analogous comparison with the dihydrazones of dihydrotestosterone, 2α-methyldihydrotestosterone, and testosterone, it is possible to conclude that the properties and yields of the symmetrical dihydrazones are little affected by the presence of a double bond at C_4 and by substituents either at C_2 or C_{17}. An exception is formed by the low yields of the symmetrical dihydrazones of 17α-ethyl-2α-methyltestosterone and the yields of the phthalic-acid-substituted dihydrazones, which are low for all groups.

Experimental

The hydrazones and symmetrical dihydrazones of 2α-methyltestosterone and its 17α-methyl and 17α-ethyl homologs were synthesized in a similar manner to the hydrazones of 2α-methyldihydrotestosterone [8] by heating a methanolic solution of the hydroxyketone concerned (I) with the appropriate acid hydrazide for 5 hr. In the case of the preparation of the hydrazones (II), a slight excess of the acid hydrazide was taken, and in the case of the symmetrical dihydrazones (III), a slight excess of the hydroxyketones. Then the resulting mixture was diluted with water. The precipitate was filtered off, washed with water, and purified by various methods:

a) where the product was insoluble in ether, heating with ether freed it from unreacted hydroxyketone;

b) if the precipitate was soluble in ether, the solvent was distilled off, and the product was dissolved in a small amount of ethyl acetate and precipitated by the addition of petroleum ether or hexane;

c) if purification by method b did not give a crystalline product, the solvent was distilled off completely, the residue was dissolved in a small amount of methanol, and water was added.

The hydrazones and symmetrical dihydrazones obtained are given in Tables 1–6.

Summary

Hydrazones and symmetrical dihydrazones of 2α-methyltestosterone and its 17α-methyl and 17α-ethyl derivatives have been synthesized.

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