ether concentrate,[21] and 5 ml. of dry pyridine in 10 ml. of dry benzene was added dropwise at 5–10° with agitation a solution of 3.5 g. (0.026 mole) of sulfur monochloride in 10 ml. of dry benzene over a period of 1.25 hr. White, crystalline pyridine hydrochloride soon precipitated. The addition of more benzene (10 ml.) was necessary to loosen the crystalline mass. After the reaction mixture had come to room temperature, it was stoppered and allowed to stand overnight. Water (50 ml.) was added and the mixture was shaken for 15 min. The benzene layer was separated and the aqueous layer extracted with 10 ml. of benzene. The benzene layers were combined and washed successively with 40 ml. of 1 *N* sulfuric acid, 40 ml. of 1 *N* sodium bicarbonate, and thrice with 40-ml. portions of water. After the benzene solution was filtered and dried over anhydrous sodium sulfate, the solvent was removed *in vacuo* at 55–60° under nitrogen. When the solvent ceased to distil, the pressure slowly was reduced to 34 mm. The crude product (7.9 g.) was fractionated at 0.021 mm. under nitrogen. The portion that distilled at 83.2–88.5° was essentially pure di(methylthiomethyl) disulfide and that which distilled at 90.2–111° was impure trisulfide. Redistillation of the latter fraction under the same conditions gave pure di(methylthiomethyl) trisulfide. Distillation was discontinued to avoid decomposition when the residue did not distil upon raising the bath temperature to 165°. The residue (2.3 g., 35.4%) was impure tetrasulfide. The method of solvent extraction[5,10,22] previously employed for the isolation and purification of higher polysulfides was used for this compound. Extraction with absolute alcohol, filtration of the alcohol solution, and removal of the solvent at room temperature *in vacuo* and under nitrogen gave the alcohol-soluble tetrasulfide. From this substance, after extraction with absolute chloroform and removal of the solvent under the same conditions, the di(methylthiomethyl) tetrasulfide was obtained as a pale yellow, moderately viscous oil with the usual garliclike odor. The yield was 1.39 g. (21.4%).

Di(methylthiomethyl) Pentasulfide.—To a suspension of 12.1 g. (0.051 mole) of potassium pentasulfide in 100 ml. of anhydrous ether, protected from moisture and previously flushed with dry nitrogen, was added a solution of 9.8 g. (0.101 mole) of chloromethyl methyl sulfide in 50 ml. of anhydrous ether over a period of 0.5 hr. at room temperature, with magnetic stirring. The reaction mixture was flushed again with dry nitrogen, stoppered, and allowed to react at room temperature for 13 days. During this time, the mixture was stirred 8 hr. daily for 9 days. The solid component changed from a coarse, orange-red powder to a pale yellow crystalline material. The reaction mixture was filtered under slight vacuum, the solid residue was washed with several 10-ml. portions of ether, and the washings were combined with the filtrate. The resultant ether solution of the pentasulfide was washed with three 50-ml. portions of water, dried over anhydrous sodium sulfate, filtered, and the ether removed by distillation at 34–40° under a slight vacuum and in a nitrogen atmosphere. The residue was taken to, and kept at, 50° and about 35 mm. for 10 min. The yield of crude pentasulfide was 10 g. (70%). By extracting the crude product with absolute ethanol (distilled over magnesium) to remove the alcohol-soluble impurities, and by subjecting the residue to a high vacuum at room temperature to eliminate the last traces of solvent, the pentasulfide was obtained as a pale yellow, slightly viscous oil with the usual garliclike odor. The yield was 3.9 g. (27.3%). The pentasulfide was stable with respect to autodesulfuration on standing at room temperature.

Di(methylthiomethyl) Polysulfide Products Higher than Pentasulfide.[20]—To a solution of 7.4 g. (0.079 mole) of methylthiomethyl mercaptan in 25 ml. of dry benzene was added a solution of 5.3 g. (0.039 mole) of sulfur monochloride in 15 ml. of dry benzene according to the procedure described earlier for the tetrasulfide. No pyridine was used. Copious evolution of hydrogen chloride gas took place at the beginning of the reaction. When the reaction mixture had reached room temperature, however, only a little hydrogen chloride gas was evolved which gave a weak test with blue litmus paper and with ammonia. With the exception that the benzene solution had to be washed six times with 50-ml. portions of ice–water to obtain a negative test for chloride ion, the procedure for working up the reaction mixture and removing the solvent was the same as that used for the tetrasulfide. The weight of the crude oil was 7.6 g. An attempt to distil it under vacuum (0.08 mm.) in a nitrogen atmosphere gave evidence of decomposition, accompanied by an increase in pressure to 0.1 mm. Two small quantities of oil, 1.4 g. and 1.3 g., presumably impure di- and trisulfide, were collected. When the bath temperature had reached 185° and the vapor 123°, distillation ceased and the pressure dropped to 0.08 mm. The residue was a clear, yellow-orange, moderately viscous oil (3.5 g.) with a mild odor not resembling the previous polysulfides. The oil soon became opalescent and, on standing at room temperature, slowly underwent autodesulfuration with the separation of well defined crystals of rhombic sulfur, identified by melting point (109.1–111.5°) and molecular weight (found, 256, 257; calcd. for S_8, 256). Shaking the polysulfidic material with acetone produced the same transformation in much less time. The autodesulfuration which took place on standing at room temperature was observed over a period of time. At intervals, the clear, supernatant oil was carefully removed from the crystals of sulfur, and its composition determined by elemental analysis. The results are given in Table I. At the end of 3 days, the composition of the polysulfide corresponded to that of di(methylthiomethyl) decasulfide. It corresponded to that of an octasulfide at the end of 24 days, and thereafter remained constant.

Acknowledgment.—The authors are grateful to Dr. D. Stanley Tarbell of the University of Rochester for his helpful suggestions; to Dr. W. Davidson for the molecular weight determinations; to Mr. F. Bissett of our laboratory for the gas chromatography and spectrophotometric determinations; to Mr. C. DiPietro of the Analytical Laboratory for the microanalyses; and to Mr. A. Deacutis for the preparation of potassium pentasulfide.

(21) The concentrate was an approximately 61% solution of the mercaptan in dry ether.

(22) J. S. Thomas and R. W. Riding, *J. Chem. Soc.*, **125**, 2460 (1924).

The Formation of Thiachroman as a Major Product in the Claisen Rearrangement of Allyl Phenyl Sulfide[1]

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Under conditions effecting the Claisen rearrangement of allyl phenyl ethers, thia analogs afford mainly the corresponding propenyl phenyl sulfides (prototropic isomerization).[2] Only recently, however, the observations of Kwart and Hackett[3] suggested that, through amine catalysis, the thia analogs also may be induced to follow the path of the Claisen rearrangement; *viz.*, allyl phenyl sulfide (I), dissolved in a high-boiling amine, was converted (15–20%) into 2-methyl-2,3-dihydrobenzothiophene (II) by a single distillation (atmospheric pressure).

During the course of our studies[1,4] a convenient preparation of II was sought and we followed, essentially, the method of Kwart and Hackett. In addition to isolating the desired compound we found for the

(1) This study is part of a series dealing with the nature of organic sulfur groups and is supported by grants from the Petroleum Research Fund. The preceding paper is by C. Y. Meyers, G. Lombardini, and L. Bonoli, *J. Am. Chem. Soc.*, **84**, 4603 (1962). (a) Inquiries should be directed to C. Y. Meyers, Department of Chemistry, University of Southern California, Los Angeles 7, Calif.

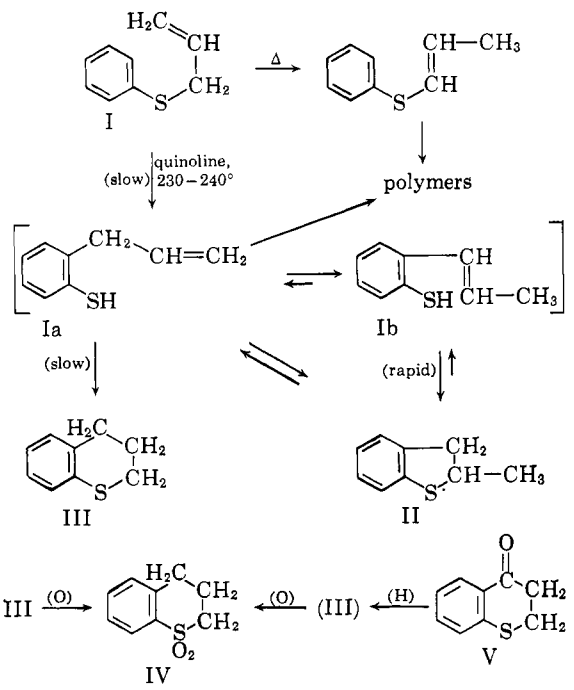
(2) E. N. Karaulova, D. Sh. Meilanova, and G. D. Gal'pern, *Zh. Obshch. Khim.*, **27**, 3034 (1957).

(3) H. Kwart and C. M. Hackett, *J. Am. Chem. Soc.*, **84**, 1754 (1962).

(4) C. Y. Meyers, C. Rinaldi, and L. Bonoli, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, Abstracts of meeting, p. 4M.

first time another major Claisen product, the isomeric thiachroman (III).[5] From these observations a new and simple preparation of thiachromans is offered, further evidence of the greater stability of six- than five-membered cyclic sulfides is suggested, and more information regarding the Claisen path of this reaction is provided.

In several experiments involving two- to four-hour refluxing of equimolar quantities of I and quinoline, conversions of about 25% into II and about 30% into III were realized. The latter was identified by its b.p. 125–127° (14–15 mm.) [lit.[6a] b.p. 128–130° (15 mm.)] and its almost quantitative transformation (one-hour reflux with excess hydrogen peroxide in acetic acid) to the 1,1-dioxide (IV), m.p. 89.5–90° (from water, then ligroin; lit.[7] m.p. 88–89°). Moreover, III was prepared directly from thiachromanone (V)[8] by reduction,[9] then converted to the 1,1-dioxide, melting point the same as that of IV either alone or in mixtures with it.



The isolation of III in this study, but not in that reported by Kwart and Hackett, may reasonably be explained by comparing their respective reaction procedure and results with our own. Their *single distillations* of solutions of I and quinoline (or N,N-diethylaniline) yielded II along with mainly unchanged I and small or trace amounts of propenyl phenyl sulfide and thiophenol. All of these have boiling points lower than or very close to that of the amine solvent.[10] In our studies the initial mixture was allowed to *reflux for several hours*, the quinoline was then converted into its hydrochloride, and the sulfur-containing products were removed by ether extraction and separated by fractional distillation. In this way both II [b.p 113–114° (15 mm.); lit.[11] b.p. 118–120° (21 mm.); 1,1-dioxide, m.p. 116–117°; lit.[11] m.p. 115–115.5°] and III were detected and isolated. Only a very small amount of lower-boiling material was isolated, the balance of I being represented as high-boiling fractions.[12]

Significantly, the observed per cent of conversion of I into II was more or less the *same* from the single distillation (when much unchanged I but no III was obtained) and from the several-hour reflux (when virtually no I but much III was isolated). This suggests that the formation of II is rapid but involves reversible reactions (or a reaction cycle), while the reaction leading to III is slow but unidirectional. The formation of III experimentally[12b] from II offers additional evidence for this mechanism.

This reasoning is justified by related observations. Neither Ia nor Ib has been isolated from these reactions. If Ia is formed it may be tautomerized[13] to Ib and, as suggested,[3] the latter rapidly cyclized to II which is detected early. Moreover, II would be the expected (Markownikoff) product from direct cyclization of Ia, although its formation by this route may be less important because of the lower reactivity of the nonconjugated double bond and because the amount of Ia is depleted by its isomerization to Ib. While III cannot be formed directly from Ib it may be formed by the cyclization of Ia. The formation of III, then, would be slow not only because of reasons just mentioned, but because III is not the preferred (Markownikoff) product. Finally, it should be noted that cyclic six-membered sulfides exhibit much less strain than the corresponding five-membered systems.[14] While II is reasonably cleaved under these conditions,[12b,15] re-forming Ia and Ib, III is stable and through its continuous formation becomes the major product when the mixture is allowed to reflux over an extended period.

A very recent report,[16] of the formation of six-membered sultones rather than the expected five-membered ones and explained on the basis of the greater stability of the former (the latter being strained), virtually parallels the observations and conclusions arising from

(5) The oxy analogs of II (2-methyl-2,3-dihydrobenzofurans) and III (chromans) are important side-products observed following the Claisen rearrangement of allyl phenyl ethers. See L. I. Smith, *Chem. Rev.*, **27**, 287 (1940); and D. S. Tarbell, *Org. Reactions*, **2**, 15–19 (1944).

(6) (a) J. von Braun, *Ber.*, **43B**, 3220 (1910); (b) C. Angelini and G. Grandolini, *Ann. chim.* (Rome), **46**, 235 (1956), report b.p. 124–126° (10 mm.).

(7) F. G. Bordwell and W. H. McKellin, *J. Am. Chem. Soc.*, **73**, 2251 (1951).

(8) F. Krollpfeiffer and H. Schultze, *Ber.*, **56B**, 1819 (1923).

(9) Satisfactory yields were obtained by a simple reflux with amalgamated zinc in hydrochloric acid (until tests with 2,4-dinitrophenylhydrazine were negative) and the product isolated in the subsequent steam-distillate. The Wolff–Kishner method (ref. 7) and lithium aluminum hydride (ref. 6b) have also been used.

(10) Compound III has an appreciably higher boiling point, and, even if it were present in small amounts, it probably would not have been detected in the distillate. We found that when a mixture of quinoline containing 20% of III was distilled in common equipment appreciable amounts of III appeared in the distillate only after a large part of the quinoline had been distilled.

(11) E. N. Karaulova, D. Sh. Meilanova, and G. D. Gal'pern, *Dokl. Akad. Nauk SSSR*, **123**, 99 (1958).

(12) (a) The propenyl phenyl sulfide that probably was formed is easily converted into polymeric material (ref. 2, 3). (b) From a mixture of II and quinoline that was refluxed for several hours there was isolated unchanged II, small amounts of III, and polymeric material representing about one-third of the original charge of II.

(13) The well known tautomerization of allylbenzenes to propenylbenzenes (*e.g.*, eugenol to isoeugenol) occurs in a matter of minutes in alkaline medium.

(14) C. Y. Meyers, S. Ghersetti, and A. Mangini, 140th National Meeting of the American Chemical Society, Chicago, Ill., September, 1961, Abstracts of meeting, p. 5T.

(15) H. D. Hartough and S. L. Meisel, "Compounds with Condensed Thiophene Rings," Interscience Publishers, Inc., New York, N. Y., 1954, pp. 34 ff.

(16) W. E. Truce, D. N. Burdge, and R. J. Steltenkamp, *J. Org. Chem.*, **27**, 3913 (1962).

this study of the cyclic sulfides. Similarly, the facile cleavage of cyclic five-membered sulfones under conditions not affecting the six-membered systems was attributed to ring strain in the former.[4]

The isolation of both II and III in this study provides greater evidence that the classical Claisen rearrangement product (Ia) is the initial intermediate formed directly from I (*cf.* ref. 5). However, since neither we nor Kwart have actually isolated this classical product (or Ib) under conditions leading to the formation of II and now also III, this evidence may be circumstantial and an alternate initial path from I cannot yet be definitely precluded.

The Claisen route, with the initial formation of Ia and Ib as *very reactive transients* (*i.e.*, nonisolable)[17] derives further support from related studies. There are indications that benzenesulfenyl anions (ArS^-) are much more reactive nucleophiles than phenoxy anions; *e.g.*, PhS^- attacks benzothiophene 1,1-dioxide forming quantitatively the β-PhS-adduct, while PhO^- is completely unreactive with this substrate.[18] Much greater mesomeric delocalization of the negative charge in the phenoxy systems reasonably accounts for this and similar observations.[19] It follows rationally that while *o*-allylphenols can be isolated from usual Claisen rearrangements, the corresponding thiols may simply cyclize too rapidly to be detected *per se* especially under the high-temperature and alkaline conditions employed.

It has been suggested[20] that I initially might cyclize directly into III-anion which then is reversibly transformed into the anions of Ia, Ib, and II, all in equilibrium, but irreversibly into III by proton abstraction. The experimental facts—sequence of formation of II and III, cleavage of II but not III under these conditions, etc.—together with independent evidence of the greater stability of six- than five-membered cyclic systems containing a sulfur atom[4,14-16] do not support this argument.

A closer examination of these reactions, necessarily under less vigorous conditions, should prove interesting and fruitful.

(17) While this was suggested by Kwart to explain the absence of Ia, no supporting evidence was offered.

(18) F. G. Bordwell and W. H. McKellin, *J. Am. Chem. Soc.*, **72**, 1985 (1950).

(19) See C. C. Price and S. Oae, "Sulfur Bonding," The Ronald Press Co., New York, N. Y., 1962, p. 25.

(20) The authors gratefully acknowledge a referee's suggestion.

Azasteroids. IV. Microbiological Dehydrogenation of C-Ring Azasteroids[1]

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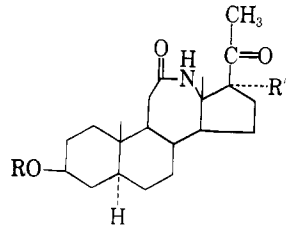
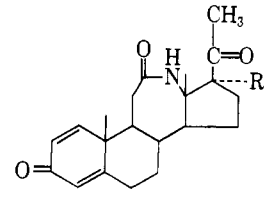
Azasteroids have attracted some attention as a direction in which to search for steroid hormone analogs. Introduction of nitrogen into ring C (with concurrent homoannulation) has been reported by Mazur[2,3] and Zderic.[4,5] All our attempts to convert suitable precursors to A-ring unsaturated compounds by chemical methods have failed—for example, bromination-dehydrobromination,[6] selenium dioxide oxidation,[7] and heating with dichlorodicyanoquinone[8]—and Zderic has mentioned having the same experience.

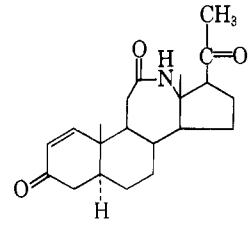
We have now found that fermentation of 12a-aza-3β-hydroxy-C-homo-5α-pregnane-12,20-dione (I) with *Nocardia sp.* A.T.C.C. 14558 gave 12a-aza-C-homo-1,4-pregnadiene-3,12,20-trione (II). Compound II was obtained in two polymorphic forms having identical solution infrared spectra. The structure was confirmed by quantitative hydrogenation and by n.m.r. spectrum. The latter showed the typical complex pattern in the 350–450-c.p.s. region due to interaction of the C-4 proton with the C-2 proton (itself part of an AB system). Similarly, fermentation of 3β-acetoxy-12a-aza-17α-hydroxy-C-homo-5α-pregnane-12,20-dione (III) with *Nocardia sp.* A.T.C.C. 14559 gave 12a-aza-17α-hydroxy-C-homo-1,4-pregnadiene-3,12,20-trione (IV), with typical n.m.r. spectrum in the 350–450-c.p.s. region. A different result was obtained by fermenting 3β-acetoxy-12a-aza-C-homo-5α-pregnane-12,20-dione (V) with *Arthrobacter sp.* A.T.C.C. 14560 which yielded 12a-aza-C-homo-5α-pregn-1-ene-3,12,20-trione (VI); the n.m.r. spectrum showed the AB pattern of a Δ^1-3-ketone.



I, R = R′ = H
III, R = Ac, R′ = OH
V, R = Ac, R′ = H



II, R = H
IV, R′ = OH



VI

It is interesting that the ultraviolet spectra of all products showed a hypsochromic shift of about 4 mμ usually associated with 11-keto steroids. To our knowledge, there is only one previous example of direct conversion of a ring A/B saturated steroid 3-alcohol derivative to a $\Delta^{1,4}$-3-ketone by fermentation.[9]

(1) Part III, R. H. Mazur, *J. Org. Chem.*, **28**, 248 (1963).

(2) R. H. Mazur, *J. Am. Chem. Soc.*, **82**, 3992 (1960).

(3) R. H. Mazur, *ibid.*, **81**, 1454 (1959).

(4) J. A. Zderic, H. Carpio, and D. C. Limon, *J. Org. Chem.*, **27**, 1125 (1962).

(5) J. A. Zderic and J. Iriarte, *ibid.*, **27**, 1756 (1962).

(6) E. S. Rothman and M. E. Wall, *J. Am. Chem. Soc.*, **78**, 1744 (1956).

(7) C. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956).

(8) D. Burn, D. N. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

(9) V. E. Origoni, Neil E. Rigler, and J. J. Goodman, U. S. Patent 3,047,468 (July 31, 1962).