

STEROIDS HAVING SULFUR-SUBSTITUENT GROUPS*

Ken'ichi Takeda

Shionogi Research Laboratory, Shionogi & Co., Ltd.,

Fukushima-ku, Osaka, 553 Japan

A study was made of various methods for introducing a sulfur function into a steroid for the purpose of synthesizing cortisol having its 11β -hydroxyl replaced by a thiol group.

While our efforts failed to yield the target compound, introduction of the sulfur function led to some interesting observations which we would like to report here.

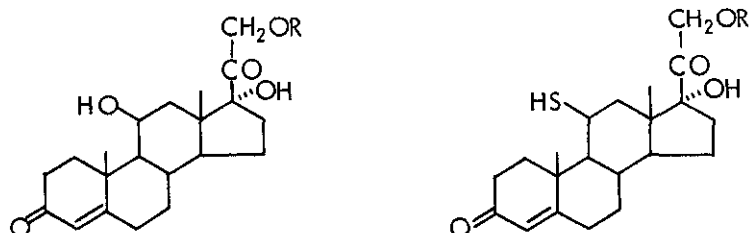
- I. Introduction
- II. Substitution of 16-bromo-17-oxosteroids
- III. Introduction of sulfur through the opening of an epoxy ring
- IV. Properties of the thiocyanato hydrin and episulfide ring
- V. Other reactions
- VI. Conclusion

* This paper was presented as the Presidential address at the 96th Annual Meeting of the Pharmaceutical Society of Japan at Nagoya, on April 5, 1976

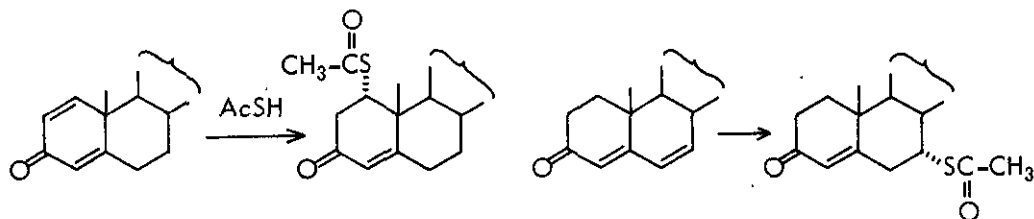
1. Introduction

In around 1950, a method was found for separating diosgenin from a Mexican species of *Dioscorea* in high yield and this opened up a way for the highly economical synthesis of steroid hormones. Also, as corticosteroids could be readily synthesized from diosgenin or hecogenin, the use of this hitherto expensive compound as a therapeutic drug become possible.

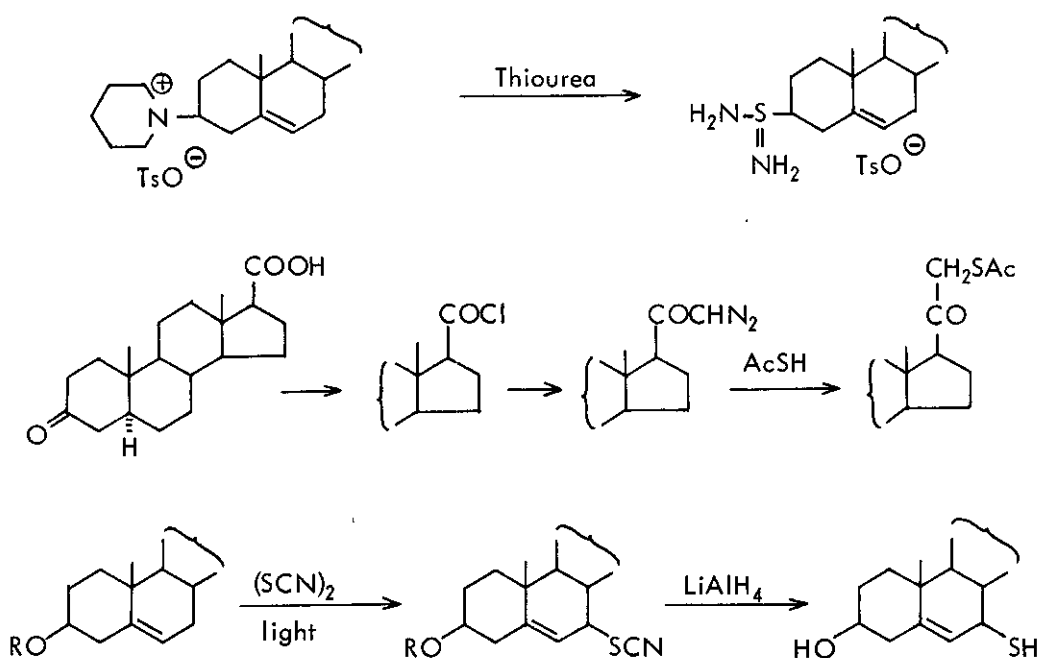
It was this achievement that prompted us to attempt a new modification of cortisol by replacing the 11β -hydroxyl group, which was known to be essential for its biological activity, with an 11β -thiol group.



At that time the literature dealing with introduction of a sulfur function into a steroid was quite limited; there was known the addition of thiolacetic acid to dienone,¹ substitution of 3-pyridinium tosylate with thiourea,² and synthesis of 21-acetylthio-5 α -pregnane-3,20-dione through reaction of thiolacetic acid on diazoketone.³ Frederiksen



et al.⁴ had also reported that the irradiated reaction of cholesterol with thiocyanogen, a pseudohalogen, gave 7-thiocyanate which in turn was reduced to 7-thiol.

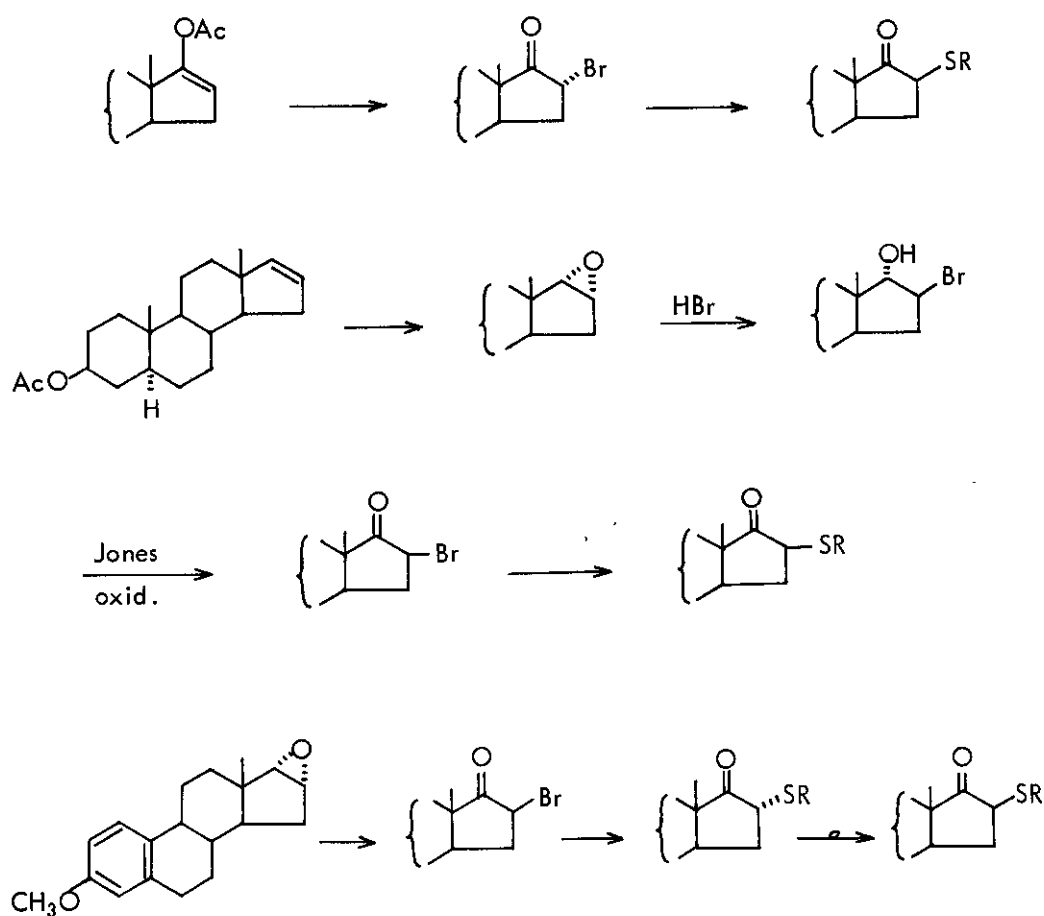


All attempts to obtain the compound having a sulfur function at C₁₁-position, for instance, addition of thiocyanogen to a 9(11)-olefin or replacement of 11a-ol tosylate by a sulfur nucleophile, were unsuccessful, perhaps due to severe steric hindrance at the 11 position of the steroid. We therefore next examined the reaction between 16-bromide and a sulfur nucleophile.

II. Substitution of 16-bromo-17-oxosteroids

We first tried the substitution reaction of alkylthiol or thiolacetic acid on 16-bromo-17-oxosteroids,^{5,6} with which there appeared to be little risk of steric hindrance. With 16 α -bromo-17-oxosteroid of either the estrane or androstane type, substitution reactions with these reagents afforded acetylthio and alkylthio derivatives of inverted β -configuration. When the reaction was carried out on 16 β -bromoandrostane-17-one,

however, the products were invariably 16β -alkylthio or acetylthio derivatives of retained configuration. On the contrary, similar reaction of 16β -bromoestrone with an aromatized A-ring resulted in formation of the corresponding alkylthio or acetylthio derivative of inverted α -configuration, which could be isolated by recrystallization as a pure substance.⁷



R = Ac or Alkyl

The α -substitution product of the estrane type compound, however, could be epimerized fairly easily to the β -isomer. NMR studies on the androstane compound re-

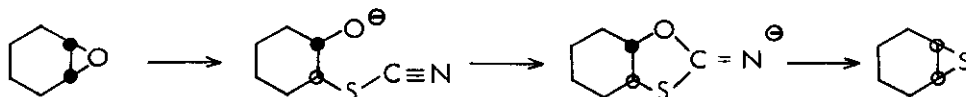
vealed that the reaction of 16 β -bromide at low temperature proceeds first to form a product having an α -substituent of inverted configuration and that thermal and base-catalyzed epimerization takes place at room temperature. An explanation for this is that an aromatic A-ring will exert influence even as far as the 16- and 17-positions to affect the conformational mobility there, and thus higher stability is conferred on the α -derivative in the estrane compound than in the androstane one. It is quite noteworthy that the A-ring has influence extending to the D-ring.

As the failure of our attempt at substitution at the 11-position was attributable to steric hindrance, we decided to try further possibilities.

III. Introduction of sulfur through the opening of an epoxy ring

(a) Ring opening with the use of thiocyanic acid

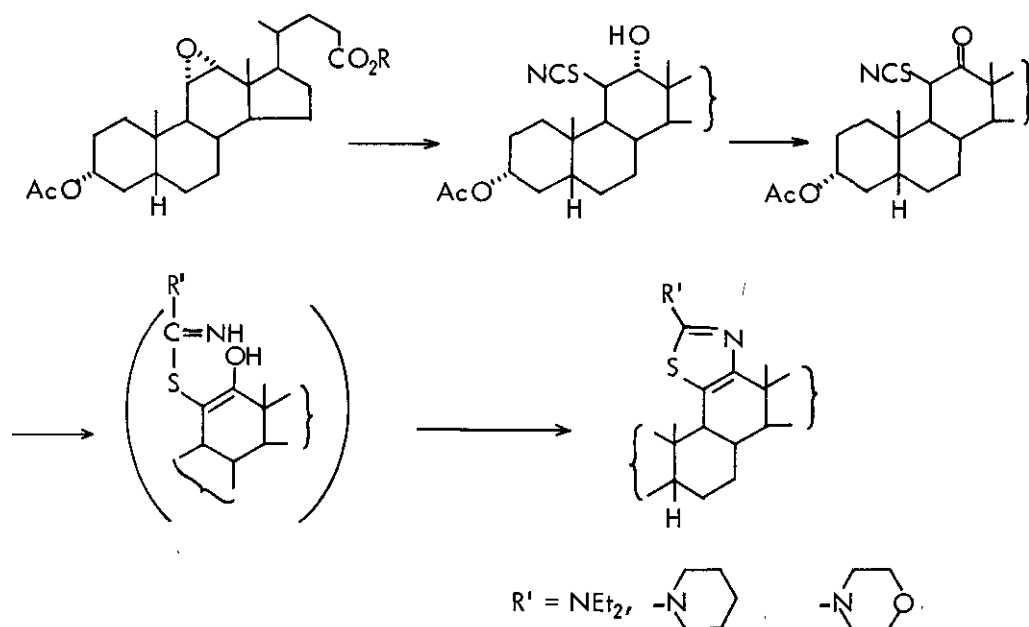
E. E. van Tamelen⁸ reported that he obtained an episulfide via a thiocyanato hydrin through treatment of cyclohexan-oxide with alkali thiocyanates. With steroidal 2,3-epoxide, however, this reaction gave episulfide only in poor yield. We therefore



studied the opening of an epoxy ring at various positions in a steroid by treatment with thiocyanic acid.

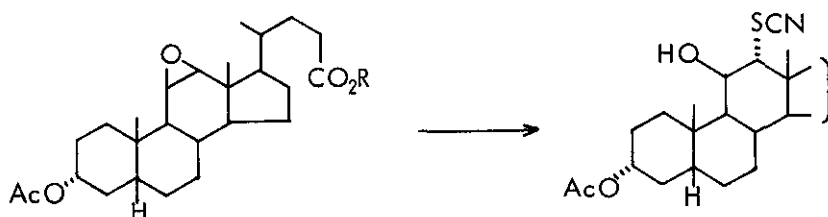
We first examined on a reaction of 11 α ,12 α -epoxide for introduction of thiocyanate at 11 β , and obtained 11 β -thiocyanato-12 α -ol through trans-diaxial opening of the ring. Treatment of this with an alkali regenerated the parent epoxide. The structure

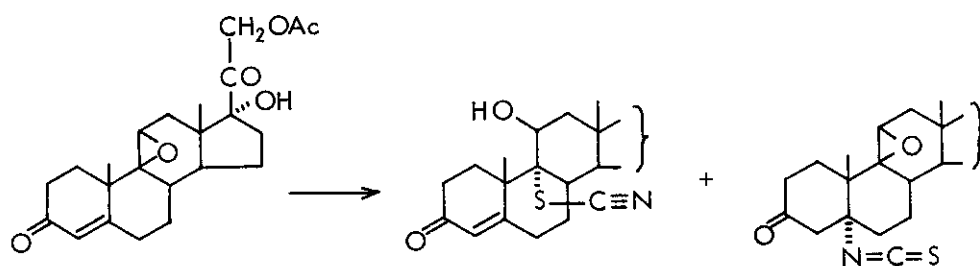
of the thiocyanato hydrin was confirmed by oxidation and desulfurization leading to the known 12-oxocholanic acid. The intermediate, thiocyanato ketone, on treatment with secondary amine was found to afford a steroidal thiazole fused at 11- and 12-positions.⁹



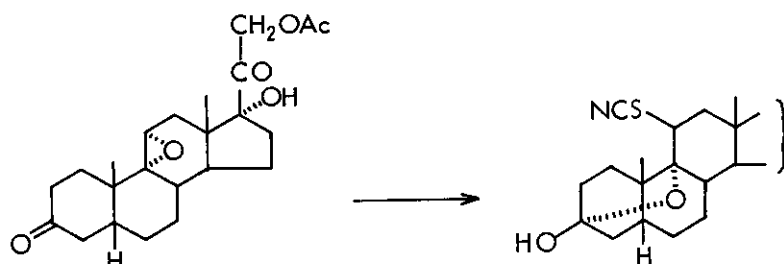
Similarly the 11 β ,12 β -epoxide afforded 11 β -hydroxy-12 α -thiocyanate.

Treatment of 9 β ,11 β -epoxide with thiocyanic acid gave 9 α -thiocyanato-11 β -ol, but the same treatment in the presence of a Δ^4 -3-one system afforded a compound with an isothiocyanato group attached at the 5 α -position.¹⁰



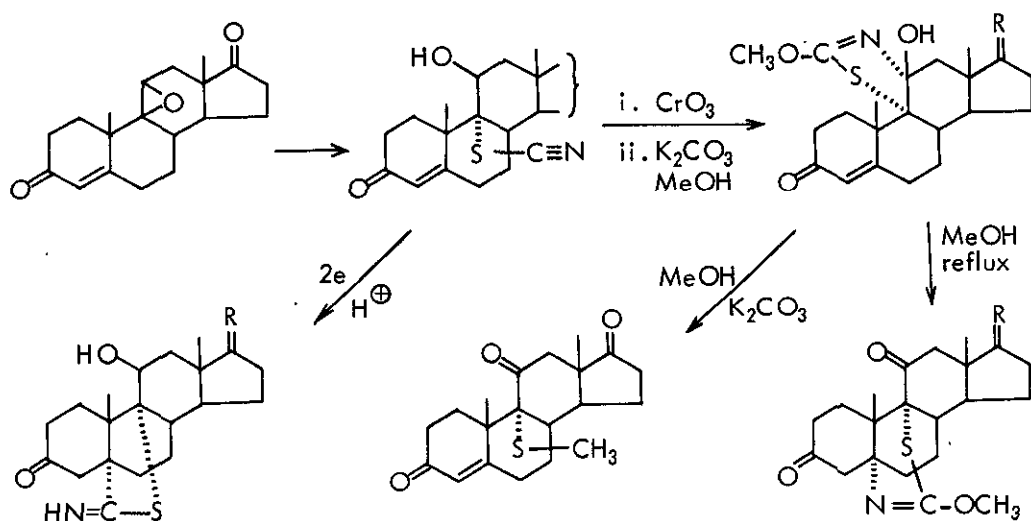


At almost the same time Mosettig and Kawasaki of NIH, U. S. A., who were probably aiming at synthesis of the same target compound as ours, reported successful ring opening of 9β,11β-epoxide with the use of thiocyanic acid.¹¹ They also found that with 9α-hydroxy-11β-thiocyanate, obtained through reaction with 3-oxo-9α,11α-epoxy 5β-steroids, there was formed a hemi-ketal bond between the 9α-hydroxyl group and the 3-ketone.

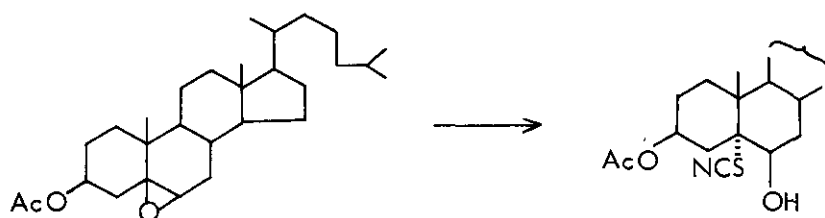


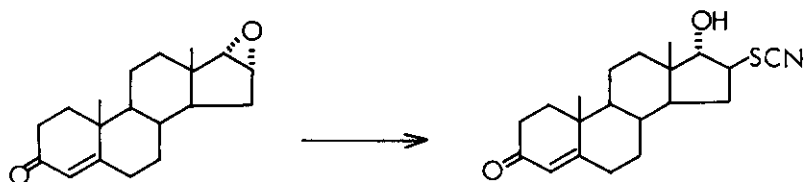
Meanwhile, Mosettig¹² in his joint study with Kitagawa, Ueda, and Kawasaki applied the same reaction to Δ⁴-3-oxo-9β,11β-epoxy steroid and oxidized the hydroxyl group at the 11-position in the resulting thiocyanato hydrin to ketone. He found that the subsequent treatment of the ketone with potassium carbonate in aqueous methanol gave a thiazolino derivative. Further treatment under the same conditions gave a 9α-methylthio derivative. He also reported that reflux of the thiazolino derivative in methanol solution afforded a thiazino derivative, the 6-membered ring arising through

opening of the thiazolino ring with simultaneous addition of the imino group to the conjugated enone. In a similar experiment we obtained a 5 α -carboimide derivative through electrolytic reduction of Δ^4 -3-oxo-9 α -thiocyanato-11 β -hydroxy steroid.¹³ This derivative could be converted into thiolactone by hydrolysis with hydrochloric acid.

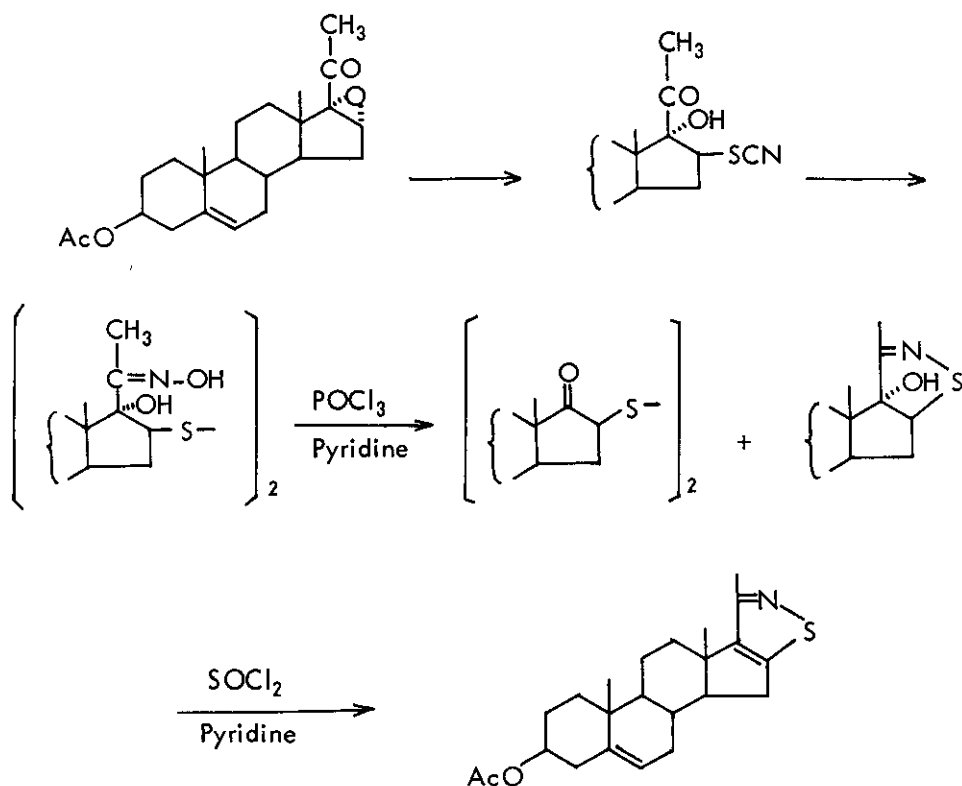


Epoxide rings at other positions, too, were opened by treatment with thiocyanic acid, to afford 5 α -thiocyanato-6 β -ol in the case of 5 β ,6 β -epoxide, 6 β -thiocyanato-5 α -ol in the case of 5 α ,6 α -epoxide¹⁴ and 16 β -thiocyanato-17 α -ol in the case of 16 α ,17 α -epoxide,¹⁵ each invariably in high yield.

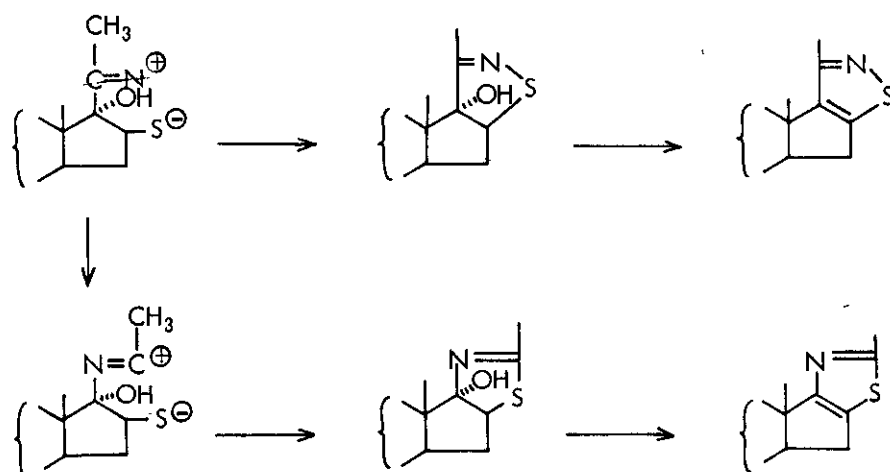




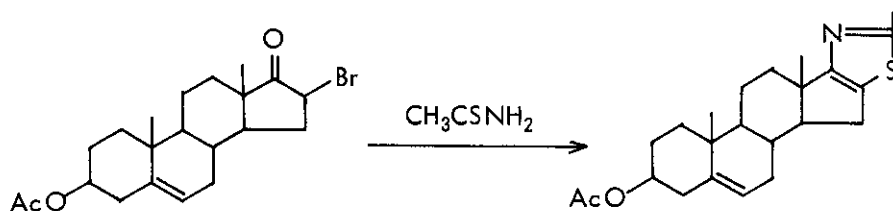
A similar experiment was also made with a pregnane derivative having an acetyl side chain at the 17-position, and the reaction that took place was exactly the same. The 16 β -thiocyanato-17 α -hydroxypregnenolone thus obtained was treated with hydroxylamine affording a mixture of 16-mercapto-20-oxime and its dimer. Beckmann rearrangement of the mixture with POCl₃-pyridine gave a 16-mercapto-17-one dimer and a by-product thought to arise from ring closure.¹⁵ Reduction of the dimer with LiAlH₄ afforded



16 β -mercapto-17 β -ol. Dehydration of the above byproduct gave a heteroaromatic compound, and in the course of its formation isothiazole should be obtained if the ring is closed prior to the Beckmann rearrangement, while ring closure after the Beckmann rearrangement should give a thiazole derivative. To identify its structure, therefore,



we treated 16 β -bromo-17-ketone with thioacetamide by the usual method for formation of a thiazole ring, and found that the resultant product was different from the heteroaromatic byproduct. On the basis of this observation and further study of physical properties we proved that it was an isothiazole derivative.¹⁶

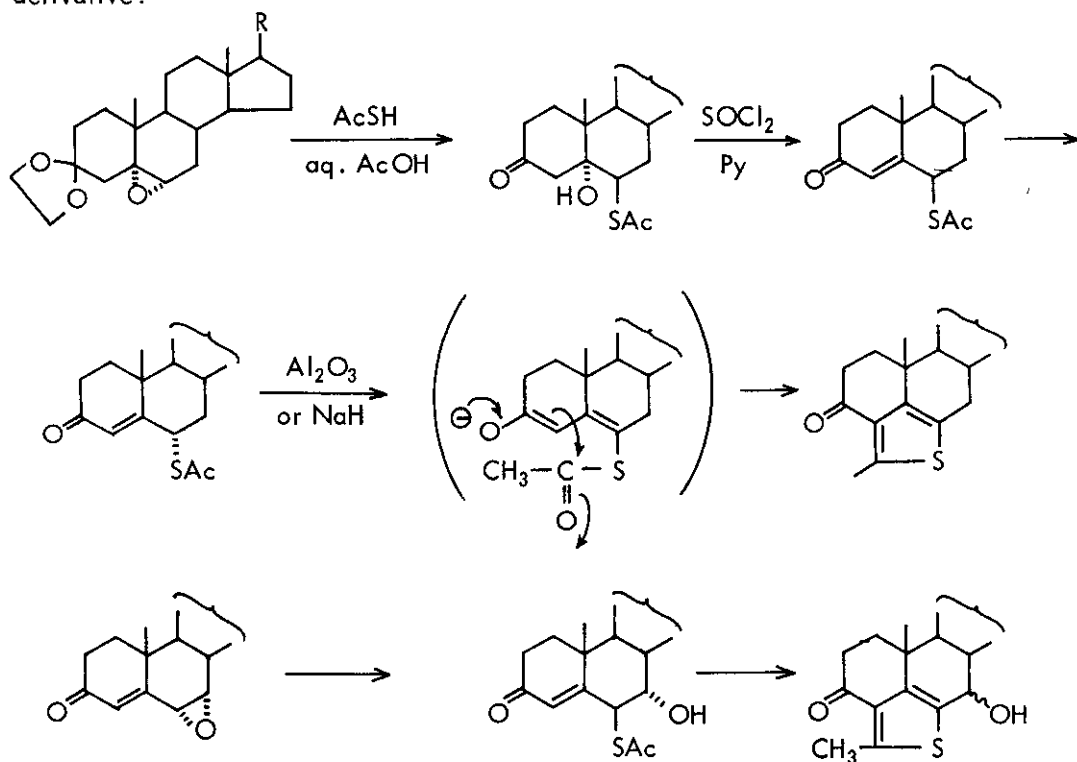


(b) Opening of epoxy ring with thiolacetic acid

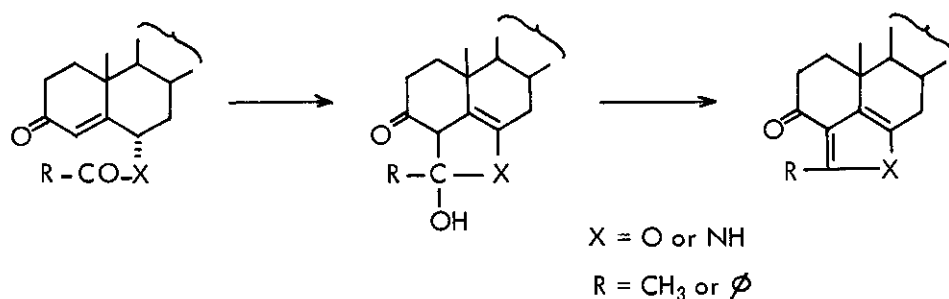
The opening of an epoxy ring is possible not only with thiocyanic acid but also with

thiolacetic acid. For instance, the 6 β -acetylthio-5 α -ol derivative can be obtained by opening the 5 α ,6 α -epoxide of cholesteryl acetate with thiolacetic acid.

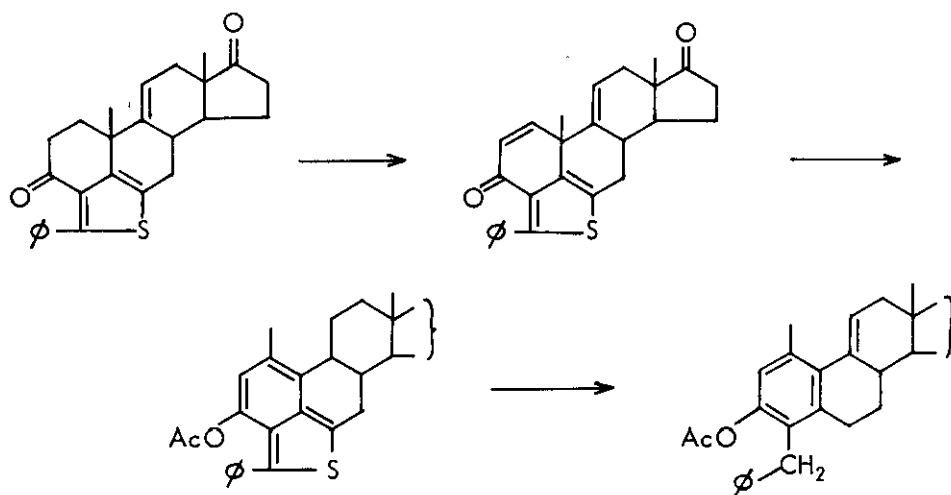
This reaction is also applicable to 3,3-ethylenedioxy-5 α ,6 α -epoxide. Ring opening of the compound with thiolacetic acid, followed by hydrolysis of the ketal moiety and dehydration with SOCl₂-pyridine gave 6 β -acetylthio-4-en-3-one, which was isomerized to 6 α -acetylthio-4-en-3-one with an acid. Further treatment of this product with alumina or sodium hydride causes intramolecular dehydration-cyclization between the 4- and 6-positions of the steroid with formation of a thiophene derivative.¹⁷ With 6 α ,7 α -epoxypregn-4-ene-3,20-dione a thiophene derivative can be obtained as a product of intramolecular cyclization by a similar route through the 6 β -acetylthio-7 α -hydroxy derivative.¹⁸



This cyclization reaction is similarly applicable to compounds having a 6 α -benzoylthio, 6 α -acetoxy, 6 α -benzoyloxy or 6 α -acetylamino group as substituent at the 6-position to afford the corresponding phenylthiopheno, methylfurano, phenylfurano or methylpyrrolo derivative.¹⁹



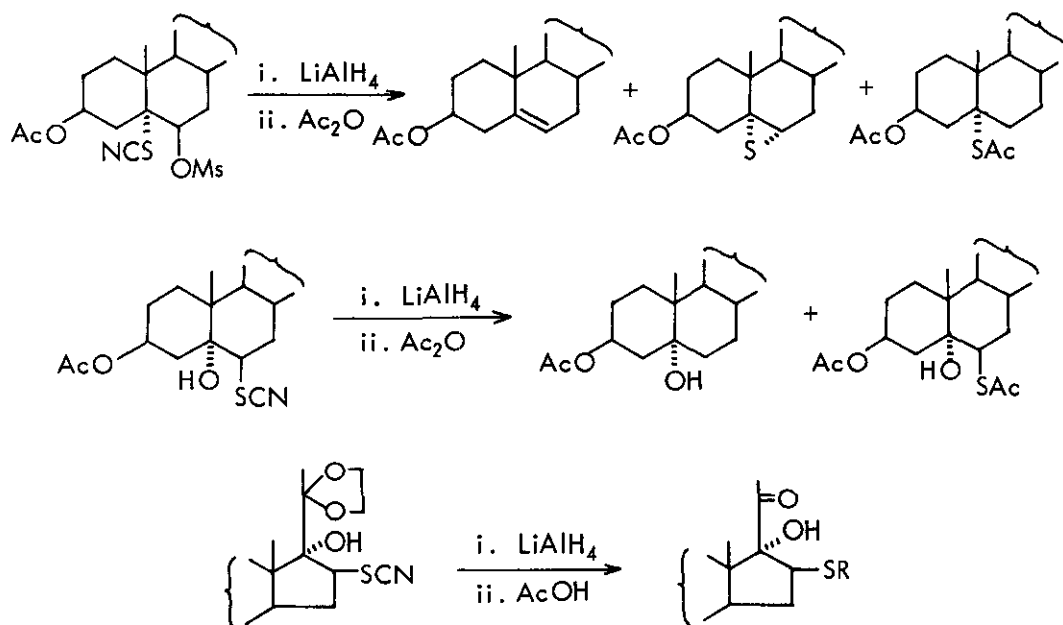
When the fused $\Delta^{1,9(11)}$ -bisdehydro derivative of phenylthiophene is treated with boron trifluoride in acetic anhydride-acetic acid, aromatization of the A-ring readily occurs, with migration of methyl at the 10-position and formation of a benzo-c-thiophene derivative. In order to clarify the structure of this compound, this was converted to 1-methyl-4-benzyl- $\Delta^{9(11)}$ -dehydroestrone acetate by desulfurization, but no maleic anhydride addition product known to be characteristic of such structure was obtainable.²⁰



IV. Properties of the thiocyanato hydrin and episulfide ring

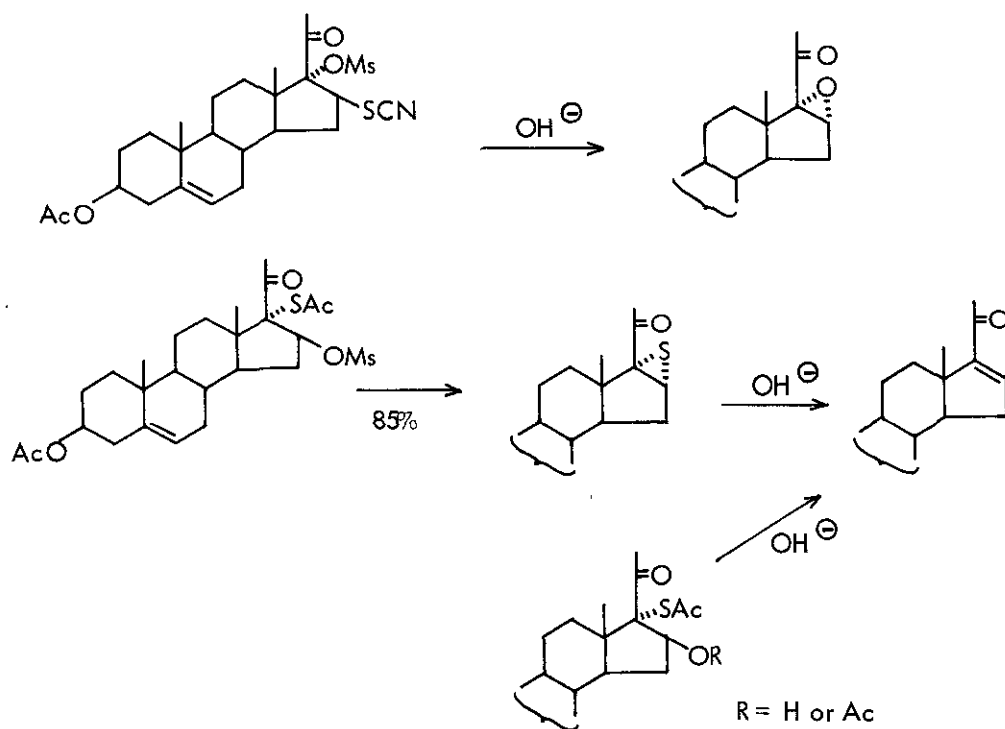
(a) Some reactions of thiocyanato hydrin

LiAlH_4 reduction of thiocyanato hydrin itself, or its derivatives in which the hydroxyl group is mesylated or substituted by halogen should yield the respective thiol derivatives. In fact, treatment of 5 α -thiocyanato-6 β -ol-mesylate with LiAlH_4 followed by acetylation gave cholesteryl acetate, episulfide, and the target compound 5 α -thiol acetate in roughly equal amounts. Similarly, 5 α -hydroxy-6 β -thiol and 5 α -hydroxy derivatives are obtainable from 5 α -hydroxy-6 β -thiocyanate.¹⁴

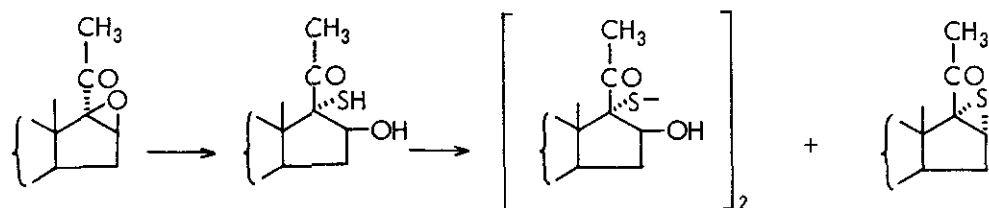


A similar reaction is also utilized with the 20-ethylene ketal compound of 16 β -thiocyanato-17 α -hydroxy-5 α -pregnan-20-one to afford a 16 β -thiol-17 α -hydroxy derivative.¹⁵ Chemists in the U.S.S.R.²¹ have recently been studying similar reactions at the 16- and 17-position in greater detail, and, for instance, it has been reported by A. V.

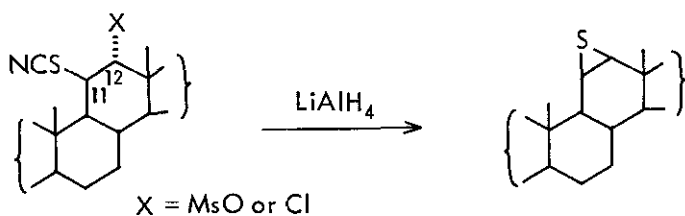
Kamernitskii et al.^{21e} that the 16 β -thiocyanato-17 α -mesyloxy compound affords α -epoxide when treated with a base, whereas the 16 β -mesyloxy-17 α -acetylthio compound gives 16 α ,17 α -episulfide. On the other hand, 16 β -hydroxy or 16 β -acetoxy derivatives give the 16,17-unsaturated compound with a base.



H. Hofmeister et al. of Schering AG, Germany²² subjected 17 α -pregnenolone-16 β ,17 β -epoxide and analogous compounds having a modified A-ring to ring opening with hydrogen sulfide and subsequently treated the resultant 16 β -hydroxy-17 α -thiol derivative with mesyl chloride under heating in pyridine to obtain 16 α ,17 α -episulfide and S-dimer.

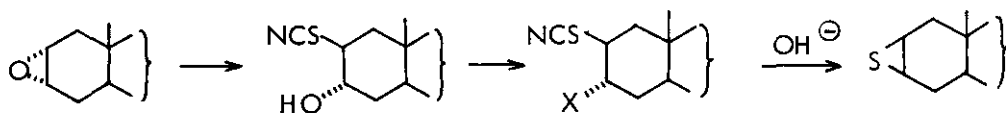


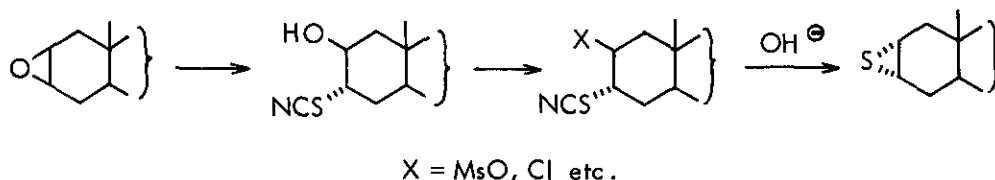
Things are, however, somewhat different with the 11 β -thiocyanato-12 α -hydroxy compound, from which 11 β ,12 β -episulfide only could be obtained; neither was the thiol derivative obtainable even by treatment of the 12 α -ol mesylate or 12 α -chloride with LiAlH_4 .²³



(b) Synthesis of episulfide

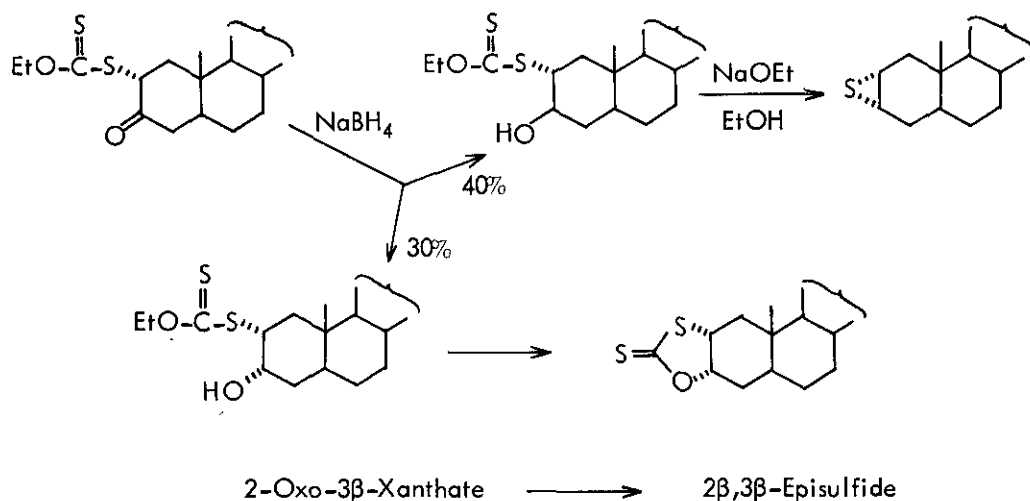
Before attempting reductive ring opening of episulfide we first studied methods for synthesizing the latter. As already mentioned, the general method involves 3-step conversions; ring opening of epoxide with thiocyanic acid, mesylation or halogenation of the formed hydroxyl group, and then treatment of the product with an alkali. In the course of this procedure double inversion of configuration takes place with resultant formation of β -episulfide from α -epoxide and α -episulfide from β -epoxide at the same position.





Among the thiocyanato hydrins at various positions which we studied, 2,3-thiocyanato hydrin alone could be converted into episulfide in a high yield simply by direct alkali treatment.²⁴ On the other hand, in the case of thiocyanato hydrin at positions 3 and 4 on the steroidal A-ring, only regeneration of epoxide occurred under the same conditions. From these facts it appears that conformational interconversion of the A-ring, especially at the 2- and 3-positions, should be very similar to that of the cyclohexane ring itself. For instance, the 2,3-mercapto-ol derivative having either 2 β -O, 3 α -S or 2 β -S, 3 α -O configuration which are both in diaxial relation to each other is able to form the corresponding acetonide under mild conditions.

Another known method for synthesis of episulfide is that utilizing oxo-xanthate.²⁵



This is not very favorable in terms of yield since, while reduction of the ketone with sodium borohydride and subsequent treatment with sodium ethoxide results in conversion to episulfide of the reduced compound having an equatorial hydroxyl group, the compound with an axial configuration is converted into an oxathiolane derivative. This method is, however, applicable to synthesis of labile compounds such as cholest-4-en-2 α ,3 α -episulfide.²⁶ Similarly 2-oxo-3 β -xanthate is converted to 2 β ,3 β -episulfide.

Recently Guy et al.²⁷ reported that they could obtain 2 α ,3 α -episulfide by alkali treatment of 2 β -chloro-3 α -thiocyanate produced through reaction of 5 α -cholest-2-ene with thiocyanogen chloride. Using this method we carried out synthesis of various methyl-substituted episulfides from methyl-substituted 5 α -androst-2-en-17 β -ol.²⁸

There are also reports dealing with the reaction of iodine thiocyanate on 5 α -cholest-2-ene,²⁹ and with the treatment of 5 α -cholestan-2 α ,3 α -epoxide with phosphine sulfide and trifluoroacetic acid,³⁰ both yielding 2 β ,3 β -episulfide.

(c) Properties of the episulfide ring

The results of our various experiments on the reductive ring opening of 11 β ,12 β -episulfide are shown in Table 1. They show that practically no reaction takes place under mild conditions, while treatment under drastic conditions effects desulfurization with resultant formation of an unsaturated compound.²³ Treatment with Raney nickel in dioxane affords a saturated compound through desulfurization and reduction, while treatment with *p*-toluenesulfonic acid and acetic anhydride gives $\Delta^9(11)$ -12 β -thiol acetate.³¹ Thus, our attempts at reductive ring opening of 11 β ,12 β -episulfide were unsuccessful. We considered that this failure was attributable to steric hindrance, so we next studied the possibility of reductive ring opening of episulfides at various other positions.

Table 1. Ring Opening Reactions with 11 β ,12 β -Epithio Ring

Reagent	Product
HCl-dioxane, HBr-dioxane, Na-amalgam, Na ₂ S, CrCl ₂ , H ₂ /Pt, LiAlH ₄ in THF or Bu ₂ O, LiAlH ₄ -AlCl ₃	No reaction
HBr-AcOH, Zn-AcOH, Clemmensen- reduction Na-MeOH, Li-EtNH ₂ -liq. NH ₃ , I ₂ -EtOH	Δ^{11} -ene
Ni-dioxane	Desulfurized saturated compound
Ac ₂ O-pTsOH in AcOH	$\Delta^{9(11)}$ -ene-12 β -SAc

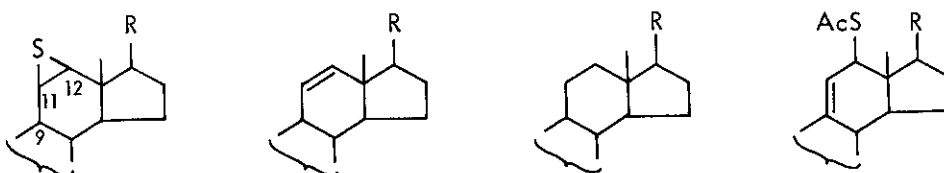


Table 2-a¹⁴ shows the results of reduction of 5 α ,6 α -episulfide with LiAlH₄, while in Table 2-b^{24b} are given the results of ring opening reactions conducted with 2 α ,3 α - and 2 β ,3 β -episulfides with the same reagent.

As seen from the tables, the reactions are invariably accompanied by formation of desulfurized unsaturated compounds, and the yields of the respective reaction products depend on the nature of the solvent used as well as on the reaction conditions. In the reductive ring opening with LiAlH₄, the mode of ring opening varies according to the

Table 2. Reductive Ring Opening of Episulfide with LiAlH_4 a. Ring Opening of 5 α ,6 α -Epithio-5 α -cholestane

Solvent	Recovered material	$\Delta^{5(6)}$ -ene	5 α -Thiol compd.
Ether (reflux)	53	36	1
Ether : THF (1 : 1) (r.t.)	51	37	1
Ether : THF (1 : 1) (reflux)	7	39	35

b. Ring Opening of 2,3-Epithio-5 α -cholestane

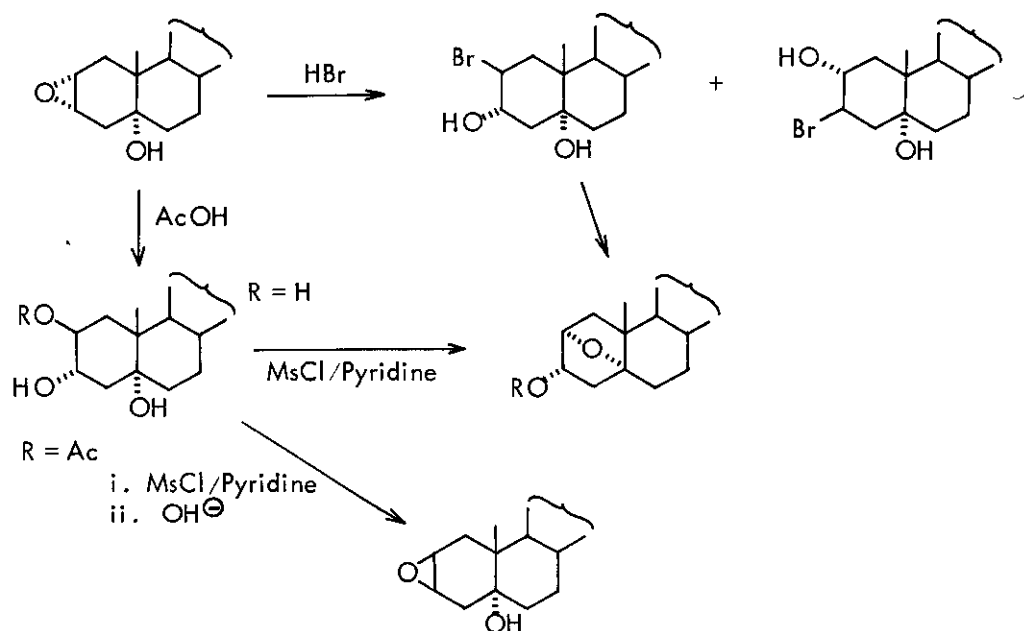
Compound	Solvent	Recovered material	Δ^2 -ene	Thiol compd.
2 β ,3 β	Ether : THF (1 : 1)	-	16	60 (2 β)
2 α ,3 α	"	62	17	-
2 α ,3 α	THF	-	42	40 (3 α)

position and configuration of the epithio ring, while optimum conditions vary according to the individual compounds.

V. Other reactions

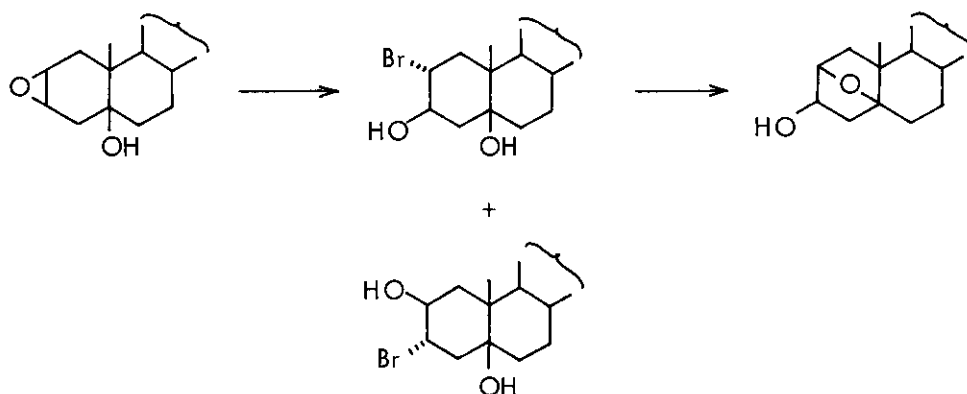
(a) Synthesis of 2,5-bridged compound

In the process of converting 5 α -hydroxy-2 α ,3 α -epoxide into 5 α -hydroxy-2 β ,3 β -epoxide for the intended synthesis of 5 α -hydroxy-2 α ,3 α -episulfide we obtained 2 α ,5 α -oxygen-bridged compound as an unexpected byproduct.³² Being interested in this reaction, we studied it closely and found that prolonged treatment of 5 α -hydroxy-2 α ,3 α -epoxide with HBr in a two phase CH_2Cl_2 solution system afforded 3 α -hydroxy-2 α ,5 α -

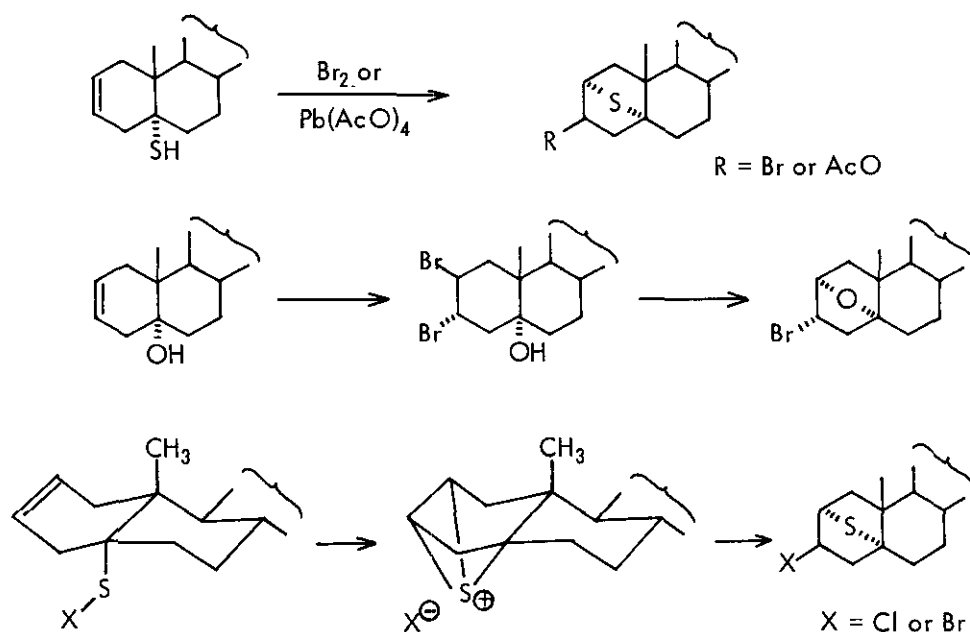


epoxide accompanied by a small amount of 3 β -bromo-2 α ,5 α -diol through transient formation of 2 β -bromo-3 α ,5 α -diol.

A similar reaction with 5 β -hydroxy-2 β ,3 β -epoxide gave the 3 β -hydroxy-2 β ,5 β -epoxy compound, accompanied by formation of a fairly large quantity of diequatorial bromohydrin, presumably due to the intramolecular hydrogen bonding in the parent epoxide.



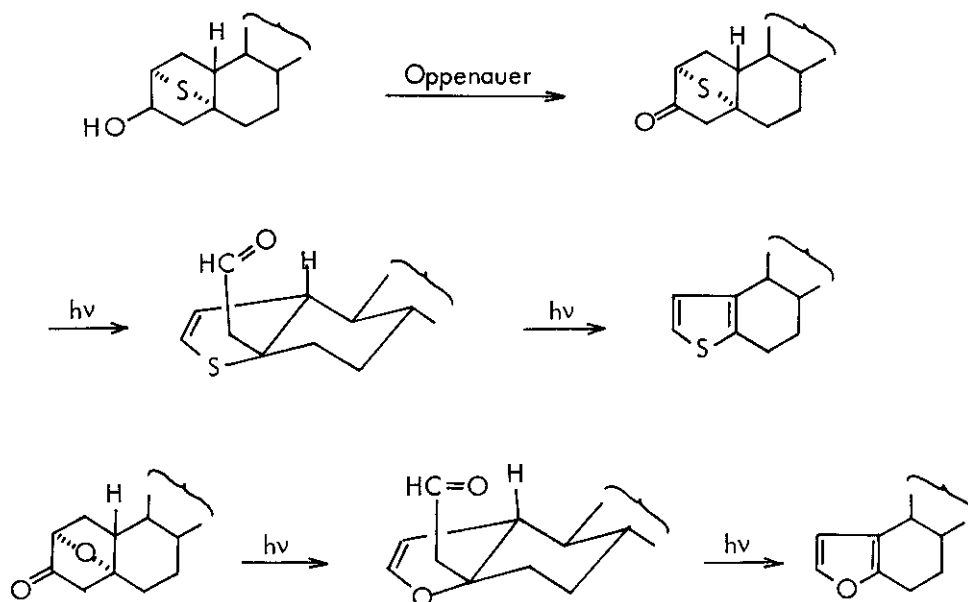
Various experiments were next performed in anticipation that the use of 5 α -thiol derivatives would afford 2 α ,5 α -episulfides, and the results revealed that the most efficient route to 3 β -substituted 2 α ,5 α -episulfide was to treat Δ^2 -ene-5 α -thiol derivative³³ with bromine or lead tetraacetate, this at the same time representing the shortest route. Similar treatment of Δ^2 -5 α -hydroxy steroid with Br₂ gave the 3 α -bromo-2 α ,5 α -epoxy compound. The 2 α ,5 α -episulfide compound synthesized from the 5 α -thiol derivative has its substituent at the 3-position in β -configuration, this presumably having resulted from addition of sulfenyl halide occurring in the course of the reaction to the double bond with resultant formation of episulfonium halide and substitution in the next stage by halogen anion from the β -side.³⁴ Reaction of lead tetraacetate on Δ^2 -5 α -thiol steroid resulted in introduction of an acetoxy group into the 3 β -position. Hydrolysis of the compound, followed by Oppenauer oxidation gave a 3-keto derivative.



(b) Photo-chemical reaction with 2,5-bridged compound

The reaction described above, when applied to 19-norsteroid, affords 19-nor-3 β -hydroxy-2 α ,5 α -episulfide. Oppenauer oxidation of this to 3-ketone and subsequent irradiation bring about α -fission at the C₂-C₃ bond yielding the 5-formylmethyl-3-thia-A-norestr-1-ene derivative. It also gives rise to δ -H abstraction and resultant elimination of acetaldehyde with formation of a thiophene ring.

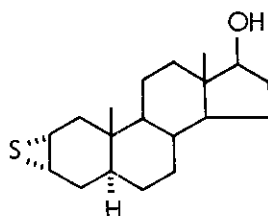
Similar treatment of 19-nor-3-oxo-2 α ,5 α -epoxide compound affords the steroid with a furan ring, although the yield is low.³⁴



VI. Conclusion

Despite all the experiments which we have described above, our attempts to synthesize the 11 β -thiol analogue of cortisol were unsuccessful, and this report is consequently rather inconclusive. This disappointment has, however, awakened us anew to the com-

plicated nature of steroid chemistry, such as dependence of chemical properties of the episulfide ring according to its position and configuration, and steric influence by environment around the steroid nucleus. Further, it should be mentioned that in examining the hormonal activity of these sulfur-containing steroids it was discovered that 2 α ,3 α -epithio-5 α -androstan-17 β -ol showed an interesting biological activity,³⁵ a factor which caused us to divert from the original target and accounts in part for the admittedly inconclusive aspect of the present report.



ACKNOWLEDGMENT: We wish to express our thanks to Prof. Kametani of the Tohoku University, Institute of Pharmaceutical Science, to whom we owe this opportunity, and also our gratitude for the kind cooperation rendered by Dr. Taichiro Komeno.

References

1. R. M. Dodson, and R. C. Tweit, J. Am. Chem. Soc., 1959, 81, 1224
2. L. C. King, R. M. Dodson, and L. A. Sublusky, J. Am. Chem. Soc., 1948, 70, 1176
3. C. Djerassi and A. L. Nussbaum, J. Am. Chem. Soc., 1953, 75, 3700
4. E. Frederiksen and Sv. Liisberg, Chem. Ber., 1955, 88, 684
5. K. Takeda, T. Komeno, N. Tokutake, and Y. Kanematsu, Chem. Pharm. Bull., 1964, 12, 905

6. K. Takeda, T. Komeno, N. Tokutake, and Y. Kanematsu, Chem. Pharm. Bull., 1965, 13, 687
7. N. Tokutake, Private Communication
8. E. E. van Tamelen, J. Am. Chem. Soc., 1951, 73, 3444
9. K. Takeda and T. Komeno, Chem. Pharm. Bull., 1960, 8, 468
10. K. Takeda, T. Kubota, and J. Kawanami, Chem. Pharm. Bull., 1960, 8, 615
11. T. Kawasaki and E. Mosettig, J. Org. Chem., 1962, 27, 1374
12. I. Kitagawa, Y. Ueda, T. Kawasaki, and E. Mosettig, J. Org. Chem., 1963, 2228
13. K. Takeda, K. Igarashi, and M. Narisada, Steroids, 1964, 4, 305
14. T. Komeno, Chem. Pharm. Bull., 1960, 8, 672
15. T. Komeno, Chem. Pharm. Bull., 1960, 8, 680
16. K. Takeda and T. Komeno, Chem. Pharm. Bull., 1962, 10, 1173
17. K. Takeda, T. Komeno, and S. Ishihara, Chem. Pharm. Bull., 1963, 11, 500
18. K. Takeda, T. Komeno, and S. Ishihara, Chem. Pharm. Bull., 1964, 12, 1433
19. T. Komeno, S. Ishihara, K. Takigawa, H. Itani, and H. Iwakura, Chem. Pharm. Bull., 1969, 17, 2586
20. T. Komeno and K. Takigawa, Chem. Pharm. Bull., 1970, 18, 43
21. a: A. A. Akhrem, A. M. Turta, and E. P. Prokofév, Izv. Akad. Nauk SSSR, Ser Khim, 1971, 2558. b: ibid., 1971, 1124. c: A. A. Akhrem, A. M. Turta, and Z. I. Istomina, ibid., 1972, 1354. d: A. A. Akhrem, Z. I. Istomina, and A. M. Turta, ibid., 1973, 895. e: A. V. Kamernitskii, A. M. Turta, and T. K. Ustynyuk, ibid., 1975, 132
22. H. Hofmeister, G. A. Hoyer, G. Cleve, H. Laurent, and R. Wiechert, Chem. Ber., 1976, 109, 185

23. K. Takeda, T. Komeno, and J. Kawanami, Chem. Pharm. Bull., 1960, 8, 621
24. a: K. Takeda and T. Komeno, Chem. and Ind. (London), 1962, 1793. b: K. Takeda, T. Komeno, J. Kawanami, S. Ishihara, H. Kadokawa, H. Tokura, and H. Itani, Tetrahedron, 1965, 21, 329. c: P. D. Klimstra, E. F. Nutting, and R. E. Counsell, J. Med. Chem., 1966, 9, 693
25. C. Djerassi and D. A. Lightner, Chem. and Ind. (London), 1962, 1236
26. T. Komeno and H. Itani, Chem. Pharm. Bull., 1970, 18, 608
27. P. G. Guy and I. Pearlson, Chem. and Ind. (London), 1967, 1255
28. T. Komeno, S. Hayashi, S. Ishihara, H. Itani, H. Iwakura, and K. Takeda, Ann. Rept. Shionogi Res. Lab., 1969, 19, 3
29. J. C. Hinshaw, Tetrahedron Letters, 1972, 3567
30. T. H. Chan and J. R. Finkenbine, Internat. J. Sulfur Chem., 1973, 8, 45
31. T. Komeno, Chem. Pharm. Bull., 1960, 8, 668
32. T. Komeno, H. Itani, H. Iwakura, and K. Nabeyama (née Takigawa), Chem. Pharm. Bull., 1970, 18, 1145
33. T. Komeno, M. Kishi, and K. Nabeyama, Tetrahedron, 1971, 27, 1503
34. M. Kishi and T. Komeno, Tetrahedron, 1971, 27, 1527
35. a: T. Miyake and A. Tanaka, Ann. Rept. Shionogi Res. Lab., 1969, 19, 20
b: T. Miyake, T. Hori, and T. Suzuki, Endocrinol. Japan, 1973, 20, 157

Received, 23rd July, 1976