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Utilization of Derivatives of Thiazolidine-2-thione: Esterification

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The reaction between acid chlorides and alcohols in the presence of the thallium (I) salt of thiazolidine-2-thione (TTT) was explored. Three possible pathways for this reaction were investigated. Conditions were established under which esterification took place rapidly and in good yield.

Keywords——thallium(I) salt of thiazolidine-2-thione; esterification; acylation; epiandrosterone 3-hexadecanoate; dihydrolanosterol 3-decanoate; 1-adamantanol hexadecanoate

Anti-tumor activity is often increased by the acylation of alcoholic tumor-inhibitory substances,[2] and in the course of our studies on tumor-inhibitory compounds, it seemed desirable to develop a new esterification procedure.

We therefore tried the use of the thallium (I) salt of thiazolidine-2-thione (TTT) in reactions between fatty acid chlorides and alcohols, because the double activation mechanism shown in Fig. 1 was expected to operate on the basis of the affinity[3] of the thallium atom in TTT for chlorine.

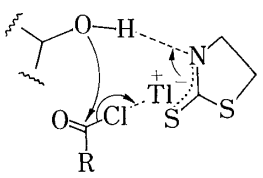


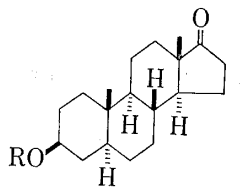
Fig. 1

The alcohols **1**—**9**, on treatment with five mol equivalents of TTT and acid chloride, gave the desired esters **10**—**20** (Method A). The acid chlorides used were butanoyl, decanoyl, and hexadecanoyl chlorides. These reactions gave good yields, except in the cases of the alcohols **6**, **7**, and **9**. The results are shown in Table 1. Further additions of equivalent molar amounts of TTT and acid chloride were required in the slow reactions (see entries 4, 5, 10, and 11 in Table 1), although esterlification without further additions of the reagents could be achieved by "Method B," as described later.

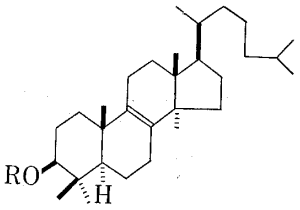
In these reactions, competitive formation of the N-acylthiazolidine-2-thione[4] always occurred, resulting in the appearance of a yellow color[4] during the reaction, and some of the N-acylthiazolidine-2-thiones were isolated and characterized. The three hypothetical pathways shown in Chart 1 were explored. Path 1 involves the double activation transition state that we initially expected. Path 2 represents a mechanism in which the N-acylthiazolidine-2-thione reacts as the actual esterification reagent. In path 3, the N-acylthiazolidine-2-thione simply acts as a hydrogen chloride acceptor.

First, a mixture of epiandrosterone (**1**) and N-butanoylthiazolidine-2-thione (**21**) (5 equiv.) was heated in hot benzene, but 91% of the alcohol **1** and 90% of the amide **21** were recovered. In view of the possibility of catalysis by TTT or thallous chloride formed during the reaction, the alcohol **1** was treated with the amide **21** (5 equiv.) and TTT (5 equiv.) in hot benzene, but monitoring by thin layer chromatography (TLC) for 30 min showed no change. Addition of

1) Location: *Uji, Kyoto, 611, Japan.*
2) E. Fujita and Y. Nagao, *Bioorg. Chem.*, **6**, 287 (1977).
3) Y. Nagao, M. Ochiai, K. Kaneko, A. Maeda, K. Watanabe, and E. Fujita, *Tetrahedron Lett.*, **1977**, 1345; S. Uemura, S. Tanaka, and M. Okano, *Bull. Inst. Chem. Res., Kyoto Univ.*, **55**, 273 (1977).
4) Y. Nagao, K. Kawabata, K. Seno, and E. Fujita, *J.C.S. Perkin I*, in press.

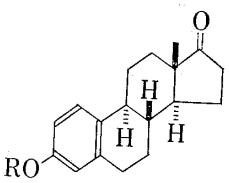


1: R=H
10: R=$CO(CH_2)_2CH_3$
11: R=$CO(CH_2)_8CH_3$
12: R=$CO(CH_2)_{14}CH_3$



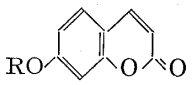
2: R=H

13: R=$CO(CH_2)_8CH_3$



3: R=H

14: R=$CO(CH_2)_2CH_3$



4: R=H
15: R=$CO(CH_2)_{14}CH_3$

$CH_3(CH_2)_3OR$

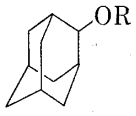
5: R=H
16: R=$CO(CH_2)_{14}CH_3$

CH_3CH_2CHOR
CH_3

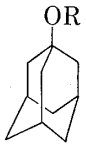
6: R=H
17: R=$CO(CH_2)_{14}CH_3$

$(CH_3)_3COR$

7: R=H
18: R=$CO(CH_2)_{14}CH_3$



8: R=H
19: R=$CO(CH_2)_{14}CH_3$



9: R=H
20: R=$CO(CH_2)_{14}CH_3$

Table I. Esterification of Alcohols by Method A

Entry	Alcohol	Acid chloride[a] (Mol Equiv.)	TTT (Mol Equiv.)	Time (min)	Ester	Yield(%) of ester
1	**1**	B 5	5	30	**10**	75
2	**1**	D 5	5	30	**11**	72
3	**1**	H 5	5	80	**12**	71
4	**2**	D 18	18	85	**13**	96
5	**3**	B 17	17	60	**14**	98
6	**4**	H 5	5	10	**15**	95
7	**5**	H 5	5	10	**16**	81
8	**6**	H 5	5	10	**17**	49
9	**7**	H 5	5	10	**18**	20
10	**8**	H 14	14	40	**19**	84
11	**9**	H 17	17	50	**20**	36

a) B: butanoyl chloride. D: decanoyl chloride. H: hexadecanoyl chloride.

thallous chloride (5 equiv.) and heating for a further 30 min resulted in recoveries of 97% of the alcohol **1** and 98% of the amide **21**. Thus, path 2 was excluded.

Treatment of epiandrosterone (**1**), butanoyl chloride (3 equiv.) and N-butanoylthiazolidine-2-thione (**21**) (3 equiv.) in hot benzene for 30 min gave a 70% yield of the butanoyl ester **10**. Similar treatment of the alcohol **1** with hexadecanoyl chloride (3 equiv.) and the amide **22** (3 equiv.) resulted in the formation of the hexadecanoyl ester **12** in 71% yield. These findings support path 3.

Although we were not able to obtain direct evidence for path 1, the participation of path 1 in this esterification is suggested by the finding that in all of the reactions by Method A, the formation of thiazolidine-2-thione was detected by TLC or by nuclear magnetic resonance (NMR) spectrometry.

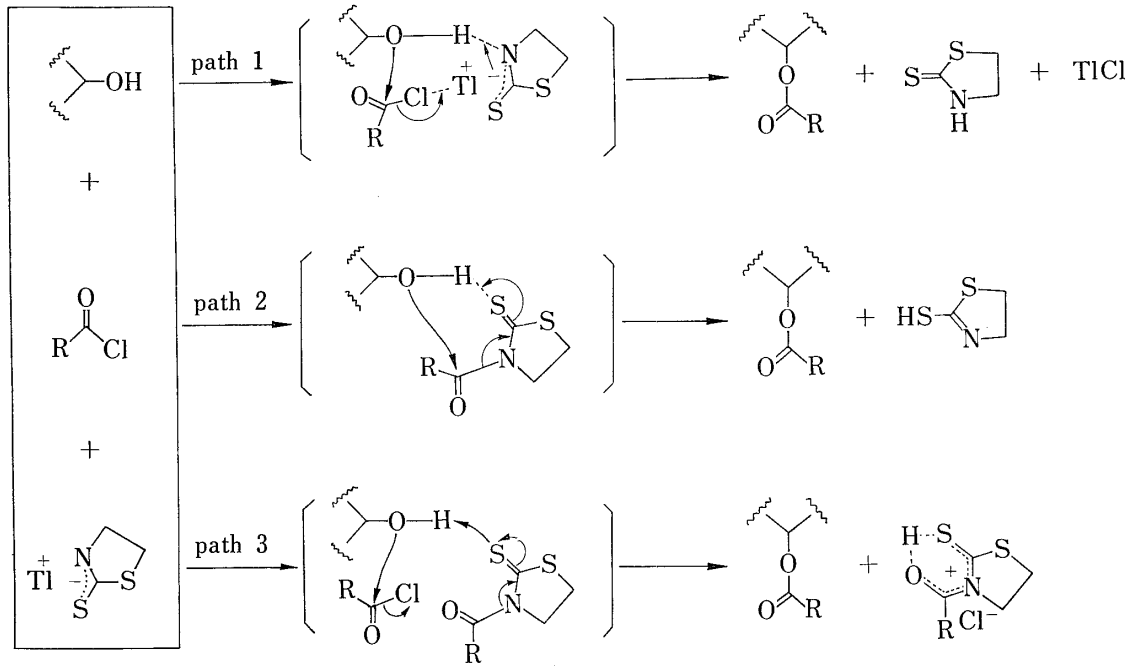
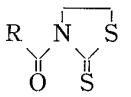


Chart 1

Thus, significant participation of path 1 in the esterification by Method A is likely for the more reactive alcohols, *e. g.*, **1**, **4**, and **5**, while for the less reactive alcohols, *e. g.*, **2**, **3**, **8**, and **9**, path 3 is presumed to be mainly involved, beacause the reaction between TTT and acid chloride is more rapid than esterification of the alcohol.



21: R=$CH_3(CH_2)_2$
22: R=$CH_3(CH_2)_{14}$

Since we were interested in esterification under conditions favoring path 3, we carried out further studies on the reactions of the alcohol **3** or **8**, which showed a relatively low reactivity in Method A. Preliminary formation of the N-acylthiazolidine-2-thione **21** or **22** by the reaction of TTT (3 equiv.) and excess butanoyl chloride (9 equiv.) or hexadecanoyl chloride (7 equiv.) in hot benzene for 20 min, followed by addition of the alcohol **3** or **8** with heating gave the ester **14** in 94% yield in 120 min or the ester **19** in 89% yield in 40 min.

We repeated the reactions by Method B, a development of Method A, for all of the alchols, **1**—**9**. Method B is a procedure in which both paths 1 and 3 should be involved: the alcohol

Table II. Esterification of Alcohols by Method B

Alcohol	Acid chloride[a] (Mol Equiv.)	TTT (Mol Equiv.)	Time (min)	Ester	Yield (%) of ester
1	B 6	3	15	**10**	97
1	D 6	3	15	**11**	94
1	H 6	3	15	**12**	93
2	D 20	10	30	**13**	94
3	B 20	3	30	**14**	83
4	H 5	3	10	**15**	87
5	H 6	3	30	**16**	80
6	H 6	3	30	**17**	70
7	H 6	3	30	**18**	18
8	H 7	3	30	**19**	98
9	H 9	3	50	**20**	58

a) B: butanoyl chloride. D: decanoyl chloride. H:hexadecanoyl chloride.

is treated with TTT and excess acid chloride in hot benzene. This method gave good yields of the desired esters within relatively short times without further additions of the reagents, except in the case of the tertiary alcohols (see Table II).

The reaction proceeds rapidly and gives good yields of esters, and the chloride anion formed during the reaction is largely removed as a precipitate of thallous chloride. Thus, we have developed a new procedure for the esterification of higher fatty acids, utilizing TTT.

Experimental

Melting points were determined with a Yanagimoto microapparatus and are uncorrected. Infrared (IR) spectra were measured on a Jasco A-202 spectrophotometer. NMR spectra were taken with a JEOL JMN-FX100 instrument in $CDCl_3$; signals are given as ppm from TMS as an internal standard. Mass spectra were determined on JEOL JMS-OISG or JEOL JMS-D300 double-focusing mass spectrometers. Extracts were dried over anhydrous Na_2SO_4. A mixture of Kieselgel 60 (70—230 mesh) (Merck) and silicic acid (Mallinckrodt) (3: 1) was used for column chromatography. All alcoholic compounds (except for dihydrolanosterol **2**[5]) were purchased from Nakarai Chemicals Co., Kyoto, Japan, and Wako Pure Chemical Ind. Ltd. Osaka, Japan.

Thallium (I) Salt of Thiazolidine-2-thione (TTT)[3]——A solution of thiazolidine-2-thione (4.986 g, 1.1 mol equiv.) in EtOH (200 ml) was added dropwise to a solution of thallium (I) acetate (10 g) in EtOH (400 ml) over 10 min with stirring, during which time a white crystalline precipitate appeared. Stirring was continued for a further 30 min at room temperature. The precipitate was filtered off and washed with large amounts of water, ethanol, and ether to give white crystals (9.778 g, 80%), mp 187—189° (dec.).

General Acylation Procedure by Method A——(1) Butanoyl chloride (185 mg, 5 mol equiv.) was added to a suspension of epiandrosterone (**1**) (101 mg) and TTT (562 mg, 5 mol equiv.) in benzene (10 ml). The mixture was stirred at 85° (bath temperature) for 30 min under N_2. The solid material (TlCl) was filtered off and washed with CH_2Cl_2. The filtrate combined with the washings (CH_2Cl_2), after addition of water, was extracted with a large amount of CH_2Cl_2. The extract was washed with brine, dried, and concentrated *in vacuo* to leave a yellowish residue, which was chromatographed on a silica gel column, eluting successively with *n*-hexane–CH_2Cl_2 (7: 3), *n*-hexane–CH_2Cl_2 (1: 9), and CH_2Cl_2. The first eluate gave N-butanoylthiazolidine-2-thione **21** as a yellowish oil (172 mg). The second eluate afforded epiandrosterone 3-butanoate (**10**) as colorless crystals (94 mg, 75%); recrystallization from CH_2Cl_2–MeOH gave colorless prisms (72 mg). The third eluate gave thiazolidine-2-thione, contaminated with a small amount of the butanoyl ester **10**. The presence of thiazolidine-2-thione in the third eluate was shown by comparison of the NMR spectrum with that of the authentic compound.

(2) Butanoyl chloride (197 mg, 5 mol equiv.) was added to a suspension of estrone (**3**) (100 mg) and TTT (598 mg, 5 mol equiv.) in benzene (10 ml). After stirring at 85° for 20 min, a thin-layer chromatogram of the reaction mixture showed the presence of the starting alcohol **3**. Thus, further amounts of both TTT (359 mg, 3 mol equiv.) and butanoyl chloride (118 mg, 3 mol equiv.) in benzene (2 ml) were added four times at 10 min intervals. During this time (40 min), the mixture was heated at 85° with stirring under N_2. The reaction mixture was treated as above to give estrone 3-butanoate (**14**) (123 mg, 98%) as colorless crystals. Recrystallization from CH_2Cl_2–MeOH gave colorless prisms (91 mg).

General Acylatien by Method B——(1) Butanoyl chloride (220 mg, 6 mol equiv.) was added to a suspension of epiandrosterone (**1**) (100 mg) and TTT (333 mg, 3 mol equiv.) in benzene (10 ml). The mixture was stirred at 85° for 15 min under N_2. Usual work-up gave a crude product consisting of N-butanoylthiazolidine-2-thione (**21**) and epiandrosterone 3-butanoate (**10**) contaminated with thiazolidine-2-thione. Purification of **10** was performed by chromatography on a silica gel-$AgNO_3$ (10: 1) column with CH_2Cl_2 (yield 120 mg, 97%), followed by recrystallization from CH_2Cl_2–MeOH to give colorless prisms (104 mg).

(2) Butanoyl chloride (788 mg, 20 mol equiv.) was added to a suspension of estrone (**3**) (100 mg) and TTT (359 mg, 3 mol equiv.) in benzene (10 ml). After stirring at 85° for 30 min, the reaction mixture was treated as usual to give estrone 3-butanoate (**14**) (104 mg, 83%) as colorless prisms.

Physical Data for Each N-Acylthiazolidine-2-thione——N-Butanoylthiazolidine-2-thione **21**: a yellowish oil. *Anal.* Calcd for $C_7H_{11}ONS_2$: M, 189.028. Found: M^+ *m/e*: 189.030. IR $\nu_{max}^{CHCl_3}$: 1700 cm^{-1}. NMR δ: 0.97 (3H, t, J=7 Hz, $C\underline{H}_3$–$(CH_2)_2$–C(=O)–S–), 1.43—2.03 (2H, m, CH_3–$C\underline{H}_2$–CH_2–C(=O)–O–), 3.30 (2H, t, J=7 Hz, S=C(N(–CH_2)–$\underline{CH}_2$)(S–$\underline{CH}_2$)), 4.60 (2H, t, J=7 Hz, S=C(S–CH_2)(N(–$\underline{CH}_2$)–CH_2)), 3.23 (2H, t, J=7 Hz, –$C\underline{H}_2$–C(=O)–S–). N-Decanoylthiazolidine-2-thione: a yellowish oil. Spectral data were identical with those of an authentic sample.[4] N-Hexade-

5) E. Fujita, Y. Nagao, and K. Kaneko, *Chem. Pharm. Bull.*, **26**, 3743 (1978).

canoylthiazolidine-2-thione **22**: yellowish needles mp 59.5—60° (from MeOH). Physical data were identical with those of an authentic sample.[4]

Physical Data for Each Ester——Epiandrosterone 3-butanoate (**10**): colorless prisms (from CH_2Cl_2–MeOH), mp 151—152°. *Anal.* Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07; M, 360. Found: C, 76.42; H, 10.28; M^+ *m/e*: 360. IR ν_{max}^{KBr}: 1725 cm^{-1}. NMR δ: 0.86 (6H, s, C-10-CH_3 and C-13-CH_3), 0.95 (3H, t, J=8 Hz, –O–C–$(CH_2)_2$–$C\underline{H}_3$), 4.44—4.88 (1H, m, C-3-H). Epiandrosterone 3-decanoate (**11**): colorless plates (from CH_2Cl_2–MeOH), mp 69.5—70°. *Anal.* Calcd for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88; M, 444. Found: C, 78.19; H, 11.07; M^+ *m/e*: 444. IR ν_{max}^{KBr}: 1735 cm^{-1}. NMR δ: 0.86 (9H, brs, C-10-CH_3, C-13-CH_3, and –O–C–$(CH_2)_8$–$C\underline{H}_3$), 4.44—4.88 (1H, m, C-3-H). Epiandrosterone 3-hexadecanoate (**12**): colorless plates (from CH_2Cl_2–MeOH), mp 82.5—83°. *Anal.* Calcd for $C_{35}H_{60}O_3$: C, 79.49; H, 11.44; M, 528. Found: C, 79.20; H, 11.65; M^+ *m/e*: 528. IR ν_{max}^{KBr}: 1740 cm^{-1}. Dihydrolanosterol 3-decanoate (**13**): colorless plates (from THF–acetone–MeOH), mp 65—66.5°. *Anal.* Calcd for $C_{40}H_{70}O_2$: C, 82.40; H, 12.11; M, 582. Found: C, 82.27; H, 12.36; M^+ *m/e*: 582. IR ν_{max}^{KBr}: 1730 cm^{-1}. NMR δ: 2.29 (2H, t, J=7 Hz, –O–C–$C\underline{H}_2$–$(CH_2)_7$–CH_3), 4.28—4.60 (1H, quartet-like, C-3-H). Estrone 3-butanoate (**14**): colorless prisms (from CH_2Cl_2–MeOH), mp 103—104.5°. *Anal.* Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29; M, 340. Found: C, 77.41; H, 8.37; M^+ *m/e*: 340. IR ν_{max}^{KBr}: 1755, 1735, 1600, 1585, and 1495 cm^{-1}. NMR δ: 0.91 (3H, s, C-13-CH_3), 1.04 (3H, t, J=7 Hz, –O–C–$(CH_2)_2$–$C\underline{H}_3$), 6.77 (1H, s, C-4-H), 6.82, 7.24 (2H, AB type, J=8 Hz, C-2-H and C-1-H). Umbelliferone 7-hexadecanoate (**15**): colorless needles (from CH_2Cl_2–MeOH), mp 79—79.5°. *Anal.* Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.76; H, 9.19. IR ν_{max}^{KBr}: 3090, 3070, 1725, 1620, and 1510 cm^{-1}. NMR δ: 0.86(3H, triplet-like, –O–C–$(CH_2)_{14}$–$C\underline{H}_3$), 2.58 (2H, t, J=8 Hz, –O–C–$C\underline{H}_2$–$(CH_2)_{13}$–CH_3), 6.36, 7.01 (2H, AB type, J=10 Hz, –$C\underline{H}$=$C\underline{H}$–C–O–), 6.95—7.49 (3H, aromatic protons). Butyl hexadecanoate (**16**): colorless oil. *Anal.* Calcd for $C_{20}H_{40}O_2$: M, 312.303. Found: M^+ *m/e*: 312.303. IR $\nu_{max}^{CHCl_3}$: 1725 cm^{-1}. NMR δ: 0.94 (6H, t, J=6 Hz, $C\underline{H}_3$–$(CH_2)_{14}$–C–O–$(CH_2)_3$–$C\underline{H}_3$), 2.28 (2H, t, J=8 Hz, –CH_2–$C\underline{H}_2$–C–O–), 4.06 (2H, t, J=6 Hz, –CH_2–$C\underline{H}_2$–O–C–). *sec*-Butyl hexadecanoate (**17**): colorless oil. *Anal.* Calcd for $C_{20}H_{40}O_2$: M, 312.303. Found: M^+ *m/e*: 312.300. IR $\nu_{max}^{CHCl_3}$: 1715 cm^{-1}. NMR δ: 0.88 (6H, t, J=8 Hz, CH_3–$(CH_2)_{14}$–C–O–CH$<^{CH_3}_{CH_2-CH_3}$), 1.22 (3H, d, J=6 Hz, –C–O–CH$<^{Et}_{CH_3}$), 2.26 (2H, t, J=7 Hz, –CH_2–$C\underline{H}_2$–C–O–), 4.82 (1H, h, J=6 Hz, –C–O–C$\underline{H}<^{Et}_{CH_3}$). *t*-Butyl hexadecanoate (**18**): colorless needles (from CH_2Cl_2), mp <30°. *Anal.* Calcd for $C_{20}H_{40}O_2$: M, 312.303. Found: M^+ *m/e*: 312.300 IR $\nu_{max}^{CHCl_3}$: 1720 cm^{-1}. NMR δ: 0.86 (3H, triplet-like, –O–C–$(CH_2)_{14}$–$C\underline{H}_3$), 1.41 (9H, s, $(CH_3)_3$≡C–O–C–), 2.17 (2H, t, J=5 Hz, –O–C–$C\underline{H}_2$–CH_2–). 2-Adamantanol hexadecanoate (**19**): colorless plates (from CH_2Cl_2-acetone-MeOH), mp 48.5—49°. *Anal.* Calcd for $C_{26}H_{46}O_2$: C, 79.94; H, 11.87; M, 390.3498. Found: C, 80.04; H, 11.87; M^+ *m/e*: 390.3480. IR ν_{max}^{KBr}: 1735 cm^{-1}. NMR δ: 0.85 (3H, triplet-like, –O–C–$(CH_2)_{14}$–$C\underline{H}_3$), 2.30 (2H, t, J=7 Hz, –O–C–$C\underline{H}_2$–), 4.84 (1H, brs, 1/2W=7 Hz, >$C\underline{H}$–O–C–). 1-Adamantanol hexadecanoate (**20**): colorless plates (from THF–acetone–MeOH), mp 35—35.5°. *Anal.* Calcd for $C_{26}H_{46}O_2$: C, 79.94; H, 11.87; M, 390.3498. Found: C, 79.66; H, 11.90; M^+ *m/e*: 390.3463. IR ν_{max}^{KBr}: 1735 cm^{-1}. NMR δ: 0.86 (3H, triplet-like, –O–C–$(CH_2)_{14}$–$C\underline{H}_3$), 2.18 (2H, t, –O–C–$C\underline{H}_2$–CH_2–).

Treatment of Epiandrosterone (1) with N-Butanoylthiazolidine-2-thione (21)——N-Butanoylthiazolidine-2-thione (**21**) (384 mg, 5 mol equiv.) was added to a suspension of epiandrosterone (**1**) (118 mg) in benzene (10 ml). The mixture was stirred at 85° for 30 min under N_2 and treated as usual to give a crude yellowish substance; chromatography on a silica gel column gave the starting compounds, N-butanoylthiazolidine-2-thione (**21**) (346 mg, 90%), and epiandrosterone (**1**) (107 mg, 91%).

Treatment of Epiandrosterone (1) with N-Butanoylthiazolidine-2-thione (21) in the Presence of TTT Chloride——TTT (556 mg, 5 mol equiv.) was added to a suspension of epiandrosterone (**1**) (100 mg) and

N-butanoylthiazolidine-2-thione (**21**) (325 mg, 5 mol equiv.) in benzene (10 ml). The mixture was stirred at 85° for 30 min in N_2. After addition of thallium (I) chloride (412 mg, 5 mol equiv.), the mixture was further heated at 85° for 30 min with stirring. Usual work-up of the reaction mixture gave a crude yellowish substance; separation on a silica gel column resulted in recovery of N-butanoylthiazolidine-2-thione (**21**) (319 mg, 98%) and epiandrosterone (97 mg, 97%).

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