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The Syntheses of Some Androstano[2,3-*g*]pteridines

FUMIO YONEDA,[1a] SHINOBU FUKAZAWA, and SADAO NISHIGAKI[1b]

Faculty of Pharmaceutical Sciences, Kumamoto University[1a] and School of Medicine, Keio University[1b]

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Reaction of 17β-hydroxy-5α-androstan-3-one morpholine or pyrrolidine enamine with 6-amino-5-nitrosopyrimidines or 6-amino-5-phenylazopyrimidines led to the formation of the corresponding androstano[2,3-*g*]pteridines. These steroidal pteridines were also prepared by the Isay's pteridine synthesis from 17β-hydroxy-5α-androstan-2,3-dione and the corresponding 5,6-diaminopyrimidines.

It was of interest to prepare pteridinosteroids with several types of pteridines which are linear with respect to the A and B rings of the steroids, since some other heterocyclic-fused steroids[2] maintained, modified, or accentuated some of the hormonal activities. Such a [2,3-*g*]-fused pteridinosteroid, 17β-acetoxy-5α-androstano[2,3-*g*]-2',4'-diaminopteridine, has first been prepared by Bardos, *et al.*[3] whose method consisted of the condensation of 17β-acetoxy-2α-bromo-5α-androstan-3-one with 2,4,5,6-tetraaminopyrimidine bisulfite. Recently, we reported the successful synthesis of some [2,3-*g*]-fused androstanopteridines, consisting of treatment of 6-amino-5-(1,2-diethoxycarbonylhydrazino)pyrimidines with 17β-hydroxy-5α-androstan-3-one morpholine enamine (3-morpholino-2-androstanolene).[4] This paper describes another convenient syntheses of some androstano[2,3-*g*]pteridines.

Weinstock, *et al.*[5] investigated the ability of an enamine to condense with a 6-amino-5-nitrosopyrimidine and succeeded in synthesis of 4-amino-2-phenylcyclopenta[*g*]pteridine by heating 1-pyrrolidinocyclopentene with 4,6-diamino-5-nitroso-2-phenylpyrimidine. First, we have extended this procedure to the preparation of steroidal pteridines.

The starting material for this synthesis, 3-morpholino-2-androstanolene (I) was prepared by the general procedure of Heyl and Herr[6]: Refluxing of 17β-hydroxy-5α-androstan-3-one with morpholine in dry benzene formed the corresponding enamine (I). The completion of the reaction was ascertained by infrared spectrum by the complete disappearance of CO-absorption at 1700 cm^{-1} and the appearance of the C=C-absorption at 1640 cm^{-1}. 3-Pyrrolidino-2-androstanolene (II) was similarly prepared from 17β-hydroxy-5α-androstan-3-one and pyrrolidine. Heating I with 6-amino-4-hydroxy-5-nitroso-2-phenylpyrimidine at 210° for 30 min gave 17β-hydroxy-5α-androstano[2,3-*g*]-4'-hydroxy-2'-phenylpteridine (IV) in quantitative yield. Similarly, compound I or II with 2,4,6-triamino-5-nitrosopyrimidine and 6-amino-1,3-dimethyl-5-nitrosouracil led to 17β-hydroxy-5α-androstano[2,3-*g*]-2',4'-diaminopteridine (V) and 17β-hydroxy-5α-androstano[2,3-*g*]-1',3'-dimethyllumazine (VI), respectively. (The above is referred to as Method A.)

Next, 6-amino-5-phenylazopyrimidines instead of 6-amino-5-nitrosopyrimidines have been used for the synthesis of these androstano[2,3-*g*]pteridines. Heating I with 6-amino-4-hydroxy-2-methyl-5-phenylazopyrimidine afforded successfully 17β-hydroxy-5α-androstano-[2,3-*g*]-4'-hydroxy-2'-methylpteridine (III). Similarly, treatment of I with 6-amino-4-

1) Location: *a*) 5, *Oe-honmachi, Kumamoto*; *b*) 35, *Shinanomachi, Shinjuku-ku, Tokyo.*
2) R.E. Counsell and P.D. Klimstra, "Medicinal Chemistry," 3rd Ed., Part II, ed. by A. Burger, Wiley-Interscience, New York, 1970, p. 923.
3) S.P. Raman, Z.F. Chmielewicz, T.J. Bardos, R.B. Gabbard, and A. Segaloff, *J. Med. Chem.*, **7**, 678 (1964).
4) F. Yoneda, S. Fukazawa, and S. Nishigaki, *Chem. Commun.*, **1971**, 83.
5) J. Weinstock, R.Y. Dunloff, J.E. Carevic, J.G. Williams, and A.J. Villani, *J. Med. Chem.*, **11**, 618 (1968).
6) F.W. Heyl and M.E. Herr, *J. Am. Chem. Soc.*, **75**, 1918 (1953).

hydroxy-2-phenyl-5-phenylazopyrimidine and 5-phenylazo-2,4,6-triaminopyrimidine under similar conditions yielded compounds IV and V, respectively (Method B).

When the corresponding *p*-nitrophenylazopyrimidines, which may have stronger reactivity, were used in the above reaction, the yields of the products were considerably increased as expected (Method C). Used 5-*p*-nitrophenylazopyrimidines are as follows: 6-amino-4-hydroxy-5-*p*-nitrophenylazo-2-phenylpyrimidines, 6-amino-4-hydroxy-2-methyl-5-*p*-nitrophenylazopyrimidine and 5-*p*-nitrophenylazo-2,4,6-triaminopyrimidine.

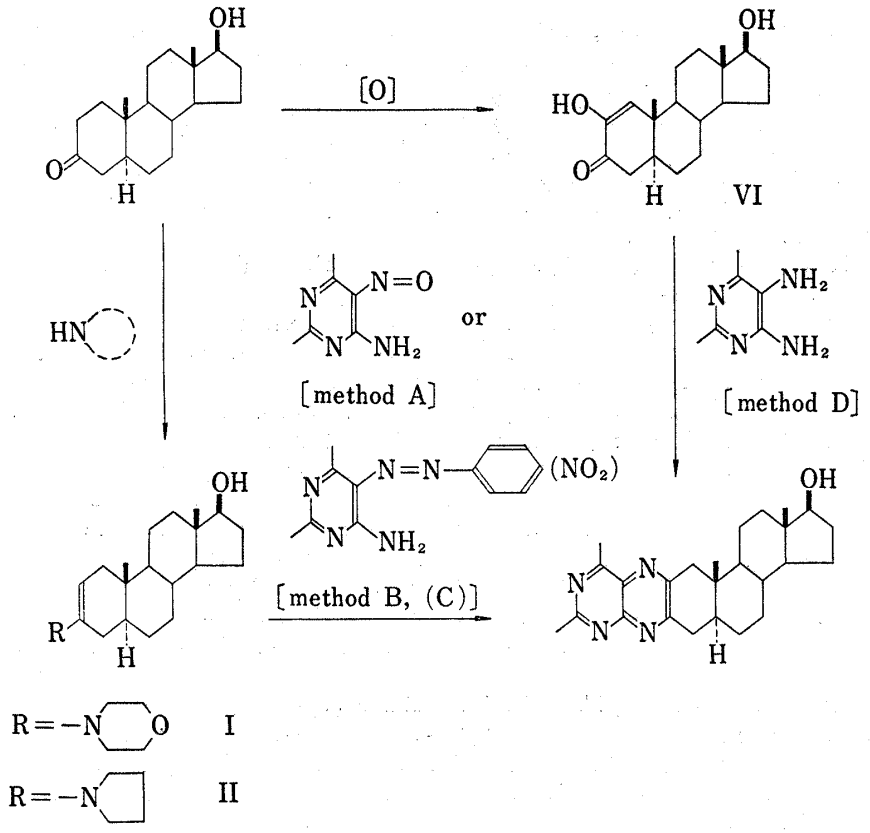

Chart 1

The structures of some of these steroidal pteridines were confirmed by the Isay's pteridine synthesis from 17*β*-hydroxy-5*α*-androstan-2,3-dione (VII)[7] and the corresponding 5,6-diaminopyrimidines. Compound VII was prepared by the oxygen oxidation of 17*β*-hydroxy-5*α*-androstan-3-one in *t*-buthanol in the presence of potassium *t*-buthoxide. Treatment of VII with 5,6-diamino-1,3-dimethyluracil in acetic acid gave compound VI, which was identical in all respects with the authentic sample synthesized by Method A. Similarly, treatment of VII with 5,6-diamino-4-hydroxy-2-methyl- and 5,6-diamino-4-hydroxy-2-phenylpyrimidine formed compounds III and IV, respectively (Method D).

Experimental[8]

3-Morpholino-2-androstanolene (17*β*-Hydroxy-5*α*-androstan-3-one Morpholine Enamine) (I)——17*β*-Hydroxy-5*α*-androstan-3-one[9] (2.0 g, 0.0068 mole) and morpholine (3.0 g, 0.035 mole) were dissolved in 100 ml of dry benzene and refluxed for 3 hr. The course of the reaction was followed by noting the amount of H_2O collected in a Bidwell–Sterling moisture trap. The reaction mixtute was concentrated to dryness *in vacuo* to give almost pure product, mp 166—170°, in quantitative yield. This compound was extremely sensitive to moisture and was immediately offered for the next step without recrystallization.

7) G. Ohta, T. Takegoshi, K. Ueno, and M. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **13**, 1445 (1965).
8) All melting points are uncorrected.
9) A. Butenandt, K. Tscherning, and G. Hanisch, *Chem. Ber.*, **68**, 2097 (1935).

3-Pyrrolidino-2-androstanolene (II)——This compound was prepared in the same manner from 17β-hydroxy-5α-androstan-3-one and pyrrolidine. mp 135—139°. This compound was more sensitive to moisture than compound I.

17β-Hydroxy-5α-androstano[2,3-*g*]-4′-hydroxy-2′-methylpteridine (III)——Method B: A mixture of I (0.50 g, 0.0014 mole) and 6-amino-4-hydroxy-2-methyl-5-phenylazopyrimidine (0.23 g, 0.001 mole) was heated with occasional stirring at 260° for 35 min. The brown reaction mixture was diluted with ether, the precipitated powder collected by filtration and washed with ether. Recrystallization from acetone gave 0.26 g (56.5%) of yellow powder, mp 276—280° (decomp.). $[\alpha]_D^{20}=+67°$ ($c=1.00$, $CHCl_3$). Its mass spectrum showed a strong parent ion at *m/e* 408. *Anal.* Calcd. for $C_{24}H_{32}O_2N_4$: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.39; H, 7.84; N, 13.95.

Method C: A mixture of I (0.20 g, 0.00056 mole) and 6-amino-4-hydroxy-2-methyl-5-*p*-nitrosophenylazopyrimidine (0.10 g, 0.00037 mole) was heated with occasional stirring at 300° for 5 min. After cooling, the reaction mixture was treated with ether to precipitate pale brown powder. Recrystallization from acetone gave pale yellow powder, mp 275° (decomp.), in quantitative yield.

Method D: A solution of 5,6-diamino-4-hydroxy-2-methylpyrimidine (0.14 g, 0.001 mole) and 17β-hydroxy-5α-androstan-2,3-dione (0.40 g, 0.0013 mole) in 10 ml of AcOH was refluxed for 1 hr at about 150°. The solution was evaporated to dryness and the residue was recrystallized from acetone to give 0.23 g (74.7%) of yellow powder, mp 275° (decomp.).

17β-Hydroxy-5α-androstano[2,3-*g*]-4′-hydroxy-2′-phenylpteridine (IV)——Method A: A mixture of I (0.50 g, 0.0014 mole) and 6-amino-4-hydroxy-5-nitroso-2-phenylpyrimidine (0.30 g, 0.0014 mole) was heated with occasional stirring at 200—210° for 30 min. The reaction mixture was gradually changed into a brown resin. After cooling, the resin product was washed with ether to separate yellow powder. Recrystallization from ether gave yellow powder, mp 286—289° (decomp.), in quantitative yield. $[\alpha]_D^{20}=+50°$ ($c=1.01$, $CHCl_3$). Its mass spectrum revealed a strong parent ion at *m/e* 470. *Anal.* Calcd. for $C_{29}H_{34}O_2N_4+H_2O$: C, 71.28; H, 7.43; N, 11.47. Found: C, 71.21; H, 7.47; N, 11.21.

Method B: A mixture of I (0.50 g, 0.0014 mole) and 6-amino-4-hydroxy-2-phenyl-5-phenylazopyrimidine (0.22 g, 0.00076 mole) was heated at 250° for 25 min. After cooling, the brown mixture was diluted with ether to separate the crude product, which was collected by filtration, washed with ether and recrystallized from EtOAc to give 0.31 g (87%) of pale yellow powder, mp 286—289° (decomp.).

Method C: A mixture of I (0.50 g, 0.0014 mole) and 6-amino-4-hydroxy-5-*p*-nitrophenylazo-2-phenylpyrimidine (0.35 g, 0.001 mole) was heated with occasional stirring at 300° for 7 min. Treatment of the reaction mixture in the same manner described above gave 0.44 g (90.3%) of pale yellow powder, mp 285—289° (decomp.).

17β-Hydroxy-5α-androstano[2,3-*g*]-2′,4′-diaminopteridine (V)——Method A: A mixture of the pyrrolidine enamine (II) (0.04 g, 0.00026 mole) and 2,4,6-triamino-5-nitrosopyrimidine (0.04 g, 0.00026 mole) was heated with occasional stirring at 270° for 20 min. After cooling, the crude product was washed with ether and recrystallized from EtOAc to give 0.08 g (75.4%) of yellow powder, mp 329—331° (decomp.). $[\alpha]_D^{20}=+53°$ ($c=0.41$, $CHCl_3$). The mass spectrum showed a strong parent peak at *m/e* 408. *Anal.* Calcd. for $C_{23}H_{32}ON_6$: C, 67.62; H, 7.90; N, 20.57. Found: C, 67.90; H, 7.83; N, 20.38.

Method B: A mixture of I (0.50 g, 0.0014 mole) and 5-phenylazo-2,4,6-triaminopyrimidine (0.23 g, 0.01 mole) was heated with occasional stirring at 280° for 25 min. The dark brown solid was treated with ether, the brown powder was separated by filtration, and recrystallized from EtOAc to give 0.24 g (58.5%) of yellow powder, mp 330° (decomp.).

17β-Hydroxy-5α-androstano[2,3-*g*]-1′,3′-dimethyllumazine (VI)——Method A: A mixture of II (0.90 g, 0.0049 mole) of 6-amino-1,3-dimethyl-5-nitrosouracil (0.35 g, 0.001 mole) was heated with occasional stirring at 200° for 10 min. Violet color of nitrosouracil was faded away and changed into dark red. After cooling, the dark red solid was washed with ether and a small amount of MeOH and collected by filtration to give pale yellow powder. Recrystallization from MeOH gave 0.35 g (42.1%) of colorless needles, mp 287—290° (decomp.). $[\alpha]_D^{20}=+53°$ ($c=1.00$, $CHCl_3$). Its mass spectrum revealed a strong parent ion at *m/e* 438. *Anal.* Calcd. for $C_{25}H_{34}O_3N_4+H_2O$: C, 65.76; H, 7.95; N, 12.27. Found: C, 65.97; H, 7.93; N, 12.04.

Method D: A solution of VII (0.30 g, 0.001 mole) and 5,6-diamino-1,3-dimethyluracil (0.47 g, 0.0028 mole) in 10 ml of AcOH was refluxed at about 150° for 1 hr. The solution was evaporated to dryness, the residue extracted with ether, and the ether extracts were evaporated to give 0.3 g (68.5%) of colorless powder. Recrystallization from ether gave colorless needles, mp 287—290° (decomp.).

17β-Hydroxy-5α-androstane-2,3-dione (VII)——A solution of potassium *t*-buthoxide prepared from potassium (1.00 g, 0.026 g atom) and *t*-buthanol (50 ml) was stirred under oxygen at room temperature until there was no further uptake of the gas. A solution of 17β-hydroxy-5α-androstan-3-one (0.88 g, 0.003 mole) in *t*-buthanol (30 ml) was then added and stirring under oxygen was continued for 1 hr. The reaction mixture was neutralized with AcOH and concentrated *in vacuo*. The residue was filtered, washed with H_2O and dried. Recrystallization from EtOH–H_2O (1:1) gave colorless needles of 17β-hydroxy-5α-androstan-2,3-dione, mp 107°, as its enol form in quantitative yield. $[\alpha]_D^{20}=+63°$ ($c=1.01$, $CHCl_3$). Its mass spectrum showed a strong parent ion at *m/e* 304. *Anal.* Calcd. for $C_{19}H_{28}O_3+1/2\ H_2O$: C, 72.81; H, 9.33. Found: C, 72.79; H, 9.05.

Preparation of 6-Amino-5-*p*-nitrophenylazopyrimidines——*p*-Nitroaniline (2.3 g, 0.017 mole) was dissolved in 10% HCl (40 ml) and $NaNO_2$ (1.15 g, 0.017 mole) was added gradually under cooling with ice water. On the other hand, 6-amino-4-hydroxy-2-phenylpyrimidine (3.00 g, 0.017 mole) was dissolved in 3N AcOH (75 ml), to this solution the prepared diazonium chloride solution was added dropwise under stirring. After neutralization with NaOAc and maintaining overnight at room temperature, the precipitated crystals were collected by filtration, washed with H_2O and recrystallized from DMF to give yellow crystals, mp >320°. *Anal.* Calcd. for $C_{16}H_{12}O_3N_6$: C, 57.14; H, 3.60; N, 24.99. Found: C, 57.38; H, 3.45; N, 25.27.

In the same manner, 6-amino-4-hydroxy-2-methyl-5-*p*-nitrophenylazopyrimidine, mp>320°, (yellow crystals. *Anal.* Calcd. for $C_{11}H_{10}O_3N_6$: C, 48.17; H, 3.68. Found: C, 48.47; H, 3.48) and 5-*p*-nitrophenylazo-2,4,6-triaminopyrimidine, mp>320°, (orange-red powder. *Anal.* Calcd. for $C_{10}H_{10}O_2N_8+H_2O$: C, 41.09; H, 4.14; N, 38.34. Found: C, 40.85; H, 3.94; N, 38.13) were synthesized.