benzamide (**48**) (14.0 g, 0.0475 mole) in redistilled $POCl_3$ (100 ml), and the mixture was heated under reflux for 0.5 hr. The excess $POCl_3$ was removed under reduced pressure. A $CHCl_3$ solution of the residue was washed (aqueous K_2CO_3, H_2O). The solution was dried (Na_2SO_4) and the $CHCl_3$ was removed. The residue was exhaustively extracted with boiling Skellysolve B. The combined extracts were reduced in volume and cooled to yield 10.5 g (80.2%) of **65** as pale yellow needles, mp 129.5–132°.

5-(2-Anilinophenyl)tetrazoles.—All of the tetrazoles in Table I were prepared from the corresponding nitriles by the general procedure of Finnegan, *et al.*,[11] as illustrated for 5-[2-(2,6-dichloro-3-methylanilino)phenyl]tetrazole (**14**) as follows. A mixture of 2-(2,6-dichloro-3-methylanilino)benzonitrile (9.0 g, 0.0325 mole), NaN_3 (2.54 g, 0.039 mole), and NH_4Cl (2.09 g, 0.039 mole) in DMF (65 ml) was heated, with stirring, at an oil bath temperature of 127° for 17 hr. The DMF was removed under reduced pressure and the residue was suspended in cold H_2O (300 ml) which was acidified to pH 2 with concentrated HCl (beware of any liberated HN_3). The solid product was collected and recrystallized from aqueous MeOH (Norit) to give **14** (8.6 g, 82.7%) as yellow needles: mp 207–208.5° dec; uv maxima (95% EtOH, 0.01 *N* in HCl), 280 mμ (ε 7510), 329 mμ (ε 7360).

5-[2-(3-Trifluoromethylanilino)phenyl]tetrazole (**4**), mp 205–207°, had uv maxima (95% EtOH, 0.01 *N* in HCl), 287 mμ (ε 16,200), 336 mμ (ε 7500).

Alternative Preparation of 5-[2-(3-Trifluoromethylanilino)-phenyl]tetrazole (4).—A solution of 5-(2-bromophenyl)tetrazole[27] (5.0 g, 0.0222 mole) in dry hexamethylphosphoramide (20 ml) was added slowly to a cooled (ice–water), stirred suspension of NaH (1.80 g of a 59.4% NaH dispersion in mineral oil, 0.0446 mole of NaH) in hexamethylphosphoramide (20 ml). When the vigorous evolution of H_2 had ceased, 3-trifluoromethylaniline (3.58 g, 0.0222 mole) was added to the reaction mixture. The temperature of the mixture was slowly raised under N_2. At about 120° a further gaseous evolution occurred. When this reaction had subsided, the mixture was then heated at 185° for 1.5 hr. The cooled reaction mixture was diluted (cold H_2O, 400 ml). The resulting solution was acidified to pH 2 with concentrated HCl. The acidified mixture was extracted ($CHCl_3$, four 100-ml portions). The combined extracts were washed (cold H_2O, 100 ml). The $CHCl_3$ solution was then extracted with 10% aqueous NaOH (two 50-ml portions). The combined NaOH extracts were acidified to pH 2 with concentrated HCl. The resulting mixture was extracted ($CHCl_3$, four 50-ml portions). The combined $CHCl_3$ extracts were washed (H_2O, 50 ml), dried (Na_2SO_4), and filtered, and the filtrate was reduced to dryness. The brown oily residue (8.0 g) was purified by chromatography on silicic acid (300 g). The crude product was introduced onto the column in a mixture of Me_2CO (5 ml) and C_6H_6 (25 ml). The column was eluted with Me_2CO–C_6H_6 (1:20). After the first 400-ml fraction, the eluate was collected in 300-ml fractions. A buff, crystalline solid (1.9 g, 28% yield) was obtained after the removal of the solvent from fractions 2–4, inclusive. The solid had mp 198–202°, with mmp 202–205° with authentic 5-[2-(3-trifluoromethylanilino)phenyl]tetrazole (**4**). The solid was recrystallized from aqueous EtOH to give buff crystals, mp 205–207° (ir spectrum identical with authentic **4**).

A repeat of the above reaction using 5-(2-chlorophenyl)-tetrazole[27] in place of the 5-(2-bromophenyl)tetrazole gave **4** in 34.5% yield. A repeat using 5-(2-chlorophenyl)tetrazole (0.0222 mole), NaH (0.0666 mole), and 3-trifluoromethylaniline (0.0444 mole) gave **4** in 46% yield.

1-Methyl-5-[2-(3-trifluoromethylanilino)phenyl]tetrazole (XVIII) and 2-Methyl-5-[2-(3-trifluoromethylanilino)phenyl]-tetrazole (XIX).—A cooled (ice–water bath) suspension of 5-[2-(3-trifluoromethylanilino)phenyl]tetrazole (10.0 g) in Et_2O (100 ml) was treated with an ethereal solution of excess CH_2N_2. Excess CH_2N_2 and Et_2O were removed. Fractional recrystallization of the residue from MeOH gave two products. The first product (9.4 g) was recrystallized from MeOH to give colorless crystals of XIX, mp 119.5–121°, nmr peak ($CDCl_3$) at δ 4.39 (3 H singlet, $CH_3N<$).

Anal. Calcd for $C_{15}H_{12}F_3N_5$: C, 56.41; H, 3.79; N, 21.94. Found: C, 56.24; H, 3.87; N, 21.95.

The second product (0.9 g) was recrystallized from cyclohexane to give pale yellow crystals of XVIII, mp 116–117.5°, nmr peak ($CDCl_3$) at δ 4.18 (3 H singlet, $CH_3N<$).

Anal. Calcd for $C_{15}H_{12}F_3N_5$: C, 56.41; H, 3.79; N, 21.94. Found: C, 56.32; H, 3.98; N, 21.99.

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Steroids. CCCX.[1] Structure–Activity Relationship of Some Steroidal Hypnotic Agents

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A total of 62 steroids, some of them new, and belonging to different chemical classes were studied for hypnotic activity. A few members of the 5α- and 5β-pregnane and 19-norpregnane class were outstanding as hypnotic agents, markedly surpassing 21-hydroxy-5β-pregnane-3,20-dione and the commonly known short-acting barbiturates in potency. These compounds were particularly effective when given intravenously in nonaqueous solvents, *i.e.*, glycols or dimethyl sulfoxide. About half of the compounds were either inactive or gave rise to CNS stimulation. The water-soluble succinates of the potent pregnane derivatives were uniformly less effective and slower acting than the free alcohol and ketone forms. Pregn-4-enes, pregn-5-enes, and the few androstane- and estrane-type steroids studied exhibited negligible hypnotic activity.

Certain classes of hormonal and nonhormonal steroids are known to possess significant influence on the central nervous system of mammals. A large number of these compounds exhibit hypnotic effects,[3,4] while some produce CNS stimulation with convulsions.[4,5] The first observations of Selye[6] on the sedative and hypnotic actions of progesterone and some other pregnanes were followed by efforts concerned with the synthesis of therapeutically useful anesthetic steroids. Main emphasis was placed on the synthesis

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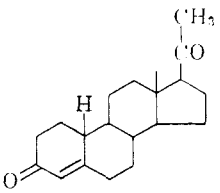
and biological exploration of water-soluble, ester salts of pregnane-type steroids[7] which resulted in the therapeutic application of the sodium semisuccinate of 21-hydroxy-5β-pregnane-3,20-dione (hydroxydione, **22**,[8] Table I) as an intravenous anesthetic agent. More recent studies[4] and a comprehensive review[3] of this subject have dealt with the structure and hypnotic-activity correlations of several classes of steroids, mostly water-soluble, ester salts of pregnanes. However, no clinically useful new compounds superior to hydroxydione have emerged from these studies.

In the present paper, a pharmacological reevaluation of several previously described, pregnane-type steroids is reported in addition to the preliminary biological testing of some new steroidal compounds possessing hypnotic properties. The results obtained with 62 steroids are given in Tables I–IV. Emphasis has been placed on increasing potency and obtaining rapid onset of hypnotic action following intravenous administration, because these properties of previously studied compounds were found not to be "ideal."

Chemistry.—The new routes to 19-nor steroids recently developed in these laboratories[9] have permitted access to many compounds not readily available from the old methods, which involved high-temperature pyrolysis and reaction of aromatic compounds in liquid ammonia.

Several attempts were made to prepare 19-nordeoxycorticosterone acetate (**63b**) from 19-norprogesterone



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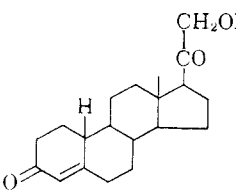
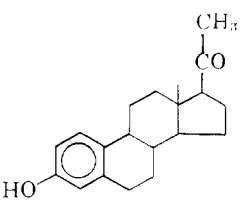


63a, R = H
b, R = Ac



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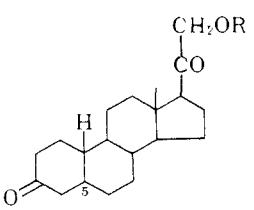

5β-H series	5α-H series
65a, R = H	**66a**, R = H
b, R = Ac	**b**, R = Ac
c, R = $CO(CH_2)_2CO_2H$	**c**, R = $CO(CH_2)_2CO_2H$
52, R = $CO(CH_2)_2CO_2Na$	**50**, R = $CO(CH_2)_2CO_2Na$

(44) by direct iodination with calcium oxide and iodine, using either *t*-butyl hydroperoxide or azobisisobutyronitrile[10] as a catalyst. The yield was never very good in these reactions. Functionalization of 19-norprogesterone (**44**) at C-21 was performed in better yield, by the Ringold–Stork procedure,[11] *i.e.*, reaction with iodine and calcium oxide in tetrahydrofuran (containing peroxides) and methanol solution. After reaction, the mixture was not isolated but immediately treated with potassium acetate in acetone. The crude product was then hydrolyzed with methanolic sodium bicarbonate. Careful chromatography of this mixture afforded, apart from 15% of 19-nordeoxycorticosterone (**63a**), 52% of starting **44** and 25% of 17β-acetylestra-1,3,5(10)-trien-3-ol (**64**).

Catalytic hydrogenation of **63a** with 5% palladium on charcoal in 5% ethanolic potassium hydroxide gave a mixture of the *cis* (5β-H) (**65a**, 70%) and the *trans* (5α-H) (**66a**, 30%) isomers. These compounds were separated conveniently by crystallization of their acetates (**65b**, **66b**). It is worthwhile to mention here that when the alkaline solution of the mixture obtained after hydrogenation, *i.e.*, **65a** and **66a**, was exposed a few minutes to air, in the presence of the catalyst, the main product isolated seemed to be a side-chain degradation product.

Mild, alkaline hydrolysis of the 21-acetoxy function of **65b** provided the free alcohol **65a**. Further esterification of **65a** with succinic anhydride in pyridine gave the hemisuccinate (**65c**), of which the sodium salt (**52**) was prepared.

As mentioned previously (*vide supra*), the 5α isomer (**66a**) was also obtained by catalytic hydrogenation of **63a**. Its hemisuccinate (**66c**) and the corresponding sodium salt (**50**) were also prepared. Although both isomers (**65c**, **66c**) have very similar physical properties, the molecular amplitude[12] of their optical rotatory dispersion curves and the molecular ellipticity[12] of their circular dichroism curves are quite different (see Experimental Section) and permit a safe assignment of the configuration at position 5.

The synthesis of several other new steroids examined in this work is straightforward and is described in detail in the Experimental Section.

Methods. Swiss albino mice (20–30 g) and young albino rats (100–150 g) (Simonsen Labs, Gilroy, Calif.) were used in the bulk of the experiments. The animals were injected either intraperitoneally or intravenously. The majority of the ester salts of steroids were dissolved in distilled H_2O and were injected intravenously in volumes not exceeding 0.1 ml/mouse and 0.4 ml/rat, and intraperitoneally in volumes not exceeding 0.5 ml/mouse and 2 ml/rat.

The free alcohols and ketones were dissolved in glycols (propylene glycol, or polyglycol 400[E], Dow) or DMSO (Crown-Zellerbach) or were suspended (carboxymethylcellulose, Tween 20). The glycol solutions were given intravenously; the total amount of solvent varied from 2.0–2.5 ml/kg. On intraperitoneal administration, the total amounts of solvent used ranged from 2–5 ml/kg. The end point for hypnosis was the

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TABLE I

5β-PREGNANES

No.	Compound	Min anesthetic dose, mg/kg[a] Mouse	Rat	Min lethal dose, mg/kg[a] Mouse	Rat	Solvents; notes
1	3α-Hydroxy-5β-pregnane	>50 iv				40–50 mg, ataxia, sedation
2	5β-Pregnan-20-one	>20 iv				Poor soly limits study of higher doses
3	3α,20α-Dihydroxy-5β-pregnane	(7.0 iv)	(>40 ip)	(7.0 iv)	(>40 ip)	Ataxia, convulsion, irreg respiration
4	3α,20β-Dihydroxy-5β-pregnane			(10 iv)[c]		Convulsions, tremor, sedation in 5–12 mg/kg iv
5	3α-Hydroxy-5β-pregnan-20-one	(2.5 iv), 2.3 iv	1.13 iv	(20 iv), 66 ± 10 iv[c]	27.5 ± 2.4 iv[c]	Jerks, tremor, dyspnea at 5–10 mg in DMSO
6	3α-Hydroxy-5β-pregnan-20-one acetate	320 ip				Corn oil
7	5β-Pregnane-3,20-dione	28 ip + 50,[b] (9 iv), 9 iv		80–320 ip + 200, (10–20 iv), 56 iv		Polyglycol 400; cat EEG, 20 mg is effective; CMC
8	3α,17α-Dihydroxy-5β-pregnan-20-one	320 ip, >40 iv		160–320		Polyglycol 400; 20 mg iv, sedation, convulsions
9	3α-Hydroxy-5β-pregnane-11,20-dione	20Δ,[d] <50[b] ip, 5 iv	1.25 iv	>200, 160 ± 22 iv	68 ± 6.7 iv[c] Δ	Polyglycol 400, CMC
10	21-Hydroxy-5β-pregnane-3,20-dione	14 iv, >200 oral				Ataxia, dyspnea
11	3α,6α-Dihydroxy-5β-pregnan-20-one	160 ip		40 ip		Polyglycol 400; 80 mg, sedation
12	3α,11α-Dihydroxy-5β-pregnan-20-one	>80 ip		40 ip		Polyglycol 400
13	5β-Pregnane-3,11,20-trione	320 ip, <40 iv		160 ip		Tween 20 suspension; convulsions at 40 mg iv
14	3α-Hydroxy-5β-pregn-16-en-20-one	>320[b] ip		160 ip		Sedation from 80 mg and above; Polyglycol 400
15	3α-Hydroxy-18-methyl-5β-pregnan-20-one	2.5 iv		40 iv		Ataxia, excitation, twitching
16	3α,11α-Dihydroxy-5β,17β-H-pregnan-20-one	40 iv				Ataxia, excitation, twitching
17	3α,11β-Dihydroxy-5β-pregnan-20-one	40 iv				
18	20-Fluoro-22-homo-3α-hydroxy-5β-pregn-17(20)-en-21-one	40 iv				
19	Sodium 3α,20β-dihydroxy-5β-pregnane dihemisuccinate	(35 iv)		(>35 iv)		
20	Sodium 3α-hydroxy-5β-pregnan-20-one hemisuccinate	40 ip, <20 iv		>320 ip		Water; sl convulsions
21	21-Hydroxy-5β-pregnane-3,20-dione hemisuccinate	28 iv				Ataxia, jerks, tremors, opisthotonos
22	Sodium 21-hydroxy-5β-pregnane-3,20-dione hemisuccinate (hydroxydione)	60 ip, 39 iv	80 ip	640 ip, 160 iv		Water; cat EEG, 20 mg ip effective
23	Sodium 3α-hydroxy-5β-pregnane-11,20-dione hemisuccinate	40 ip, >20 iv		640 ip		Water; sedation at 20 mg iv
24	Sodium 17α,21-dihydroxy-5β-pregnane-3,20-dione 21-hemisuccinate	>160 ip, >40 iv				
25	3α-Hydroxy-5β-pregnan-20-one dichloroacetate	10 iv				1 min delay, ataxia, opisthotonos
26	3α-Hydroxy-5β-pregnan-20-one tetrahydropyranyl ether	>25 iv, >400 oral				Rigidity, tremors on iv injection

[a] Numbers in parentheses refer to doses effective in DMSO (volume of DMSO varied from 1 to 2.5 ml/kg). [b] Carboxymethylcellulose suspension. [c] LD_{50}. [d] Δ refers to polyglycol 400.

loss of righting reflex and diminuation or loss of lid and cornea reflexes. Minimal hypnotic doses were determined using groups of five animals or more per dose level at 1:2- or 1:1.5-dose increments. The minimal effective dose refers to the minimal dose capable of producing loss of righting in at least 50% of the animals in a group. Sodium hemisuccinates were administered either dissolved in H_2O or in propylene glycol–H_2O. The glycol solutions which were given intravenously varied from 2.0–2.5 ml/kg.

TABLE II

5α-PREGNANES

No.	Compound	Min anesthetic dose, mg/kg Mouse	Rat	Min lethal dose, mg/kg Mouse	Rat	Solvents; notes
27	3α-Hydroxy-5α-pregnan-20-one	2.5 iv	2.5 iv	20 iv	15 mg iv	Rabbit ED_{min} 2 mg/kg LD_{min} 7 mg/kg
28	3β-Hydroxy-5α-pregnan-20-one	200 ip		<40 iv		CMC
29	5α-Pregnane-3,20-dione	>200 ip, >40 iv				CMC
30	3β-Hydroxy-5α-pregnane-11,20-dione	160 ip[a]		160 ip		Polyglycol 400; 40–80 mg, sedation
31	5α,6α-Oxido-5α-pregnane-3β,17α-21-triol-20-one	>160 ip				
32	Sodium 3β-hydroxy-5α-pregnane-11,20-dione hemisuccinate	160 ip, >40 iv		>640 ip		Water; sl sedation

[a] Carboxymethylcellulose suspension.

TABLE III

PREGN-4-ENES

No.	Compound	Min anesthetic dose, mg/kg[a] Mouse	Min lethal dose, mg/kg[a] Mouse	Solvents; notes
33	Pregn-4-ene-3,20-dione (progesterone)	60 iv,[b] (>75 iv)	100 iv, (>75 iv)	Ataxia, convulsions, dyspnea, sedation, stupor
34	21-Sodium 11β,21-dihydroxypregn-4-ene-3,20-dione hemisuccinate	160 ip, >40 iv[b]	1280 ip	Water; cat EEG, effective dose 10 mg, convulsions

[a] Numbers in parentheses refer to doses effective in DMSO (volume of DMSO varied between 1 and 2.5 ml/kg). [b] Carboxymethylcellulose suspension.

TABLE IV

PREGN-5-ENES

No.	Compound	Min anesthetic dose, mg/kg Mouse	Min lethal dose, mg/kg Mouse	Solvents; notes
35	3β-Hydroxypregn-5-en-20-one	>200 ip	>200 ip	CMC
36	3β-Hydroxypregn-5-en-20-one formate	>200 ip		CMC
37	3β-Hydroxypregn-5-en-20-one benzoate	>200 ip		CMC
38	Sodium 3β-Hydroxypregn-5-en-20-hemisuccinate	160 ip, 40 iv	>320 ip	Sedation at 40 mg/kg
39	20β-(Dimethylamino)ethoxylpregn-5-en-3β-ol	28 iv		Convulsions, dyspnea, no sleep at 20 mg/kg
40	3β-Hydroxy-16α,17α-oxidopregn-5-en-20-one acetate	200 ip		CMC; decrease motor activity

A few compounds were injected intraperitoneally to cats with chronical electrode implants. Changes of electrocortical activity (EEG) characteristic of sedation and sleep and blockade of the cortical-arousal reaction following high-frequency stimulation of the midbrain reticular formation were noted. The minimal effective doses producing the above characteristic changes are presented in the tables.

Results

5β-Pregnanes (Table I). The most potent compounds given intravenously in nonaqueous solvents were in order of decreasing activity: 3α-hydroxy-5β-pregnan-20-one (epipregnanolone, **5**), 3α-hydroxy-18-methyl-5β-pregnan-20-one (**15**),[13] 3α-hydroxy-5β-pregnane-11,20-dione (**9**),[14] 5β-pregnane-3,20-dione (**7**),[15] and 21-hydroxy-5β-pregnane-3,20-dione (**10**).[8] The corresponding sodium semisuccinate salts of **5**, **9**, and **10** (**20**, **22**, and **23**) were considerably weaker and, in contrast to the rapid onset of action observed with the free alcohols and ketones, their effect took place only after a latency of a few minutes as was noted in earlier reports for water-soluble steroidal hypnotics.[3,4,5,16] The dichloroacetate of **5** was quite potent,[17] but still less so than the original compounds and also showed some delay in onset of action.

Some active members of this group, *e.g.*, the two pregnanediols **3**[18] and **4**[19] produced, in addition to sedation, ataxia and convulsions, with marked respiratory impairment and acute toxicity.

Eliminating either the hydroxy or keto functions from 3α-hydroxy-5β-pregnan-20-one at C-3 or C-20 results in inactive compounds (**1**, **2**).

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The differences between the minimal hypnotic and minimal lethal doses are very marked with several potent compounds of this group. For example, **5**[20] shows a ratio of 28 for these doses, while **9** offers an even more marked separation amounting to 32. Also favorable, but less pronounced lethal *vs.* hypnotic dose ratios were found on intraperitoneal administration of these steroids or with the water-soluble ester salt forms.

It is remarkable that, except for hydroxydione (**22**), which was reported to be orally effective, none of the potent members of this group can produce sleep on mice following oral administration. In general, 40–80 times larger doses than those effective intravenously were inactive when given orally.

Introduction of a hydroxyl group at C-6, C-11, or C-17 (**11**[21], **12**,[22] and **8**[23]) or more than two oxo groups (**13**)[14] in 5β-pregnanes uniformly leads to a marked drop in potency. A double bond at C-16 (**14**)[24] similarly abolished efficacy.

It is interesting that while the change of the 3α-hydroxy in the 5β-pregnane series to a 3-oxo group (**7**) results in a moderate reduction of potency, there is a more marked loss of activity with this structural change in the 5α-pregnane series (**29**).[25] A change of the steric position of the 3-OH in the 5β-series resulted in only moderate diminution of potency,[7] while in the 5α-series it led to two hypnotically very weak compounds (**28**)[25] and (**30**).[26]

5α-Pregnanes (Tables II).—Only one compound (**27**)[27] of the six in this class proved to be hypnotically potent. Its activity on mice and rats is equivalent to that of the 5β-epimer (**5**), and it was only slightly less potent in rabbits. A marked loss of potency occurs when the steric position of the 3-hydroxy group is altered. 3β-Hydroxy-5α-pregnan-20-one (**28**) proved to be ineffective below 200 mg/kg when given intraperitoneally. Atkinson, *et al.*,[4] found the suspension of this compound to be convulsant on intravenous administration, while Figdor, *et al.*,[7] reported it to be a moderately potent hypnotic when given in the same form. A 3-oxo instead of a 3α-hydroxy group also markedly diminishes efficacy (**29**). Only very moderate activity was found with the 11-oxo derivative of 3β-hydroxy-5α-pregnan-20-one (**30**) and its sodium hemisuccinate derivative (**32**). Multiple substitution in addition to the 3 and 20 substituents on the 5α-pregnane skeleton with a 5α,6α-oxido group and C-17 and C-21 hydroxyl groups resulted in an inactive compound (**31**).[28]

Pregn-4-enes (Table III).—The few pregn-4-enes were uniformly less potent than the saturated pregnanes. Although large doses of progesterone (**33**), variously administered, produced light sleep, the doses were close to the toxic range. Although corticosterone semisuccinate (**34**) was only moderately active in mice, it produced EEG changes of sedation and slow-wave sleep at 10 mg/kg in the cat.

Pregn-5-enes (Table IV). This group did not show significant hypnotic activity. Pregnenolone (**35**) was previously reported to be inactive as a hypnotic agent in mice.[4] Its formate (**36**) and its benzoate (**37**) were inactive intraperitoneally in carboxymethylcellulose (CMC) up to 200 mg/kg, while the sodium hemisuccinate (**38**) was slightly effective, producing sleep at 160 mg/kg when administered in propylene glycol solution. Acute toxicity was not marked with this compound, with mice surviving at 320 mg/kg intraperitoneally.

The 20β-dimethylaminoethyl derivative of pregnanolone (**39**)[13] was the most potent compound of this group (minimal-effective dose, 28 mg/kg intravenously). However, in doses smaller than those producing sleep, it exhibited marked side effects, *e.g.*, convulsions, dyspnea. The 16α,17α-oxido derivative of pregnanolone in the acetate form (**40**)[17] was only moderately potent at the 200-mg/kg level, where it was found to produce sedation.

Of the above pregn-5-ene derivatives, only pregnenolone was tested previously by others and was found to be inactive as a hypnotic agent in mice.[4]

19-Norpregnanes and Related Compounds (Table V).—This group includes (a) 19-nor derivatives of a few hypnotically potent pregnanes, (b) other 19-nor steroids of the 5β-pregnane, pregn-4-ene, and pregn-5-ene type, and (c) some 19-hydroxy steroids. Within the first group, elimination of the CH_3 group at C-19 produced no change of the hypnotic activity as compared to 3α-hydroxy-5β-pregnan-20-one and 5β-pregnane-3,20-dione (**41** and **42**). These norpregnanes were as potent as their parent compounds (**5**, **7**). The corresponding succinate sodium salts (**51**, **52**) of these nor steroids were also fairly effective intraperitoneally. While the sodium hemisuccinate salt of the 3β-hydroxy-19-nor-5α-pregnan-20-one (**50**) was found to be inactive, the 19-nor derivative of 5α-pregnane-3,20-dione (**43**) is more potent than its 19-methylated analog (**29**); the latter was found inactive when given up to 200 mg intraperitoneally in CMC suspension. Atkinson, *et al.*,[4] found the same agent to be convulsant on intravenous administration. 19-Norprogesterone (**44**)[29] was slightly less potent than progesterone itself. No such comparison is available between retroprogesterone (not included in this study) and the corresponding 19-nor derivative (**45**).[13] The latter seems to be inactive, hypnotically, and also highly toxic.

Three derivatives, containing 19-hydroxy groups or a 6,19-oxido moiety, were either inactive at the 200-mg dose level, or were convulsant (**46**,[30] **47**,[31] **48**[30,31]).

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TABLE V

19-NORPREGNANES AND RELATED COMPOUNDS

No.	Compound	Min anesthetic dose, mg/kg Mouse	Rat	Min lethal dose, mg/kg Mouse	Rat	Solvents; notes
41	3α-Hydroxy-5β,19-norpregnan-20-one	2.5–5.0 iv		20 iv		Propyleneglycol; twitching
42	5β-19-Norpregnane-3,20-dione	20 ip, 10 iv	20 ip, 100 oral	80 ip, 40 iv	80 ip	Polyglycol 400; Tween 20 suspension
43	5α-19-Norpregnane-3,20-dione	40 ip, >20 iv	>80 ip[a]	40 ip		Polyglycol 400; sedation at 40 and 80 mg
44	19-Norpregn-4-ene-3,20-dione (19-norprogesterone)	160 ip	>80 ip[a]			Propyleneglycol; sedation
45	19-Norretroprogesterone	>40 iv		28 iv[b]		Propyleneglycol
46	19-Hydroxypregn-4-ene-3,20-dione	>200 mg ip				CMC; sedated at 100 mg
47	3β,19-Dihydroxypregn-5-en-20-one	>200 ip, 40 iv[b]				CMC; convulsions and dyspnea at 200 mg, convulsions
48	6,19-Oxidopregn-4-ene-3,20-dione	>200 mg, >40 iv[b]				CMC; convulsions at 200 mg, convulsions and sedation
49	7-Fluoro-5α-B-homo-19-norpregnane-3,20-dione	>40 iv				Weakness, stupor
50	Sodium 3β-hydroxy-5α-19-norpregnan-20-one hemisuccinate	>320 ip, >40 iv				Water
51	Sodium 3α-hydroxy-5β-19-norpregnan-20-one hemisuccinate	40 ip		160 ip		Water; cat EEG
52	Sodium 21-hydroxy-5β-19-norpregnane-3,20-dione hemisuccinate	40 ip		160 ip		Water; cat EEG; 10 mg ip effective
53	3β,17α-Dihydroxy-19-norpregn-4-en-20-one 17-acetate	>40 iv				

[a] Carboxymethylcellulose suspension. [b] All animals die following 40 mg/kg but no loss of righting reflex occurs preceding the lethal effect.

TABLE VI

ANDROSTANES, ESTRANES, AND ETHIOCHOLANES

No.	Compound	Min anesthetic dose, mg/kg Mouse	Min lethal dose, mg/kg Mouse	Solvents; notes
54	3α-Tetrahydropyranoxy-5α-androstan-17-one	40 iv		Spasms, gasping respiration
55	3β-Acetoxy-19-hydroxyandrost-5-en-17-one	>400 ip	<400 ip	CMC; convulsions
56	17α-Ethynyl-5β-androstane-3α,17β-diol	40 iv		Sedation, tremors, dyspnea at 20–40 mg
57	16-(Methylene-N-piperidyl)-5α-androstan-3β-ol-17-one	>320 ip		CMC
58	2-Methylene(dimethylamino)-17α-methyl-5α-androstan-17β-ol-3-one	320 ip		CMC
59	3β-Hydroxy-5,19-cycloandrost-6-en-17-one	>200 ip		CMC
60	5α-Chloro-3β,6β,17β-trihydroxyandrostan-19-oic acid 6β,19-lactone 3,17-diacetate	160 ip		Warm propyleneglycol (poor solubility)
61	3α-Hydroxy-5β-androstan-17-one (ethiocholanolone)	40 iv		
62	17α-Hydroxy-5α-estr-2-ene	320 ip	320 ip	Polyglycol 400; convulsions

B-Homo-7-fluoro-5α-19-norpregnane-3,20-dione (**49**)[32] produced muscular weakness and stupor, but no sleep at 40 mg/kg, the highest dose level permitted by the limited solubility. A 19-norpregn-4-ene with a 17α-acetoxy substituent (**53**)[13] proved to be ineffective.

Androstanes, Estranes, and Ethiocholanes (Table VI).—3α-Tetrahydropyranoxy-5α-androstan-17-one (**54**) and 17α-ethynyl-5β-androstane-3α,17β-diol (**56**), at 40 mg/kg iv, produced sleep and sedation, as well as tremors and dyspnea. A substituted 5α-chloroandrostan-19-oic acid (**60**)[27] was effective intraperitoneally, while substitution at C-2 and/or C-6 (**55**),[31] C-16 (**57**),[13] C-17 (**58**),[33] and C-19 (**59**)[34] produced inactive forms. Ethiocholanolone (**61**) was hypnotic at 40 mg/kg intravenously; 17α-hydroxyestr-2-ene (**62**)[13] at 320 mg/kg intraperitoneally, the minimal lethal dose, showed no hypnotic activity.

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Discussion.—Aqueous suspensions of these steroids were neither optimally nor immediately effective. Such results may be related to the physical–chemical properties of suspensions in complex biological systems. The use of nonaqueous solutions is an attempt to alter the distributions of these compounds in a way conductive to increased hypnotic action.

Considering the minimal effective hypnotic doses of epipregnanolone (**5**), it is about two to three times more effective when given intravenously in solution than in suspension, the latter having been reported earlier by Figdor, *et al.*[7] Much higher efficacy (nine times) in solution, including marked toxicity, was found with 3α,20α-dihydroxy-5β-pregnane (**3**) as compared to its suspension.[7] Some of the other hypnotic pregnanes did not, however, show higher efficacy in propylene glycol. 5β-Pregnane-3,20-dione (**7**) was only slightly more effective (9 *vs.* 12 mg/kg) while progesterone (**33**) and 21-hydroxy-5β-pregnane-3,20-dione (**10**) were found slightly less potent in solution. Nonaqueous solutions and suspensions of many free steroidal alcohols and ketones, however, seem to be uniformly more effective (two to five times) than the water-soluble ester salts.

In the study by Atkinson, *et al.*,[4] when a 25-min sleep duration was the end point, the higher efficacy of the free compounds (in the suspension form) as compared to the water-soluble ester salt forms, was not apparent. The difference is probably due to the rapid uptake and metabolic elimination of the free steroidal alcohols and ketones as distinguished from the ester salts which are hydrolyzed before becoming effective and, at the equipotent dose level, also exhibit more sustained action. Substituents other than 11-oxo or 21-hydroxy, *i.e.*, 6,11,17-hydroxy, when added to the C-3 and C-20 oxygen functions interfere with hypnotic potency, confirming the results of earlier studies. None of the few derivatives of the pregn-4-ene and pregn-5-ene series studied was highly effective with the exception of corticosterone hemisuccinate, which, although ineffective in mice, proved to be effective in the cat, producing EEG changes characteristics of sedation. Although, Overbeek[35] reported sedative and anticonvulsant effects with a series of androstanes, none of the compounds listed in Table VI exhibited significant activity. No analgetic activity has been assigned, so far, to any of the compounds of the pregnane type.

Experimental Section[36]

3α-Hydroxy-5β-pregnane (**1**).—$NH_2NH_2 \cdot H_2O$ (200 ml) was carefully added to a cold solution of 2.5 g of Na in 375 ml of anhydrous ethylene glycol. The solution was cooled to room temperature, and 2.5 g of 3α-hydroxy-5β-pregnan-20-one (1.5 g) was added. The mixture was heated at 130° for 3 hr. By slow distillation of NH_2NH_2, the temperature was raised to 180° and maintained for 8 hr. The temperature was raised to 210° and maintained for an additional 8 hr. After cooling, excess H_2O was added, and the product was extracted with EtOAc. The crude product (1.5 g) was purified by chromatography on 50 g of Al_2O_3. Crystallization (from aqueous MeOH) of the fractions eluted with C_6H_6–$CHCl_3$ (7:3) afforded 500 mg of **1**: mp 144–145°; $[\alpha]_D$ +24°; ν_{max} 3275 cm^{-1}; nmr, 33 (18-H), 56 (19-H), 151 (hydroxyl), 200–235 (3β-H, axial) cps. *Anal.* ($C_{21}H_{36}O$) C, O.

5β-Pregnan-20-one (**2**).—Na (4 g) was dissolved in 715 ml of anhydrous ethylene glycol. After cooling, $NH_2NH_2 \cdot H_2O$ (115 ml) was slowly added to this solution. After adding 1.5 g of 20β-hydroxy-5β-pregnan-3-one hemisuccinate, the mixture was heated at 130° for 3 hr. By distillation of NH_2NH_2, the temperature was raised to 180° and maintained for 8 hr. More NH_2NH_2 was then removed by distillation until the temperature reached 210°. After heating for 8 hr at this temperature, the mixture was allowed to cool, excess H_2O was added, and the product was extracted with EtOAc. The amorphous material, in 30 ml of Me_2CO, was oxidized at 5° with 2 ml of 8 *N* chromic acid.[37] By addition of H_2O, extraction with CH_2Cl_2, decolorization with charcoal, and crystallization from MeOH–H_2O, 400 mg of **2** was obtained; mp 114–115°; $[\alpha]_D$ +110°; ν_{max} 1700 cm^{-1}; nmr, 37 (18-H), 56 (19-H), 121 (21-H). *Anal.* ($C_{21}H_{34}O$) C, H, O.

5β-Pregnan-20-one could also be obtained by hydrogenation of a mixture of 5β-pregn-2-en-20-one and 5β-pregn-3-en-20-one in EtOAc at 2.11 kg/cm^2 (30 psi) (5% Pd–C). The material was purified by chromatography on alumina and crystallization from MeOH.

3α,20β-Dihydroxy-5β-pregnane (**4**).—A solution of 20 g of progesterone (**33**) in 500 ml of 5% ethanolic KOH was hydrogenated at 2.81 kg/cm^2 (20 g of 5% Pd–C). The filtered solution was neutralized with HCl, concentrated *in vacuo*, poured into H_2O, and extracted with CH_2Cl_2. The crude mixture of 5α- and 5β-pregnane-3,20-diones showed *no* ultraviolet absorption at *ca.* 240 mμ. It was dissolved in 500 ml of MeOH and reduced at 0–5° with 20 g of $NaBH_4$ in 50 ml of H_2O. After 20 hr at room temperature, the product was precipitated with H_2O and extracted with CH_2Cl_2. The crude mixture melted at 131–133°. Recrystallizations from MeOH provided the pure 5β-isomer (5 g), mp 236–237°, $[\alpha]_D$ +32°, ν_{max} 3280 cm^{-1}. The diacetate crystallized from Me_2CO–hexane; mp 109–110°; $[\alpha]_D$ +68° (Me_2CO); ν_{max} 1730, 1250 cm^{-1} [diol: lit.[15] mp 239–240°, $[\alpha]_D$ +25° (EtOH); diacetate: mp 110°, $[\alpha]_D$ +68 ± 4° (Me_2CO)].

3α-Hydroxy-5β-pregnan-20-one (**5**) had already been prepared by several procedures.[20] The method preferred was the selective reduction of 5β-pregnane-3,20-dione (**7**) with lithium tri-*t*-butoxyaluminum hydride as follows. Compound **7** (12.4 g) in 250 ml of anhydrous THF was reduced at room temperature with 15 g of lithium tri-*t*-butoxyaluminum hydride during 48 hr. A 1:1 H_2O–HOAc solution was then added, and the mixture was extracted with EtOAc. The product (11.7 g) was isolated by chromatography on 350 g of alumina and crystallization from Me_2CO–hexane to afford 5 g of 3α-hydroxy-5β-pregnan-20-one (**5**): mp 149–150°; $[\alpha]_D$ +109°; ν_{max} 3300, 1700 cm^{-1}. The acetate (**6**) was prepared by the usual technique and recrystallized from MeOH; mp 97–98°; $[\alpha]_D$ +115°; ν_{max} 1733, 1711, 1258 cm^{-1}.

Partial reduction of 5β-pregnane-3,7-dione with $NaBH_4$ or oxidation of 3α,20β-dihydroxy-5β-pregnane 3-hemisuccinate or the 3-monoacetate, followed, in both cases, by alkaline hydrolysis, also gave **5**.

5β-Pregnane-3,20-dione (**7**) was obtained by oxidation of a suspension of 15 g of pure **4** in 250 ml of Me_2CO at 5° with 20 ml of 8 *N* chromic acid.[37] Addition of H_2O and extraction with EtOAc gave 12.4 g of **7**, mp 114–116°, $[\alpha]_D$ +105°.[11]

3α,11α-Dihydroxy-5β,17βH-pregnan-20-one (**16**) was prepared by lithium tri-*t*-butoxyaluminum hydride reduction of an isomeric mixture, at C-17, of 11α-hydroxy-5β,17ξ-pregnane-3,20-

(35) G. A. Overbeek, Proceedings of the International Congress on Hormonal Steroids, Milan, 1962, Excerpta Medica, International Congress Series No. 51, 43 (1962).

(36) Microanalyses were done by Dr. A. Bernhardt, Max Planck Institut, Mülheim, Germany. Melting points (corrected) were determined in capillary tubes with a Mel-Temp apparatus. Rotations were taken in $CHCl_3$ at concentrations *ca.* c = 1, between 16 and 22° with a 1-dm tube at sodium D line (589 mμ). Infrared spectra were taken with a Perkin-Elmer, Model 21, NaCl prism. Ultraviolet absorption spectra (uv) were obtained with a Beckman spectrophotometer, Model DU. The optical rotatory dispersion (ORD) curves were measured with a Rudolph photoelectric spectropolarimeter. The circular dichroism (CD) curves were obtained with a Rousset-Jouan dichrograph, at the University of Strasbourg, through the courtesy of Professor G. Ourisson. The nmr spectra were recorded at 60 Mc using a 5–8% w/v solution of the steroid in $CDCl_3$ containing TMS as an internal reference. Resonance frequencies are quoted as cycles per second downfield from TMS reference and are accurate to ±0.5 cps. Where analyses are indicated only by symbols of elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(37) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

dione[38] in THF. On chromatography of the product on alumina, elution with EtOAc–Et_2O (4:1), and crystallization from Et_2O, **16** was isolated (mp 110–115° dec; $[\alpha]_D$ −60°; ν_{max} 3330, 1700 cm^{-1}), slightly contaminated by its 17α-H isomer.

3α,11β-Dihydroxy-5β-pregnan-20-one (17) was prepared as described by Rosenkranz, *et al.*[39]

Sodium 3α,20β-Dihydroxy-5β-pregnane Dihemisuccinate (19).—3α,20β-Dihydroxy-5β-pregnane (500 mg) dissolved in pyridine was heated on the steam bath for 1 hr with excess succinic anhydride. The dihemisuccinate was isolated by pouring the solution into cold, dilute, aqueous HCl, extracting with EtOAc, shaking the EtOAc solution with $NaHCO_3$, and acidifying the aqueous, alkaline extract. The crude precipitate of the free acid hemisuccinate was collected by filtration and purified by recrystallization from Et_2O–hexane. The pure compound was obtained as fine needles: mp 125–127°; $[\alpha]_D$ +55°; ν_{max} 3000–3600, 1745, 1710 cm^{-1}. *Anal.* ($C_{29}H_{44}O_8$) C, H.

The **disodium salt** of this hemisuccinate was prepared in MeOH with the stoichiometric quantity of $NaHCO_3$ in H_2O. Evaporation to dryness gave a soluble white powder, $[\alpha]_D$ +59° (H_2O).

Sodium 3α-Hydroxy-5β-pregnan-20-one Hemisuccinate (20).—3α-Hydroxy-5β-pregnan-20-one (**5**) (1 g) in anhydrous pyridine (40 ml) was heated on the steam bath for 1 hr with 1 g of succinic anhydride. Addition of cold, dilute HCl and extraction with CH_2Cl_2 furnished a crystalline residue (1.2 g) which, when dissolved in C_6H_6, could not be extracted by aqueous $NaHCO_3$. A pure sample was prepared by crystallization from CH_2Cl_2–Et_2O: mp 130°; $[\alpha]_D$ +97°; ν_{max} 3390, 1740, 1710 cm^{-1}. *Anal.* Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15; O, 19.11. Found: C, 71.02; H, 9.12; O, 19.59.

By dissolving the free hemisuccinate (1 g) in MeOH (50 ml), adding a stoichiometric amount of $NaHCO_3$ in H_2O (30 ml), concentrating (*in vacuo*), and chilling, the **sodium salt (20)** crystallized as fine needles. Purification by recrystallization from MeOH–H_2O gave material, very sparingly soluble in H_2O, which decomposed at 210–220° without melting (softening): $[\alpha]_D$ +90° (H_2O).

Sodium 3α-Hydroxy-5β-pregnane-11,20-dione Hemisuccinate (23).—3α-Hydroxy-5β-pregnane-11,20-dione (3 g) in anhydrous pyridine (50 ml) was heated on the steam bath with succinic anhydride (3 g) for 30 min, then left 20 hr at room temperature. The mixture was poured into cold, dilute, aqueous HCl and extracted with CH_2Cl_2. The residue, obtained by evaporation of the solvent, was redissolved in EtOAc and repeatedly extracted with 5% aqueous $NaHCO_3$. The combined alkaline extracts were acidified with dilute HCl. The free acid hemisuccinate was extracted with CH_2Cl_2 and the crude, crystalline acid hemisuccinate (2.3 g, mp 155–158°), obtained by evaporation of the solvent *in vacuo*, was further purified by crystallization from CH_2Cl_2–Et_2O: mp 161–163°; $[\alpha]_D$ +106°; ν_{max} 3330, 1740, 1710 cm^{-1}. *Anal.* ($C_{25}H_{36}O_6$) C, H, O.

The **sodium salt (23)** was prepared as described for **20**. It was obtained as an amorphous powder without definite melting point (decomposition), very soluble in water, $[\alpha]_D$ +79° (H_2O).

21-Sodium 17α,21-Dihydroxy-5β-pregnane-3,20-dione Hemisuccinate (24).—A solution of 17α,21-dihydroxy-5β-pregnane-3,20-dione 21-monoacetate[40] (1 g, mp 200–204°, $[\alpha]_D$ +54°) in MeOH (500 ml) was hydrolyzed by treating with $NaHCO_3$ (1 g) in H_2O (50 ml) at room temperature for 2 hr under N_2. By neutralization (dilute aqueous HCl), concentration (*in vacuo*), and isolation with CH_2Cl_2, a crystalline, homogeneous residue (0.8 g) was obtained. It was dissolved in 20 ml of pyridine and treated with 1 g of succinic anhydride in 20 ml of pyridine at room temperature for 20 hr. The steroid was then isolated by adding cold, dilute HCl, extracting with CH_2Cl_2, and removing the solvent. The residue crystallized from MeOH–H_2O to afford the pure sample: mp 182–184°; $[\alpha]_D$ +50°; ν_{max} 3450, 1725 cm^{-1}.

Anal. Calcd for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.65; H, 8.30.

The **sodium salt (24)** was prepared as mentioned previously. This salt was obtained as an amorphous powder with $[\alpha]_D$ +41° (in MeOH); it forms colloidal solutions in H_2O.

3α-Hydroxy-5β-pregnan-20-one Dichloroacetate (25).—Compound **5** (900 mg) in dry C_6H_6 (500 ml) and dichloroacetyl chloride (2 ml) were heated to reflux for 3 hr, poured into saturated $NaHCO_3$, and extracted with CH_2Cl_2. It was purified by crystallization from MeOH to provide 1 g of pure **25**: mp 116–117°; $[\alpha]_D$ +103°; ν_{max} 1750, 1700 cm^{-1}. *Anal.* ($C_{25}H_{34}Cl_2O_3$) C, H, Cl.

3α-Hydroxy-5β-pregnan-20-one Tetrahydropyranyl Ether (26).—Compound **5** (1 g), dihydropyran (0.5 ml), and *p*-toluenesulfonic acid hydrate (20 mg) in dry C_6H_6 (80 ml) were stirred for 30 min at room temperature, poured into saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2, followed by chromatography on alumina. The fractions eluted with C_6H_6 crystallized from MeOH and provided 900 mg of pure **26**: mp 115–116°; $[\alpha]_D$ +88; ν_{max} 1710 cm^{-1}; nmr, 37 (18-H), 55 (19-H), 126 (21-H), 200–245 (–OCH$_2$– and 3β-H), ~284 (–OCHO–) cps. *Anal.* Calcd for ($C_{26}H_{42}O_3$) C, H, O.

Sodium 3β-hydroxy-5α-pregnane-11,20-dione hemisuccinate (32) was prepared by heating 1 g of the free 3β-hydroxy steroid with 1 g of succinic anhydride and 40 ml of anhydrous pyridine on the steam bath for 1 hr. After leaving for 20 hr at room temperature the solution was added to cold, dilute, aqueous HCl (excess) and extracted with EtOAc. The material which dissolved was then separated into neutral and acid fractions by repeated extractions with saturated $NaHCO_3$. By acidifying the combined, alkaline extracts and reextracting with EtOAc, a crude acid fraction (369 mg) was obtained. Crystallization from CH_2Cl_2–Et_2O yielded 300 mg of pure 3β-hydroxy-5α-pregnane-11,20-dione acid hemisuccinate: mp 206–208°; $[\alpha]_D$ −76°; ν_{max} 3450, 1730, 1710 cm^{-1}. *Anal.* ($C_{25}H_{36}O_7$) C, H, O.

The **sodium salt (32)**, prepared by the usual technique (*vide supra*), was a white powder, soluble in water, $[\alpha]_D$ +68° (MeOH).

21-Sodium 11β,21-Dihydroxypregn-4-ene-3,20-dione Hemisuccinate (34).—Corticosterone (2 g) and 2 g of succinic anhydride in 50 ml of anhydrous pyridine were heated on the steam bath for 5 min, left at room temperature for 20 hr, poured into excess cold dilute HCl, and extracted with EtOAc. Fractionation into neutral and acid parts by repeated extractions with saturated $NaHCO_3$, acidification of the aqueous alkaline solution, reextraction of the precipitated material with EtOAc, and crystallization from MeOH–Et_2O gave 1.5 g of a crude acid hemisuccinate, mp 178–180°. An analytical sample was prepared by recrystallization from MeOH–Et_2O: mp 182–184°; $[\alpha]_D$ +171°; λ_{max} 242 mμ (log ε 4.20); ν_{max} 3470, 1755, 1725 cm^{-1}. *Anal.* ($C_{25}H_{34}O_7$) C, H, O.

The **sodium salt (34)** was an amorphous, white powder, soluble in H_2O, $[\alpha]_D$ +158° (H_2O), λ_{max} 248 mμ (log ε 4.16).

Sodium 3β-Hydroxypregn-5-en-20-one Hemisuccinate (38).—Pregn-5-en-3β-ol-20-one (2 g), succinic anhydride (2 g), and 50 ml of anhydrous pyridine were heated on the steam bath for 1 hr and poured into cold dilute HCl. The precipitate was extracted with EtOAc. Repeated extraction of the EtOAc solution with 5% aqueous $NaHCO_3$ furnished, upon acidification, only a negligible fraction of the total hemisuccinate. The EtOAc layer gave, after concentration and crystallization of the residue from CH_2Cl_2–Et_2O, 1.8 g of pure 3β-hydroxypregn-5-en-20-one acid hemisuccinate: mp 197–199°; $[\alpha]_D$ +72°; ν_{max} 3150, 1730, 1690 cm^{-1}. *Anal.* ($C_{25}H_{36}O_5$) C, O; H: calcd, 8.71; found, 9.12.

The **sodium salt (38)** was prepared as described for **20**; it decomposed at 200–220° without melting and showed $[\alpha]_D$ +67° (MeOH).

3α-Hydroxy-5β-19-norpregnan-20-one (41).—A solution of 1.5 g of 19-norprogesterone in 100 ml of 5% MeOH–KOH was hydrogenated at 2.11 kg/cm^2 for 1 hr (5% Pd–C). Filtration and evaporation gave a crude mixture of isomers which, upon repeated crystallizations from MeOH, yielded 760 mg of pure 5β-19-norpregnane-3,20-dione (**42**),[9] mp 134–136°, $[\alpha]_D$ +115°, ν_{max} 1710 cm^{-1}. A solution of 1 g of **42** in 40 ml anhydrous THF was treated with 2 g of lithium tri-*t*-butoxyaluminum hydride at 10° for 2 days, then added to 1:1 aqueous AcOH and extracted with CH_2Cl_2. The crude product (700 mg) was chromatographed on 30 g of neutral Al_2O_3. By elution with C_6H_6 and crystallizing from Et_2O–hexane, 300 mg of **41** was obtained; mp 105–106°; $[\alpha]_D$ +116°; ν_{max} 3280, 1710 cm^{-1}; nmr, 37 (18-H), 126 (21-H), 158 (hydroxyl), 200–230 (axial 3β-H) cps. *Anal.* ($C_{20}H_{32}O_2 \cdot H_2O$) C, H.

Sodium 3β-Hydroxy-5α-19-norpregnan-20-one Hemisuccinate

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(**50**).[41]—19-Norpregn-4-ene-3,20-dione (1 g) was dissolved in 4 ml of pyridine, 100 mg of $NaBH_4$ was added, and the mixture was shaken until the solids dissolved. After 7 hr at room temperature, dilute HCl was added, and the product was extracted with C_6H_6. The organic layer was washed twice with dilute HCl, then witn H_2O. Evaporation and crystallization from Me_2CO–hexane gave 300 mg of 3β-hydroxy-5α-19-norpregnan-20-one. This compound (200 mg) was converted into the acid hemisuccinate by treatment with succinic anhydride (2 g) in pyridine (40 ml) at 20° for 20 hr. Crystallization from Me_2CO–hexane gave the pure sample, mp 189–190°, $[\alpha]_D$ +12°. *Anal.* ($C_{24}H_{36}O_5$) C, H, O.

The **sodium salt** was prepared by titration of a solution (in MeOH) with 2 *N* aqueous NaOH and evaporation. Dissolution in H_2O, filtration, and evaporation to dryness gave hygroscopic crystals melting above 300°; $[\alpha]_D$ +1° (H_2O).

Sodium 21-Hydroxy-5β-19-norpregnane-3,20-dione Hemisuccinate (**52**).—21-Hydroxy-5β-19-norpregnane-3,20-dione acetate (**65b**) (0.7 g), 800 ml of MeOH, 1.0 g of $KHCO_3$, and 150 ml of H_2O were left at room temperature for 20 hr, neutralized with dilute HCl, concentrated to half volume at 30° *in vacuo*, and extracted with CH_2Cl_2. Evaporation of the solvent *in vacuo* at low temperature afforded an amorphous residue (0.6 g) which was directly esterified in 40 ml of pyridine by adding 1 g of succinic anhydride, heating the mixture on the steam bath for 5 min, and leaving it at room temperature overnight. Addition of cold dilute HCl and extraction with CH_2Cl_2 gave a residue which was partitioned between Et_2O–CH_2Cl_2 (4:1) and 5% aqueous $NaHCO_3$. The combined alkaline extracts were acidified with HCl, whereupon a solid acid hemisuccinate precipitated. It was extracted with CH_2Cl_2 and washed until neutral, and the solvent was removed at reduced pressure. The crude compound (0.8 g) was purified from CH_2Cl_2–Et_2O to provide 685 mg of **21-hydroxy-5β-19-norpregnane-3,20-dione acid hemisuccinate** (**65c**): mp 167–169°; $[\alpha]_D$ +111°; CD (c 0.002, dioxane), $[\theta]_{324}$ ±0, $[\theta]_{291}$ +2200, $[\theta]_{238}$ ±0; ν_{max} 3570–3120, 1755, 1710, 1160 cm^{-1}. *Anal.* ($C_{24}H_{34}O_6$) C, H.

The **sodium salt** (**52**) was prepared as above. It was obtained as an amorphous powder, which decomposed above 200° without melting and had $[\alpha]_D$ +103° (in H_2O) and a strong α-ketol (TPTZ) test.

21-Hydroxy-5β-19-norpregnane-3,20-dione Acetate (**65b**).—A solution of 970 mg of 19-nordeoxycorticosterone (**63a**) in 30 ml of EtOH was added to a prehydrogenated suspension of 0.6 g of 5% Pd–C in 200 ml of 5% EtOH–KOH, taking precautions for complete exclusion of air during this addition. The hydrogenation proceeded smoothly for 30 min, with uptake of 1 mole. The mixture was acidified with aqueous HCl before opening the apparatus. The material was isolated with CH_2Cl_2. An amorphous mixture of isomers was obtained, the 5β isomer being the predominant component as shown by tlc. It was directly acetylated at room temperature during 20 hr with 10 ml of Ac_2O and 5 ml of anhydrous pyridine. Addition of H_2O and extraction with CH_2Cl_2 gave a crystalline residue (1.05 g). Recrystallization (CH_2Cl_2–Et_2O) of the crude acetate mixture furnished 700 mg of **65b**: mp 184–185°; $[\alpha]_D$ +109°; ORD (c 0.0007, MeOH), $[\Phi]_{600}$ +480°, $[\Phi]_{302}$ +8890°, $[\Phi]_{295}$ +5770°; ν_{max} 1750, 1730, 1705, 1230 cm^{-1}. *Anal.* ($C_{22}H_{32}O_4$) C, H, O.

21-Hydroxy-5α-19-norpregnane-3,20-dione Acetate (**66b**).—The hydrogenation of 19-nor-11-deoxycorticosterone acetate (**63b**) (100 mg) in EtOH (80 ml) with 5% Pd–C (50 mg) was carried out with smooth absorption of 1 mole of H_2. The crude, hydrogenated material proved to be (silica gel) a mixture of two isomers, the less polar one (probably the 5α isomer) predominating. Recrystallization from CH_2Cl_2–Et_2O afforded 15 mg of pure **66b**: mp 163–165°; $[\alpha]_D$ +121°; ORD (*c* 0.0006, MeOH), $[\Phi]_{600}$ +430°, $[\Phi]_{307}$ +10,600°, $[\Phi]_{300}$ +9500°; ν_{max} 1755, 1730, 1715, 1240 cm^{-1}. *Anal.* ($C_{22}H_{32}O_4$) C, H.

(41) We are indebted to Dr. I. T. Harrison, Syntex Research, Palo Alto, Calif., for this experiment.

21-Hydroxy-5α-19-norpregnane-3,20-dione Acid Hemisuccinate (**66c**).—The hydrogenation of 100 mg of the free alcohol (**63a**) in 50 ml of EtOH with 50 mg of 5% Pd–C proceeded with H_2 uptake of 1 mole. The amorphous, crude, hydrogenated product (87 mg) was an isomeric mixture with the less polar component (5α isomer) predominating (silica gel). It was dissolved in pyridine and treated with 150 mg of succinic anhydride at room temperature for 24 hr. Ice-cold dilute HCl was then added, the product was extracted with CH_2Cl_2, and the CH_2Cl_2 solution was repeatedly extracted with 5% aqueous $NaHCO_3$. The combined alkaline extracts were acidified. The material which precipitated was extracted with CH_2Cl_2, and the solvent was removed *in vacuo*. The crude acid hemisuccinate (95 mg) crystallized from CH_2Cl_2–Et_2O to furnish the pure sample: mp 167–168°; $[\alpha]_D$ +112°; CD (*c* 0.002, dioxane), $[\theta]_{332}$ ±0, $[\theta]_{289}$ +15,100, $[\theta]_{270}$ ±0; ν_{max} 3450, 1750, 1725, 1720 cm^{-1}. *Anal.* ($C_{24}H_{34}O_6$) C, H, O.

19-Nor-11-deoxycorticosterone (**63a**).[42]—19-Norprogesterone (**44**)[29] (26 g) was iodinated in batches of 2 g by stirring at room temperature with 15 ml of THF (peroxide content equivalent to 10 mg of I_2/ml), 9 ml of MeOH, 3 g of CaO, and 3 g of I_2. Iodine disappeared in about 2 hr. The product was extracted with CH_2Cl_2 and washed with sodium thiosulfate and H_2O, and the solvent was removed at 30° *in vacuo*. The residues from 13 batches were dissolved in dry Me_2CO (2.5 l.), and heated to reflux with 50 g of anhydrous KOAc for 60 hr. Concentration to a small volume, addition of H_2O, and extraction with CH_2Cl_2 gave a residue which was hydrolyzed with 2 l. of MeOH, 25 g of $KHCO_3$, and 300 ml of H_2O for 20 hr at room temperature. Neutralization with dilute HCl, concentration under vacuum, and extraction with CH_2Cl_2 furnished a product (25 g), which was chromatographed on 300 g of silica gel. The fractions eluted with C_6H_6–EtOAc (95:5) yielded 13.5 g of starting **44** and 6.6 g of a crystalline compound: mp 233–237°; $[\alpha]_D$ +148° (pyridine); λ_{max} 280 mμ (log ε 3.40); ν_{max} 3250, 1690, 1625, 1590 cm^{-1}. This compound was shown to be 17β-acetylestra-1,3,5(10)-trien-3-ol (**64**)[43] by mixture melting point and ir comparison with an authentic sample. The more polar, amorphous fractions from the chromatogram gave a strong α-ketol test. They were combined (4.8 g) and rechromatographed on 200 g of silica. Elution with C_6H_6–EtOAc gave 1.32 g of crystalline and 2.82 g of amorphous **63a**. The crystalline compound showed mp 130–132°; $[\alpha]_D$ +133°; λ_{max} 240 mμ (log ε 4.23); ν_{max} 3390, 1725, 1660, 1615 cm^{-1}, in agreement with the published data.[42]

3α-Tetrahydropyranoxy-5α-androstan-17-one (**54**).—A solution of 1 g of **5**, dihydropyran (0.5 ml), and 20 mg of *p*-toluenesulfonic acid hydrate in 50 ml of dry C_6H_6 was stirred for 5 min. It was then poured into 5% aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The product was purified by chromatography on alumina, followed by crystallization from MeOH of the fractions (0.9 g) eluted with C_6H_6. The pure compound (**54**) presented mp 115–116°; $[\alpha]_D$ +88°; ν_{max} 1710 cm^{-1}; nmr, 37 (18-H), 55 (19-H), 126 (21-H), 200–245 (–CH_2O– + 3β-H), ~284 (–O-CHO–) cps. *Anal.* ($C_{26}H_{42}O_3$) C, H, O.

17α-Ethinyl-5β-androstane-3α,17β-diol (**56**).—Purified acetylene was bubbled through 200 ml of dry THF for 2 hr. Without stopping the acetylene stream, 25 ml of 3 *N* ethereal MeMgBr was slowly added and the acetylene stream continued for 5 hr. A solution of 2 g of 5α-hydroxy-5β-androstan-17-one (**62**) in a few milliliters of THF was then added, and the mixture was allowed to reflux for 2 hr. Addition to ice-cold, saturated, aqueous NH_4Cl and extraction with CH_2Cl_2 gave 2.15 g of a crude product which was purified by chromatography on alumina. Crystallization from Et_2O–hexane furnished 1.8 g of **56**, mp 171–172°; $[\alpha]_D$ −37°; ν_{max} 3240, 2080 cm^{-1}. *Anal.* ($C_{21}H_{32}O_2$) C, H.

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