TABLE I

CONDENSATIONS

Bromobenzyl alcohol	Phenol	Product Substituted 4-hydroxydiphenylmethane	Yield, %	M.p., °C. This work	M.p., °C. Lit.[8]	Analyses Bromine, % Calcd.	Analyses Bromine, % Found
Para	Phenol	4[1]-Bromo	48–53	64.5–65.0		30.37	30.31
				85.0–85.5	82–83		30.30
Ortho	Phenol	2[1]-Bromo	41	83.6–84.2	71–73	30.37	30.38
Para	2,6-Dibromo	3,5,4[1]-Tribromo	40–44	88.0–88.2	81–82	56.95	56.73
Ortho	2,6-Dibromo	3,5,2[1]-Tribromo	27	89.4–89.8	78–80	56.95	56.78

TABLE II

CONDENSATIONS

Compound condensed	Method of preparation	Product 4-Hydroxy-4′-bromodiphenylmethane M.p., °C.	Yield, %	Analyses, % Bromine, calcd. 30.37 Found
p-Bromobenzyl alcohol	Grignard	64.5-65.0	48-53	30.30
		85.0-85.5		30.33
p-Bromobenzyl chloride	Alcohol + concd. HCl	64.5-65.0	48	30.39
		85.0-85.5		30.40
p-Bromobenzyl chloride	Chlorination of *p*-bromotoluene	64.5-65.0	47.2	30.30
		85.0-85.5		30.25
p-Bromobenzyl bromide	Bromination of *p*-bromotoluene	64.5-65.0	50.1	30.29
		85.0-85.5		30.28

fonyl esters were recrystallized from alcohol and the α-naphthylurethans from ligroin, b.p. 60–90°, Table III.

The benzoyl ester made from either crystalline form of 4-hydroxy-4′-bromodiphenylmethane showed identical melting points; mixtures gave no depression.

The benzenesulfonyl esters made from 4-hydroxy-4′-bromodiphenylmethane exhibited dimorphism. Mixed melting points of the two forms were between the melting points of the separate forms.

The ketone 4-hydroxy-4′-bromobenzophenone,[9] m.p. 191° and 4-hydroxy-2′-bromobenzophenone,[10] m.p. 114° were prepared by the condensation of phenetole with the appropriate bromobenzoyl chloride followed by splitting of the ether by hydrobromic acid. The ketones were reduced by the Huang-Minlon modification of the Wolff–Kishner reduction.[11]

TABLE III

DERIVATIVES

Substituted 4-hydroxydiphenylmethanes	Melting point, °C.	Benzoyl ester Analyses Bromine, % Lit.[8]	Calcd.	Found	Benzenesulfonyl ester M.p., °C.	Analyses, Bromine, % Calcd.	Found	α-Naphthylurethan M.p., °C.	Analyses, Bromine, % Calcd.	Found
4[1]-Bromo	126.5–127.0	118.5–120	21.77	22.19	68.0–68.4	19.82	19.68	139.0-140.0	18.62	18.49
					79.5–80		19.71			
2[1]-Bromo	76.0–76.5	64–65	21.77	22.46	54.0-54.5	19.82	19.61	151.8–152.4	18.62	18.51
3,5,4[1]-Tribromo	147.0–147.8	144–145	45.67	45.93	141.0–141.4	42.74	42.53	162.5–163.0	40.65	40.60
3,5,2[1]-Tribromo	107.6–108.0	.....	45.67	45.41	133.2–133.8	42.74	42.49	159.4–160.0	40.65	40.57

Microscopic examination of a melt of either of the dimorphic forms seeded at one side of the melt by crystals of the high melting form and at the other side by crystals of the low melting form showed two typical crystal formations meeting at a common boundary. On standing the boundary moved toward the side seeded with the lower melting crystal until all the unstable form had been consumed.

Benzoyl, benzenesulfonyl esters and α-naphthylurethans were prepared by the usual procedures and recrystallized to constant melting points. The benzoyl and benzenesul-

Debromination of the hydroxybromodiphenylmethanes was carried out using Raney nickel.[12]

(9) P. J. Montagne, *Chem. Weekblad.*, **14**, 526 (1917).

(10) P. J. Montagne, *Rec. trav. chim.*, **42**, 509 (1923).

(11) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946).

(12) E. Schwenk, D. Papa and H. Ginsberg, *Ind. Eng. Chem., Anal. Ed.*, **15**, 576 (1943).

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Formation and Ring-Opening of Alkene Sulfides

BY EUGENE E. VAN TAMELEN

A mechanism for the transformation of a 1,2-epoxide to a 1,2-sulfide by alkali thiocyanates is proposed, and experimental evidence supporting this mechanism is presented. A synthesis of cyclopentene sulfide, the preparation of which fails by the above method, is described. Various conversions which point to a *trans* ring-opening of cyclohexene sulfide are presented.

A considerable bulk of evidence concerning the mechanism of 1,2-epoxide formation from 1,2-halohydrins and the ring-opening of epoxides has been accumulated in recent years.[1a] On the other hand, the closely related 1,2-sulfides have been subjected only to a more general type of investigation; studies of the steric and mechanistic aspects of their chemistry have been limited thus far to the direction of ring-opening of propylene sulfide.[1b]

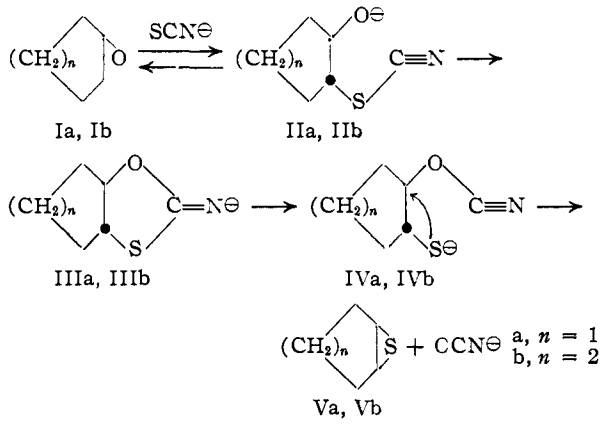
It is the purpose of this work to (1) obtain some evidence relating to the mechanism of 1,2-sulfide formation from 1,2-oxides and (2) determine the stereochemical course of the ring opening of 1,2-sulfides leading to products of the type A-C-C-S-B.

Several methods of preparing 1,2-sulfides have been recorded, among which may be mentioned the treatment of 1,2-halothiocyanates or dithiocyanates with sodium sulfide[2]; the ring-closure of 2-chlorothiols by means of weakly alkaline buffered

(1) (a) For a recent review by S. Winstein and R. Henderson, see R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 1; (b) W. Davies and W. E. Savige, *J. Chem. Soc.*, 317 (1950).

(2) M. M. Delépine, *et al.*, *Bull. soc. chim. France*, **27**, 740 (1920); **29**, 136 (1921); **33**, 703 (1923).

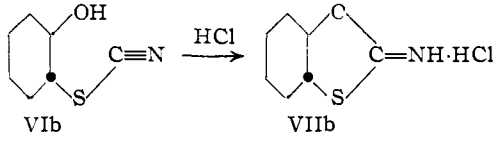
solutions[3]; thermal dehydration of 2-hydroxymercaptans[4]; and direct sulfurization of olefins with ethyl tetrasulfide.[5] By far the most widely used method, however, is the direct conversion of 1,2-oxides to 1,2-sulfides through the use of an alkali thiocyanate.[6] A plausible mechanism for this reaction, applied below to the alicyclic series, involves the following intermediates.[7]



It should be pointed out that this sequence is also rational in a stereochemical sense. The ring-opening of cyclohexene oxide has been shown to proceed, in all cases studied, with exclusive Walden inversion in acid, neutral or basic media[1]; thus, in the reaction under consideration, the ring-opening of this oxide leads to the anion of *trans*-2-hydroxycyclohexylthiocyanate IIb. S→O migration of the cyano group *via* the form IIIb yields the anion of *trans*-2-mercaptocyclohexyl cyanate IVb; the latter is favorably oriented for a *trans* ring-closure to cyclohexene sulfide Vb and cyanate ion, analogous to epoxide formation from 2-halocyclohexanols, for which the *trans* configuration is also requisite.[8]

Support for this mechanism was gained first of all by an investigation in the cyclo*pentane* series. Application of this scheme to cyclopentene oxide Ia involves the intermediate form IIIa, the skeleton of which consists of two five-membered rings fused in the *trans* sense. This ring system has been amply demonstrated to involve a considerable amount of strain[9,10]; in fact only one such case has been recorded.[9] Thus form IIIa was predicted to represent a difficultly obtainable or prohibited molecular state, and the preparation of cyclopentene sulfide *via* this sequence should be very slow or fail entirely. Step Ia → IIa should offer no obstacle, since displacement occurs more readily on the cyclopentane than on the cyclohexane ring, as Brown has recently emphasized.[11] Actually it was found that treatment of cyclopentene oxide with potassium thiocyanate under conditions equivalent to, or more vigorous than, those which bring about a 73% yield of cyclohexene sulfide, gave only recovered oxide Ia. That the attack of thiocyanate ion on Ia led to intermediate IIa at least in part, is clear from the gradually acquired basicity of the reaction medium; this observation is paralleled by the well-known ring-opening of oxides by the alkali halides, this reaction type also leading to a basic medium.[12] A very small amount of higher boiling product was isolated, which may have contained some IIa (protonated) or Va, but the material was not formed in quantity sufficient for fractionation.

Additional support for the mechanism proposed above arose from the preparation of protonated derivatives corresponding in structure to forms IIb and IIIb and the demonstration that each could be transformed into cyclohexene sulfide Vb. *trans*-2-Hydroxycyclohexyl thiocyanate VIb was prepared in fair yield through the ring-opening of Ib with thiocyanic acid. The slow addition of a dilute aqueous solution of potassium hydroxide to a well-stirred solution of VIb in ethanol gave a 69% yield of cyclohexene sulfide, Vb. Similar treatment of *trans*-2-hydroxy*cyclopentyl* thiocyanate VIa did not lead to the corresponding sulfide, but gave only colored material which decomposed upon attempted distillation under reduced pressure. The crystalline *trans*-hydrochloride VIIb was readily prepared by saturating VIb with dry hydrogen chloride gas; the reaction is an intramolecular modification of a general method of Knorr[13] for preparing the hydrochlorides of thiocarbonic acid-iminoesters from equimolar quantities of an alcohol and an aliphatic or aromatic thiocyanate. Liberation of the free iminoester through the action of an equimolar quantity of



aqueous sodium hydroxide upon VIIb, followed by the slow addition of a second mole of base under controlled conditions, led to a good yield of sulfide Vb, presumably *via* the intermediate IIIb. It should be emphasized that the addition of strong alkali to either VIb or VIIb must be made under carefully controlled conditions, since the resulting sulfide is easily polymerized by aqueous base.[14]

Knorr[13] has reported that the free acyclic thiocarbonic acid-iminoesters are completely stable substances which are capable of withstanding distillation. It was found in the present study, however, that the free base corresponding to VIIb *spontaneously eliminated cyanic acid in ether solution at room temperature* with the formation of cyclo-

(3) J. Coltof, U. S. Patent 2,183,860 (1939).

(4) W. A. Lazier and F. K. Signaigo, U. S. Patent 2,396,957 (1946).

(5) S. O. Jones and E. E. Reid, THIS JOURNAL, **60**, 2452 (1938).

(6) (a) I. G. Farbenind., French Patent 797,621 (1936); (b) H. R. Snyder, J. M. Stewart and J. B. Ziegler, THIS JOURNAL, **69**, 2672 (1947); (c) C. C. J. Culvenor, W. Davies and K. Pausacker, *J. Chem. Soc.*, 1050 (1946).

(7) Each of the forms II, III and IV is presumed to be in equilibrium with the corresponding protonated structure.

(8) P. D. Bartlett and R. H. Rosenwald, THIS JOURNAL, **56**, 1990 (1934).

(9) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 935 (1934).

(10) W. E. Grigsby, J. Hind, J. Chanley and F. H. Westheimer, THIS JOURNAL, **64**, 2606 (1942).

(11) H. C. Brown, R. S. Fletcher and R. B. Johannesen, *ibid.*, **73**, 212 (1951).

(12) J. N. Brönsted, M. Kilpatrick and M. E. Kilpatrick *ibid.*, **51**, 428 (1929).

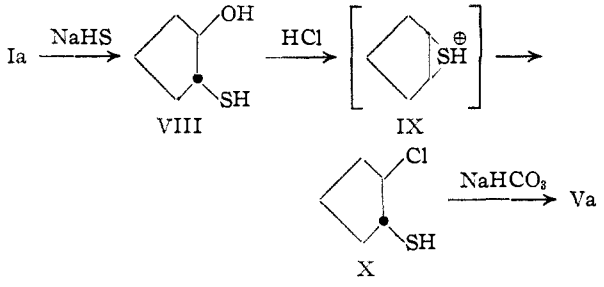
(13) A. Knorr, *Ber.*, **49**, 1735 (1916).

(14) C. C. J. Culvenor, W. Davies and N. S. Heath, *J. Chem. Soc.*, 282 (1949).

hexene sulfide. This facile transformation demonstrates a significant driving force for the formation of 1,2-sulfides and provides additional support for the reaction scheme presented above.

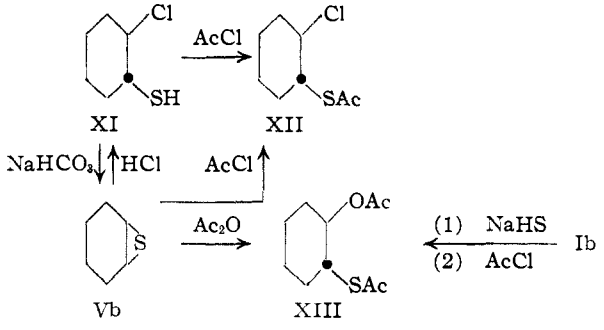
That the ring system represented by IIIa is sterically prohibited was also shown by the failure of *trans*-2-hydroxycyclopentyl thiocyanate VIa to give the thiocarbonic acid-iminoester upon treatment with hydrogen chloride. Prolonged standing of the reaction mixture gave only polymeric material, which would be expected to form by the intermolecular condensation of VIa.

At this point, it became of interest to prepare the hitherto unknown cyclopentene sulfide Va, unobtainable by the above route. The synthesis was accomplished through the following sequence, starting with cyclopentene oxide. Ring cleavage of Ia by sodium hydrogen sulfide in methanol



gave a fair yield of *trans*-2-hydroxycyclopentanethiol VIII. Stirring the latter with concentrated hydrochloric acid at room temperature led to a 61% yield of 2-chlorocyclopentanthiol X. The ease with which this reaction is brought about may be attributed to a sulfonium ion[15] intermediate IX; this structure, upon nucleophilic attack by chloride ion, would lead to a chlorothiol of the desired *trans* configuration. That the latter actually is *trans* was shown by its conversion to the desired sulfide Va by aqueous sodium bicarbonate. Cyclopentene sulfide undergoes decomposition to trimethylsulfonium iodide through the action of methyl iodide, as does cyclohexene sulfide.[14]

Evidence for the stereochemical course of the ring-opening of 1,2-sulfides was gained through the study of three cases, each of which can best be interpreted in terms of a Walden inversion. The results are summarized in the scheme below.



The action of hydrochloric acid on cyclohexene sulfide, previously reported by Culvenor, Davies and Heath,[14] leads to 2-chlorocyclohexanethiol XI. This material is readily converted back in good yield to Vb by sodium bicarbonate at room temperature. This result indicates a *trans* configuration for XI, since, by analogy with oxide formation, only that form is favorably oriented for an intramolecular nucleophilic displacement. Secondly, the ring-opening of Vb with acetyl chloride[14] yields *trans*, rather than *cis*, 2-chlorocyclohexanethiol acetate XII, since the same material is obtained upon acetylation of XI, which is, of course, *trans*. Finally, the diacetate of 2-hydroxycyclohexanethiol XIII resulting from the opening of Vb with acetic anhydride must be *trans*, in that XIII was also obtained by the conversion of cyclohexene oxide to 2-hydroxycyclohexanethiol XV[16] by sodium hydrogen sulfide, followed by acetylation.[14] The intermediate XV is assigned the *trans* configuration, which would result from the demonstrated mode of ring-opening of oxides, as was pointed out earlier.

Culvenor, *et al.*,[14] have reported that the reaction of acetic acid with Vb yields 26% of 2-acetoxycyclohexanethiol and 48% of 2-mercaptocyclohexyl 2-acetoxycyclohexyl sulfide. Numerous attempts to repeat this work under a variety of conditions led in our hands only to the latter product.

Experimental[17]

Cyclohexene Sulfide (Vb).—The material was prepared by a modification of the method of Snyder, *et al.*[6] Ninety-eight grams (one mole) of cyclohexene oxide was divided into two equal portions and one portion added to a solution of 121 g. of potassium thiocyanate in 100 ml. of water and 75 ml. of 95% ethanol. After standing for three to four hours, the second portion of oxide was added and the solution stirred for 36 hours at room temperature. After this time a considerable amount of potassium cyanate had precipitated, which was identified by suitable qualitative tests.[18] The supernatant layer of sulfide which had formed was extracted with 50 ml. of ether; the ether extract was washed twice with saturated sodium chloride solution. After drying over sodium sulfate, the material was distilled through a short Vigreux column. After redistillation of the forerun, the sulfide boiling over the range 71.5–73.5° (21 mm.) amounted to 83.5 g. (73%); $n^{25}D$ 1.5311. The physical constants reported for this material are: b.p. 83–87° (46 mm.), $n^{20}D$ 1.5292[6b]; b.p. 67–68° (16 mm.), $n^{20}D$ 1.5309.[6c]

When cyclopentene oxide (b.p. 99–101°) was subjected to identical (except for the omission of ethanol) reaction conditions, or heated at 60° for 15 hours, about 80% of the starting material could be recovered. When the reaction was attempted in the presence of ethanol, potassium cyanate did not precipitate, and again no sulfide could be isolated. In this case, however, cyclopentene oxide could be recovered only with difficulty, since the flask contents remained homogeneous and the oxide could not be readily separated from the ethanol by distillation. The oxide used was prepared according to the method of Osterberg[19] from *trans*-2-chlorocyclopentanol.[20]

***trans*-2-Hydroxycyclohexyl Thiocyanate (VIb).**—The method is similar to that used by Wagner-Jauregg[21] for the preparation of 2-hydroxyethyl thiocyanate. Seventy-three grams (0.75 mole) of potassium thiocyanate was dissolved in 250 ml. of water, and the solution was transferred, along with 250 ml. of ether and excess crushed ice, to a two-liter separatory funnel. After cooling thoroughly by shaking, 100 g. of 85% phosphoric acid was added in several portions

(15) P. D. Bartlett and C. G. Swain, THIS JOURNAL, **71**, 1406 (1949).

(16) C. C. J. Culvenor, W. Davies and N. S. Heath, *J. Chem. Soc.*, 278 (1949).

(17) All boiling points are uncorrected.

(18) F. D. Treadwell and W. T. Hall, "Analytical Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1937, p. 360.

(19) A. E. Osterberg, "Organic Syntheses," Col. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 179.

(20) H. B. Donahoe and C. A. Vanderwerf, *ibid.*, Vol. 30, p. 24.

(21) T. Wagner-Jauregg, *Ann.*, **561**, 87 (1949).

while shaking was continued. The dark red, ethereal solution of thiocyanic acid was quickly separated, and to it was added 24.5 g. (0.25 mole) of cyclohexene oxide, cooled to about 0°. The reaction mixture was kept packed in ice until the red color was discharged (about ten minutes was required). A small amount of hydroquinone was added,[22] and the ether solution was dried over sodium sulfate. Distillation gave 18.6 g. (48%) of a slightly yellow, viscous oil, b.p. 148–152° (7 mm.), $n^{25}D$ 1.5307.

Anal. Calcd. for $C_7H_{11}OSN$: C, 53.47; H, 7.05; S, 20.39; N, 8.21. Found: C, 53.68; H, 6.79; S, 20.27; N, 7.82.

Conversion of VIb to Cyclohexene Sulfide Vb.—Fourteen grams (0.09 mole) of VIb dissolved in 7 ml. of ethanol was stirred vigorously while a solution of 5.0 g. of 85% potassium hydroxide in 10 ml. of water was added dropwise over a period of 75 minutes. During the addition the reaction flask was cooled externally by water at room temperature. Stirring was continued for 15 hours, after which the mixture was extracted with ether; the extract was washed with sodium chloride solution and dried over sodium sulfate. Distillation gave 6.0 g. (69%) of cyclohexene sulfide, b.p. 67–69° (16 mm.), which was converted to trimethylsulfonium iodide, dec. 215° (reported dec. 215°) by methyl iodide.[14]

***trans*-2-Hydroxycyclopentyl Thiocyanate (VIa).**—The procedure described above was used, except that the reactants after mixing were allowed to stand for two hours in a cold room. The yield of product boiling at 133–134° (7 mm.) was 56%; $n^{25}D$ 1.5238. VIa and VIb exhibited absorption in the infrared at 2.92 μ and at 4.65 μ, characteristic, respectively, of the hydroxyl and cyanide groups.

Anal. Calcd. for C_6H_9OSN: C, 50.42; H, 6.33; S, 22.39; N, 9.78. Found: C, 50.79; H, 6.27; S, 22.34; N, 9.92.

Upon treatment of VIa with base under conditions similar to those described under VIb above, a dark-colored reaction mixture formed, which gave, upon extraction, only undistillable material.

***trans*-2-Imino-4,5,6,7,8,9-hexahydro-1,3-benzoxathiole Hydrochloride (VIIb).**—2-Hydroxycyclohexyl thiocyanate VIb (3.14 g., 0.02 mole) was placed in a 25-ml. erlenmeyer flask outfitted with an inlet tube for hydrogen chloride gas extending to the bottom of the flask and an outlet tube protected at one end by Drierite. Care was taken to exclude moisture as much as possible throughout the entire operation. Dry hydrogen chloride was bubbled rapidly through the flask, which was kept cool in an ice-bath, until the liquid became immobile (about ten minutes was required). Anhydrous ether was added and the flask contents crystallized by scratching. The ethereal suspension was returned to the ice-bath and saturated with hydrogen chloride. After standing for several hours the solid hydrochloride was filtered and washed well with anhydrous ether. After drying, the microcrystals weighed 3.35 g. (89%). An analytical sample was prepared by recrystallizing a portion of the material several times from dry ether–dry methanol. The dry, pure material (dec. above 220°) is not hygroscopic.

Anal. Calcd. for $C_7H_{12}OSNCl$: C, 43.42; H, 6.20; S, 16.56. Found: C, 43.42; H, 5.87; S, 17.07.

trans-2-Hydroxycyclopentyl thiocyanate VIa upon similar treatment, appeared to remain unchanged. Upon standing overnight, however, the material had become very viscous; it did not crystallize upon standing, scratching or the addition of ether.

Conversion of VIIb to Cyclohexene Sulfide Vb (A).—Seventeen grams of the hydrochloride VIIb was dissolved in 50 ml. of water and a solution of 12.1 g. of potassium carbonate in 25 ml. of water was added with stirring. The free base precipitated as an oil and was extracted with ether. Upon standing overnight the solution had deposited a considerable amount of white, powdery solid (cyamelide). Upon removal of the ether on the steam-bath, the solution became semisolid due to the precipitation of more cyamelide. The mixture was extracted with ether and the extracts dried. Distillation gave cyclohexene sulfide, b.p. 68–70° (17 mm.), which was converted to trimethylsulfonium iodide as before. The yield of sulfide was poor (20–30%) probably because of the polymerizing action of the free cyanic acid formed; the former is known to be polymerized by many acids.[14] The cyamelide was identified by its physical properties and by depolymerization to cyanic acid.

(B) Thirteen and three-tenths grams (0.069 mole) of VIIb was dissolved in 30 ml. of water. Upon the slow addition of a solution of 2.75 g. of sodium hydroxide in 20 ml. of water, with stirring, the free base separated. Twenty-five ml. of ether was added, and a solution of 2.40 g. of sodium hydroxide dissolved in 25 ml. of water was added dropwise with cooling and vigorous stirring over a period of one hour. The ether layer was washed twice with saturated sodium chloride solution, dried and distilled. The cyclohexene sulfide, b.p. 67–70° (16 mm.), amounted to 5.8 g. (74%) and was converted to trimethylsulfonium iodide to establish its identity.

***trans*-2-Hydroxycyclopentanethiol (VIII).**—A solution of 0.2 mole of sodium hydrogen sulfide in methanol was prepared according to the directions of Culvenor, *et al.*[16] Cyclopentene oxide (16.8 g., 0.2 mole) was added in one lot to the sodium hydrogen sulfide solution cooled in ice, and hydrogen sulfide was bubbled through for one hour after the addition. After standing at room temperature overnight, the solution was diluted with 100 ml. of water, and 75 ml. of 1 *N* sulfuric acid was stirred in. Three chloroform extractions were combined, washed with dilute, aqueous sodium bicarbonate, and the product was then isolated by distillation. Seven and one-half grams (32%) of the hydroxylthiol was collected, boiling over the range 103–123° (18 mm.); a considerable amount of higher boiling residue remained in the stillpot. The entire fraction, upon redistillation, boiled at 92–94° (15 mm.); $n^{25}D$ 1.5190.

Anal. Calcd. for $C_5H_{10}OS$: C, 50.80; H, 8.53. Found: C, 50.51; H, 8.23.

***trans*-2-Chlorocyclopentanethiol (X).**—*trans*-2-Hydroxycyclopentanethiol (17.8 g.) was stirred for 12 hours at room temperature with 100 ml. of concentrated hydrochloric acid. The product was extracted with chloroform, and the combined extracts were washed twice with water. Distillation gave 12.5 g. (61%) of product, b.p. 51.0–51.5° (5 mm.).

Anal. Calcd. for C_5H_9SCl: S, 23.45. Found: S, 24.00.[23]

Cyclopentene Sulfide (Va).—Ten and four-tenths grams of *trans*-2-chlorocyclopentanthiol was stirred for 90 minutes with a mixture of 12 g. of sodium bicarbonate in 120 ml. of water and 30 ml. of ethanol. The sulfide was then extracted with 30 ml. of ether. After washing the extract with sodium chloride solution and drying, distillation yielded 5.75 g. (75%) of cyclopentene sulfide, b.p. 69–70° (65 mm.), $n^{25}D$ 1.5222. Upon standing with dry methyl iodide for several days, the sulfide was converted to trimethylsulfonium iodide, dec. 215°.

Anal. Calcd. for C_5H_8S: C, 59.94; H, 8.05; S, 32.01. Found: C, 60.15; H, 7.79; S, 31.63.

Ring-closure of *trans*-2-Chlorocyclohexanethiol (XI).—The reaction was carried out as described above, using 7.2 g. of XI, prepared according to Culvenor, *et al.*[14] The entire product, except for a small amount of undistillable residue, boiled at 60.0–61.5° (12 mm.), and the yield was 4.85 g. (76%). The sulfide was converted to trimethylsulfonium iodide for identification.

***trans*-2-Chlorocyclohexanethiol Acetate (XII).**—Seven and one-half grams (0.05 mole) of *trans*-2-chlorocyclohexanethiol XI was added slowly with cooling to 7 ml. of acetyl chloride. The solution was refluxed for two hours and distilled directly, yielding 8.1 g. (84%) of the acetate, b.p. 127–129° (14 mm.), $n^{25}D$ 1.5178. Repetition of the directions of Culvenor, *et al.*,[14,24] for the preparation of XII from cyclohexene sulfide and acetyl chloride afforded a liquid boiling at 126–127° (13 mm.), $n^{25}D$ 1.5181, which gave the following analysis: Calcd. for $C_8H_{13}OSCl$: Cl, 18.39. Found: Cl, 18.00. The infrared spectra of the esters were identical (2–12 mμ).

***trans*-2-Hydroxycyclohexanethiol Diacetate (XIII).**—A solution composed of 12.0 g. of cyclohexene sulfide, 20 ml. of dry pyridine and 20 ml. of acetic anhydride was heated on the steam-bath for 15 hours. Water was added gradu-

(22) Hydroquinone has been used to stabilize 2-hydroxyethyl thiocyanate (see ref. 21).

(23) The carbon and chlorine analyses (45.91 and 22.58, respectively) varied significantly from those calculated for X, but agreed with those calculated for a mixture of X and Va. It was noted that X, after standing for several days in a sealed container, released hydrogen chloride upon exposure to the atmosphere.

(24) Culvenor (ref. 14) reported a boiling point of 110° (20 mm.) for the same product.

ally to the hot, dark reaction product in order to decompose the excess acetic anhydride. After cooling, the mixture was extracted with chloroform. Distillation gave, after a forerun of several drops, 10.5 g. (46%) of diester, b.p. 143–146° (16 mm.), $n^{25}D$ 1.4936. The infrared spectrum was identical with that of XIII prepared by acetylation[14] of *trans*-2-hydroxycyclohexanethiol obtained by the ring-opening of cyclohexene oxide with sodium hydrogen sulfide.[16] The latter material possessed the following physical constants: b.p. 147–150° (19 mm.), $n^{25}D$ 1.4940.

Acknowledgment.—The author wishes to express his gratitude to Mr. Donald Johnson for the infrared spectra used in this investigation.

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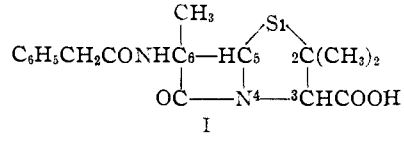
[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH, DIVISION OF ORGANIC CHEMISTRY]

Homologs of Penicillin Degradation Products. I. α-Methylpenaldic Acid Derivatives

BY HOMER E. STAVELY[1] AND MARY BERESTECKI

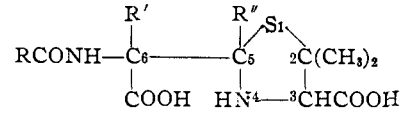
Some alkyl substituted penaldic acid derivatives were prepared as intermediates for attempted syntheses of penicillin homologs. Racemic α-methylbenzylpenaldic acid diethyl acetal was resolved *via* the brucine salts and the D- and L-forms were converted into the corresponding oxazolones, methyl esters and amides. The preparation of α-methylbenzylpenaldic acid diethyl dithioacetal and α-methylphenylpenaldic acid diethyl acetal is described.

This series of papers will describe the preparation and reactions of some compounds which theoretically could be derived by degradation from the unknown substance 6-methylbenzylpenicillin (I). The eventual goal of this work was the synthesis of I.



I

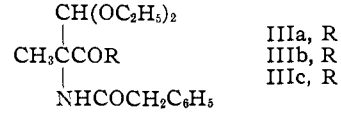
The final step of many unsuccessful attempts to synthesize a penicillin has been closure of the β-lactam ring, a penicilloic acid derivative (IIa) being the penultimate compound in the synthesis.[2]



IIa, R′, R″ = H
IIb, R′ = CH_3, R″ = H
IIc, R′ or R″ = alkyl or aryl

Since most of the monocyclic and bicyclic β-lactams known are heavily substituted with alkyl or aryl groups[3] it might be expected that a penicilloic acid derivative having alkyl or aryl radicals on carbon atoms 5 and/or 6 (IIc) could be β-lactamized more readily than the unsubstituted derivative.[4]

As the first step in the synthesis of penicillin homologs with substituents on carbon atom 6, the preparation of certain α-methylpenaldic acid derivatives was undertaken. Heilbron and his associates[5] were the first to report the preparation of DL-α-phenylacetylamido-α-diethoxymethylpropionic acid (IIIa) (α-methylbenzylpenaldic acid diethyl acetal) by reaction of DL-phenylacetylalanine[6] with ethyl orthoformate in hot acetic anhydride. The British investigators found that the acetal group of IIIa possessed an unusual degree of stability, since it was unaffected by dilute acid and failed to form a 3,5-dinitrophenylhydrazone or a semicarbazone under mild conditions. Treatment with a warm solution of dinitrophenylhydrazine in dilute sulfuric acid degraded the acid but the product was the dinitrophenylosazone of methylglyoxal. In the reaction with phenylacetylalanine, ethyl orthoformate might conceivably have reacted with the active methylene of the phenylacetyl residue, but the isolation of this osazone proved that the reaction product had structure IIIa. This conclusion has been further strengthened by the successful synthesis of DL-α-benzamido-α-diethoxymethylpropionic acid (α-methylphenylpenaldic acid diethyl acetal) from benzoylalanine by the same procedure in this Laboratory.



IIIa, R = OH
IIIb, R = OCH_3
IIIc, R = NH_2

In the present work a number of alkaloids were utilized in unsuccessful attempts to resolve the racemic acid IIIa, but the resolution was finally accomplished with the aid of brucine in dilute aqueous solution. The separation of the two diastereoisomeric brucine salts was aided by the fact that the more soluble salt apparently has a negative differential solubility, since heating the cold mother liquor caused an oily precipitation which redissolved on cooling. Decomposition of the insoluble crystalline salt by the usual methods afforded an acid with an $[\alpha]D$ of $-10.5 \pm 1°$ (chloroform) and $[\alpha]D$ $+9.6 \pm 1°$ in normal sodium hydroxide. Decomposition of the first mother liquor gave the slightly optically impure optical antipode, $[\alpha]D$ $+8.8°$ in chloroform, $[\alpha]D$ $-9.2°$ in normal sodium hydroxide, but the rotation could be raised somewhat by crystallization from aqueous ethanol. The L configuration has been tentatively assigned to the acid forming the insoluble brucine salt, since this form has a dextro rotation in alkaline solution, as is the case with L(+)-benzoylalanine and other L(+)-acylamino acids.

(1) Pharmaceutical Research Division, Commercial Solvents Corporation, Terre Haute, Indiana.

(2) H. T. Clarke, J. R. Johnson and R. Robinson, editors, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, pp. 849–891.

(3) See Chapter XXVI, "The Chemistry of Penicillin," for an excellent review of β-lactam chemistry.

(4) This has been borne out by the recent synthesis of a 5-phenyl penicillin derivative by J. C. Sheehan, *et al.*, THIS JOURNAL, **72**, 3828 (1950).

(5) Ref. 2, pp. 502, 765, 838. The work mentioned was reported in detail in C.P.S. 105 by J. R. Catch, A. H. Cook and I. M. Heilbron, dated July 4, 1944.

(6) G. J. Shiple and C. P. Sherman, *J. Biol. Chem.*, **53**, 463 (1922).