SUMMARY

1. The new diguaianolide anabsin has been isolated from *Artemisia absinthium*, and its structure has been established on the basis of chemical transformations and an analysis of ^1H and ^{13}C NMR spectra.

2. The structures of absinthin and of anabsinthin have been reconsidered.

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SYNTHESIS AND STUDY OF HYDRAZONES OF 17α-HYDROXYPROGESTERONE AND 17α-HYDROXYPREGNA-4,6-DIENE-3,20-DIONE AND THEIR 17α-ACYLATED DERIVATIVES

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It has been shown that under mild conditions the reactions of 17α-hydroxy 3,20-diones of the pregnane series with acid hydrazides lead to the formation of 3-monohydrazones, while under severe conditions 3,20-dihydrazones are formed regardless of whether a C_4–C_5 ethylenic bond or a chain of conjugation of C_4–C_5 and C_6–C_7 ethylenic bonds is present in the steroid molecule. The reaction of 17α-acetoxy 3,20-diketones of the pregnane series with acid hydrazides takes place only with the formation of 3-monohydrazones. An investigation of the gestagenic action of some of the compounds synthesized has shown that the presence of a 3-keto group in the steroids of the pregnane series is not necessary for the retention of this effect. The replacement of the keto group at carbon atom 3 by an azomethine group does not abolish the gestagenic action.

According to the literature [1], a necessary condition for gestagenic action is the presence in the pregnane molecule of a 3-keto group and a C_4–C_5 ethylenic bond conjugated with it. Until now, it has been considered [1] that various changes connected with the replacement or reduction of the carbonyl group at C_3 either deprive the compound of gestagenic activity or greatly weaken it. However, it has been shown for a number of androstane compounds [2-6] that the replacement of an oxygen by a nitrogen atom at C_3 in androstane hydroxy ketones leads to an enhancement of biological activity.

A study of the reaction of the keto groups in an androstane 3,17-diketone with acid hydrazides [7] has shown that if the steroids include saturated rings A and B or a C_4–C_5 ethylenic bond conjugated with the 3-keto group, the reaction takes place at both carbonyls with the formation of dihydrazones. In this case, monohydrazones cannot be obtained by any changes whatever in the ratio of the initial components [7]. The presence in ring A of the

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TABLE 1. Hydrazones of 17α-Hydroxyprogesterone Derivatives

Compound	R	R_1	Yield, %	mp, °C	Empirical formula	IR spectrum, cm^{-1}							
						νCO, amide I	δNH, amide II	νC–N, amide III	νC=O at C_{20}	νC–O–C	νC=N		$(CH_2)_n$
I	H		30	189–192	$C_{27}H_{35}N_3O_3$	1670	1550	1280	1700	—	1540	3040	—
II	$\underset{\underset{O}{\Vert}}{C}-CH_3$	H	70	150–153	$C_{24}H_{31}N_2O_4$	1690	1520	1270	1720	1210	1570	—	—
III	H		58	242–246	$C_{29}H_{40}O_4N_2Cl$	1690	1550	1285	1710	—	1590	—	—
IV	$\underset{\underset{O}{\Vert}}{C}-CH_3$		68	286–290	$C_{29}H_{38}N_3O_4$	1690	1550	1300	1710	1230	1540	3300	—
V	H	C_6H_{13}	17,8	169–173	$C_{28}H_{44}N_2O_3$	1690	1550	1280	1710	—	1540	—	745
VI	H	C_5H_{11}	66	131–133	$C_{27}H_{42}N_2O_3$	1690	1540	1290	1710	—	1560	—	740

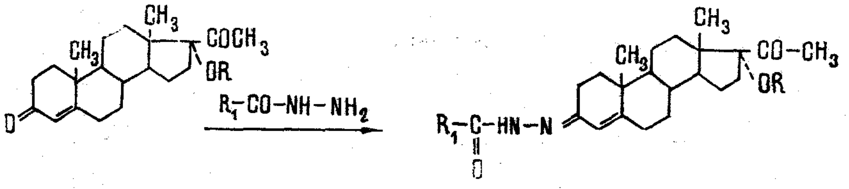
TABLE 2. Hydrazones of Derivatives of 17α-Hydroxy-Δ^6-progesterone

Compound	R	R_1	Yield, %	mp, °C	Empirical formula	IR spectrum, cm⁻¹							
						ν CO, amide I	δNH, amide II	ν C—N, amide III	ν CO at C_{20}	ν C—O—C	ν C=N		$(CH_2)_n$
VII	H		30	185—188	$C_{27}H_{33}N_3O_3$	1660	1530	1280	1700	—	1590	2990	—
VIII	$\underset{\underset{O}{\|}}{C}-CH_3$	H	60	190—192	$C_{24}H_{32}N_2O_4$	1690	1515	1280	1710	1220	1530	—	—
IX	H		77	244—246	$C_{31}H_{40}O_3N_2Cl$	1690	1550	1285	1710	—	1590	—	—
X	$\underset{\underset{O}{\|}}{C}-CH_3$		51,72	207—210	$C_{31}H_{35}N_2O_5Cl$	1690	1540	1260	1710	1230	1600	—	—
XI	$\underset{\underset{O}{\|}}{C}-CH_3$	C_6H_{13}	38	137—140	$C_{30}H_{44}O_4N_2$	1680	1535	1265	1710	1220	1560	—	740
XII	$\underset{\underset{O}{\|}}{C}-CH_3$	H	45	228—230	$C_{24}H_{33}N_2O_4$	1690	1560	1270	1710	1230	1590	—	—
XIII	$\underset{\underset{O}{\|}}{C}-CH_3$		57,7	280—283	$C_{29}H_{36}N_3O_4$	1670	1520	1300	1730	1250	1570	3050	—
XIV	$\underset{\underset{O}{\|}}{C}-CH_3$	CH_3	78	186—188	$C_{25}H_{34}N_2O_4$	1670	1520	1250	1710	1220	1570	—	—
XV	$\underset{\underset{O}{\|}}{C}-CH_3$	C_5H_{11}	70	126—128	$C_{29}H_{42}N_2O_4$	1670	1535	1270	1730	1225	1600	—	760

steroid skeleton of two ethylenic bonds conjugated with the carbonyl group at C_3 leads to the formation of only the monohydrazone at C_{17}.

In the pregnane derivatives that we are investigating, there are one or two double bonds in rings A and B conjugated with the carbonyl group at C_3, and it was of interest to see what influence they exert on the reactivity of the 3-keto group. Furthermore, in the compounds under investigation the reactivity of the carbonyl at C_{20} is lowered because of the screening effect of the methyl groups at C_{13} and C_{20} and of the 17α-hydroxy or -acetoxy groups.

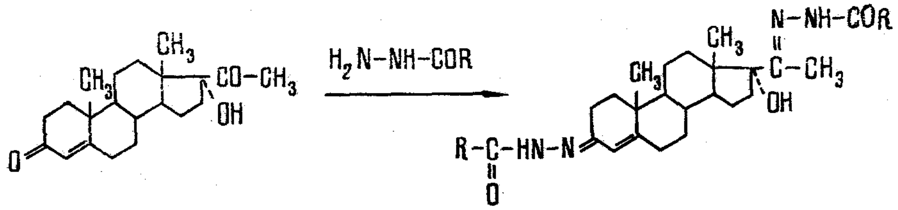
Our investigations have shown that on boiling in low-boiling aliphatic alcohols the reaction of the above-mentioned pregnane compounds took place with the formation of 3-monohydrazones in accordance with the scheme given below.



The reaction with 17α-hydroxypregna-4,6-diene-3,20-dione takes place similarly (Tables 1 and 2).

It follows from the results obtained that on heating in methanolic solution, acid hydrazides react only with the 3-keto group on progesterone derivatives. Thus, a C_4-C_5 ethylenic bond in ring A or a C_4-C_5, C_6-C_7 chain of conjugated ethylenic bonds in rings A and B, unlike $\Delta^{1,4}$-conjugation [8], has practically no influence on the reactivity of the 3-keto group.

Raising the temperature permits 17α-hydroxyprogesterone 3,20-dihydrazone to be obtained in accordance with the scheme given below.



The reaction takes place similarly with 17α-hydroxypregna-4,6-diene-3,20-dione (Tables 3 and 4).

If the 17α-hydroxy group is acylated, then, because of steric factors, the formation of hydrazones is possible only at carbon atom 3, regardless of the conditions of performing the reaction.

The compositions and structures of the hydrazones obtained were shown with the aid of elementary analysis and IR spectrometry. The absorption bands observed in the spectra agree with literature figures for analogous functional groups [10]. Consequently, the reactivity of the 3-keto groups, even though it is lowered as a consequence of the conjugation effect, is nevertheless higher than the reactivity of the C_{20} keto group.

In view of the identical stereoisomeric structural skeletons of the androstane hydroxy ketones and the pregnane derivatives, it might be assumed that an increase in the density of the electron cloud at C_3 of the steroid molecule connected with the replacement of oxygen by nitrogen should lead, if not to an enhancement, at least to a retention of the biological properties of derivatives of the pregnane series.

To evaluate the gestagenic properties of the compounds obtained we used the Clauberg test [11]. The experiments were performed on sexually immature female rabbits weighing 0.6-0.8 kg.

Results on the gestagenic activity of some of the hydrazones of the pregnane series that we synthesized are given in Table 5. On analyzing them, it is possible to arrive at the conclusion that the replacement of oxygen by nitrogen at C_3 of the pregnane molecules leads to a retention of the gestagenic activity of the compounds.

The specific action of the 17α-acetoxy-Δ^6-progesterone 3-caproylhydrazone obtained exceeds that of progesterone.

TABLE 3. 17α-Hydroxyprogesterone Dihydrazones

Compound	R	Yield, %	mp, °C	Empirical formula	IR spectrum, cm⁻¹						
					νCO, amide I	δNH, amide II	νC-N, amide III	νC=N	νNH	OH	$(CH_2)_n$
XV	H	60	233–235	$C_{23}H_{34}O_3N_4$	1690	1515	1270	1540	3200	3420	—
XVI	C_5H_{11}	59	165–167	$C_{33}H_{54}O_3N_4$	1670	1520	1300	1520	3200	3420	740
XVII	C_6H_{13}	71,4	140–143	$C_{35}H_{58}O_3N_4$	1690	1550	1290	1560	3250	3420	760
XVIII	CH_3	27	267–272	$C_{23}H_{36}O_3N_4$	1690	1540	1250	1560	3250	3400	—

TABLE 4. 17α-Hydroxy-Δ^6-progesterone Dihydrazones

Compound	R	Yield, %	mp, °C	Empirical formula	IR spectrum, cm⁻¹						
					νCO, amide I	δNH, amide II	νC-N, amide III	νC=N	νNH	$(CH_2)_n$	OH
XIX	H	80	238–240	$C_{23}H_{32}O_3N_4$	1695	1530	1270	1555	3250	—	3400
XX	CH_3	19,5	340–343	$C_{25}H_{36}O_3N_4$	1670	1510	1285	1530	3250	—	3420
XXI	C_5H_{11}	60,1	157–159	$C_{33}H_{52}O_3N_4$	1670	1510	1290	1530	3200	760	3400
XXII	C_6H_{13}	48,5	124–127	$C_{35}H_{56}O_3N_4$	1670	1510	1280	1530	3200	760	3420
XXIII		29	180–182	$C_{35}H_{40}O_3N_4$	1665	1520	1275	1580	3250	—	3420
XXIV		40	222–224	$C_{33}H_{38}O_3N_6$	1660	1530	1270	1555	3260	—	3400

TABLE 5. Gestagenic Activities of Some 17α-Hydroxyprogesterone Derivatives

Substance tested	Dose, mg (equivalent to progesterone)	Index of progestagenic proliferation (Clauberg test) the following numbers of days after the administration of the substance			
		3	7	10	14 days
Progesterone	1,0	3,60	1,50	0	—
	0,8	3,40	0	—	—
	0,6	3,20	—	—	—
	0,4	3,00	—	—	—
	0,2	1,00	—	—	—
	0,1	0,33	—	—	—
I	1,0	1,12	—	—	—
VII	1,0	1,17	—	—	—
XIII	1,0	0,66	—	—	—
VI	1,0	0,50	—	—	—
XУ	1,0	3,50	3,00	2.20	1,10
	0,8	2,37	2.20	1,10	—
	0.6	2,17	1,50	—	—
	0,4	1,17	1,80	—	—
	0,2	1,30	—	—	—
	0,1	0,50	—	—	—

EXPERIMENTAL

The results of the elementary analysis of the compounds described agreed with the calculated figures.

17α-Hydroxypregn-4-ene-3,20-dione 3-Isonicotinoylhydrazone (I). A mixture of 0.5 g of 17α-hydroxypregesterone, 0.75 g of isonicotinic acid hydrazide, and 30 ml of methanol was boiled for 5 h. After cooling, the reaction mixture was poured into salted water and the precipitate was filtered off, washed with water, and dried. The resulting hydrazone was purified by crystallization from benzene, which yielded 0.3 g of 17α-hydroxypregn-4-ene-3,20-diene 3-isonicotinoylhydrazone (I) (30% of theoretical) with mp 189-192°C.

The following were obtained similarly: 17α-hydroxypregna-4,6-diene-3,20-dione 3-isonicotinoylhydrazone (VII), 17α-hydroxypregn-4-ene-3,20-dione 3-enanthoylhydrazone (V), 17α-hydroxypregn-4-ene-3,20-dione 3-caproylhydrazone (VI), 17α-acetoxypregn-4-ene-3,20-dione 3-formylhydrazone (II), and 17α-acetoxypregna-4,6-diene-3,20-dione 3-formylhydrazone (VIII).

17α-Hydroxypregna-4,6-diene-3,20-dione 3-p-Chlorophenoxyacetylhydrazone (IX). A mixture of 0.2 g of 17α-hydroxypregna-4,6-diene-3,20-dione, 0.3 g of p-chlorophenoxyacetic acid hydrazide, and 5 ml of glycol was heated in Wood's metal bath at 200°C for 5 h. After cooling, the reaction mixture was poured into salted water and the precipitate was filtered off and washed with water. The hydrazone synthesized was purified by crystallization from ether. This gave 0.25 g of 17α-hydroxypregna-4,6-diene-3,20-dione 3-p-chlorophenoxyacetylhydrazone (IX) (77% of theoretical) with mp 244-246°C.

The following were obtained similarly: 17α-hydroxypregn-4-ene-3,20-dione 3-p-chlorophenoxyacetylhydrazone (III); 17α-acetoxypregna-4,6-diene-3,20-dione 3-p-chlorophenoxyacetylhydrazone (X); 17α-acetoxypregna-4,6-diene-3,20 - dione 3-acetylhydrazone (XIV); 17α-acetoxypregna-4,6-diene-3,20-dione 3-enanthoylhydrazone (XI); 17α-acetoxypregna-4,6-diene-3,20-dione 3-isonicotinoylhydrazone (XIII); 17α-acetoxypregn-4-ene-3,20-dione 3-isonicotinoylhydrazone (IV); 17α-acetoxypregna-4,6-diene,3-20-dione 3-formylhydrazone (XII); and 17α-acetoxypregna-4,6-diene-3,20-dione 3-caproylhydrazone (XXV).

17α-Hydroxypregna-4,6-diene-3,20-dione Di(acetylhydrazone) (XX). To 0.2 g of 17α-hydroxypregna-4,6-diene-3,20-dione in 5 ml of ethylene glycol was added 0.2 g of acetic acid hydrazide. The reaction mixture was heated at 200-210°C for 5 h. After cooling, the mixture was poured into salted water, and the precipitate was filtered off and dried. The substance was purified by crystallization from benzene. This gave 0.05 g of 17α-hydroxypregna-4,6-diene-3,20-dione di(acetylhydrazone) (XX) with mp 340-346°C (19.5% of theoretical).

The following were obtained similarly: 17α-hydroxypregna-4,6-diene-3,20-dione di(caproylhydrazone) (XXIII); 17α-hydroxypregn-4-ene-3,20-dione di(caproylhydrazone) (XVI); 17α-hydroxypregn-4-ene-3,20-dione di(enanthoylhydrazone) (XVII); 17α-hydroxypregna-4,6-diene-3,20-dione di(isonicotinoylhydrazone) (XXIV); and 17α-hydroxypregn-4-ene-3,20-dione di(acetylhydrazone) (XVIII).

17α-Hydroxypregn-4-ene-3,20-dione Di(formylhydrazone) (XV). A mixture of 0.2 g of 17α-hydroxypregn-4-ene-3,20-dione, 0.2 g of formic acid hydrazide, and 3 ml of methanol was boiled for 5 h. After cooling, the reaction mixture was poured into salted water, and the precipitate was filtered off and dried. The dihydrazone obtained was crystallized from ether. This gave 0.15 g of 17α-hydroxypregn-4-ene-3,20-dione di(formylhydrazone) (60% of theoretical) with mp 233-235°C.

17α-Hydroxypregna-4,6-diene-3,20-dione di(formylhydrazone) was obtained similarly.

SUMMARY

1. It has been established that under mild conditions the reaction of 17α-hydroxy 3,20-diones of the pregnane series with acid hydrazides leads to the formation of 3-monohydrazones and under severe conditions 3,20-dihydrazones are formed regardless of whether a C_4-C_5 ethylene bond or a chain of conjugation of C_4-C_5 and C_6-C_7 ethylenic bonds is present in the steroid molecule.

2. It has been shown that the reaction of 17α-acetoxy 3,20-diketones of the pregnane series with acid hydrazides leads to the formation only of the 3-hydrazones.

3. A study of the gestagenic action of some of the compounds synthesized has shown that the presence in steroids of the pregnane series of a 3-keto group is not essential for the retention of its effect. The replacement of the keto group on carbon atom 3 by an azomethine group is accompanied by retention of the gestagenic action.

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