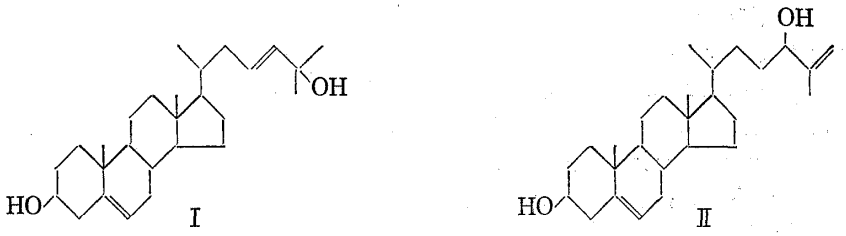

Chart

in *R. palmata* seems to suggest that I and II might be biosynthesized from desmosterol *via* photosensitized oxygenation or related mechanism. However, the possibility that these diols (I and II) would be artifact produced from desmosterol during air-drying of algae or extraction/isolation procedures, should be also considered.

Experimental

The algae were harvested at Muroran bay, Hokkaido, Japan, and identified by Profs. T. Nakamura and M. Tatewaki, Hokkaido University. Extraction of sterols and the analysis of their trimethylsilyl ethers by GC-MS were carried out as previously described.[2] Mass chromatography was performed with Shimadzu-LKB 9000 Gas Chromatograph-Mass Spectrometer equipped with GC-MASS PAC-300 DG data processing system; OKITAC-4300C minicomputer with 12K core, a typewritten digital plotter, a magnetic disk and an interface. For details see Fig. 2 legend.

Acknowledgement We are indebted to Profs. T. Nakamura, and M. Tatewaki, Hokkaido University, for collection and identification of algae. Thanks are also due to Shimadzu Co., Ltd. for analysis by mass chromatography.

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Studies on the Synthesis of Cardiotonic Steroids. II.[1] Synthesis of 17β-(3-Furyl)-5β,14β-androstane-3β,14β-diol

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17β-(3-Furyl)-5β,14β-androstane-3β,14β-diol, a promissing relay compound leading to digitoxigenin, was synthesized starting with 3β-acetoxy-5β-pregn-14-en-20-one.

Our continuous interest in the exploration of new synthetic routes to naturally occurring cardenolide led us to establish the effective synthetic method of the title compound,[3] since the compound is known to be convertible to digitoxigenin.[4] The starting material employed for this objective was 3β-acetoxy-5β-pregn-14-en-20-one (**1**) that proved the attractive intermediate in our previous digitoxigenin synthesis.[1] Derivation of furan ring from the side chain of **1** and subsequent formation of 14β-hydroxy group have completed the present approach as described below.

1) Part I: E. Yoshii, T. Koizumi, H. Ikeshima, K. Ozaki, and I. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **23**, 2496 (1975).
2) Location: *Gofuku, Toyama, 930, Japan.*
3) H. Minato and T. Nagasaki, *J. Chem. Soc.* (*C*), **1966**, 337.
4) J.M. Ferland, Y. Lefebvre, R. Deghenghi, and K. Wiesner, *Tetrahedron Letters*, **1966**, 3617.

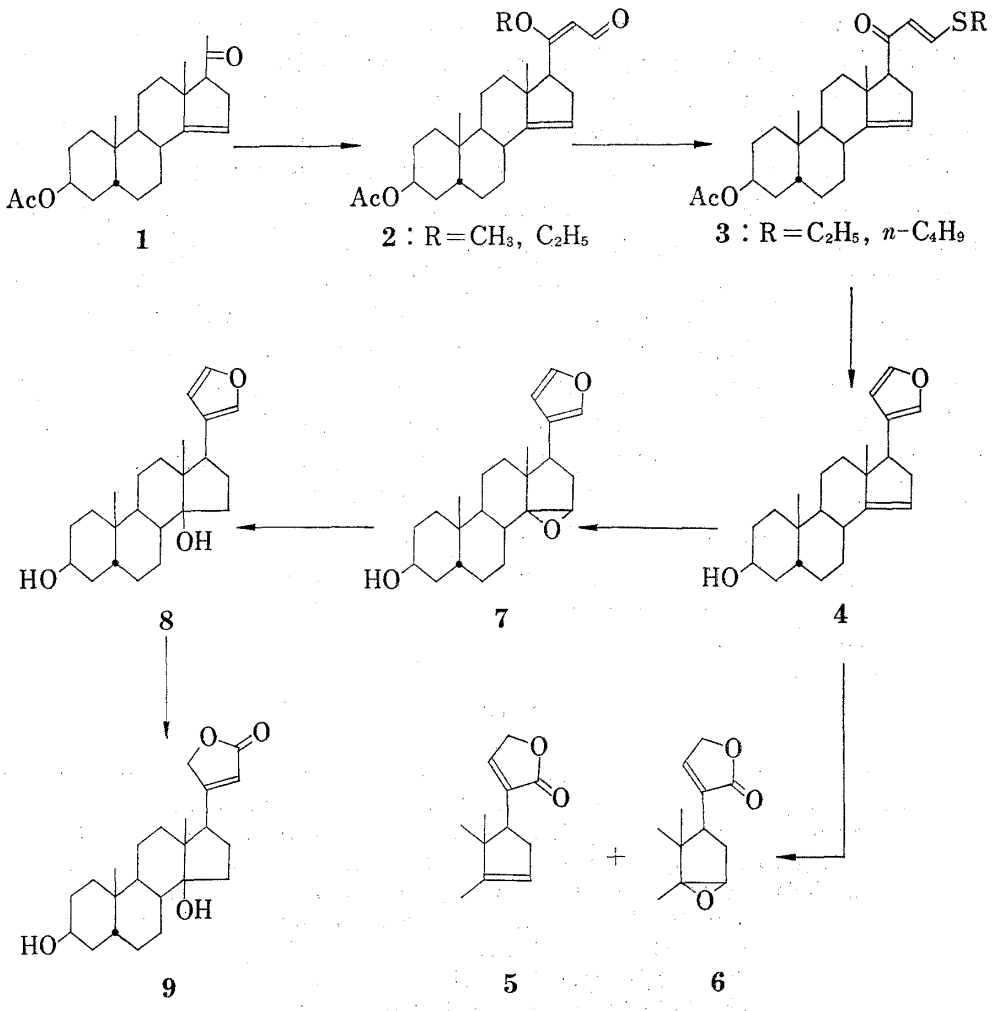

Chart 1

For building 17β(3-furyl)-androstane structure from **1** we decided to employ the furan synthesis of Garst and Spencer,[5] since the reaction sequence was expected to allow the presence of the olefinic bond. Accordingly the synthesis of the required 21-alkylthiomethylidene derivative of **1** (**3**) was first investigated. After several attempts the following two step reaction was found to be superior in yield and in experimental convenience over the existing methods[6] in the case of 20-ketopregnanes. First, **1** was formylated with orthoformate after the method of Bernstein[7] to give β-alkoxy-α,β-unsaturated aldehyde (**2**). The subsequent reaction of **2** with a mercaptan occurred in benzene containing p-toluenesulfonic acid under mild condition giving **3** in good yield. The course of this acid catalyzed reaction could be rationalized as initial formation of the hemithioacetal followed by loss of alcohol. The reaction of **3** with dimethylsulfonium methylide generated from trimethylsulfonium iodide proceeded smoothly,[8] yielding unstable 2-alkylthio-2,5-dihydrofuran intermediate[9] which on desulfurization with mercuric chloride gave 3β-hydroxy-17β(3-furyl)-5β-pregn-14-en-20-one (**4**).

5) M.E. Garst and T.A. Spencer, *J. Am. Chem. Soc.*, **95**, 250 (1973).
6) R.E. Ireland and J.A. Marshall, *J. Org. Chem.*, **27**, 1615 (1962).
7) J.P. Dusza, J.P. Joseph, and S. Bernstein, *J. Am. Chem. Soc.*, **86**, 3908 (1964).
8) The authors of ref. 5 used the fluoroborate stating that the iodide was unsuitable. But experiments at our hand showed no merit of the use of the fluoroborate.
9) See ref. 5 for the structure of intermediate. By our model experiments this type of steroidal thiodihydrofurans was found to be stable under basic conditions, but once isolated they gradually lost mercaptan forming furan ring.

The next step which was the formation of 14β-hydroxy group from 14-double bond of **4** could be achieved in principle through 15α-halo-14β-hydrin, either by its catalytic hydrogenolysis[1] or by hydride reduction of the epoxide obtained thereof.[10] In both paths, the halohydrin should be selectively made without the oxidation of the furan ring. The reaction of aqueous N-bromosuccinimide with **4** followed by alumina chromatography produced 14β,15β-epoxy butenolide (**5**) and 14-olefinic butenolide (**6**) showing that the furan ring is more reactive to this particular haloimide. On the contrary, N-iodosuccinimide of softer character was found to attack the 14-double bond preferentially giving the crude iodohydrin which showed no carbonyl band. At this stage, of the two methods leading to **8** the reductive cleavage of an epoxide derivable from iodohydrin was attempted, since it was considered that under the condition of hydrogenolysis the furan ring might not survive. Thus the epoxide (**7**) obtained by dehydroiodination of the iodohydrin with potassium acetate was reduced with lithium aluminum hydride in refluxing ether to give 17β-(3-furanyl)-5β,14β-androstane-3β,14β-diol (**8**), the structure of which was supported by spectroscopic data including infrared (IR), proton magnetic resonance (PMR), and mass spectrum (MS).

The short step synthesis of **8**[11] thus established from readily available steroid, coupled with the work of Ferland, *et al.*[4] provides a new effective synthetic method of digitoxigenin (**9**) as well as isodigitoxigenin.[4]

Experimental

Melting points were determined with Yanagimoto micro melting point apparatus and uncorrected. Infrared spectra(IR) were recorded on Nippon Bunko IR-S spectrometer and were calibrated using 1603 cm^{-1} polystyrene band. The 60-MHz proton magnetic resonance spectra(PMR) were taken with Jeol H-60 or PMX-60 spectrometer using tetramethylsilane as internal standard. Chemical shifts are reported in ppm(δ) from tetramethylsilane. Mass spectra were obtained with Jeol JMS-01SG-2 instrument at 75 eV ionization potential. For column chromatography Merck silica gel with 0.06—0.20 mm particles or Merck alumina was used. Thin-layer chromatography(TLC) was conducted with Merck Silica gel G.

3β-Acetoxy-20-methoxy-21-formyl-5β-pregna-14,20-diene(2, R=CH_3)——To an ice cold solution of 2.17 g of 3β-acetoxy-5β-pregn-14-en-20-one(**1**) in 43.5 ml of trimethyl orthoformate was added with stirring 1.06 ml of 70% perchloric acid. After 5 min, 3.0 ml of pyridine was added followed by ice water, and the mixture was extracted with ether. The ether solution was washed with 5% $NaHCO_3$ and water, dried on $MgSO_4$, and evaporated. The residue was chromatographed on 20 g of silica gel, eluting with *n*-hexane and *n*-hexane–benzene mixtures to give 2.12 g of 2(R=CH_3). Analytical sample was recrystallized from *n*-hexane, mp 157—160°. IR (KBr) cm^{-1}: 1728, 1655, 1600. PMR (CCl_4)δ: 0.83 (18-CH_3), 0.96 (19-CH_3), 1.95 (CH_3COO), 3.66 (OCH_3), 4.91 (3α-H), 5.09 (15-H), 5.34 (21-H, d, J=7 Hz), 9.63 (CHO, d, J=7 Hz). *Anal.* Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.89; H, 8.84. 20-Ethoxy compound (**2**, R=C_2H_5) was obtained in comparable yields by the same procedure. But it could not be crystallized and was isolated by alumina chromatography.

3β-Acetoxy-21-alkylthiomethylidene-5β-pregn-14-en-20-one (**3**)——To a solution of 350 mg of *p*-toluenesulfonic acid in 350 ml of benzene was added 4.65 g of 2(R=C_2H_5) followed by 1 g of *n*-butanethiol. The mixture was gradually heated to the boiling point with stirring and kept at this temperature for 5 min. The solution was cooled to room temperature, washed with 2% K_2CO_3 and water, and dried on $MgSO_4$. The crude product obtained after evaporation of the solvent was chromatographed on silica gel, eluting with *n*-hexane and *n*-hexane–benzene mixtures. 4.03 g of *n*-butylthiovinyl ketone (**3**, R=*n*-C_4H_9) which showed single spot on TLC was obtained as pale yellow glass. PMR ($CDCl_3$)δ: 6.15 (d, J=15 Hz), 7.70 (d, J=15 Hz). By similar procedure (30—40°, 10 min) ethylthio derivative (**3**, R=C_2H_5) was prepared, mp 128—130° colorless cubes from acetone. IR (KBr) cm^{-1}: 1725, 1660, 1545. PMR ($CDCl_3$) δ: 0.85 (18-CH_3), 1.00 (19-CH_3), 2.05 (CH_3COO), 6.15 (d, J=15 Hz), 7.65 (d, J=15 Hz). *Anal.* Calcd. for $C_{26}H_{38}O_3S$: C, 72.52; H, 8.89. Found: C, 72.77; H, 9.08.

3β-Hydroxy-17β(3-furyl)-5β-androst-14-ene (**4**)——Dimsyl sodium prepared from 1.65 g of 50% NaH and 15 ml of dimethyl sulfoxide was diluted with 30 ml of dry tetrahydrofuran and cooled to −10°. To this solution was added with stirring 7.0 g of trimethylsulfonium iodide dissolved in 30 ml of dimethyl sulfoxide. After 10 min, 4.03 g of 3 (R=C_4H_9) in 5 ml of tetrahydrofuran was introduced to the methylide solution and the stirring at −5—0° was continued for 1 hr. The reaction mixture was poured into ice water and extracted

10) For general discussion, see; F. Sondheimer, *Chemistry in Britain*, **1965**, 454.

11) This compound was previously prepared by di-isobutylaluminum hydride reduction of digitoxingenin.[3]

with ether. The ether solution was washed with water, dried on $MgSO_4$, and then stirred with 0.6 g of $HgCl_2$ for 1 hr. The precipitate was filtered off and the filtrate was washed with 5% $NaHCO_3$ and water, dried on $MgSO_4$, and evaporated. The oily residue was chromatographed on silica gel to give 1.98 g of **4** which was crystallized from MeOH, mp 117—119°. IR (KBr) cm^{-1}: 3380, 1500, 1030, 880, 780. PMR ($CDCl_3$)δ: 0.68 (18-CH_3), 1.00 (19-CH_3), 4.08 (3α-H), 5.20 (15-H), 6.25 (22-H), 7.17 (21-H), 7.39 (23-H). *Anal.* Calcd. for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 81.12; H, 9.66.

Reaction of 4 with aqueous NBS——To a solution of 100 mg of **4** in 3 ml of acetone were added 0.3 ml of water and 0.03 ml of 70% perchloric acid, followed by the addition of 51.3 mg of NBS. The mixture was kept at room temperature in the dark for 1.5 hr and then treated with aq. $Na_2S_2O_3$. It was extracted with dichloromethane and the crude product obtained by evaporating the solvent was chromatographed on 6 g of alumina. Elution with benzene afforded 40.3 mg of unreacted **4**, 12 mg of **5** and 16 mg of **6**. **5**, mp 198—210° (benzene). IR (KBr) cm^{-1}: 1755. PMR ($CDCl_3$)δ: 4.10 (3α-H), 4.77 (23-H), 5.15 (15-H), Mass Spectrum *m/e*: 356 (M^+). **6**, mp 236—238°. PMR ($CDCl_3$) δ: 0.88 (18-CH_3), 1.00 (19-CH_3), 3.51 (15α-H), 4.10 (3α-H), 4.76 (23-H), 7.38 (22-H). Mass Spectrum *m/e*: 372 (M^+). *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.33; H, 8.85.

3β,14β-Dihydroxy-17β(3-furanyl)-5β-androstane (8)——A solution of 500 mg of **4** in 30 ml of acetone was treated with 3 ml of water, 0.5 ml of 70% perchloric acid and 400 mg of NIS for 10 min. The crude iodohydrin obtained by the same work-up described above was refluxed with 25 ml of dry methanol and 1.0 g of anhydrous potassium acetate for 1 hr. The solution was concentrated by a rotary evaporator, extracted with ether. The ether solution was washed with water, dried on $MgSO_4$ and evaporated. The residue was chromatographed on 20 g of alumina (basic, activity II) to give 150 mg of glassy epoxy furan (**7**), IR: no carbonyl; PMR ($CDCl_3$): 3.47 ppm (15α-H), and 233 mg of unreacted **4**. A solution of **7** obtained here in 20 ml of dry ether was refluxed with 350 mg of lithium aluminum hydride for 5 hr. The product isolated by usual work-up was chromatographed on alumina (neutral, activity II, 8 g) to give 90 mg of **8** as prisms from benzene–MeOH, mp 204—205° (lit.[3] 208—209°), and 24 mg of unreacted **7**. IR(KBr) cm^{-1}: 3440, 1500, 1020, 875, 790. PMR ($CDCl_3$)δ: 0.70 (18-CH_3), 0.94 (19-CH_3), 4.10 (3α-H), 6.42 (22-H), 7.15 (21-H), 7.25 (23-H). Mass Spectrum *m/e*: 358 (M^+). *Anal.* Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.99; H, 9.55.