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Synthesis of 14,15-Epoxyisobufadienolides[1]

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In order to clarify the structure–activity relationship of the cardiotonic steroids the synthesis of the 14,15-epoxyisobufadienolides, in which C-17 is linked to 6-position of the α-pyrone ring, has been undertaken. When refluxed with triphenyltin hydride in xylene, pregna-14,16-dien-20-ones underwent selective hydrogenation to yield the corresponding Δ^{14}-unsaturated compounds. Condensation with ethyl orthoformate followed by cyclization with malonic acid gave the Δ^{14}-isobufadienolides. Subsequent treatment with N-bromoacetamide and then with alumina resulted in formation of the desired 14β,15β-epoxyisobufadienolides (VIIIa, b). The epimeric 14α,15α-epoxides (VIa, b) were also prepared with the object of comparing the biological activity.

The structure–activity relationship of the cardenolide and bufadienolide has recently been investigated by several workers and in consequence some structural factors essential for cardiotonic activity have been elucidated.[3] However, significance of the linked position of the α-pyrone ring to the steroid nucleus has not yet been clarified. From this point of view the authors have already prepared the 16-methylisobufadienolides.[4] The physiological activity of the positional isomer of resibufogenin seemed to be of particular interest to us. The present paper deals with the preparation of the epimeric 14,15-epoxyisobufadienolides employing the pregn-16-en-20-ones as the starting material.

The authors have previously reported that the synthesis of the thermodynamically less stable 14,17-*cis*-isobufadienolide would be somewhat difficult due to facile epimerization at C-17 during formation of the α-pyrone ring.[5] Hence the preparation of the titled compound having 14β,17β-configuration was undertaken by way of the Δ^{14}-17β-isobufadienolide. For this purpose an initial project was focused to the synthesis of 3β-acetoxypregna-5,14-dien-20-one (IIIa) employing the $\Delta^{5,14,16}$-unsaturated compound (IIa), derivable from 3β-acetoxypregna-5,16-dien-20-one (Ia) in three steps.[6] Selective hydrogenation of the Δ^{16}-double bond in the $\Delta^{14,16}$-diene system has recently been developed by Yoshii, *et al.* with use of triphenyltin hydride in toluene.[7] However, the proposed procedure is somewhat tedious and inconvenient in that the reagent must be added several times in a sealed tube. These difficulties could be overcome by refluxing in xylene under a stream of nitrogen gas, and in consequence the $\Delta^{5,14}$-diene (IIIa) was afforded in the yield of 60%. In a similar fashion 3β-acetoxypregna-14,16-dien-20-one (IIb) could also be led to the corresponding Δ^{14}-unsaturated compound (IIIb).

1) This paper constitutes Part IV of the series entitled "Studies on Cardiotonic Steroid Analogs"; Part III: T. Nambara, K. Shimada, S. Goya, and N. Sakamoto, *Chem. Pharm. Bull.* (Tokyo), **18**,617 (1970).
2) Location: *Aobayama, Sendai.*
3) T. Shigei, M. Katori, H. Murase, and S. Imai, *Experientia*, **20**, 572 (1964); S. Imai, H. Murase, M. Katori, M. Okada, and T. Shigei, *Jap. J. Pharmacol.*, **15**, 62 (1965); T. Shigei and S. Mineshita, *Experientia*, **24**, 466 (1968); Ch. Tamm, "Proceedings of the 1st International Pharmacological Meeting," Vol. 3, ed. by W. Wilbrandt, Pergamon Press, Oxford, 1963, p. **11.**
4) T. Nambara, K. Shimada, S. Goya, and J. Goto, *Chem. Pharm. Bull.* (Tokyo), **16**, 2236 (1968).
5) T. Nambara, K. Shimada, S. Goya, and N. Sakamoto, *Chem. Pharm. Bull.* (Tokyo), **18**, 617 (1970).
6) A.J. Solo and B. Singh, *J. Org. Chem.*, **30**, 1658 (1965).
7) E. Yoshii and M. Yamasaki, *Chem. Pharm. Bull.* (Tokyo), **16**, 1158 (1968).

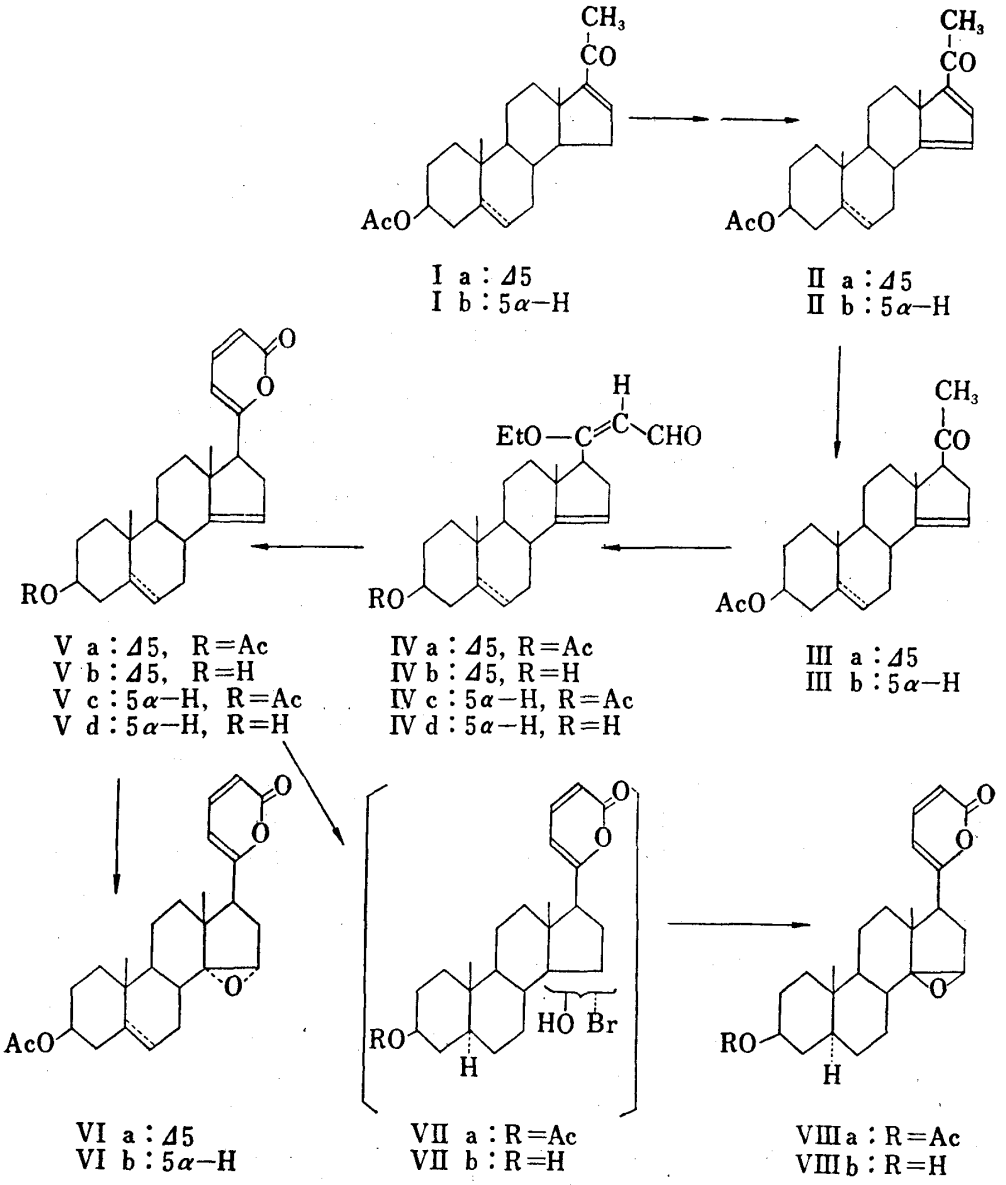

Chart 1

The formation of the pyrone ring was performed according to the method previously established.[4] Treatment of IIIa with ethyl orthoformate gave 3β-acetoxy-20-ethoxy-21-formylpregna-5,14,20-triene (IVa), which on condensation with malonic acid followed by cyclization was converted into the desired α-pyrone derivative (Va). Three Δ^{14}-isobufadienolides (Vb,c,d) lacking the acetyl group at C-3 and/or the double bond between C-5 and C-6 could also be synthesized from the pregn-14-en-20-ones (IIIa,b) through condensation with ethyl orthoformate and then with malonic acid in the same manner as mentioned above.

Treatment of Va with one mole of monoperphthalic acid gave the 14,15-epoxide (VIa) in 60% yield, whose structure was definitely established by inspection of the nuclear magnetic resonance (NMR) spectra. A new signal assignable to a proton on the epoxy-bearing carbon appeared at 3.5 ppm along with loss of a peak due to vinyl proton at C-15. Configuration of the epoxy group was tentatively assigned to be α, since it is well documented in the literatures that as for the 17β-substituted steroid the per-acid attacks the Δ^{14}-double bond from the rear side to give the α-epoxide.[8] It is of interest that the epoxidation takes place preferentially

8) H. Ishii, *Chem. Pharm. Bull.* (Tokyo), **10**, 354 (1962); H. Hasegawa, Y. Sato, and K. Tsuda, *ibid.*, **11**, 1275 (1963).

at Δ^{14}-double bond rather than Δ^{5}, when a limited amount of the reagent is used.[7] The 14α,15α-epoxide (VIb) having no unsaturation was similarly prepared by treatment with the per-acid in the same way.

Then the project was directed to the preparation of the epimeric β-epoxide. Treatment of Vc with N-bromoacetamide in acetone gave the 14,15-bromohydrin (VIIa), which in turn was passed through a column of alumina[9] resulting in formation of the 14β, 15β-epoxyisobufadienolide acetate (VIIIa). However, difficulties were encountered in the subsequent step involving hydrolysis of the 3-acetate. When treated with potassium bicarbonate in methanol, undesired cleavage of the α-pyrone ring was accompanied to a considerable extent. On brief treatment with N-bromoacetamide and subsequent chromatography on alumina Vd was readily transformed into the desired 14β,15β-epoxyisobufadienolide (VIIIb).

Configurational assignment was supported by the following evidences. It is sufficiently substantiated that as for the two epimeric 17β-substituted 14,15-epoxides the 18-methyl proton signal of the α-epoxide appears at higher field than that of the β-epimer.[10] In actuality the 18-methyl proton of the α-epoxide resonates at 0.79 ppm, while that of its epimer at 0.98 ppm. In addition it has already been reported that the chemical shift and splitting pattern of the ring protons of the α-pyrone in the bufadienolide are influenced to a certain extent by alteration of the C/D-ring fusion and the neighboring substituents.[11] Indeed there can be seen differences in chemical shift with *ca.* 0.2 ppm and in coupling constants ($J_{H21,22}$, $J_{H22,23}$) with 2—4 cps between the two epimeric 14,15-epoxyisobufadienolides.

Recently it has been demonstrated that the furanosteroid derived from the corresponding cardenolide exhibits the cardiotonic activity.[12] This finding implys that the oxygen function attached to C-21 may possibly have a particular significance for the physiological activity. It is hoped that pharmacological examination of the 14,15-epoxyisobufadienolides will provide the more precise knowledge on the structural requirements for the cardiotonic activity.

Experimental[13]

3β-Acetoxypregna-5,14-dien-20-one (IIIa)——To a solution of IIa (400 mg) in xylene (4 ml) was added $(C_6H_5)_3SnH$ (870 mg) and the resulting solution was refluxed under a stream of N_2 for 2 hr. Then $(C_6H_5)_3SnH$ (400 mg) was added and further refluxed for 2 hr. The reaction product was extracted with MeOH and chromatographed on silica gel (4 g). Elution with benzene and recrystallization of the eluate (300 mg) from MeOH gave IIIa (240 mg) as colorless needles. mp 158—161°. $[\alpha]_D^{24}$ −46.8° (c=0.12). *Anal.* Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.26; H, 9.05. NMR (4% solution in $CDCl_3$) δ: 0.87 (3H, s, 18-CH_3), 1.03 (3H, s, 19-CH_3), 2.00 (3H, s, 3β-$OCOCH_3$), 2.13 (3H, s, 21-CH_3), 5.13 (1H, half-band width=5 cps, 15-H), 5.38 (1H, m, half-band width=9 cps, 6-H). ORD (c=0.20, MeOH) $[\alpha]^{24}$: +98° (350), +725° (309) (peak), 0° (294), −1353° (265) (trough), −1255° (250).

3β-Acetoxy-20-ethoxy-21-formyl-17β-pregna-5,14,20-triene (IVa)——To a solution of IIIa (150 mg) in ethyl orthoformate (5 ml) was added a few drops of $HClO_4$ dropwise under ice-cooling over a period of 20 min. After addition of several drops of pyridine to decompose the perchlorate, the resulting solution was extracted with ether. The organic layer was washed with cold 5% HCl, 5% $NaHCO_3$ and H_2O successively, and dried over anhydrous Na_2SO_4. On usual work-up a crystalline product was obtained. Recrystallization from MeOH gave IVa (130 mg) as colorless leaflets. mp 185—186.5°. $[\alpha]_D^{24}$ −140.3° (c=0.07). *Anal.* Calcd. for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80. Found: C, 76.12; H, 8.60. NMR (4% solution in $CDCl_3$) δ: 3.80

9) P. Hofer, H. Linde, and K. Meyer, *Helv. Chim. Acta*, **45**, 1041 (1962).
10) K. Tori, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, **29**, 1136 (1964).
11) L. Gsell and Ch. Tamm, *Helv. Chim. Acta*, **52**, 551 (1969).
12) T. Minesita, R. Hirota, S. Kimoto, M. Uno, and Y. Uemura, *Ann. Rept. Shionogi Res. Lab.*, **18**, 94 (1968).
13) All melting points were taken on a micro hot-stage apparatus and uncorrected. The optical rotations were measured in $CHCl_3$ unless otherwise stated. The thin-layer chromatography (TLC) plates were prepared by the Stahl's procedure using silica gel HF (E. Merck AG) as adsorbent. The rotatory dispersion curves were obtained on Nihon-Bunko Model ORD/UV-5 recorder. The nuclear magnetic resonance (NMR) spectra were run on Hitachi Model H-60 spectrometer at 60 Mc: the chemical shifts are quoted as ppm downfield from $(CH_3)_4Si$ as an internal standard. Abbreviation used s=singlet, d=doublet, q=quartet and m=multiplet.

(2H, q, J=6.5 cps, $-OCH_2Me$), 4.60 (1H, m, 3α-H), 5.22 (1H, m, 15-H), 5.45 (1H, m, 6-H), 5.50 (1H, d, J=8 cps, $>C=C<^{CHO}_{H}$), 9.80 (1H, d, J=8 cps, -CHO).

3β-Hydroxy-20-ethoxy-21-formyl-17β-pregna-5,14,20-triene (IVb)——To a solution of IVa (50 mg) in MeOH (5 ml) was added 5% K_2CO_3 (1 ml), and the resulting solution was refluxed for 1 hr. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with H_2O and dried over anhydrous Na_2SO_4. On usual work-up a crystalline product was obtained. Recrystallization from MeOH gave IVb (30 mg) as colorless needles. mp 203—205°. $[\alpha]_D^{24}$ −70.4° (c=0.18). *Anal.* Calcd. for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.89; H, 9.37.

6-(3β-Acetoxyandrosta-5,14-dien-17β-yl)-2-pyrone (Va)——To a solution of IVa (200 mg) in pyridine (5 ml) were added a trace of morpholine and malonic acid (100 mg), and the resulting solution was refluxed for 4 hr. The reaction mixture was diluted with $CHCl_3$, washed with 5% HCl, H_2O and dried over anhydrous Na_2SO_4. On usual work-up the residue obtained was submitted to the preparative TLC using benzene–AcOEt (50:1) as developing solvent. The adsorbent corresponding to the spot (*Rf* 0.21) was eluted with CH_2Cl_2–AcOEt. Recrystallization of the eluate from MeOH gave Va (26 mg) as colorless plates. mp 213.5—215°. $[\alpha]_D^{20}$ −85.3° (c=0.14). *Anal.* Calcd. for $C_{26}H_{32}O_4$: C, 76.44; H, 7.90. Found: C, 76.20; H, 7.63. NMR (4% solution in $CDCl_3$) δ: 0.85 (3H, s, 18-CH_3), 1.05 (3H, s, 19-CH_3), 2.01 (3H, s, 3β-$OCOCH_3$), 4.65 (1H, m, 3α-H), 5.20 (1H, m, 15-H), 5.45 (1H, m, 6-H), 6.05 (1H, d, J=6 cps, 23-H), 6.16 (1H, d, J=9 cps, 21-H), 7.30 (1H, q, J=6, 9 cps, 22-H).

6-(3β-Hydroxyandrosta-5,14-dien-17β-yl)-2-pyrone (Vb)——IVb (130 mg) was treated with malonic acid (65 mg), pyridine (5 ml) and a trace of morpholine in the same manner as described in Va. The crude product obtained was submitted to the preparative TLC using benzene–AcOEt (4:1) as developing solvent. The adsorbent corresponding to the spot (*Rf* 0.50) was eluted with CH_2Cl_2–AcOEt. Recrystallization of the eluate from MeOH gave Vb (30 mg) as colorless needles. mp 239—242°. $[\alpha]_D^{15}$ −202.7° (c=0.11). *Anal.* Calcd. for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25. Found: C, 78.45; H, 8.26. NMR (4% solution in $CDCl_3$) δ: 5.23 (1H, m, 15-H), 5.45 (1H, m, 6-H), 6.05 (1H, d, J=6 cps, 23-H), 6.16 (1H, d, J=9 cps, 21-H), 7.30 (1H, q, J=6, 9 cps, 22-H).

6-(3β-Acetoxy-14α,15α-epoxyandrost-5-en-17β-yl)-2-pyrone (VIa)——To a solution of Va (35 mg) in $CHCl_3$ (2 ml) was added a solution (1 ml) of monoperphthalic acid (18 mg/ml) in ether and allowed to stand at 4° for 16 hr. The reaction mixture was diluted with $CHCl_3$, washed with KI, $Na_2S_2O_3$, $NaHCO_3$ solutions and H_2O successively, and dried over anhydrous Na_2SO_4. On usual work-up the residue obtained was submitted to the preparative TLC using benzene–AcOEt (9:1) as developing solvent. The adsorbent corresponding to the spot (*Rf* 0.22) was eluted with CH_2Cl_2–AcOEt. Recrystallization of the eluate from MeOH gave VIa (28 mg) as colorless needles. mp 242—245°. $[\alpha]_D^{17}$ −34.9° (c=0.11). *Anal.* Calcd. for $C_{26}H_{32}O_5$: C, 73.56; H, 7.60. Found: C, 73.74; H, 7.47. NMR (4% solution in $CDCl_3$) δ: 0.82 (3H, s, 18-CH_3), 1.05 (3H, s, 19-CH_3), 2.01 (3H, s, 3β-$OCOCH_3$), 3.49 (1H, d, J=2 cps, 15β-H), 4.65 (1H, m, 3α-H), 5.35 (1H, m, 6-H), 5.95 (1H, d, J=7 cps, 23-H), 6.17 (1H, d, J=9 cps, 21-H), 7.30 (1H, q, J=7, 9 cps, 22-H).

3β-Acetoxy-5α-pregn-14-en-20-one (IIIb)——IIb (700 mg) was treated with $(C_6H_5)_3SnH$ (2.2 g) in xylene in the same manner as described in IIIa. Recrystallization from MeOH gave IIIb (400 mg) as colorless needles. mp 127—129°. $[\alpha]_D^{24}$ +35.1° (c=0.10). *Anal.* Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.91; H, 9.44. NMR (4% solution in $CDCl_3$) δ: 0.85 (3H, s, 18-CH_3), 0.89 (3H, s, 19-CH_3), 2.00 (3H, s, 3β-$OCOCH_3$), 2.10 (3H, s, 21-CH_3), 4.60 (1H, m, 3α-H), 5.15 (1H, m, 15-H), ORD (c=0.17, MeOH) $[\alpha]^{18}$: +70° (350), +1070° (309) (peak), 0° (290), −1810° (260) (trough), −1650° (250).

3β-Acetoxy-20-ethoxy-21-formyl-17β-pregna-14,20-diene (IVc)——IIIb (60 mg) was treated with ethyl orthoformate (5 ml) and $HClO_4$ in the same manner as described in IVa. Recrystallization from MeOH gave IVc (30 mg) as colorless leaflets. mp 153.5—155°. $[\alpha]_D^{27}$ −63.6° (c=0.11). *Anal.* Calcd. for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24. Found: C, 74.71; H, 8.56.

3β-Hydroxy-20-ethoxy-21-formyl-17β-pregn-14-en-20-one (IVd)——IVc was treated with K_2CO_3 in aq. MeOH in the same manner as described in IVb. Recrystallization from acetone–hexane gave IVd as colorless prisms. mp 180—184°. NMR (4% solution in $CDCl_3$) δ: 3.67 (1H, m, 3α-H), 3.70 (2H, q, J=6.5 cps, $-OCH_2Me$), 5.19 (1H, m, 15-H), 5.50 (1H, d, J=8 cps, $>C=C<^{CHO}_{H}$), 9.85 (1H, d, J=8 cps, -CHO). The analytical sample could not be obtained and therefore the crude product was submitted to further elaboration without purification.

6-(3β-Acetoxyandrost-14-en-17β-yl)-2-pyrone (Vc)——IVc (200 mg) was treated with malonic acid (100 mg), pyridine (5 ml) and a trace of morpholine in the same manner as described in Va. The crude product obtained was submitted to the preparative TLC using benzene–AcOEt (50:1) as developing solvent. The adsorbent corresponding to the spot (*Rf* 0.20) was eluted with CH_2Cl_2–AcOEt. Recrystallization of the eluate from MeOH gave Vc (30 mg) as colorless needles. mp 194—196°. $[\alpha]_D^{24}$ −15.9° (c=0.13). *Anal.* Calcd. for $C_{26}H_{34}O_4$: C, 76.06; H, 8.34. Found: C, 75.89; H, 8.42. NMR (4% solution in CCl_4) δ: 0.85 (3H, s, 18-CH_3), 0.90 (3H, s, 19-CH_3), 1.97 (3H, s, 3β-$OCOCH_3$), 4.60 (1H, m, 3α-H), 5.17 (1H, m, 15-H), 5.88 (1H, d, J=6 cps, 23-H), 6.03 (1H, d, J=9 cps, 21-H), 7.20 (1H, q, J=6, 9 cps, 22-H).

6-(3β-Hydroxyandrost-14-en-17β-yl)-2-pyrone (Vd)——IVd (160 mg) was treated with malonic acid (90 mg), pyridine (5 ml) and a trace of morpholine in the same manner as described in Va. The crude product obtained was submitted to the preparative TLC using benzene–AcOEt (4:1) as developing solvent. The adsorbent corresponding to the spot (*Rf* 0.50) was eluted with CH_2Cl_2–AcOEt. Recrystallization of the eluate from MeOH using active charcoal gave Vd (50 mg) as colorless plates. mp 217—218.5°. $[\alpha]_D^{27}$ −66.7° (c=0.05). *Anal.* Calcd. for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75. Found: C, 78.22; H, 8.50. NMR (4% solution in $CDCl_3$) δ: 0.83 (6H, s, 18-CH_3, 19-CH_3), 3.50 (1H, m, 3α-H), 5.15 (1H, m, 15-H), 6.02 (1H, d, J=6 cps, 23-H), 6.15 (1H, d, J=9 cps, 21-H), 7.25 (1H, q, J=6, 9 cps, 22-H).

6-(3β-Acetoxy-14α,15α-epoxyandrostan-17β-yl)-2-pyrone (VIb)——Vc (30 mg) was treated with monoperphthalic acid (20 mg) in the same manner as described in VIa. The crude product obtained was submitted to the preparative TLC using benzene–CH_2Cl_2 (1:1) as developing solvent. The adsorbent corresponding to the spot (*Rf* 0.30) was eluted with CH_2Cl_2–AcOEt. Recrystallization of the eluate from acetone gave VIb (22 mg) as colorless needles. mp 261—265°. $[\alpha]_D^{20}$ 0° (c=0.23). *Anal.* Calcd. for $C_{26}H_{34}O_5$: C, 73.21; H, 8.04. Found: C, 73.35; H, 7.77. NMR (4% solution in $CDCl_3$) δ: 0.79 (3H, s, 18-CH_3), 0.88 (3H, s, 19-CH_3), 2.01 (3H, s, 3β-$OCOCH_3$), 3.49 (1H, d, J=2 cps, 15β-H), 4.65 (1H, m, 3α-H), 5.92 (1H, d, J=7 cps, 23-H), 6.15 (1H, d, J=10 cps, 21-H), 7.25 (1H, q, J=7, 10 cps, 22-H).

6-(3β-Acetoxy-14β,15β-epoxyandrostan-17β-yl)-2-pyrone (VIIIa)——To a solution of Vc (24 mg) dissolved in acetone (5 ml) and H_2O (1 ml) N-bromoacetamide (13 mg) was added and stirred for 16 hr at room temperature. The reaction mixture was extracted with ether and washed with 5% Na_2SO_3, H_2O and dried over anhydrous Na_2SO_4. The crude bromohydrin (VIIa) (20 mg) was chromatographed on Al_2O_3 (300 mg). The eluates with benzene–AcOEt (1:1) were collected and submitted to the preparative TLC using benzene–AcOEt (9:1) as developing solvent. The adsorbent corresponding to the spot (*Rf* 0.20) was eluted with CH_2Cl_2–AcOEt and recrystallization of the eluate from MeOH gave VIIIa (10 mg) as colorless needles. mp 180—181.5°. $[\alpha]_D^{16}$ −237.1° (c=0.07). *Anal.* Calcd. for $C_{26}H_{34}O_5$: C, 73.21; H, 8.04. Found: C, 73.44; H, 7.78. NMR (4% solution in $CDCl_3$) δ: 0.88 (3H, s, 19-CH_3), 0.98 (3H, s, 18-CH_3), 2.02 (3H, s, 3β-$OCOCH_3$), 3.51 (1H, s, 15α-H), 4.70 (1H, m, 3α-H), 6.10 (1H, d, J=10 cps, 23-H), 6.35 (1H, d, J=6 cps, 21-H), 7.30 (1H, q, J=6, 10 cps, 22-H).

6-(3β-Hydroxy-14β,15β-epoxyandrostan-17β-yl)-2-pyrone (VIIIb)——Vd (24 mg) was treated with N-bromoacetamide (13 mg) in the same manner as described in VIIIa except that the reaction time was 4 hr. The crude bromohydrin (VIIb) (20 mg) was chromatographed on Al_2O_3 (300 mg). The eluates with AcOEt were collected and submitted to the preparative TLC using benzene–CH_2Cl_2–AcOEt (16:4:3) as developing solvent. The adsorbent corresponding to the spot (*Rf* 0.22) was eluted with CH_2Cl_2–AcOEt and recrystallization of the eluate from acetone gave VIIIb (18 mg) as colorless needles. mp 238—239.5°. $[\alpha]_D^{17}$ −232° (c=0.18). *Anal.* Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.88; H, 8.37. NMR (4% solution in $CDCl_3$) δ: 0.85 (3H, s, 19-CH_3), 0.98 (3H, s, 18-CH_3), 3.50 (1H, s, 15α-H), 3.50 (1H, m, 3α-H), 6.10 (1H, d, J=10 cps, 23-H), 6.35 (1H, d, J=6 cps, 21-H), 7.30 (1H, q, J=6, 10 cps, 22-H).

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