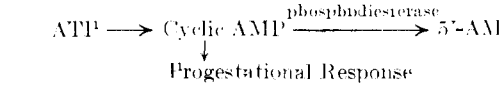
Scheme II



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°; λ_{max}^{Nujol} 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.

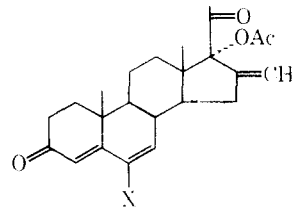
Preparation of 6-Acetamino-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate

G. Teutsch,[1] E. L. Shapiro, and H. L. Herzog

Natural Products Research Department, Schering Corporation, Bloomfield, New Jersey 07003

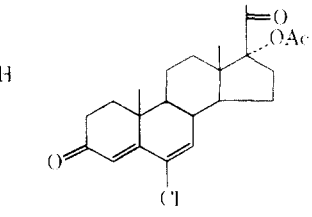
Received February 27, 1970

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

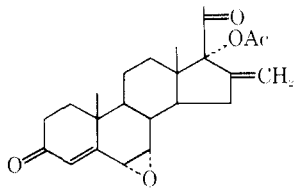


1

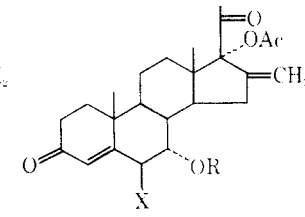
a, X = Cl
b, X = NHCOCH$_3$



2

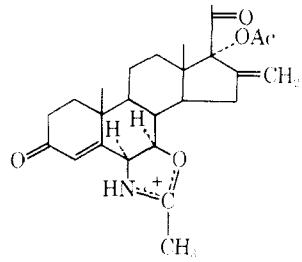


3



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, U. 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. Mazar, *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).

2β,3β-epoxy steroids in the presence of BF_3 or $HClO_4$. This method has been extended for the purpose of the present synthesis.

The starting epoxide, 6α,7α-epoxy-16-methylene-17α-hydroxy-4-pregnene-3,20-dione 17-acetate (**3**), was prepared by selective saponification of the chlorodiacetate **4a**[7] with concomitant oxide formation. In a first experiment, the *trans* diaxial opening of the 6α,7α-epoxide ring by MeCN was effected with the aid of $SnCl_4$ as a Lewis acid. 6β-Acetamino-7α,17α-dihydroxy-16-methylene-4-pregnene-3,20-dione 17-acetate (**4c**), was obtained in 40% yield. In addition to this compound, we also isolated 10% of the 6β-chloro analog **4b**, which upon acetylation (Ac_2O) in pyridine, gave the corresponding acetate **4a**. Chlorhydrin **4b** most likely arose from the presence of HCl resulting from the partial hydrolysis of $SnCl_4$. Acetylation of **4c** led to the acetamino acetate **4d**. In order to obtain **4d** in one step, and simultaneously, to circumvent the formation of **4b**, the epoxide **3** was treated with a mixture of MeCN and Ac_2O in the presence of *p*-TSA at room temperature. The reaction was slower than that catalyzed by $SnCl_4$, but afforded **4d** smoothly, in 38% yield. When BF_3 etherate was used instead of *p*-TSA, no steroidal acetamide could be isolated. The assignment of configurations at C_6 and C_7 was made in accordance with the rule of diaxial opening of epoxides,[9] and is supported by nmr data, namely the lack of any noticeable coupling of the C_6 proton with the C_4 vinylic proton, and the small coupling (2 Hz), between the C_7 and C_8 protons. Elimination of the 7-acetate from **4d** was more facile than in the 6β-chloro analog **4a**. A comparative experiment showed that under identical reaction conditions (*p*-TSA in $CHCl_3$ at 60°), **4d** was transformed quantitatively to 6-acetamino-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-acetate (**1b**), within 1 hr, whereas only 30% of **4a** was transformed to **1a** after 24 hr. This striking difference in reactivity is best explained by invoking the very favorable participation of the acetamino group in the acetate elimination, as represented by a possible intermediate species, such as **5**.

Experimental Section[10,11]

6α,7α-Epoxy-16-methylene-17α-hydroxy-4-pregnene-3,20-dione 17-Acetate (3).—To a solution of **4a** (5 g) in CH_2Cl_2 (62.5 ml) and MeOH (75 ml) was added a solution of NaOH (1.6 g) in H_2O (7.5 ml). The reaction mixture was left at 25° for 20 min. After the usual work-up ($CHCl_3$), crystallization from EtOAc–Et_2O afforded **3**: 2.45 g (57.3%); mp 250–254°; $[\alpha]D$ −104.7°; λ_{max} 240 mμ (ε 15,980); ν_{max} 1735, 1720, 1680, and 1625 cm^{-1}; nmr, δ 3.34 and 3.50 (J = 3.5 Hz, 6-H, 7-H) and 6.14 (s, 1, 4-H) ppm. *Anal.* ($C_{24}H_{30}O_5$) C, H.

6β-Acetamino-7α,17α-dihydroxy-16-methylene-4-pregnene-3,20-dione 17-Acetate (4c).—To a solution of **2** (398 mg) in CH_3CN (26 ml), $SnCl_4$ (1.1 ml) was added. After 15 min at 25°, the reaction mixture was worked up in the usual manner (CH_2Cl_2). Separation by preparative tlc afforded **4c**: 160 mg (41%); mp 230–231°; $[\alpha]D$ −36°; λ_{max} 239 mμ (ε 13,560); ν_{max} 3330, 3230, 1740, 1715, 1680, 1665, 1650, and 1635 cm^{-1}; nmr, δ 1.98 (s, 3, $NHCOCH_3$), 3.22 (7-OH), 4.58 (6-H), 6.00 (s, 1, 4-H), and 6.19 (m, 1, $NHCOCH_3$) ppm; *m/e* ($C_{26}H_{35}O_6N$) 457.

In addition to **4c**, chlorhydrin **4b**, 41 mg (10%) was isolated and characterized by comparison with an authentic sample.

6β-Acetamino-7α,17α-dihydroxy-16-methylene-4-pregnene-3,20-dione 7,17-Diacetate (4d). A. From 3.—Epoxide **3** (2.45 g) was added to a solution of *p*-TSA (2.4 g) in Ac_2O (60 ml) and MeCN (120 ml). The reaction mixture was kept at room temperature for 3.5 hr. After work-up in the usual way ($CHCl_3$), crystallization in Et_2O afforded the acetamino acetate **4d**: 1.16 g (38%); mp 238–241°; $[\alpha]D$ −82.7°; λ_{max} 237 mμ (ε 13,100); ν_{max} 3350, 1745, 1720, 1680, 1660, and 1520 cm^{-1}; nmr, δ 1.95 (s, 3, $NHCOCH_3$), 4.50 (6-H), 5.00 (7-H) ppm; *m/e* ($C_{28}H_{37}O_7N$) 499.

B. From 4c.—To a solution of **4c** (80 mg) in pyridine (2 ml), Ac_2O (0.4 ml) was added. After 2 days at room temperature, extraction with CH_2Cl_2 afforded 89 mg of crude material, which upon recrystallization in *i*-Pr_2O yielded pure **4d** (50 mg).

6-Acetamino-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate (1b).—A solution of **4d** (1.0 g) and *p*-TSA (20 mg) in $CHCl_3$ previously shaken with $CaCl_2$ (30 ml), was kept at 60° for 1 hr. The solution was then washed ($NaHCO_3$), dried, and evaporated to a residue. Crystallization from EtOAc–Et_2O, afforded **1b**, 783 mg (89%). One more crystallization, MeOH, gave the analytical sample: mp 191–193°; $[\alpha]D$ −124.9°; λ_{max} 288 mμ (ε 16,950); ν_{max} 3350, 1720, 1705, 1665, 1645, 1595 and 1520 cm^{-1}; nmr, δ 2.10 (s, 3, $NHCOCH_3$), 6.00 (s, 1, 4-H), 6.45 (d, 1, 7-H), 7.03 (m, 1, $NHCOCH_3$). *Anal.* ($C_{25}H_{33}O_5N$) C, H, N, *m/e* (439).

Biological Data.[12]—In the progestational assay carried out by the method of McPhail,[13] **1b** was found to have less activity than progesterone, whereas **1a** is 77 times as active as progesterone. In the intact rat antiandrogenic screen[14] **1b** was also inactive.

Acknowledgments.—We are grateful to Mr. M. Yudis and Mrs. H. Marigliano for the interpretation of the nmr spectra, and to Dr. T. Traubel for the mass spectra.

(12) The authors express their appreciation to Dr. R. Neri and staff for carrying out the biological tests.

(13) M. K. McPhail, *J. Physiol. (London)*, **83**, 145 (1934).

(14) R. O. Neri, M. D. Monahan, J. G. Meyer, B. A. Afonso, and I. A. Tabachnick, *Eur. J. Pharmacol.*, **1**, 438 (1967).

(9) A. Furst and Pl.A. Plattner, Abstracts of Papers, 12th International Congress Pure and Applied Chemistry, New York, N. Y., 1951, p 409.

(10) All melting points are uncorrected. Rotations are in dioxane at 26°, uv spectra are of MeOH solutions and ir spectra are in Nujol. Nmr spectra were recorded in $CDCl_3$, using Me_4Si as internal standard. Mass spectra were determined on a CEC 21-103 spectrometer using a heated inlet at a temperature of 230–240°; elemental analyses were by the Physical Organic Chemistry Department of the Schering Corporation. Where analyses are indicated only by symbols, analytical results obtained for these elements were within ±0.4% of the theoretical values. Although all other physical data are in excellent agreement with the proposed structures of the acetamino conpounds, C analyses were consistently low. This phenomenon was also observed in other N-containing steroids, *i.e.*, D. Cheron and F. Winternitz, Thesis of D. Cheron, Montpellier, France, 1965.

(11) The term "usual work-up" denotes: the reaction mixture was poured into H_2O, extracted with either CH_2Cl_2 or $CHCl_3$ (as indicated in parentheses). The organic layer was washed with dilute acid or base, as the case may be, dried ($MgSO_4$), and taken to dryness.

Ring-D-Bridged Steroid Analogs. VIII. Testosterone Analogs[1]

A. J. SOLO, J. N. KAPOOR,
Department of Medicinal Chemistry

AND P. HEBBORN
Department of Biochemical Pharmacology, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214

Received November 29, 1969

Recently, there has been considerable interest in determining the details of the structural requirements

(1) (a) This investigation was supported, in part, by the National Institute of Arthritis and Metabolic Diseases under Grant AM-006900; (b) part VII: A. J. Solo, B. Singh, and J. N. Kapoor, *Tetrahedron*, **25**, 4579 (1969).