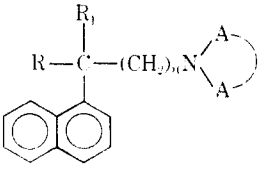
TABLE I
1-NAPHTHYLALKYLCARBAMATES



Compd	R	R1	NCH2	Reflux time, hr	Yield, %[a]	Bp (mm), °C	Formula[b]
1	*i*-C_3H_7	$NHCO_2Et$	$(CH_3)_2N(CH_2)_2$	8	65.6	*c*	$C_{21}H_{30}N_2O_2$
2	*i*-C_7H_7	$NHCO_2Et$	*d*	8	78.4	*c*	$C_{24}H_{34}N_2O_2$
3	H	CH_2NHCO_2Et	$(CH_3)_2N(CH_2)_2$	3	65.4	190–192 (0.3)	$C_{19}H_{26}N_2O_2$
4	CH_3	CH_2NHCO_2Et	$(CH_3)_2N(CH_2)_2$	8	56.2	*c*	$C_{20}H_{28}N_2O_2$
5	*i*-C_3H_7	CH_2NHCO_2Et	$(CH_3)_2N(CH_2)_2$	5	77	*c*	$C_{22}H_{32}N_2O_2$
6	*sec*-C_4H_9	CH_2NHCO_2Et	$(CH_3)_2N(CH_2)_2$	5	39.2	*c*	$C_{23}H_{34}N_2O_2$
7	$(CH_3)_2N(CH_2)_2$	CH_2NHCO_2Et	$(CH_3)_2N(CH_2)_2$	8	74	*c*	$C_{25}H_{35}N_3O_2$
8	*i*-C_3H_7	CH_2NHCO_2Et	$CH_3(C_2H_5)N(CH_2)_2$	5	82.2	*c*	$C_{25}H_{34}N_2O_2$
9	*i*-C_3H_7	CH_2NHCO_2Et	$(C_2H_5)_2N(CH_2)_2$	5	82	*c*	$C_{24}H_{36}N_2O_2$
10	*sec*-C_4H_9	CH_2NHCO_2Et	$(C_2H_5)_2N(CH_2)_2$	5	60.8	*c*	$C_{25}H_{38}N_2O_2$
11	*i*-C_3H_7	CH_2NHCO_2Et	$(i\text{-}C_3H_7)_2N(CH_2)_2$	5	60	*c*	$C_{26}H_{40}N_2O_2$
12	CH_3	CH_2NHCO_2Et	*e*	8	53.3	*c*	$C_{22}H_{30}N_2O_2$
13	*i*-C_3H_7	CH_2NHCO_2Et	*e*	5	63.4	*c*	$C_{24}H_{34}N_2O_2$
14	*sec*-C_4H_9	CH_2NHCO_2Et	*e*	5	48.8	*c*	$C_{25}H_{36}N_2O_2$
15	*e*	CH_2NHCO_2Et	*e*	8	41	*c*	$C_{27}H_{39}N_3O_2$
16	H	CH_2NHCO_2Et	*d*	3	81.5	215–218 (0.5)	$C_{22}H_{30}N_2O_2$
17	CH_3	CH_2NHCO_2Et	*d*	5	67	*c*	$C_{23}H_{32}N_2O_2$
18	*i*-C_3H_7	CH_2NHCO_2Et	*d*	5	81.4	*c*	$C_{25}H_{36}N_2O_2$
19	*d*	CH_2NHCO_2Et	*d*	5	80	*c*	$C_{29}H_{43}N_3O_2$
20	CH_3	CH_2NHCO_2Et	*f*	5	88	*c*	$C_{22}H_{30}N_2O_3$
21	*i*-C_3H_7	CH_2NHCO_2Et	*f*	5	55.7	*c*	$C_{24}H_{34}N_2O_3$
22	*f*	CH_2NHCO_2Et	*f*	10	66.4	*c*	$C_{27}H_{39}N_3O_4$
23	CH_3	CH_2NHCO_2Et	$(CH_3)_2N(CH_2)_3$	5	80.2	*c*	$C_{21}H_{30}N_2O_2$
24	*sec*-C_4H_9	CH_2NHCO_2Et	$(CH_3)_2N(CH_2)_3$	3	43.5	*c*	$C_{24}H_{36}N_2O_2$
25	*i*-C_3H_7	CH_2NHCO_2Et	*g*	3	66.6	*c*	$C_{26}H_{38}N_2O_2$
26	*sec*-C_4H_9	CH_2NHCO_2Et	*h*	3	92.7	*c*	$C_{26}H_{38}N_2O_2$
27	*sec*-C_4H_9	CH_2NHCO_2Et	$(CH_3)_2N(CH_2)_4$	5	56.6	*c*	$C_{25}H_{38}N_2O_2$
28	*i*-C_3H_7	CH_2NHCO_2Et	*i*	5	80.4	*c*	$C_{27}H_{40}N_2O_2$
29	*i*-C_3H_7	CH_2NHCO_2Et	*j*	4	76.2	*c*	$C_{26}H_{38}N_2O_3$

[a] Crude product. [b] All compounds were analyzed for C, H, N and the analytical results were within ±0.4% of the theoretical values. [c] Waxy product. [d] 2-Piperidinoethyl. [e] 2-(1-Pyrrolidinyl)ethyl. [f] 2-Morpholinoethyl. [g] 3-Piperidinopropyl. [h] 3-Morpholinopropyl. [i] 4-Piperidinobutyl. [j] 4-Morpholinobutyl.

29 prolonged pentobarbital sleeping time at 40 mg/kg ip. However, this effect had only slight pharmacological significance. Compounds **12** and **20** displayed some activity in the antireserpine test but were less active than imipramine. In none of the other assays did the compounds exert any noteworthy activity.

Experimental Section[8]

The intermediate amines were prepared as previously described.[1]

Ethyl 1-Naphthylalkylcarbamates.—A solution of the appropriate amine (0.1 mol) and $ClCO_2Et$ (0.15 mol) in anhydrous C_6H_6 (190 ml) was refluxed in the presence of K_2CO_3 (0.15 mol). The reaction mixture was extracted with 10% HCl, the acid solution made alkaline with 10% NaOH, and the precipitate which formed extracted (Et_2O). The ethereal solution was washed (H_2O) until neutral, dried (Na_2SO_4), and evaporated to dryness to give an oily or waxy product.

Acknowledgments.—The authors wish to thank Dr. R. Perego for performing microanalyses, Mr. G. Bietti for assistance in preparing the compounds, and Miss L. Tomasi and Miss C. Bacci for carrying out the pharmacological tests.

(8) Boiling points are uncorrected.

Synthesis and Endocrine Activity of Some 3-Aza-*A*-homopregnenes

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The nucleotide, cyclic 3′,5′-adenosine monophosphate (cyclic AMP), is a naturally occurring intracellular constituent that has been shown to influence a wide variety of physiological functions.[1-3] Hormones and

(1) M. A. Rizack, *J. Biol. Chem.*, **239**, 392 (1964).
(2) E. W. Sutherland and T. W. Rall, *Pharmacol. Rev.*, **12**, 265 (1960).
(3) S. Tarui, K. Nanaka, Y. Ikura, and K. Shima, *Biochem. Biophys. Res. Commun.*, **13**, 329 (1963).

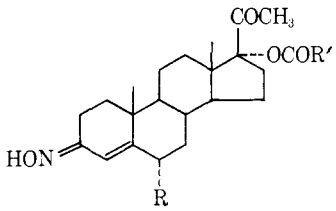
neurohormones increase the tissue concentration of cyclic AMP at target cells, thus indicating[4] that this cyclic nucleotide may be responsible in mediating the response of the hormones. Haynes and Berthet[5] have shown cyclic AMP to be a mediator for the action of ACTH on steroidogenis in the adrenal cortex. Similarly, Marsch and Savard[6] have demonstrated that cyclic AMP acts as a mediator of the stimulatory action of LH on steroidogenesis.

We became interested in exploring these observations from a synthetic point of view and chose 17α-acetoxyprogesterone and 6α-methyl-17α-acetoxyprogesterone for our molecular modifications. Conversion of the 3-ketone into the oxime followed by Beckmann rearrangement to an *A*-homo lactam (Scheme I) would impart a certain amount of basicity to the steroid molecule which could conceivably bind to 3′,5′-cyclic nucleotide phosphodiesterase, the enzyme that catalyzes the hydrolysis of cyclic AMP to 5′-AMP. Bases such as theophylline and caffeine have been shown[7] to inhibit 3′,5′-cyclic nucleotide phosphodiesterase thus building up the intracellular concentration of cyclic AMP for physiological activity.

The oximes and their Beckmann rearranged products were synthesized according to the procedure outlined in the Experimental Section. The spectral data confirm the structural assignment. The physical properties of these compounds are summarized in Tables I and II.

TABLE I

3-OXIMINO PROGESTINS



Compd[a]	R	R′	Recrystn[b] solvent	Mp, °C	Formula[c]
1	H	CH_3	A	240–241	$C_{23}H_{33}NO_4$
2	H	C_2H_5	M	205–209	$C_{24}H_{35}NO_4$
3	H	$(CH_2)_4CH_3$	M	189–192	$C_{27}H_{41}NO_4$
4	CH_3	CH_3	M	215–218	$C_{24}H_{35}NO_4$
5	CH_3	C_2H_5	M–W	122–124	$C_{25}H_{37}NO_4$
6	CH_3	$(CH_2)_4CH_3$	M–W	97–98	$C_{28}H_{43}NO_4$

[a] All compounds showed uv absorption at 240 mμ. [b] A, acetone; M, methanol; W, water. [c] Acceptable C, H, N values were obtained for all compounds.

The progestational response of these compounds was determined by the Clauberg test[8] and the endometrial response was scored according to the index of McPhail.[9] The individual responses are tabulated in Table III. Compounds **4** and **9** were the most potent compounds in the series. On a milligram basis, **4** was about 10 times as potent as **1** which lacks the 6α-Me group. Similarly, **9** was also about 10 times as potent as the corresponding lactam **7** without the 6α-Me group. Interestingly, the

SCHEME I

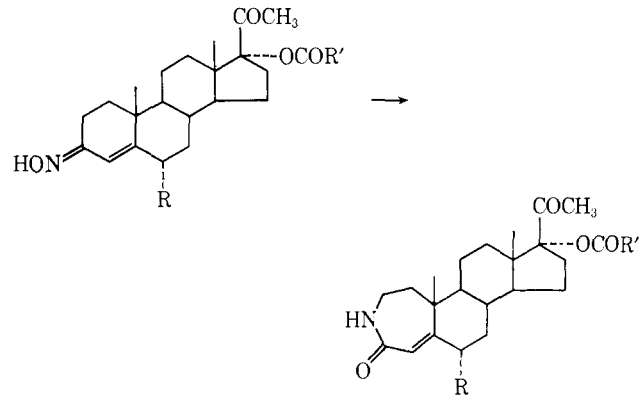
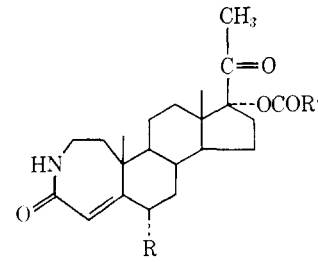


TABLE II

3-AZA-*A*-HOMO LACTAMS



Compd[a]	R	R′	Recrystn[b] solvent	Mp, °C	Formula[c]
7	H	CH_3	A-H	274–277	$C_{23}H_{33}NO_4$
8	H	$(CH_2)_4CH_3$	A	224–227	$C_{27}H_{41}NO_4$
9	CH_3	CH_3	EA-E	184–186	$C_{24}H_{35}NO_4$
10	CH_3	$(CH_2)_4CH_3$	H	87–90	$C_{28}H_{43}NO_4$

[a] All compounds showed uv absorption around 220 mμ. [b] A, acetone; EA, ethyl acetate; E, ether; H, hexane. [c] Acceptable C, H, N values were obtained for all compounds.

TABLE III

PROGESTATIONAL RESPONSE OF RABBIT UTERUS

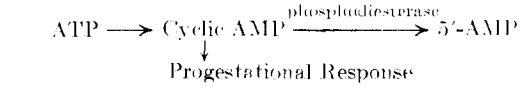
Compd no.	Dose, mg/kg	McPhail index
1	5.0	2.6
2	5.0	1.1
3	5.0	0.3
4	0.5	3.1
5	5.0	3.3
6	5.0	2.7
7	5.0	2.5
8	5.0	0
9	0.5	3.0
10	5.0	1.2

oxime **4** and its corresponding lactam **9** are equally potent and marks the first time, to our knowledge, that an azasteroid **9** has imparted such a potent endocrine activity. Introduction of a long-chain fatty ester at C-17 in both series (6H and 6α-Me) decreases the activity precipitously.

No data are available at present on the mode of action of these types of steroids but it is possible, judging from their progestational response, that these compounds act at the 3′,5′-cyclic nucleotide phosphodiesterase level thus inducing a sufficient build-up of cyclic AMP for the observed response (Scheme II). The necessity of 6α-Me group to enhance the progestational response suggests the β face interaction with

(4) R. C. Haynes, Jr., E. W. Sutherland, and T. W. Rall, *Recent Progr. Horm. Res.*, **16**, 121½(1960).
(5) R. C. Haynes, Jr. and L. Berthet, *J. Biol. Chem.*, **225**, 115 (1957).
(6) J. M. Marsch and K. Savard, *Steroids*, **8**, 133 (1966).
(7) R. W. Butcher and E. W. Sutherland, *J. Biol. Chem.*, **237**, 1244 (1962).
(8) C. Clauberg, *Zentralbl. Gynaekol.*, **54**, 2757 (1930).
(9) M. K. McPhail, *J. Physiol. (London)*, **83**, 145 (1935).

Scheme II



phosphodiesterase. Also, both **4** and **9** must have common binding sites.

Experimental Section

All melting points were taken on a Fisher–Johns melting point apparatus and are uncorrected. The uv and ir data were obtained on a Cary Model 11 and Beckmann IR-5 spectrophotometers, respectively. The nmr spectra were determined on a Varian A-60 spectrometer in $CDCl_3$ using TMS as an internal standard (0 ppm). All parts per million values are the center of the signals. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Where analyses are indicated only by symbols of the elements, (Tables I and II), analytical results obtained for those elements were within ±0.4% of the theoretical value.

General Method. Oximes. 3-Oximino-17α-acetoxypregn-4-ene-3,20-dione (1).—A solution containing 1.0 g of 17α-acetoxyprogesterone, 250 mg of $HONH_3^+ \cdot Cl^-$, and 5 ml of C_5H_5N was heated on a steam bath for 1.5 hr. The mixture was poured into a large amount of ice–water and the crude oxime thus precipitated was collected by filtration. Recrystallization from MeOH gave 1.0 g of 1: mp 240–241°; $[\alpha]D$ +97.6°; λ_{max}^{KBr} 3.02, 5.75, 5.82 6.1 μ; λ_{max}^{EtOH} 240 mμ; nmr ($CDCl_3$) 0.70 ppm (C-18), 1.11 (C-19), 2.06 (C-21), 2.12 (C-17 OAc), 5.89 (C-4 anti), and 6.6 (C-4 Syn).

General Method. Beckmann Rearrangements. 3-Aza-17α-acetoxy-A-homo-4a-pregnene-4,20-dione (7).—To a solution containing 4.0 g of **1** in 30 ml of purified dioxane was added 5 ml of $SOCl_2$. The mixture was stirred at room temperature for 1.5 hr and poured into a large amount of ice water. The excess acid was neutralized with $NaHCO_3$ and the solution was extracted with CH_2Cl_2. The organic layer was washed (H_2O), dried (Na_2SO_4), and filtered. The filtrate was evaporated to give a brown oil which could be recrystallized from acetone–hexane to give 1.4 g of **8**: mp 274–277°; $[\alpha]$ +15.9°; $\lambda_{max}^{CHCl_3}$ 3.1, 5.75, 5.80 6.05 μ; λ_{max}^{EtOH} 221 mμ; nmr ($CDCl_3$) 0.67 ppm (C-18), 1.15 (C-19), 2.04 (C-21), and 2.09 (C-17 OAc).

Acknowledgment.—I wish to thank Dr. I. Scheer for his encouragement and interest, and Dr. R. P. Blye of our Division of Pharmacology for the biological data.

Preparation of 6-Acetamino-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate

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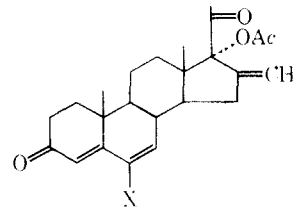
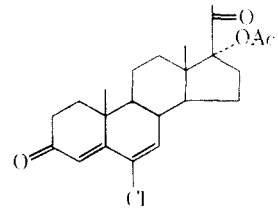
Much attention has been devoted in recent years to 6-substituted 6-dehydroprogesterone analogs, among which 6-chloro-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-acetate (**2**) (chlormadinone), has found wide use as the progestational factor in contraceptives and has been clinically investigated for independent antifertility action.[2] Following the discovery of the large progestagenic potentiating effect of a 16-methylene substituent,[3] active interest has developed in this new

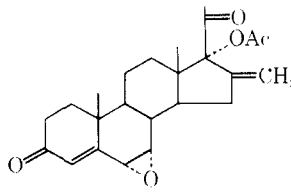


1

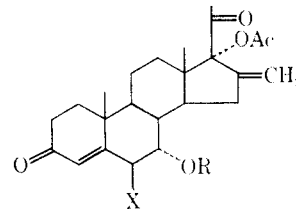
a, X = Cl
b, X = $NHCOCH_3$



2

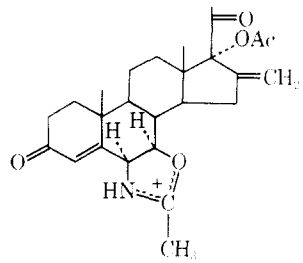


3



4

a, X = Cl; R = Ac
b, X = Cl; R = H
c, X = NHAc; R = H
d, X = NHAc; R = Ac



5

class of compounds, both for their potential progestagenic[4] and antiandrogenic[5] activities.

In the present communication we wish to report briefly on the synthesis, as well as progestational and antiandrogenic evaluation, of the 6-acetamino analog **1b**.

The synthetic procedure used, in essence, was the one outlined earlier by Brückner and coworkers[6] for the synthesis of **2**, and subsequently modified for the synthesis of the 16-methylene homolog **1a**, by Shapiro and coworkers.[7a] It involved the opening of a 6α,7α-epoxide with a nucleophile, followed by the elimination of the 7α function with *p*-TSA[7b] to introduce the 6,7 double bond. The use of MeCN as a nucleophile for the acid-catalyzed opening of epoxides to acetamino alcohols has been reported recently by Julia and coworkers,[8] who applied their finding to the opening of 5α,6α-, 5β,6β-, and

(1) Post-Doctoral Fellow, 1968 and 1969.

(2) For a review in this field see E. Diczfalusy, *Amer. J. Obst. Gynecol.*, **100**, 136 (1968) and ref therein.

(3) E. Shapiro, T. Legatt, L. Weber, M. Steinberg, A. Watnick, M. Eisler, M. Gilmore Hennessey, C. T. Coniglio, W. Charney, and E. P. Oliveto, *J. Med. Chem.*, **5**, 975 (1962), and ref therein.

(4) (a) H. J. Mannhardt, F. v. Werder, K. H. Bork, H. Metz, and K. Brückner, *Tetrahedron Lett.*, 21 (1960); (b) K. H. Bork, K. Brückner, F. Jahn, H. J. Mannhardt, and F. v. Werder, German Patent 1,156,407 (1963); (c) V. Petrow, U.S. Patent 3,117,966 (1964); (d) K. Syhora nd R. Mazac, *Collect. Czech. Chem. Commun.*, **31**, 2768 (1966); (e) Z. Cekan, M. Seda, J. Mikulaskova, and K. Syhora, *Steroids*, **8**, 205 (1966); (f) E. P. Oliveto, R. Rausser, and E. B. Hershberg, U.S. Patent 3,312,692 (1967); (g) D. Burn, M. Lester, and V. Petrow, U.S. Patent 3,375,167 (1968).

(5) (a) S. Rocky and R. Neri, *Fed. Proc.*, **27**, 624 (1968); (b) C. Casmer, F. Fielder, and R. Neri, Northeast Conference of Comparative Endocrinology, Boston University, Boston, Mass., 1968.

(6) K. Brückner, B. Hampel, and U. Johnsen, *Chem. Ber.*, **94**, 1225 (1961).

(7) (a) E. L. Shapiro, H. L. Herzog, and L. Weber, U.S. Patent 3,493,588 (Feb 3, 1970); (b) The acid medium utilized in U.S. Patent 3,493,588 is HCl–$CHCl_3$.

(8) (a) S. Julia and G. Bourgery, *C. R. Acad. Sci., Ser. C.*, **264**, 333 (1967); (b) S. Julia, G. Bourgery, and J. J. Frankel, *ibid.*, **267**, 1861 (1968).