4,4',6,6'-Tetrachloro-2,2'-diphenol. *o,o'*-Biphenol (50 g, 0.269 mole), SO_2Cl_2 (302 g, 2.24 mole), and 200 ml of C_6H_6 were refluxed for 16 hr. The C_6H_6 was distd off. Recrystn from C_6H_6–C_6H_{14} gave 75.0 g (86%) of 4,4',6,6'-tetrachloro-2,2'-diphenol, mp 166–172°, lit.[21] mp 178°.

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Analgetic 1-Oxidized-2,6-methano-3-benzazocines

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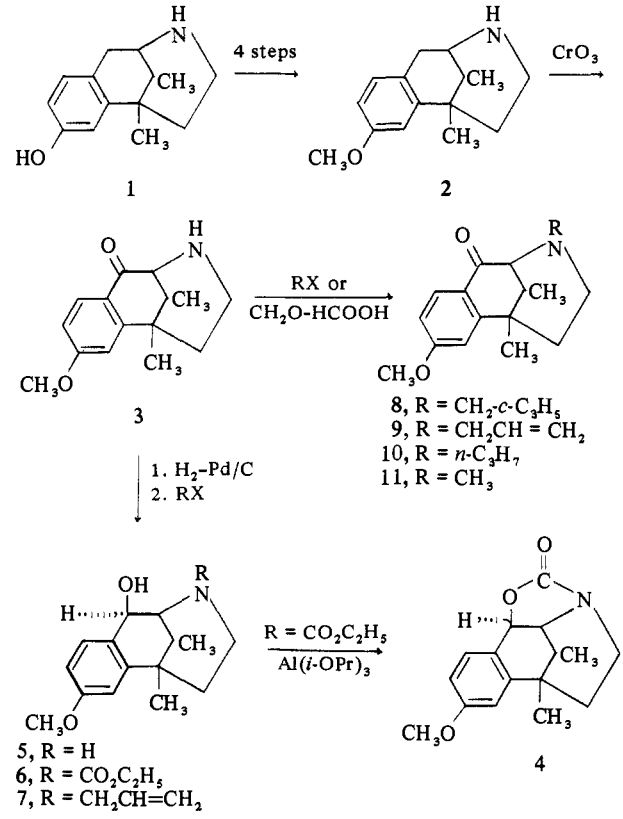
Direct introduction of oxygen on the benzylic carbon of 8-methoxy-2,6-methano-3-benzazocines is described. *N*-Alkyl derivatives have been prepared and one compound, 3-cyclopropylmethyl-3,4,5,6-tetrahydro-8-hydroxy-6(e),11(a)-dimethyl-2,6-methano-3-benzazocin-1(2*H*)-one, has been found to have a noteworthy profile with respect to narcotic antagonist and agonist activities.

In the course of our work on the 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-8-ols, it became desirable to modify the parent ring system by introduction of an oxygen function at position one. A search of the literature revealed that some examples of benzylic position oxidized morphine-like structures existed.[1] None of the authors reported any biological data on these compounds.† Since it is well documented that introduction of a hydroxyl group para to the phenethylamine moiety in morphine-like structures generally enhances analgetic activity, and, further, since we could find only one example[1b] of a related compound bearing both a phenolic hydroxyl and an oxidized benzylic functionality, we prepared a series of such derivatives of 1,2,3,4,5,6-hexahydro-6(e),11(a)‡-dimethyl-2,6-methano-3-benzazocine for evaluation as potential analgetic agents.

Chemistry. The introduction of oxygen at the benzylic position of the compounds referred to above had been achieved in three ways: (1) intramolecular acylation;[1a] (2) photooxidation;[1c] (3) CrO_3 oxidation.[1b] Of these, the first was rejected because it was felt that the synthesis would be too extensive, and the second was rejected because of probable poor yield. This left the third choice, and a suitable substrate for the oxidation was determined in part by literature precedent and in part by our synthetic objectives. Rapoport and Masamune[1b] reported that whereas dihydrodesoxycodeine could be oxidized by CrO_3 in aqueous sulfuric acid, heroin could not be, and since we wished to prepare a series of *N*-alkyl derivatives, the logical starting material was 1,2,3,4,5,6-hexahydro-8-methoxy-6(e),-

Scheme I



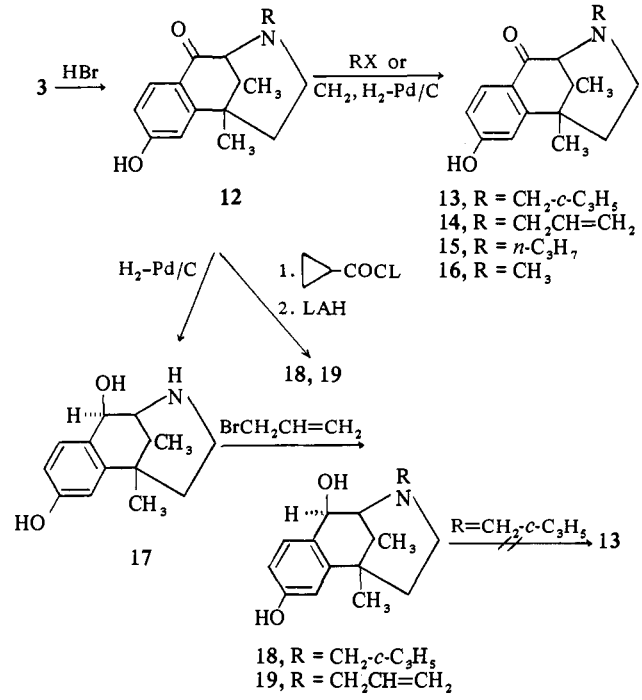
†A recent report by Ziering, *et al.*,[2] which prompted us to report our work, gives data on one such compound.

‡a stands for axial and e for equatorial. Configurations are with respect to the hydroaromatic ring. This nomenclature was adopted in this laboratory when the cis-trans nomenclature became unwieldy for some 2,6-methano-3-benzazocines.

11(a)-dimethyl-2,6-methano-3-benzazocine, **2** (Scheme I). This material could be conveniently prepared in quantity by diacetylating the norbase **1**,[3] removing the *O*-acetyl group with NaOH, methylating with $(CH_3)_2SO_4$, and removing the *N*-acetyl group with HCl. No purification of intermediates is necessary and the overall yield is 75%. It was found that **2** could be oxidized to **3** in a simple procedure that consistently gives 80–90% yields. The structure of **3** was established by ir and uv spectra, and elemental analysis. Alkylation of **3** with an alkyl halide (*vide infra*) or with CH_2O-HCOOH produced **8–11**. Reduction of **3** with H_2 over palladium gave **5**. The stereochemistry of the benzylic position in **5** was established by N-acylation with $ClCO_2C_2H_5$ to give **6** followed by $Al(i\text{-}OPr)_3$-catalyzed intramolecular transesterification[4] to give **4**. Alkylation of **5** gave **7**.

Compound **3** could be demethylated smoothly to **12** (Scheme II). Compound **12** was alkylated by the usual procedures to give **13–16**. In this connection it is interesting to note that the usual procedure for introducing an *N*-cyclopropylmethyl group[5] (acylation by cyclopropanecarboxylic acid chloride followed by LAH reduction of the resulting amide) is inapplicable to **12** since the product, quite predictably, is **18**. Oxidation of this material to **13** could not be achieved by Collins' reagent,[6] DMSO-acetic anhydride,[7] or MnO_2.[1b] Therefore, in order to prepare **13**, a direct alkylation procedure was required. However, it is known that cyclopropylmethyl bromide prepared by the procedure of Van Braun, *et al.*,[8] cannot be expected to yield homogenous material.[9] We found that the bromide prepared by the procedure of Meek and Rowe[10] gave the desired **13** in excellent yield and in easily purified form. Use of the corresponding chloride (obtained as an 85% pure commercial sample) was unsatisfactory.

Scheme II



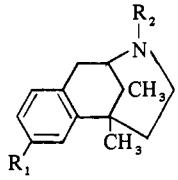
Compound **12** was reduced catalytically to **17** which in turn was alkylated to give **19**. The stereochemistry of the benzylic position in compounds **17–19** is that expected by analogy with the corresponding reduction of **3**, and was confirmed by the values of the C-1–C-2 coupling constants.

Pharmacology. Compounds were assayed for narcotic antagonist activity *vs.* meperidine by the method of Harris and Pierson,[11] and for agonist activity in the acetylcholine-induced writhing procedure of Collier, *et al.*[12] The data are shown in Table I. Data for some corresponding unoxidized compounds are included for comparison. The activity of most of the compounds tested is not particularly remarkable. As expected the ethers **7**, **8**, and **10** are less active in both tests than their phenolic counterparts **19**, **13**, and **15**, respectively. Actually, the inactivity of **10** is somewhat surprising in view of the activity of **15**, and the unoxidized counterpart. Of greater interest are compounds **13**, **14**, and **15**. Note that in these three compounds introduction of a carbonyl oxygen has greatly reduced narcotic antagonist activity, while agonist activity remains essentially unchanged. Compound **13** is particularly noteworthy in this regard, possessing an antagonist activity similar to pentazocine and an agonist activity similar to cyclazocine.

Experimental Section

All melting points are uncorrected. Where analyses are indicated only by the symbols of the elements, analytical results obtained for

Table I. Narcotic Antagonist and Agonist Activities of Some Oxidized 6(e),11(a)-Dimethyl-2,6-methano-3-benzazocines



Compound	Q	R_1	R_2	AD_{50},[a] mg/kg	ED_{50},[b] mg/kg
7	CHOH	CH_3O	$CH_2CH{=}CH_2$	37	117
8	>C=O	CH_3O	CH_2-*c*-C_3H_5	48	14
10	>C=O	CH_3O	*n*-C_3H_7	Inact[c]	Inact[d]
13	>C=O	HO	CH_2-*c*-C_3H_5	7.2	0.16
14	>C=O	HO	$CH_2CH{=}CH_2$	1.6	1.5
15	>C=O	HO	*n*-C_3H_7	1.8	3.2
16	>C=O	HO	CH_3	29	23
18	CHOH	HO	CH_2-*c*-C_3H_5	11	10
19	CHOH	HO	$CH_2CH{=}CH_2$	1	4.8
Metazocine	CH_2	HO	CH_3		0.54
	CH_2	HO	*n*-C_3H_7	0.02	6.4
Cyclazocine	CH_2	HO	CH_2-*c*-C_3H_5	0.02	0.15
	CH_2	HO	$CH_2CH{=}CH_2$	0.05	7.1
Pentazocine	CH_2	HO	$CH_2CH{=}C(CH_3)_2$	3.9	2.2

[a] Narcotic antagonism *vs.* meperidine in the rat, subcutaneous administration. [b] Agonist activity in the acetylcholine-induced writhing screen in the mouse, subcutaneous administration. [c] At a screening dose of 80 mg/kg. [d] At a screening dose of 100 mg/kg.

Table II. Compounds Obtained by Alkylation of 3, 5, 12, and 17

Compound	Mp, °C	Recrystallization solvent	Formula	Analyses
7·HCl	239 dec	*i*-PrOH-Et_2O	$C_{18}H_{25}NO_2$·HCl	C, H, N
8·HCl	192-193	EtOH-Et_2O	$C_{19}H_{25}NO_2$·HCl	C, H, N
9·HCl	205-207	EtOAc	$C_{18}H_{23}NO_2$·HCl	C, H, N
10·HCl	223-225	EtOH-Et_2O	$C_{18}H_{25}NO_2$·HCl	C, H, N
13	249-252	MeOH	$C_{18}H_{23}NO_2$	C, H, N
13·HCl	272-276	EtOH	$C_{18}H_{23}NO_2$·HCl	C, H, N
13·CH_3SO_3H	257-258	MeOH-Et_2O	$C_{18}H_{23}NO_2$·CH_3SO_3H	C, H, N
14·HCl	252 dec	*i*-PrOH	$C_{17}H_{21}NO_2$·HCl	C, H, N
15	219-222	EtOH	$C_{17}H_{23}NO_2$	C, H, N
19	148-150	Hexane–acetone	$C_{17}H_{23}NO_2$	C, H, N

these elements were within ±0.4% of the theoretical values.

1,2,3,4,5,6-Hexahydro-8-methoxy-6(e),11(a)-dimethyl-2,6-methano-3-benzazocine (2). One mole (217 g) of 1,2,3,4,5,6-hexahydro-6(e),11(a)-dimethyl-2,6-methano-3-benzazocine-8-ol‡ was heated on a steam bath for 1.5 hr with 700 ml of Ac_2O and concentrated *in vacuo*. After addition of 100 ml of H_2O, the solution was reconcentrated. This residue was dissolved in 600 ml of EtOH, and a solution of 44 g of NaOH in 100 ml of H_2O was added. This was warmed on a steam bath for 2 hr and allowed to stand overnight. Concentration *in vacuo* left a residue § which was dissolved in a solution of 44 g of NaOH in 600 ml of H_2O and cooled. Dimethyl sulfate (120 ml) was added at a moderate rate, and the mixture was stirred for 1.5 hr. The product was extracted with Et_2O, and the organic layer washed twice with 100 ml of 1 *N* NaOH and once with H_2O. After drying and removal of the Et_2O, the resulting syrup# was stirred and refluxed for 24 hr with 1 l. of H_2O and 500 ml of concentrated HCl. The cooled solution was extracted twice with Et_2O, and the aqueous layer was concentrated *in vacuo*. The residue was dissolved in H_2O, made strongly basic with 35% NaOH, and extracted several times with Et_2O. The combined extracts were washed with H_2O, dried, filtered, and treated with 200 ml of 5 *N* HCl in EtOH. After cooling, the product was filtered and washed with Et_2O, mp 206-209°, yield 200 g, 75% overall. A sample recrystallized from EtOH melted at 208-210°.** *Anal.* ($C_{15}H_{21}NO$·HCl) C, H, N.

3,4,5,6-Tetrahydro-8-methoxy-6(e),11(a)-dimethyl-2,6-methano-3-benzazocine-1(2*H*)-one (3). Concentrated H_2SO_4 (180 ml) was added to ice and more ice was added until the total volume was 2 l. A solution of 53.5 g (0.2 moles) of **2** in about half of the above acid was stirred. A solution of 26.4 g of CrO_3 in the other half of the acid was added all at once to the stirred solution of **2**. The resulting mixture, which contained a gummy precipitate, was stirred and heated on a steam bath for 2 hr. The now homogeneous reaction mixture was cooled in ice while 500 ml of concentrated NH_4OH was added at a fairly rapid rate. When the mixture had returned to room temperature it was extracted with three 500-ml portions of Et_2O. The partially emulsified extracts were filtered through filter-cel. The small amount of H_2O in the filtrate was separated. The Et_2O layer was washed with H_2O, dried, filtered, and evaporated to give 42 g (86%) of a syrup. This material is of adequate purity (tlc indicated one trace impurity) for subsequent transformations. A sample was purified as the hydrochloride (recrystallized from EtOH), mp 268-270°, ir (KBr) 1670 cm^{-1}, uv (EtOH) ϵ_{297} 16,400, ϵ_{231} 10,500. *Anal.* ($C_{15}H_{19}NO_2$·HCl) C, H, N.

1,2,3,4,5,6-Hexahydro-8-methoxy-6(e),11(a)-dimethyl-2,6-methano-3-benzazocin-1-ol (5). A solution of 27.3 g of **3** in 800 ml of AcOH was reduced in the presence of 10% Pd on charcoal at room temperature. The catalyst and solvent were removed, and the glassy residue was dissolved in acetone. Cooling and scratching yielded 19.5 g, mp 180-182°. Dilution of the mother liquors with Et_2O gave an additional 8.0 g, mp 174-176°. A sample was recrystallized from acetone, mp 173-174°, nmr ($CDCl_3$) δ 5.05 (d, 1, *J* = 6 Hz, >CHOH). *Anal.* ($C_{15}H_{21}NO_2 \cdot C_2H_4O_2$) C, H, N.

§ This residue (1a) sometimes crystallized. Recrystallization of a sample from EtOAc afforded white crystals, mp 192-194°. *Anal.* ($C_{16}H_{21}NO_2$) C, H, N.

#This residue (1b) also crystallized at times. Recrystallization from hexane gave crystals, mp 77-84°. *Anal.* ($C_{17}H_{23}NO_2$) C, H, N. The same compound was prepared, presumably as a syrup, by a different route by May.[13]

**The crude base has been prepared by a different method by May and Eddy.[14]

A sample was converted to the hydrochloride, mp 219-221° (EtOH-Et_2O). *Anal.* ($C_{15}H_{21}NO_2$·HCl) C, H, N.

Ethyl 1,2,3,4,5,6-Hexahydro-1-hydroxy-8-methoxy-6(e),11(a)-dimethyl-2,6-methano-3-benzazocine-3-carboxylate (6). Reaction of 10.5 g of **5** with 4.0 g of ethyl chloroformate in 25 ml of $CHCl_3$ and 3.0 g of NaOH in 25 ml of H_2O, followed by work-up of the $CHCl_3$ layer and crystallization of the residue from hexane, gave **6**. Recrystallization from hexane gave material with mp 131-132°. *Anal.* ($C_{18}H_{25}NO_4$) C, N; H: calcd, 7.89; found, 8.49.

3a,4,5,9b-Tetrahydro-7-methoxy-4(a),5(e)-dimethyl-3,5-ethanonaphth[2,1-*d*]oxazol-2(3*H*)-one (4). A solution of 5.8 g of **6** in toluene with 0.5 g of Al(*i*-OPr)$_3$ added was slowly distilled until the vapor temperature reached 110°. The solution was washed with dil HCl and aqueous $NaHCO_3$. The solvent was removed, and the residue was crystallized from EtOH, mp 135-136°. *Anal.* ($C_{16}H_{19}NO_3$) C, H, N.

3,4,5,6-Tetrahydro-8-methoxy-3,6(e),11(a)-trimethyl-2,6-methano-3-benzazocin-1(2*H*)-one (11). Crude **3** (5.9 g), 3 ml of 35% aqueous CH_2O, and 3 ml of HCOOH were warmed on a steam bath for 1 hr. Water, Et_2O, and concentrated NH_4OH were added, and the soln was shaken. The Et_2O layer was washed with water, dried, filtered, and concentrated. The residue was crystallized from EtOH, mp 109-112°. *Anal.* ($C_{16}H_{21}NO_2$) C, H, N.

3,4,5,6-Tetrahydro-8-hydroxy-6(e),11(a)-dimethyl-2,6-methano-3-benzazocin-1(2*H*)-one (12). A mixture of 24.6 g of **3** and 125 ml of 48% HBr was refluxed for 5 hr, cooled, and made basic with concentrated NH_4OH. The crystalline product was filtered and washed with H_2O. Recrystallization from MeOH gave mp 280-282°. *Anal.* ($C_{14}H_{17}NO_2$) C, H, N.

3,4,5,6-Tetrahydro-8-hydroxy-3,6(e),11(a)-trimethyl-2,6-methano-3-benzazocin-1(2*H*)-one (16). A mixture of 11.5 g of **12**, 4 ml of 35% aqueous CH_2O, and EtOH to 200-ml total volume was reduced in the presence of 10% palladium on charcoal at room temperature. Removal of the catalyst and solvent left a residue which could be crystallized from EtOH. Recrystallization gave material melting at 224-228°. *Anal.* ($C_{15}H_{19}NO_2$) C, H, N.

1,2,3,4,5,6-Hexahydro-6(e),11(a)-dimethyl-2,6-methano-3-benzazocin-1(e),8-diol (17). A solution of 2.3 g of **12** in 100 ml of AcOH was reduced in the presence of 10% palladium on charcoal at 45°. Removal of the catalyst and solvent left a glassy residue which was taken up in about 15 ml of 1:1 DMF-H_2O. Addition of NH_4OH and cooling precipitated the product. Recrystallization from DMF gave material with mp 255-256°, nmr (CF_3COOH) δ 5.43 (d, 1, *J* = 5.5 Hz, >CHOH). *Anal.* ($C_{14}H_{19}NO_2$) C, H, N.

3-Cyclopropylmethyl-1,2,3,4,5,6-hexahydro-6(e),11(a)-dimethyl-2,6-methano-3-benzazocin-1(e),8-diol (18). A solution of 9.25 g of **12** in 130 ml of C_5H_5N was treated with 8.4 g of cyclopropanecarboxylic acid chloride, stirred 4 hr, and left to stand overnight. The solvent was removed, and the residue partitioned between H_2O and Et_2O. The Et_2O layer was washed with dil HCl and aqueous $NaHCO_3$. After drying, filtration, and solvent removal, the residue was reduced with 4.5 g of LAH in 150 ml of refluxing THF for 4 hr. Addition of 9 ml of H_2O followed by filtration and extraction of the residue with boiling THF and removal of solvent gave a residue which was converted to the hydrochloride and recrystallized from *i*-PrOH-Et_2O, mp 230° dec, nmr (D_2O) δ 5.67 (d, 1, *J* = 6 Hz, >CHOH). *Anal.* ($C_{18}H_{25}NO_2$·HCl) C, H, N.

General Procedure for Alkylation of 3, 5, 12, and 17 to Give 7-10, 13-15, and 19. For each 0.01 mole of starting norbase, 0.01 mole of $NaHCO_3$, 25 ml of DMF, and a 10% excess of alkyl halide (allyl bromide, cyclopropylmethyl bromide, *n*-propyl iodide) is used. The reaction mixture is refluxed for 2-4 hr and the DMF removed. Partitioning of the residue between H_2O and $CHCl_3$ followed by filtration if product crystallizes at this point or by drying and evapora-

tion of the $CHCl_3$ gives the product. The requisite physical data for the compounds prepared in this way are shown in Table II.

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17-Aminoacylamido Steroid Antidepressants

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Nine new examples of 17β-aminoacylamido steroids were synthesized in order to extend the exploratory study reported earlier. Four of these compounds corresponding to the L-alaninamido, β-alaninamido, L-threoninamido, and dimethylaminoacetamido derivatives showed antidepressant activity in screening tests in mice.

Since an initial study[1] showed that certain aminoacylamido steroids have a bioactivity measurable as antidepressant effect in mice, further synthetic work was done to help define the structural features required for the activity. This paper extends the study to eight new 17β-aminoacylamido-5-androsten-3β-ols and one example of a 4-androsten-3-one.

In order to learn the effect of *N*-alkyl substituents, four different *N*-methyl derivatives of 17β-glycinamido-4-androsten-3β-ol were made using three synthetic routes. In one approach, condensation of chloroacetic anhydride with 17β-amino-5-androsten-3β-ol (**1**) under mild conditions gave 17β-chloroacetamido-5-androsten-3β-ol (**2**), which upon aminolysis with methylamine, dimethylamine, or trimethylamine led to the desired products **3a**, **4**, or **5**, respectively.

In another approach, the intermediate 17β-*N*-benzyloxycarbonyl(Z)sarcosinamido-5-androsten-3β-ol (**3b**) was obtained by condensation of Z-sarcosine pentachlorophenyl ester with the steroid amine **1**, and the amine-protecting group was subsequently cleaved with sodium in liquid ammonia[2] to obtain **3a**.

A different isomer was obtained by first methylating the amine **1** and coupling the secondary amine with phthalylglycine *p*-nitrophenyl ester (NPE) to give the 17β-*N*-phthalylglycinamido-5-androsten-3β-ol (**6a**). Removal of the protecting group of **6a** was accomplished with hydrazine in DMF to obtain the desired 17β-(glycyl-*N*-methylamido)-5-androsten-3β-ol (**6b**).

In order to vary the functional group in the steroid nucleus, 17β-methylamino-4-androsten-3-one was prepared and coupled with an N-protected glycine active ester.[3] In this case the presence of the conjugated ketone precluded the use of the protecting groups described above. However, the *tert*-butoxycarbonyl (BOC) group was satisfactory. The keto amine and BOC-glycine NPE gave the amide **7a**. Removal of the BOC group with HCl-EtOAc led to the desired 17β-(glycyl-*N*-methylamido)-4-androsten-3-one (**7b**).

Table I. Antidepressant Activity in Mice[a]

Compound	Dose, mg/kg	Activity
3a	50 po	0
4	50 po	+2
5	50 ip	0
6b	50 ip	0
7b	50 ip	0
8b	30 po	+1
9b	50 po	+2
	50 ip	+3
10b	50 ip	0
11b	45 po	+1
	45 ip	+2
Amitriptyline (positive control)	25 po	+2

[a] This test used four mice per dose level, plus four as negative control and four as positive (amitriptyline) control. All mice were pretreated with a monoamine oxidase inhibitor as described by Everett[4] and the test compounds were given as single doses, either per os or intraperitoneally, using 1% methylcellulose suspensions. Four hours later each mouse received a DOPA challenge dose as described by Everett, and the behavior was observed. In the rating system, +1 indicates that the animals were uniformly more active than negative controls, +2 indicates marked increased activity, while +3 denotes full activity including aggressive behavior.

By similar procedures, isomers involving only the position of the side-chain amine were obtained as 17β-alaninamido-5-androsten-3β-ol (**8b**)† and 17β-(β-alaninamido)-5-androsten-3β-ol (**9b**). Another way of testing the biological effect of the position of the amino group was with the triglycyl derivative **10b**, which could be compared with the mono- and diglycyl compounds described earlier.[1]

The threoninamido analog **11b** was made because it is functionally similar to the active serinamido compound previously reported.[1]

The products were tested for antidepressant activity in

† All optically active amino acids are of the L configuration.