

"chair" form as the most probable structure for at least the *cis*-isomer of piperylene. The *trans*-iso-

mer apparently reacts largely in the "boat" form. AKRON, OHIO RECEIVED JULY 7, 1942

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Hydrogenolysis of Sulfur Compounds by Raney Nickel Catalyst

BY RALPH MOZINGO, DONALD E. WOLF, STANTON A. HARRIS AND KARL FOLKERS

Contemplated investigations of the structures of natural products containing sulfur¹ have led us to study the action of Raney nickel catalyst on representative sulfur compounds. The present paper describes the hydrogenolysis of aliphatic and aromatic sulfides and disulfides and the extension of the reaction to sulfones and sulfoxides.

Raney nickel catalyst prepared in the usual way² contains hydrogen which is not lost when the nickel is stored in the absence of oxygen, and this hydrogen is fully capable of reaction with hydrogen acceptors. The hydrogen may be collected as the gas by heating the catalyst in the absence of oxygen. Whether this hydrogen is held by simple solution in the nickel, by chemical combination as nickel hydride,³ or by so-called "adsorption" on the surface of the nickel is not known. The hydrogen is present, however, in considerable amount varying with the method of preparing the catalyst. It was found that 4 g. of Raney nickel catalyst may contain between 170 and 460 ml. of hydrogen depending upon the final temperature used in its preparation. It is hydrogenolysis by this hydrogen which is the basis of the present investigation.

It has been known that traces of catalyst poisons may be removed by treating compounds containing them with pyrophoric Raney nickel catalyst at room temperature or slightly above.⁴ However, the fate of the sulfur containing compounds, when these are the poisons, has not been determined.

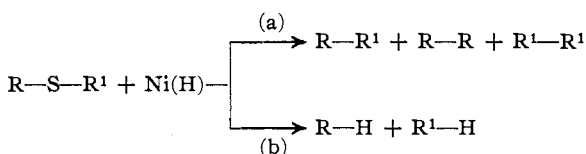
(1) During a collaborative study of biotin by Dr. du Vigneaud and his co-workers of the Biochemistry Staff of the Cornell University Medical College and certain members of the Research staff of Merck & Co., Inc., it was thought that the application of a method for the replacement of sulfur by hydrogen atoms, under study in our laboratories, might be applied to the structural investigation of biotin. For the description of the use of this reaction in the preparation of desthiobiotin from biotin and the role of this compound in the final determination of the structure of biotin, see du Vigneaud, Melville, Folkers, Wolf, Mozingo, Keresztesy and Harris, *J. Biol. Chem.*, **146**, 475 (1942).

(2) "Organic Syntheses," **21**, 15 (1941).

(3) Bougault, Cattelain and Chabrier, *Bull. soc. chim.*, [5] **5**, 1699 (1938).

(4) Adkins, "Reactions of Hydrogen," The University of Wisconsin Press, Madison, Wisconsin, 1937, p. 28.

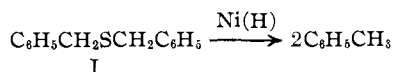
Recently, it was reported that Raney nickel catalyst in neutral or alkaline solution removes sulfur from aliphatic sulfhydryl compounds and disulfides, forming first nickel mercaptides which then decompose to yield sulfur-free compounds.⁵ In the present work, it was found that an active Raney nickel catalyst alone, in the presence of a solvent at moderate temperature, removes either reduced or oxidized sulfur by cleavage from the remainder of the organic molecule. Two courses for the reaction of a sulfide may be postulated. In the first of these the nickel is considered to function as a metal, removing the sulfur in a Wurtz-type reaction according to equation (a). Alternately, in the presence of sufficient Raney nickel catalyst to contain an excess of hydrogen, the reaction may take the course represented by equation (b).



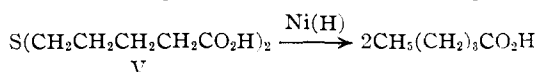
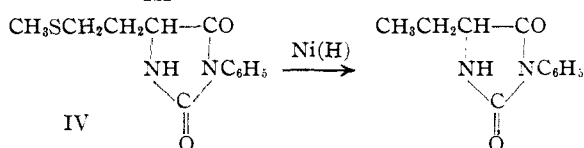
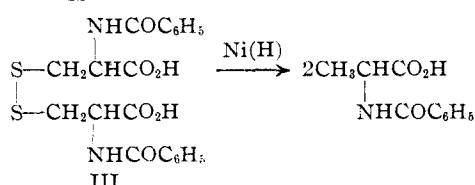
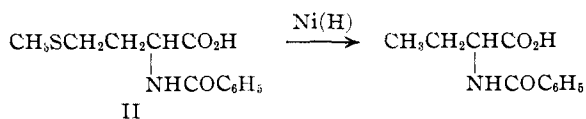
Similar paths could be postulated for the reactions of disulfides, sulfoxides and sulfones. Using aliphatic and aromatic sulfides, disulfides, sulfoxides and sulfones with sufficient Raney nickel catalyst to contain a large excess of hydrogen only the reaction (b) has been observed. That is, in every case, the rupture of the carbon-sulfur bond was accompanied by the formation of a new carbon-hydrogen bond and combination of the organic radicals did not occur. Sulfhydryl compounds would, of course, give the same product by either mechanism (a) or (b) since R¹ is a hydrogen atom.

When benzyl sulfide (I) was treated with Raney nickel catalyst in boiling ethanol, but in the absence of a hydrogen atmosphere, an 85% yield of toluene was obtained. Compounds of more complicated structure such as benzoylmethionine

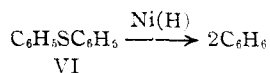
(5) Bougault, Cattelain and Chabrier, *Bull. soc. chim.*, [5] **7**, 781 (1940).



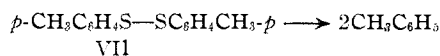
(II), benzoylcystine (III), methionine phenylhydantoin (IV), and δ,δ' -thiodivaleric acid (V) were prepared and subjected to the hydrogenolysis reaction. The corresponding sulfur-free compounds were obtained in good yields.



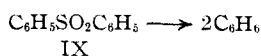
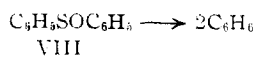
The ease with which a carbon-sulfur bond in an aromatic sulfide is cleaved by Raney nickel catalyst is of interest. Simply refluxing the compound in ethanol solution with Raney nickel catalyst is sufficient to effect hydrogenolysis. The conditions are mild enough that the benzenoid nucleus does not react with hydrogen. For example, diphenyl sulfide (VI) was converted into benzene in a 68% yield. Likewise, di-*p*-tolyl di-



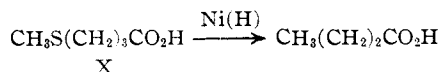
sulfide (VII) gave an 87% yield of toluene.



A similar ease of cleavage was observed also in the case of oxidized sulfur compounds. An experiment with diphenyl sulfoxide (VIII) gave a 75% yield of benzene and a similar one with diphenyl sulfone (IX) gave a 65% yield of benzene.



While most of the reactions were carried out in ethanol, the hydrogenolysis of γ -methylmercaptobutyric acid (X) was carried out quite as



well in methanol to give a 95% yield of butyric acid. The time and temperature of heating in these first experiments are probably greatly in excess of those necessary for complete reaction. When methyl *p*-tolyl sulfide was added to Raney nickel catalyst in 70% ethanol, the temperature rose nine degrees in two minutes. After ten minutes, the ethanol-toluene-water azeotrope was distilled quickly (twenty minutes). The toluene recovered amounted to 93% of the theoretical yield.

Some difficulty was encountered in separating the products from the large amounts of nickel present. This has resulted in rather low yields in some cases. Under the conditions used the only reaction observed with compounds containing no easily reducible groups was direct cleavage of the carbon-sulfur bonds and the formation of carbon-hydrogen bonds in their place. This hydrogenolysis reaction, therefore, offers a convenient means for the removal of sulfur in structure and synthetic work.

Since the benzoyl-*l*(-)-cystine used in this reaction was prepared from *l*(-)-cystine isolated from a natural source, the configuration of benzoyl derivative must be the same. And, since the asymmetric center was not disturbed in the reaction with nickel, the product must have the same absolute configuration as the starting material. Any deviation in rotation can be due only to temperature or to racemization of the starting material, or product, through effect of *pH*. The observed specific rotation in alcohol was $(\alpha)^{25\text{D}} +9.7^\circ$. The rotation of benzoyl-*l*(+)-alanine in alcohol is $(\alpha)^{20\text{D}} +10.5^\circ$.⁶ The product is, therefore, benzoyl-*l*(+)-alanine and the cystine from which it is derived is that one having this same absolute configuration. Thus, independent evidence is offered that the two amino acids belong to the same configurational series. The slightly low rotation and melting point indicate that there was a small amount of racemization by the alkali used in the various steps of the process; this alters the degree of rotation and not its direction.

The methionine used was synthetic *dl*-methionine. The configuration of this acid in relation to α -aminobutyric acid was not determined, but

(6) Pope and Gibson, *J. Chem. Soc.*, **101**, 939 (1912).

its resolution and configuration is under study and will be reported later.

The authors wish to express their thanks to Messrs. Claude Spencer, Arthur Greslin, Glen Arth and Robert Anderson for their assistance throughout this investigation and to Messrs. D. F. Hayman, Wilhelm Reiss, H. S. Clark and R. N. Boos and Mrs. E. H. Meiss for carrying out the microanalyses.

Experimental Part

Preparation of Raney Nickel Catalyst.—The catalyst was prepared in the usual way² except the final heating of the reaction mixture after the addition of the alloy was carried out at 80° for one hour or at 50° for one hour.

The hydrogen contained in the catalyst was determined by heating the catalyst to 220° in butyl phthalate suspension, the hydrogen being swept into a gas buret by means of carbon dioxide and the carbon dioxide removed by solution in 50% potassium hydroxide solution. The hydrogen collected in this way amounted to about 160–170 ml. per 4-g. sample of catalyst when the catalyst was heated to 80° in its preparation. When the final heating was conducted at 50°, the volume of hydrogen was about 470 ml. per 4 g. of catalyst.

Hydrogenolysis of Benzyl Sulfide.—A solution of 2 g. of benzyl sulfide in 150 ml. of ethyl alcohol was refluxed two hours with about 20 g. of Raney nickel catalyst. The mixture was diluted to 500 ml. with water and distilled until no more alcohol came over. The distillate was diluted with water and distilled. The azeotrope, water-alcohol-toluene, which came over was diluted with water and yielded 1.47 g. (85% of the theoretical yield) of toluene, boiling at 105–108°.

Hydrogenolysis of δ,δ' -Thiodivaleric Acid.—A solution of 2.5 g. of δ,δ' -thiodivaleric acid⁷ in 140 ml. of 75% ethyl alcohol was refluxed for five hours with 25–30 g. of Raney nickel catalyst. The nickel was removed by centrifugation and washed three times with dilute sodium hydroxide solution. After removal of the alcohol from the combined solutions, the resulting solution was made strongly acid with sulfuric acid. Distillation gave 0.0203 mole (94% of the theoretical) of acid by titration.

The anilide prepared from the acid by heating with aniline melted at 62.5–63.5° after recrystallization from acetone-water. The melting point of valerianilide is 63°.⁸

The *p*-phenylphenacyl ester⁹ melted at 67–68° (from acetone-water).

Anal. Calcd. for C₁₉H₂₀O₃: C, 77.00; H, 6.80. Found: C, 77.20; H, 6.67.

The melting point of the *p*-phenylphenacyl ester prepared from known *n*-valeric acid was found to be 67–68°.

γ -Methylmercaptobutyric Acid.—The ether solution of β -methylmercaptoethylmalonic acid obtained as an intermediate in a preparation of *dl*-methionine¹⁰ was evaporated

to dryness and the residue distilled under reduced pressure. The γ -methylmercaptobutyric acid boiled at 143–144° (16 mm.).

Anal. Calcd. for C₆H₁₀O₂S: C, 44.77; H, 7.52. Found: C, 45.06; H, 7.58.

Hydrogenolysis of γ -Methylmercaptobutyric Acid.—A solution of 4.3 g. of γ -methylmercaptobutyric acid in 100 ml. of 75% ethyl alcohol was refluxed with about 25 g. of Raney nickel catalyst for five hours. The nickel was extracted with dilute alkali and the alcohol removed from the extracts. The solution was made acid with sulfuric acid and steam distilled. Titration of the distillate showed 72.5% of the theoretical amount of butyric acid.

The anilide, prepared from the salt left after evaporation of the solution from the titration, melted at 94.5–95° after recrystallization from dilute alcohol. The melting point of *n*-butyranilide is given as 96°.⁸

Anal. Calcd. for C₁₀H₁₃ON: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.63; H, 8.08; N, 8.59.

When the above reaction was repeated using methanol in place of the dilute ethyl alcohol, a 95% yield of butyric acid was obtained.

Hydrogenolysis of Benzoyl-*l*(-)-cystine.—To a suspension of 25–35 g. of Raney nickel catalyst in 125 ml. of alcohol and 10 ml. of water was added 2.0 g. of benzoyl-*l*(-)-cystine, m. p. 178–180°. The mixture was refluxed for one and one-quarter hours and cooled. The material was transferred to a centrifuge bottle and the nickel separated and washed six times by resuspension in dilute sodium hydroxide solution and centrifugation. The combined extracts were evaporated to dryness at 40–50° under reduced pressure and taken up in water. The water solution was acidified to congo red and continuously extracted with chloroform. The chloroform solution was evaporated and the product crystallized from water to constant melting point. The yield was 1.40 g. (81% of the theoretical yield) of benzoyl-*l*(+)-alanine,¹¹ m. p. 144–145°; (α)^{25D} +9.7° (C = 1.9% in ethanol).

Anal. Calcd. for C₁₀H₁₁O₃N: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.37; H, 5.95; N, 7.57.

Hydrogenolysis of Benzoyl-*dl*-methionine.—A solution of 2.3 g. of benzoyl-*dl*-methionine¹² (m. p. 150–152°) in 140 ml. of 75% ethyl alcohol was heated under reflux with 25–30 g. of Raney nickel catalyst for five hours. The nickel was removed and washed with dilute alkali. After removal of the alcohol from the combined extracts, the solution was acidified with sulfuric acid and continuously extracted with ether. Evaporation of the ether and recrystallization of the residue from ether-benzene gave 1.55 g. (84% of the theoretical) of *dl*- α -(benzoylamino)-butyric acid, m. p. 145–146°. The melting point for this compound is given as 145–146°.¹³

Anal. Calcd. for C₁₁H₁₈O₃N: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.52; H, 6.16; N, 6.66.

***dl*-Methionine Phenylhydantoin.**—A cold solution of 5 g. of methionine in 33.6 ml. of 1 *N* sodium hydroxide and 100 ml. of water was prepared and 4 g. of phenyl isocyanate

(7) Köggl and de Man, *Z. physiol. Chem.*, **269**, 81 (1941).

(8) Robertson, *J. Chem. Soc.*, **115**, 1211 (1919).

(9) Drake and Bronitsky [THIS JOURNAL, **52**, 3715 (1930)] observed 63.5° for the melting point of this compound.

(10) "Organic Syntheses," **14**, 58 (1934).

(11) Fischer, *Ber.*, **32**, 2455 (1899).

(12) Windus and Marvel, THIS JOURNAL, **53**, 3493 (1931); Hill and Robson, *Biochem. J.*, **30**, 250 (1936).

(13) Fischer and Mouneyrat, *Ber.*, **33**, 2383 (1900).

was added in small portions with thorough shaking over a period of forty-five minutes. The solution was allowed to stand two hours longer and acidified to congo red with 2 *N* sulfuric acid. The solid which precipitated was removed by filtration.

The wet solid was suspended in 400 ml. of 25% hydrochloric acid and heated on a steam-bath overnight in a beaker. The solution was cooled and filtered. The filter cake was washed with ice water. The *dl*-methionine phenylhydantoin was recrystallized twice from ethyl alcohol-water and melted at 109–110°. The yield was 5.9 g. (70% of the theoretical amount).

Anal. Calcd. for $C_{12}H_{14}O_2SN_2$: C, 57.58; H, 5.64; N, 11.19. Found: C, 57.69; H, 5.73; N, 11.42, 11.44.

Hydrogenolysis of *dl*-Methionine Phenylhydantoin.—A solution of 107.2 mg. of *dl*-methionine phenylhydantoin in 65 ml. of 70% ethyl alcohol was refluxed six hours with about 5 g. of Raney nickel catalyst. The nickel was removed by centrifugation and washed four times with alcohol. The solution was evaporated to dryness and the residue taken up in alcohol and again centrifuged to remove some insoluble material. Recrystallization from water gave 67.1 mg. (77% of the theoretical yield) of *dl*-3-phenyl-5-ethylhydantoin melting at 123–123.5°. ¹⁴

Anal. Calcd. for $C_{11}H_{12}O_2N_2$: C, 64.69; H, 5.92. Found: C, 64.75; H, 5.88.

Hydrogenolysis of Methyl *p*-Tolyl Sulfide.—Two grams of methyl *p*-tolyl sulfide and 25–30 g. of Raney nickel catalyst were refluxed in 135 ml. of 70% ethyl alcohol for five hours. The toluene recovered amounted to 1.16 g. (87% of the theoretical yield) and gave benzoic acid, m. p. 121–122°, on alkaline permanganate oxidation.

The above reaction was repeated at room temperature. When the nickel was added to the sulfide solution, the temperature rose rapidly from 28 to 37°. After ten minutes the mixture was diluted with water and the water-alcohol-toluene azeotrope distilled as rapidly as possible (20 min.). The yield of toluene obtained was 1.24 g. (93% of the theoretical amount) boiling at 106–109°.

Hydrogenolysis of Di-*p*-tolyl Disulfide.—Two grams of di-*p*-tolyl disulfide in 135 ml. of 75% ethyl alcohol was treated with 25–30 g. of Raney nickel catalyst in the same manner as the benzyl sulfide. After heating for five hours, the yield of toluene was 1.31 g. (87% of the theoretical yield) boiling at 105–109°.

(14) Mouneyrat [*Ber.*, **33**, 2395 (1900)] found the melting point of this compound to be 126–127° d. (cor.).

Hydrogenolysis of Phenyl Sulfide.—Two grams of phenyl sulfide in 135 ml. of 75% alcohol with 25–30 g. of Raney nickel catalyst was heated for four and one-half hours. The yield of benzene recovered in the same manner as the toluene from benzyl sulfide was 1.14 g. (68% of the theoretical yield) boiling at 79–80°.

Hydrogenolysis of Diphenyl Sulfoxide.—Two grams of diphenyl sulfoxide in 135 ml. of 75% ethyl alcohol was refluxed for five hours with 25–30 g. of Raney nickel catalyst. The benzene, b. p. 79–80°, was recovered in the same manner as in previous experiments and amounted to 1.14 g. (75% of the theoretical yield).

Hydrogenolysis of Diphenyl Sulfone.—Two grams of diphenyl sulfone was refluxed in 135 ml. of 75% ethyl alcohol with 25–30 g. of Raney nickel catalyst for six hours. The yield of benzene was 0.93 g. (65% of the theoretical amount).

Summary

Certain representative sulfur-containing compounds, *i. e.*, aliphatic and aromatic sulfides, disulfides, sulfones and sulfoxides, have been submitted to hydrogenolysis by the hydrogen contained in Raney nickel catalyst in the absence of added hydrogen. They have been found to undergo cleavage with the replacement of the sulfur atom by two hydrogen atoms.

The following transformations have been accomplished with yields of 65–95% of the theoretical amount: dibenzyl sulfide, di-*p*-tolyl sulfide, and methyl *p*-tolyl sulfide each into toluene; δ, δ' -thiodivaleric acid into valeric acid; γ -methylmercaptobutyric acid into butyric acid; benzoyl methionine and benzoyl cystine into α -benzoylaminobutyric acid and benzoyl alanine, respectively; methionine phenylhydantoin into 3-phenyl-5-ethylhydantoin; phenyl sulfide, diphenyl sulfoxide and diphenyl sulfone each into benzene.

Independent evidence is offered that the absolute configuration of *l*(–)-cystine is the same as that of *l*(+)-alanine.