[Chem. Pharm. Bull. 15(4) 523~527 (1967)]

UDC 547.92.07

Katsujiro Ueno, Kazunaga Obata, and Masao Shimizu : Investigations on Steroids. Ⅷ.*1 Synthesis of Steroidal [2,3-*c*]furazans of Pregnane Series.

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A number of steroids of pregnane series with a heterocycle fused at the 2,3-positions were synthesized recently. Progestational activities of [3,2-*c*]pyrazoles related to progesterone[1] and anti-inflammatory activities of [2,3-*d*]isoxazoles, [3,2-*c*]pyrazoles, [3,2-*d*]-thiazoles, [2,3-*d*]imidazoles, [2,3-*d*]triazoles, and [3,2-*d*]pyrimidines related to cortisol[1b,2] were reported, indicating that the activities are dependent specifically on the structure of the heterocycle. In view of the anabolic activities associated with certain androstano-[2,3-*c*]furazans,[3] preparation of [2,3-*c*]furazans related to progesterone and to cortisol was undertaken to evaluate the effect produced by fusion of a furazan ring.

The method of synthesis employed the same sequence of reactions as used previously for other steroidal furazans.[4] Oxidation of 5α-pregnane-3,20-dione 20-ethylene ketal (Ⅰ) with oxygen in the presence of potassium *tert*-butoxide, followed by oximation gave the 2,3-dione dioxime (Ⅱa). The same compound was obtained, alternatively, by oximation of the 2-hydroxyimino-3-ketone (Ⅱb) which was prepared by nitrosation of Ⅰ. Furazan ring formation by heating the dioxime (Ⅱa) with alkali in ethylene glycol at 180° and subsequent removal of the ketal group afforded 20-oxo-5α-pregnano[2,3-*c*]furazan (Ⅳ).

For the synthesis of the corresponding 4,5-unsaturated compound (Ⅶ), the 2-hydroxymethylene-20β-hydroxy-3-ketone (Va)[5] was treated with sodium nitrite and acetic acid to give the 2-hydroxyimino-3-ketone (Vb). Oximation of Vb, followed by ring closure with alkali, gave the furazan (Ⅵ), which was oxidized to yield the 20-ketone (Ⅶ).

Similarly, 2-hydroxymethylene-17α,20;20,21-bismethylenedioxy-11β-hydroxypregn-4-en-3-one[6] (Ⅷa) was converted to the 2,3-dione dioxime (Ⅷc), *via* the 2-hydroxyimino-3-ketone (Ⅷb). Since the bismethylenedioxy moiety was unstable to treatment with alkali at 180°, the dioxime (Ⅷc) was converted to the furazan N-oxide (Ⅸ, 2′-oxide and/or 5′-oxide) by treatment with sodium hypochlorite. Deoxygenation of the N-oxide with triethyl phosphite and subsequent removal of the protective group furnished the furazan (Ⅺ).

The spectral data of the compounds described above were consistent with the assigned structures.

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1) *a*) Belgian Patent, 633906 (1963); *b*) German Patent, 1152101 (1963).

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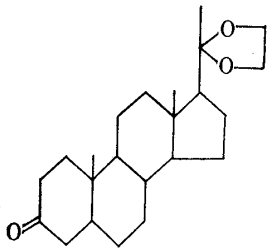
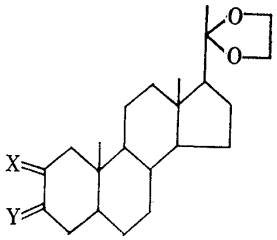
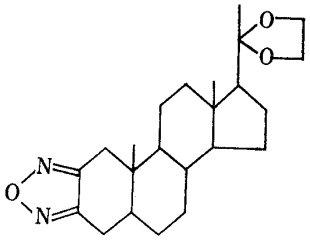


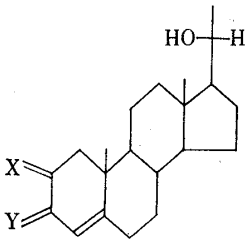
I



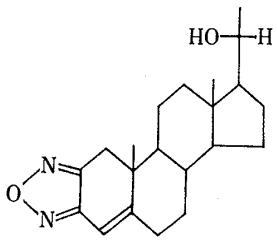
IIa : X=Y=NOH
IIb : X=NOH, Y=O



III



Va : X=CHOH, Y=O
Vb : X=NOH, Y=O
Vc : X=Y=NOH



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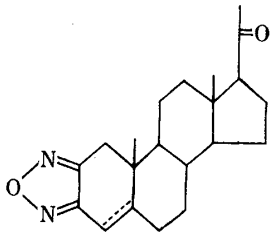
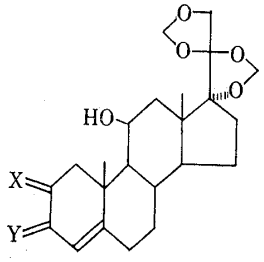
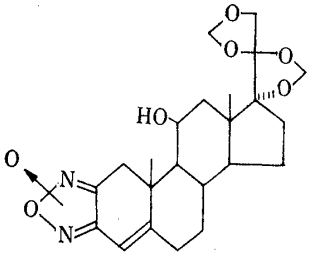


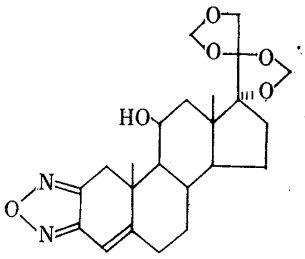
IV : 4,5α-saturated
VII : 4,5-unsaturated



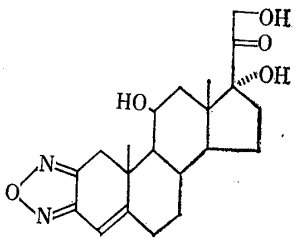
VIIIa : X=CHOH, Y=O
VIIIb : X=NOH, Y=O
VIIIc : X=Y=NOH



IX



X



XI

Chart 1.

The detailed biological activities of the compounds will be reported elsewhere, but preliminary findings are presented.*3 Compound Ⅳ is devoid of progestational activity and compound Ⅶ is 0.2 times as progestational as progesterone by Clauberg assay. Compound Ⅺ has an anti-inflammatory activity of 2.5 times hydrocortisone acetate in the rat systemic granuloma assay. All the compounds were administered subcutaneously.

Experimental*4

2-Hydroxyimino-5α-pregnane-3,20-dione 20-Ethylene Ketal (IIb)——To a solution of *tert*-BuOK (0.34 g. of K and 15 ml. of *tert*-BuOH) was added a solution of 5α-pregnane-3,20-dione 20-ethylene ketal[7] (I, 1.0 g.) in *tert*-BuOH (50 ml.). A solution of *tert*-BuONO (0.34 g.) in *tert*-BuOH (8 ml.) was then added with stirring under nitrogen over 17 min. and stirring was continued for 2 hr. The reaction mixture was poured into H_2O (250 ml.) and extracted with ether. The ethereal solution was washed with water, dried and evaporated. The residue was mixed with benzene to separate a solid (0.315 g.) which was crystallized from $CHCl_3$–MeOH to give IIb, m.p. 254~263°(decomp.), $[\alpha]_D$ +65.6°(c=1.09, pyridine). UV λ_{max} mμ (ε): 243 (7170). IR ν_{max} cm^{-1}: 3135, 1715, 1620, 1060, 1045, 975, 954. *Anal.* Calcd. for $C_{23}H_{35}O_4N$: C, 70.92; H, 9.06; N, 3.60. Found: C, 71.04; H, 8.85; N, 3.72.

2,3-Dihydroxyimino-5α-pregnan-20-one 20-Ethylene Ketal (IIa)——a) To a solution of hydroxylamine in MeOH prepared from hydroxylamine hydrochloride (0.174 g.), sodium acetate (0.33 g.) and MeOH (10 ml.), was added a solution of IIb (0.195 g.) in pyridine (5 ml.) and the mixture was refluxed for 1 hr. Evaporation of the solvent and dilution of the residue with water separated a solid (0.11 g.) melting at 240~241.5° (decomp.) which was crystallized from MeOH to afford IIa, m.p. 240~241°(decomp.), $[\alpha]_D$ +66.2°(c=0.55, pyridine). UV λ_{max} mμ (ε): 240 (6550). IR ν_{max} cm^{-1}: 3390, 3190, 1065, 1045, 942, 922. *Anal.* Calcd. for $C_{23}H_{36}O_4N_2$: C, 68.28; H, 8.97; N, 6.93. Found: C, 68.41; H, 9.07; N, 7.06.

b) A solution of *tert*-BuOK (0.54 g. of K and 25 ml. of *tert*-BuOH) was stirred under oxygen at room temperature and to this was added a solution of I (1.0 g.) in *tert*-BuOH (50 ml.). The mixture was stirred for 1 hr., while 64 ml. of oxygen (theory 67 ml.) was absorbed. The solution was neutralized with 20% AcOH and a solution of hydroxylamine prepared from hydroxylamine hydrochloride (1.55 g.), sodium acetate (2.74 g.) and MeOH (45 ml.) was added. After refluxing for 1 hr., the reaction mixture was concentrated and diluted with water to separate IIa (1.03 g.), m.p. 235~237°(decomp.). Two crystallizations from MeOH gave a pure sample, m.p. and mixed m.p. 242~243°(decomp.).

20-Oxo-5α-pregnano[2,3-*c*]furazan 20-Ethylene Ketal (III)——A mixture of IIa (0.18 g.), KOH (0.05 g.) and ethylene glycol (5 ml.) was heated at 180~190° for 15 min. The reaction mixture was diluted with water to separate a solid (0.105 g.), m.p. 196~202°. Chromatography of the product in benzene solution over alumina, followed by crystallization from acetone–MeOH gave III, m.p. 202~205.5°, $[\alpha]_D$ +62.5°(c=0.87). UV λ_{max} mμ (ε): 217 (4810). IR ν_{max} cm^{-1}: 1585, 1495, 1002 (furazan); 1055, 1040 (ketal). *Anal.* Calcd. for $C_{23}H_{34}O_3N_2$: C, 71.47; H, 8.87; N, 7.25. Found: C, 71.64; H, 8.90; N, 7.21.

20-Oxo-5α-pregnano[2,3-*c*]furazan (IV)——A mixture of III (0.50 g.) and 80% AcOH (30 ml.) was heated at 100° for 30 min. The reaction mixture was concentrated and the residue was diluted with water to separate a crude product which was dissolved in benzene and filtered through a column of alumina (10 g.). Evaporation of the solvent and crystallization of the residue from acetone afforded IV (0.375 g.). Recrystallization from the same solvent gave a pure sample, m.p. 205.5~208.5°, $[\alpha]_D$ +138.3°(c=1.19). UV λ_{max} mμ (ε): 217 (4670). IR ν_{max} cm^{-1}: 1590, 1499, 1002 (furazan); 1703 (20-ketone). *Anal.* Calcd. for $C_{21}H_{30}O_2N_2$: C, 73.64; H, 8.83; N, 8.18. Found: C, 73.59; H, 8.94; N, 7.98.

2-Hydroxyimino-20β-hydroxypregn-4-en-3-one (Vb)——To a solution of 2-hydroxymethylene-20β-hydroxypregn-4-en-3-one[5] (Va, 3.20 g.) in MeOH (60 ml.) was added an aqueous solution (12 ml.) of $NaNO_2$ (2.57 g.). To the ice-cooled mixture was added AcOH (10 ml.) with stirring during 8 min. and stirring was continued for 1 hr, at room temperature. The mixture was diluted with water and the separated product was crystallized from AcOEt to give Vb, m.p. 213~214°(decomp.) in 35.6% yield. Recrystallization from the same solvent gave an analytical sample with the same m.p., $[\alpha]_D$ +79.0°(c=0.86, pyridine). UV λ_{max} mμ (ε): 264 (14580). IR ν_{max} cm^{-1}: 3350, 1679, 1614, 1025, 983, 939, 880, 868. *Anal.* Calcd. for $C_{21}H_{31}O_3N$: C, 73.00; H, 9.05; N, 4.05. Found: C, 73.02; H, 9.04; N, 4.31.

*3 The biological activities were determined by Mr. A. Kasahara and his associates in this Laboratory.

*4 Melting points are uncorrected. IR spectra were taken in a KBr-disc, and UV spectra in EtOH. Unless otherwise stated, optical rotations were measured in $CHCl_3$. Microanalyses were performed by Mr. B. Kurihara and Miss K. Hanawa in this Laboratory.

7) J. A. Edwards, J. C. Orr, A. Bowers: J. Org. Chem., **27**, 3378 (1962).

2,3-Dihydroxyiminopregn-4-en-20β-ol (Vc)——A solution of Vb (0.30 g.) in MeOH (10 ml.) and pyridine (1 ml.) was mixed with hydroxylamine hydrochloride (90 mg.) in water (1 ml.) and the mixture was refluxed for 30 min. The reaction mixture was diluted with water and the separated product (0.29 g.) was crystallized from MeOH to give Vc, m.p. 244~245°(decomp.), $[\alpha]_D$ +108.6°(c=0.90, pyridine). UV λ_{max} mμ (ε): 230 (14490), 261 (14100). IR ν_{max} cm^{-1}: 3530, 3340~3100, 1616, 1100, 1027, 991, 958, 927, 867. *Anal.* Calcd. for $C_{21}H_{32}O_3N_2$: C, 69.97; H, 8.95; N, 7.77. Found: C, 69.96; H, 8.93; N, 8.06.

20β-Hydroxypregn-4-eno[2,3-*c*]furazan (VI)——Treatment of Vc (2.75 g.) in ethylene glycol (15 ml.) with KOH (0.63 g.) as described for III gave a crude product (1.38 g.). Recrystallization from MeOH afforded a pure sample of VI, m.p. 192~193.5°, $[\alpha]_D$ +145.6°(c=0.88). UV λ_{max} mμ (ε): 255~256 (10840). IR ν_{max} cm^{-1}: 1625, 851 (Δ^4); 3600, 1103 (OH); 1575, 1510, 999 (furazan). *Anal.* Calcd. for $C_{21}H_{30}O_2N_2$: C, 73.64; H, 8.83; N, 8.18. Found: C, 73.56; H, 8.69; N, 8.07.

20-Oxopregn-4-eno[2,3-*c*]furazan (VII)—— To a solution of VI (1.58 g.) in acetone (50 ml.) was added 8*N* CrO_3-H_2SO_4 solution[8] (1.70 ml.) under ice-cooling. The reaction mixture was diluted with water and the separated product was collected. After chromatography in benzene solution over alumina, the product was crystallized from MeOH to give VII (0.90 g.), m.p. 152~153°, $[\alpha]_D$ +256.4°(c=1.00). UV λ_{max} mμ (ε): 255~256 (10840). IR ν_{max} cm^{-1}: 3040, 1625 (Δ^4); 1698 (C=O); 1573, 1511, 1001 (furazan). *Anal.* Calcd. for $C_{21}H_{28}O_2N_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.27; H, 8.49; N, 8.20.

2-Hydroxyimino-17α,20;20,21-bismethylenedioxy-11β-hydroxypregn-4-en-3-one (VIIIb)——To an ice-cooled mixture of AcOH (170 ml.) and water (17 ml.) was added 2-hydroxymethylene-17α,20;20,21-bismethylenedioxy-11β-hydroxypregn-4-en-3-one[5] (VIIIa, 4.90 g.) in $CHCl_3$ (60 ml.). An aqueous solution (20 ml.) of $NaNO_2$ (1.56 g.) was added with stirring over 15 min. and stirring was continued for 1 hr. The reaction mixture was diluted with water and extracted with $CHCl_3$. The $CHCl_3$-solution was washed with water, 5% $NaHCO_3$-solution and water, dried and evaporated. The residue (4.8 g.) was used without purification for the next reaction. Crystallization of a portion of the residue from AcOEt and then from ether-AcOEt gave a pure sample of VIIIb, pale yellow needles, m.p. 227~228°(decomp.), $[\alpha]_D$ −6.1°(c=1.06, pyridine). UV λ_{max} mμ (ε): 265~266 (13710). IR ν_{max} cm^{-1}: 3530~3440, 3310, 1677, 1614, 1097, 985, 942, 872. *Anal.* Calcd. for $C_{23}H_{31}O_7N \cdot \frac{1}{2}H_2O$: C, 62.42; H, 7.29; N, 3.17. Found: C, 62.41, 62.37; H, 7.05, 7.10; N, 3.13

2,3-Dihydroxyimino-17α,20;20,21-bismethylenedioxypregn-4-en-11β-ol (VIIIc)——As described for Vc, VIIIb (0.38 g.) was oximated to give the crude dioxime (0.31 g.), m.p. 260°(decomp.). Crystallization from MeOH gave a pure sample of VIIIc, pale yellow needles, m.p. 264~265°(decomp.), $[\alpha]_D$ +58.8°(c=1.09, pyridine). UV λ_{max} mμ (ε): 231 (13420), 261~262 (14170). IR ν_{max} cm^{-1}: 3610, 3370, 3160, 1623, 1097, 1010~910, 872. *Anal.* Calcd. for $C_{23}H_{32}O_7N_2$: C, 61.59; H, 7.19; N, 6.25. Found: C, 61.35; H, 7.18; N, 6.35.

11β-Hydroxy-17α,20;20,21-bismethylenedioxypregn-4-eno[2,3-*c*]furazan N-Oxide (IX)——A solution of sodium hypochlorite was prepared by introducing Cl_2-stream into an aqueous 10% NaOH-solution and the solution was added with stirring to an ice-cooled solution of VIIIc (0.38 g.) in a mixture of an aqueous 6% NaOH-solution and MeOH (1:1, 44 ml.) until there was no further precipitation. The reaction mixture was diluted with water and the precipitate was collected, washed with water, dried and dissolved in $CHCl_3$. The solution was filtered through silica gel (2 g.) and concentrated *in vacuo*. Crystallization of the residue from AcOEt gave IX (0.22 g.), m.p. 225~226°(decomp.). Recrystallization from acetone-AcOEt afforded an analytical sample, pale yellow prisms, m.p. 226.5~227.5°(decomp.), $[\alpha]_D$ +33.4°(c=0.98). UV λ_{max} mμ (ε): 233~234 (17050), 269~270 (8040); inflexion: 227 (16520), 244 (12010). IR ν_{max} cm^{-1}: 3510, 1636, 1472, 1097, 986, 941. *Anal.* Calcd. for $C_{23}H_{30}O_7N_2$: C, 61.87; H, 6.77; N, 6.27. Found: C, 61.63; H, 6.87; N, 6.29.

11β-Hydroxy-17α,20;20,21-bismethylenedioxypregn-4-eno[2,3-*c*]furazan (X)——A suspension of IX (0.98 g.) in triethyl phosphite (10 ml.) was heated under nitrogen at 140~150° for 1.5 hr. The clear solution obtained was diluted with aqueous 10% H_2SO_4-solution to destroy the excess reagent. The precipitated product, whose IR spectrum indicated the presence of a phosphate group (ν_{max}: 1250 cm^{-1}), was dissolved in a methanolic 2% KOH-solution (60 ml.) and the solution was refluxed for 45 min. Dilution with water gave a precipitate which was dissolved in AcOEt and the solution was filtered through alumina (3 g.). Removal of the solvent *in vacuo* and crystallization of the residue from acetone-MeOH gave X (0.58 g.), m.p. 230~232°. An analytical sample, recrystallized from MeOH, melted at 232~233.5°, $[\alpha]_D$ +57.3°(c=0.94). UV λ_{max} mμ (ε): 256 (10340); inflexion: 225 (7300). IR ν_{max} cm^{-1}: 3490, 1637, 1583, 1510, 1090, 1018, 990, 941, 863. *Anal.* Calcd. for $C_{23}H_{30}O_6N_2$: C, 64.17; H, 7.02; N, 6.51. Found: C, 64.07; H, 7.16; N, 6.37.

20-Oxo-11β,17α,21-trihydroxypregn-4-eno[2,3-*c*]furazan (XI)——A suspension of X (1.01 g.) in an aqueous 60% HCOOH-solution (120 ml.) was heated with occasional shaking at 100° for 35 min. The resulting solution was concentrated below 45° *in vacuo* and diluted with water to separate a precipitate (0.87 g.), whose IR spectrum indicated the presence of a formate group (ν_{max}: 1700, 1170 cm^{-1}). To a solution of

8) K. Bowden, I. M. Heilbron, E. R. H. Jones, B. C. L. Weedon: J. Chem. Soc., **1946**, 39.

the precipitate in MeOH (18 ml.) was added dropwise a 0.5*M* sodium methoxide solution (6.70 ml.) at room temperature under nitrogen. After being stirred for 12 min., the mixture was neutralized with AcOH, concentrated below 40° ***in vacuo*** and diluted with water to give a precipitate (0.87 g.). This was dissolved in $CHCl_3$ and chromatographed over silica gel (34.7 g.). Fractions eluted with $CHCl_3$ (100 ml.) and with $CHCl_3$–acetone (9:1, 300 ml.) were discarded. From the subsequent fractions eluted with $CHCl_3$–acetone (9:1, 100 ml.; 1:1, 200 ml.) was obtained a product which was crystallized from hexane–AcOEt to give XI (0.45 g.). Recrystallization from the same solvent mixture gave an analytical sample, m.p. 200~202°(sintered at 190°), $[\alpha]_D$ +194.2°(c=1.24, EtOH). UV λ_{max} mμ (ε): 256 (10510); inflexion 225 (7810). IR ν_{max} cm^{-1}: 3450, 1710, 1628, 1575, 1511, 1118, 1096, 1055, 1043, 1006, 897, 861. *Anal.* Calcd. for $C_{21}H_{28}O_5N_2$: C, 64.93; H, 7.27; N, 7.21. Found: C, 64.90; H, 7.03; N, 7.17.

The authors thank Dr. T. Ishiguro, the President of this Company for his interest and encouragement.

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UDC 541.127

Masaichiro Masui and Hidenobu Ohmori: Method for Obtaining the Rate Constant of a Reversible Reaction.

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When a homogeneous chemical reaction is followed by the change of some physical property, a pseudo-first-order kinetic treatment is usually applied because of its mathematical simplicity, and the apparent rate constant is generally calculated by a graphical method. Roseveare,[1] however, pointed out that in a reaction in which the rate is represented by the equation, $dx/dt=k(a-x)\pm k'(b-x)$, where a and b are constants, a straight line is obtainable by an ordinary first-order plot of $\ln(a-x)$ *vs.* time, or by Guggenheim's plot. Thus, when the above methods are applicable, it must be a scertained whether there is any contribution from the second term.

Further, we recognized that the above treatments for a reaction expressed by a rate expression, $-dx/dt=k(a-x)-k'x^2$, also gave an almost linear plot from which an approximate rate constant k was obtainable.

In a reversible reaction (1),

$$X \underset{}{\overset{k}{\rightleftarrows}} Y + Z \qquad (1)$$

the forward rate constant, k, can be obtained from eq. (2)

$$\ln \frac{x_0^2 - x x_e}{x_0(x-x_e)} = k\left(\frac{x_0+x_e}{x_0-x_e}\right)t \qquad (2)$$

where x expresses the concentration of X at time t and the subscripts 0 and e refer to the initial and equilibrium concentrations, respectively.[2] The concentration of Y and Z are zero when $t=0$. When β represents the amount of some physical property of X at time t, which is proportional to the concentration, $\beta=ax$ where a is a proportionality constant. Thus eq. (2) becomes

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*1 Toneyama, Toyonaka-shi, Osaka (枡井雅一郎, 大森秀信).

1) W. E. Roseveare: J. Am. Chem. Soc., **53**, 1651 (1931).

2) A. Frost, R. G. Pearson: "Kinetics and Mechanisms," 2nd Ed. p. 187. John Wiley & Sons, Inc., London.