67–75°. Purification by sublimation gave a sample melting at 87–88° which did not depress the melting point of an authentic sample.[3]

The ether solution containing the alkali-insoluble portion from the Grignard gave an oily solid (5.3 g.) melting at 57–69°. Sublimation under reduced pressure gave the white 2,2-dimethylchromanone melting at 87–88° and gave no depression with an authentic sample.

The 2,4-dinitrophenylhydrazone crystallized from ethanol–ethyl acetate melted at 225–226°.

Anal. Calcd. for $C_{17}H_{16}N_4O_5$: C, 57.32; H, 4.53; N, 15.72. Found: C, 57.31; H, 4.65; N, 15.37.

A mixture with the 2,4-dinitrophenylhydrazone of authentic 2,2-dimethylchromanone showed no depression.

IOWA CITY, IOWA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Reaction of Thiacyclopropanes (Olefin Sulfides) and Thiacyclobutanes with Organolithium Compounds[1]

BY F. G. BORDWELL, HARRY M. ANDERSEN AND BURNETT M. PITT

RECEIVED SEPTEMBER 29, 1953

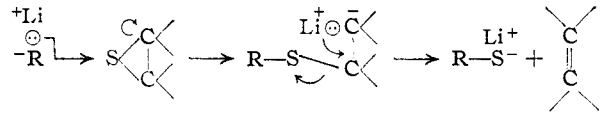
Alkyl- and aryllithium reagents were found to effect a 1,2-elimination reaction with thiacyclopropanes giving rise to olefins and lithium mercaptides. This reaction constitutes a new method for preparing thiols; it is chiefly useful for preparing thiophenols. With thiacyclobutane ring opening occurred, but attack of R^- (or Ar^-) was again on sulfur rather than on carbon (thiacyclopentane gave no reaction). The reaction gave a mixture of products, which can be formulated as coming from the initial substance, $RSCH_2CH_2CH_2Li$. Lithium aluminum hydride reacted with thiacyclopropanes to give secondary lithium mercaptides.

Thiacyclopropanes (olefin sulfides) react with some nucleophilic reagents including lithium diethylamide,[2a] primary and secondary amines,[2b] and mercaptide ions[2b,c] to give products of ring opening which are comparable to those formed from epoxides. In the course of a program of study of the methods of synthesis and reactions of divalent sulfur compounds, an attempt was made to prepare mercaptans by the reaction of thiacyclopropanes with organometallic compounds in a manner analogous to the formation of alcohols by the coupling of epoxides with Grignard reagents or organolithium compounds. However, the reactions did not proceed as anticipated. Alkyl- or aryllithium reagents appropriated the sulfur from the thiacyclopropane molecule to form alkyl or aryl mercaptides and olefins.

The reaction of phenyllithium with 2-thiabicyclo-[4,1,0]heptane (cyclohexene sulfide) gave 60% of thiophenol (as the lithium salt) and 52% of cyclohexene. Butyllithium gave 63% of 1-butanethiol and 67% of cyclohexene. Similarly, 81% of thiophenol was obtained from phenyllithium and methylthiacyclopropane (propylene sulfide). From comparable experiments using thiacyclopropane (ethylene sulfide) 51% of thiophenol and 27% of 1-butanethiol were obtained.

The reaction of aryllithium reagents and the readily available propylene sulfide[3] constitutes a new method for preparing thiophenols. It serves as an alternative to the reaction of aryl Grignard reagents and sulfur (S_8), which is awkward due to the insolubility of sulfur in ether, and usually gives very poor yields. The method has also been applied in our laboratory to the preparation of *m*- and *p*-dimethylaminothiophenols in yields of 70–80%.[4]

These reactions probably can best be formulated as an attack by the alkyl- or arylcarbanion on sulfur, facilitated by coördination of sulfur with the lithium cation. Breaking of the carbon–sulfur



bond gives rise to an electron pair which can simultaneously or subsequently initiate a 1,2-elimination reaction to form the olefin and liberate the sulfur in the form of lithium mercaptide. The attack of the incipient carbanion on sulfur in olefin sulfides and on carbon in olefin oxides may be rationalized by pointing to the fact that (1) sulfur is more electropositive and polarizable than oxygen, (2) the carbon–sulfur dipole is small, and (3) divalent sulfur in disulfides, sulfenyl halides, etc., is known to be susceptible to attack by nucleophilic agents in displacement type reactions. A similar difference in susceptibility to attack was observed between chlorine and bromine in reactions with phenyllithium.[5] Whereas 1,2-dichlorides react with the elimination of hydrogen chloride (nucleophilic attack on hydrogen), 1,2-dibromides, such as cyclohexene dibromide, react with the elimination of bromine (nucleophilic attack on bromine).

Reactions of thiacyclopropanes with Grignard reagents were less clear-cut. Although an 87% yield of cyclohexene was obtained by the reaction of phenylmagnesium bromide and cyclohexene

(1) This investigation was supported by the American Petroleum Institute as part of Research Project 48B. An account of this work was presented at the Milwaukee Meeting of the American Chemical Society, March, 1952.

(2) (a) H. Gilman and L. A. Woods, THIS JOURNAL, **67**, 1843 (1945); (b) H. R. Snyder, J. M. Stewart and J. B. Ziegler, *ibid.*, **69**, 2672, 2675 (1947); (c) C. C. J. Culvenor, W. Davies and N. S. Heath, *J. Chem. Soc.*, 282 (1949).

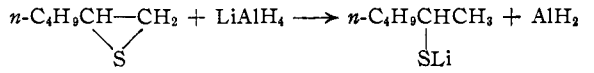
(3) French Patent 797,621; *C. A.*, **30**, 7122 (1936); C. C. J. Culvenor, W. Davies and K. H. Pausacker, *J. Chem. Soc.*, 1050 (1946); F. G. Bordwell and H. M. Andersen, THIS JOURNAL, **75**, 4959 (1953).

(4) Pierre J. Boutan, unpublished results.

(5) G. Wittig and G. Harborth, *Ber.*, **77B**, 306 (1944).

sulfide, no thiophenol was isolated and the nature of the sulfur containing product was not established. From the reaction with butylmagnesium bromide 19% of cyclohexene and 5% of 1-butanethiol were isolated; benzylmagnesium chloride gave 13% of cyclohexene, 12% of benzyl mercaptan and 5% of benzyl disulfide.

The reaction of thiacyclopropanes with lithium aluminum hydride was also found to proceed smoothly. Butylthiacyclopropane gave 2-hexanethiol, methylthiacyclopropane gave 2-propanethiol and cyclohexene sulfide gave cyclohexanethiol. No evidence for the formation of primary thiols in these reactions was obtained. These

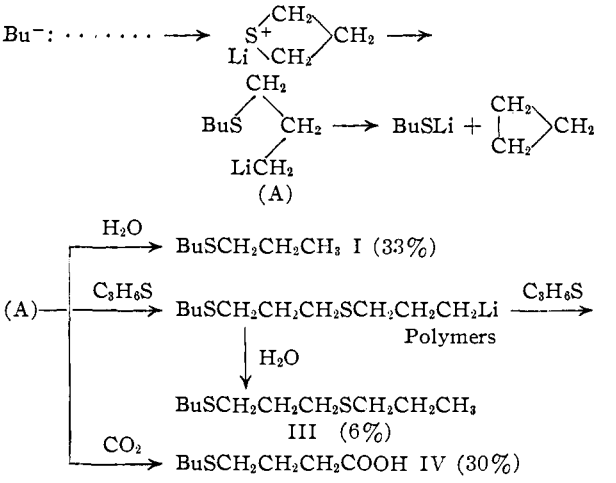


observations are consistent with attack of aluminohydride ion (AlH_4^-) on either the primary carbon or on sulfur with fission of the primary alkyl–sulfur bond.

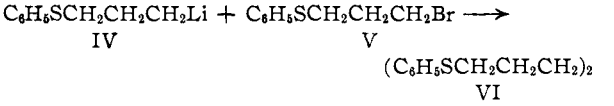
Trimethylene oxide has been shown to react with Grignard and lithium reagents about as readily and in the same manner as does ethylene oxide.[6] Similarly, it was found in the present investigation that thiacyclobutane (trimethylene sulfide), like the thiacyclopropanes, underwent an exothermic reaction with butyl- or phenyllithium. However, the reaction again differed from that of the oxygen analog in that attack occurred on sulfur rather than carbon. Strain in the thiacyclobutane ring is indicated by this exothermic reaction, since thiacyclopentane failed to undergo any reaction even under "forcing" conditions.

Hydrolysis of the reaction mixture from thiacyclobutane and butyllithium gave 33% of *n*-butyl *n*-propyl sulfide (I), 11% of 1-butanethiol (II), and 6% of a substance believed to be 4,8-dithiadodecane (III). These products seem to be best rationalized by assuming an attack of an incipient butylcarbanion on sulfur to give an intermediate (A), which reacts to some extent by an intramolecular displacement of ^-SBu to give cyclopropane and II (as the lithium mercaptide), and to some extent with more thiacyclobutane giving III (after hydrolysis) and polymers. The presence of (A) was substantiated by carbonation of the reaction mixture to give 30% of 3-(butylthio)-butyric acid (IV). No attempt was made to identify the gaseous product as cyclopropane, but this formulation seems very probable in view of the formation of 1-butanethiol and by analogy with the reaction of γ-iodopropyl phenyl ether with magnesium in butyl ether which has been shown to give phenol and cyclopropane.[7]

The reaction of thiacyclobutane with phenyllithium resembled that with butyllithium in the



formation of thiophenol (12%) and phenyl propyl sulfide (7%). In addition some 1,6-bis-(phenylthio)-hexane (VI) was isolated. The latter product probably arises from the coupling of γ-(phenylthio)-propyllithium (IV) and γ-(phenylthio)-propyl bromide (V), since the reaction of V with lithium in ether solution gave VI. In the reaction of phenyllithium with thiacyclobutane the source of V must



be a metal–halogen interchange between γ-(phenylthio)-propyllithium (IV) and unreacted bromobenzene (used for the preparation of phenyllithium). The coupling of IV and V was unexpected, since V cannot be present in very high concentration and alkyllithium reagents do not usually couple readily with alkyl halides. It is possible that γ-(phenylthio)-propyl bromide may be unusually susceptible to attack by nucleophilic agents, since in the reaction of 1,3-dibromopropane with sodium phenyl mercaptide appreciable amounts of 1,3-bis-(phenylthio)-propane were formed even when one-half mole of potassium phenyl mercaptide was added slowly to one mole (100% excess) of 1,3-dibromopropane.

Experimental[8]

Butyllithium and Cyclohexene Sulfide.—*n*-Butyllithium was prepared by the reaction of 60.0 g. (0.44 mole) of *n*-butyl bromide with 8.6 g. (1.23 g. atom) of lithium at −10° to 0° according to the procedure of Gilman, *et al.*[9] To the resulting ether solution of *n*-butyllithium was added 21.0 g. (0.18 mole) of cyclohexene sulfide[10] dissolved in 30 ml. of ether. The addition required about one-half hour and was accompanied by gentle refluxing. The mixture was stirred 2 hours more and was then allowed to stand overnight. It was next poured upon an equal volume of ice-water, the layers separated, and the ether layer washed twice with 2 *N* sodium hydroxide; the washings were combined with the aqueous phase. The ether phase was washed with water until the washings were neutral, dried over Drierite, and distilled to yield 9.8 g. (67%) of cyclohexene. The latter was characterized by reaction with 2,4-dinitrobenzenesulfenyl chloride

(6) C. G. Derick and D. W. Bissell, THIS JOURNAL, **38**, 2478 (1916); S. Searles, *ibid.*, **73**, 124 (1951).

(7) R. Paul, *Compt. rend.*, **192**, 964 (1931); the Grignard reagent is a likely intermediate in this reaction. H. Gilman and R. McCracken, *Rec. trav. chim.*, **46**, 463 (1927), reported an 81% yield of Grignard reagent from γ-chloropropyl phenyl ether on the basis of titration. We isolated an 82% yield of phenol on hydrolysis of this "Grignard reagent," so apparently this reaction also follows a course similar to that observed by Paul. See also, N. Rabjohn and M. S. Cohen, THIS JOURNAL, **74**, 6290 (1952), regarding the instability of Grignard reagents from γ-bromopropyl ethers.

(8) Microanalyses were by Misses Joyce Sorenson and Constance Brauer.

(9) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, THIS JOURNAL, **71**, 1499 (1949).

(10) C. Culvenor, W. Davies and K. Pausacker, *J. Chem. Soc.*, 1050 (1946).

to yield 2-chlorocyclohexyl-2′,4′-dinitrophenyl sulfide, m.p. 116–118°.[11] No depression of m.p. was observed when mixed with an authentic sample. The aqueous phase obtained above was acidified with hydrochloric acid to precipitate 1-butanethiol as an oil, which was separated. The aqueous phase was washed with pentane, the pentane washings combined with the oil, dried over Drierite, and distilled to yield 10.2 g. (63%) of 1-butanethiol, b.p. 95–97°. The latter was characterized as *n*-butyl 2,4-dinitrophenyl sulfide, m.p. 66–68°. No depression of m.p. was observed when mixed with an authentic sample.

Phenyllithium and Cyclohexene Sulfide.—This reaction and the work-up were carried out in the same way as described for *n*-butyllithium and cyclohexene sulfide, except that 40.0 g. (0.25 mole) of bromobenzene and 3.5 g. (0.50 g. atom) of lithium were used to prepare the phenyllithium. Cyclohexene, b.p. 80–82°, was isolated in 52% yield and again characterized as 2-chlorocyclohexyl 2′,4′-dinitrophenyl sulfide, m.p. 116–118°. The latter derivative was obtained in 62% yield. Thiophenol was isolated in 60% yield, b.p. 70–73° (33 mm.), characterized as 2,4-dinitrophenyl phenyl sulfide, m.p. 119–121° (no depression of m.p. with authentic sample).

The reactions of phenyllithium with thiacyclopropane and methylthiacyclopropane, and of butyllithium with thiacyclopropane were run in an analogous manner with the results already mentioned in the Discussion.

Grignard Reagents and Cyclohexene Sulfide.—Addition of cyclohexene sulfide to an ether solution containing an equimolar quantity of phenylmagnesium bromide gave 87% of cyclohexene. The other product consisted of a sulfur-containing oil from which no discrete product was obtained. The oil failed to crystallize or to form a solid sulfone on oxidation with hydrogen peroxide in acetic acid. Its properties showed no improvement after a molecular distillation.

Five per cent. of 1-butanethiol and 19% of cyclohexene were isolated from the reaction of butylmagnesium bromide and cyclohexene sulfide; the actual yield of cyclohexene was probably considerably higher.

Using benzylmagnesium bromide 12% of benzyl mercaptan, 5% of benzyl disulfide and 13% of cyclohexene were isolated. The remaining product consisted of a viscous oil which distilled at 140–172° (1.5 mm.), but yielded no discrete fraction.

Reduction of Butylthiacyclopropane with Lithium Aluminum Hydride.—The butylthiacyclopropane was prepared in 52% yield from 1-hexene oxide and thiourea according to the method described for methylthiacyclopropane.[12] A solution of 34.6 g. (0.3 mole) of butylthiacyclopropane in twice its volume of anhydrous ether was slowly added with mechanical stirring over a 30-min. period to 5.7 g. (0.15 mole) of lithium aluminum hydride dissolved in 200 ml. of anhydrous ether. The mixture was refluxed for 2 hr. and 300 ml. of water added very slowly. The aluminum hydroxide was dissolved in 150 ml. of 10% sulfuric acid and the ether layer separated and the aqueous phase extracted twice with 50-ml. portions of ether. The combined ether fraction was washed free of acids, dried over anhydrous sodium sulfate and distilled. The fraction boiling at 136–138° weighed 25.3 g. (73%). The refractive index, $n^{25}D$ 1.4418, and infrared absorption pattern of this sample agreed well with that of a pure sample of 2-hexanethiol prepared from 2-hexyl *p*-toluenesulfonate and thiourea.[13]

A 72% yield of 2-propanethiol, identified as its disulfide ($n^{20}D$ 1.4911, 1.4916 reported[14]), was obtained by a similar procedure using methylthiacyclopropane. Starting with cyclohexene sulfide, cyclohexanethiol was obtained.

Butyllithium and Thiacyclobutane.—A solution of 22.2 g. (0.30 mole) of thiacyclobutane in 50 ml. of ether was slowly added to the lithium reagent prepared from 51 g. (0.55 mole) of *n*-butyl chloride and 7 g. of lithium in 300 ml. of ether. An exothermic reaction took place during the 30-min. addition period. The mixture was heated further for one hour, allowed to stand for 16 hours, and then hydrolyzed by slow addition of a solution prepared from 80 ml. of concd. hydrochloric acid and 250 ml. of water. The ether layer was separated, the aqueous layer washed with ether, and the combined extract dried over anhydrous magnesium sulfate. Distillation through a short Vigreux column gave 2.5 g. (11% based on thiacyclobutane) of 1-butanethiol, b.p. 94–98°; 13 g. (33%) of butyl propyl sulfide, b.p. 157–158°; 1.9 g. (6%) of 4,8-dithiadodecane, b.p. 145–148° (15 mm.); and a higher boiling residue.

1-Butanethiol was characterized by preparation of butyl 9-phenylxanthyl sulfide, m.p. 51–52°, as a derivative.[15]

An authentic sample of butyl propyl sulfide was prepared by addition of 37 g. (0.3 mole) of *n*-propyl bromide to 27 g. (0.3 mole) of 1-butanethiol in 300 ml. of 10% potassium hydroxide. The bromide was added with vigorous stirring and external heating during one-half hour, and the mixture was heated at reflux for an additional hour. On cooling, the sulfide was extracted with ether, dried over anhydrous potassium carbonate and distilled to yield 30 g. (76%) of butyl propyl sulfide.

Anal. Calcd. for $C_7H_{16}S$: C, 63.56; H, 12.19. Found: C, 63.20, 62.98; H, 11.69, 12.29.

Shaking 1 g. of the sulfide isolated from the thiacyclobutane reaction with a solution of 3 g. of chloramine-T in 10 ml. of water in a stoppered flask for 5 minutes gave a crystalline sulfilimine. Crystallization from aqueous alcohol and finally from isopropyl ether and isopropyl alcohol gave material, m.p. 94–95°, which did not depress the m.p. of a sample prepared from the authentic sulfide.

Anal. Calcd. for $C_{14}H_{23}NO_2S_2$: C, 55.78; H, 7.69; N, 4.65. Found: C, 55.88; H, 7.50; N, 4.92.

The mercuric chloride derivatives, m.p. 91–92°, from the two samples of butyl propyl sulfide also gave no m.p. depression on admixture.

The fraction boiling at 145–148° (15 mm.) was oxidized with 5 ml. of 30% hydrogen peroxide in 20 ml. of acetic acid during 15 minutes at reflux. On dilution of the oxidation mixture with ice, 2.0 g. (74%) of **4,8-dithiadodecane 4,8-tetroxide**, m.p. 142–144°, was obtained. An analytical sample obtained by crystallization from alcohol melted at 143–144°.

Anal. Calcd. for $C_{10}H_{22}O_4S_2$: C, 44.41; H, 8.20. Found: C, 44.67; H, 8.47.

γ-(Butylmercapto)-butyric Acid.—A solution of 30 g. (0.5 mole) of potassium hydroxide in 30 ml. of water was added to 300 ml. of alcohol, followed by 27 g. (0.3 mole) of 1-butanethiol. Addition of 31 g. (0.3 mole) of γ-chlorobutyronitrile resulted in an exothermic reaction accompanied by precipitation of potassium chloride. The mixture was heated at reflux for 1.5 hours and 60 g. of potassium hydroxide in 300 ml. of water was added. Heating was continued for 3 hours and the major portion of the alcohol was then distilled off. On cooling, the mixture was twice extracted with ether. The γ-(butylmercapto)-butyric acid was separated, after acidification of the aqueous layer, by extraction into ether. After drying over anhydrous magnesium sulfate, distillation gave 40 g. (76%) of acid, b.p. 163–165° (15 mm.).

Anal. Calcd. for $C_8H_{16}O_2S$: neut. equiv., 176. Found: neut. equiv., 176.

Both preparations of γ-(butylmercapto)-butyric acid were oxidized to the corresponding sulfones with hydrogen peroxide in acetic acid. After dilution with water the sulfone was isolated by concentration on the steam-bath. Both preparations of the sulfone melted at 113–113.5° and the m.p. was not depressed on mixing.

Anal. Calcd. for $C_8H_{16}O_4S$: C, 46.13; H, 7.75. Found: C, 46.33; H, 7.69.

Phenyllithium and Thiacyclobutane.—A solution of 22.2 g. (0.3 mole) of thiacyclobutane in 50 ml. of ether was added to a solution of 26 g. (0.8 mole) of bromobenzene and 11 g. of lithium in 450 ml. of ether. The resulting reaction and work-up were comparable to that described for butyllithium. Distillation through a short Vigreux column gave 4.0 g. (12%) of thiophenol, b.p. 65–67° (15 mm.); a fraction, b.p. 90–130° (15 mm.), from which 3 g. (7%) of phenyl propyl sulfide, b.p. 215–220°, was isolated on redistillation; 7 g. of a fraction, b.p. 185–187° (15 mm.), which was not identified. The pot residue crystallized on cooling, and

(11) N. Kharasch and C. Buess, THIS JOURNAL, **71**, 2724 (1949).

(12) F. G. Bordwell and Harry M. Anderson, *ibid.*, **75**, 4959 (1953).

(13) We wish to thank Mr. William Hewett for carrying out this experiment.

(14) A. I. Vogel and D. M. Cowan, *J. Chem. Soc.*, 16 (1943).

(15) The 9-phenylxanthyl sulfides have been shown in this Laboratory to be convenient for the characterization of mercaptans. A description of this work will be published at a later date.

trituration with alcohol yielded small amounts of 1,6-bis-(phenylthio)-hexane.

The thiophenol was characterized as its 9-phenylxanthyl sulfide, m.p. 164° dec.[15]

Authentic phenyl propyl sulfide is reported to boil at 218.5–219.5°.[16] The sulfone prepared by oxidation of our crude sample (b.p. 215–220°) with hydrogen peroxide in acetic acid melted at 41.5–43.5°; Ipatieff, Pines and Friedman[16] report m.p. 44°.

γ-(Phenylthio)-propyl Bromide (V) and Lithium.—V was prepared by the slow addition of 0.5 mole of potassium phenyl mercaptide in alcohol solution to 215 g. (1.06 moles) of 1,3-dibromopropane in refluxing alcohol. The addition required 1.25 hours, after which the mixture was refluxed one-half hour more. After cooling, the potassium bromide was filtered and the filtrate diluted with several volumes of water. The product was separated and the aqueous phase extracted with ether. The combined extracts were dried over potassium carbonate and distilled to yield 99.3 g. (0.49 mole) of unreacted 1,3-dibromopropane, b.p. 58–60° (16 mm.), 46.6 g. (0.20 mole, 40%) of V, b.p. 155–160° (16 mm.),[17] and 34.1 g. of pot residue which may be 1,3-bis-(phenylthio)-propane.

To 1.9 g. (0.27 g. atom) of lithium in 100 ml. of ether was added 31.1 g. (0.135 mole) of V in 60 ml. of ether while stirring. The reaction started spontaneously and the addition was complete in one hour. The mixture was stirred and refluxed 3 hours more and was then allowed to stand overnight. To detect the possible presence of any unreacted lithium reagent, it was then carbonated and extracted with 5% sodium bicarbonate. Subsequent work-up of these washings yielded none of the corresponding acid. The ether phase was dried over potassium carbonate and the ether removed from it to yield 4.4 g. (22%) of 1,6-bis-(phenylthio)-hexane (VI) as white plates, m.p. 81–82° from methanol, and 7.9 g. of an oil which gave no discrete fraction on molecular distillation, and no crystalline sulfone on oxidation with hydrogen peroxide in acetic acid.

Oxidation of VI with hydrogen peroxide in acetic acid yielded the disulfone, 1,6-bis-(phenylsulfonyl)-hexane, m.p. 112–114°.

1,6-Bis-(phenylthio)-hexane (VI).—VI was prepared by mixing 25 g. (0.1 mole) of 1,6-dibromohexane with 0.3 mole of potassium phenyl mercaptide in alcohol solution. An exothermic reaction occurred, after which the mixture was refluxed one-half hour more. The product (VI) as well as potassium bromide were separated by filtration, and the latter removed by trituration with water. After recrystallization from alcohol the product weighed 29 g. (96%) and melted at 81–82°. Mixed m.p.'s of this compound with material from the reaction of phenylithium and thiacyclobutane or with the material from the reaction of γ-(phenylthio)-propyl bromide with lithium showed no depression. The disulfone of VI, 1,6-bis-(phenylsulfonyl)-hexane (prepared in 98% yield by oxidation with hydrogen peroxide in acetic acid), also showed no depression in m.p. when mixed with the corresponding derivatives of the other samples of VI.

EVANSTON, ILLINOIS

(16) V. N. Ipatieff, H. Pines and B. S. Friedman, THIS JOURNAL, **60**, 2731 (1938).

(17) P. Cagniant and A. Deluzarche, *Compt. rend.*, **223**, 677 (1946).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MERCK & CO., INC., THE DEPARTMENT OF BACTERIOLOGY, UNIVERSITY OF CALIFORNIA, AND THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD UNIVERSITY]

α,β-Dihydroxyisovaleric Acid and α,β-Dihydroxy-β-methylvaleric Acid, Precursors of Valine and Isoleucine[1,2]

BY JOHN R. SJOLANDER, KARL FOLKERS, EDWARD A. ADELBERG AND E. L. TATUM

RECEIVED JULY 27, 1953

The synthesis and resolution of DL-α,β-dihydroxyisovaleric acid and of a DL-α,β-dihydroxy-β-methylvaleric acid are described. An optical isomer of each acid has been shown to be identical with the precursor of valine and of isoleucine previously obtained from a *Neurospora* mutant.

By the use of a mutant strain of *Neurospora crassa*, which requires valine and isoleucine for growth, an isomer of α,β-dihydroxyisovaleric acid[3] has been found to be a precursor of valine, and an isomer of α,β-dihydroxy-β-methylvaleric acid[4] has been shown to be a precursor of isoleucine. Confirmatory evidence for the structure of the precursors has now been obtained by synthesis of these two dihydroxy acids.

DL-α,β-Dihydroxyisovaleric acid,[5] the valine precursor, was prepared from ethyl DL-α,β-oxidoisovalerate[5] by hydrolysis of the ester and the oxide groups. Resolution of the acid was accomplished by formation of the diastereoisomeric quinine salts, one of which was crystalline. This crystalline salt was identical with the quinine salt of the dihydroxy acid obtained from the *Neurospora* mu-

(1) Part of this work was supported by a contract between the Office of Naval Research and the Regents of the University of California.

(2) These acids in previous reports (ref. 3, 4) were named α,β-dihydroxy-β-methylbutyric acid and α,β-dihydroxy-β-ethylbutyric acid, respectively, to emphasize their origin from the β-acetylation of a 4-carbon precursor.

(3) E. A. Adelberg and E. L. Tatum, *Arch. Biochem.*, **29**, 235 (1950).

(4) E. A. Adelberg, D. M. Bonner and E. L. Tatum, *J. Biol. Chem.*, **190**, 837 (1951).

(5) F. Kögl, H. Duisberg and H. Erxleben, *Ann.*, **489**, 191 (1931).

TABLE I

α,β-DIHYDROXYISOVALERIC ACID

	Quinine salt of synthetic α,β-dihydroxyisovaleric acid	Quinine salt of natural α,β-dihydroxyisovaleric acid
M.p., °C.	208–209 dec.	209–210 dec.
Mixed m.p., °C.	209–210 dec.	
Anal. Calcd. for $C_{23}H_{34}N_2O_6$:	Found:	Found:
C, 65.47	65.36	65.13
H, 7.47	7.21	7.23
N, 6.11	5.91	6.00
$[\alpha]^{23}D$ in MeOH	−142° (*c* 1)	−141° (*c* 1)

Infrared spectra: The spectra of the two salts as a solid mull in petrolatum were identical from 2–15 μ.

	Synthetic α,β-dihydroxyisovaleric acid	Natural α,β-dihydroxyisovaleric acid
$[\alpha]^{23}D$	−12.5° (*c* 2 in 0.1 *N* HCl)	−12.4° (*c* 2 in dilute HCl, *p*H 1)
	+ 9.5° (*c* 2 in water, *p*H 5.5–6.5)	+10° (*c* 2 in water, *p*H 5.5–6.5)

Biological activity: The two substances exhibited identical threshold concentrations for inhibition of *Escherichia coli* K-12, and supported in each case the same growth rate of valine-less *E. coli* 6B9.