[Chem. Pharm. Bull.
16(7)1200—1209(1968)]

UDC 547.92.07 : 547.735.7

A Novel Synthesis of Steroidal[2,3-*c*]thiophenes

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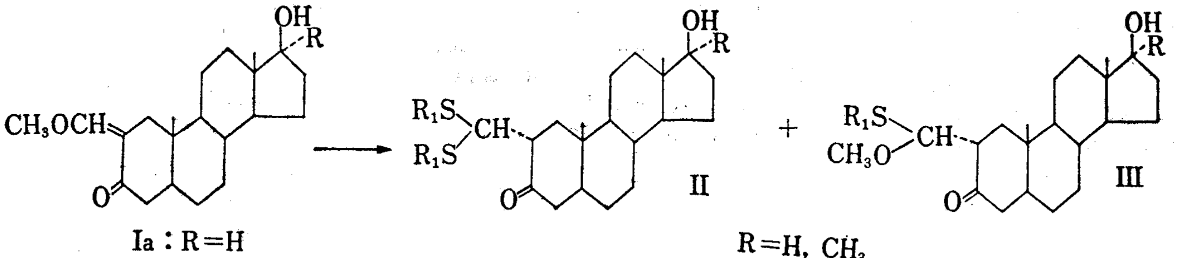
(Received August 21, 1967)

Steroids with a thiophene ring fused to the 2,3 positions were synthesized. Condensation of 2-methoxymethylene-3-ketosteroids (Ia, Ib) with ethyl thioglycolate in the presence of sodium methoxide yielded the tetrahydrothiophene derivatives (Va, Vb), which were dehydrated to the corresponding androstano[2,3-*c*]thiophene carboxylates (VIa, VIb) by treatment of acids. Hydrolysis, followed by decarboxylation of the carbethoxythiophenes gave the corresponding androstano[2,3-*c*]thiophenes (Xa, Xb). Similarly androst-4-eno[2,3-*c*]thiophenes and androstano[16,17-*c*]thiophenes were prepared.

The appearance of 17β-hydroxy-17α-methyl-5α-androstano[3,2-*c*]pyrazole (Stanazolol)[2] as a therapeutically useful anabolic drug led to the synthesis of analogous steroids with a heterocyclic ring fused onto ring A in several laboratories.[3] In a course of the investigation concerning with addition of alkylmercaptans to α,β-unsaturated steroid ketones, we have been interested in the biological activity of some steroidal fused heterocycles containing sulfur atom. This paper describes a novel synthesis of steroidal[2,3-*c*]thiophene derivatives by an extension of thiophene synthesis recently reported by Tilak, *et al.*[4]

Nucleophilic addition of aklylmercaptan *e.g.* methyl-, ethyl-, benzyl- and phenylmercaptan to 2-methoxymethylene-3-ketosteroids (I) in the presence of sodium methoxide readily afforded the thioacetal (II) and the hemithioacetal (III) of 2-formyl-3-oxosteroids.[5]



Ia : R=H
Ib : R=CH_3

R=H, CH_3
R_1=alkyl, aryl

Chart 1

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[1] Location: *Kami-Ebie 2, Fukushima-ku, Osaka.*

[2] R.O. Clinton, A.J. Manson, F.W. Stonner, H.C. Neumann, R.G. Christiansen, R.L. Clarke, J.H. Ackerman, D.F. Page, J.W. Dean, W.B. Dickinson, and C. Carabateas, *J. Am. Chem. Soc.*, **83**, 1478 (1961).

[3] *a*) A.J. Manson, F.W. Stonner, H.C. Neumann, R.G. Christiansen, R.L. Clarke, J.H. Ackerman, J.W. Dean, D.K. Phillips, G.O. Potts, A. Arnold, A.L. Beyler, and R.O. Clinton, *J. Med. Chem.*, **6**, 1 (1963); *b*) H. Antaki and V. Petrow, *J. Chem. Soc.*, **1951**, 901; *c*) C. Orr, M.L. Franco, A.D. Cross, and F. Sondheimer, *Steroids*, **3**, 1 (1961); *d*) G. Ohta, T. Takegoshi, K. Ueno, and M. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **12**, 1445 (1965); *e*) J.A. Zderic, O. Halpern, H. Carpio, A. Bowers, and H.J. Ringold, *Chem. & Ind.* (London), **1960**, 1625; *f*) P. Ruggieri, C. Gandolfi, D. Chairamonti, and U. Guzzi, *Gazz. Chim. Ital.*, **95**, 257 (1965).

[4] B.D. Tilak, H.S. Desai, and S.S. Gupte, *Tetrahedron Letters*, **1966**, 1953.

[5] Details of this work will be published in the near future.

It was of interest that the addition of ethyl thioglycolate with I[2,6] under the same condition in place of alkylmercaptan resulted in a simultaneous cyclization to form the tetrahydrothiophene derivatives (Va and Vb) in approximately 70% yield.

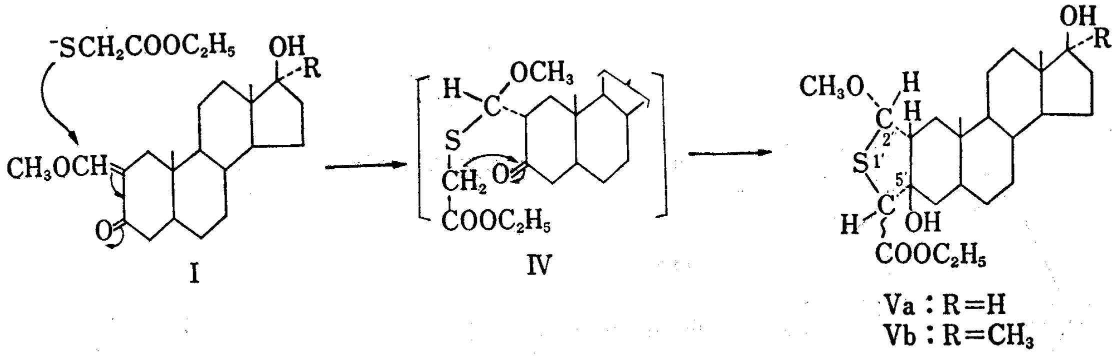

Chart 2

The course of the reaction may involve a nucleophilic attack of thioglycolate anion on the 2-methoxymethylene carbon atom and a concomitant intramolecular aldol condensation of the presumable intermediate (IV) led to the compound having a tetrahydrothiophene ring (V) as shown in Chart 2. The ring juncture of the tetrahydrothiophene ring to ring A may be assumed to be thermodynamically more stable *cis* form as that of hydrindane.[7] The nuclear magnetic resonacne (NMR) spectrum of Va showed a doublet at 4.97 τ (J=8.2 cps), two singlets at 5.69 τ and 6.73 τ indicative of the 2'-,5'-protons and 2'-OCH_3 group, respectively. On the basis of comparison with the coupling constant between the C-2 and C-3 protons in *cis* isomer of N-acetyl-3-methylproline ester,[8] it was concluded that the methoxy group at C-2' is placed in the *trans* relation with respect to the 2β-hydrogen.

By mild treatment with *p*-toluenesulfonic acid in benzene or with hydrochloric acid in acetic acid the compound (Va) was dehydrated to afford ethyl 17β-hydroxyandrostano[2,3-*c*]thiophene-5'-carboxylate (VIa), wihch showed ultraviolet absorption at 264 mμ characteristic of thiophene ring and a singlet peak at 2.95 τ due to the C-2' proton. Thereby the hydroxy group *in situ* on the tetrahydrothiophene ring was postulated to place at C-3' as a result of the above-mentioned aldol condensation. Likewise, ethyl 17β-hydroxy-17α-methylandrostano[2,3-*c*]thiophene-5'-carboxylate (VIb) was also obtained from the corresponding 2-methoxymethylene-17α-methyl- steroid (Vb). On the other hand, prolonged treatment of the tetrahydrothiophene derivative (Vb) with *p*-toluenesulfonic acid or hydrochloric acid did not afford the desired product (VIb) but exclusively transformed to the 17-*gem*-dimethyl product (VII), whose infrared spectrum exhibited bands at 1383 and 1359 cm^{-1} characteristic of 17-*gem*-dimethyl group. The NMR spectrum of this compound agreed well with the rearrangement structure (VII).[3a)]

After hydrolyzing the thiophene carboxylates (VIa, VIb and VII) with 10% ethanolic potassium hydroxide, the resulting carboxylic acids (VIIIa, VIIIb and IX) were each subjected to decarboxylation on heating with copper powder in quinoline at 210° to furnish the final products, androstano[2,3-*c*]thiophenes (Xa, Xb and XI). In the NMR spectrum of Xa, two protons at 3.17 τ were assigned to the hydrogens in the thiophene ring, while ultraviolet absorption maximum at 248 mμ was also characteristic of thiophene structure. The structures of Xb and XI were also proved in the same manner. Upon heating the 17α-methyl-carboxylic

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6) *a*) L.H. Knox and E. Velarde, *J. Org. Chem.*, **27**, 3925 (1962); *b*) J. Schmitt, J.J. Panouse, A. Hallot, P.J. Cornu, H. Pluchet, and P. Comoy, *Bull. Soc. Chim. France*, **1964**, 2753.

7) E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, "Conformational Analysis," Interscience Publishers, New York, 1965, p. 226.

8) A.B. Mauger, F. Irreverre, and B. Witkop, *J. Am. Chem. Soc.*, **88**, 2019 (1966).

acid derivative (VIIIb) over 300° without copper as the catalyst, decarboxylation was accompanied with the rearrangement of 18-methyl group to give the 17,17-dimethyl-18-norandrost-13-eno[2,3-*c*]thiophene (XI), whose thermal rearrangement has some analogy with that of 17*β*-hydroxy-17*α*-methylandrostan-3-one.[9]

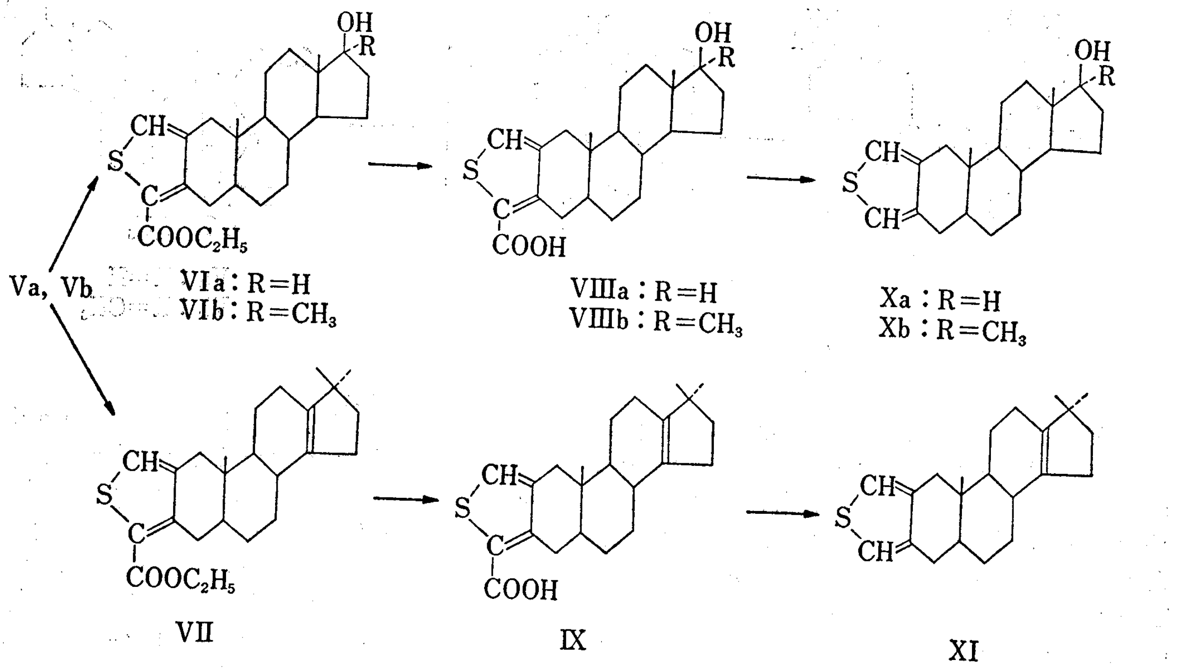

Chart 3

As an alternative route to synthesis of the androstano[2,3-*c*]thiophenes, the similar addition reaction to 3-methoxymethylene-2-oxosteroids as mentioned above was available, in which 2-oxosteroid (XII), prepared from 3-hydroxymethylene-17*β*-hydroxyandrostan-2-one[10] by refluxing in methanolic hydrochloric acid, was treated with ethyl thioglycolate, followed by treatment with hydrochloric acid in acetic acid to give 17*β*-acetoxyandrostano[2,3-*c*]thiophene-2′-carboxylate (XV). After hydrolysis of the ester (XV) with alkali and decarboxylation

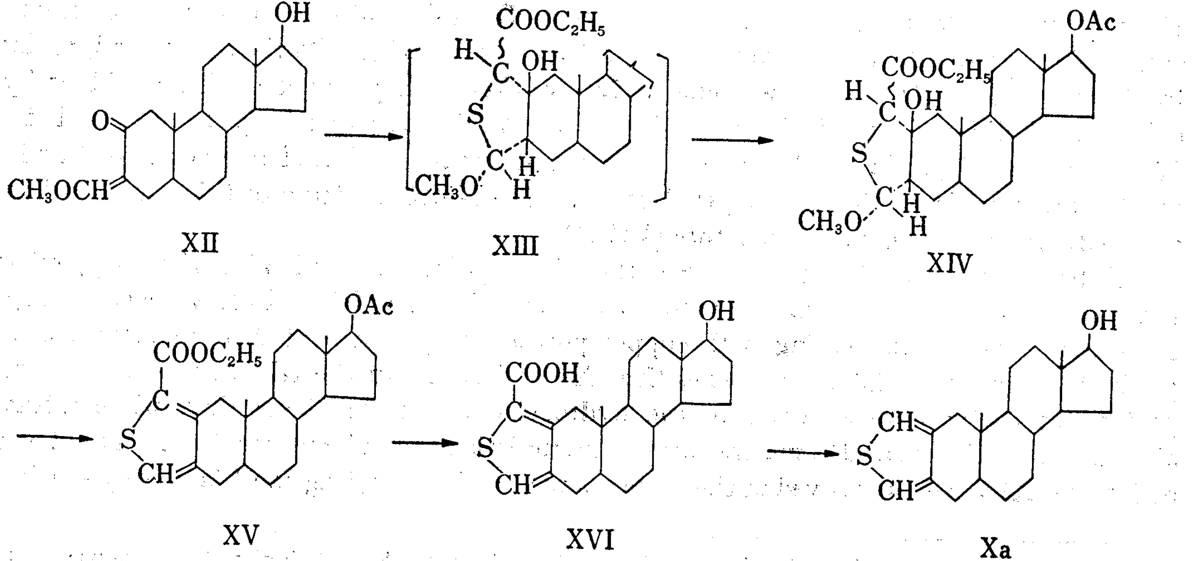

Chart 4

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[9] K. Ueno, *Chem. Pharm. Bull.* (Tokyo), 12, 92 (1964).

[10] R.L. Clarke and S.J. Daum, *J. Org. Chem.*, 30, 3786 (1965).

of the resulting carboxylic acid (XVI) on heating, androstano[2,3-*c*]thiophene (Xa) was obtained, which was proved to be quite identical with that prepared from Ia.

The condensation product (XIII) of 3-methoxymethylene-2-oxosteroid (XII) with ethyl thioglycolate was failed to crystallize, which was characterised as its acetate (XIV). The configuration of the 5′-methoxy group was assigned by means of NMR spectroscopy as follows.

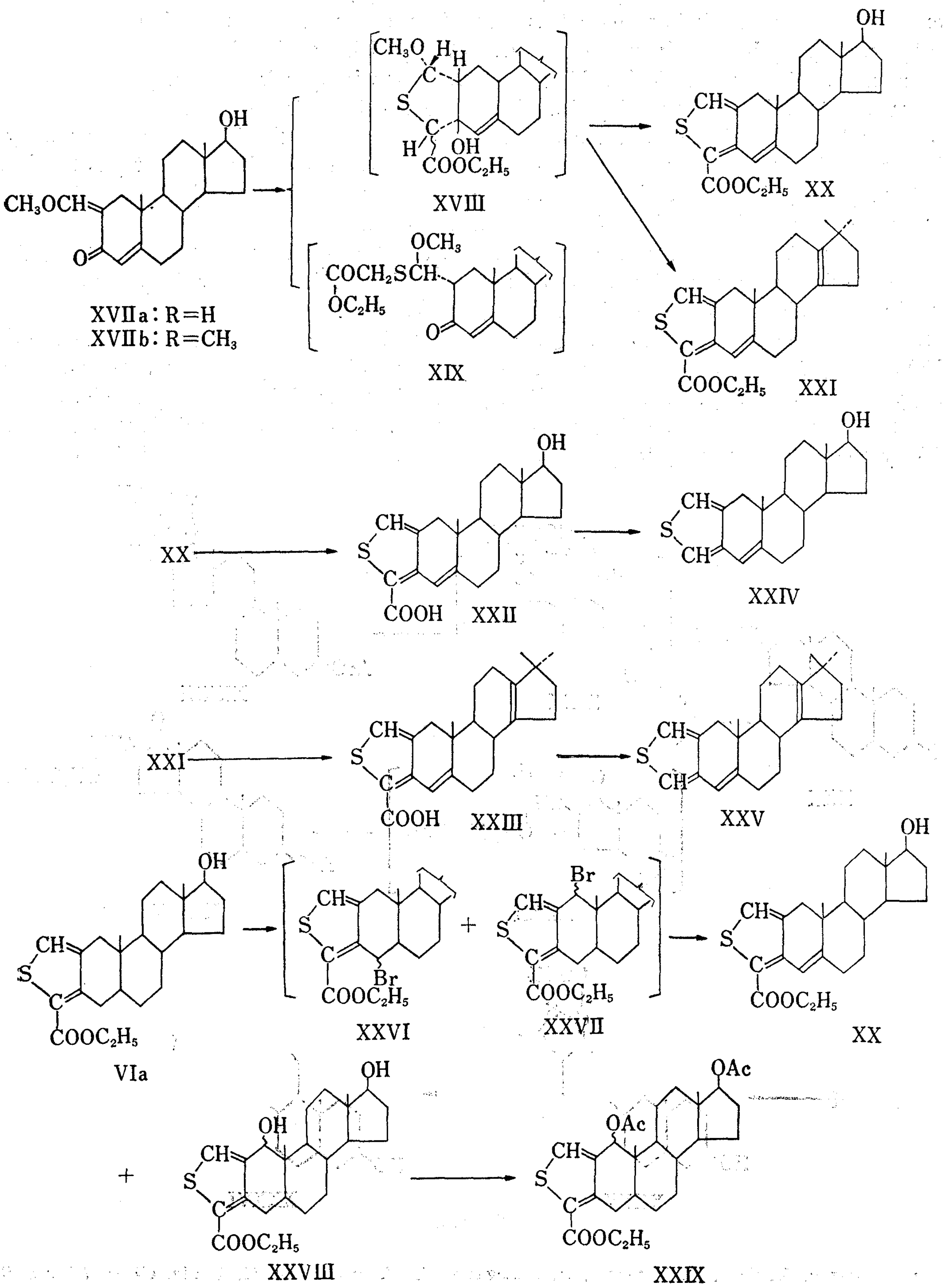

Chart 5

The signal of the 19-methyl group appeared in 0.25 ppm lower field than that of unsubstituted 5α-androstane at C-2. Accordingly, the 2-hydroxy group of the acetate (XIV) is in 1,3-diaxial relation to the 19-methyl group,[11] whereas 5′-methoxy group of the acetate (XIV) was suggested to be α-configuration on the basis of coupling constant (J=8.0 cps) between the 5′-proton and the adjacent 3β-proton as discussed for Va.

Moreover, also the corresponding androst-4-eno[2,3-*c*]thiophenes (XXIV and XXV) were prepared by the similar method as that of androstanes. Condensation of 2-methoxymethylene-17β-hydroxyandrost-4-en-3-one (XVIIa) with ethyl thioglycolate, followed by treatment with *p*-toluenesulfonic acid, gave ethyl 17β-hydroxyandrost-4-eno[2,3-*c*]thiophene-5′-carboxylate (XX) in only 3% yield. From the NMR spectra of the reaction products of XVIIa and XVIIb with ethyl thioglycolate, it was suggested that there remains mainly an addition product (XIX) along with a small amounts of the cyclization product (XVIII) in the reaction. Thus, the attack of the carbanion to C-3 carbonyl in the conjugated system seems to be more depressed than that of the saturated system.

An attempt to introduce a double bond at the 4,5 positions of the androstano[2,3-*c*]thiophene (Xa) by bromination with N-bromosuccinimide, followed by dehydrobromination with lithium chloride/lithium carbonate, was unsuccessful. However, applying this method to the thiophene carboxylate (VIa), it gave the androst-4-eno[2,3-*c*]thiophene-5′-carboxylate (XX) and 1ξ,17β-dihydroxyandrostano[2,3-*c*]thiophene-5′-carboxylate (XXVIII) in 20% and 16% yields, respectively. Diacetate (XXIX) of the latter exhibited a sharp singlet at 4.31 τ indicated a proton of C-1 bearing an acetoxy group. The 1-hydroxy derivative (XXVIII) is likely to generate from hydrolysis of the corresponding 1-bromo compound (XXVII).

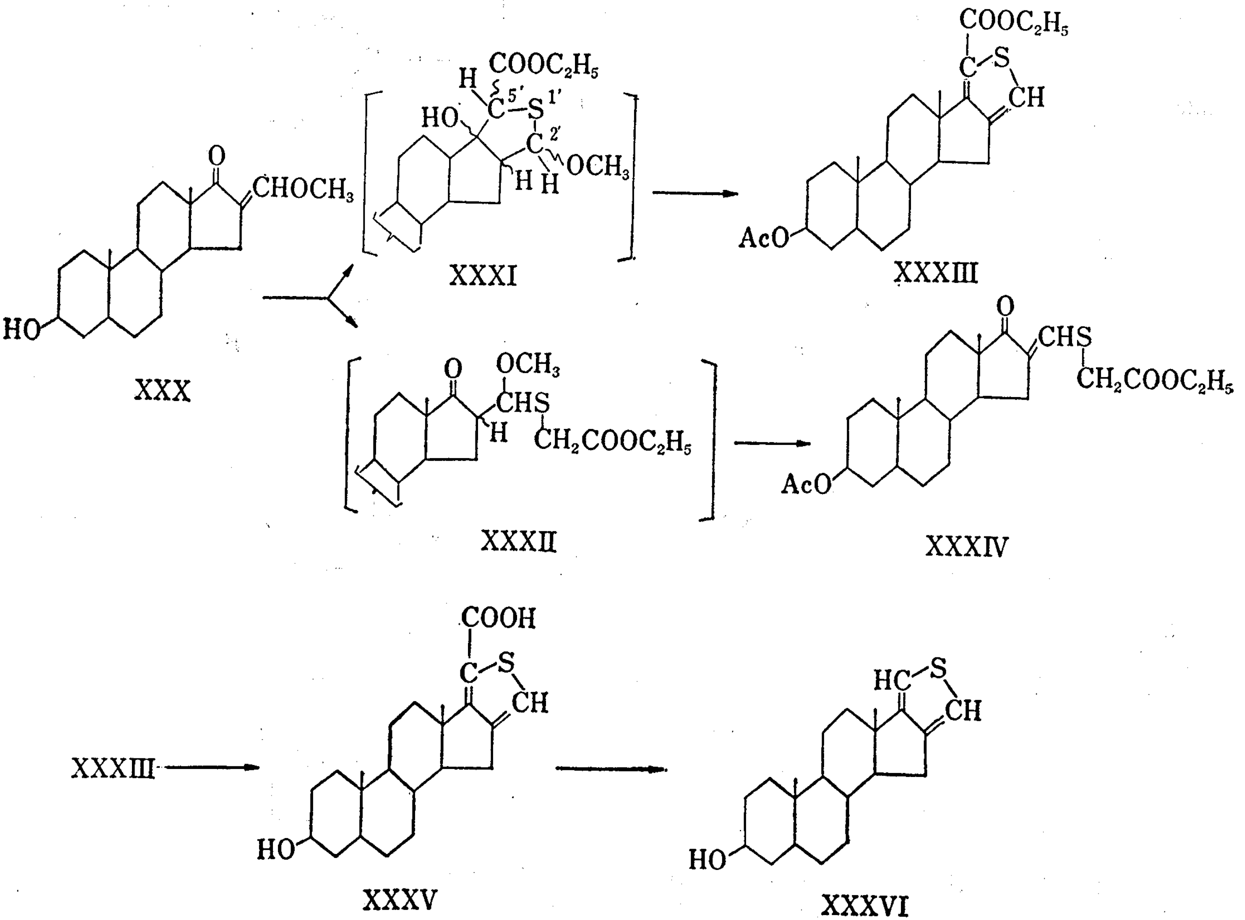

Chart 6

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[11] Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962).

Although several synthesis of steroids of androstane series with heterocycle fused at the C-16 and -17 positions have been reported,[12] it is noteworthy further to report a new type of the steroidal 16,17-heterocycles, androstano[16,17-*c*]thiophenes prepared under the similar condition as that for the androstano[2,3-*c*]thiophenes.

The addition of ethyl thioglycolate with the methoxymethylene derivative (XXX) prepared from 3β-hydroxy-16-hydroxymethylene-5α-androstan-17-one[13] by brief refluxing in methanol containing a few drops of concentrated hydrochloric acid, resulted in an oily product which was, without purification, treated with hydrochlolic acid in acetic acid and then chromatographed on silica gel to afford ethyl 3β-acetoxyandrostano[16,17-*c*]thiophene-5′-carboxylate (XXXIII) as a minor product together with the ethoxycarbonylmethylthiomethylene compound (XXXIV). Hydrolysis followed by decarboxylation of the former in the usual manner furnished the final product, 3β-hydroxy-5α-androstano[16,17-*c*]thiophene (XXXVI) as shown in Chart 6.

The intermediate having tetrahydrothiophene ring (XXXI) was not isolated in this reaction, but only the thioglycolate adduct (XXXII) was obtained as crystalline form. The latter compound however did not proceed to further cyclization to give the compound (XXXIII).

The biological activities of the steroidal thiophenes described in this paper will be reported elsewhere.

Experimental[14]

Preparation of 2-Methoxymethylene-3-oxosteroids——After 2-hydroxymethylene-3-oxosteroid (20 millimoles) was refluxed in MeOH (100 ml) containing a few drops of HCl for 2 min, pyridine (1 ml) was added to the mixture. Removal of the solvent gave the corresponding 2-methoxymethylene-3-oxosteroid. The crude product was used, without purification, for the next procedure in this work.

Condensation of 2-Methoxymethylene-3-oxosteroids with Ethyl Thioglycolate, and Dehydration of the Condensation Products with Acids. Ethyl 2′α-Methoxy-3β, 17β-dihydroxyandrostano[2α,3α-*c*]tetrahydrothiophene-5′ξ-carboxylate(Va)——To a solution of 2-methoxymethylene-17β-hydroxyandrostan-3-one (Ia) (mp 200—206°, 3 g) in ethyl thioglycolate (30 ml) was added 1.5 g of MeONa. After stirring for 3 hr at room temperature and standing overnight, water was added and the product was extracted with ether. The solvent was washed with water, dried and evaporated. The residual oily product was dissolved in 30 ml of hexane. On standing the solution deposited 2.5 g of colorless needles. Recrystallization from acetone gave the tetrahydrothiophene derivative (Va), mp 219—221°, $[\alpha]_D$ $-112.7°$ ($c=1.05$). IR ν_{max} cm^{-1}: 3380 (OH), 1719 (CO). NMR[15] τ: 9.37 (18-CH_3), 9.27 (19-CH_3), 8.82 (t, $J=7.0$, $-CH_2C\underline{H}_3$), 6.73 (OCH_3), 5.90 (q, $J=7.0$, $-C\underline{H}_2CH_3$), 5.69 (5′ξ-H), 4.97 (d, $J=8.2$, 2′β-H) (in DMSO-d_6). *Anal.* Calcd. for $C_{25}H_{40}O_5S$: C, 66.33; H, 8.91; S, 7.08. Found: C, 66.54; H, 8.99; S, 7.02.

Ethyl 17β-Hydroxyandrostano[2,3-*c*]thiophene-5′-carboxylate (VIa)——A solution of Va (3.0 g) and *p*-TsOH (0.6 g) in benzene was refluxed for 1 hr. After cooling, the benzene layer was washed with 5% $NaHCO_3$ and water, dried and evaporated. Recrystallization of the crude product from MeOH-ether gave the [2,3-*c*]thiophene carboxylate (VIa) (2.55 g) as colorless needles, mp 141—144°, $[\alpha]_D$ $+75.9°$ ($c=1.33$). UV λ_{max} mμ (ε): 264 (14500). IR ν_{max} cm^{-1}: 3480 (OH), 1690 (CO), 1619 (thiophene ring). NMR τ: 9.28 (19-CH_3), 9.24 (18-CH_3), 8.64 (t, $J=7.0$, $-CH_2C\underline{H}_3$), 8.42 (OH), 6.36 (17α-H), 5.68 (q, $J=7.0$, $-C\underline{H}_2CH_3$), 2.95 (2′-H). *Anal.* Calcd. for $C_{24}H_{34}O_3S \cdot \frac{1}{2}CH_3OH$: C, 70.29; H, 8.67; S, 7.66. Found: C, 70.55; H, 8.42; S, 7.83.

Ethyl 2′α-Methoxy-3β,17β-dihydroxy-17α-methylandrostano[2α,3α-*c*]tetrahydrothiophene-5′ξ-carboxylate (Vb)——Vb (1.3 g) was prepared from 2-methoxymethylene-17β-hydroxy-17α-methylandrostan-3-one (Ib) (mp 166—173°, 2.0 g) by the similar method as described in (Va). Recrystallization from ether-hexane

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12) *a*) K. Brückner, K. Irmscher, F. Werder, K.H. Bork, and H. Metz, *Chem. Ber.*, **94**, 2897 (1961); *b*) P. Ruggieri, C. Gandolfi, and D. Chiaramonti, *Gazz. Chim. Ital.*, **93**, 289 (1963).

13) L.H. Knox, U.S. Patent 3088954 [*C.A.*, **59**,11613 (1963)].

14) Melting points are uncorrected. IR spectra were determined in KBr disk and UV spectra in EtOH solution. Optical rotations were measured in $CHCl_3$ solution at *ca.* 20° unless otherwise indicated. NMR spectra were recorded on a Varian A-60 spectrometer in $CDCl_3$ containing tetramethylsilane as internal standard.

15) Abbreviation used s=singlet, d=doublet, and q=quartet. Coupling constants *J* are given in cps.

afforded an analytical sample, mp 148—150°, $[\alpha]_D$ −121.3° (c=1.13). IR ν_{max} cm^{-1}: 3500 (OH), 1716 (CO). NMR τ: 9.23 (18- and 19-CH_3), 8.90 (17α-CH_3), 8.78 (t, J=7.0, -$CH_2C\underline{H}_3$), 6.71 (OCH_3), 5.87 (q, J=7.0, -$C\underline{H}_2CH_3$), 5.66 (5′ξ-H), 4.95 (d, J=8.2, 2′β-H) (in DMSO-d_6). *Anal.* Calcd. for $C_{26}H_{42}O_5S$: C, 66.91; H, 9.07; S, 6.87. Found: C, 67.22; H, 9.15; S, 6.61.

Ethyl 17β-Hydroxy-17α-methylandrostano[2,3-*c*]thiophene-5′-carboxylate (VIb)——To a solution of Vb (2.0 g) in AcOH (50 ml) was added 5 ml of 9% HCl–ether and the mixture was stirred at room temperature for 1 hr. After diluted with water, the crude product was extracted with ether. The ethereal solution was washed with 5% Na_2CO_3, water and dried. Evaporation of the solvent and crystallization of the residue from ether–hexane afforded 1.6 g of the androstano[2,3-*c*]thiophene carboxylate (VIb), mp 113—117°, $[\alpha]_D$ +56.5° (c=1.07). UV λ_{max} mμ (ε): 264 (14400). IR ν_{max} cm^{-1}: 3440, 3470 (OH), 1684 (CO). NMR τ: 9.28 (19-CH_3), 9.13 (18-CH_3), 8.77 (17α-CH_3), 8.65 (t, J=7.0, -$CH_2C\underline{H}_3$), 8.47 (OH), 5.68 (q, J=7.0, -$C\underline{H}_2$-CH_3), 2.95 (2′-H). *Anal.* Calcd. for $C_{25}H_{36}O_3S$: C, 72.02; H, 8.71; S, 7.70. Found, C. 71.82; H, 8.68; S, 7.57.

Ethyl 17,17-Dimethyl-18-norandrost-13-eno[2,3-*c*]thiophene-5′-carboxylate (VII)——A solution of IVb (1.0 g) and p-TsOH (0.2 g) in benzene was refluxed for 1 hr. Working up as described for (VIa) gave a colorless needles. Recrystallization from MeOH afforded the 17-*gem*-dimethylandrostano[2,3-*c*]thiophene-5′-carboxylate (VII) (0.68 g), mp 132—134°, $[\alpha]_D$ +35.6° (c=1.44). UV λ_{max} mμ (ε): 263 (14600). IR ν_{max} cm^{-1}: 1683 (CO), 1533(thiophene ring), 1383, 1359 (17-*gem*-dimethyl). NMR τ: 9.32 (19-CH_3), 9.02 (17-*gem*-dimethyl), 8.64 (t, J=7.0, -$CH_2C\underline{H}_3$), 5.67 (q, J=7.0, -$C\underline{H}_2CH_3$), 2.93 (2′-H). *Anal.* Calcd. for $C_{25}H_{34}O_2S$: C, 75.33; H, 8.57; S, 8.04. Found: C, 75.12; H, 8.38; S, 7.97.

Ethyl 2β-Hydroxy-5′α-methoxy-17β-acetoxyandrostano[2α,3α-*c*]tetrahydrothiophene-2′ξ-carboxylate (XIV) and Ethyl 17β-Acetoxyandrostano[2,3-*c*]thiophene-2′-carboxylate (XV)——To a solution of 3-methoxymethylene-17β-hydroxyanhydrostan-2-one (XII) in ethyl thioglycolate (10 ml) and anhydrous dioxane (20 ml) was added 1 g of MeONa and the mixture was stirred at room temperature for 5 hr. After standing overnight, the reaction mixture was worked up as described in (Va). The reasulting crude product was dissolved in hexane and chromatographed on silica gel. Elution with petroleum ether–benzene (1:1) afforded the crude condensation product (XIII) (4.1 g).

Acetate of XIII——The crude product of XIII (0.5 g) was acetylated with acetic anhydride and pyridine in usual way. Recrystallization from hexane gave 0.2 g of the acetate (XIV) as needles, mp 129—131°, $[\alpha]_D$ −127° (c=0.52). IR ν_{max} cm^{-1}: 3490 (OH), 1730 ($OCOCH_3$), 1715 ($COOC_2H_5$). NMR τ: 9.22 (18-CH_3), 8.96 (19-CH_3), 8.71 (t, J=7.0, -$CH_2C\underline{H}_3$), 7.97 ($OCOCH_3$), 6.58 (OCH_3), 6.02 (2′-H), 5.76 (q, J=7.0, -$C\underline{H}_2$-CH_3), 5.38 (17α-H), 4.78 (d, J=8.0, 5′-H). *Anal.* Calcd. for $C_{27}H_{42}O_6S$: C, 65.55; H, 8.56; S, 6.48. Found: C, 65.73; H, 8.65; S, 6.51.

Acid Treatment of XIII——The condensation product (XIII) (3.0 g) mentioned above was dissolved in the mixture of AcOH (30 ml) and 9% HCl–ether (0.5 ml). The mixture was refluxed for 4 hr and diluted with water. After working up as described for VIa, the resulting crude product was chromatographed on silica gel. Elution with benzene afforded an oily product which was recrystallized from hexane to give the androstano[2,3-*c*]thiophene-2′-carboxylate (XV) (1.5 g), mp 176—179°, $[\alpha]_D$ +58.3° (c=0.86). UV λ_{max} mμ (ε): 264 (12900). IR ν_{max} cm^{-1}: 1736 ($OCOCH_3$), 1695 ($COOC_2H_5$). NMR τ: 9.26 (19-CH_3), 9.19 (18-CH_3), 8.64 (t, J=7.0, -$CH_2C\underline{H}_3$), 7.96 ($OCOCH_3$), 5.69 (q, J=7.0 -$C\underline{H}_2CH_3$), 5.38 (17α-H), 2.94 (5′-H). *Anal.* Calcd. for $C_{26}H_{36}O_4S$: C, 70.23; H, 8.16; S, 7.21. Found: C, 70.52; H, 8.22; S, 7.42.

Hydrolysis of XV with 2% KOH–EtOH gave ethyl 17β-hydroxyandrostano[2,3-*c*]thiophene-2′-carboxylate. Recrystallization from hexane–acetone gave a pure crystal, mp 197—200°, $[\alpha]_D$ +88.1° (c =0.52). UV λ_{max} mμ (ε): 264 (14000). *Anal.* Calcd. for $C_{24}H_{34}O_3S$: C, 71.60; H, 8.51; S, 7.97. Found: C, 71.32; H, 8.25; S, 8.06.

Ethyl 17β-Hydroxyandrost-4-eno[2,3-*c*]thiophene-5′-carboxylate (XX)——To a solution of XVII (mp 140—149°, 5.0 g) in ethyl thioglycolate (8 ml) and dioxane (20 ml) was added 1.5 g of MeONa. The mixture was then sitrred at room temperature for 3 hr. After standing overnight, the reaction mixture was worked up as described in (IVa). The resulting crude product was dissolved in hexane and chromatographed on silica gel. Elution with petroleum ether–benzene (1:1) gave an oily substance, whose NMR spectrum showed a doublet at 4.86 τ (J=3.0), singlet at 6.56 τ and singlet at 6.63 τ due to -$SC\underline{H}OCH_3$, OCH_3 and -$SC\underline{H}_2CO$- groups, respectively. The oily product was dissolved in benzene (50 ml) and p-TsOH (0.6 g) was added. The mixture was refluxed for 30 min, diluted with water. The crude product, isolated by usual working up, was purified with chromatography on silica gel. The eluate with benzene–ether (1:1) was recrystallized from CH_3CN to give the androst-4-eno[2,3-*c*]thiophene carboxylate (XX) (0.2 g), mp 166—169°, $[\alpha]_D$ +37.6° (c=1.01). UV λ_{max} mμ (ε): 293 (19500), 313 (12100), shoulder at 285 (15300) and 325 (10800). IR ν_{max} cm^{-1}: 3470 (OH), 1692, 1672 (CO). NMR τ: 9.21 (18-CH_3), 9.08 (19-CH_3), 8.64 (t, J=7.0, -$CH_2C\underline{H}_3$), 8.52 (OH), 6.33 (17α-H), 5.68 (q, J=7.0, -$C\underline{H}_2CH_3$), 3.00 (2′- and 4-H). *Anal.* Calcd. for $C_{24}H_{32}O_3S$: C, 71.96; H, 8.05; S, 8.01. Found: C, 71.86; H, 7.93; S, 7.92.

Ethyl 17,17-Dimethyl-18-norandrost-4,13-dieno[2,3-*c*]thiophene-5′-carboxylate (XXI)——The analogous reaction of XVIIb (mp 168—174°, 3.0 g) as in (XX) and recrystallization from MeOH–ether gave the 17-*gem*-dimethylandrostano[2,3-*c*]thiophene (XXI) (0.15 g), mp 145—148°, $[\alpha]_D$ −58.9° (c=0.36). UV λ_{max} mμ (ε): 293 (19400), 314 (15600), shoulder at 284 (18900) and 323 (13900). IR ν_{max} cm^{-1}: 1690 (CO), 1365, 1343 (17-*gem*-dimethyl). NMR τ: 9.10 (19-CH_3), 9.02 (17-*gem*-dimethyl), 8.64 (t, J=7.0, -$CH_2C\underline{H}_3$), 5.66

(q, J=7.0, $-C\underline{H}_2CH_3$), 2.98 (2′- and 4-H). *Anal.* Calcd. for $C_{25}H_{32}O_2S$: C, 75.71; H, 8.13; S, 8.05. Found: C, 75.69; H, 8.02; S, 8.15.

Addition Product (XXXII) of 3β-Hydroxy-16-methoxymethyleneandrostan-17-one (XXX) with Ethyl Thioglycolate and 3β-Acetoxy-16-carbethoxymethylthiomethyleneandrostan-17-one (XXXIV)——The 16-methoxymethylene derivative (XXX) (mp 205—211°,[16] 5 g) in anhydrous dioxane (30 ml) was treated with ethyl thioglycolate (10 ml) and MeONa (2.0 g) to give an oily product. After addition of hexane (30 ml) the crude crystalline was precipitated. Repeated crystallization from ether afforded the addition product (XXXII) (2.5 g),mp 142—145°, $[\alpha]_D$ +80.0° (c=0.52). IR ν_{max} cm^{-1}: 3450 (OH), 1741 ($COOC_2H_5$), 1710 (17-CO). NMR τ: 9.17 (18- and 19-CH_3), 8.71 (t, J=7.0, $-CH_2C\underline{H}_3$), 6.45 (3α-H), 5.05 (d, J=2.5, $-C\underline{H}(OCH_3)S-$). *Anal.* Calcd. for $C_{25}H_{40}O_5S$: C, 66.34; H, 8.91; S, 7.08. Found: C, 66.07; H, 8.87; S, 7.26.

Treatment of the addition product (XXXII) with 9% HCl-ether and AcOH furnished only the conjugated ketone (XXXIV), which was recrystallized from hexane to yield a pure crystal, mp 122—123.5°, $[\alpha]_D$ −21.2° (c=1.23). UV λ_{max} mμ (ε): 298 (19400). IR ν_{max} cm^{-1}: 1730 ($OCOCH_3$ and $COOC_2H_5$), 1700 (17-CO), 1577 (C-C). NMR τ: 9.13 (18- and 19-CH_3), 8.71 (t, J=7.0, $-CH_2C\underline{H}_3$), 7.98 ($OCOCH_3$), 6.44 ($SC\underline{H}_2CO$), 5.77 (q, J=7.0, $-C\underline{H}_2CH_3$), 5.32 (3α-H), 2.62 (=CHS-). *Anal.* Calcd. for $C_{26}H_{38}O_5S$: C, 67.50; H, 8.28; S, 6.93. Found: C, 67.88; H, 8.16; S, 6.84.

Ethyl 3β-Acetoxyandrostano[16,17-*c*]thiophene-5′-carboxylate (XXXIII)——The reaction product of XXX (6.5 g) with ethyl thioglycolate (10 ml) in dioxane (30 ml) in the presence of MeONa (2.0 g) was heated with the mixture of 9% HCl-ether (0.5 ml) and (15 ml) on a water bath for 3 hr. After working up, the resulting crude product was purified by chromatography on silica gel. Elution with petroleum ether-benzene (2:3) yielded the androstano[16,17-*c*]thiophene carboxylate (0.08 g) as colorless needles, which was recrystallized from CH_3CN to give an analytical sample, mp 196—198.5°, $[\alpha]_D$ +33.8° (c=0.86). UV λ_{max} mμ (ε): 259 (14000), shoulder at 280 (6700). IR ν_{max} cm^{-1}: 1739 ($OCOCH_3$), 1703 ($COOC_2H_5$). NMR τ; 9.11 (19-CH_3), 8.96 (18-CH_3), 8.64 (t, J=7.0, $-CH_2C\underline{H}_3$), 7.98 ($OCOCH_3$), 5.69 (q, J=7.0, $-C\underline{H}_2CH_3$), 5.34 (3α-H), 3.04 (2′-H). *Anal.* Calcd. for $C_{26}H_{36}O_4S$: C, 70.23; H, 8.16; S, 7.21 Found: C, 70.66; H, 7.86; S, 7.38.

Further elution with benzene and recrystallization from hexane afforded the conjugated ketone (XXXIV) (0.83 g), mp 122—123.5°, which was identical with that obtained above.

Hydrolysis of the [2,3-*c*]- and [16,17-*c*] Thiophene Carboxylate with Alkali 17β-Hydroxyandrostano[2,3 *c*]thiophene-5′-carboxylic Acid (VIIIa)——A solution of VIa (2.5 g) in 10% KOH-EtOH (60 ml) was refluxed for 10 min. The solution was poured into water and acidified with 10% HCl. The resulting precipitate was collected by filtration, washed with water and dried. Recrystallization from MeOH gave 2.1 g of VIIIa as colorless needles, mp 292—296° (decomp.), $[\alpha]_D$ +72.5° (c=0.83, dioxane). UV λ_{max} (ε): 263 (13600). IR ν_{max} cm^{-1}: 3300, 3660 (OH), 1683 (COOH), 1620 (thiophene ring). *Anal.* Calcd. for $C_{22}H_{30}O_3S\cdot\frac{1}{2}H_2O$: C, 67.31; H, 8.22; S, 8.17. Found: C, 67.79; H, 8.17; S, 7.93.

Hydrolysis of VIb, VII, XV, XX, XXI and XXXIII were each performed in the same way as in (VIa), and afforded VIIIb, IX, XVI, XXII, XXIII and XXXV, respectively. Their physical constants, spectroscopic data and analytical values were as follows:

a) 17β-Hydroxy-17α-methylandrostano[2,3-*c*]thiophene-5′-carboxylic acid (VIIIb): recryst. from MeOH, mp 297—299° (decomp.), $[\alpha]_D$ +52.5° (c=0.88, dioxane). UV λ_{max} mμ (ε): 263 (13500). IR ν_{max} cm^{-1}: 3420, 3470 (OH), 1684 (COOH). *Anal.* Calcd. for $C_{23}H_{32}O_3S$: C, 71.09; H, 8.30; S, 8.25. Found: C, 70.75; H, 8.17; S, 8.08.

b) 17,17-Dimethyl-18-norandrost-13-eno[2,3-*c*]thiophene-5′-carboxylic acid (IX): recryst. from CH_3CN, mp 242—253° (decomp.), $[\alpha]_D$ +46.2° (c=1.0, dioxane). UV λ_{max} mμ (ε): 263 (14000). IR ν_{max} cm^{-1}: 1660 (COOH), 1380, 1358 (17-*gem*-dimethyl). *Anal.* Calcd. for $C_{23}H_{30}O_2S$: C, 74.55; H, 8.16; S, 8.65. Found: C, 74.71; H, 8.07; S, 8.49.

c) 17β-Hydroxyandrostano[2,3-*c*]thiophene-2′-carboxylic acid (XVI): recryst. from CH_3CN, mp 286.5—287.5° (decomp.), $[\alpha]_D$ +83.9° (c=0.87, dioxane). UV λ_{max} mμ (ε): 264 (12200). IR ν_{max} cm^{-1}: 1661 (COOH), 1542 (thiophene ring). *Anal.* Calcd. for $C_{22}H_{30}O_3S\cdot\frac{1}{2}H_2O$: C, 68.89; H, 8.15; S, 8.36. Found: C, 69.24; H, 8.21; S, 8.31.

d) 17β-Hydroxyandrost-4-eno[2,3-*c*]thiophene-5′-carboxylic acid (XXII): recryst. from CH_3CN, mp 273—275° (decomp.), $[\alpha]_D$ +45.3° (c=0.99, dioxane). UV λ_{max} mμ (ε): 285—292 (16500), 312 (12300), shoulder at 323 (10500) IR ν_{max} cm^{-1}: 1690, 1650 (COOH). *Anal.* Calcd. for $C_{22}H_{28}O_3S$: C, 70.93; H, 7.18; S, 8.61. Found: C, 70.64; H, 7.38; S, 8.38.

e) 17,17-Dimethyl-18-norandrost-4,13-dieno[2,3-*c*]thiophene-5′-carboxylic acid (XXIII): recryst. from acetone-CH_3CN, mp 278—280° (decomp.), $[\alpha]_D$ −63.4° (c=0.35, dioxane). UV λ_{max} mμ (ε): 292 (19000), 312 (15100), shoulder at 284 (18900) and 323 (13000). IR ν_{max} cm^{-1}: 1677 (COOH). *Anal.* Calcd. for $C_{23}H_{28}O_2S\cdot\frac{1}{3}H_2O$: C, 73.82; H, 7.63; S, 8.57. Found: C, 73.90; H, 7.51; S, 8.49.

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[16] The pure methoxymethylene derivative had mp 209—212° (from MeOH), $[\alpha]_D$ −70.5° (c=1.16). UV λ_{max} mμ (ε): 267 (20,610). *Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.36; H, 9.17. Ref. 13 reported mp 204—206° and $[\alpha]_D$ 0°.

f) 3β-Hydroxyandrostano[16,17-*c*]thiophene-5′-carboxylic acid (XXXV): recryst. from acetone, mp 319—321° (decomp.), $[\alpha]_D$ +38 8° (c=0.76, dioxane). UV λ_{max} mμ (ε): 258 (12000), shoulder at 280 (6700). IR ν_{max} cm^{-1}: 1700 (COOH). *Anal.* Calcd. for $C_{22}H_{30}O_3S$: C, 70.55; H, 8.07; S, 8.56. Found: C, 70.80; H, 8.13; S, 8.32.

Decarboxylation of [2,3-*c*]- and [16,17-*c*]Thiophene-carboxylic Acids with Copper Powder and Quinoline. 17β-Hydroxyandrostano[2,3-*c*]thiophene (Xa): To a solution of VIIIa (0.5 g) in quinoline (0.2 ml) was added 0.4 g of copper powder. The reaction mixture was heated at 210° for 10 min. After vigorous gas evolution was observed, the mixture was cooled, and dissolved in $CHCl_3$. The filtrate from the solution was washed with 5% HCl, water and dried. After removal of the solvent, the resulting oily product was chromatographed on silica gel. Elution with petroleum ether-benzene (1:1) afforded 0.4 g of the androstano[2,3-*c*]thiophene (Xa), which was recrystallized from hexane to furnish a pure sample as colorless needles, mp 138—141°, $[\alpha]_D$ +69.7° (c=1.18). UV λ_{max} mμ (ε): 240 (7900), 248 (8400), shoulder at 255 (5600). IR ν_{max} cm^{-1}: 3376 (OH). NMR τ: 9.26 (19-CH_3), 9.25 (18-CH_3), 8.53 (OH), 6.35 (17α-H), 3.17 (2′- and 5′-H). *Anal.* Calcd. for $C_{21}H_{30}OS$: C, 76.31; H, 9.15; S, 9.70. Found: C, 75.95; H, 8.92; S, 9.78.

Propionate of the Androstano[2,3-*c*]thiophene (Xa)———The 17β-hydroxy compound (Xa) in pyridine was treated with propionic anhydride at room temperature. The product was crystallized from ether-MeOH to give the propionate, mp 152—154°, $[\alpha]_D$ +50.2° (c=1.08). *Anal.* Calcd. for $C_{24}H_{34}O_2S$: C, 74.56; H, 8.86; S, 8.29. Found: C, 74.64; H, 8.77; S, 8.34.

Decarboxylation of 17β-hydroxyandrostano[2,3-*c*]thiophene-2′-carboxylic acid (XVI) gave the androstano[2,3-*c*]thiophene (Xa), mp 138—141°, which was identical with the sample obtained above.

Decarboxylation of VIIIb, IX, XXII, XXIII and XXXV was carried out in the same manner as in VIIIa with copper powder in quinoline. The reaction each afforded the thiophene derivatives, Xb, XI, XXIV, XXV and XXXVI, respectively. Their physical constants, spectroscopic data, and analytical values were as follows:

a) 17β-Hydroxy-17α-methylandrostano[2,3-*c*]thiophene (Xb)——recryst. from hexane as colorless needles, mp 118.5—120°, $[\alpha]_D$ +43.6° (c=1.12). UV λ_{max} mμ (ε): 240 (7600), 248 (8100), shoulder at 255 (5400). NMR τ: 9.25 (19-CH_3), 9.12 (18-CH_3), 8.77 (17α-CH_3), 8.68 (OH), 3.16 (2′-and 5′-H). *Anal.* Calcd. for $C_{22}H_{32}OS$: C, 76.69; H, 9.36; S, 9.31. Found: C, 76.67; H, 9.21; S, 9.18.

b) 17,17-Dimethyl-18-norandrost-13-eno[2,3-*c*]thiophene (XI): recryst. from hexane, mp 140—143°, $[\alpha]_D$ +4.7° (c=1.05). UV λ_{max} mμ (ε): 240 (7400), 247 (7900), shoulder at 254 (5400). IR ν_{max} cm^{-1}: 1379, 1357 (17-*gem*-dimethyl). NMR τ: 9.30 (19-CH_3), 9.03 (17-*gem*-dimethyl), 3.16 (2′- and 5′-H). *Anal.* Calcd. for $C_{22}H_{30}S$: C, 80.92; H, 9.26; S, 9.82. Found: C, 81.21; H, 9.17; S, 9.68.

c) 17β-Hydroxyandrost-4-eno[2,3-*c*]thiophene (XXIV): recryst. from CH_3CN, mp 139.5—141.5°, $[\alpha]_D$ +132° (c=1.09). UV λ_{max} mμ (c): 259 (17500), shoulder at 251 (16600), 267 (15100). IR ν_{max} cm^{-1}: 3260 (OH). NMR τ: 9.22 (18-CH_3), 9.09 (19-CH_3), 8.56 (OH), 6.33 (17α-H), 3.22 (2′- and 5′-H). *Anal.* Calcd. for $C_{21}H_{28}OS$: C, 76.78; H, 8.95; S, 9.76. Found: C, 76.93; H, 8.81; S, 9.48.

d) 17,17-Dimethyl-18-norandrost-4,14-dieno[2,3-*c*]thiophene (XXV): recrysyt. from ether-CH_3CN, mp 107—110°, $[\alpha]_D$ +33.0° (c=0.30). UV λ_{max} mμ (ε): 258 (18300), shoulder at 251 (17000) and 267 (16000). IR ν_{max} cm^{-1}: 1366, 1356 (17-*gem*-dimethyl). NMR τ: 9.11 (19-CH_3), 9.02 (17-*gem*-dimethyl), 3.79 (4-H), 3.20 (2′- and 5′-H). *Anal.* Clacd. for $C_{22}H_{28}S$: C, 81.42; H, 8.70; S, 9.88. Found: C, 81.63; H, 8.80; S, 9.58.

e) 3β-Hydroxyandrostano[16,17-*c*]thiophene (XXXVI): recryst. from hexane, mp 151—152.5°, $[\alpha]_D$ +27.2° (c=0.86). UV λ_{max} mμ (ε): 245 (7730). NMR τ: 9.13 (19-CH_3), 9.04 (18-CH_3), 8.48 (OH), 6.41 (3α-H), 3.34 and 3.24 (2′- and 5′-H). *Anal.* Calcd. for $C_{21}H_{30}OS$: C, 76.31; H, 9.15; S, 9.70. Found: C, 75.86; H, 9.22; S, 9.35.

Bromination and Dehydrobromination of Ethyl 17β-Hydroxyandrostano[2,3-*c*]thiophene-5′-carboxylate (VIa)——A solution of VIa (2.5 g) and N-bromosuccinimide (1.28 g) in CCl_4 (50 ml) was refluxed for 40 min and the resulting precipitate was filtered off. After evaporation of the filtrate, the oily residue was heated at 90—95° with lithium chloride (1.25 g) and lithium carbonate (0.75 g) in dimethylformamide for 45 min. The reaction mixture was poured into water and extracted with ether. The ether extract was treated in the usual way to give an oily residue, which was chromatographed on silica gel. Elution with 2% ether in benzene gave a crystalline product. Repeated crystallization from CH_3CN afforded a pure crystal (0.5 g), mp 166—169°, whose melting point and IR spectrum were identical with that of the compound (XX) obtained from XVIIa.

Further elution with 10% ether in benzene gave ethyl 1ξ,17-dihydroxyandrostano[2,3-*c*]thiophene-5′-carboxylate (XXVIII) (0.35 g) as prisms. Recrystallization from MeOH furnished an analytical sample, mp 118—121°, $[\alpha]_D$ +51.7° (c=0.90). UV λ_{max} mμ (ε): 264 (13900). IR ν_{max} cm^{-1}: 3550, 3400 (OH), 1678 (CO). NMR: 9.39 (19-CH_3), 9.25 (18-CH_3), 8.64 (t, J=7.0, $-CH_2C\underline{H}_3$), 8.35 (1ξ,17β-OH), 6.35 (17α-H), 5.51 (1ξ-H), 5.67 (q, J=7.0, $-C\underline{H}_2CH_3$), 2.54 (2′-H). *Anal.* Calcd. for $C_{24}H_{34}O_4S$: C, 66.63; H, 8.50; S, 7.12. Found: C, 66.54; H, 8.22; S, 7.30.

Diacetate of XXVIII——The diol (XXVIII) was acetylated with Ac_2O and pyridine in usual way. Recrystallization from hexane gave the diacetate (XXIX), mp 139—141°, $[\alpha]_D$ +141.5° (c=1.19). UV λ_{max} mμ (ε) 263 (14100). IR ν_{max} cm^{-1}: 1730 ($OCOCH_3$), 1692 ($COOC_2H_5$). NMR τ: 9.30 (19-CH_3), 9.21

(18–CH_3), 8.65 (t, J=7.0, –$CH_2C\underline{H}_3$), 8.02 and 7.97 ($OCOCH_3$), 5.67 (q, J=7.0, –$C\underline{H}_2CH_3$), 5.35 (17α–H), 4.31 (1ξ–H), 2.37 (2′–H). *Anal.* Calcd. for $C_{28}H_{38}O_6S$: C, 66.90; H, 7.62; S, 6.38. Found: C, 66.75: H, 7.40; S, 6.47.

Pyrolysis of 17β-Hydroxyandrostano[2,3-*c*]thiophene-5′-carboxylic Acid (VIIIa)——VIIIa (1.12 g) was placed in a 10 ml test tube and heated on metal bath at 300° for 15 min. The crude product was dissolved in benzene and chromatographed on silica gel. Elution with benzene furnished the androstano[2,3-*c*]thiophene (Xa) (0.32 g), which was identified by mixed melting point and comparison of the IR spectra with the compound prepared in VIIIa.

Pyrolysis of 17β-Hydroxy-17α-methylandrostano[2,3-*c*]thiophene-5′-carboxylic Acid (VIIIb)——Pyrolysis of VIIIb (1.0 g) was carried out in the same way as described above. The crude product was chromatographed on silica gel and eluted with petroleum ether–benzene (1:1) to afford the 17-*gem*-dimethylandrostano[2,3-*c*]thiophene (0.2 g), which was identical with the sample obtained in Xb.

Acknowledgement——The authors are very grateful to Dr. S. Ose, Director of this laboratory, for his encouragement and also to the members of Analytical Center of this laboratory for microanalysis and the NMR measurements.