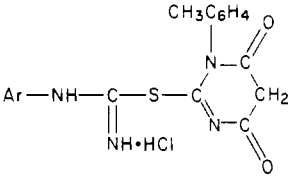
Table II.
***S*-((Arylamino)formimidoyl)-1-(*p*-tolyl)-2-thiobarbituric Acid Hydrochlorides**[a]



Ar	mp, °C	yield, %
C_6H_5	140	85
o-$CH_3C_6H_4$	157	82
p-$CH_3C_6H_4$	150	80
p-$CH_3OC_6H_4$	143	79
o-$CH_3OC_6H_4$	149	75
p-ClC_6H_4	143	81

[a] All these compounds gave elemental analyses (C, H, N, S) within ±0.30 of the calculated values.

Other *S*-((arylamino)formimidoyl)-2-thiobarbituric acid hydrochlorides and *S*-((arylamino)formimidoyl-1-(*p*-chlorophenyl)-2-thiobarbituric acid hydrochlorides synthesized by condensing 2-thiobarbituric acid and 1-(*p*-chlorophenyl)-2-thiobarbituric acid with different arylcyanamide hydrochlorides are summarized in Table I.

By a similar procedure several *S*-((arylamino)formimidoyl-1-(*p*-tolyl)-2-thiobarbituric acid hydrochlorides were synthesized and are given in Table II.

Acknowledgment

We are thankful to Prof. R. C. Aggrawal, Head of the Department of Chemistry, Banaras Hindu University, Varanasi, India, for providing the laboratory facilities.

Registry No. I (Ar = C_6H_5), 64119-04-6; I (Ar = o-$CH_3C_6H_4$), 64119-05-7; I (Ar = m-$CH_3C_6H_4$), 64119-06-8; I (Ar = p-$CH_3C_6H_4$), 64119-07-9; I (Ar = o-ClC_6H_4), 64119-11-5; I (Ar = m-ClC_6H_4), 64119-12-6; I (Ar = p-ClC_6H_4), 64119-13-7; I (Ar = o-$CH_3OC_6H_4$), 64119-08-0; I (Ar = p-$CH_3OC_6H_4$), 64119-09-1; II (R = H), 504-17-6; II (R = p-ClC_6H_4, 28921-30-4; II (R = $CH_3C_6H_4$), 28921-28-0; IV (Ar = C_6H_5, R = H), 93084-87-8; IV (Ar = o-$CH_3C_6H_4$, R = H), 93084-88-9; IV (Ar = m-$CH_3C_6H_4$, R = H), 93084-89-0; IV (Ar = p-$CH_3C_6H_4$, R = H), 93084-90-3; IV (Ar = o-ClC_6H_4, R = H), 93084-91-4; IV (Ar = m-ClC_6H_4, R = H), 93084-92-5; IV (Ar = p-ClC_6H_4, R = H), 93084-93-6; IV (Ar = o-$CH_3OC_6H_4$, R = H), 93084-94-7; IV (Ar = p-$CH_3OC_6H_4$, R = H), 93084-95-8; IV (Ar = C_6H_5, R = p-ClC_6H_4), 93110-21-5; IV (Ar = m-$CH_3OC_6H_4$, R = p-ClC_6H_4), 93084-96-9; IV (Ar = p-$CH_3OC_6H_4$, R = p-ClC_6H_4), 93084-97-0; IV (Ar = m-ClC_6H_4, R = ClC_6H_4), 93084-98-1; IV (Ar = p-ClC_6H_4, R = p-ClC_6H_4), 93084-99-2; IV (Ar = C_6H_5, R = p-$CH_3C_6H_4$), 93085-00-8; IV (Ar = o-$CH_3C_6H_4$, R = p-$CH_3C_6H_4$), 93085-01-9; IV (Ar = p-$CH_3C_6H_4$, R = p-$CH_3C_6H_4$), 93085-02-0; IV (Ar = p-$CH_3OC_6H_4$, R = p-$CH_3C_6H_4$), 93110-22-6; IV (Ar = o-$CH_3OC_6H_4$, R = p-$CH_3C_6H_4$), 93085-03-1; IV (Ar = p-ClC_6H_4, R = p-$CH_3C_6H_4$), 93110-23-7; acetone, 67-64-1.

Literature Cited

(1) Krall, H. R. H.; Sahasrabudhey, *J. Indian Chem. Soc.* **1942**, *19*, 345.
(2) Miller, Ellis; Crossley, F. S.; Munch, J. C.; Hartung, W. H. *J. Am. Chem. Soc.* **1936**, *58*, 1090-1.
(3) Lee, John, *J. Am. Chem. Soc.* **1938**, *60*, 993-6.
(4) Bergman, Ernst. *British Patent* 381 551, 1943.
(5) Dai Nippon Pharmaceutical Co., Inc., Japan; *Chem. Abstr.* **1963**, *59*, 10077*e*.

Received for review May 23, 1983. Revised manuscript received March 9, 1984. Accepted July 16, 1984.

Synthesis of 20-Acetamido-3-aza-*A*-homo-4α-pregnen-4-one

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A synthetic approach for the preparation of 20-acetamido epimers of 3-aza-*A*-homo-4α-pregnen-4-one is described.

When cultures of human leukemia cells were treated with 3β-hydroxy-13α-amino-13,17-seco-5α-androstan-17-oic acid 13,17-lactam, an increased proliferating actvivity was exhibited (*1*). On the other hand, 3,17α-diaza-*A*,*D*-dihomoandrost-4α-ene-4,17-dione showed antitumor activity (*2*).

In view of the importance of such compounds we desired to effect the synthesis of steroidal lactams containing a second CONH group out of the steroid nucleus, namely, 20α-acetamido- and 20β-acetamido-3-aza-*A*-homo-4α-pregnen-4-one.

Experimental Section

Melting points were determined on a Fisher Johns melting point apparatus and are uncorrected. The IR spectra were recorded with a Perkin-Elmer 521 in solid-phase potassium bromide. The NMR spectra were determined with a Varian Associates XL-100 instrument using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Elemental analyses were performed by the Analytical Laboratory of Nuclear Research Center "Democritos", Analytical results obtained for those elements were within ±0.4% of the theoretical values.

20*α*-Acetamido-4-pregnen-3-one (IV). A 1.3-g sample of 3β-hydroxy-20α-aminopregnene (*3*) was dissolved in 10 mL of pyridine and 10 mL of acetic anhydride and left at room temperature overnight. After that time it was poured into ice water and the precipitate collected by filtration (1.48 g). The crude material was hydrolyzed selectively at $C_{(3)}$, 70 mL of 5% methanolic potassium hydroxide solution at room temperature being used with stirring for 30 min. The reaction mixture was diluted with water and the precipitate collected by filtration to yield 3β-hydroxy-20α-acetamido-5-pregnene, 1.28 g (homogeneous as judged by TLC).

A solution of 6.8 mmol of 3β-hydroxy-20α-acetamido-5-pregnene in 500 mL of dry toluene and 45 mL of cyclohexanone was distilled slowly until 50 mL of solvent was removed. An aluminum isopropoxide solution 2 g in 20 mL of dry

0021-9568/85/1730-0134$01.50/0

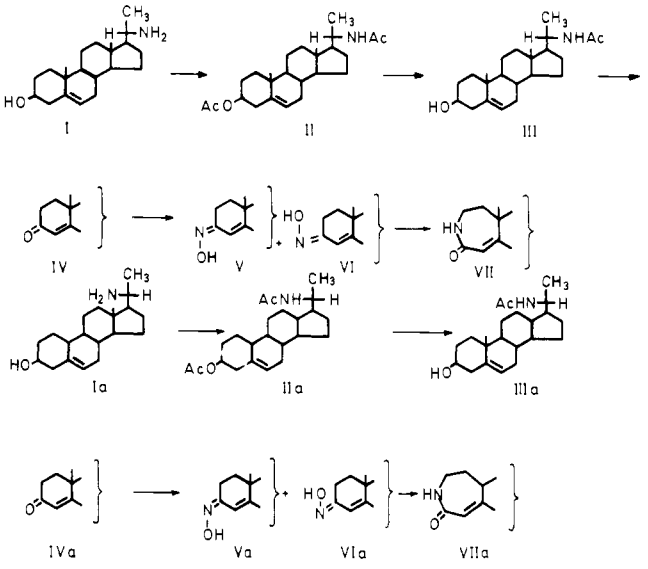
Table I. NMR Data of Prepared Compounds in $CDCl_3$[a]

	δ								J, Hz	
							NH			
compd	$C_{(4)}H$	$C_{(18)}H_3$	$C_{(19)}H_3$	$C_{(21)}H_3$	$C_{(20)}H$	$NCOOCH_3$	amine	lactam	$C_{(20)}HNH$	$C_{(20)}HC_{(21)}H_3$
IV	5.73	0.77	1.18	1.15	4.00	1.94	5.33		8.8	6.6
IVa	5.72	0.75	1.18	1.07	4.02	1.95	5.32		9.29	6.37
VII	5.72	0.75	1.14	1.14	3.99	1.94	5.34	6.32	(broad)	6.59
VIIa	5.73	0.73	1.14	1.06	4.00	1.94	5.35	6.26	9.29	6.36

[a] The assignments of the protons attached to the asymmetric $C_{(20)}$ center were confirmed by double resonance experiments. Thus, in compound IVa, for example, irradiation at 4.02 δ ($C_{(20)}$ methine) reduced the doublets at 1.07 δ ($C_{(21)}$ methyl) and 5.32 δ (amide NH) to singlet peaks.

toluene was added and the mixture was refluxed for 10 h and left to stand at room temperature overnight. The mixture was filtered to remove the precipitate containing the aluminum. The filtrate was steam distillated until all the cyclohexanone was removed. The residue was extracted with chloroform and washed with water. Solvent was removed and the residue was crystallized from ether to yield compound IV in 76% yield: mp 209–211 °C; IR 3300 (NH), 1640 (CO), 1620 (C=C) cm^{-1}.

Anal. ($C_{23}H_{35}NO_2$) C, H, N.



20β-Acetamido-4-pregnen-3-one (IVa). Under the same reaction conditions as for IV, 20β-acetamido-4-pregnen-3-one in 57% yield was obtained: mp 268–270 °C; IR 3340 (NH), 1650 (CO), 1620 (C=C) cm^{-1}.

Anal. ($C_{23}H_{35}NO_2$) C, H, N.

20α-Acetamido-3-aza-A-homo-4α-pregnen-4-one (VII). A 2-g sample of ketone IV was dissolved in a mixture of 70 mL of dry ethanol and 70 mL of dry pyridine. Hydroxylamine (1.5 g) was added to this solution and the mixture was heated under reflux for 2.5 h. The solution was poured into ice water and the resulting precipitate was collected by filtration, washed with water, and dried to yield 87% of oximes V and VI.

Unresolved 20α-acetamido-4-pregnen-3-one oxime (1.8 g) was dissolved in 120 mL of purified dioxane; 5 mL of purified thionyl chloride was added dropwise. The mixture was kept at room temperature, stirred for 2 h, poured into a solution of 25% ammonium hydroxide, and extracted with chloroform. The organic layer was washed with water and dried over sodium sulfate, and the solvent was removed under reduced pressure, yielding solid material, which on TLC gave three spots.

This residue was chromatographed on a column of silica gel prepared with chloroform. Elution with chloroform gave a mixture of syn and anti oximes. Further elution of the column with chloroform–methanol (9:1) gave the 20α-acetamido-3-aza-*A*-homo-4α-pregnen-4-one in 25% yield. Crystallization from ethyl acetate gave the final product: mp 274–276 °C; IR 3280 (NH), 1630 (CONH) cm^{-1}.

Anal. ($C_{23}H_{36}N_2O_2$) C, H, N.

20β-Acetamido-3-aza-A-homo-4α-pregnen-4-one (VIIa). Similar reaction conditions as for the 20β-acetamido-4-pregnen-3-one oxime produced VIIa in 33% yield after column chromatography. Crystallization from ethyl acetate gave the final product: mp > 300 °C; IR 3340, 3300 (NH), 1650 (CONH) cm^{-1}.

Anal. ($C_{23}N_{36}N_2O_2$) C, H, N.

Registry No. I, 5035-10-9; II, 60534-25-0; III, 5035-11-0; IIIa, 5035-12-1; IV, 92420-64-9; IVa, 92420-65-0; V, 92420-66-1; Va, 92420-67-2; VI, 92420-68-3; VIa, 92420-69-4; VII, 92420-70-7; VIIa, 92456-16-1.

Literature Cited

(1) Politis, G.; Camoutsis, Ch.; Catsoulacos, P. *Methods Find. Exp. Clin. Pharmacol.* **1982**, *4*, 402–6.
(2) Papageorgiou, A.; Camoutsis, Ch.; Catsoulacos, P. *Oncology*, in press.
(3) Van de Woode, G.; Van Hove, L. *Bull. Soc. Chim. Belg.* **1987**, *76*, 566–78.

Received for review April 9, 1984. Accepted June 25, 1984.