Tetrahedron. Vol. 30, pp. 2135 to 2142. Pergamon Press 1974. Printed in Great Britain

THIOSTEROIDS—XXXV[1]

DIASTEREOMERS OF STEROIDAL THIOLSULFINATES

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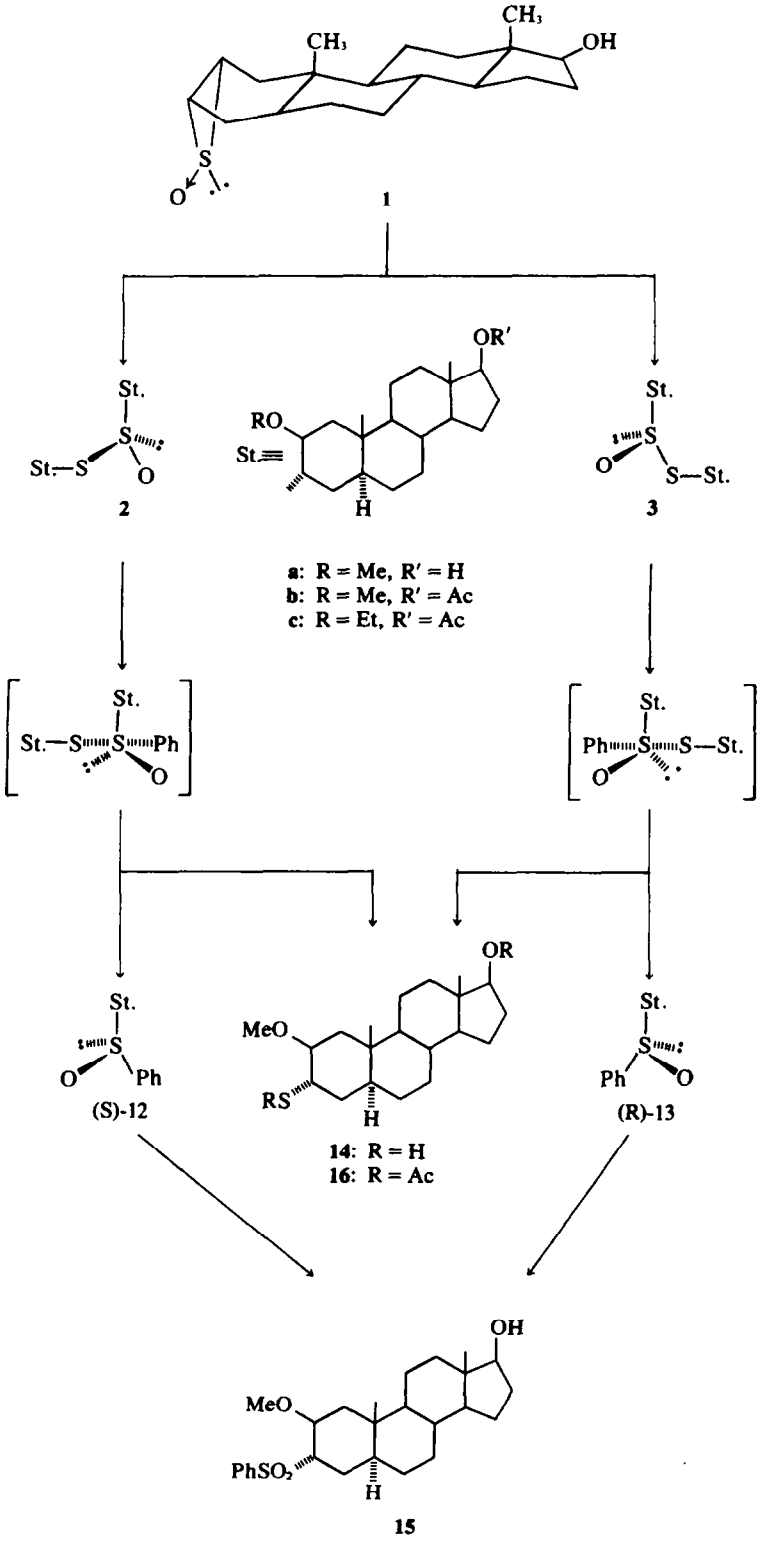
(*Received in Japan* 5 *November* 1973; *Received in the UK for publication* 12 *Feburary* 1974)

Abstract—17β-Hydroxy-5α-androstan-2α,3α-anti(R)-episulfoxide on treatment with methanol and ethanol in the presence of a trace amount of sulfuric acid gave diastereomers of bis((2β-methoxy- and 2β-ethoxy-17β-hydroxy-5α-androstan-3α-yl) disulfide S-monoxides respectively. The absolute configuration of the compounds was established by their Grignard reactions leading to diastereomeric phenyl sulfoxides stereoaspecifically.

The resolution of cystine (±) S-monoxides by Savige *et al.*[2] in 1964 demonstrated that thiolsulfinates have a stable pyramidal configuration at the sulfinyl sulfur like other trivalent sulfur compounds bearing the semipolar S–O bond, e.g. sulfoxides and sulfinate esters. They also found that the oxidation of diaryl disulfides with optically active (+) percamphoric acid yielded the corresponding thiolsulfinates showing positive specific rotation,[3] and assigned the (*R*) absolute configuration to the compounds by means of conversion to benzylsulfoxides having the established configuration.[4] Kice and Large[5] also reported a similar asymmetric synthesis of (+) phenyl benzenethiolsulfinate derivatives as well as the acid- and nucleophile-catalyzed racemization of the compounds. While these and later studies in this field have dealt with aryl and aralkyl benzenethiolsulfinates, little is known on optically active alkyl alkanethiolsulfinates. In our continuing studies on epithiosteriods, we encountered the formation of diastereomeric thiolsulfinates from a steroidal episulfoxide and were interested in their configurational assignments, since the absolute configuration of the steroid itself was already established. We now wish to present the results obtained in the investigation.

17β - Hydroxy - 5α - androstan - 2α,3α - anti(*R*) - episulfoxide (**1**) has been considered to be a key intermediate in a metabolic path of 17β - hydroxy - 5α - androstan - 2α,3α - episulfide, a compound showing potent anti-estrogenic and modest androgenic activities,[6] since the episulfoxide is readily isolable either by the incubation of the episulfide with a microsome fraction of rat liver homogenate or by oxidation of the episulfide with m-chloroperbenzoic acid.[7] The anti(*R*) configuration at the sulfinyl sulfur in **1** has been assigned on the basis of its PMR and CD spectra, compared with those of the corresponding 2β,3β-anti(*S*)-episulfoxide, and from consideration of a plausible mechanism involving attack of the reagents from the less crowded site of the S atom.[7,8] Support for this assignment has been recently furnished by X-ray analysis on a single crystal of **1**,[9] obtained by recrystallization from methanol. In a separate experiment an attempted recrystallization from ethanol, whereby **1** was allowed to stand in ethanol at room temperature for 2 days, resulted in the decomposition of **1** to yield two main products. Acetylation of the mixture, followed by preparative TLC afforded mobile **2c** and polar **3c** in yields of 19% and 61% respectively. On addition of a trace amount of conc sulfuric acid to the solvent, acceleration of the reaction was distinctly observed so that the reaction under very mild conditions (at 0° for 30 min), followed by treatment similar to that described above, gave the same products; 24% yield of **2c** and 62% yield of **3c**. A similar acid-catalyzed reaction of **1** in methanol also afforded less polar **2a** and more polar **3a** in yields of 24% and 62% respectively, acetylation of which gave the corresponding acetates **2b** and **3b**. In all cases examined, PMR spectra of the compounds thus obtained exhibit signals due to alkoxy groups originating from the solvent employed in the reaction, indicating introduction of the groups into the molecules. As can be seen in Table 1, the IR spectra show intense absorption bands at 1080–1090 cm^{-1} characteristic of a thiolsufinate and the M_D difference in each pair of the compounds reveals that the polar compounds (**3a–3c**) are more dextrotatory than the mobile ones (**2a – 2c**) by a margin of from 525 to 756 M_D units. The compounds exhibit CD maxima near 250 nm, presumably corresponding to the absorption bands in their UV spectra (Experimental), in addition to CD maxima opposite in sign at a shorter wave length (near 205 nm). Furthermore, the CD maxima for **2a–2c** are opposite in sign to those observed for **3a–3c** at each wave length, suggesting a diastereomeric relationship between **2a–2c** and **3a–3c**.


CH3
CH3
OH
S
O
1
OR'
RO
St.
St.
St.—S
S
O
2
H
St.
O
S
S—St.
3
a: R = Me, R' = H
b: R = Me, R' = Ac
c: R = Et, R' = Ac
St.
St.—S
S
Ph
O
St.
Ph
S
S—St.
O
OR
MeO
RS
H
St.
O
S
Ph
(S)-12
St.
Ph
S
O
(R)-13
14: R = H
16: R = Ac
OH
MeO
PhSO2
H
15

SCHEME 1.

Table 1. Physical data of steroidal thiolsulfinates

Compd	M.p.	MD	$\nu_{S=O}$	CD Spectra in MeOH (nm) [θ]
2a	176	+121	1090	(322) 0, (255) +19640, (230sh) +920, (220·5) 0, (205) −50680.
3a	176	+646	1081	(330) 0, (256) −16300, (235) −10340, (224·5) −16370, (218) 0, (205sh) +49300, (197) +80800.
2b	165	−7	1077	(325) 0, (254) +23330, (227sh) +10240, (220·5) 0, (205) −78900, (200) −84900.
3b	171	+749	1080	(330) 0, (257) −16550, (235) −10440, (227·5) −16350, (218·5) 0, (200) +76800.
2c	165	+120	1077	(310) 0, (252) +19400, (230sh) +9200, (221) 0, (208) −44000, (200) −29000.
3c	173	+781	1078	(325) 0, (260) −10570, (235) −6340, (225) −10920, (218) 0.
21a	228	−359	1062	(320) 0, (225) +20500, (232) +10700, (227·5) +11800, (219) 0, (202) −75000, (199) −67000.
22a	185	+581	1063	(320) 0, (255) −19000, (235) −12800, (225) −16400, (217) 0, (200) +74000.
21b	233	−479	1063	(345) 0, (266) +30600, (238) +13600, (229) +19100, (222) 0, (210) −100000.
22b	198	+858	1075	(325) 0, (267) −30000, (240)− 12200, (228) −23000, (222) 0, (210) +94000.

Based on these spectral findings coupled with both the elemental analysis and the mass spectra, a partial structure of bis(2β-alkoxy-3α-yl) disulfide S-monoxide, a thiolsulfinate, was assigned to the compounds. This assumption was also in agreement with Kondos' observation[10] where the acid-catalyzed ring-opening reaction of episulfoxides proceeds with attack of nucleophile and produces the corresponding thiolsulfinates by the dehydrative dimerization of the initially formed (or transient) sulfenic acids because of their instabilities. Of our compounds, the structures of **2a** and **3a** were confirmed by their independent multi-step synthesis starting from 2β,3β-epoxy-5α-androstan-17-one (**4**). Thus the ring-cleavage reaction of **4** with thiocyanic acid gave thiocyanatohydrin **5**, the C_{17}-keto group in which was protected by conversion to ethyleneketal **6**. LAH reduction of **6** afforded mercapto-ol **7**, which was transformed to disulfide **8** by reaction with iodine in the presence of triethyl amine. At this stage, O-methylation of the 2β-OH group in **8** was effected using sodium hydride and methyl iodide, and bis(2β-methoxy-17,17-ethylenedioxy-5α-androstan-3α-yl) disulfide (**9**) was obtained in 48·5% overall yield from **4**. The structure of **9** was evidenced by its PMR spectrum (OMe: 3·33 ppm). After acid-hydrolysis of **9**, reduction of the ketone **10**, thus obtained with lithium aluminum tri(t-butoxy)hydride proceeded smoothly without affecting the S–S linkage, affording bis(2β-methoxy-17β-hydroxy-5α-androstan-3α-yl) disulfide (**11a**) in 94·6% yield from **9**. Oxidation of **11a** with 1 mole of m-chloroperbenzoic acid furnished in high yields equal amounts of the thiolsulfinates **2a** and **3a**, identical with those prepared from the episulfoxide **1** respectively. It should be noted that these results provide not only evidence of the gross structures of the thiolsulfinates, except for the configuration about the sulfinyl sulfur, but also the first example of trans diaxial cleavage by nucleophile of an episulfoxide ring fused to a cyclohexane system. Kondo *et al.*[10] have observed that the ring-opening reaction of episulfoxides of isomeric 2-butenes and stilbenes proceeds with inversion of configuration at the point of nucleophile attack.

The assignment of the absolute configuration of the thiolsulfinates remained to be solved. This was carried out in the following way* since we considered the spectroscopic data which we had obtained to be of no use for the purpose. Thus treatment of **2a** with phenyl magesium bromide in tetrahydrofuran at 0° gave phenyl sulfoxide **12**, $[\alpha]_D$ −37°, and 3α-thiol **14** both in quantitative yields. On the other hand, **3a** on the same treatment afforded phenyl sulfoxide **13**, $[\alpha]_D$ +107°, different from **12** in all respects, and the same 3α-thiol **14**, both in high yields. The structure of **14** was characterized by its conversion to the identical O,S-diacetate **16** in each case. Oxidation of both **12** and **13** with m-chloroperbenzoic acid yielded the same phenyl sulfone **15**, indicating that these sulfoxides are also diastereomers which are epimeric at the asymmetric sulfur. CD Spectral data for the sulfoxides thus obtained are listed in Table 2.

The benzenesulfinyl chromophore is inherently dissymmetric and the chirality of alkyl aryl sulfoxides has been rationalized to the relevant Cotton effect. Mislow *et al.*[11] reported that (*R*) alkyl *p*-tolyl sulfoxides, derived by Grignard reaction of the

*Vinkler *et al.* found that in the Grignard reaction of phenyl benzenethiolsulfinate benzyl magnesium chloride attacks the sulfinyl sulfur to give benzyl sulfoxide and thiol, while phenyl magnesium bromide reacts with the sulfenyl sulfur affording phenyl sulfide and thiolsulfinate arising from the initially formed sulfenic acid. (Ref 18) In our case, in contrast, (*R*)-thiolsulfinates **3a** and **22a** on treatment with benzyl magnesium chloride gave a mixture of nearly equal amounts of diastereomeric thiolsulfinates as well as disulfide. If the reagemt attacks the sulfenyl sulfur in the compounds, benzyl sulfide and thiolsulfinates are expected to be formed. In the reaction of **22a**, the formation of a detectable amount of 3α-benzylthio-5α-androstan-17β-ol could not be observed by monitoring on TLC.

Table 2. CD Spectra of phenyl sulfoxides

Sulfoxide	CD Maxima in cyclohexane (nm) [θ]	Assigned configuration
12	(261) −54200, (240·5) 0, (221) +96300	(S)
13	(260) +49700, (240) 0, (222) −98900	(R)

sulfinate esters having an (*S*) configuration established by X-ray analysis, gave rise to positive Cotton effects at around 250 nm in their ORD curves. Later, Jones and Green[12] prepared both diastereomers of 3α-phenylsulfinyl-5α-cholestanes, whose structures are very similar to those of our compounds, and studied pyrolytic elimination in each isomer. The reactions gave a mixture of 5α-cholest-2-ene and -3-ene, the composition of which varied with the substrate. They assigned the absolute configuration of the sulfoxides by consideration of the relationship between the product ratio in each reaction and relative stabilities of the transition states leading to the isomeric olefins. In the ORD curves they also observed that the (*R*)-sulfoxide showed a positive Cotton effect at around 260 nm in accord with Mislows' observation, and the (*S*)-sulfoxide exhibited a negative Cotton effect in the same region. From these data, the sign of the CD maxima at 260 nm observed in our compounds, as shown in Table 2, allows us straightforwardly to assign the (*S*) configuration to **12** and the (*R*) configuration to **13**.

Since the reaction of sulfinate esters with Grignard reagent is known to proceed by S_N2 type nucleophilic attack at the sulfinyl sulfur and hence to produce sulfoxides configurationally inverted at the sulfur atom,[11,13] thiolsulfinates also are expected to react in a similar way.[4] Consequently, the (*S*)* configuration for thiolsulfinate **2a** and the (*R*)* configuration for **3a** can be assigned. The assignment is supported by the following consideration of the CD spectral data.

It is of interest that the phenyl sulfoxides **12** and **13** exhibit another CD maxima opposite in sign at shorter wave length (220 nm) as shown in Table 2, though Stirling[14] has found in (−) benzyl *p*-tolyl sulfoxide a negative CD maximum at 220 nm besides a positive CD maximum at 250 nm. The Cotton effect observed at 220 nm is reasonably considered to arise from the sulfinyl chromophore, reflecting the chirality at sulfur. Although correlation of the configuration of alkyl alkanethiolsulfinates, the chromophore of which is also inherently dissymmetric, to the relevant Cotton effect has not hitherto been discussed, the chiroptic properties of the compounds are governed by two asymmetric factors: the chirality of the skewed conformations of the C–S–SO–C bonds and that of the asymmetric sulfinyl sulfur. Of the two Cotton effects observed with the thiolsulfinates (Table 1), the Cotton effect at the shorter wave length (205 nm) appears to correspond to the electronic transition of the sulfinyl chromophore, by analogy with a dislkyl sulfoxide.[11] In this sense, it should be noted that the negative Cotton effect observed at 205 nm in **2a** is changed to the positive Cotton effect at 220 nm in **12** whereas the positive CD maximum at 205 nm in **3a** is converted to the negative CD maximum at 220 nm in **13**, these indicating the occurrence of inversion of configuration at the sulfinyl sulfur in the reactions **2a** → **12** and **3a** → **13**.

As for the conformation of (*S*)-**2** and (*R*)-**3**, there are two possible forms for each compound, as shown in Fig 1. Exner *et al.*[15] have recently determined the dipole moments of alkyl and aryl benzenethiolsulfinates and concluded that these have a preferred conformation in which the energy of electrostatic repulsion between lone pair–lone pair electrons on adjacent *S* atoms is minimized. In this connection, the conformation A for (*S*)-**2** and the conformation A′ for (*R*)-**3** may be preferable, in agreement with the antipodal relationship between them observed in their CD spectra.

The results that oxidation of disulfide **11a** gives equal amounts of thiolsulfinates (*S*)-**2a** and (*R*)-**3a** indicates that the steroidal moieties in **11a** do not significantly affect the formation of each compound and hence that the steric environments of the sulfinyl groups are comparable in **2a** and **3a**. Under conditions more drastic rather than those used in the acid-catalyzed reaction of episulfoxide **1**, both **2a** and **3a** were stable and not interconvertible. The presence of hydrochloric acid instead of sulfuric acid, however caused equilibration in which equal

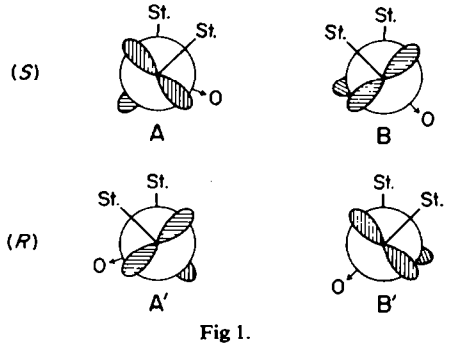
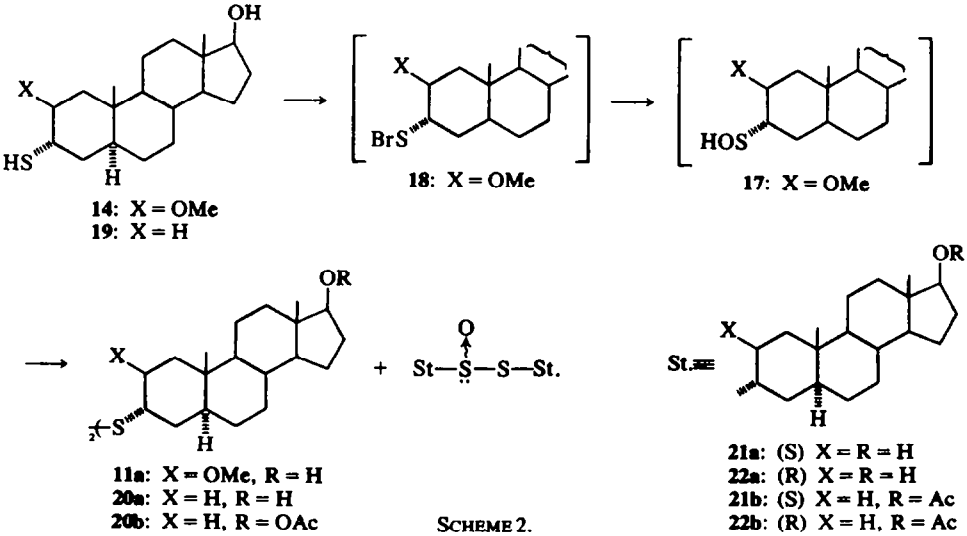


Fig 1.

*It must be noted that the sequence used in assigning configuration of thiolsulfinates is thiol-S, O, C_3, pair of electrons while that of phenyl sulfoxides is O, Ph, C_3, pair of electrons.

amounts of **2a** and **3a** were formed starting from either **2a** or **3a**, suggesting that these have the same thermodynamic stabilities. According to the mechanism postulated by Kondo *et al.*,[10] the reaction of **1** leading to **2a** and **3a** is considered to involve the formation of 3α-sulfenic acid **17** as a transient intermediate. Therefore, the dehydrative dimerization of **17**, which contains only a divalent sulfur substituent devoid of chirality at the sulfur, is expected to give equal amounts of **2a** and **3a**. In fact, however, polar (*R*)-**3a**, whose configuration at the sulfur is apparently inverted from that of the parent episulfoxide **1**, was found to predominate over mobile (*S*)-**2a**. The observed inversion of configuration in going from **1** to **3a** is also supported by the CD spectral data, where **1** exhibited two negative CD maxima at 220 and 210 nm with elipticities of −13620 and −11410 respectively.[7] For the observed predominance of **3a** over **2a** the following explanation seemed attractive in view of the stereochemical course of the reaction. In the main course of the reaction, the sulfinyl S-anion developing by attack of nucleophile on **1** may react in a concerted manner with the formed sulfenic acid to yield the product configurationally inverted at the sulfinyl sulfur. However, we had to exclude this possible interpretation since we could demonstrate that the situation is not peculiar to the ring-opening reaction of **1** by the dehydrative dimerization of the sulfenic acid generated from the corresponding thiol, which lacks the chirality at sulfur, instead of episulfoxide **1**. Thus, 2β-methoxy-3α-mercapto-5α-androstan-17β-ol (**14**) was brominated in carbon tetrachloride and the product was further treated with aqueous tetrahydrofuran. These reactions are thought to proceed through sulfenyl bromide **18** and sulfenic acid **17**,[16] although the compounds were not isolated in the pure state because of their instability. As expected, a mixture of **2a** and **3a** was obtained in 30% yield in addition to disulfide **11a** as the main product, which appears to be formed in the first step of the combined reactions. It was again found that **3a** predominated over **2a** in a ratio similar to that found in the reaction of **1**. Furthermore, 3α-mercapto-5α-androstan-17β-ol (**19**), in which a lack of the axial 2β-substituent does not presumably bring about a deformation of the A-ring, was treated successively with bromine and then water in the same way as described above. In this case, a mixture of diastereomeric thiolsulfinates **21a** and **22a** was obtained in 14% yield besides disulfide **20a** as the main product. The assignments of the (*S*) configuration at the sulfinyl sulfur in **21a** and the (*R*) configuration in **22a** were ascertained by comparison of the CD spectra with those of **2a** and **3a** respectively (Table 1). The observed product ratio of **21a** to **22a** was also 1:2·5, nearly the same as obtained starting from **14**. On the other hand, disulfide **20a** on oxidation with *m*-chloroperbenzoic acid afforded a 1:1 mixture of **21a** and **22a** in keeping with the result in the oxidation of disulfide **11a**. The formation of thiolsulfinates in the combined reaction of thiols **14** and **19** is roughly comparable with that in the dimerization of sulfenic acid and the reactions are very similar to the acid-catalyzed racemization of optically active thiolsulfinates. In the latter reaction Kice and Cleveland[17] found that O-exchange is considerably slower than racemization, and concluded that the rate determining step is the initial formation of the original oxygen containing sulfenic acid formed by nucleophilic attack on the sulfenyl sulfur and that the sulfenic acid is highly reactive as nucleophile toward its counterpart, a sulfenyl derivative. These considerations do not directly answer the question why the (*R*)-thiolsulfinate predominates over the



SCHEME 2.

(*S*)-isomer. Consequently, we speculate that in the course of the dehydrative dimerization of the transient sulfenic acid the transition state leading to the (*R*)-isomer would be less influenced than that leading to the (*S*)-isomer by complex stereoelectronic factors arising from repulsions among the steroidal residue, the lone pairs of electrons at the sulfurs, and the sulfinyl moieties with restricted rotation about the C–S(OH) · · · S(O)–C bonds, although these cannot be estimated at present because of their complexity.

EXPERIMENTAL

M.ps were measured on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined in 1% EtOH-$CHCl_3$ with a Perkin–Elmer polarimeter, type 141. Unless otherwise stated, IR spectra were recorded in Nujol mulls by use of a Koken DS-201B spectrophotometer and PMR spectra on $CDCl_3$ solns with a Varian A-60 spectrometer, TMS serving as internal standard. CD and UV curves were measured with a Jasco Model ORD/UV-5 equipped with CD. Mass spectra were observed with a Hitachi RMU-6 mass spectrometer (70 eV). For preparative TLC, silica gel G or GF (E. Merck Co.) was used as an adsorbent.

The reaction of 17β-*hydroxy*-5α-*androstan*-2α,3α-*anti* (R)-*episulfoxide* (1)

(a) *With* MeOH. **1** was recovered unchanged after prolonged standing in abs MeOH at room temp.

(b) *With conc* H_2SO_4-MeOH. To a cooled and stirred soln (40 ml) of conc H_2SO_4 in MeOH (0·02% v/v), 315 mg **1** was added portionwise. After being stirred for 30 min at 0°, the mixture was concentrated *in vacuo* and diluted with water. Extraction with CH_2Cl_2 gave 320 mg of white solid, which was purified by preparative TLC (CH_2Cl_2–acetone = 5:1) to yield 81 mg (24%) of **2a** as the more mobile fraction and 209 mg (62%) of **3a** as the less mobile fraction. Both were recrystallized from acetone–hexane to give pure crystals respectively. **2a**, m.p. 174·5–176·5°, $[\alpha]_D^{21}$ + 17·6° (*c* = 1·045), ν_{max}: 3327, 1090 cm^{-1}; λ_{max}^{MeOH} 252 nm (ε 6370); PMR (δ ppm): 0·72 (s, 18-H × 2), 0·97 (s, 19-H × 2), 3·32 (s, OMe), 3·34 (s, OMe), 3·35–3·93 (m, 2α-, 3β-, and 17α-H × 2). (Found: C, 69·42; H, 9·59; S, 9·54. $C_{40}H_{66}O_3S_2$ requirs: C, 69·52; H, 9.63; S, 9·28%). **3a**, m.p. 175–176°, $[\alpha]_D^{21}$ + 93·6° (*c* = 1·001), ν_{max}: 3330, 1110, 1081, 1069 cm^{-1}; λ_{max}^{MeOH} 252 nm (ε 2480); PMR (δ): 0·73 (s, 18-H × 2), 0·98 (s, 19-H × 2), 3·33 (s, OMe), 3·35 (s, OMe), 3·35–3·93 (m, 2α-, 3β-, and 17α-H × 2). (Found: C, 69·42; H, 9·45; S, 9·29. $C_{40}H_{66}O_3S_2$ requires: C, 69·52; H, 9·63; S, 9·28%).

In a separate experiment the crude product from reaction (b) was treated with Ac_2O in pyridine overnight at room temp, worked up in the usual way and purified by preparative TLC (cyclohexane–AcOEt = 2:1) to give 19·5% of **2b** as the more mobile fraction and 55% of **3b** as the less mobile fraction respectively after recrystallization from acetone–hexane. **2b**, m.p. 163–165°, $[\alpha]_D^{23.5}$ − 0·9° (*c* = 0·543), ν_{max}^{KBr}: 1735, 1245, 1077 cm^{-1}, λ_{max}^{MeOH} 252 nm (ε 2620). (Found: C, 67·96; H, 9·08; S, 8·22. $C_{44}H_{70}O_7S_2$ requires: C, 68·17; H, 9·10; S, 8·27%). **3b**, m.p. 170–171°, $[\alpha]_D^{23.5}$ + 96·8° (*c* = 1·007), ν_{max}^{KBr}: 1737, 1245, 1080 cm^{-1}, λ_{max}^{MeOH} 252 nm (ε 2390). (Found: C, 68·15; H, 9·09; O, 14·37; S, 8·31. $C_{44}H_{70}O_7S_2$ requires: C, 68·17; H, 9·10; O, 14·45; S, 8·27%).

(c) *With* EtOH. **1** (300 mg) was dissolved in 20 ml EtOH with warming, allowed to stand at room temp for 43 h, then concentrated to dryness *in vacuo*. The residue was treated with 1·5 ml Ac_2O in 4 ml pyridine overnight at room temp and worked up in the usual way. Preparative TLC (cyclohexane–AcOEt = 3:1) of the product afforded 70 mg (18·7%) of **2c** as the less polar fraction and 229 mg (61·3%) of **3c** as the more polar one respectively after recrystallization from acetone–hexane. **2c**, m.p. 163–165°, $[\alpha]_D^{23.5}$ + 15·0° (*c* = 0·982), ν_{max}: 1738, 1229, 1077 cm^{-1}, λ_{max}^{MeOH} 252 nm (ε 2830). PMR (δ): 0·77 (s, 18-H × 2), 0·98 (s, 19-H × 2), 1·18 (t, *J* = 7 H_z, OCH_2CH_3 × 2), 2·02 (s, OAc × 2), 3·50 (q, *J* = 7 H_z, OCH_2CH_3 × 2), 3·33–3·83 (m, 2α- and 3β-H × 2), 4·58 (m, 17α-H × 2). (Found: C, 68·18; H, 9·16; S, 7·84. $C_{46}H_{74}O_7S_2$ requires: C, 68·78; H, 9·29; S, 7·98%). **3c**, m.p. 171–173°, $[\alpha]_D^{22.5}$ + 97·4° (*c* = 1·037), ν_{max}: 1739, 1227, 1078 cm^{-1}, λ_{max}^{MeOH} 253 nm (ε 2130). PMR (δ): 0·79 (s, 18-H × 2), 0·99 (s, 19-H × 2), 1·17 (t, *J* = 7 H_z, OCH_2CH_3 × 2), 2·02 (s, OAc × 2), 3·50 (q, *J* = 7 H_z, OCH_2CH_3 × 2), 3·67–4·08 (m, 2α- and 3β-H × 2), 4·55 (m, 17α-H × 2). MS (*m/e*): 786 (M^+-O), 754 (M^+-SO). (Found: C, 69·08; H, 9·19; O, 13·49; S, 8·05. $C_{46}H_{74}O_7S_2$ requires: C, 68·78; H, 9·29; O, 13·94; S, 7·98%).

(d) *With conc* H_2SO_4-EtOH. **1** (321 mg) was treated with 44 ml soln of conc H_2SO_4 in EtOH (£·02 v/v) for 6 h at 0° and worked up as described above. Acetylation of the product, followed by preparative TLC gave 59 mg (14·8%) of **2c** and 196 mg (49%) of **3c**.

3α - *Thiocyanato* - 17,17 - *ethylenedioxy* - 5α - *androstan* - 2β - *ol* (6)

Compound **5** (524 mg) easily prepared by the reaction of oxide **4** with HSCN, was mixed with 13 ml dry benzene, 1 ml ethylene glycol and 25 mg *p*-TsOH·H_2O and the mixture was refluxed for 4 h with the removal of water. The residual crystals extracted with CH_2Cl_2 were recrystallized from acetone-hexane to yield 522 mg (88·2%) of **6**, m.p. 192–194°, $[\alpha]_D^{23}$ + 14·8° (*c* = 0·946), ν_{max}: 3556, 2159, 1101, 1035 cm^{-1}. (Found: C, 67·40; H, 8·46; N, 3·53; S, 8·26. $C_{22}H_{33}NO_3S$ requires: C, 67·48; H, 8·50; N, 3·58; S, 8·19%).

3α - *Mercapto* - 17,17 - *ethylenedioxy* - 5α - *androstan* - 2β - *ol* (7)

To a stirred and cooled suspension of 70 mg LAH in 60 ml dry THF, 2·015 g **6** in 55 ml THF was added dropwise and the mixture was stirred at room temp for 5 h. Work-up in the usual way gave 1·415 g (75·1%) of crystals, which were recrystallized from acetone-hexane to afford pure **7**, m.p. 143–144°, $[\alpha]_D^{24}$ + 18·4°(*c* = 0·425), ν_{max}: 3245, 2574, 1306, 1120, 1023 cm^{-1}. (Found: C, 69·14; H, 9·32 ; S, 8·50. $C_{21}H_{34}O_3S$ requires: C, 68·81; H, 9·35; S, 8·75%).

Bis(2β - *hydroxy* - 17,17 - *ethylenedioxy* - 5α - *androstan* - 3α - *yl*) *disulfide* (8)

A mixture of 860 mg I_2 in 70 ml MeOH, 0·95 ml triethylamine and then 1·239 g **7**, was stirred at room temp for 1 h while **8** crystallized out. After the addition of water, deposited crystals were collected by filtration, dried, and recrystallized from MeOH to give 935 mg (75·7%) of **8**, m.p. 266–268°, $[\alpha]_D^{24}$ − 49·3° (*c* = 1·021), ν_{max}: 3478, 3355, 1306, 1167 cm^{-1}. (Found: C, 68·58; H, 9·31; S, 8·68. $C_{42}H_{66}O_6S_2$ requires: C, 69·00; H, 9·10; S, 8·77%).

Bis(2β - *methoxy* - 17,17 - *ethylenedioxy* - 5α - *androstan* 3α - *yl*) *disulfide* (9)

To a stirred mixture of 876 mg **8**, and 220 mg NaH in

30 ml glyme was added 0·5 ml (3 molar equiv.) methyl iodide dropwise over 3 h at room temp and the mixture was stirred for 4 h more. Water was added, and crystals which deposited were collected by filtration, dried, and recrystallized from acetone to give 871 mg (95·7%) of **9**, m.p. 226–228°, $[\alpha]_D^{24}$ − 82·6° (c = 1·014), ν_{max}: 1305, 1106, 1079 cm^{-1}. (Found: C, 69·77; H, 9·39; S, 8·34. $C_{44}H_{70}O_6S_2$ requires: C, 69·21; H, 9·29; S, 8·45%).

Bis(2β - methoxy - 17 - oxo - 5α - androstan - 3α - yl) disulfide (**10**)

A mixture of **9** (776 mg), 35 ml AcOH and 5 ml H_2O was heated on a water-bath for 1·5 h. After addition of water, deposited solid was collected by filtration, washed with water, dried, and recrystallized from acetone-hexane to yield 675 mg (98·4%) of **10**, m.p. 197–198°, $[\alpha]_D^{24}$ + 0·4° (c = 1·032), ν_{max}: 1736, 1091 cm^{-1}. PMR (δ): 0·85 (s, 18-H), 0·96 (s, 19-H), 3·20 (m, 3β-H), 3·32 (s, OMe), 3·60 (m, $W_{h/2}$ = 7 Hz, 2α-H). (Found: C, 71·54; H, 9·42; S, 9·50. $C_{40}H_{62}O_4S_2$ requires: C, 71·59; H, 9·31; S, 9·56%).

Bis(2β - methoxy - 17β - hydroxy - 5α - androstan - 3α - yl) disulfide (**11a**)

To a stirred suspension of 750 mg LiAl (t-BuO)$_3$H in 15 ml dry THF, 300 mg **10** was added portionwise at room temp. The mixture was stirred for 1 h, concentrated *in vacuo*, acidified with HCl, and extracted with CH_2Cl_2. After evaporation of the solvent, the residual solid (310 mg) was recrystallized from MeOH to give 290 mg (96·3%) of **11a**, m.p. 189–193, 217–221°, $[\alpha]_D^{24}$ − 75·7° (c = 0·199), ν_{max}^{KBr}: 3467, 1074 cm^{-1}, λ_{max}^{EtOH} 251 nm (ε 300), CD(EtOH): (nm) [θ]: (335) 0, (258) − 3190, (235) − 1710, (203) − 40300, (200) − 40000. PMR (δ): 0·71 (s, 18-H × 2) 0·94 (s, 19-H × 2), 3·20 (m, $W_{h/2}$ = 7 Hz, 3β-H × 2), 3·31 (s, OMe × 2), 3·60 (m, 2α- and 17α-H × 2). (Found: C, 71·07; H, 9·89; O, 9·23; S, 9·73. $C_{40}H_{66}O_4S_2$ requires: C, 71·22; H, 9·78; O, 9·49; S, 9·51%).

Acetylation of **11a** with Ac_2O in pyridine in the usual way, followed by recrystallization of the product from acetone gave pure **11b**, m.p. 205–207°, $[\alpha]_D^{24}$ − 67·2° (c = 1·023), ν_{max}: 1730, 1250 cm^{-1}. (Found: C, 69·69; H, 9·32; S, 8·36. $C_{44}H_{70}O_6S_2$ requires: C, 69·02; H, 9·29; S, 8·43%).

Bis(17β - hydroxy - 5α - androstan - 3α - yl) disulfide (**20a**)

To a soln of 500 mg (1 molar equiv) I_2 in 20 ml MeOH, a soln of 600 mg **19** and 400 mg (2 molar equiv) triethylamine in 20 ml MeOH–CH_2Cl_2 (1:1) was added dropwise at room temp for 10 min. The soln was stirred for 10 min and worked up in the usual way. The product was recrystallized from MeOH to afford 600 mg (quantitative) **20a**, m.p. 219–221°, $[\alpha]_D^{23}$ + 18·0° (c = 0·544), ν_{max}^{KBr}: 3436, 1054 cm^{-1}, λ_{max}^{MeOH} 250 nm (ε 380), CD(MeOH): (nm) [θ]: (300) 0, (255) − 410, (240) − 330, (210) − 7200, (201) 0. (Found: C, 72·77; H, 10·18; S, 10·09. $C_{38}H_{62}O_2S_2 \cdot CH_3OH$ requires: C, 72·40; H, 10·28; S, 9·90%).

Treatment of **20a**, with Ac_2O in pyridine overnight at room temp gave **20b**, which was recrystallized from acetone to give pure crystal, m.p. 226–228°, $[\alpha]_D^{24}$ + 24·7° (c = 0·542), ν_{max}^{KBr}: 1730, 1240 cm^{-1}. PMR (δ): 0·78 (s, 18-H × 2), 0·80 (s, 19H × 2), 2·02 (s, OAc × 2), 3·20 (m, $W_{h/2}$ = 8 Hz, 3β-H × 2), 4·60 (m, 17α-H × 2). (Found: C, 71·89; H, 9·46; S, 9·06; $C_{42}H_{66}O_4S_2$ requires: C, 72·17; H, 9·52; S, 9·16%).

Thiolsulfinate by the oxidation of disulfide

(a) *From* **11a**. To a soln of 200 mg **11a** in 5 ml CH_2Cl_2 was added 67 mg (1·3 molar equiv) *m*-CPBA and the mixture was allowed to stand for 1 h at room temp, washed with Na_2CO_3 aq and dried over Na_2SO_4. After evaporation of the solvent, the residue (180 mg) was purified by preparative TLC (CH_2Cl_2–acetone = 5:1) to afford 52 mg (26%) of the more mobile **2a** and 62 mg (30%) of the less mobile **3a**.

(b) *From* **11b**. **11b** (100 mg) was treated with 32 mg *m*-CPBA in 3 ml CH_2Cl_2 as described above and the product was purified by preparative TLC (cyclohexane-AcOEt = 2:1) to give 46 mg (45%) of the less polar **2b** and 43 mg (42%) of the more polar **3b**.

(c) *From* **20a**. A mixture of 1 g **20a** and 0·46 g *m*-CPBA in 50 ml CH_2Cl_2 was treated as described above. The product separated was washed successively with MeOH and MeOH-CH_2Cl_2 (1:1) to give 260 mg **21a**. The mother liquor gave 600 mg of the residue, which was washed with MeOH to afford 420 mg **22a** as a white powder. **21a** and **22a** were recrystallized from CH_2Cl_2 respectively. **21a**, m.p. 227–228°, $[\alpha]_D^{24}$ − 58·5° (c = 0·48), ν_{max}^{KBr}: 3605, 3465, 1064 cm^{-1}, λ_{max}^{MeOH} 253 nm (ε 2220). **22a**, m.p. 184–185°, $[\alpha]_D^{24}$ + 94·7° (c = 0·282), ν_{max}^{KBr}: 3416, 1072 cm^{-1}, λ_{max}^{MeOH} 252·5 nm (ε 2430).

(d) *From* **20b**. **20b** (250 mg) in 5 ml CH_2Cl_2 was treated with 103 mg *m*-CPBA at room temp for 30 min and worked up in the usual way. Preparative TLC (CH_2Cl_2–acetone = 30:1) of the crude product gave 100 mg (39·3%) of mobile **21b** and 95 mg (37·8%) of polar **22b**. These were recrystallized from CH_2Cl_2-MeOH and CH_2Cl_2-acetone, respectively. **21b**, m.p. 232–233°, $[\alpha]_D^{23.5}$ − 67·1° (c = 0·502), ν_{max}^{KBr}: 1731, 1250, 1063 cm^{-1}. PMR (δ): 0·78 (s, 18-H × 2), 0·84, 0·86 (each s, 19-H × 2), 2·02 (s, OAc × 2), 3·38 (m, $W_{h/2}$ = 9 Hz, 3β-H), 3·97 (m, $W_{h/2}$ = 8 Hz, 3β-H), 4·60 (m, 17α-H × 2). (Found: C, 70·66; H, 9·25; S, 8·84. $C_{42}H_{66}O_5S_2$ requires: C, 70·55; H, 9·31; S, 8·95%). **22b**, m.p. 196–198°, $[\alpha]_D^{23.5}$ + 120·2° (c = 0·495), ν_{max}^{KBr}: 1732, 1248, 1075 cm^{-1}. PMR (δ): 0·78 (s, 18-H × 2), 0·84, 0·86 (each s, 19-H × 2), 2·02 (s, OAc × 2), 3·38 (m, $W_{h/2}$ = 9 Hz, 3β-H), 4·00 (m, $W_{h/2}$ = 8 Hz, 3β-H), 4·60 (m, 17α-H × 2). (Found: C, 70·37; H, 9·30; S, 8·92. $C_{42}H_{66}O_5S_2$ requires: C, 70·55; H, 9·31; S, 8·95%).

Grignard reaction of thiolsulfinates with phenyl magnesium bromide

(a) *With* **2a**. The Grignard reagent was prepared from 54 mg Mg and 366 mg bromobenzene in 2 ml dry THF in a stream of N_2 in the usual way, and diluted with 3 ml THF. To the soln 150 mg **2a** in 10 ml THF was added dropwise over a period of 30 min at 0°; during addition an insoluble white precipitate formed. After being stirred for 2 h at the same temp, NH_4Cl aq was added to the reaction mixture and the THF was removed *in vacuo*. The residue was extracted with CH_2Cl_2. The crude product was purified by preparative TLC (CH_2Cl_2–acetone = 6:1) to give 70 mg (47·5%) of **14** as the more mobile fraction, which was recrystallized from acetone–petroleum ether, m.p. 126–128°, $[\alpha]_D^{24}$ + 41·8° (c = 0·505), ν_{max}^{KBr}: 3320, 2858, 1095 cm^{-1}. PMR (δ): 0·72 (s, 18-H), 0·94 (s, 19-H), 3·00 (s, OMe), 3·20–3·75 (br. m, 2α-, 3β-, and 17α-H). (Found: C, 70·70; H, 9·71; S, 9·41. $C_{20}H_{34}O_2S$ requires: C, 70·97; H, 10·13; S, 9·46%). The less mobile fraction afforded 88 mg (47%) of **12**, which was recrystallized from acetone to give pure crystals, m.p. 184–186°, $[\alpha]_D^{23.5}$ − 37·3° (c = 0·526), ν_{max}^{KBr}: 3395, 3050, 1090, 1075, 1055, 752 cm^{-1}. PMR (δ): 0·73 (s, 18-H), 0·97 (s, 19-H), 2·91 (m, $W_{h/2}$ = 7 Hz, 3β-H), 3·23(s, OMe),

3·65 (m, 17α-H), 3·95 (m, $W_{h/2}$ = 6 H_z, 2α-H), 7·56 (m, Ph-H). (Found: C, 72·39; H, 8·81; S, 7·55. $C_{26}H_{38}O_3S$ requires: C, 72·54; H, 8·90; S, 7·43%).

(b) *With* **3a**. The reaction of PhMgBr, prepared from 27 mg Mg and 183 mg bromobenzene, with 150 mg **3a** in the same way as described above gave 67 mg (45%) of **14** and 85 mg (45·5%) of **13**, which was recrystallized from acetone to afford pure crystals, m.p. 176–177°, $[\alpha]_D^{23.5}$ + 107·3° (*c* = 0·494), ν_{max}^{KBr}: 3365, 3050, 1090, 1077, 1022, 750 cm^{-1}. PMR (δ): 0·74(s, 18-H), 0·94 (s, 19-H), 3·05 (s, OMe), 2·85–3·30 (m, 2α- and 3β-H), 3·65 (m, 17α-H), 7·56 (m, Ph-H). (Found: C, 72·68; H, 8·63; S, 7·52. $C_{26}H_{38}O_3S$ requires: C, 72·54; H, 8·90; S, 7·43%).

2β - Methoxy - 3α - phenylsulfonyl - 5α - androstan - 17β - ol (**15**)

A mixture of 50 mg **12** or **13** in 2 ml CH_2Cl_2 25 mg (1·5 molar equiv) *m*-CPBA was allowed to stand at room temp for 30 min. Usual work-up gave 50 mg (nearly quantitave) of **15**, which was recrystallized from acetone to yield pure crystals, m.p. 233–235°, $[\alpha]_D^{23.5}$ + 18·5° (*c* = 0·514), ν_{max}^{KBr}: 3483, 3085, 1303, 1145, 1075, 1052, 737 $^{-1}$. PMR (δ): 0·74 (s, 18-H), 0·92 (s, 19-H), 3·10 (s, OMe), 3·30 (m, $W_{h/2}$ = 8 H_z, 3β-H), 3·65 (m, 17α-H), 3·86 (m, 2α-H), 7·50–8·00 (m, Ph-H). (Found: C, 70·10; H, 8·69; S, 7·12. $C_{26}H_{38}O_4S$ requires: C, 69·93; H, 8·58; S, 7·17%).

2β - Methoxy - 3α - acetylthio - 5α - androstan - 17β - ol acetate (**16**)

Treatment of **14** with Ac_2O in pyridine overnight at room temp gave **16**, which was recrystallized from acetone to yield pure crystals, m.p. 118–120°, $[\alpha]_D^{23.5}$ + 24·6° (*c* = 0·395), ν_{max}^{KBr}: 1731, 1720, 1697, 1252, 1130, 625 cm^{-1}. PMR (δ): 0·76 (s, 18-H), 0·95 (s, 19-H), 2·02 (s, OAc), 2·31 (s, SAc), 3·33 (m, 2α-H), 3·38 (s, OMe), 4·00 (m, $W_{h/2}$ = 7 H_z, 3β-H), 4·60 (m, 17α-H). (Found: C, 68·11; H, 8·99; S, 7·61. $C_{24}H_{38}O_4S$ requires: C, 68·22; H, 9·07; S, 7·57%).

Isomerization of thiolsulfinates **2a** *and* **3a**

100 mg of **2a** or **3a** was dissolved in conc HCl-THF-MeOH (1:3·5:3·5) and allowed to stand overnight at room temp. The mixture was treated in the usual way and the product was purified by preparative TLC (CH_2Cl_2–acetone = 5:1) to give each 47 mg of **2a** and **3a** in both cases.

Thiolsulfinates from 3α - mercapto derivatives

(a) *From* **14**. To a soln of 200 mg **14** in 20 ml CCl_4 was added dropwise Br_2-CCl_4 soln at 0° until the color of Br_2 remained. The mixture was stirred at the same temp for 5 min then concentrated to dryness under reduced pressure at below room temp. Residual yellow solid was dissolved in aqueous THF and the soln was stirred at room temp for 5 min. The product was purified by preparative TLC (CH_2Cl_2-acetone = 5:1) to give 130 mg (65%) of **11a**, 16 mg (8%) of **2a**, and 43 mg (21%) of **3a**.

(b) *From* **19**. 250 mg **19** in 30 ml CCl_4 was treated successively with Br_2 and aqueous THF as described above. The same work-up afforded 157 mg (63%) of **20a**, 10 mg (4%) of **21a**, and 25 mg (10%) of **22a**.

Acknowledgement—The authors express their deep gratitude to Dr. K. Kuriyama for discussion on CD spectra.

REFERENCES

[1]Thiosteroids XXXIV. T. Komeno and H. Itani, *Chem. Pharm. Bull.* **21**, 335 (1973)
[2]W. E. Savige, J. Eager, J. A. Maclaren and C. M. Roxburgh, *Tetrahedron Letters* 3289 (1964)
[3]W. E. Savige and A. Fava, *Chem. Commun.* 417 (1965)
[4]L. Sagramora, P. Koch, A. Garbesi and A. Fava, *Ibid.* 985 (1967)
[5]J. L. Kice and G. B. Large, *Tetrahedron Letters* 3537 (1965); *J. Am. Chem. Soc.* **90**, 4069 (1968)
[6]T. Miyake and K. Takeda, *Except. Med. Int. Cong. Series* **132**, 616 (1966)
[7]Y. Nakamura, H. Otsuka and T. Komeno, *Ann. Rept. Shionogi Res. Lab.* **20**, 152 (1970)
[8]C. R. Johnson and D. McCants, Jr., *J. Am. Chem. Soc.* **87**, 1109 (1965); C. R. Johnson, H. Diefenbach, J. E. Keiser and J. C. Sharp, *Tetrahedron* **25**, 5649 (1969)
[9]H. Koyama and H. Nakai, to be published
[10]K. Kondo, A. Negishi and I. Ojima, *J. Am. Chem. Soc.* **94**, 5786 (1972)
[11]K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons and A. L. Ternay, Jr., *Ibid.* **87**, 1958 (1965)
[12]D. N. Jones and M. J. Green, *J. Chem. Soc.* (C) 532 (1967)
[13]H. F. Herbrandson and C. M. Cusano, *J. Am. Chem. Soc.* **83**, 2124 (1961); K. K. Andersen, *Tetrahedron Letters* 93 (1962); K. K. Andersen, W. Gaffield, N. E. Papanikolaou, J. W. Foley and R. I. Perkins, *J. Am. Chem. Soc.* **86**, 5637 (1964); M. Kobayashi and M. Terao, *Bull. Chem. Soc. Japan.* **39**, 1343 (1966)
[14]C. J. Stirling, *J. Chem. Soc.* 5741 (1963)
[15]P. Dembech, P. Vivarelli, V. Jehlicka and O. Exner, *Ibid.* Perkin II 488 (1973)
[16]E. Vinkler and F. Klivenyi, *Acta Chim. Acad. Sci. Hung.* **11**, 15 (1957)
[17]J. L. Kice and J. P. Cleveland, *J. Am. Chem. Soc.* **92**, 4757 (1970); *Ibid.* **95**, 104 (1973)
[18]E. Vinkler, F. Klivenyi and E. Klivenyi, *Acta Chim. Acad. Sci. Hung.* **16**, 247 (1958)