Selective Hydrogenation of Haloalkenes to Haloalkanes Using Rhodium Catalyst[1]

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Rhodium on alumina has been found to be a superior catalyst for the hydrogenation of a vinylic or allylic halogen-substituted olefin to a haloalkane. Yields of 40-60% chloroalkane were obtained from the hydrogenation of 1-chloropropene, allyl chloride, and 1,3-dichloropropene. Hydrogenation of 5-chlorohexene-1 gave 2-chlorohexane in 96% yield. Under hydrogenation conditions used, hydrogenolysis of the chloroalkanes did not occur when rhodium, platinum, or palladium was used as catalyst. Yields of chloroalkanes were found to be dependent on solvent, the presence of thiophene as a poison, and catalyst support. Dependency of yields on the catalyst was found to be in the following decreasing order: rhodium, palladium, platinum. Isomerization of *cis-* or *trans-*1,3-dichloropropene did not occur over rhodium catalyst in the absence of hydrogen. However, isomerization was noted in partially hydrogenated material.

In a preliminary investigation of the hydrogenation of 1,3-dichloropropene over rhodium, palladium, platinum, and platinum oxide catalysts it was found that only four products were formed. These were- 1,3 dichloropropane, propyl chloride, propane, and hydrogen chloride.

$$ClCH{=}CHCH_2Cl + H_2 \longrightarrow \begin{array}{c} ClCH_2CH_2CH_2Cl \\ CH_3CH_2CH_2Cl \\ CH_3CH_2CH_3 \\ HCl \end{array}$$

The major products obtained using palladium, platinum, and platinum oxide catalysts were propane and hydrogen chloride. It was surprising to find, however, that using rhodium catalysts afforded high yields of 1,3-dichloropropane and propyl chloride.

The reductive dehalogenation of organic halides has been previously studied. Horner, Schläfer, and Kämmerer[2] found that when using Raney nickel in alkali methanol, primary and secondary monochlorides did not react but that a vinylic or allylic chloride would undergo hydrogenolysis as the double bond was reduced. These authors also found that 1,1-dihaloalkanes and 1,2-dihaloethanes gave hydrogenolysis of the carbon-halogen bond whereas very little or none was observed with 1,3- or 1,4-dihaloalkanes. Alkyl bromides or iodides underwent hydrogenolysis as compared with none for the chlorides. When the chlorine was not allylic or vinylic only partial hydrogenolysis was observed. Hydrogenation of 4-chlorohexene-1 gave some hydrogenolysis and some 3-chlorohexane.

In connection with some other work McCullen, Henze, and Wyatt[3] carried out hydrogenation of 2-bromopropene and 1,2-dibromopropene-1 in ethanol over palladium on carbon. These authors found that a pressure drop corresponding to 1.5 equivalents of hydrogen occurred with 2-bromopropene to give a 93.4% yield of bromide ion and that one equivalent of hydrogen reacted with 1,2-dibromopropene-1 without formation of bromide ion.

Kindler, Oelschlager, and Henrich[4] studied the selective hydrogenation of the double bond in 2-allyl-4-chlorophenol over palladium catalyst. Dehalogenation of the starting material or product was the major side reaction. These authors found that solvent affected the yield of chloride ion. The following chloride ion yields were reported: methanol, 6.2%; ethanol, 8.6%; isopropyl alcohol, 3.6%; benzene, 0%; cyclohexane, 0%. Poisons also were reported to retard dehalogenation. The following chloride ion yields were found using ethanol as solvent: no poison, 8.6%; nicotinamide, 0.4%; dimethylnicotinamide, 0.8%; thiophene, 0.6%.

Baltzly and Phillips[5] studied the dehalogenation of halogen-substituted compounds over palladium on charcoal. These authors found that saturated aliphatic bromides, such as isobutyl bromide, *t*-butyl bromide, and cyclohexyl bromide, did not undergo hydrogenolysis. Aromatic halides, such as bromobenzene, allyl chloride, and benzyl chloride, were readily dehalogenated, however.

The primary purpose of the work reported here was to find procedures which would allow the selective hydrogenation of the olefinic linkage in 1,3-dichloropropene. Initially it was considered that four different reactions might be occurring in this system. These are (1) hydrogenation of the double bond, (2) hydrogenolysis of an allylic chloride, (3) hydrogenolysis of a vinylic chloride, and (4) hydrogenolysis of an alkyl chloride. It was reasoned that these four reactions might be affected differently by changes in hydrogenation conditions.

It was found that alkyl halides do not undergo hydrogenolysis using rhodium, palladium, or platinum catalyst.

Table I shows the results of such attempted hydrogenolysis. Contrary to the results of Horner, Schläfer, and Kammerer, no hydrogenolysis was noted with an alkyl bromide, 1-bromo-3-chloropropane, and 1,2,3-trichloropropane.

TABLE I

ATTEMPTED HYDROGENOLYSIS OF ALKYL HALIDES[a]

Alkyl halide	Catalyst	H2 pressure, lb./in.2	% yield HCl
$Cl(CH_2)_3Cl$	5% Rh on alumina	860	0[b]
$CH_3CH_2CH_2Cl$	5% Rh on charcoal	380	0
$CH_3CHClCH_3$	5% Rh on charcoal	815	0
$CH_3C(CH_3)ClCH_3$	5% Rh on charcoal	1000	73.4
$CH_2ClCHClCH_2Cl$	5% Rh on charcoal	800	0
$Cl(CH_2)_3Cl$	5% Pd on alumina	500	0[c]
$Cl(CH_2)_3Cl$	5% Pt on alumina	500	0[c]
$Cl(CH_2)_3Br$	5% Rh on alumina	480	0

[a] At 100° for 3 hr. [b] 88.5% 1,3-dichloropropane recovered [c] 97% 1,3-dichloropropane recovered.

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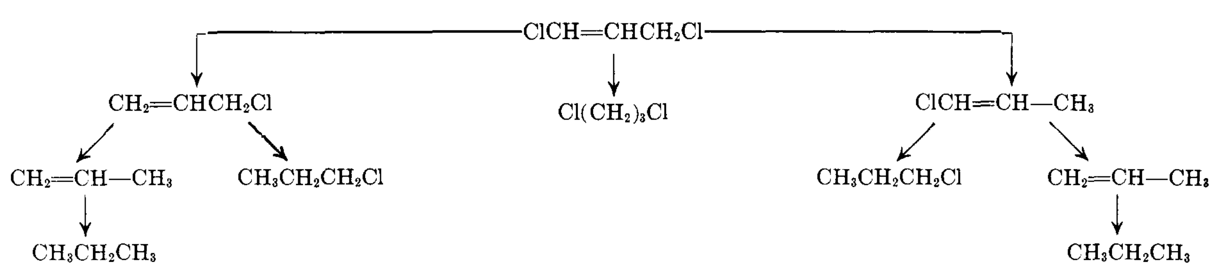
[1] A portion of this work was presented at the 18th Southwest Regional Meeting of the American Chemical Society, Dallas, Tex., December, 1962.

[2] L. Horner, L. Schläfer, and H. Kämmerer, *Ber.*, **92**, 1700 (1959).

[3] E. J. McCullen, H. R. Henze, and B. W. Wyatt, *J. Am. Chem. Soc.*, **76**, 5636 (1954).

[4] K. Kindler, H. Oelschlager, and P. Henrich, *Ber.*, **86**, 167 (1953).

[5] R. Baltzly and A. P. Phillips, *J. Am. Chem. Soc.*, **68**, 261 (1946).



Thus it is seen that in the hydrogenation of 1,3-dichloropropene the following reaction scheme is more nearly representative of reactions in this system.[6]

Hydrogenolysis of allylic and vinylic chloride are the only side reactions shown. The propyl chloride formed in the reaction can only result from 1-chloropropene or allyl chloride. The propane formed can result only from hydrogenation of propylene.

The superior selectivity of rhodium in this hydrogenation is shown in Table II, where the reaction is carried out with other noble metal catalysts. These reactions were run in cyclohexane as solvent and at the same mole ratio of catalyst metal to olefin.

TABLE II

EFFECT OF CATALYST METAL ON SELECTIVITY IN HYDROGENATION OF 1,3-DICHLOROPROPENE[a]

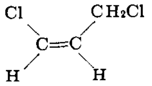
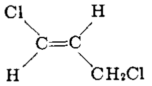
Catalyst	% yield $Cl(CH_2)_3Cl$	% yield $CH_3CH_2CH_2Cl$
5% Ru on alumina	No reaction	
5% Rh on alumina	47.9	35.4
5% Pd on alumina	19.2	33.0
5% Pt on alumina	6.1	32.2

[a] At 100° and 400–600 lb./in.² hydrogen pressure.

In Table III is shown the results of hydrogenating several chloro-substituted olefins using 5% rhodium on alumina in cyclohexane solvent. It is interesting to note that approximately the same yields of 1,3-dichloropropane and propyl chloride were obtained with the *cis* or *trans* isomer of 1,3-dichloropropene. *cis–trans* isomerization of 1,3-dichloropropene did not occur when heated in the presence of the catalyst at 105° for 2 hr. However, in an experiment where only a small amount of hydrogenation had taken place a small per cent of the olefin had isomerized. When the chlorine was substituted in a position which was not allylic or vinylic to the double bond, as in 5-chlorohexene-1, there was no hydrogenolysis of the carbon–chlorine bond.

TABLE III

HYDROGENATION OF CHLORO-SUBSTITUTED OLEFINS WITH 5% RHODIUM-ON-ALUMINA CATALYST

Olefin	T, °C.	H_2 pressure, lb./in.²	Products	% yield
$ClCH{=}CHCH_3$ *cis–trans*	100	620	$CH_3CH_2CH_2Cl$	42.4
$CH_2{=}CHCH_2Cl$	100	580	$CH_3CH_2CH_2Cl$	57.8
	100	710	$Cl(CH_2)_3Cl$	42.9
			$CH_3CH_2CH_2Cl$	31.4
	100	680	$Cl(CH_2)_3Cl$	47.0
			$CH_3CH_2CH_2Cl$	33.5
$CH_2{=}CH{-}CH_2CH_2CHClCH_3$	52	500	$CH_3(CH_2)_3CHClCH_3$	96.9

The yield of chloroalkanes, as well as the rate of hydrogenation, was affected by the catalyst support. In Table IV is shown the effect of three different supports. These experiments were all carried out at the same mole ratio of olefin to rhodium metal.

TABLE IV

EFFECT OF CATALYST SUPPORT ON SELECTIVITY IN THE RHODIUM-CATALYZED HYDROGENATION OF 1,3-DICHLOROPROPENE[a]

Catalyst	% yield $Cl(CH_2)_3Cl$
5% Rh on alumina powder[b]	47.9
5% Rh on charcoal powder[b]	37.4
0.5% Rh on 1/8-in. alumina pellets[c]	29.8

[a] In 150 g. of cyclohexane (0.334 mole of olefin) at 100° and 400–600 lb./in.² hydrogen pressure. [b] 2.4 g. of catalyst. [c] 24 g. of catalyst.

Kindler, Oelschlager, and Henrich found that in the hydrogenation of 2-allyl-4-chlorophenol certain solvents and poisons retard the dehalogenation reaction. The results on solvent effect obtained in this work agree with these authors in that the less polar solvents gave the highest yields of chloroalkane. However, the opposite effect was noted when thiophene was added as a poison. Whereas these authors found a reduction in hydrogenolysis from 8.6% to 0.6%, an increase was found in this work.

Tables V and VI show the effect of thiophene and solvents, respectively, on the selectivity in hydrogenation of 1,3-dichloropropene using rhodium catalyst.

TABLE V

EFFECT OF THIOPHENE ON SELECTIVITY IN HYDROGENATION OF 1,3-DICHLOROPROPENE USING 5% RHODIUM-ON-ALUMINA CATALYST[a]

Poison	% yield $Cl(CH_2)_3Cl$
None	45.6
Thiophene[b]	28.8

[a] In 150 g. of cyclohexane (0.334 mole of olefin and 2.4 g. of catalyst) at 100° and 700–800 lb./in.² hydrogen pressure. [b] 0.05 ml./44 g. of olefin.

Temperature was found to have only a very slight effect on the selectivity in the hydrogenation of 1,3-dichloropropene. These results are shown in Table VII.

There was no attempt made to measure carefully the rate or kinetics of the hydrogenation of the chloroalkenes. However, it was noted consistently that decrease in total pressure *vs.* time was linear and that

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(6) One referee suggested that this scheme may imply that desorption and readsorption occurs with the intermediate unsaturated species. The authors intended only to emphasize that propane and propyl chloride do not result from hydrogenolysis of 1,3-dichloropropane. The hydrogenolysis reactions may certainly proceed during one period of adsorption of 1,3-dichloropropene *via* surface intermediates.

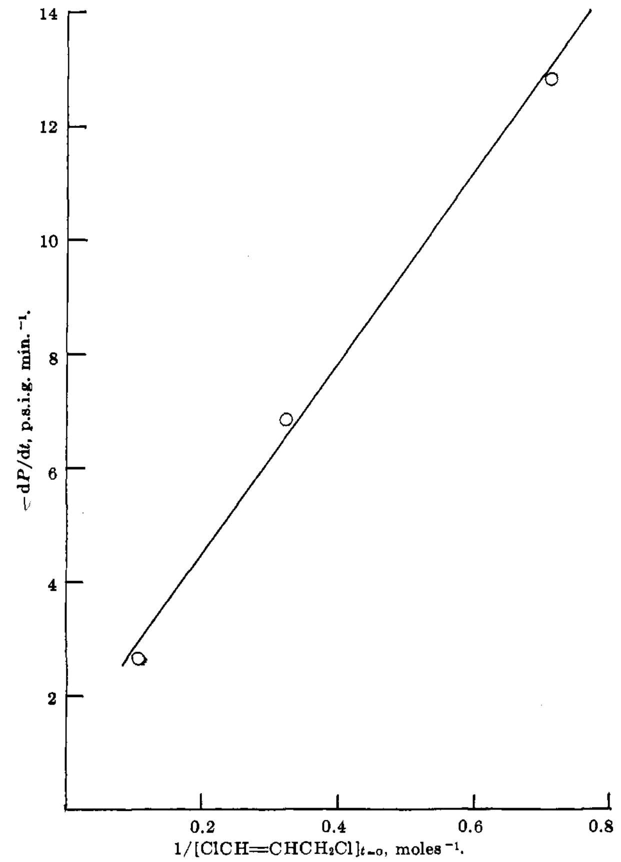

Fig. 1.—Effect of initial olefin concentration on rate of hydrogenation of 1,3-dichloropropene.

TABLE VI

EFFECT OF SOLVENT ON SELECTIVITY IN HYDROGENATION OF 1,3-DICHLOROPROPENE USING 5% RHODIUM-ON-ALUMINA CATALYST[a]

Solvent	T, °C.	% yield $Cl(CH_2)_3Cl$
1,3-Dichloropropane[b]	100	39.4
Cyclohexane	100	47.9
Diethyl ether	100	30.8
	30–35	29.9
Ethanol[c]	100	2.5
	30–35	12.1
Acetic acid[c,d]	100	2.5

[a] At 400–600 lb./in.^{2} hydrogen pressure with 150 g. of solvent, 0.334 mole of olefin, and 2.4 g. of catalyst. [b] Yield of 1,3-dichloropropane determined by weight gain in pure $Cl(CH_2)_3Cl$ recovered. Loss of 4 g. of material in handling would account for yield loss of 9.8%. [c] Reaction mixture darkened. Solvolysis of allylic chloride in 1,3-dichloropropene does not occur under these conditions. [d] Catalyst appeared degraded.

TABLE VII

EFFECT OF TEMPERATURE ON SELECTIVITY IN HYDROGENATION OF 1,3-DICHLOROPROPENE USING 5% RHODIUM ON ALUMINA[a]

T, °C.	% yield $Cl(CH_2)_3Cl$	% yield $CH_3CH_2CH_2Cl$
100	47.9	35.4
35–40	53.3	21.0

[a] In 150 g. of cyclohexane solvent (0.334 mole of olefin and 2.4 g. of catalyst) at 400–600 lb./in.^{2} hydrogen pressure.

this rate of decrease for a given experiment could be repeatedly observed, *i.e.*,

$$-dP/dt = K$$

Since one mole of gas is liberated for each mole of hydrogen consumed which is not used for saturation of the double bond, the observed pressure drops may be used as a rough measure of the relative rates of double bond hydrogenation in the various experiments. Thus it was noticed that the order of rates for reduction of the various olefins under approximately the same conditions was as follows: cyclohexene > 5-chlorohexene-1 > allyl chloride > 1-chloropropene > 1,3-dichloropropene.

The conditions under which this order was observed were about 100° in cyclohexane as solvent at about 400–600 lb./in.^{2} hydrogen pressure. These conditions afforded an almost instantaneous hydrogenation of cyclohexene and about 20 min. for completion with 1,3-dichloropropene. The presence of thiophene in the reaction mixture in trace amounts caused a very marked reduction in rate of hydrogenation of 1,3-dichloropropene over 5% rhodium on alumina powder. The effect of catalyst support on the rate of rhodium-catalyzed hydrogenation of 1,3-dichloropropene was as follows: 5% rhodium on alumina powder > 5% rhodium on charcoal powder ≫ 0.5% rhodium on $^1/_8$-in. alumina pellets.

Using cyclohexane as solvent and 5% rhodium on alumina powder it was noticed that the rate of hydrogenation of 1,3-dichloropropene was dependent on the initial concentration and that the rate was faster in the more dilute solutions. This dependency on initial concentration is shown in Fig. 1. This dependency is interpreted as indicating that in this particular system the olefin is more strongly adsorbed on the catalyst surface than hydrogen.

It was also noticed that the rate of hydrogenation of 1,3-dichloropropene using 5% rhodium on alumina powder in cyclohexane was a function of the catalyst concentration. This dependency is shown in Fig. 2.

Experimental

The catalysts used in this work were obtained from Baker and Company, Inc., and were used in the form they were received. Different batches of catalysts (different lot numbers) gave identical results.

Analysis for *cis*- and *trans*-1,3-dichloropropene and 1,3-dichloropropane was done by v.p.c. techniques on an 8 ft. by $^3/_{16}$ in. stainless steel column packed with 30% tricresyl phosphate on Celite operated at 98–100° under 4.0 lb./in.^{2} helium pressure at maximum flow rate of helium through the column under these conditions. The *cis* and *trans* isomers of 1,3-dichloropropene and 1,3-dichloropropane were well separated on this column. Calibration curves were prepared for each of the components to be analyzed. Samples injected into the column were weighed to the nearest 0.1 mg. on an analytical balance and the area of the chromatogram peaks was determined by carefully cutting out the peak and weighing the paper to the nearest 0.1 mg.

Attempted Hydrogenolysis of Haloalkanes.—The following is a typical example for attempted hydrogenolysis of various haloalkanes as reported in Table I. In most cases the formation of hydrogen chloride was the criterion used for hydrogenolysis.

To a 1410-ml. stainless steel rocking autoclave was charged 22.6 g. (0.20 mole) of 1,3-dichloropropane and 0.23 g. of rhodium catalyst (5% Rh on alumina powder). The mixture was heated to 100° and the vessel was pressurized with hydrogen to 860 lb./in.^{2}. After rocking at 100° for 3 hr. the bomb was cooled and vented through two scrubbers containing 1.0 N sodium hydroxide solution. The acidified scrubber solution did not give a precipitate with silver nitrate solution. The liquid recovered from the bomb (20.6 g., 91.2% recovery) was shown by infrared analysis to be pure 1,3-dichloropropane.

General Procedure for Hydrogenation.—All of the hydrogenations were carried out in a stainless steel rocking autoclave. The olefin, solvent, and catalyst were charged to the bomb, the bomb and contents heated to the desired temperature and then pressurized to the desired pressure with hydrogen. The pressure and temperature inside the bomb were recorded automatically *vs.* time. Hydrogenations were always carried out for a period of time after there was no further pressure drop in the system. The bomb and contents were then cooled to room temperature and vented through two gas scrubbers containing 1.0 *N* sodium hydroxide solution. This solution was then analyzed for chloride ion by the Volhard method. The contents of the bomb were then filtered to remove catalyst, weighed, and analyzed by v.p.c. for 1,3-dichloropropane. Propyl chloride was recovered by distillation of the product solution. A typical example of the hydrogenation is given subsequently for the hydrogenation of 1,3-dichloropropene in cyclohexane.

Hydrogenation of 1,3-Dichloropropene.—A mixture of *cis*- and *trans*-1,3-dichloropropene was distilled and the fraction boiling between 103° and 112° collected. This material was shown by infrared analysis to be approximately 50% *cis* isomer and 50% *trans* isomer. To a 1410-ml. stainless steel rocking autoclave was charged 0.334 mole of 1,3-dichloropropene, 150.0 g. of cyclohexane, and 2.40 g. of catalyst (5% Rh on alumina powder). The bomb and contents were heated to 100° and then pressurized with hydrogen to 500 lb/in.^{2}. After about 15 min. there was no further pressure drop. Rocking and heating were continued for an additional 2.75 hr. After this time the bomb was cooled to room temperature and vented through two scrubbers containing 1.0 *N* sodium hydroxide solution. Analysis of this solution revealed that 0.204 mole of hydrogen chloride had been formed.

The liquid obtained from the bomb (178.5 g.) was analyzed by v.p.c. for 1,3-dichloropropane. This solution was found to be 10.1% by weight 1,3-dichloropropane (0.160 mole formed). Fractionation of the solution yielded 9.26 g. of a fraction with b.p. 46.5–48° which was shown to be pure propyl chloride by infrared analysis. This corresponds to a 35.4% yield of propyl chloride and 47.9% yield of 1,3-dichloropropane.

Hydrogenation of *cis*-1,3-Dichloropropene.—A mixture of *cis*- and *trans*-1,3-dichloropropene was fractionated. The fraction boiling at 103–104°, n^{20}D 1.4691 (lit.[7] b.p. 104.3°, n^{20}D 1.4682), was isolated and shown by v.p.c. analysis to be 73% *cis* isomer by weight. This fraction was shown by infrared analysis to be greater than 98% pure *cis*- and *trans*-1,3-dichloropropene. To a 1410-ml. stainless steel bomb was charged 45.0 g. (0.385 mole of 1,3-dichloropropene) of this fraction, 150.0 g. of cyclohexane, and 2.40 g. of catalyst (5% Rh on alumina powder) and the hydrogenation procedure carried out as described previously. There was obtained a 42.9% yield of 1,3-dichloropropene and 31.4% yield of propyl chloride.

Hydrogenation of *trans*-1,3-Dichloropropene.—Distillation of a mixture of *cis*- and *trans*-1,3-dichloropropene yielded a fraction boiling at 111.5–112.0°, n^{20}D 1.4739 (lit.[7] b.p. 112.0°, n^{20}D 1.4730), which was 92% by weight *trans* isomer by v.p.c. analysis. By infrared analysis it was shown that this fraction was greater than 98% pure *cis*- and *trans*-1,3-dichloropropene. Hydrogenation of this fraction was carried out exactly as described for the *cis* isomer. There was obtained a 47.0% yield of 1,3-dichloropropane and 33.5% yield of propyl chloride.

Hydrogenation of 1-Chloropropene.—To a 1410-ml. stainless steel bomb was charged 30.0 g. (0.392 mole) of freshly distilled *cis–trans*-1-chloropropene (b.p. 31–37°), 150.0 g. of cyclohexane, and 2.40 g. of catalyst (5% Rh on alumina powder). Hydrogenation was carried out by the previously described procedure at an initial hydrogen pressure of 610 lb/in.^{2}. There was obtained a 42.4% yield of propyl chloride.

Hydrogenation of Allyl Chloride.—To a 1410-ml. stainless steel bomb was charged 30.0 g. (0.392 mole) of redistilled allyl chloride, 150.0 g. of cyclohexane, and 2.40 g. of catalyst (5% Rh on alumina powder). Hydrogenation was carried out by the previously described procedure at an initial hydrogen pressure of 580 lb./in.^{2}. There was obtained a 57.8% yield of propyl chloride.

Preparation of 5-Chlorohexene-1.—Into a 500-ml. flask fitted with a stirrer and thermometer was placed 50.0 g. (0.608 mole) of biallyl, 100 g. (36 g. of HCl, 1.0 mole) of concentrated hydrochloric acid, and 1.34 g. of zinc chloride. This mixture was stirred at room temperature for 40 hr. The organic layer was then separated, dried over anhydrous potassium carbonate, and distilled. Most of the product was unchanged biallyl. The fraction boiling at 120–123° (5.14 g.) was collected and had a refractive index of n^{25}D 1.4289 (lit.[8] b.p. 121–125°, n^{25}D 1.4279).

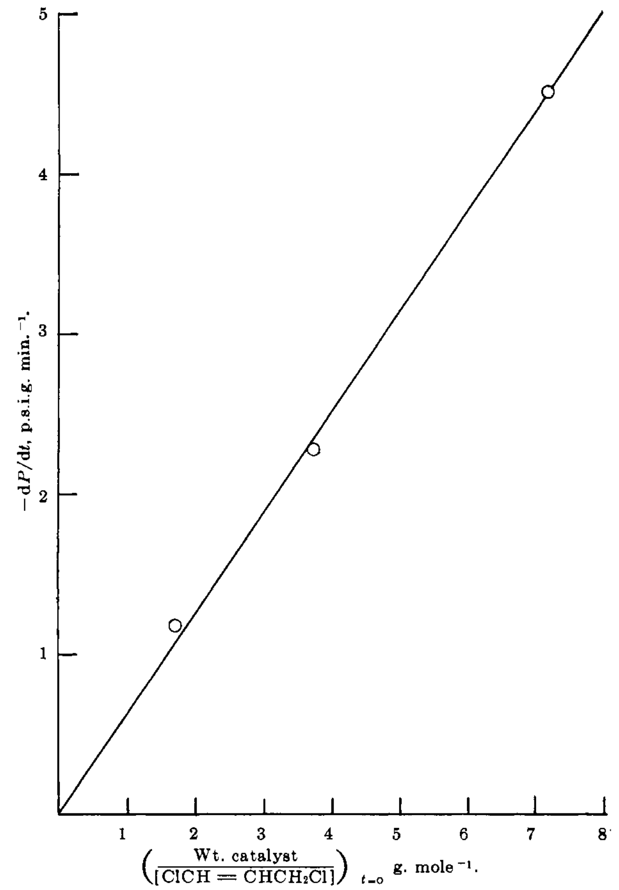

Fig. 2.—Effect of initial catalyst to olefin ratio on rate of hydrogenation of 1,3-dichloropropene.

Hydrogenation of 5-Chlorohexene-1.—To a 110-ml. stainless steel bomb was charged 5.14 g. (0.0433 mole) of 5-chlorohexene-1, 15.4 g. of cyclohexane, and 0.50 g. of catalyst (5% Rh on alumina powder). The bomb and contents were heated to 52° and pressurized to 500 lb./in.^{2} with hydrogen. After rocking and heating at this temperature for 70 min. the bomb was cooled and the gaseous portion vented through two scrubbers containing 1.0 *N* sodium hydroxide solution. A precipitate was not obtained when silver nitrate solution was added to an acidified portion of the scrubber solution. From the bomb was obtained 19.5 g. of product solution. After removal of the cyclohexane by distillation two fractions were collected. The first boiled at 80–120° (5.0 g., n^{25}D 1.4170) and was shown by analysis to be 79% 2-chlorohexane. The second boiled at 120–125° (1.10 g., n^{25}D 1.4153). Literature[9] values for 2-chlorohexane are b.p. 122.5° (754 mm.) and n^{25}D 1.4142. The yield of 2-chlorohexane was 96.9%.

Attempted *cis–trans* Isomerization of 1,3-Dichloropropene over 5% Rh on Alumina Powder in Absence of Hydrogen.—Into a flask fitted with a reflux condenser was placed 20.0 g. of *cis*-rich 1,3-dichloropropene (area % of *cis* and *trans* by v.p.c., 87.4% *cis* and 12.6% *trans*) and 2.00 g. of 5% Rh on alumina powder. The mixture was heated at reflux temperature (about 105°) for 160 min. After this time analysis of the mixture revealed 87.7% *cis* isomer and 12.3% *trans* isomer.

***cis–trans* Isomerization of 1,3-Dichloropropene over 5% Rh on Alumina Powder in Presence of Hydrogen.**—To a Paar apparatus was charged 24.4 g. (0.220 mole) of *cis*-rich 1,3-dichloropropene (analysis by v.p.c., 74.4% *cis* and 25.6% *trans*) and 2.00 g. of 5% Rh on alumina powder. The vessel was pressurized to 50 lb./in.^{2}

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[7] E. H. Huntress, "Organic Chlorine Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 653.

[8] F. Cortese, *J. Am. Chem. Soc.*, **52**, 1519 (1930).

[9] E. H. Huntress, "Organic Chlorine Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 1066.

with hydrogen and after about 30 min. shaking at room temperature the pressure had dropped to 47 lb./in.^{2}. The hydrogenation was stopped and analysis of the mixture revealed that 25.0% of the 1,3-dichloropropene had been converted and the remaining 1,3-dichloropropene was 73.0% *cis* and 27.0% *trans*. This corresponds to 1.9 ± 0.4% isomerization of *cis* to *trans* isomer in the unchanged 1,3-dichloropropene.

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The Microbial Hydroxylation of Tomatidine[1a,b]

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The steroidal alkaloid tomatidine has been hydroxylated by the fungus *Helicostylum piriforme* to yield 7α,11α-dihydroxytomatidine, 7α-hydroxytomatidine, and 9α-hydroxytomatidine. The proofs for their structures are discussed.

With the successful microbial hydroxylation of the steroidal alkaloid solasodine,[3a] it became of interest to study the effect of the fungus *Helicostylum piriforme* on tomatidine (I), the 5,6-dihydro C-25 epimer of solasodine. We previously had observed[3b] that the reduction of the double bond in the steroidal sapogenin, diosgenin, to the 5,6-dihydro derivative, tigogenin, had hindered its hydroxylation entirely.

With tomatidine, however, the hydroxylation proceeded smoothly to give the triol, 7α,11α-dihydroxytomatidine (IIa), in fairly good yields (25–30%). A lesser amount (*ca.* 5%) of the monohydroxylated compound, 7α-hydroxytomatidine (IIB), and a very small amount (*ca.* 0.5%) of 9α-hydroxytomatidine (IIC) also were isolated.

The assignment of a 3β,7α,11α-triol formulation to IIA is based on the degradation of the triol IIA to the known allopregnane derivatives, allopregnane-3β,7α,-11α-triol-20-one triacetate (Va) and allopregnane-3,7,11,20-tetrone (Vc). For the removal of the side chain,[4] the amorphous tetraacetate (IIa) was isomerized with boiling glacial acetic acid to a resinous pseudoderivative (IIIa) which could not be resolved by alumina chromatography. The reaction product, without further efforts at purification, was oxidized with chromic acid and the acyloxy side chain removed by treatment with boiling acetic acid.[5] Although the products crystallized at this stage, chromatography over alumina failed to resolve them into homogeneous components. The mixture, therefore, was hydrogenated in ethyl acetate over palladium–barium sulfate, whereupon an absorption of about 1.6 moles of hydrogen occurred, and the product became resolvable through alumina chromatography. The purified component agreed in properties with an authentic specimen of 3β,7α,11α-trihydroxyallopregnan-20-one triacetate[6] (Va). For further confirmation, the triol Vb also was oxidized to the known allopregnane-3,7,11,20-tetrone[6] (Vc). In the course of the separation of Va through chromatography, paper chromatographic spot tests of the various fractions indicated the presence of a second component concentrated mainly in the mother liquors after removal of Va. Accordingly the mother liquors were combined, hydrolyzed with base, and chromatographed over Florisil. The crystalline dihydroxyallopregnane (Vd) thus obtained was then oxidized to the known allopregnane-3,11,20-trione[6] (Ve). Apparently, the 7α-hydroxyl moiety in the triol IIA had partially dehydrated during the course of the degradation.

The structure of the diol IIB also was determined by its degradative conversion into the known 3β-acetoxyallopregnane-7,20-dione[7] (Vf) and into 3β,7α-dihydroxyallopregnane-20-one (Vg). For the conversion into Vf, the crude acetate IIb (acetic anhydride–pyridine, 15 hr. at room temperature) was isomerized as usual with glacial acetic acid and the pseudoproduct chromatographed over alumina to yield O,N-diacetylhydroxypseudo- (IIIb) and O,O,N-triacetylpseudotomatidine (IIIc). The 7α-hydroxyl is not completely acetylated under these conditions of acetylation.[8] Barton and Laws[9] have observed the same phenomenon in regard to the acetylation of ergost-22-ene-3β,7α-diol. The subsequent oxidation and acid hydrolysis (acetic acid) of IIIb and the reduction of the resultant 16-dehydro derivative (IVa) affords the known 3β-acetoxyallopregnane-7,20-dione[7] (Vf). For conversion of IIB into 3β,7α-dihydroxyallopregnan-20-one (Vg), the acetylation is conducted under more vigorous conditions (acetic anhydride–pyridine, 1 hr. at steam-bath temperature) to the O,O,N-triacetyl derivative (IIb) and submitted to the usual degradative procedure (IIb → IIIc → IVb → Vh).

The resistance of IIB toward acetylation, its relationship to the triol IIA, and its molecular rotation data[10] (ΔM_D −39) all support our assignment of a 7α configuration.

The structure of compound IIC was unequivocally established as 9α-hydroxytomatidine by its degradative conversion in the usual manner (IIc → IIId →

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(1) (a) In remembrance of the late Dr. Erich Mosettig of this Institute; (b) a preliminary account of portions of this work was published in *J. Org. Chem.*, **26**, 4181 (1961).

(2) Visiting Scientist (1960–1962), National Institutes of Health.

(3) (a) Y. Sata and S. Hayakawa, *J. Org. Chem.*, **28**, 2739 (1963); (b) S. Hayakawa and Y. Sato, *ibid.*, **28**, 2742 (1963).

(4) Y. Sato, N. Ikekawa and E. Mosettig, *ibid.*, **24**, 893 (1959).

(5) A. F. B. Cameron, K. M. Evans, J. C. Hamlet, J. S. Hunt, P. C. Jones, and A. G. Long, *J. Chem. Soc.*, 2807 (1955).

(6) C. Djerassi, O. Mancera, J. Romo, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 3505 (1953). We thank Dr. P. G. Holton of Syntex, S.A., Mexico, for providing us with an authentic specimen of the triacetate.

(7) W. Klyne, *J. Chem. Soc.*, 3449 (1951).

(8) L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romero, and T. Utne; *J. Am. Chem. Soc.*, **74**, 3309 (1952).

(9) D. H. R. Barton and G. F. Laws, *J. Chem. Soc.*, 52 (1954).

(10) ΔM_D = M_D (7ξ-hydroxytomatidine) − M_D (tomatidine) = −39. Cited values for 7α-OH, −59, and for the 7β-OH, +110. From L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 179.