10 g. of phosphorus pentasulfide was added after heating for an hour. After four hours of refluxing, the mixture was cooled, extracted with ether and the ether extracts dried over calcium chloride. Distillation gave the crude hydrocarbon, which was purified by refluxing over sodium. Rectification yielded 40.8 g. (53%) of 2-methyl-5-*t*-butylthiophene, b.p. 74–75° (19 mm.).

The chloromercuri derivative melted at 195°.

Anal. Calcd. for $C_9H_{13}HgClS$: C, 27.76; H, 3.35. Found: C, 28.01; H, 3.59.

5-*t*-Butyl-2-thiophenecarboxylic Acid.—5-*t*-Butyl-2-methylthiophene (24 g.) (0.15 mole) reacted with N-bromosuccinimide followed by hexamethylenetetramine in the manner indicated above under 5-isopropyl-2-thiophenecarboxylic acid to give the aldehyde, a small portion of which was converted to a semicarbazone melting at 215–216° (recrystallized from alcohol).

Anal. Calcd. for $C_{10}H_{15}N_3OS$: C, 53.33; H, 6.66; N, 18.66. Found: C, 53.14; H, 6.47; N, 18.56.

The crude aldehyde was then oxidized with alkaline potassium permanganate to give the crude acid. Recrystallization from alcohol–water yielded 8.4 g. (31%) of 5-*t*-butyl-2-thiophenecarboxylic acid, m.p. 127–128°. A mixed melting point with a sample obtained in an analogous manner from the 2-methyl-5-*t*-butylthiophene resulting from Friedel–Crafts reaction showed no depression.

Anal. Calcd. for $C_9H_{12}O_2S$: C, 58.69; H, 6.52. Found: C, 58.70; H, 6.33.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

The Mechanism of Halide Reductions with Lithium Aluminum Hydride. II. Reduction of 2-Chloro-2-phenylpropionic Acid[1,2]

BY ERNEST L. ELIEL AND JEREMIAH P. FREEMAN

Optically active 2-chloro-2-phenylpropionic acid and its methyl ester are readily reduced to active 2-phenyl-1-propanol by lithium aluminum hydride in either tetrahydrofuran or ether solution with 37–67% racemization. α-Methylstyrene oxide is not an intermediate, as it is reduced to 2-phenyl-2-propanol. 2-Phenyl-1,2-propanediol is a by-product of the reduction of 2-chloro-2-phenylpropionic acid and is formed with complete inversion of configuration. Formation of the glycol probably proceeds through an α-lactone intermediate. The alcohol may be formed by way of the primary reduction product, 2-chloro-2-phenyl-1-propanol, assumed to undergo a hydride shift with loss of hydrogen chloride to form 2-phenylpropanal which in turn is reduced to 2-phenyl-1-propanol.

The amazing versatility of lithium aluminum hydride[3] as a reducing agent in organic chemistry has stimulated considerable interest in the manner in which this reagent acts. Shortly after it became known that halides,[4,5] epoxides[5–7] and certain *p*-toluenesulfonates[8–10] can be reduced with lithium aluminum hydride in such a way as to replace a carbon–halogen or carbon–oxygen bond by carbon–hydrogen, Trevoy and Brown[6] demonstrated an inversion mechanism in the reduction of cyclic epoxides. They suggested the AlH_4^- anion to be the active species in the reduction which appears to be of the classical S_N2 type. Cram[10] showed that the reduction of the *p*-toluenesulfonates of the stereoisomeric 3-phenyl-2-butanols, 3-phenyl-2-pentanols and 2-phenyl-3-pentanols involves double inversion of configuration and postulated a "phenonium ion" intermediate. Alexander[9] obtained optically active 3-deutero-*trans*-*p*-menthane by the reduction of 1-menthyl *p*-toluenesulfonate with lithium aluminum deuteride. However, no work has been reported on the mechanism of the reduction of *halides* with lithium aluminum hydride, beyond the qualitative observation that primary halides react more rapidly than secondary, while tertiary halides produce mainly olefins.[4,6] This again points to an S_N2 mechanism which is also supported by the fact that optically active α-phenethyl chloride yields active α-deuteroethylbenzene upon reduction with lithium aluminum deuteride.[1,11]

It was the object of the present study to investigate the steric course of the reduction of a tertiary halide with lithium aluminum hydride. To accomplish this objective, a halide had to be chosen which was sufficiently reactive to be reduced, which could be obtained in a state of known optical purity, and which, upon reduction, would give a compound of known maximum rotation. Such a compound is 2-chloro-2-phenylpropionic acid (I).

Preliminary experiments with the racemic chloro-acid (I) indicated that it was readily reduced to 2-phenyl-1-propanol (II) in about 30% yield by means of lithium aluminum hydride in tetrahydrofuran solution. 2-Phenyl-1,2-propanediol (III) (about 25%) was also obtained in the reduction, as well as small amounts of 2-phenylpropanal (IV) and acetophenone.[12] Reduction of the active chloro-acid (I) revealed that the 2-phenyl-1-pro-

(1) First paper in this series: E. L. Eliel, THIS JOURNAL, **71**, 3970 (1949).

(2) Presented before the Organic Division of the American Chemical Society at Cleveland, Ohio, April 11, 1951.

(3) W. G. Brown in R. Adams, "Organic Reactions," John Wiley and Sons, Inc., Vol. VI, New York, N. Y., 1951, p. 469.

(4) J. E. Johnson, R. H. Blizzard and H. W. Carhart, THIS JOURNAL, **70**, 3664 (1948).

(5) R. F. Nystrom and W. G. Brown *ibid.*, **70**, 3738 (1948).

(6) L. W. Trevoy and W. G. Brown, *ibid.*, **71**, 1675 (1949).

(7) D. A. Prins, *ibid.*, **70**, 3955 (1948); P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta*, **31**, 1885 (1948); **32**, 265 (1949), P. A. Plattner, H. Heusser and M. Feurer, *ibid.*, **31**, 2210 (1948); **32**, 587 (1949).

(8) H. Schmid and P. Karrer, *ibid.*, **32**, 1371 (1949); P. Karrer and G. Widmark, *ibid.*, **34**, 34 (1951); P. Karrer, H. Asmis, K. N. Sareen and R. Schwyzer, *ibid.*, **34**, 1022 (1951).

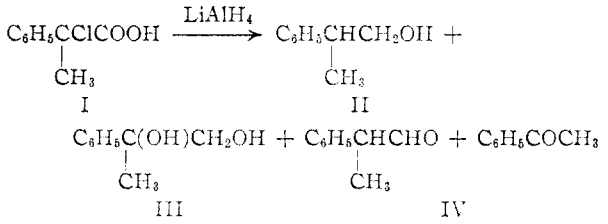
(9) E. R. Alexander, THIS JOURNAL, **72**, 3796 (1950).

(10) D. J. Cram, Meeting of the American Chemical Society, Chicago, Ill., September 6, 1950, Abstracts pp. 49N, 50N.

(11) The estimates of the optical purity of the α-phenethyl chloride used in our earlier investigation (ref. 1) are in error. Gerrard [*J. Chem. Soc.*, 741 (1946)] obtained α-phenethyl chloride with $[\alpha]_D^{16}$ +93.5°; thus the chloride used in the lithium aluminum deuteride reduction was at most about 52% pure. This does not affect the conclusions of the earlier paper (ref. 1) which were of a qualitative nature only.

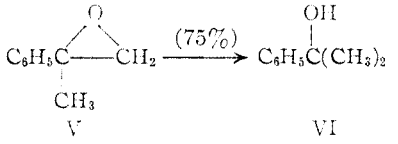
(12) Since an excess of lithium aluminum hydride was employed in the reduction, the carbonyl compounds cannot have been present in the reaction mixture but must have originated during the isolation process.

panol (II) was about 61–67% racemized, while the 2-phenyl-1,2-propanediol (III) was formed with nearly complete inversion.



Surprisingly, the reduction of the chloro-acid (I) with lithium aluminum hydride also proceeded readily in *ether* solution to give substantially the same products as in tetrahydrofuran, except that the alcohol II (69% yield) was racemized to the extent of 43% only and very little glycol (III) was isolated. Similarly, active methyl 2-chloro-2-phenylpropionate, obtained from the optically active parent acid I and diazomethane, could be reduced with lithium aluminum hydride in ether solution to 2-phenyl-1-propanol (II) in 62% yield with 37% racemization.

Since it was suspected that α-methylstyrene oxide (V) might be an intermediate in the reduction of the chloro-acid (I), this epoxide was submitted to lithium aluminum hydride treatment in a separate experiment. 2-Phenyl-2-propanol (VI) was the only product isolated, and there was no material whose boiling point corresponded to 2-phenyl-1-propanol (II).



Experimental[13]

Atrolactic Acid.—The acid was synthesized from acetophenone by a combination of methods described in the literature,[14,15] and resolved by means of either quinine[16] or active α-phenethylamine[17] to the extent of 70–80%.[18]

***dl*-2-Chloro-2-phenylpropionic Acid.**[19]—Treatment of 20 g. of atrolactic acid with 500 ml. of fuming hydrochloric acid yielded 17.1 g. (77%) of the chloro-acid melting at 72–74°. Recrystallization from benzene–petroleum ether (b.p. 30–60°) (89% recovery) raised the melting point to 73.5–74.5° (lit.[19] 73–74°).

(+)- and (−)-2-Chloro-2-phenylpropionic Acid.[16,20]—Finely powdered anhydrous[21] (−)-atrolactic acid (129 g., 0.78 mole, $[\alpha]_D$ −28.1° in acetone) was slurried with 387 g. (3.25 moles) of thionyl chloride. After four hours, the clear, red solution was concentrated *in vacuo* at room temperature. Dry benzene was added to the residue, and the vacuum distillation was continued at room temperature until as much of the excess thionyl chloride as possible was removed. The residue was allowed to crystallize in a refrigerator overnight and the crystals were separated from the adherent oil by vacuum filtration through a sintered-glass funnel under dry nitrogen. The filtration took several hours and the remaining crystals were slightly pink. After they had been stored for several days in a vacuum desiccator over potassium hydroxide, the color had changed to light yellow and the material weighed 40 g. Two recrystallizations from petroleum ether (b.p. 30–60°) with the aid of Norite gave 23.0 g. (16%) of (−)-2-chloro-2-phenylpropionic acid, m.p. 68–71°, $[\alpha]^{27}D$ −21.0 ± 0.2° in benzene (α = −1.39 ± 0.01°, l = 2 dm., c = 33.2 g./l.), optical purity 80%. (The values for the rotation of optically pure material given in the literature are 26.0°[16] and 26.3°.[22]) The sign of rotation is reversed in *ether* solution. A sample with $[\alpha]^{24}D$ +22.9 ± 0.2° in benzene had $[\alpha]^{23}D$ −4.13 ± 0.12° in ether.

Anal. Calcd. for $C_9H_9O_2Cl$: Cl, 19.2; neut. equiv.,[23] 92.3. Found: Cl, 19.1, 19.2; neut. equiv., 93.4, 94.1.

Reduction of 2-Chloro-2-phenylpropionic Acid.—The reduction of 22.2 g. (0.12 mole) of (−)-2-chloro-2-phenylpropionic acid, $[\alpha]^{27}D$ −21.0 ± 0.2° (optical purity 80%) in 100 ml. of tetrahydrofuran was carried out by means of 9.5 g. (0.25 mole) of lithium aluminum hydride in 275 ml. of tetrahydrofuran.[4] The reaction time was 24 hours. Fractional distillation of the reaction product through an eight-inch helix-packed column at 16 mm. pressure gave 1.7 g. of forerun and 4.7 g. (29%) of 2-phenyl-1-propanol, b.p. 111–116°, $[\alpha]^{26}D$ +3.63 ± 0.01° (α = +7.33°, homogeneous, l = 2 dm., d^{25} 1.005). Since infrared analysis showed the alcohol to contain about 10% of 2-phenylpropanol, assumed to be racemic, the optical purity is estimated at 26.5% based on a maximum rotation value $[\alpha]^{20}D$ +15.75°.[24] In other runs (see Table I) the 2-phenyl-1-propanol was purified by conversion to the acid phthalate which was separated from non-alcoholic impurities by carbonate extraction and then hydrolyzed without prior crystallization.

The residue, upon high-vacuum distillation, yielded 3.6 g. (20%) of 2-phenyl-1,2-propanediol, b.p. 84–88° (0.02 mm.), m.p. 33–43°, $[\alpha]D$ +7.09 ± 0.08° (α = +0.80 ± 0.01°, l = 2 dm., c = 63.7 g./l. in absolute ether), optical purity *ca.* 79%. Crystallization from absolute ether–petroleum ether (b.p. 30–60°) raised the specific rotation to +8.18 ± 0.08°; a second recrystallization from the same solvent pair gave material melting at 47–48°, $[\alpha]^{22}D$ +8.99 ± 0.18° (α = 1.04 ± 0.02°, l = 2 dm., c = 57.8 g./l. in absolute ether). The twice recrystallized material appeared to be optically pure, as further recrystallization did not alter the melting point or rotation. It was also noted that the material obtained in the second recrystallization and the residue from the mother liquors of the same recrystallization had identical ultraviolet spectra in alcohol solution, indicating that the once recrystallized material was chemically pure and that the second recrystallization merely served to separate the (+)-enantiomorph from the racemate.

The forerun of the distillation, upon treatment with semicarbazide acetate, in some instances yielded 2-phenylpropanal semicarbazone, m.p. 150–152° (lit.[25] 153–154°) and in others acetophenone semicarbazone, m.p. 193–195°, undepressed by admixture with an authentic specimen.

The results of various reductions of active and racemic 2-chloro-2-phenylpropionic acid with lithium aluminum hydride are summarized in Table I.

Methyl (+)-2-Chloro-2-phenylpropionate.—Six and two-tenths grams of 2-chloro-2-phenylpropionic acid, $[\alpha]^{24}D$ +22.9 ± 0.14° (α = +1.745 ± 0.01°, l = 2 dm., c = 38.0 g./l. in benzene), optical purity 87%, was converted to the methyl ester by treatment with a slight excess of diazomethane in ether solution. Concentration followed by vacuum distillation yielded 5.8 g. (87%) of the ester collected at 121.5–122.5° (12 mm.), $n^{25}D$ 1.5192, d^{23} 1.169, $[\alpha]^{23}D$ +6.54 ± 0.02° (α = +15.30 ± 0.05°, l = 2 dm., homogeneous). From this the specific rotation of the optically pure ester is calculated to be 7.5°.

(13) All melting points are uncorrected. The symbols D and L as used in this work are intended only to imply a generic relationship to D(−)- [or L(+)-] α-phenethyl alcohol.

(14) K. Freudenberg, J. Todd and R. Seidler, *Ann.*, **501**, 213 (1932).

(15) A. McKenzie and G. W. Clough, *J. Chem. Soc.*, **101**, 393 (1912).

(16) A. McKenzie and G. W. Clough, *ibid.*, **97**, 1016 (1910).

(17) L. Smith, *J. prakt. Chem.*, [2] **84**, 738 (1911).

(18) Literature values of the specific rotation of atrolactic acid in water at slightly varying concentrations and temperatures range from 50 to 56°: ref. 16, 17, 20 also A. McKenzie and A. Ritchie, *Ber.*, **70**, 30 (1937).

(19) G. Merling, *Ann.*, **209**, 19 (1881).

(20) E. Ott and K. Krämer, *Ber.*, **68**, 1655 (1935).

(21) The atrolactic acid should be recrystallized from benzene, and not from water, lest it be obtained in the form of the hemihydrate.

(22) A. McKenzie and G. W. Clough, *J. Chem. Soc.*, **97**, 2564 (1910).

(23) The chloro-acid hydrolyzes so rapidly that it consumes two equivalents of base (ref. 16).

(24) J. B. Cohen, J. Marshall and H. E. Woodman, *J. Chem. Soc.*, **107**, 899 (1915). According to our data on the reduction of 2-phenylpropionic acid, this value is about 15% too low.

(25) M. Tiffeneau, *Ann. chim.*, [8] **10**, 352 (1909).

TABLE I

REDUCTION OF 2-CHLORO-2-PHENYLPROPIONIC ACID WITH LITHIUM ALUMINUM HYDRIDE

Run no.	Reaction Solvent	Time, hr.	Chloro acid $[\alpha]_D$	O.P. %[26]	2-Phenyl-1-propanol Yield, %	$n^{25}D$	$[\alpha]_D$	O.P. %[26]	Yield, %	2-Phenyl-1,2-propanediol M.p., °C.	$[\alpha]_D$	O.P. %[2]
1	THF	24	−21.0	80	29	1.5245	+3.63	26.5	20	33–43	+7.09	79
2	THF	24	+3.95	15	38	....	−0.89	5.8	15.1	liq.[27]	*ca.* −2	..
3	THF	24	0	..	25[28]	1.5239	0	..	26	44–45[29]	0	..
4	Ether[30]	2	+10.7	41	43.5	1.5245	−3.46	22.6	0[31]	....	....	..
5	Ether[30]	2	0	..	69.5[28]	1.5265	0	..	trace	44–46[29]	0	..

Reduction of Methyl 2-Chloro-2-phenylpropionate. (A).—A solution of 11.6 g. (0.059 mole) of the ester, $[\alpha]^{23}D$ +4.33 ± 0.04° (optical purity 57.5%) was added to 4.6 g. (0.12 mole) of lithium aluminum hydride in 180 ml. of ether.[30] After one hour refluxing, the reaction mixture was treated with water and acid and worked up in the usual way. The residue was converted to the phthalate and the alcoholic constituent isolated as described above. There was obtained 5.0 g. (62%) of (−)-2-phenyl-1-propanol, b.p. 106–111° (12 mm.), $n^{25}D$ 1.5254, $[\alpha]^{27}D$ −5.49 ± 0.02° (α = −10.98 ± 0.04°, l = 2 dm., homogeneous), optical purity 36%. Its infrared spectrum was identical with that of an authentic sample of the racemate. A similar reduction of the racemic chloro-ester gave *dl*-2-phenyl-1-propanol purified by vacuum distillation rather than through the phthalate (identified by its 3-nitrophthalate, m.p. 146.5–148.5°, not depressed by admixture with an authentic sample) in 61% yield. Only a very small amount of high-boiling material was found.

The non-alcoholic fraction (1.4 g.) upon treatment with semicarbazide acetate, yielded 0.4 g. of acetophenone semicarbazone, m.p. 191–194° (without recrystallization), undepressed by admixture of an authentic sample. There was no evidence for the presence of 2-phenylpropanal.

(B).—A solution of 2.0 g. (0.053 mole) of lithium aluminum hydride in 120 ml. of absolute ether was added slowly to a stirred solution of 19.8 g. (0.1 mole) of methyl *dl*-2-chloro-2-phenylpropionate in 100 ml. of absolute ether which was maintained near room temperature by water cooling. Stirring was continued for 15 minutes after the addition of the hydride was complete. After addition of 30 ml. of water and 75 ml. of 10% sulfuric acid, the layers were separated and the ether layer was washed successively with water, sodium carbonate solution and water, dried over sodium sulfate and concentrated. Hydrogen chloride fumes were evolved during concentration. Fractional distillation of the residue yielded 1.6 g. (12%) of 2-phenylpropanal, b.p. 97–101° (23 mm.), $n^{25}D$ 1.5162, identified by its semicarbazone, melting point and mixture melting point 148–150°, after one crystallization from ethanol. The higher-boiling material weighed 2.75 g. and distilled over a wide range of temperature; a considerable residue was left in the distillation flask.

When the reaction was carried out in the same manner except that the reflux period was extended to one hour after which the metal complexes were destroyed by 30 minutes warming with 100 ml. of a 10% sodium hydroxide solution diluted with 50 ml. of water, no hydrogen chloride fumes were observed in the concentration step. In this case very little if any 2-phenylpropanal was isolated; instead there was obtained 2.4 g. (18%) of material boiling at 84–88° (13 mm.), $n^{20}D$ 1.5202, which appeared to be α-methylstyrene oxide (V).

Optical Stability of 2-Phenyl-1-propanol on Treatment with Lithium Aluminum Hydride.—To 3.8 g. (0.1 mole) of lithium aluminum hydride in 125 ml. of tetrahydrofuran was added a solution of 8.0 g. (0.59 mole) of (−)-2-phenyl-1-propanol, α = −2.375 ± 0.01° (l = 2 dm., homogeneous). The solution was boiled under reflux for 25 hours. During part of this time it was also stirred mechanically. The usual isolation procedure[4] then led to the recovery of 7.1 g. of material of which 3.7 g., collected at 97–99° (6 mm.), had $n^{25}D$ 1.5231, α −2.31 ± 0.01° (l = 2 dm., homogeneous) and 2.7 g., collected at 99° (6 mm.), had $n^{25}D$ 1.5225, α −2.435 ± 0.01° (l = 2 dm., homogeneous). Thus the alcohol was not racemized to any extent.

Reduction of (+)-Atrolactic Acid.—A solution of 4.5 g. (0.027 mole) of (+)-atrolactic acid, $[\alpha]^{27}D$ +34.7 ± 0.1° (α = +2.91 ± 0.01°, l = 2 dm., c = 42.0 g./l. in acetone), optical purity *ca.* 95%[16,18] in 50 ml. of ether was added to 2.3 g. (0.06 mole) of lithium aluminum hydride in 85 ml. of ether. The usual procedure[30] was followed, the reaction mixture being worked up with base. The product was collected at 87–88° (0.03 mm.) and weighed 2.9 g. (69%). It melted at 45–47° and had $[\alpha]D$ +8.42 ± 0.08° (α = 1.135 ± 0.01°, l = 2 dm., c = 67.6 g./l. in ether). From this, the specific rotation of the pure compound in ether solution is calculated to be *ca.* +8.85°. Actually, when the material was crystallized to constant melting point and rotation, it had $[\alpha]D$ +8.94 ± 0.08°, m.p. 47.5–48.5°.

A similar reduction of *dl*-atrolactic acid gave *dl*-2-phenyl-1,2-propanediol in 76% yield. After two recrystallizations from ether–pentane, the racemate melted at 43–44°.[29]

α-Methylstyrene Oxide.—Preparation of this oxide by peracid oxidation of α-methylstyrene[32] gave material contaminated with the highly undesirable 2-phenylpropanal. The epoxide was therefore prepared from the olefin through the iodohydrin[33] in 12% over-all yield. It boiled at 84–85° (14 mm.) and had $n^{20}D$ 1.5205.

Reduction of α-Methylstyrene Oxide.—A solution of 13.0 g. (0.09 mole) of the epoxide in 50 ml. of tetrahydrofuran was added to 3.8 g. (0.1 mole) of lithium aluminum hydride in 65 ml. of the same solvent. The usual procedure was followed[4] with a total reaction time of 24 hours. Distillation of the product gave 9.9 g. (75%) of a fraction boiling at 95–97° (15 mm.); no higher-boiling material appeared to be present. The product as distilled melted at 23–25°; recrystallization from petroleum ether (b.p. 30–60°) raised the melting point to 30–31.5° and the substance did not depress the melting point of an authentic specimen of 2-phenyl-2-propanol prepared from phenylmagnesium bromide and acetone[34] in 77% yield. The authentic specimen boiled at 95–96° (15 mm.) and melted at 31–32° after recrystallization.

***dl*-2-Phenylpropionic Acid.**[35]—To a well-stirred solution of 24.7 g. (0.184 mole) of *dl*-2-phenylpropanal[36] and 69 g. (0.406 mole) of silver nitrate in 110 ml. of ethanol and 110 ml. of water, a solution of 25.8 g. (0.645 mole) of sodium hydroxide in 520 ml. of water was added over a period of 1.5 hours. The suspension was then heated on a steam-bath with continued stirring for another hour.[37] The silver and silver oxide were removed by vacuum filtration and washed with water and ether. The filtrate was twice extracted with *ca.* 200 ml. of ether. The aqueous layer was distilled until the organic solvents were removed, then acidified with hydro-

(26) Optical purity.

(27) Attempted crystallization yielded only the racemate, m.p. 44–45°. *dl*-2-Phenyl-1,2-propanediol is a racemic *compound*, since it was found that the (+)-enantiomorph depresses the melting point of the racemate to 25–30° on admixture.

(28) Identified by the 3-nitrophthalate, m.p. 143.5–145.5° (lit.[24] 147°) and the phthalate, m.p. 78–79° (lit.[24] 79°), undepressed by admixture of an authentic specimen.

(29) R. Stoermer, *Ber.*, **39**, 2297 (1906), reports 44.5°. The mixture melting point of our sample with an authentic specimen prepared as described below was not depressed.

(30) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 2548 (1947). Basic decomposition was employed in run 4.

(31) The high-boiling material was collected over a wide temperature range and did not crystallize.

(32) S. Danilov and E. Venus-Danilova, *Ber.*, **60**, 1059 (1927).

(33) M. Tiffeneau, *Ann. chim.*, [8] **10**, 186 (1909).

(34) Tissier and Grignard, *Compt. rend.*, **132**, 1184 (1901).

(35) H. D. Kay and H. S. Raper, *Biochem. J.*, **16**, 469 (1922).

(36) Purchased from Verona Chemical Company. Infrared spectral analysis shows that this material contains a few per cent. of acetophenone.

(37) Method of M. Délépine and P. Bonnet, *Compt. rend.*, **149**, 39 (1909).

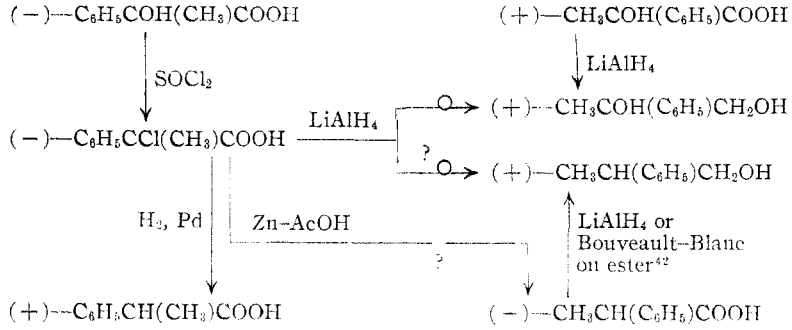


Fig. 1

chloric acid and extracted with two 200-ml. portions of ether. The ether solution was dried over sodium sulfate, concentrated and the residue distilled *in vacuo*. The hydratropic acid boiled at 144–147° (11 mm.) and weighed 20.5 g. (74%). The neutral fraction upon distillation gave *ca.* 2 g. (8%) of acetophenone, b.p. 80–82° (11 mm.), $n^{25}D$ 1.5285, semicarbazone m.p. 196.5–197° (without recrystallization) not depressed by admixture with acetophenone semicarbazone.

(−)-2-Phenylpropionic Acid.—Resolution of the *dl*-acid by means of quinine was found less efficient than indicated in the literature.[38] The resolved acid boiled at 146–147° (11 mm.) and had $[\alpha]^{27.5}D$ −16.5 ± 0.1° (homogeneous, α = −36.25°, l = 2 dm.); $[\alpha]^{29}D$ −13.5° (in USP chloroform, α = −0.965 ± 0.01°, l = 2 dm., c = 35.55 g./l.) and $[\alpha]^{29}D$ −14.3° (in 95% ethanol, α = −0.925 ± 0.01°, l = 2 dm., c = 32.6 g./l.). From the rotation in alcohol and chloroform,[39] the optical purity is calculated to be 17.6–17.7%, thus the specific rotation of the pure compound[40] is 93.6 ± 0.6°.

Reduction of (−)-2-Phenylpropionic Acid.—The reduction of 22.0 g. (0.147 mole) of the (−)-acid, optical purity 17.7%, in 200 ml. of ether by means of 7.1 g. (0.15 mole) of lithium aluminum hydride in 250 ml. of ether[30] yielded 17.9 g. (90%) of 2-phenyl-1-propanol boiling at 105–106° (11 mm.), $n^{25}D$ 1.5230, $[\alpha]^{25.5}D$ +3.18 ± 0.01° (α = +6.37 ± 0.02°, l = 2 dm., homogeneous). The optical purity calculated on the basis of literature data[24] is 20.6%, thus there was no racemization[41]; in fact the data indicate that the maximum rotation of 2-phenyl-1-propanol is about 15% higher than indicated in the literature.[24]

Optical Purity and Relative Configuration of Materials.—The minimum specific rotation of 2-chloro-2-phenylpropionic acid (I) in benzene solution is 26.3°.[23] The maximum rotation can be calculated as 26.6°, since reduction of the acid with a rotation of 21.0° gives 2-phenyl-1,2-propanediol (III) of 79% optical purity. The degree of optical purity of the starting chloro-acid (I) used in this investigation is therefore not subject to doubt.

For the main product, 2-phenyl-1-propanol (II), the minimum rotation[24] is 15.25°. No maximum value is available, but if it is *assumed* that lithium aluminum hydride reduction of 2-phenylpropionic acid proceeds without racemization, the true specific rotation appears to be about 15% higher than the above value. This variation would not be sufficient to affect any conclusions arrived at below. With respect to the configurational relationship of 2-chloro-2-phenylpropionic acid (I) and 2-phenyl-1-propanol (II), it is known that catalytic reduction of (−)-2-chloro-2-phenylpropionic acid (I) gives rise to (+)-2-phenylpropionic acid while chemical reduction with zinc and acetic acid gives the (−)-enantiomorph.[20] Since (−)-2-phenylpropionic acid has the same configuration as (+)-2-phenyl-1-propanol (II) (shown in this work as well as previously[42]) which in turn is obtained by lithium aluminum hydride reduction of (−)-2-chloro-2-phenylpropionic acid (I), the hydride reduction is stereochemically equivalent to metal–acid reduction and different from catalytic reduction. This does not, however, give any clue as to the relative configurations.[43]

Reduction of (+)-methyl-2-chloro-2-phenylpropionate, which can be obtained from the dextrorotatory parent acid (I) by diazomethane treatment presumably without change of configuration and optical purity, also gives rise to (−)-2-phenyl-1-propanol (II).

The relative configuration and maximum rotation of the second major reduction product, 2-phenyl-1,2-propanediol (III) were established by obtaining it through lithium aluminum hydride reduction of atrolactic acid of known optical purity. The maximum rotation thus calculated[44] was 8.85° and agrees satisfactorily with the value actually found after crystallization to constant melting point and rotation (8.94°). Configurationally, the (+)-glycol (III) is related to (+)-atrolactic acid which upon thionyl chloride treatment yields (+)-2-chloro-2-phenylpropionic acid (I), presumably with retention of configuration. Hence the reduction of the levorotatory chloroacid (I), which gives rise to the dextrorotatory glycol (III) must involve inversion. The degree of inversion is calculated from the optical purity data to be 99%.

The configurational relationships are summarized in Fig. 1 and some of the optical purity data are shown in Table I.

Discussion

Reaction Path.—Any adequate reaction mechanism must account for the following facts: (1) 2-chloro-2-phenylpropionic acid and its methyl ester are reduced to halogen-free products more readily than either α-phenethyl chloride[1] or chloroacetic acid and its ethyl ester.[45] (2) One of the products of reduction of the acid (I) is 2-phenyl-1,2-propanediol (III) formed with complete in-

(38) P. A. Levene, L. A. Mikeska and K. Passoth, *J. Biol. Chem.*, **88**, 33 (1930).

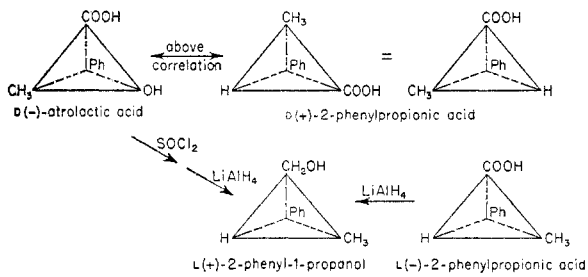
(39) H. S. Raper, *J. Chem. Soc.*, **123**, 2558 (1923), reports $[\alpha]^{20}D$ +81.1° in ethanol; +76.2° in chloroform.

(40) H. I. Bernstein and F. C. Whitmore, THIS JOURNAL, **61**, 1326 (1939), report d^{20} 1.097, $[\alpha]^{25.5}D$ +86.1, but do not claim their material to be completely resolved.

(41) This is in agreement with the findings of D. S. Noyce and D. B. Denney, *ibid.*, **72**, 5743 (1950), for the reduction of active 2-methylbutyric acid.

(42) P. A. Levene, R. E. Marker and A. Rothen, *J. Biol. Chem.*, **100**, 589 (1933).

(43) V. Prelog, Abstracts, XIIth International Congress of Pure and Applied Chemistry, New York, N. Y., 1951, p. 401, has proposed an ingenious argument by means of which the configuration of (−)-atrolactic acid can be related to that of D(−)-mandelic acid. The latter in turn has been related to D(−)-α-phenethyl alcohol: K. Mislow, THIS JOURNAL, **73**, 3954 (1951). D(−)-α-phenethyl alcohol has been correlated in at least two independent ways with D(+)-2-phenylpropionic acid: E. Bergmann, *Helv. Chim. Acta*, **20**, 601 (1937); P. A. Levene, A. Rothen and M. Kuna, *J. Biol. Chem.*, **120**, 797 (1937); H. R. Snyder and J. H. Brewster, THIS JOURNAL, **71**, 291 (1949); P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **93**, 751 (1931); also ref. 40. If Prelog's argument is valid, the configurations are related as follows:



It is apparent that the conversion of D(−)-atrolactic acid to L(+)-2-phenyl-1-propanol involves an odd number of inversions. This is consistent with the scheme postulated in Fig. 1 where one inversion is assumed to occur in the reduction step. We feel that this correlation lends further support to the reaction mechanism given in the discussion part.

(44) Assuming the specific rotation of optically pure atrolactic acid in acetone to be 36.5° (ref. 16). This is probably within about 5% of the correct value (ref. 18).

(45) C. E. Sroog, C. M. Chih, F. A. Short and H. M. Woodburn, THIS JOURNAL, **71**, 1710 (1949).

version of configuration. (3) Both the acid (I) and its methyl ester give rise to 2-phenyl-1-propanol (II) in approximately the same yield and with partial racemization; the configurational relationship of II to I is the same, regardless of whether the free acid or its methyl ester is reduced. It appears to us that the mechanism shown in Fig. 2 best accounts for all the facts.

According to this mechanism, the salt formed from the chloro-acid (I) and lithium aluminum hydride may undergo an internal displacement (with inversion) to the α-lactone (VII) which is then further reduced in the normal manner,[5] *i.e.*, with acyl–oxygen fission and without inversion. The formation of α-lactone intermediates has been postulated to account for the kinetic and optical course of other displacement reactions of α-halo-acids,[46] and such an intermediate may be responsible for the abnormally rapid hydrolysis of 2-chloro-2-phenylpropionic acid (I).[23] To our knowledge, the present case is the first instance where the hypothetical α-lactone intermediate accounts for a *single* inversion.

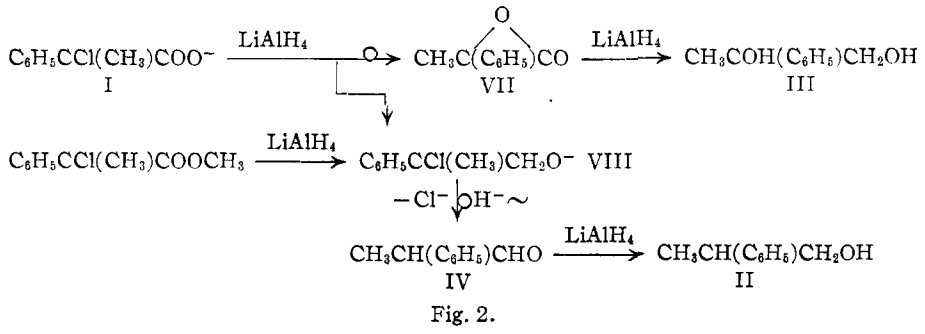


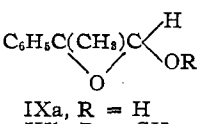
Fig. 2.

An alternative path of reduction open to the chloro-acid (I) and the only path available for the methyl ester leads to the chlorohydrin anion VIII which is then assumed to undergo a hydride shift with loss of chloride ion to form 2-phenylpropanal (IV). An analogy for this type of shift is available in the reaction of chlorohydrins and α-chloro-ketones with alkylmagnesium halides.[47,48] While the stereochemistry of this shift is not yet quite clear,[47] it appears to proceed with predominant inversion of configuration. This is therefore assumed in the conversion of VIII into IV, and consequently the over-all transformation of I or its methyl ester into II. Reference to Fig. 1 shows that if this assumption is correct, catalytic reduction of I proceeds with partial retention of configuration and chemical reduction with partial inversion, a consequence which does not seem unreasonable. Moreover, the assumption that conversion of (−)-I to (+)-II involves inversion of configuration is consistent with the recent assignment of the D-configuration to (−)-atrolactic acid,[14,43] since (+)-2-phenyl-1-propanol belongs to the L-series.[43]

The lack of complete stereospecificity in the reduction of I or its methyl ester to II is a matter of some concern. Reduction of I to VIII would not be expected to involve racemization, nor would the reduction of IV to II, in view of the fact that the reduction of 2-phenylpropionic acid to 2-phenyl-1-propanol (II) [in which 2-phenylpropanal (IV) is necessarily a fleeting intermediate] is stereospecific. Partial racemization thus appears to take place in the transformation of the chlorohydrin VIII to the aldehyde IV. An analogy for this is available in the lack of stereospecificity in the reaction of *cis*- and *trans*-1-methyl-2-chlorocyclopentanol with methylmagnesium bromide which involves a methyl shift and leads to 2-methylcyclopentanone, regardless which geometric isomer is employed as the starting material.[49]

Experimental evidence for the postulated hydride shift was obtained when methyl 2-chloro-2-phenylpropionate was reduced by the slow addition of one-half mole of lithium aluminum hydride in ether solution. This is the amount calculated for the partial reduction of the ester to the chlorohydrin VIII. When the reaction mixture was decomposed with acid, the crude reaction product contained a very unstable chlorine compound, as evidenced by the evolution of hydrogen chloride during concentration of the ether solution of the product. Distillation of the residue yielded 2-phenylpropanal (IV) in 11% yield; no 2-phenyl-1-propanol (II) was isolated from this reaction. Basic decomposition of the reaction mixture led to α-methylstyrene oxide (V) in 18% yield. It seems likely that both the aldehyde (II) and the epoxide (V) were formed from the primary reaction product 2-chloro-2-phenyl-1-propanol (VIII) during the isolation process.

Other reaction paths leading to II can be envisaged, such as a nucleophilic displacement of chlorine by hydrogen[4–6]; dehydrohalogenation[4,6] followed by hydrogenation,[50] intervention of an organo-lithium compound,[6] alkyl–oxygen fission of the α-lactone (VII), or alkyl–oxygen fission of an intermediate cyclic hemiacetal (IXa) in the case of the acid or epoxy-ether (IXb) in the case of the ester. However, such mechanisms appear less likely than the one proposed because of unfavorable steric and electronic factors, because they do not adequately account for the partial preservation of optical activity, or because there is no analogy for them in the literature.



IXa, R = H
IXb, R = CH_3

Acknowledgment.—We wish to thank Professor Christopher L. Wilson of The Ohio State University for the recording and interpreting of

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the infrared spectra. We are also indebted to E. I. du Pont de Nemours and Company for a generous gift of tetrahydrofuran.

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Cacao Oxidase

BY R. G. MOORES, DOROTHY M. GRENINGER AND I. I. RUSOFF

The isolation and properties of cacao oxidase are presented. The oxidizing enzyme in cacao is a polyphenol oxidase similar to the oxidases in mushrooms and sweet potatoes. It has a high activity in the oxidation of 4-substituted catechol compounds. The oxidase is inactivated rapidly by wet heat and by cyanides and sulfides.

Fermentation is the most important step in the tropical processing of cacao beans. This processing produces a stable product and aids in the development of desirable flavor and color. Many of the changes which the bean undergoes during the fermentation process are obscure. Some changes are due to yeasts, molds and bacteria which decompose the mucilaginous substances or pulp surrounding the bean, while others are due to the natural enzymes of the bean which develop color and flavor during fermentation. These changes resemble those which occur in the browning of many fruits and vegetables due to the enzymatic oxidation of phenolic substances.

Fresh unfermented cacao beans are purple or white and have a harsh, astringent flavor attributed to the phenolic constituents. Cacao oxidase apparently initiates and hastens oxidative reactions involving the phenolic compounds, which in cacao are predominantly catechins, anthocyanins and related tannins. These oxidative reactions appear to be responsible for the decrease in astringent flavor and purple color during fermentation and, therefore, are important in the production of high-quality cacao products.

The enzymatic oxidation processes in cacao have been discussed by Brill,[1] Ciferri[2] and Knapp,[3] but no precise description of the oxidase is available. This paper describes the isolation and properties of cacao oxidase.

Measurement of Oxidase Activity.—Several techniques for the estimation of oxidase activity are available. Colorimetric methods using reagents such as pyrogallol,[4] guaiacol,[5] indophenol[6] and *o*-phenylenediamine have been used. With pyrogallol, the cacao enzyme used in the present work formed purpurogallin, a colored product with a maximum absorption at 305 millimicrons. A crude cacao enzyme had a purpurogallin number of 9 compared to a figure of 0.26 for whole mushroom and the value of 96 reported by Keilin[4] for the purest mushroom oxidase. The cacao oxidase also formed colored products with guaiacol, 2,6-dichlorobenzenoneindophenol and *o*-phenylenediamine. The colorimetric methods were found valuable for qualitative tests or semiquantitative estimations, but they lack reliability for quantitative measurements.

Manometric methods have been used to measure enzyme activity.[7] In the present work, oxygen uptake measurements were made with a Barcroft–Warburg apparatus on a system including cacao enzyme, *p*H 6 buffer, and different substrates. Under these conditions, the enzyme had greater activity with *p*-cresol than with catechol or cacao tannin.

The ascorbic acid–catechol method of Sreerangachar[8] was found to be the most reproducible method for measuring cacao oxidase. The test system contains the enzyme material, a *p*H 5 buffer, catechol or other phenol as substrate and ascorbic acid. Air is drawn through the mixture at a constant rate for a fixed period of time at 40°. Rate studies indicated that a 10-minute reaction gave reproducible results. As the catechol is oxidized, it in turn oxidizes the ascorbic acid, loss of which is followed analytically by indophenol titration. The loss of ascorbic acid is a measure of the enzyme activity of the sample for the oxidation of the substrate. An average deviation of 5% was observed between duplicate measurements using the following procedure.

Oxidase Method.—Pipet 5 ml. of *p*H 5 buffer (McIlvain 0.1 *M* citric acid and 0.2 *M* disodium phosphate) and 5 ml. of ascorbic acid–catechol solution (0.1% ascorbic acid plus 0.5% catechol) into a 200 mm. × 30 mm. test-tube. Weigh cacao or enzyme sample in a small glass cup (10 × 15 mm.) and transfer to the test-tube.

Insert a rubber stopper having a 5-mm. glass tube inlet extending to the bottom of the test-tube and a glass tube outlet at the top. Transfer the reaction vessel to a water-bath held at 40°. Connect the inlet tube to another tube containing water at 40° and the outlet tube through a flowmeter to a vacuum line. Pull air through the reaction vessel at the rate of 8 l. per hour. At 10 minutes reaction time pipet 5 ml. of the mixture into a 125-ml. erlenmeyer flask containing 1 ml. of 20% H_3PO_4. This drop in *p*H stops the oxidation reaction. Measure the excess ascorbic acid which should be not less than 50% of the total by titrating with indophenol solution (0.1% sodium 2,6-dichlorobenzenoneindophenol standardized with 0.01 *N* sodium thiosulfate in the presence of H_3PO_4).

Run a control reaction with each series of tests using 5 ml. of both the ascorbic acid–catechol and buffer solutions, titrating exactly as described above. Subtract the titration of the sample from the control titration, multiply by 2 and calculate the milligrams of ascorbic acid oxidized by 1 g. of sample on the basis of 1 ml. 0.01 *N* thiosulfate solution = 0.88 mg. ascorbic acid.

Cacao samples were prepared for oxidase measurement by drying beans from fresh pods under vacuum at 45°, hand

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