tracts were evaporated to dryness *in vacuo* and the solid residue was recrystallized from THF–petroleum ether to give 1.1 g (54%) of a solid: mp 167–168° dec; ir, 3.05 (s) with shoulders at 3.0 and 3.15 (assigned to NHOH), 5.75 (sydnone CO), and 6.2 μ (aromatic). *Anal.* Calcd for $C_8H_7N_3O_3$ (IIf): N, 21.75. Found: N, 21.41.

3-[*p*-(N,O-Diacetylhydroxylamino)phenyl]sydnone (IIg).—A mixture of 1 g of IIf and 15 ml of Ac_2O was heated at 100° for 3 hr. The reaction mixture was evaporated to dryness under reduced pressure and the residual solid was recrystallized from acetone (Darco)–petroleum ether to give 0.82 g (57%) of a solid: mp 171–173°; ir, 3.2 (sydnone C–H), 5.55 (sydnone CO), 5.73 (O-Ac superimposed by second sydnone CO peak), and 5.9 μ (N-Ac). *Anal.* Calcd for $C_{12}H_{11}N_3O_5$ (IIg): C, 51.98; H, 3.97; N, 15.16. Found: C, 52.15; H, 4.38; N, 15.25.

Reduction of 3-[*p*-(Hydroxylamino)phenyl]sydnone (IIf).—A mixture of 0.5 g of IIf and 2 g of Fe powder was added to 50 ml of 2% AcOH at 95° and refluxed for 12 min. The reaction mixture was worked up as described for IIb, and 0.32 g (70%) of a solid, mp 195–196° dec, was isolated. It was identified as IIb by mixture melting point and ir analysis.

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11-Alkylated Steroids. VI. 11β-Hydroxy-11α-methyl-5β-pregnan-20-one

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As part of a continuing study of the chemical and biological properties of 11-alkylated steroids,[1] we prepared a representative 3-deoxypregnane of this series, namely, 11β-hydroxy-11α-methyl-5β-pregnan-20-one. Two convergent syntheses, the one originating with an 11-oxo steroid and the other with an 11β-hydroxy-11α-methyl steroid, established the structure of the product.

3α-Hydroxy-5β-pregnane-11,20-dione[2] was converted to the methanesulfonate, which upon treatment with boiling 2,4,6-trimethylpyridine gave a low-melting solid, difficult to purify, presumed[3] to be largely 5β-pregn-2-ene-11,20-dione. Ketalization of the crude material with ethylene glycol afforded the 20-monoketal, which was treated with ethereal methyllithium. The 20,20-ethylenedioxy-11α-methyl-5β-pregn-2-en-11β-ol thus obtained was converted by catalytic hydrogenation and hydrolysis to the desired 11β-hydroxy-11α-methyl-5β-pregnan-20-one.

A more efficient synthesis was that originating with 11β-hydroxy-11α-methyl-5β-pregnane-3,20-dione,[4] which was converted in good yield to the 3,3-ethylene mercaptal by the use of ethanedithiol and boron trifluoride etherate in glacial acetic acid.[5,6] Hydrogenolysis of this thioketal with Raney nickel[7] in ethanol afforded 11β-hydroxy-11α-methyl-5β-pregnan-20-one in good yield.

Biological Information.—The sedative or mild tranquilizing activity of 11β-hydroxy-11α-methyl-5β-pregnane-3,20-dione[4] in humans was about equivalent to that of an equal dose of meprobamate.[8] The compound was selected for clinical trial on the basis of its activity in mice in the motor activity assay of Dews.[9] In contrast, 11β-hydroxy-11α-methyl-5β-pregnan-20-one was essentially inactive in the Dews assay.

Experimental Section[10]

3α-Hydroxy-5β-pregnane-11,20-dione Methanesulfonate.—A mixture of 25 g of 3α-hydroxy-5β-pregnane-11,20-dione, 100 ml of pyridine, and 16 ml of methanesulfonyl chloride was stirred, with ice-bath cooling, for 3 hr and then poured into ice–water. The crude product was recovered by CH_2Cl_2 extraction and chromatographed over Florisil. Elution with Me_2CO gave 22.67 g of white crystalline product, mp 123–139°, a sample of which was recrystallized several times from Me_2CO–petroleum ether to mp 153–155°, $[\alpha]_D$ +120° (*c* 1, $CHCl_3$). *Anal.* ($C_{22}H_{34}O_5S$) C, H, S.

5β-Pregn-2-ene-11,20-dione.—3α-Hydroxy-5β-pregnane-11,20-dione methanesulfonate (22.1 g) was refluxed for 3 hr with 120 ml of 2,4,6-trimethylpyridine and then allowed to stand at room temperature overnight. The mixture was poured into 500 ml of ice-cold 3 *N* H_2SO_4, the product was taken up in CH_2Cl_2, and the CH_2Cl_2 extracts were washed with 1 *N* H_2SO_4 and H_2O. Chromatography on Florisil gave 16.1 g of crude product, mp 76–107°, eluted with 5% Me_2CO–petroleum ether. Recrystallization from petroluem ether gave a low yield of an analytical sample, mp 108–111°, $[\alpha]_D$ +84° (*c* 1, Me_2CO). *Anal.* ($C_{21}H_{30}O_2$) C, H, double bond.

20,20-Ethylenedioxy-5β-pregn-2-en-11-one.—Crude 5β-pregn-2-ene-11,20-dione (mp 76–107°, 13.4 g) was refluxed overnight with 40 ml of ethylene glycol, 0.5 g of *p*-toluenesulfonic acid monohydrate, and 200 ml of C_6H_6 through a Dean–Stark trap. After cooling, the mixture was washed with aqueous 4% $NaHCO_3$, dried (Na_2SO_4), and evaporated to an orange oil. Chromatography over Florisil afforded 12.0 g of crude product in the 5% Me_2CO–petroleum ether eluate fractions. Only 2.73 g of product was recovered from a petroleum ether recrystallization. Subsequent recrystallization from acetone–petroleum ether containing a drop of pyridine afforded an analytical sample, mp 143–148°, $[\alpha]_D$ +53° (*c* 1, Me_2CO). *Anal.* ($C_{23}H_{34}O_3$) C, H.

11β-Hydroxy-11α-methyl-5β-pregnan-20-one.—Crude 20,20-ethylenedioxy-5β-pregn-2-en-11-one (8.7 g) in 100 ml of C_6H_6 was treated with 200 ml of 0.6 *M* ethereal MeLi at room temperature overnight. Washing with H_2O, followed by evaporation of the organic solution, gave an oil that still showed ir C=O absorption. It was re-treated twice with MeLi to give 9.9 g of partly crystalline 20,20-ethylenedioxy-11α-methyl-5β-pregn-2-en-11β-ol that was not purified, since the recrystallization experience with the earlier unsaturated compounds in this series was unsatisfactory.

Hydrogenation of 6.15 g of the crude ketal that contained some residual 11-ketone was carried out in 250 ml of MeOH, using 0.5 g of PtO_2 at 2200 torr for several hours. The catalyst was filtered off and the filtrate was treated with 25 ml of 1 *N* HCl at room temperature overnight. After removal of the MeOH, the products were taken up in CH_2Cl_2, washed with H_2O, and chromatographed on Florisil (elution with 5% Me_2CO–petroleum ether) to give 1.36 g of 11β-hydroxy-11α-methyl-5β-pregnan-20-one, mp 119–122°, after recrystallization from petroleum ether.

11β-Hydroxy-11α-methyl-5β-pregnane-3,20-dione 3-Ethylene Mercaptal.—11β-Hydroxy-11α-methyl-5β-pregnane-3,20-dione

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(10) Melting points were determined on a Fisher-Johns block and not further corrected. Ir spectra were consistent with the structures stated. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.3% of the theoretical values. Petroleum ether refers to a product, bp 60–70°, of the Skelly Corp. called Skellysolve B. Florisil is a synthetic magnesium silicate product of the Floridin Co.

(10.0 g) was dissolved in a mixture of 60 ml of AcOH and 10 ml of ethanedithiol, 1 ml of BF_3-etherate was added, and the solution was allowed to stand at room temperature for 8 min. It was poured onto a mixture of ice and H_2O giving an oily mass which solidified after about 1 hr. The solid was recovered by filtration and washed thoroughly (H_2O, $NaHCO_3$) and the filter cake was pressed dry overnight by means of a rubber dam. The crude product (13.43 g) was dissolved in hot acetone, treated with Norit, and crystallized from Me_2CO-petroleum ether to yield 8.56 g of material, mp 170–172°. Recrystallization from Me_2CO–H_2O gave an analytical sample, mp 173.2–175.0°. *Anal.* ($C_{21}H_{38}O_2S_2$) C, H.

11β-Hydroxy-11α-methyl-5β-pregnan-20-one.—11β-Hydroxy-11α-methyl-5β-pregnane-3,20-dione 3-ethylene mercaptal suspended in 400 ml of 75% EtOH was heated at reflux overnight with about 40 g of Raney Ni. After cooling, the nickel was filtered and the filtrate was evaporated to about 50 ml, whereupon 2.34 g of material crystallized. Recrystallization from petroleum ether afforded an analytical sample, mp 121.2–123.0°. *Anal.* ($C_{22}H_{36}O_2$) C, H.

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New Compounds

Some Derivatives of 1-Aminoadamantane

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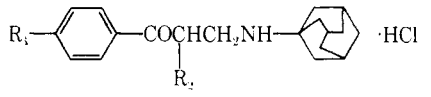
Recent interest in the pharmacology of 1-aminoadamantane and especially its application as an antiviral agent[1-3] prompted us to prepare some 1-(3,3-diarylpropylamino)adamantanes (Tables I–III) for testing for antiviral and also for CNS activity.

TABLE I

1-(3-ARYL-3-OXOPROPYLAMINO)ADAMANTANE HYDROCHLORIDES

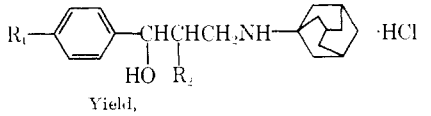


R_1	R_2	Yield, %	Mp, °C	Solvent[a]	Formula[b]
H	H	62.5	215	A	$C_{19}H_{26}ClNO$
H	CH_3	52.4	188–190	B	$C_{20}H_{28}ClNO$
Cl	H	56.5	225–226	C	$C_{19}H_{25}Cl_2NO$
NO_2	H	82.4	233–235	B	$C_{19}H_{25}ClN_2O_3$
CH_3O	H	41.4	205–207	B	$C_{20}H_{28}ClNO_2$
CH_3	H	66.0	213	C	$C_{20}H_{28}ClNO$

[a] Solvents: A, MeOH–Et_2O; B, MeOH–EtOAc; C, $CHCl_3$–EtOAc. [b] All compounds were analyzed for C, H, Cl, N.

TABLE II

1-(3-ARYL-3-HYDROXYPROPYLAMINO)ADAMANTANE HYDROCHLORIDES

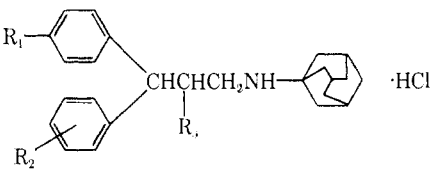


R_1	R_2	Yield, %	Mp, °C	Solvent[a]	Formula[b]
H	H	90.0	299–301	A	$C_{19}H_{28}ClNO$
H	CH_3	93.5	306–307	B	$C_{20}H_{30}ClNO$
Cl	H	87.5	316–318	C	$C_{19}H_{27}Cl_2NO$
NO_2	H	86.6	309–310	C	$C_{19}H_{27}ClN_2O_3$
CH_3O	H	72.0	86–87	D	$C_{20}H_{29}NO_2$[c]

[a] Solvents: A, MeOH–Et_2O; B, MeOH; C, MeOH–EtOAc; D, aqueous MeOH. [b] All compounds were analyzed for C, H, Cl, N except where noted otherwise. [c] This product was isolated and analyzed as a free base (for C, H, N only).

TABLE III

1-(3,3-DIARYLPROPYLAMINO)ADAMANTANE HYDROCHLORIDES



R_1	R_2	R_3	Yield, %	Mp, °C[a]	Formula[b]
H	H	H	76.2	302–304	$C_{25}H_{32}ClN$
H	H	CH_3	51.0	272	$C_{26}H_{34}ClN$
Cl	H	H	67.7	304–306	$C_{25}H_{31}Cl_2N$
Cl	Cl	H	63.0	322	$C_{25}H_{30}Cl_3N$
CH_3O	CH_3O	H	23.0	305	$C_{27}H_{36}ClNO_2$
CH_3	CH_3	H	73.9	315	$C_{27}H_{36}ClN$
H	OH	H	65.0	319–320	$C_{25}H_{32}ClNO$

[a] All products were recrystallized from MeOH–EtOAc. [b] All compounds were analyzed for C, H, Cl, N.

Experimental Section[4]

General Procedures. Mannich Condensation.—A mixture of aminoadamantane hydrochloride (prepared from adamantane[5] by the method of Stetter, *et al.*[6]) (1.0 mol), the appropriate alkyl aryl ketone (1.1 mol), 37% aqueous HCHO (1.5 mol), and concentrated HCl (1 ml) was heated under reflux for 4 hr. After standing at room temperature for 3 more hr, the reaction mixture was diluted (Me_2CO–Et_2O) and the crystalline reaction product was filtered off and purified by crystallization.

Reduction.—The hydrochloride of the Mannich ketone (1.0 mol) was dissolved in six times its weight of 80% aqueous MeOH, some aqueous NaOH was then added in order to liberate the free base, then $NaBH_4$ (0.5 mol) and the reaction mixture was allowed to stand at room temperature for 3 hr. After dilution (H_2O) the reaction product was extracted into $CHCl_3$, dried (Na_2SO_4), and filtered and dry HCl was introduced into the

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