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

George Flouret, Wayne Cole,* and Ursula Biermacher

Organic Research Department, Research Division, Abbott Laboratories, North Chicago, Illinois 60064.
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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]

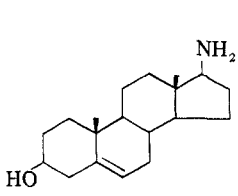
The threoninamido analog **11b** was made because it is functionally similar to the active serinamido compound previously reported.[1]

The products were tested for antidepressant activity in

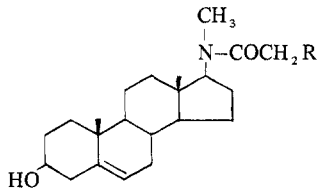
† All optically active amino acids are of the L configuration.

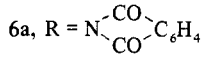
mice by a screening method described by Everett,[4] which was the same method previously used for steroid screening.[1] The data are described in Table I.

The effect of N-methylation was surprising. When compared to 17β-glycinamido-5-androsten-3β-ol which had +2 activity,[1] the sarcosinamido analog **3a** was essentially inactive while the 17β-dimethylaminoacetamido-5-androsten-3β-ol (**4**) again showed +2 activity. The trimethylammonium salt **5** was inactive, although this could be interpreted as a requirement for lipid solubility of active compounds.

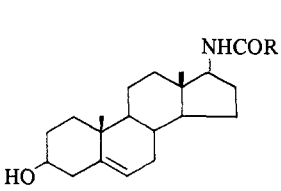


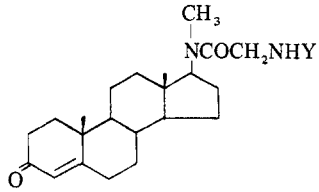
1



6a, R = 

6b, R = NH_2





2, R = CH_2Cl
3a, R = $CH_2N(H)CH_3$
3b, R = CH_2NCH_3 (|) $COOCH_2C_6H_5$
4, R = $CH_2N(CH_3)_2$
5, R = $CH_2N^+(CH_3)_3Cl^-$
8a, R = $CH(CH_3)NHCOOCH_2C_6H_5$
8b, R = $CH(CH_3)NH_2$
9a, R = $CH_2CH_2NHCOOCH_2C_6H_5$
9b, R = $CH_2CH_2NH_2$
10a, R = $CH_2(NHCOCH_2)_2N$
10b, R = $CH_2(NHCOCH_2)_2NH_2$
11a, R = $CHCHOHCH_3$ (|) $NHCOOCH_2C_6H_5$
11b, R = $CH(NH_2)CHOHCH_3$

7a, Y = *tert*-C_4H_9OCO
7b, Y = H

The activity of the dimethylaminoacetamido compound **4** showed that there was no structural requirement for a natural amino acid residue in the side chain. This conclusion is consistent with the earlier observation[1] that active compounds were obtained with either the L-seryl or the D-seryl residue in the side chain.

The effect of lengthening the side chain was also interesting. The triglycyl amide **10b** was essentially inactive, although this may again represent a loss of sufficient lipid solubility.

Compounds having the alanyl (**8b**), β-alanyl (**9b**), and threonyl (**11b**) residues at the side-chain position showed weak to fair activities comparable to the active compounds previously reported.[1]

Variations derived from 17β-*N*-methylaminoandrostenes were not active. Thus, although a 3-keto example (**7b**) was studied, no conclusion about the desirability of this structural feature was made, since it was in an inactive series.

Experimental Section

Tlc systems (silica gel G plates with MeOH–$CHCl_3$) were used for purity tests, and ir spectra were obtained for structure confirmation. A Thomas-Hoover apparatus was used for mp determinations with capillary tubes. Elemental analyses as indicated by C, H, N, Cl, and S were within ±0.4% of theoretical values. The following abbreviations were employed: DCC, dicyclohexylcarbodiimide; DCU, dicyclohexylurea; Z, *N*-benzyloxycarbonyl; BOC, *N*-*tert*-butoxycarbonyl; NPE, *p*-nitrophenyl ester.

17β-Chloroacetamido-5-androsten-3β-ol (2). A solution of the amine **1** (1.448 g, 5 mmoles) in 20 ml of $CHCl_3$ was cooled to −10°, stirred, and treated with Et_3N (0.8 ml, 5.5 mmoles) and a soln of chloroacetic anhydride (0.855 g, 5 mmoles) in 10 ml of $CHCl_3$. The mixture was stirred 5 min at −10° and 30 min at room temp, and then diluted with $CHCl_3$–EtOH to obtain a clear soln. The soln was extracted with 1 *N* HCl, H_2O, and satd NaCl soln, dried (Na_2SO_4), and evapd. The solid residue was dissolved in 200 ml of EtOAc, and the soln was filtered to remove solid by-products concentrated to 80 ml, and diluted with 50 ml of hexane. The yield of crystalline amide was 1.35 g (76%), mp 201–203°, $[\alpha]^{25}D$ −66° (*c* 0.46, EtOAc–$CHCl_3$, 2:3). *Anal.* ($C_{21}H_{32}NO_2Cl$) C, H, N, Cl.

Pentachlorophenyl *N*-Benzyloxycarbonylsarcosinate. Z-Sarcosine (19.6 g, 88 mmoles) and pentachlorophenol (25.7 g, 97 mmoles) in 176 ml of EtOAc were treated with DCC[5] (90 mmole) at 0° for 1 hr and at room temp for 3 hr.[6] AcOH (0.5 ml) was added and, after 15 min, the mixt was filtered to remove DCU by-product. The filtrate was evapd to a solid product, which was recrystd from EtOAc–pentane to yield 39.2 g (94%), mp 114–116°. Recrystallization (EtOAc) gave an analytical sample, mp 115–116°. *Anal.* ($C_{17}H_{12}NO_4Cl_5$) C, H, N.

17β-*N*-Benzyloxycarbonylsarcosinamido-5-androsten-3β-ol (3b). A mixt of the amine **1** (0.579 g, 2 mmoles), 6 ml of $CHCl_3$, and Z-sarcosine pentachlorophenyl ester (1.036 g, 2.2 mmoles) was stirred until clear, kept at 25° for 16 hr, diluted with Et_2O, and cooled to crystallize the product, 0.944 g, mp 145–147°. Recrystallization (EtOAc) afforded **3b**, 0.861 g (87%), mp 146–148°, $[\alpha]^{26}D$ −84.5° (*c* 1, EtOH). *Anal.* ($C_{30}H_{42}N_2O_4$) C, H, N.

17β-Sarcosinamido-5-androsten-3β-ol (3a). A suspension of the chloroamide **2** (1.0 g, 2.74 mmoles) in 20 ml of MeOH was saturated with $MeNH_2$. This gave a clear soln which, after 16 hr, gave prismatic needles of the product. This was washed (EtOH–Et_2O) to yield 0.55 g (56%), mp 231–234°, and a second crop, 0.18 g (18%), mp 230–233°. A sample was recrystd (EtOH), mp 233–234°, $[\alpha]^{25}D$ −106.5° (*c* 1, DMF). *Anal.* ($C_{22}H_{36}N_2O_2$) C, H, N.

The same product was obtained when a soln of **3b** (0.45 g, 0.9 mmole) in dioxane was added to liquid NH_3 (freshly distd from Na) (400 ml) and reduced with Na until a faint blue color persisted. The NH_3 was evapd, the residue extd with $CHCl_3$–MeOH–H_2O, and the organic layer concd. The product crystd from EtOH, yielding 0.228 g (70%), mp 229–232°. A recrystallized sample gave mp 232–233°.

17β-*N*,*N*-Dimethylglycinamido-5-androsten-3β-ol (4). A suspension of the chloroamide **2** (1.0 g, 2.74 mmoles) in 40 ml of MeOH was satd with Me_2NH. The soln was kept at room temp for 16 hr and then concentrated to a solid residue. The Et_2O-washed crude solid weighed 0.835 g. A soln of this material in MeOH was treated with a basic resin (Rexyn RG 1) and filtered, and the filtrate concentrated to a residue, which was crystallized from EtOH to give 0.667 g (63%), mp 208–210°, $[\alpha]^{25}D$ −86.8° (*c* 1, DMF). *Anal.* ($C_{23}H_{38}N_2O_2$) H, N; C: calcd, 73.75; found, 73.20.

17β-Trimethylammonioacetamido-5-androsten-3β-ol Chloride (5). A suspension of **2** (0.674 g, 1.85 mmoles) in 14 ml of MeOH was satd with Me_3N and the resulting soln kept for 3.5 hr at room temp, during wich time the product precipitated. Separation and recrystallization (MeOH) gave 0.5 g (63%), mp 288°, $[\alpha]^{25}D$ −99° (*c* 1, AcOH–H_2O 1:1). *Anal.* ($C_{24}H_{41}N_2O_2Cl$) C, H, N.

17β-(Phthalylglycyl-*N*-methylamido)-5-androsten-3β-ol (6a). A suspension of 17β-methylamino-5-androsten-3β-ol[7] (0.304 g, 1 mmole) and phthalylglycine NPE (0.36 g, 1.1 mmoles) in 4 ml of DMS was warmed to a clear soln and then kept 16 hr at room temp. Et_2O was added to improve crystallization of the product. After 1 hr, the crystals were separated and recrystallized (EtOH–Et_2O) to yield 235 mg (48%) of **6a**, mp 289–291°, $[\alpha]^{25}D$ −113° (*c* 1, $CHCl_3$). *Anal.* ($C_{30}H_{38}H_2O_4$) C, H, N.

The same product was also made by the reaction of 17β-methylamino-5-androsten-3β-ol (0.304 g, 1 mmole) in 8 ml of $CHCl_3$ and 0.16 ml of Et_3N with a soln of phthalylglycyl chloride (1.1 mmoles) in 2 ml of $CHCl_3$. After 10 min, the mixt was washed with 1 *N* HCl, H_2O, dried (Na_2SO_4), and evapd. The residue was recrystallized (EtOH–Et_2O) to give 0.42 g (85%) of **6a**, mp 288–289°.

17β-(Glycyl-*N*-methylamido)-5-androsten-3β-ol *p*-Toluenesulfonic Acid Salt (6b). A suspension of **6a** (1.18 g, 2.4 mmoles)

in 10 ml of DMF and 1.4 ml of NH_2NH_2 became clear after a few min and began to crystallize at 1 hr. After 3 hr, the solid was separated, washed with Et_2O, dissolved in MeOH, treated with a basic resin (Rexyn 201), and filtered, and the filtrate was concentrated to give the basic product. Crystallization from $CHCl_3$–Et_2O gave 0.382 g (1.01 mmoles) of the basic amide, mp 196–199°. This was dissolved in EtOH–$CHCl_3$, treated with *p*-toluenesulfonic acid (0.2 g, 1.05 mmoles), concentrated, and crystallized (EtOH–Et_2O) to yield the salt, 0.43 g (33%), mp 273–275°; recrystd to yield 0.367 g (29%), mp 278–280°, $[\alpha]^{26}D$ −90° (*c* 1, MeOH). *Anal.* ($C_{29}H_{44}N_2O_5S$) C, H, N.

17β-(*tert*-Butoxycarbonylglycyl-*N*-methylamido)-4-androsten-3-one (7a). BOC-glycine *N*-hydroxysuccinimide ester (1.089 g, 4 mmoles) was added to a soln of 17β-methylamino-4-androsten-3-one[7] (1.206 g, 4 mmoles) in 4 ml of DMF. After 16 hr at room temp, the mixt was diluted with 75 ml of H_2O, and the solid ppt was separated, washed (H_2O), and dried *in vacuo* to give 0.92 g (50%) of product. Recrystallization (EtOAc) gave 0.416 g (22%) of **7a**, mp 179–181°, $[\alpha]^{24}D$ −65° (*c* 2, $CHCl_3$) and 0.324 g (12%) of product, mp 177–181°. *Anal.* ($C_{27}H_{42}N_2O_4$) C, H, N.

17β-(Glycyl-*N*-methylamido)-4-androsten-3-one HCl Salt (7b). A soln of **7a** (0.72 g, 1.78 mmoles) in 20 ml of EtOAc was satd with dry HCl. After 30 min, the solvent was evaporated under reduced pressure, and the residue (vacuum-dried) was dissolved in EtOH and precipitated with Et_2O. The Et_2O-washed ppt was dried *in vacuo* to give 0.562 g (78%) of product, $[\alpha]^{25}D$ +29.5° (*c* 1, EtOH). *Anal.* ($C_{22}H_{35}N_2O_2Cl \cdot 0.5H_2O$) C, H, N, Cl.

17β-*N*-Benzyloxycarbonylalaninamido-5-androsten-3β-ol (8a). The amine **1** (0.29 g, 1 mmole) was added to a soln of Z-alanine NPE (0.361 g, 1.05 mmoles) in 0.5 ml of DMF. Swirling gave a clear soln which slowly crystallized. The Et_2O-washed crystals (0.5 g) were recrystallized (EtOH–hexane) to yield 0.36 g (72%) of **8a**, mp 118–120°, $[\alpha]^{25}D$ −78° (*c* 1, $CHCl_3$). *Anal.* ($C_{30}H_{42}N_2O_4$) C, H, N.

17β-Alaninamido-5-androsten-3β-ol (8b). A soln of **8a** (0.218 g, 0.44 mmole) in 2 ml of dioxane was added to liquid NH_3 (300 ml, freshly distd from Na) and 40 ml of dioxane. After reduction with Na, the soln was evapd, and the residue was dissolved in $CHCl_3$ plus a few milliliters of MeOH. The organic phase was washed with H_2O, dried (Na_2SO_4), and concentrated to a crystalline product, which was recrystallized from EtOH–hexane to yield 0.088 g (55%) of **8b**, mp 233–235°, $[\alpha]^{26}D$ −102° (*c* 1, EtOH). *Anal.* ($C_{22}H_{36}N_2O_2$) C, H, N.

***N*-Benzyloxycarbonyl-β-alanine *p*-Nitrophenyl Ester.** A soln of Z-β-alanine (4.68 g, 21 mmoles), *p*-nitrophenol (3.52 g, 25 mmoles), and DCC (4.35 g, 21 mmoles) in 63 ml of EtOAc was stirred at 0° for 0.5 hr and at 25° for 4 hr. The filtered mixt was concd and crystallized from EtOH–hexane to yield 6.25 g (86%), mp 91–93°. *Anal.* ($C_{17}H_{16}N_2O_6$) C, H, N.

17β-(*N*-Benzyloxycarbonyl-β-alaninamido)-5-androsten-3β-ol (9a). The above *p*-nitrophenyl ester (0.379 g, 1.1 mmoles) was added to a soln of the amine **1** (0.29 g, 1 mmole) in 3 ml of $CHCl_3$, stirred until homogeneous, and held for 16 hr at room temp. The oily product obtained by concentration *in vacuo* was crystallized from EtOAc and washed (Et_2O) to yield 0.368 g, mp 123–124°; recrystn gave 0.32 g (65%), mp 125–127°, $[\alpha]^{25}D$ −46.4° (*c* 1, EtOH). *Anal.* ($C_{30}H_{42}N_2O_4$) C, H, N.

17β-(β-Alaninamido)-5-androsten-3β-ol *p*-Toluenesulfonic Acid Salt (9b). A soln of **9a** (0.78 g, 1.57 mmoles) in 10 ml of dioxane was added to 500 ml of liquid NH_3 containing 60 ml of dioxane and reduced with Na (see procedure for **3a**). The product crystallized from EtOH–hexane yielding 0.505 g (89%) of the basic amide. This was converted to its salt by treatment in EtOH with *p*-toluenesulfonic acid (0.3 g), giving **9b** (0.395 g, 53%), mp 239–240°, $[\alpha]^{25}D$ −79° (*c* 1, MeOH). *Anal.* ($C_{29}H_{44}N_2O_5S$) C, H, N.

17β-*N*-Phthalylglycylglycylglycinamido-5-androsten-3β-ol (10a). This was made *via* five steps. The amine **1** (4.35 g, 15 mmoles) and *N*-phthalylglycine NPE (5.22 g, 16 mmoles) in 50 ml of $CHCl_3$ were warmed to a clear soln, held for 16 hr at room temp, and concentrated, and the product was crystallized (90 ml of EtOAc) to yield 4.29 g (60%) of **17β-*N*-phthalylglycinamido-5-androsten-3β-ol**, mp 265–267°, $[\alpha]^{25}D$ −102° (*c* 1, $CHCl_3$). *Anal.* ($C_{29}H_{36}N_2O_4$) C, H, N.

Removal of the blocking group with NH_2NH_2 in EtOH (see procedure for **10b**) and crystallization from EtOH gave (90%) 17β-glycinamido-5-androsten-3β-ol, mp 258–260°.[1] Reaction of this intermediate (2.772 g, 8 mmoles) and *N*-phthalylglycine NPE (2.87 g, 8.8 mmoles) in 16 ml of DMF for 16 hr, and addition of H_2O precipitated a crude product, which, after washing (H_2O), drying, and recrystallizing ($CHCl_3$–Et_2O–EtOH), yielded 3.84 g, (90%) of **17β-*N*-phthalylglycylglycinamido-5-androsten-3β-ol**, mp 246–248°, $[\alpha]^{25}D$ −30° (*c* 0.5, $CHCl_3$). *Anal.* ($C_{31}H_{39}N_3O_5$) C, H, N.

Cleavage of the latter compd (3.202 g, 6 mmoles) with 1.2 ml of NH_2NH_2 in 8 ml of DMF and crystallization from EtOH–$CHCl_3$–Et_2O gave 1.937 g (80%) of 17β-glycylglycinamido-5-androsten-3β-ol,[1] mp 293–295°. A mixt of this product (0.202 g, 0.5 mmole) and *N*-phthalylglycine NPE (0.18 g, 0.55 mmole) in 2 ml of DMF was warmed to obtain a clear soln. After 15 hr at room temp, the solid product which separated was washed with Et_2O and dried to give 0.332 g, mp 289–282°; recrystn (MeOH–$CHCl_3$) afforded 0.18 g (64%) of **10a**, mp 278–281°, $[\alpha]^{25}D$ −51° (*c* 1, DMF). *Anal.* ($C_{33}H_{42}N_4O_6$) C, H, N.

17β-Glycylglycylglycinamido-5-androsten-3β-ol (10b). A suspension of **10a** (0.887 g, 1.55 mmoles) in 1.5 ml of DMF was treated with 0.3 ml (9 mmoles) of NH_2NH_2, giving a clear soln which slowly crystd. After 4 hr, the crystals were collected, washed (Et_2O), dissolved in MeOH, filtered through a basic resin (Rexyn RG 1), and concd to a solid residue. Recrystallization (EtOH–$CHCl_3$) afforded 0.49 g (73%) of **10b**, mp 236–238°, $[\alpha]^{25}D$ −69° (*c* 1, DMF). *Anal.* ($C_{25}H_{40}N_4O_4$) C, H, N.

17β-*N*-Benzyloxycarbonylthreoninamido-5-androsten-3β-ol (11a). To a soln of the amine **1** (0.724 g, 2.5 mmoles) in 10 ml of dioxane was added Z-threonine *N*-hydroxysuccinimide ester (0.922 g, 2.63 mmoles) in 2 ml of dioxane. The mixt became clear and then slowly crystallized. The product was separated after 5 hr and washed (Et_2O) to give 1.3 g, mp 117–119°; recrystn (dioxane) yielded 1.1 g (84%) of **11a**, mp 122–123°, $[\alpha]^{25}D$ −81.5° (*c* 1, $CHCl_3$). *Anal.* ($C_{31}H_{44}N_2O_5$) C, H, N.

17β-Threoninamido-5-androsten-3β-ol (11b). A soln of **11a** (1.048 g, 2 mmoles) in dioxane (10 ml plus 5-ml wash) was added to a mixt of 1 l. of liquid NH_3 (distd from Na) and 20 ml of dioxane. After reduction with Na and evaporation, the residue was dissolved in 200 ml of hot EtOH and filtered, and the soln was diluted with 500 ml of H_2O. The ppt was collected, washed (H_2O), air-dried, and recrystallized (14 ml of hot EtOH plus 3 ml of H_2O) to yield 0.4 g (46%) of **11b**, mp 201–202°, $[\alpha]^{25}D$ −71° (*c* 1, EtOH). *Anal.* ($C_{23}H_{38}N_2O_3 \cdot C_2H_5OH$) C, H, N.

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