STEROIDS HAVING SULFUR-SUBSTITUENT GROUPS*

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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

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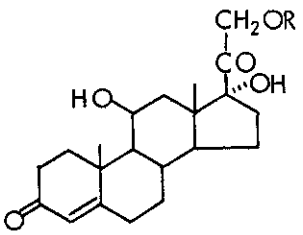
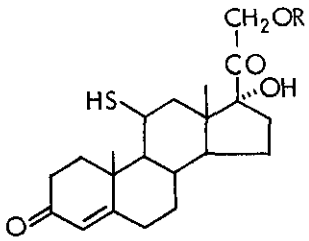
I. Introduction

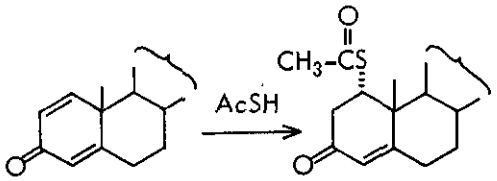
In around 1950, a method was found for separating diosgenin from a Mexican species of *Dioscorea in high yield and this opened up a way for the highly economical synthesis* of steroid hormones. Also, as corticosteroids could be readily synthesized from diosgenin or hecogenin, the use of this hitherto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

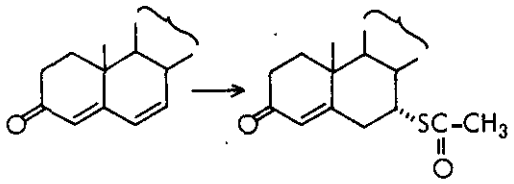
It was this achievement that prompted us to attempt a new modification of cortisol by replacing the 11β-hydroxyl group, which was known to be essential for its biological activity, with an 11β-thiol group.



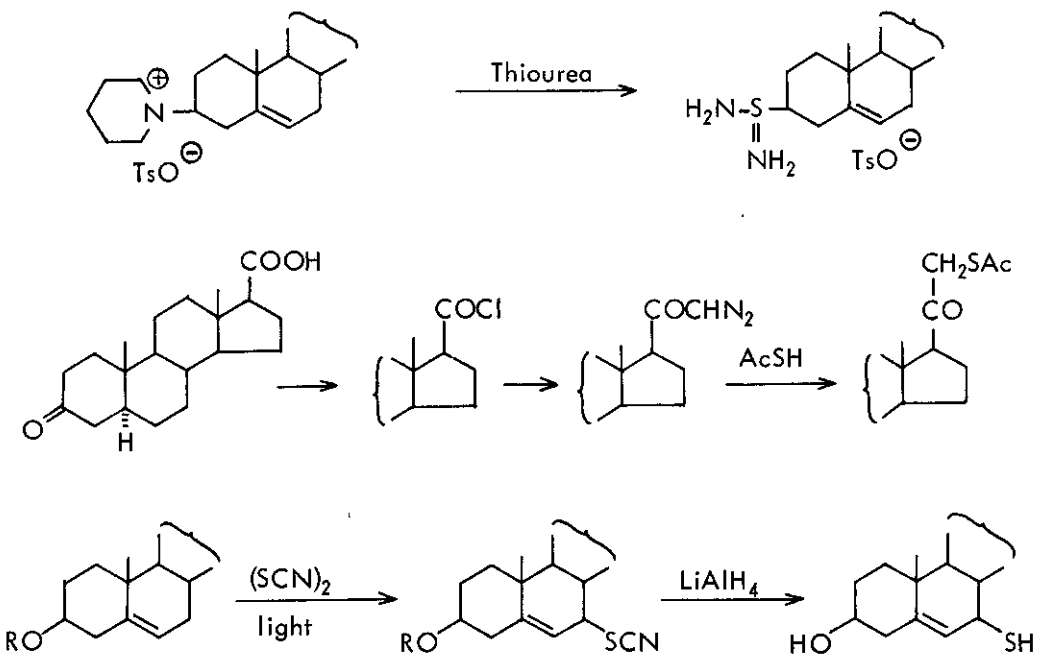


At that time the literature dealing with introduction of a sulfur function into a steroid was quite limited; there was known the addition of thiolacetic acid to dienone,[1] substitution of 3-pyridinium tosylate with thiourea,[2] and synthesis of 21-acetylthio-5α-pregnane-3,20-dione through reaction of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

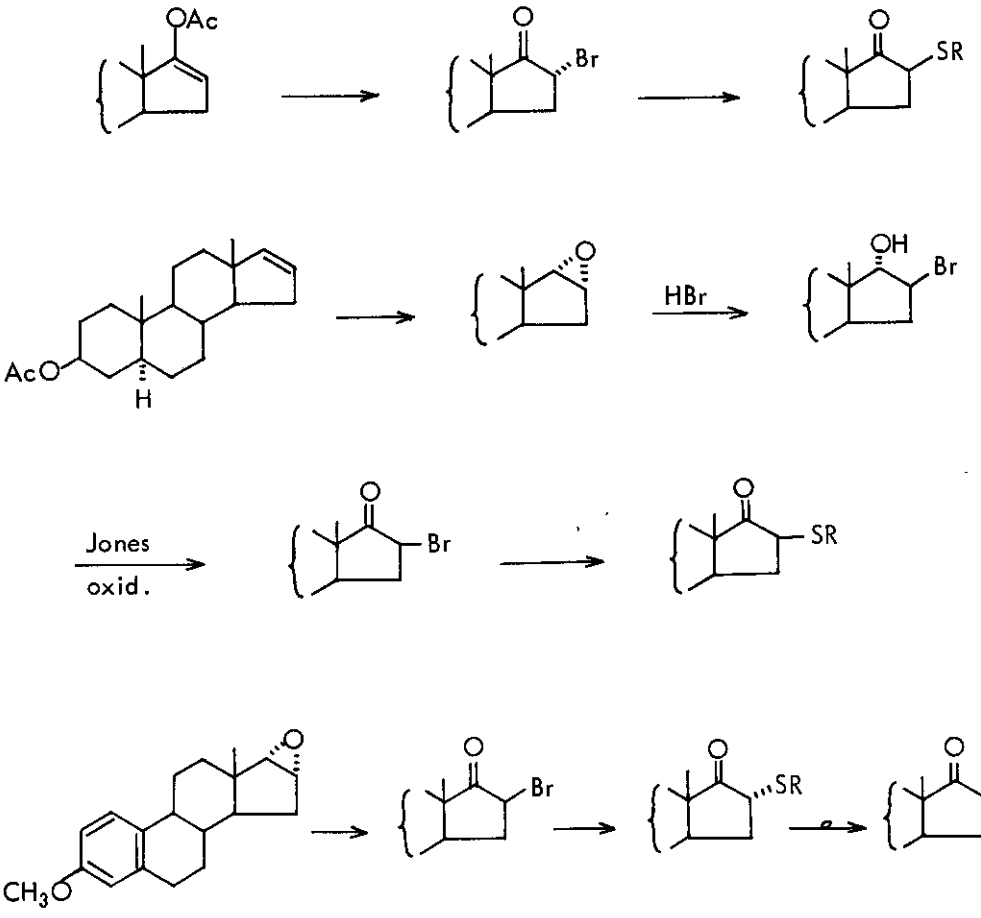


All attempts to obtain the compound having a sulfur function at C_{11}-position, for instance, addition of thiocyanogen to a 9(11)-olefin or replacement of 11α-ol tosylate by a sulfur nucleophile, were unsuccessful, perhaps due to severe steric hindrance at the 11 position of the steroid. We therefore 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 16α-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 16β-bromoandrostan-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-

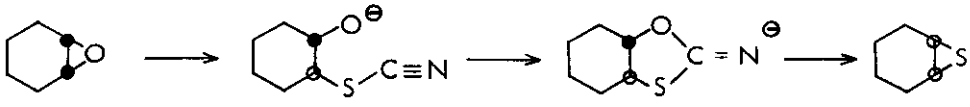
vealed that the reaction of 16β-bromide at low temperature proceeds first to form a product having an α-substituent of inverted configuration and that thermal and base-catalyzed epimerization takes place at room temperature. An explanation for this is that an aromatic A-ring will exert influence even 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

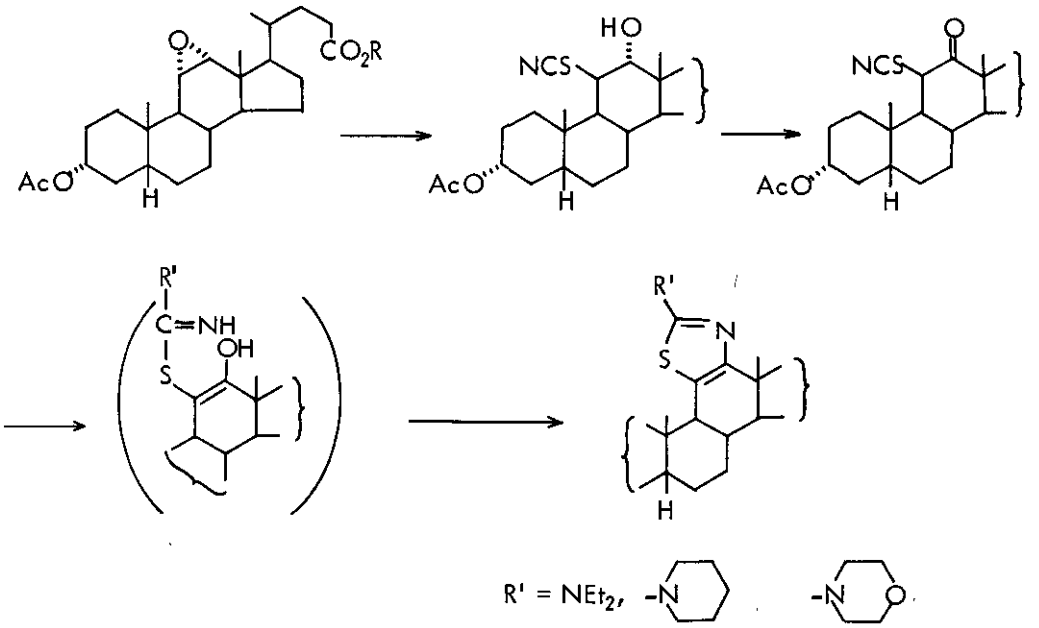
E. E. van Tamelen[8] reported that he obtained an episulfide via a thiocyanato hydrin through treatment of cyclohexan-oxide with alkali thiocyanates. With steroidal 2,3-epoxide, however, this reaction gave episulfide only in poor yield. We therefore



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

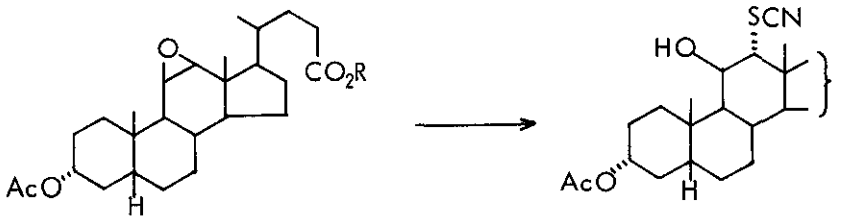
We first examined on a reaction of 11α,12α-epoxide for introduction of thiocyanate at 11β, and obtained 11β-thiocyanato-12α-ol through trans-diaxial opening of the ring. Treatment of this with an alkali regenerated the parent epoxide. The structure

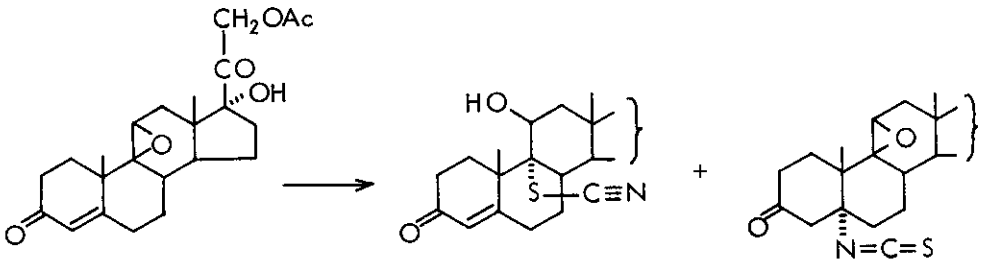
of the thiocyanato hydrin was confirmed by oxidation and desulfurization leading to the known 12-oxocholanic acid. The intermediate, thiocyanato ketone, on treatment with secondary amine was found to afford a steroidal thiazole fused at 11- and 12-positions.[9]



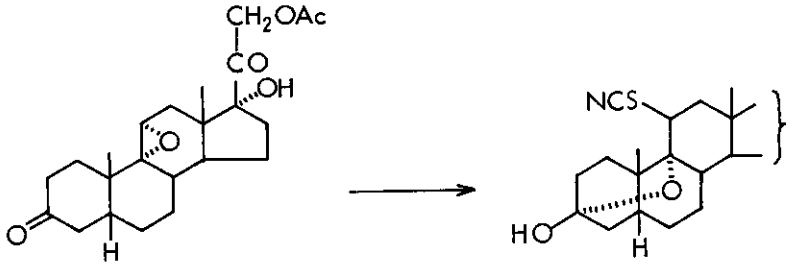
Similarly the 11β,12β-epoxide afforded 11β-hydroxy-12a-thiocyanate.

Treatment of 9β,11β-epoxide with thiocyanic acid gave 9a-thiocyanato-11β-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 5a-position.[10]



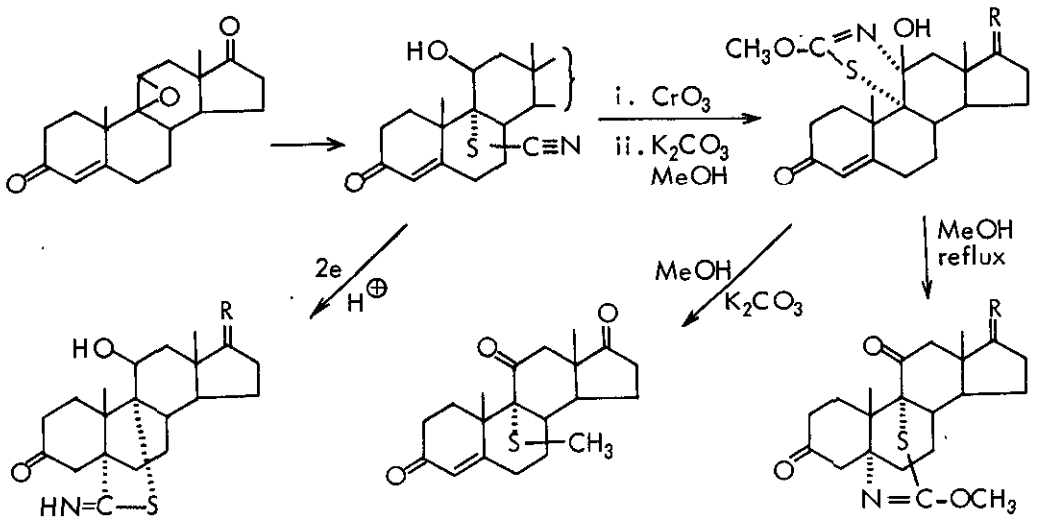


At almost the same time Mosettig and Kawasaki of NIH, U. S. A., who were probably aiming at synthesis of the same target compound as ours, reported successful ring opening of 9β,11β-epoxide with the use of thiocyanic acid.[11] They also found that with 9α-hydroxy-11β-thiocyanate, obtained through reaction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

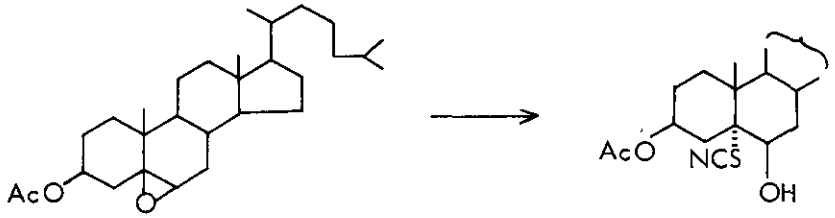


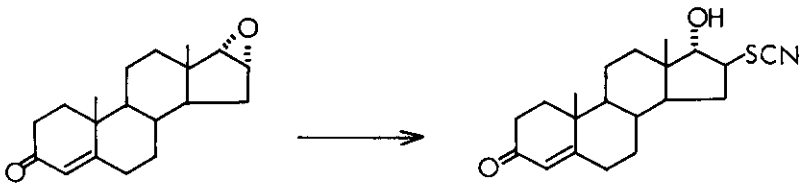
Meanwhile, Mosettig[12] in his joint study with Kitagawa, Ueda, and Kawasaki applied the same reaction to Δ^4-3-oxo-9β,11β-epoxy steroid and oxidized the hydroxyl group at the 11-position in the resulting thiocyanato hydrin to ketone. He found that the subsequent treatment of the ketone with potassium 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 5α-carboimide derivative through electrolytic reduction of Δ^4-3-oxo-9α-thiocyanato-11β-hydroxy steroid.[13] This derivative could be converted into thiolactone by hydrolysis with hydrochloric acid.

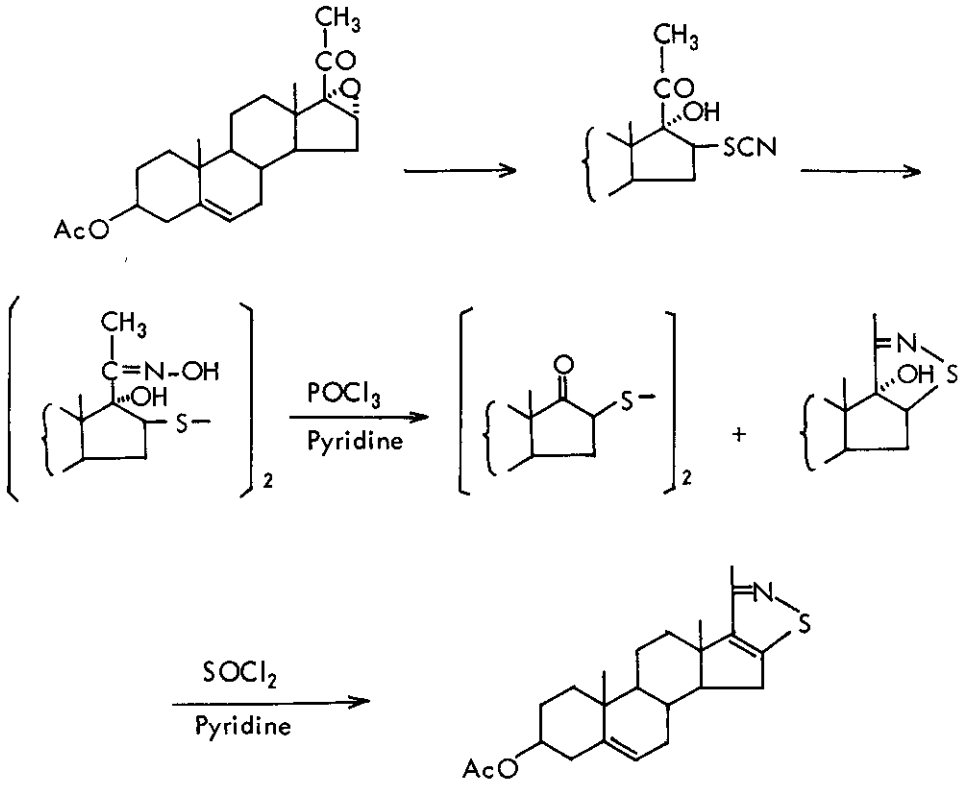


Epoxide rings at other positions, too, were opened by treatment with thiocyanic acid, to afford 5α-thiocyanato-6β-ol in the case of 5β,6β-epoxide, 6β-thiocyanato-5α-ol in the case of 5α,6α-epoxide[14] and 16β-thiocyanato-17α-ol in the case of 16α,17α-epoxide,[15] each invariably in high yield.

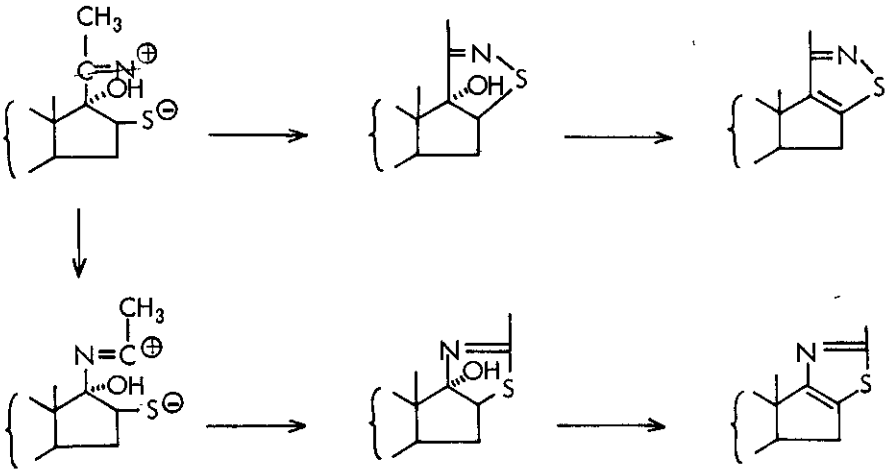




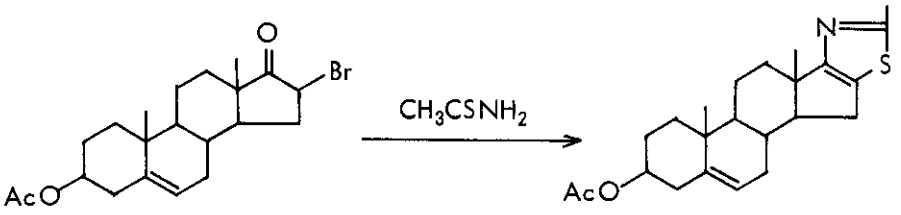
A similar experiment was also made with a pregnane derivative having an acetyl side chain at the 17-position, and the reaction that took place was exactly the same. The 16β-thiocyanato-17α-hydroxypregnenolone thus obtained was treated with hydroxylamine affording a mixture of 16-mercapto-20-oxime and its dimer. Beckmann rearrangement of the mixture with $POCl_3$-pyridine gave a 16-mercapto-17-one dimer and a by-product thought to arise from ring closure.[15] Reduction of the dimer with $LiAlH_4$ afforded



16β-mercapto-17β-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 16β-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]

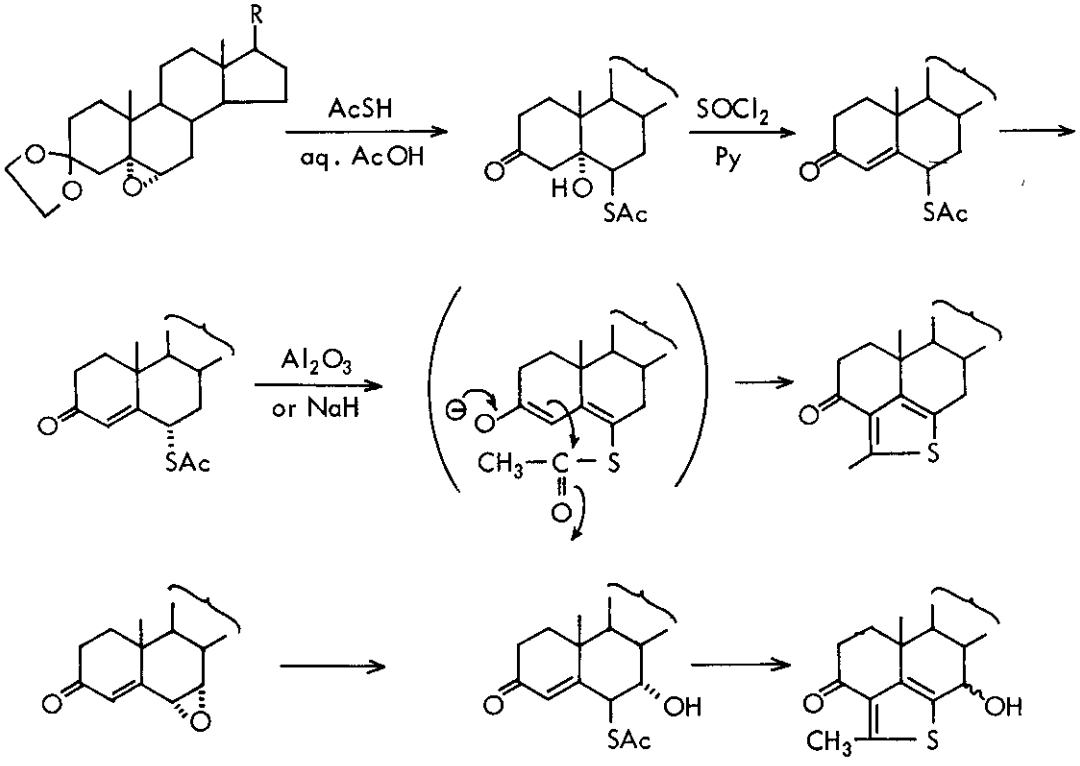


(b) Opening of epoxy ring with thiolacetic acid

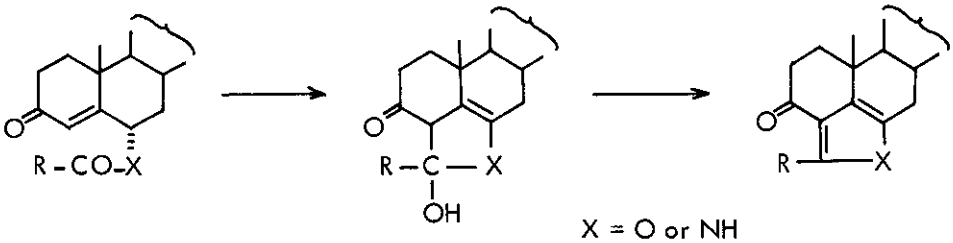
The opening of an epoxy ring is possible not only with thiocyanic acid but also with

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

This reaction is also applicable to 3,3-ethylenedioxy-5α,6α-epoxide. Ring opening of the compound with thiolacetic acid, followed by hydrolysis of the ketal moiety and dehydration with $SOCl_2$-pyridine gave 6β-acetylthio-4-en-3-one, which was isomerized to 6α-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 6α,7α-epoxypregn-4-ene-3,20-dione a thiophene derivative can be obtained as a product of intramolecular cyclization by a similar route through the 6β-acetylthio-7α-hydroxy derivative.[18]



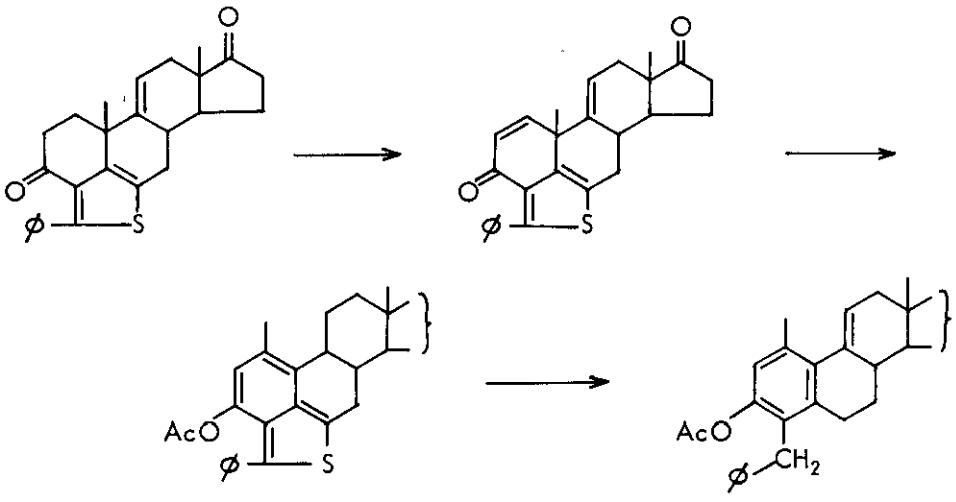
This cyclization reaction is similarly applicable to compounds having a 6α-benzoylthio, 6α-acetoxy,6α-benzoyloxy or 6α-acetylamino group as substituent at the 6-position to afford the corresponding phenylthiopheno, methylfurano, phenylfurano or methylpyrrolo derivative.[19]



X = O or NH

R = CH_3 or ∅

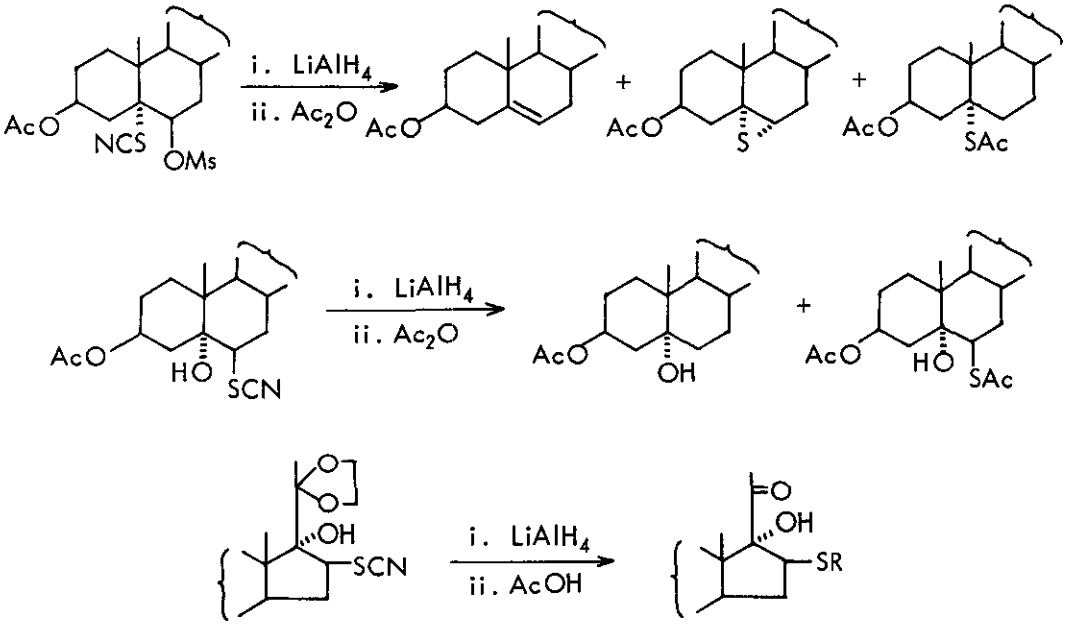
When the fused $\Delta^{1,9(11)}$-bisdehydro derivative of phenylthiophene is treated with boron trifluoride in acetic anhydride-acetic acid, aromatization of the A-ring readily occurs, with migration of methyl at the 10-position and formation of a benzo-c-thiophene derivative. In order to clarify the 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

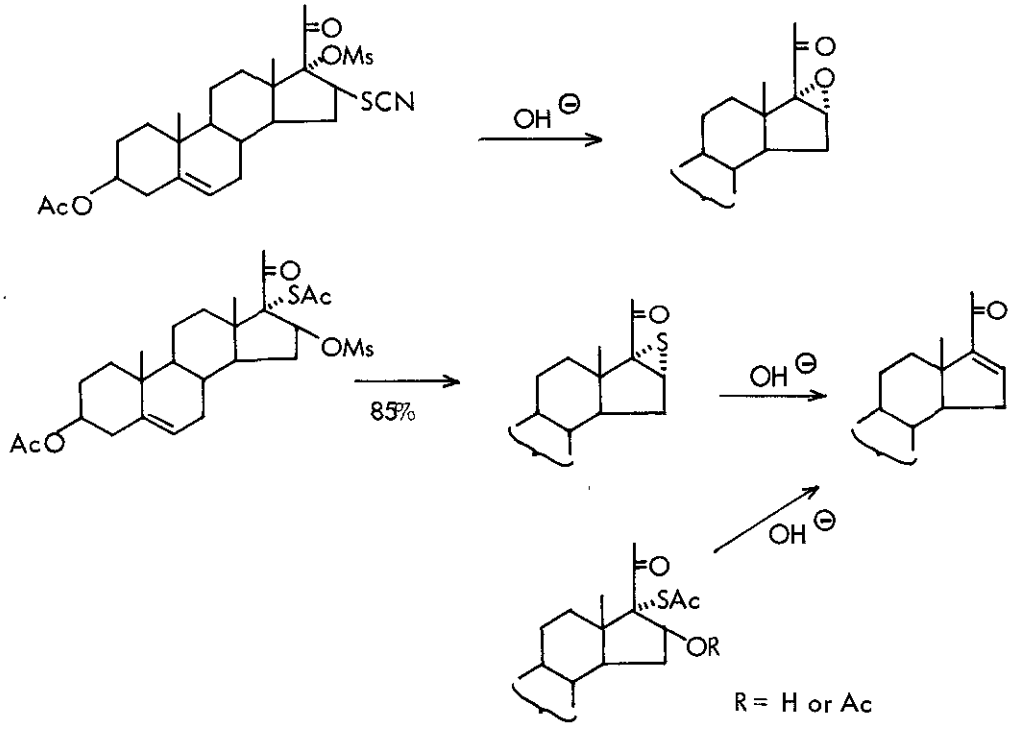
(a) Some reactions of thiocyanato hydrin

$LiAlH_4$ 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 5α-thiocyanato-6β-ol-mesylate with $LiAlH_4$ followed by acetylation gave cholesteryl acetate, episulfide, and the target compound 5α-thiol acetate in roughly equal amounts. Similarly, 5α-hydroxy-6β-thiol and 5α-hydroxy derivatives are obtainable from 5α-hydroxy-6β-thiocyanate.[14]

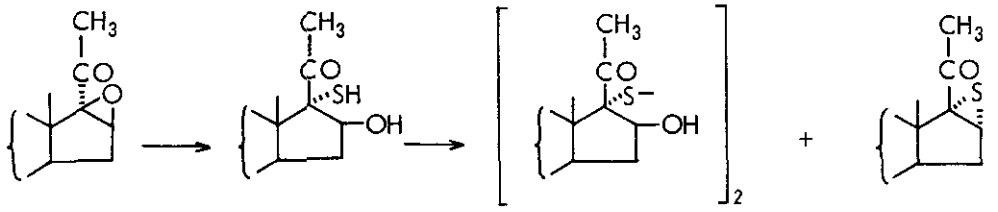


A similar reaction is also utilized with the 20-ethylene ketal compound of 16β-thiocyanato-17α-hydroxy-5α-pregnan-20-one to afford a 16β-thiol-17α-hydroxy derivative.[15] Chemists in the U.S.S.R.[21] have recently been studying similar reactions at the 16- and 17-position in greater detail, and, for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

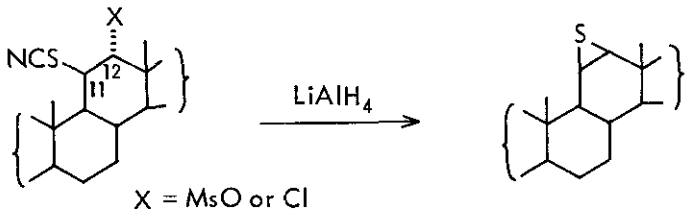
Kamernitskii et al.[21e] that the 16β-thiocyanato-17α-mesyloxy compound affords α-epoxide when treated with a base, whereas the 16β-mesyloxy-17α-acetylthio compound gives 16α,17α-episulfide. On the other hand, 16β-hydroxy or 16β-acetoxy derivatives give the 16,17-unsaturated compound with a base.



H. Hofmeister et al. of Schering AG, Germany[22] subjected 17α-pregnenolon-16β,17β-epoxide and analogous compounds having a modified A-ring to ring opening with hydrogen sulfide and subsequently treated the resultant 16β-hydroxy-17α-thiol derivative with mesyl chloride under heating in pyridine to obtain 16α,17α-episulfide and S-dimer.



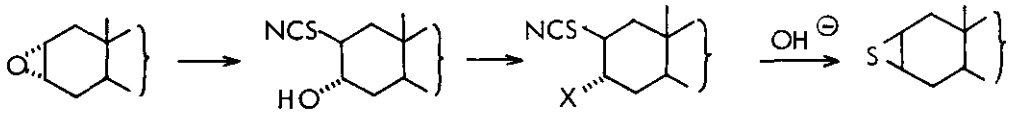
Things are, however, somewhat different with the 11β-thiocyanato-12α-hydroxy compound, from which 11β,12β-episulfide only could be obtained; neither was the thiol derivative obtainable even by treatment of the 12α-ol mesylate or 12α-chloride with $LiAlH_4$.[23]

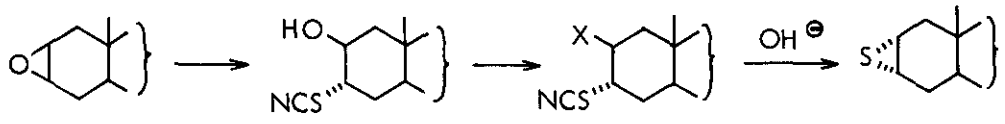


X = MsO or Cl

(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.

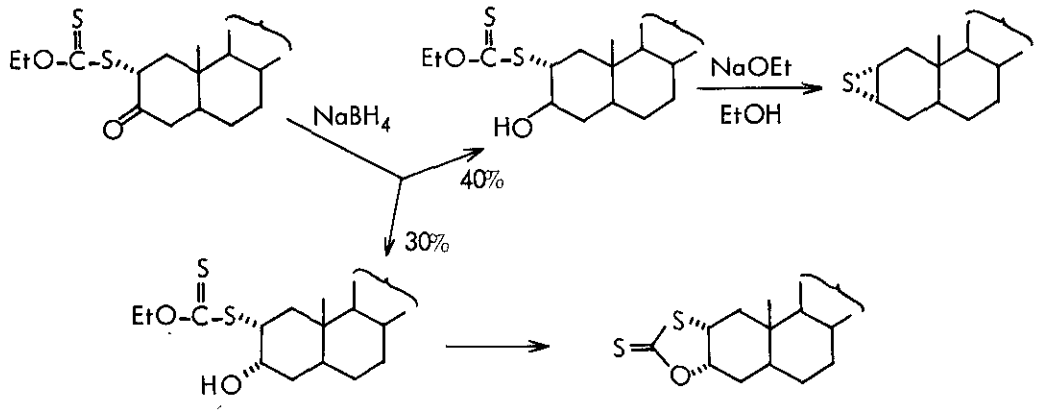




X = MsO, Cl etc.

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 2β-O, 3α-S or 2β-S, 3α-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]



2-Oxo-3β-Xanthate ⟶ 2β,3β-Episulfide

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-2α,3α-episulfide.[26] Similarly 2-oxo-3β-xanthate is converted to 2β,3β-episulfide.

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

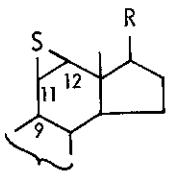
There are also reports dealing with the reaction of iodine thiocyanate on 5α-cholest-2-ene,[29] and with the treatment of 5α-cholestan-2α,3α-epoxide with phosphine sulfide and trifluoroacetic acid,[30] both yielding 2β,3β-episulfide.

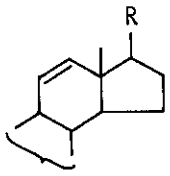
(c) Properties of the episulfide ring

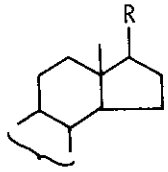
The results of our various experiments on the reductive ring opening of 11β,12β-episulfide are shown in Table 1. They show that practically no reaction takes place under mild conditions, while treatment under drastic conditions effects desulfurization with resultant formation of an unsaturated compound.[23] Treatment with Raney nickel in dioxane affords a saturated compound through desulfurization and reduction, while treatment with p-toluenesulfonic acid and acetic anhydride gives $\Delta^{9(11)}$-12β-thiol acetate.[31] Thus, our attempts at reductive ring opening of 11β,12β-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 11β,12β-Epithio Ring

Reagent	Product
HCl-dioxane, HBr-dioxane, Na-amalgam, Na_2S, $CrCl_2$, H_2/Pt, $LiAlH_4$ in THF or Bu_2O, $LiAlH_4$-$AlCl_3$	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_2O-pTsOH in AcOH	$\Delta^{9(11)}$-ene-12β-SAc







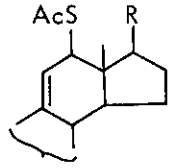


Table 2-a[14] shows the results of reduction of 5α,6α-episulfide with $LiAlH_4$, while in Table 2-b[24b] are given the results of ring opening reactions conducted with 2α,3α- and 2β,3β-episulfides with the same reagent.

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 $LiAlH_4$, the mode of ring opening varies according to the

Table 2. Reductive Ring Opening of Episulfide with $LiAlH_4$

a. Ring Opening of 5α,6α-Epithio-5α-cholestane

Solvent	Recovered material	$\Delta^{5(6)}$-ene	5α-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-5α-cholestane

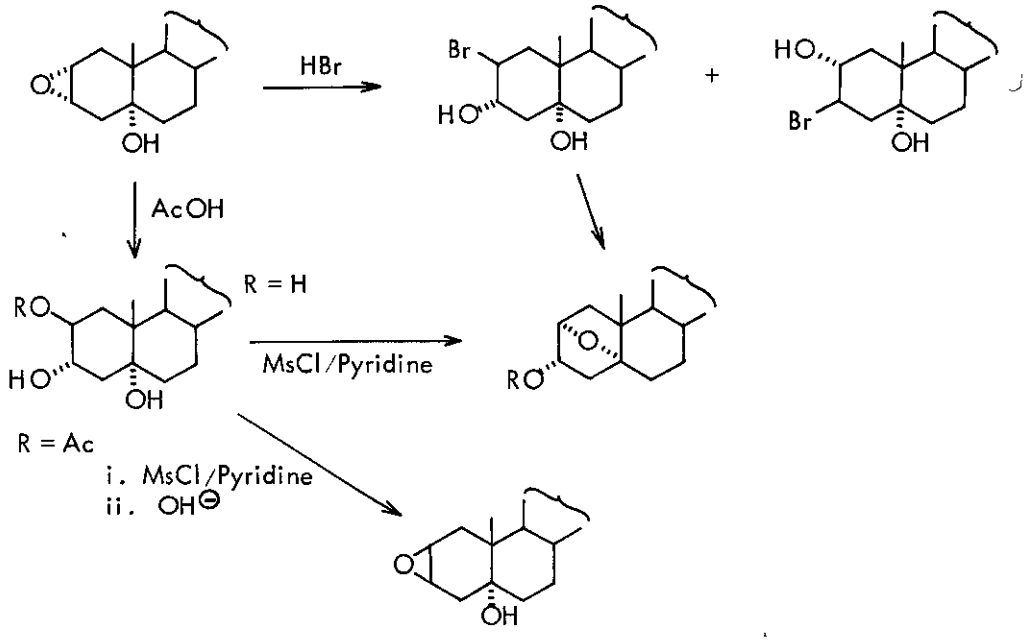
Compound	Solvent	Recovered material	Δ^{2}-ene	Thiol compd.
2β,3β	Ether : THF (1 : 1)	-	16	60 (2β)
2α,3α	"	62	17	-
2α,3α	THF	-	42	40 (3α)

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

V. Other reactions

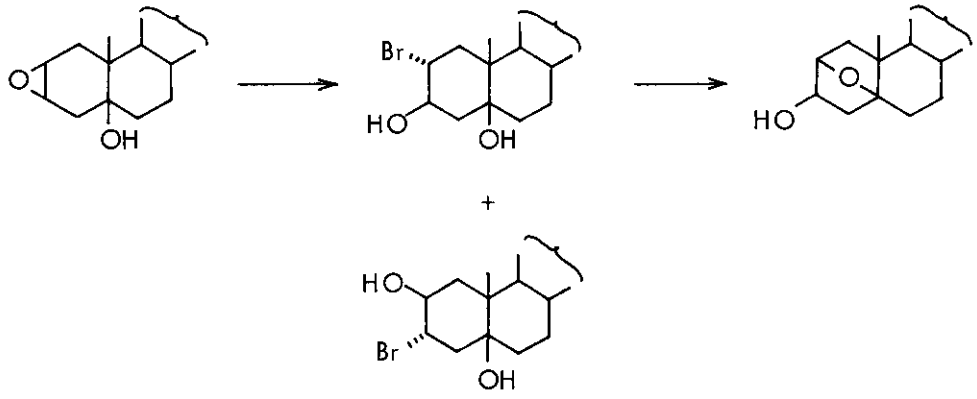
(a) Synthesis of 2,5-bridged compound

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

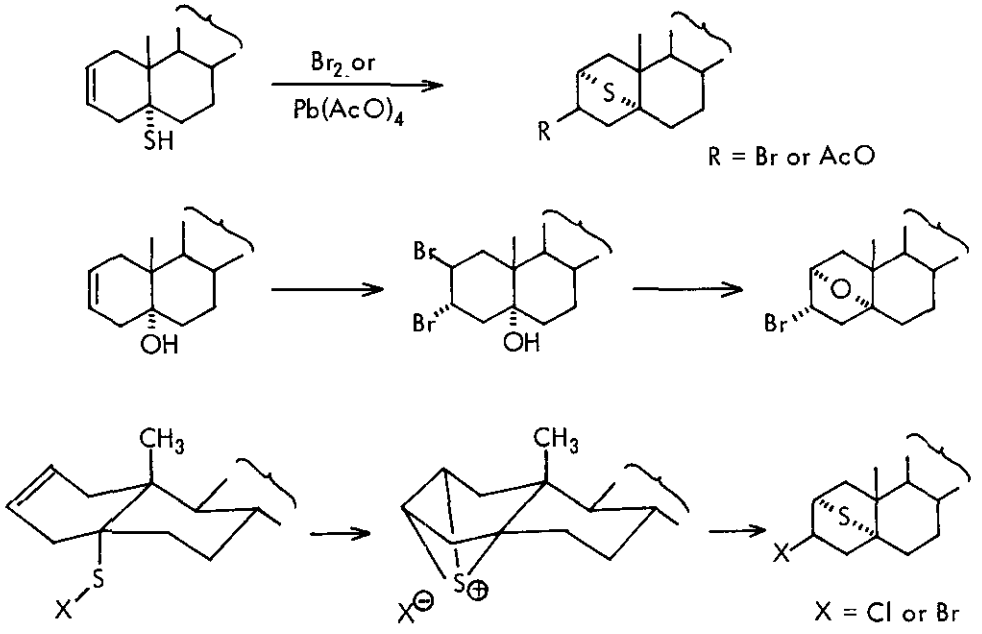


epoxide accompanied by a small amount of 3β-bromo-2α,5α-diol through transient formation of 2β-bromo-3α,5α-diol.

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



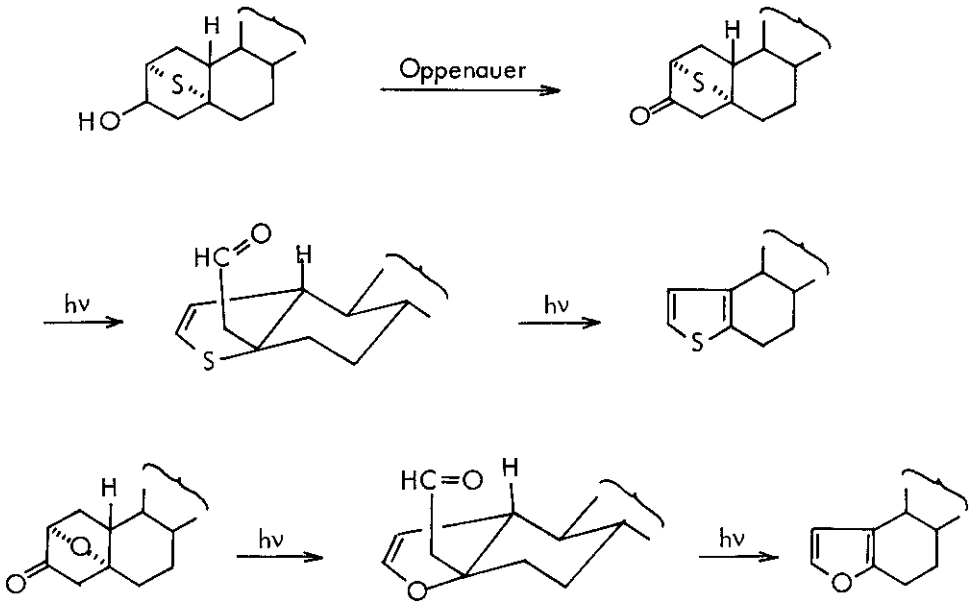
Various experiments were next performed in anticipation that the use of 5α-thiol derivatives would afford 2α,5α-episulfides, and the results revealed that the most efficient route to 3β-substituted 2α,5α-episulfide was to treat Δ^2-ene-5α-thiol derivative[33] with bromine or lead tetraacetate, this at the same time representing the shortest route. Similar treatment of Δ^2-5α-hydroxy steroid with Br_2 gave the 3α-bromo-2α,5α-epoxy compound. The 2α,5α-episulfide compound synthesized from the 5α-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^2-5α-thiol steroid resulted in introduction of an acetoxy group into the 3β-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-3β-hydroxy-2α,5α-episulfide. Oppenauer oxidation of this to 3-ketone and subsequent irradiation bring about α-fission at the C_2-C_3 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.

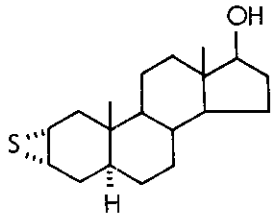
Similar treatment of 19-nor-3-oxo-2α,5α-epoxide compound affords the steroid with a furan ring, although the yield is low.[34]



VI. Conclusion

Despite all the experiments which we have described above, our attempts to synthesize the 11β-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 2α,3α-epithio-5α-androstan-17β-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.



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