[Chem. Pharm. Bull. 12(12)1433~1439(1964)]

UDC 547.931 : 547.92.07

195. Ken'ichi Takeda, Taichiro Komeno, and Shoichi Ishihara : Bile Acids and Steroids. XXVIII.*1 Thiosteroids. (13).*1 Further Study on Synthesis of 5'-Methylthieno-[4',3',2'-4,5,6]-5-en-3-one Steroids.

(*Shionogi Research Laboratory, Shionogi & Co., Ltd.*2)*)

In part Ⅷ[1] of this series, we reported that 6α-acetylthio-4-en-3-one, which was prepared from 3,3-ethylenedioxy-5α, 6α-oxide by treatment of thiolacetic acid, followed by acid-catalyzed dehydration, was converted to 5'-methylthieno[4',3',2'-4,5,6]-5-en-3-one steroids with basic alumina or sodium alcoholate. This report is concerned with an improved procedure for obtaining the 6α-acetylthio-4-en-3-one and with its thiophene formation.

An attempt to synthesize thieno steroids having ethynyl group in 19-nor series led us to take another route, because thiolacetic acid reacts with ethynyl group[2] and furthermore preparation of 3,3-ethylenedioxy-5α,6α-oxide is very difficult in 19-nor series.[3] Introduction of a bromine atom to C-6 of 4-en-3-oxo steroids is easy and has been fully studied.[4] It has also been known that 6-bromo-4-en-3-one underwent solvolysis in buffered acetic acid to give 2-acetoxy-4-en-3-one.[5] However, it was expected that acetylthio anion would directly attack C_6 due to its powerful nucleophillic character. When 6β-bromo-17β-acetoxyandrost-4-en-3-one (Ia) was treated with potassium thiolacetate in acetone or dimethylformamide, there was obtained 6α-acetylthio-17β-acetoxyandrost-4-en-3-one (Ⅱa) in a 55~62% yield. This compound was identical with the authentic sample prepared from 3,3-ethylenedioxy-5α,6α-oxide in the previous report.[1] The similar treatment of 6β-bromo-17α-ethynyl-17β-acetoxy-19-norandrost-4-en-3-one (Ie) afforded a 6α-acetylthio compound (Ⅱe), which showed a triplet (J=1.5 c.p.s.) at 3.93 τ (proton at C-4) and an octet (J=1.5, 4.5, and 12 c.p.s.) at 5.79 τ (β-proton at C-6) in the nuclear magnetic resonance spectrum. These observed coupling constants supported the structure of 6α-acetylthio-4-en-3-one in accordance with the findings by us[1] and by Ringolds.[6] In the case of 6β-bromo-progesterone (Ic) and -19-nortestosterone acetate (Id), both 6α-acetylthio compounds obtained could not be crystallized.

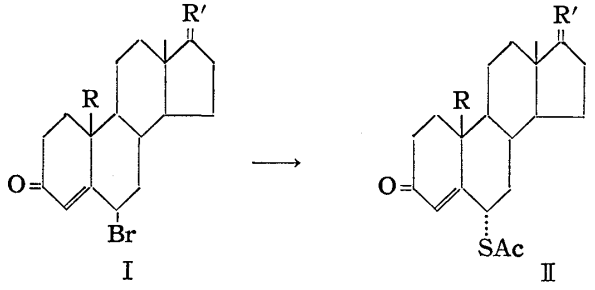
In the previous paper, we assumed that conversion of 6α-acetylthio-4-en-3-one to thieno steroids involves enolyzation of 4-en-3-one and formation of anion at C-4. This assumption made us to search for other basic reagent. Treatment of 6α-acetylthio-19-nortestosterone acetate (Ⅱd) with potassium *tert*-butoxide in *tert*-butyl alcohol gave a hydroxythieno compound (Ⅲd) in a 33.5% yield. On the other hand, by heating under reflux of the acetylthio compound (Ⅱd) with sodium hydride in toluene, yield of the

*1 Part XXVⅡ. Thiosteroids. (12), to be published in Tetrahedron.

*2 Fukushima-ku, Osaka, Japan (武田健一, 米野太一郎, 石原照一).

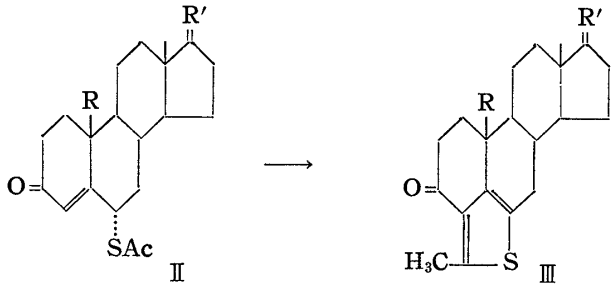
1) K. Takeda, T. Komeno, S. Ishihara : This Bulletin, **11**, 500 (1963).
2) H. Bader, L. C. Cross, I. M. Heilbron, E. R. H. Jones : J. Chem. Soc., **1949**, 619; L. N. Owen, M. U. S. Sultanbawa : *Ibid.*, **1949**, 3109; H. Behringer : Ann., **564**, 219 (1949); E. P. Kohler, H. Potter : J. Am. Chem. Soc., **57**, 1316 (1935).
3) J. A. Zderic, D. C. Limon, H. J. Ringold, C. Djerassi : J. Am. Chem. Soc., **81**, 3120 (1959).
4) L. F. Fieser, M. Fieser : "Steroids," Reinhold Publishing Co., New York, p. 288~290.
5) D. E. A. Rivett, E. S. Wallis : J. Org. Chem., **15**, 35 (1953); L. F. Fieser, M. Romero : J. Am. Chem. Soc., **75**, 4716 (1953); F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez, G. Rosenkranz : *Ibid.*, **75**, 4712 (1953); R. L. Clarke, K. Dobriner, A. Mooradian, C. M. Martini : *Ibid.*, **77**, 661 (1955); P. N. Rao, L. R. Axelrod : *Ibid.*, **82**., 2830 (1960); P. N. Rao, H. R. Gollberg, L. R. Axelrod : J. Org. Chem., **28**, 270 (1963).
6) H. J. Ringold : J. Am. Chem. Soc., **85**. 1699 (1963).

acetoxythieno compound (IIIc) increased to 56.6% and saponification of the acetoxyl group at C_{17} was not recognized. By the similar treatment of 6α-acetylthioprogesterone, IIc gave a thieno compound (IIIb) in a 65% yield and unpurified 6α-acetylthio-17α-ethynyl-19-nortestosterone acetate (IIe) gave a thieno compound (IIIe) in a 28% yield.



I

a) R=CH_3, R′=$\langle^{OAc}_{H}$
b) R=CH_3, R′=$\langle^{OCOC_2H_5}_{H}$
c) R=CH_3, R′=$\langle^{COCH_3}_{H}$
d) R=H, R′=$\langle^{OAc}_{H}$
e) R=H, R′=$\langle^{OAc}_{C\equiv CH}$
f) R=H, R′=$\langle^{OH}_{C\equiv CH}$
g) R=CH_3, R′=BMD
h) R=CH_3, R′=BMD, 11 C=O



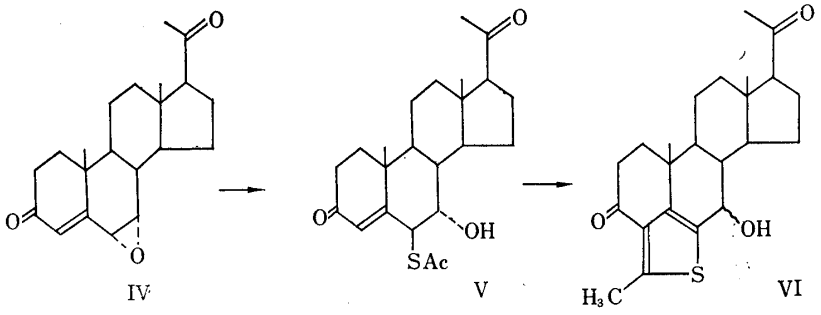
II

a) R=CH_3, R′=$\langle^{OCOC_2H_5}_{H}$
b) R=CH_3, R′=$\langle^{COCH_3}_{H}$
c) R=H, R′=$\langle^{OAc}_{H}$
d) R=H, R′=$\langle^{OH}_{H}$
e) R=H, R′=$\langle^{OAc}_{C\equiv CH}$
f) R=H, R′=$\langle^{OH}_{C\equiv CH}$
g) R=CH_3, R′=BMD
h) R=CH_3, R′=$\langle^{COCH_2OH}_{OH}$
i) R=CH_3, R′=BMD, 11 C=O

Chart 1.

In the corticoid series, this sequence was successfully applied to 6β-bromo-17,20:20,21-bismethylenedioxy-4-en-3-one (Ig and Ih) and the corresponding thieno steroids (IIIg and IIIi) were also obtained.

When 6α,7α-epoxypregn-4-ene-3,20-dione (IV) was reacted with thiolacetic acid, there was obtained 6β-acetylthio-7α-hydroxypregn-4-ene-3,20-dione (V), which was heated with sodium hydride in toluene to yield 5′-methyl-7ξ-hydroxythieno[4′,3′,2′-4,5,6]-pregn-5-ene-3,20-dione (VI) in a low yield. Configuration of the 7-hydroxyl group of this compound was ambiguous, because contribution of the hydroxyl group to the molecular rotation (ΔMD=+73) throws doubt upon the 7α-configuration.*3



IV V VI

Chart 2.

*3 According to W. Klyne (Helv. Chim. Acta, 35, 1222 (1952)), ΔMD is +182 for 7β-hydroxy-5-ene and −196 for 7α-hydroxy-5-ene. But it is doubtful whether or not application of Mils rule is reasonable in this case.

In the 17α-acetoxyprogesterone series, forced acetylation of oily 6α-acetylthio-17α-hydroxyprogesterone (IX), which was obtained from 6β-acetylthio-5α,17α-dihydroxypregnane-3,20-dione (VIII) by treatment of hydrochloric acid and acetic acid, gave an oily enol acetate (X). The structure of this compound was assumed from the ultraviolet absorption maximum at 255 mμ. The bathochromic shift (17 mμ) compared with the absorption maximum at 238 mμ of 3,5-dien-3-ol acetate showed conjugation of acetylthio group. It is interest to note that treatment of this enol acetate (X) with potassium carbonate in aqueous methanol afforded a thieno compound (XIa) in a 10% yield. In this case it is assumed that competition of both intramolecular condensation and saponification of acetylthio group results a low yield of the thieno compound. This compound

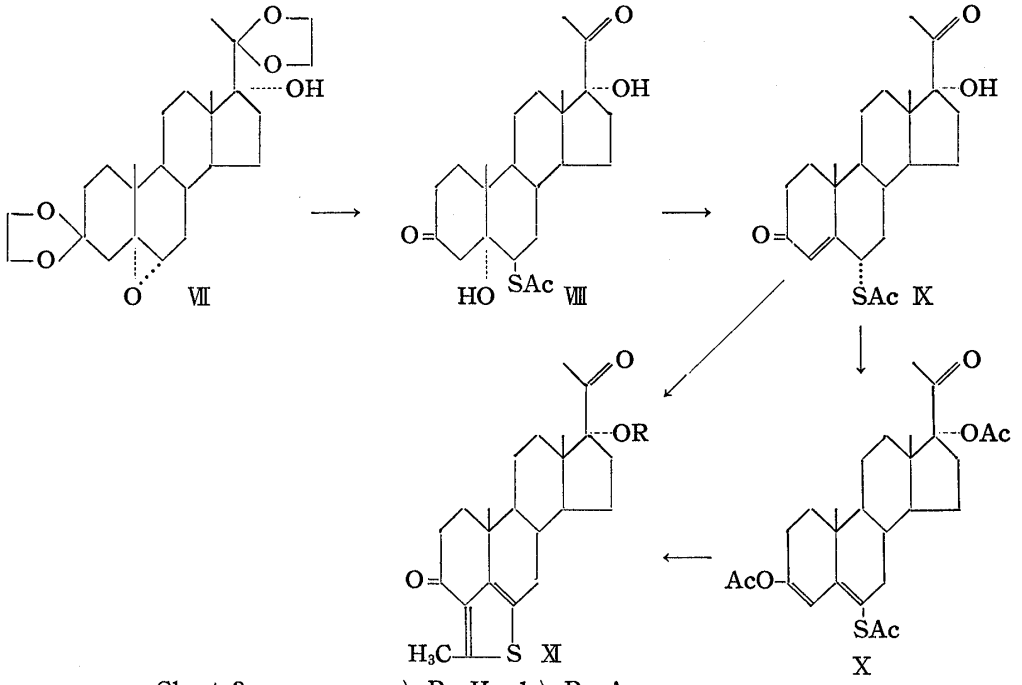


Chart 3. a) R=H, b) R=Ac

was also prepared in a 46.9% yield from 6α-acetylthio-4-en-3-one by treatment of a limited amount of sodium ethoxide in ethanol. The fact that D-homoannulation does not occur in the thieno compound (XIa) was established from the nuclear magnetic resonance data, which showed a singlet of 21-methyl protons at 7.71 τ characteristic of 17α-hydroxy-17β-methylketone.[7] Forced acetylation of this compound did not affect the 3-oxo group nor the thiophene moiety and gave 17-acetoxythieno compound (XIb). All of 5'-methylthieno[4',3',2',-4,5,6]-5-en-3-one steroids obtained here exhibited the characteristic three absorption bands in the ultraviolet (220, 268, and 304 mμ) and in the infrared spectra (1670, 1580, 1490 cm^{-1}). Biological activities of these compounds will be reported elsewhere.

Experimental*4

6α-Acetylthiotestosterone Acetate (IIa)——Bromination of testosterone acetate with NBS in CCl_4 gave

*4 All melting points were determined on a Kofler block and uncorrected. Optical rotations were measured in chloroform unless mentioned otherwise, using a Rudolf Photoelectronic Polarimeter, model 200. The ultraviolet absorption spectra were measured with a Hitachi Recording Ultraviolet spectrophotometer, EPs-2, and the infrared spectra were taken with a Koken infrared spectrophotometer, Model DS-301. The NMR spectra were run in deuteriochloroform solution with a Varian A-60 spectrometer, tetramethylsilane serving as internal standard.

7) N. R. Trenner, B. H. Arison, D. Taub, N. L. Wendler: Proc. Chem. Soc., **1961**, 214.

6β-bromotestosterone acetate (Ia), m.p. 125~127°, $[\alpha]_D^{22}$ −12.2° (c=1.103), in a 74.6% yield. UV: λ_{max}^{EtOH} 248 mμ (ε 13,900). NMR (τ): (18-H) 9.10; (19-H) 8.45; (AcO) 7.96; (17α-H) 5.37; (6α-H) 5.00 ($J_{6\alpha H:7CH_2}$= 3.5, 1.5 c.p.s); (4-H) 4.10. To a solution of the bromo compound (Ia, 2.240 g.) in acetone (60 ml.) potassium thiolacetate (1.26 g.) was added. The resulting mixture was stirred for 4 hr. at room temp., poured into H_2O, and extracted with ether-$CHCl_3$ (4:1). The extract was washed with Na_2CO_3 solution and H_2O, dried over Na_2SO_4, and evaporated. The residue was crystallized from ether-petr. ether to give 6α-acetylthiotestosterone acetate (IIa, 1.369 g., 61.8%), m.p. 180~185°, which was recrystallized from MeOH to prisms, m.p. 192~194°. The structure of this compound was confirmed by mixed melting point and comparison of the IR spectra.

6α-Acetylthiotestosterone Propionate (IIb)——Testosterone propionate (1.025 g.) was brominated with NBS (556 mg.) in CCl_4 (30 ml.). After the precipitated imide was removed by filtration, the solution was evaporated under a reduced pressure. A solution of the bromination product (Ib) in dimethylformamide (20 ml.) potassium thiolacetate (800 mg.) was added and the mixture was stirred for 30 min. at room temp. After working up as above, the product was recrystallized from MeOH to yield 6α-acetylthiotestosterone propionate (IIb, 708 mg., 56.7%) as prisms, m.p. 151~153°, $[\alpha]_D^{23}$ +40.9° (c=1.006). UV: $\lambda_{max}^{alc.}$ 235.5 mμ (ε 16,200). IR ν_{max}^{Nujol} cm^{-1}: 1731, 1696, 1675, 1610, 1190. *Anal.* Calcd. for $C_{24}H_{34}O_4S$: C, 68.86; H, 8.19; S, 7.66. Found: C, 68.71; H, 8.21; S, 7.79.

6α-Acetylthio-17α-ethynyl-17β-acetoxy-19-norandrost-4-en-3-one (IIe)——Enol acetate of 17α-ethynyl-19-nortestosterone, m.p. 166~168°, was prepared according to Iriarte, *et al.*[8] To a cooled solution of the enol acetate (1.007 g.) in CCl_4 (70 ml.) at −20°, a solution of Br_2 (425 mg.) in CCl_4 (2.5 ml.) was added dropwise at the same temp. After the solution was decolorized, Na_2CO_3 solution was added. The CCl_4-solution was washed with H_2O, dried over Na_2SO_4, and evaporated at 10~20°, under a reduced pressure. The residue was dissolved in acetone (70 ml.) and potassium thiolacetate (910 mg.) was added. The mixture was stirred for 2 hr. at room temp., poured into H_2O, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated again at 10~20° under a reduced pressure. Crystallization from ether gave an acetylthio compound (IIe, 704 mg., 65.0%), which was recrystallized from acetone-hexane to rods, m.p. 216~219° (decomp.), $[\alpha]_D^{23.5}$ −34.4° (c=0.999). UV: $\lambda_{max}^{alc.}$ 235.5 mμ (ε 17,340). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 1742, 1690 (sh), 1674, 1623, 1260, 1134, 1120, 1022. NMR: (18-H) 9.06; (OAc) 7.98; (SAc) 7.62; (≡CH) 7.39; (6β-H) octet at 5.79; (4-H) triplet at 3.93; $J_{6\beta H:7\alpha H}$=12.0 c.p.s.; $J_{6\beta H:7\beta H}$ =4.5; $J_{6\beta H:4H}$=1.5; $J_{4H:19H}$=1.5. *Anal.* Calcd. for $C_{24}H_{30}O_4S$: C, 69.53; H, 7,29; S, 7.74. Found: C, 69.54; H, 7.35; S, 7. 86.

5'-Methyl-17β-propionyloxythieno[4',3',2'-4,5,6]androst-5-en-3-one (IIIa)——A solution of 6α-acetylthiotestosterone propionate (350 mg.) in benzene-petr. ether (1:2) was absorbed on a column of alumina (10 g.) and allowed to stand overnight. The material eluted with benzene was recrystallized from aq. MeOH to yield a thieno compound (IIIa, 120 mg.), m.p. 111~113°, $[\alpha]_D^{23.5}$ −30.9° (c=1.067). UV $\lambda_{max}^{alc.}$ mμ (ε): 220.5 (12,520), 268.5 (11,390), 304 (2,290). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1665, 1572, 1493, 1186. *Anal.* Calcd. for $C_{24}H_{32}O_3S$: C, 71.96; H, 8.05; S, 8.01. Found: C, 71.80; H, 8.12; S, 8.13.

5'-Methylthieno[4', 3', 2'-4, 5, 6]pregn-5-ene-3, 20-dione (IIIb)——A mixture of 6β-bromoprogesterone (563 mg.) and potassium thiolacetate (328 mg.) in acetone (25 ml.) was stirred for 4 hr. After working up, oily 6α-acetylthio compound (452 mg.) was obtained and dissolved in toluene (20 ml.). To the solution sodium hydride*5 (103 mg.) was added and the resulting solution was heated under refiux for 4 hr. After cooling, iced H_2O was added and extracted with ether-benzene (1:1). The extracted material (412 mg.) was chromatographed over alumina (4 g.). Mineral oil was eluted with petr. ether and petr. ether-benzene. The material eluted with benzene was crystallized from ether-petr. ether to give a thieno compound (IIIb, 188 mg.), m.p. 163~164°, which was identical with the authentic sample by mixed melting point and comparison of the IR spectra.

5'-Methyl-17β-acetoxythieno[4',3',2'-4,5,6]-19-norandrost-5-en-3-one (IIIc)——19-Nortestosterone was converted to enol acetate, m.p. 159~161°, with isopropenyl acetate and H_2SO_4 (reported,[9] m.p. 169~172°). This enol acetate was brominated with NBA in a mixture of acetone and buffered AcOH according to Campbell and Babcock.[10]

A solution of 19-norandrosta-3,5-diene-3,17β-diol diacetate (1.009 g.) in acetone (120 ml.) a solution of NaOAc (1 g.) and NBA (1.06 g.) in a mixture of H_2O (20 ml.) and AcOH (1.1 ml.) was added with stirring, further agitated for 2 hr., poured into H_2O, and extracted with ether. The extract was washed with Na_2CO_3 solution and H_2O, dried over Na_2SO_4, and evaporated to give an oily bromo compound (Id, 1.14 g.). A solution of the bromide in acetone (40 ml.) potassium thiolacetate (670 mg.) was added and the resulting mixture was stirred for 4 hr. at room temp. An oily acetylthio compound (IId, 1.008 g.) was isolated by extraction with ether. This compound could not be crystallized even by using chromatography over

*5 Sodium hydride in mineral oil (50%) (supplied by Metal Hydride Inc.) was used.

8) J. Iriarte, C. Djerassi, H J. Ringold: J. Am. Chem. Soc., 81, 436 (1959).

9) R. Villotti, C. Djerassi, H. J. Ringold: *Ibid.*, 81, 4566 (1959).

10) J. A. Campbell, J. C. Babcock: *Ibid.*, 81, 4609 (1959).

Florisil and showed the absorption band at 1746, 1696(sh), 1688, 1626, 1250, and 1138 cm^{-1} in the IR spectrum. A part of this oil (215 mg.) was dissolved in toluene (10 ml.) and heated under reflux with sodium hydride (80 mg.). After working up the residue (221 mg.) extracted with ether was chromatographed over Florisil (4 g.). The material eluted with benzene-ether (9:1) was recrystallized from aq. MeOH to yield an acetoxythieno compound (IIIc, 116 mg., 56.6%) as plates, m.p. 171~172°, $[\alpha]_D^{24.5}$ −62.8° (c=0.995). UV $\lambda_{max}^{alc.}$ mμ(ε): 221.5 (12,330), 267.5 (11,140), 303 (2,200). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728; 1666, 1573, 1492, 1256, 1041. *Anal.* Calcd. for $C_{22}H_{28}O_3S$: C, 70.93; H, 7.58; S, 8.61. Found: C, 70.88; H, 7.58; S, 8.90.

5′-Methyl-17β-hydroxythieno[4′,3′,2′-4,5,6]-19-norandrost-5-en-3-one (IIId)——a) When the above acetoxythieno compound (IIIc, 120 mg.) was saponified by heating under reflux with K_2CO_3 (200 mg.) in aq. MeOH (20 ml.) for 30 min., there was obtained a hydroxythieno compound (IIId, 86 mg.), which was recrystallized from MeOH to prisms, m.p. 215~216°, $[\alpha]_D^{23.5}$ −58.7° (c=1.040). UV $\lambda_{max}^{alc.}$ mμ(ε): 221.5 (13,110), 267.5 (12,040), 303 (2,260). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3638, 3476 (ω), 1667, 1573, 1493, 1051. *Anal.* Calcd. for $C_{20}H_{26}O_2S$: C, 72.68; H, 7.93; S, 9.70. Found: C, 72.62; H, 7.92; S, 9.74.

b) A part of the oily acetylthio compound (IIc, 416 mg.) obtained above was dissolved in *t*-butyl alcohol (20 ml.) and added to a solution of K (100 mg.) in *t*-butyl alcohol (10 ml.). The mixture was left to stand overnight at room temp., poured into H_2O and extracted with ether. The material (177 mg.) extracted was chromatographed over Florisil (4 g.) and elution with benzene-ether (9:1) gave the crystals (150 mg.), which were recrystallized from MeOH to yield the same hydroxythieno compound (IIId, 118 mg., 33.5%), m.p. 215~217°, as above described.

5′-Methyl-17α-ethynyl-17β-acetoxythieno[4′,3′,2′-4,5,6]-19-norandrost-5-en-3-one (IIIe)——a) From the enolacetate of ethynyl-19-nortetosterone. The unpurified acetylthio compound (IIe, 486 mg.) described above was dissolved in toluene (20 ml.) and heated under reflux with sodium hydride (100 mg.) for 3 hr. After working up chromatography over neutral alumina (9 g.) afforded that material eluted with benzene-petr. ether (1:1, 2:1), which was recrystallized from MeOH to give a thieno compound (IIIe, 121 mg.) as prisms, m.p. 200~202° (decomp.), $[\alpha]_D^{23}$ −90.4° (c=1.059). UV $\lambda_{max}^{alc.}$ mμ(ε): 221.5 (14,380), 268 (12,610), 303 (2,320). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3308, 1741, 1667, 1575, 1492, 1256, 1034, 1021. *Anal.* Calcd. for $C_{24}H_{28}O_3S$: C, 72.69; H, 7.12; S, 8.09. Found: C, 72.93; H, 7.17; S, 7.88.

b) From the enol ether of ethynyl-19-nortestosterone. To a solution of the enol ethyl ether[11] (3.341 g.) of ethynyl-19-nortestosterone in acetone (135 ml.) successively a solution of NaOAc (2.4 g.) in H_2O (19 ml.), NBS (3.50 g.), and AcOH (2.7 ml.) were added with stirring. The mixture was agitated further for 2.5 hr. under cooling with ice, poured into H_2O, and extracted with ether. The extract was washed with Na_2CO_3 solution and H_2O, dried over Na_2SO_4, and evaporated to give an oily bromide (If, 4.57 g.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610, 3290, 1674, 1622. This oily bromide was dissolved in acetone (70 ml.) and treated with potassium thiolacetate (2.8 g.) for 3 hr. Again an oily acetylthio compound (IIf, 4.35 g.) was isolated by extraction with ether and the IR spectrum shows absorption bands at 3626, 3286, 1700, 1687, 1622, and 1130 cm^{-1} in CCl_4-solution. The oily acetylthio compound was dissolved in anhyd. EtOH (150 ml.) and a solution of NaOEt (0.156*M*, 50 ml.) was added. The dark red colored solution was allowed to stand overnight at room temp., poured into H_2O, and extracted with $CHCl_3$. The extracted material (3.57 g.) was chromatographed over Florisil (60 g.). Elution with benzene-$CHCl_3$ (1:1~1:2) afforded the oily thieno compound (IIIf, 1.73 g.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3618, 3274, 1665, 1576, 1493.

This oily thieno compound was dissolved in AcOH (20 ml.) and Ac_2O (5 ml.), and *p*-toluene sulphonic acid (180 mg.) was added. The resulting mixture was left to stand overnight at room temp., poured into iced H_2O, and extracted with CH_2Cl_2. The product was chromatographed over neutral alumina (40 g.). The material (1.50 g.) eluted with benzene-petr. ether (1:1~2:1) was recrystallized from MeOH to yield the acetoxythieno compound (IIIe, 1.372 g.), m.p. 200~202° (decomp.). This compound was in full agreement with the specimen obtained in a) by mixed melting point and comparison of the IR spectra.

5′-Methyl-17α,20:20,21-bismethylenedioxythieno[4′,3′,2′-4,5,6]pregn-5-en-3-one (IIIg)——Substance-S BMD[12] (4.00 g.) was brominated with NBS (2.00 g.) in CCl_4 (200 ml.) to yield a bromide (Ig, 3.33 g.), m.p. 170~177° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 1667, 1617, 1106, 1080. To a suspension of the bromide (Ig, 3.30 g.) of dimethylfomamide (40 ml.) potassium thiolacetate (1.70 g.) was added. The resulting mixture was stirred for 4 hr. at room temp., and poured into H_2O. The appeared precipitates were collected by filtration, washed with H_2O, and dried. This acetylthio compound (IIg) was easily soluble in MeOH and could not be crystallized. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1701, 1684, 1611, 1133, 1103, 1088.

A suspension of the acetylthio compound and sodium hydride (700 mg.) in toluene (100 ml.) was heated under reflux for 4 hr. After cooling, $CHCl_3$ was added, washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was crystallized from acetone to crystals (2.10 g.). The mother liquor was evaporated to dryness and chromatographed over Florisil. Elution with benzene-$CHCl_3$ (9:1~1:1) gave further crystals (200 mg.). The combined crystals were recrystallized from CH_2Cl_2-acetone to yield a thieno compound (IIIg, 2.202 g.), m.p. 286~287°, as prisms, $[\alpha]_D^{23.5}$ −107.5° (c=0.962). UV $\lambda_{max}^{alc.}$ mμ(ε): 221 (12,710),

11) L. H. Knox, J. A. Zderic, J. P. Ruelas, C. Djerassi, H. J. Ringold: J. Am. Chem. Soc., 82, 1230 (1960).
12) R. E. Beyler, R. M. Moriarty, F. Hoffman, L. H. Sarett: J. Am. Chem. Soc., 80, 1517 (1958).

268.5 (11,520), 304 (2,310). IR ν_{max}^{Nujol} cm^{-1}: 1673, 1569, 1494, 1096, 1090, 949. *Anal.* Calcd. for $C_{25}H_{32}O_5S$: C, 67.54; H, 7.21; S, 7.21. Found: C, 67.70; H, 7.31; S, 7.72

5′-Methyl-17α,21-dihydroxythieno[4′,3′,2′-4,5,6]pregn-5-ene-3,20-dione (IIIh)——A suspension of the above thieno compound (IIIg, 2.202 g.) in a mixture of 70% formic acid (110 ml.) and ethylene glycol (20 ml.) was heated at 100° for 2 hr. After cooling the cleared solution was poured into H_2O, and extracted with CH_2Cl_2. The extract was washed with Na_2CO_3 solution and H_2O, dried over Na_2SO_4, and evaporated. The residue was dissolved in MeOH (80 ml.) and 10% H_2SO_4 (2.5 ml.) was added. The mixture was left to stand for 2 hr. at room temp., poured into H_2O, and extrated with CH_2Cl_2. The extract was washed with Na_2CO_3 solution and H_2O, dried over Na_2SO_4, and evaporated. The residue was crystallized from MeOH to the crystals, which were further recrystallized from CH_2Cl_2-EtOH to give plates (IIIh, 431 mg.), m.p. 230~232°, $[\alpha]_D^{24}$ −18.1° (c=1.012). UV $\lambda_{max}^{alc.}$ mμ (ε): 220.5 (14,050), 268.5 (12,410), 302 (2,470). IR ν_{max}^{Nujol} cm^{-1}: 3454~3431, 1710, 1660, 1574, 1493. *Anal.* Calcd. for $C_{23}H_{30}O_4S$: C, 68.62; H, 7.51; S, 7.97. Found: C, 68.41; H, 7.48; S, 8.05.

5′-Methyl-17α, 20:20, 21-bismethylenedioxythieno[4′, 3′, 2′-4, 5, 6]pregn-5-ene-3, 11, 20-trione (IIIi)——Cortison BMD[12] (3.70 g.) was brominated with NBS (1.80 g.) in CCl_4 (200 ml.) in the same manner as described above and a bromide (Ih, 3.424 g.), m.p. 170~175° (decomp.), was obtained, IR ν_{max}^{Nujol} cm^{-1}: 1713, 1672, 1617, 1105, 1081.

This bromide was treated with potassium thiolacetate (1.62 g.) in dimethylformamide (40 ml.) and the product was recrystallized from CH_2Cl_2-MeOH to yield an acetylthio compound (IIh, 2.432 g.) m.p. 234~236°, $[\alpha]_D^{23.5}$ +140.3° (c=0.965). UV: $\lambda_{max}^{alc.}$ 233 mμ (ε 15,810). IR ν_{max}^{Nujol} cm^{-1}: 1690, 1675, 1609, 1135, 1098, 1081, 938. *Anal.* Calcd. for $C_{25}H_{32}O_7S$: C, 63.00; H, 6.77; S, 6.73. Found: C, 62.46; H, 6.87; S, 6.70. A suspension of the above thiolacetate (IIh, 2.301 g.) and sodium hydride (475 mg.) in toluene (70 ml.) was heated under reflux for 5 hr. After working up crytallization from acetone gave crystals of a thieno compound (IIIi, 1.696 g.), m.p. 260~264°. Chromatography of the mother liquor over Florisil afforded further 235 mg. of the same compound. Recrystallization of the combined crystals from CH_2Cl_2-acetone gave plates (IIIi, 1.931 g.), m.p. 263~264.5°, $[\alpha]_D^{24}$ −47.7° (c=1.005). UV $\lambda_{max}^{alc.}$ mμ (ε): 219 (12,910), 267 (11,420), 298 (2,440). IR ν_{max}^{Nujol} cm^{-1}: 1698, 1668, 1571, 1493, 1099, 1076, 942.

6β-Acetylthio-7α-hydroxypregn-4-ene-3, 20-dione (V)——6α, 7α-Epoxypregn-4-ene-3, 20-dione (IV), m.p. 174~177°, IR ν_{max}^{Nujol} cm^{-1}: 1704, 1676, 1616, 870, was prepared by monoperphthalic acid-oxidation of pregna-4,6-diene-3,20-dione.

This oxide (2.067 g.) was dissolved into thiolacetic acid (20 ml.) and allowed to stand for 31 hr. under warming at 50°. The solution was evaporated under a reduced pressure and the resulting residue was triturated in ether to yield the crystals, which were recrystallized from acetone-hexane to give an acetylthio compound (V, 1.554 g.), m.p. 236~238° (decomp.). The combined mother liquor was evaporated and chromatographed over Florisil (36 g.). Elution with benzene-ether (4:1~1:1) afforded the same crystals (276 mg.) (combined yield of V, 1.830 g.), $[\alpha]_D^{24.5}$ +269.8° (c=1.041). UV: $\lambda_{max}^{alc.}$ 244 mμ (ε 15,680). IR ν_{max}^{Nujol} cm^{-1}: 3436, 1696, 1680, 1669, 1618, 1115. *Anal.* Calcd. for $C_{23}H_{34}O_4S$: C, 68.28; H, 7.97; S, 7.93. Found: C, 68.53; H, 8.26; S, 7.65.

5′-Methyl-7ξ-hydroxythieno[4′,3′,2′-4,5,6]pregn-5-ene-3,20-dione (VI)——A suspension of the thiolacetate (V, 252 mg.) and sodium hydride (60 mg.) in toluene (10 ml.) was heated under reflux for 5.5 hr. The product was chromatographed over Florisil (5 g.). After a mineral oil was removed by elution with petr. ether, the material eluted with benzene-$CHCl_3$ was recrystallized from acetone-hexane to yield a thieno compound (VI, 25 mg.), m.p. 198~200°, $[\alpha]_D^{23.5}$ +55.3° (c=0.284). UV $\lambda_{max}^{alc.}$ mμ (ε): 221.5 (16,210), 270 (11,660), 295 (infexion, 3580). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3596, 3458, 1698, 1667, 1567, 1485, 1158, 1010, 897. *Anal.* Calcd. for $C_{23}H_{32}O_3S$: C, 71.09; H, 8.30; S, 8.25. Found: C, 71.58; H, 7.99; S, 8.21.

6β-Acetylthio-5α, 17α-dihydroxy-5α-pregnane-3, 20-dione (VIII)——5α, 6α-Epoxy-3, 3:20, 20-bisethylenedioxy-5α-pregnan-17α-ol (VII, m.p. 216~217°, $[\alpha]_D^{23.5}$ −67.0° (c=0.981): reported,[13] m.p. 216~218°, $[\alpha]_D$ −70°) was used as a starting material. This oxide (3.142 g.) was dissolved into thiolacetic acid (15 ml.) under warming and left to stand for 4.5 days at room temp. The solution was evaporated under a reduced pressure and the residue was dissolved into 80% AcOH (30 ml.). The solution was warmed on a steam bath for 20 min. The appeared crystals were collected by filtration, washed with H_2O, dried and recrystallized from acetone-hexane to yield a hydroxythiolacetate (VIII, 2.806 g.), m.p. 220~221° (decomp.), $[\alpha]_D^{23.5}$ −102.3° (c=1.102). UV $\lambda_{max}^{a.c.}$ mμ (ε): 234 (5360), 305 (160). IR ν_{max}^{Nujol} cm^{-1}: 3524 (sh), 3476 (sh), 3396, 1706 (sh), 1690, 1136, 1118, 1094. *Anal.* Calcd. for $C_{23}H_{34}O_5S$: C, 65.37; H, 8.11; S, 7.59. Found: C, 65.56; H, 8.14; S, 7.42.

5′-Methyl-17α-hydroxythieno[4′,3′,2′-4,5,6]pregn-5-ene-3,20-dione (XIa)——a) *via* the 6α-acetylthio 4-en-3-one (IX). To a solution of the hydroxythiolacetate (VIII, 829 mg.) in AcOH (15 ml.), a stream of HCl was bubbled for 10 min. Extraction with ether afforded an oily 6α-acetylthio-4-en-3-one (IX, 808 mg.), which was dissolved into abs. EtOH (40 ml.) and NaOEt in EtOH (1.83*M*, 1.1 ml.) was added. The resulting solution was allowed to stand overnight at room temp., poured into H_2O, and extracted with CH_2Cl_2. The product (633 mg.) was chromatographed over Florisil (15 g.). The material eluted with benzene-$CHCl_3$ was recrystallized from MeOH to give a thieno compound (XIa, 355 mg.), m.p. 240~242°, $[\alpha]_D^{24}$

$-47.8°$ (c=0.995). UV $\lambda_{max}^{alc.}$ mμ (ε): 221 (13,050), 268.5 (11,860), 304 (2430). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3496, 1694, 1660, 1573, 1490. NMR (τ): (18-H) 9.21; (19-H) 8.83; ($COCH_3$) 7.71; (thiophen-CH_3) 7.28; (OH) 6.98. *Anal.* Calcd. for $C_{23}H_{30}O_3S$: C, 71.46; H, 7.82; S, 8.30. Found: C, 71.49; H, 7.82; S, 8.35.

b) *via* the enol acetate (X). The oily 6α-acetylthio-4-en-3-one (Ⅷ, 1.680 g.) prepared from the thiolacetate (Ⅶ, 1.753 g.) was dissolved into a mixture of AcOH (20 ml.) and Ac_2O (10 ml.), and *p*-toluenesulfonic acid (180 mg.) was added. The mixture was left to stand overnight at room temp., poured into H_2O, and extracted with ether. The extract was washed with Na_2CO_3 solution and H_2O, dried over Na_2SO_4, and evaporated to give an oily enol acetate (X, 1.996 g.). UV: $\lambda_{max}^{alc.}$ 255 mμ (ε 17,290). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1758 (sh), 1739, 1718, 1700, 1664, 1617 (v. w), 1251, 1209, 1154, 1133. A part of this enol acetate (882 mg.) was dissolved into 80% MeOH (30 ml.) and K_2CO_3 (240 mg.) was added. The mixture was allowed to stand overnight at room temp. and treated as described above. Only the thieno compound (Ⅺa, 90 mg.), m.p. 240~242°, was obtained as crystals.

5′-Methyl-17α-acetoxythieno[4′,3′,2′-4,5,6]pregn-5-ene-3,20-dione (XIb)——The above thieno compound (Ⅺa, 1.18 g.) was dissolved into a mixture of AcOH (10 ml.) and Ac_2O (5 ml.) and *p*-toluenesulfonic acid (120 mg.) was added. The mixture was left to stand for 2 days at room temp. and poured into H_2O. The appeared crystals were collected by filtration, washed with H_2O, dried, and recrystallized from acetone-MeOH to give an acetate (Ⅺb, 1.057 g.), m.p. 267~269° (decomp.), $[\alpha]_D^{24.5}$ $-39.0°$ (c=0.981). UV $\lambda_{max}^{alc.}$ mμ (ε): 221 (12,390), 268.5 (11,320), 302 (2380). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1729, 1718 (sh), 1664, 1574, 1493. *Anal.* Calcd. for $C_{25}H_{32}O_4S$: C, 70.06; H, 7.53; S, 7.48. Found: C, 70.08; H, 7.55; S, 7.74.

Summary

By treatment of potassium thiolacetate 6β-bromo-4-en-3-one steroids were converted to 6α-acetylthio-4-en-3-ones, which were further converted to 5′-methylthieno[4′,3′,2′-4,5,6]-5-en-3-ones by heating with sodium hydride in toluene.

(Received August 29, 1964)

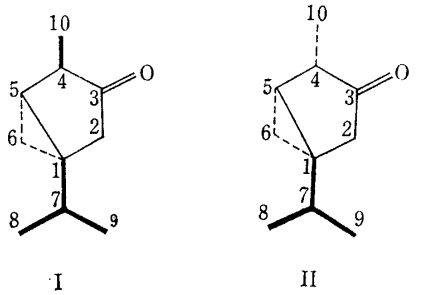
[Chem. Pharm. Bull. 12(12)1439~1446(1964)]

UDC 547.91.02 : 543.422.25

196. Kazuo Tori: Conformations of α- and β-Thujones.

(*Shionogi Research Loboratory, Shionogi & Co., Ltd.**1)

In connection with another problem in this laboratory, it became necessary to study in detail the proton magnetic resonance (NMR) spectra of α- and β-thujones (or (−)-thujone and (+)-isothujone (I and Ⅱ) respectively).*2 Thereafter, the author has published



I

II

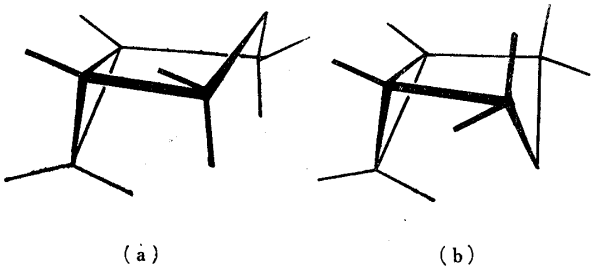


Fig. 1. Conformations of a Bicyclo-[3.1.0]hexane Ring

*1 Fukushima-ku, Osaka (通 和夫).

*2 Numbers in these compounds (I and Ⅱ) are affixed according to Bergqvist and Norin.[4]