of one-half hour while the reaction mixture was held at -5 to 0°. Stirring was continued for three hours longer. At the end of this time a thick cream-colored solid had separated. The mixture was poured over cracked ice and neutralized to litmus with 40% sodium hydroxide solution. The solid was removed by filtration, washed twice with ice-water, and dissolved in hot 2-propanol. Crystallization occurred at room temperature and after several recrystallizations a pure product, pale yellow shining platelets, was obtained, m.p. 156–157°, $[\alpha]^{24}\mathrm{D}$ 40.5 (chloroform, *c* 2.002). The recorded physical properties of *o*-nitrophenyl tetraacetyl-β-D-glucoside have been stated as m.p. 150–152°, $[\alpha]^{20}\mathrm{D}$ 45° (chloroform)[5c]; 160–162°, $[\alpha]^{20}\mathrm{D}$ 45 (chloroform)[18]; m.p. 158–159°, $[\alpha]^{20}\mathrm{D}$ 45° (chloroform)[19]; and m.p. 160.5–161.5°, $[\alpha]^{20}\mathrm{D}$ 43.0° (chloroform).[20]

Although Lindberg[18] reported the isolation of both *o*-nitro- and *p*-nitrophenyl tetraacetyl-β-D-glucoside on nitration of phenyl tetraacetyl-β-D-glucoside using nitric acid in acetic acid, we have isolated only the ortho-isomer on successive recrystallization of the crude nitration mixture. Due to the isolation of lower melting material in impure form from the mother liquors in the present nitration, we feel that the para-isomer was also produced in our experiment.

Isolation of the Aglucon.—*o*-Nitrophenyl tetraacetyl-β-D-glucoside (1.08 g.) was refluxed for one hour with 1 *N* hydrochloric acid (100 cc.). At this time the *o*-nitrophenol had been steam distilled into the condenser as bright yellow needles, m.p. 45–47°. The reported melting point of *o*-nitrophenol[21] is 45°. The nitrophenol was further characterized by bromination with aqueous bromine–potassium bromide to yield the dibromo derivative, m.p. 116–117°. The melting point of 2,4-dibromo-6-nitrophenol given in the literature[22] is 117°.

4-Nitro-1-naphthyl Tetraacetyl-β-D-glucoside.—This compound was prepared from 1-naphthyl tetraacetyl-β-D-glucoside (3 g.) in acetic anhydride in the manner described above. The mixture was stirred for 2.5 hours after addition to the nitration mixture was completed. It was then poured into sodium bicarbonate (42 g.) in ice-water, at which point a deep yellow solid separated. This was filtered, washed with ice-water and dissolved in hot 2-propanol from which it crystallized as glistening yellow needles. Two recrystallizations from alcohol yielded a pure product, m.p. 176–177°, $[\alpha]^{25}\mathrm{D}$ $-67.2°$ (chloroform, *c* 2.025).

Anal. Calcd. for $C_{24}H_{25}O_{12}N$: C, 55.29; H, 4.82; N, 2.70. Found: C, 55.28; H, 4.86; N, 2.81.

Isolation of the Aglucon.—One gram of 4-nitro-1-naphthyl tetraacetyl-β-D-glucoside was refluxed with 1 *N* hydrochloric acid (50 cc.) for approximately 12 hours. The cooled mixture contained a flocculent yellow suspension which was extracted with ether. The ether solution was extracted with 10% sodium hydroxide and the resulting orange-red solution was acidified to yield the flocculent yellow solid once again. This was extracted into ether, the solution dried over anhydrous sodium sulfate, the solvent evaporated and the yellow residue recrystallized from water as very fine yellow needles, m.p. 159–164°. The recorded melting point of 4-nitro-1-naphthol is 164°.[23] The nitronaphthol was further identified by benzoylation after the procedure of Hazlet.[14] The benzoate crystallized from acetone as small pale yellow needles, m.p. 169–170°. The melting point reported for 4-nitro-1-naphthyl benzoate[24] is 176° (cor.).

1-Nitro-2-naphthyl Tetraacetyl-β-D-glucoside.—This compound was prepared, in the manner described previously, from 2-naphthyl tetraacetyl-β-D-glucoside (3 g.) dissolved in acetic anhydride. The product, pale yellow needles, m.p. 198–199°, crystallized from benzene, darkened to a green-yellow on exposure to light, and showed no optical activity in chloroform solution.

Anal. Calcd. for $C_{24}H_{25}O_{12}N$: C, 55.49; H, 4.82; N. 2.70. Found: C, 55.50; H, 4.82; N, 2.58.

Isolation of the Aglucon.—One gram of nitro-2-naphthyl tetraacetyl-β-D-glucoside was refluxed with 1 *N* hydrochloric acid for 48 hours. The free 1-nitro-2-naphthol steam distilled and collected in the condenser, m.p. 95–98°. On recrystallization from 2-propanol, the melting point was raised to 99–100.5°. The reported melting point for 1-nitro-2-naphthol[19] is 103°. The 1-nitro-2-naphthol was further characterized by its methyl ether, m.p. 123.5–125°. The recorded melting point is 128°.[25] The methyl ether was a pale yellow solid which turned to a green-yellow on standing in light, the characteristic shown by 1-nitro-2-naphthyl tetraacetyl-β-D-glucoside.

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(19) B. Lindberg, *Acta Chem. Scand.*, **2**, 936 (1948).

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The Stereochemistry of Raney Nickel Action. III. The Stereochemical Course of Dehydroxylations in the Benzyl Alcohol Series

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Since the stereochemical path followed during the Raney nickel catalyzed desulfuration of sulfides differed from that followed during sulfone desulfuration, we have undertaken a study of the stereochemical course of Raney nickel catalyzed dehydroxylations in the benzyl alcohol series. Derivatives of atrolactic acid were converted to derivatives of 2-phenylpropionic acid with Raney nickel in refluxing ethanol with what appeared to be practically complete retention of configuration. Such slight racemization as was noted seemed due to the fact that Raney nickel slowly racemizes derivatives of 2-phenylpropionic acid in refluxing ethanol. The dehydroxylation of ethyl mandelate appeared substantially complete in the course of 20 minutes reaction time.

The occurrence of carbon–oxygen bond cleavage in benzyl alcohol or substituted benzyl alcohols under conditions of catalytic hydrogenation at elevated temperatures and pressures is well known.[1] In 1944, while studying the effect of excess Raney nickel on potentially reducible groups other than sulfur, Mozingo and co-workers found[2] that this catalyst was also capable of converting both benzyl alcohol and benzaldehyde to toluene in a short time under the mild conditions of mere refluxing in ethanol ordinarily employed in Raney nickel catalyzed desulfurations.[3] Recently the stereochemical course of reductive desulfuration was investigated[4] with the discovery that sulfides were desulfurized with complete racemization whereas

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(1) H. Adkins, "Reactions of Hydrogen with Organic Compounds Over Copper–Chromium Oxide and Nickel Catalysts," Univ. of Wisconsin Press, Madison, Wis., 1937, p. 69 ff.

(2) R. Mozingo, C. Spencer and K. Folkers, This Journal, **66**, 1859 (1944).

(3) R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, *ibid.*, **65**, 1013 (1943).

(4) W. A. Bonner, *ibid.*, **74**, 1033, 1034 (1952). These papers constituted I and II in the present series.

sulfones underwent desulfuration with apparent inversion of configuration of the carbon adjacent to the sulfur atom. In view of these unexpected and divergent results it seemed desirable to investigate the stereochemical consequences of those Raney nickel catalyzed dehydroxylations which occur under desulfurizing conditions.

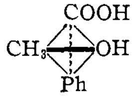
The substituted benzyl alcohol employed in the present study was atrolactic acid, which is readily obtainable[5] in both enantiomorphic forms. After establishing experimentally the fact that derivatives of both atrolactic and mandelic acids were satisfactorily dehydroxylated using Raney nickel under desulfurizing conditions, dehydroxylations were conducted on optically active derivatives of atrolactic acid.

When either the methyl or ethyl ester of (+)-atrolactic acid was refluxed in ethanol with excess Raney nickel, the 2-phenylpropionic ester obtained was found levorotatory to an extent suggesting very little racemization. Similar dehydroxylations accompanied by a reversal in the sign of rotation were noted with (−)-atrolactic esters. Since the esters obtained after dehydroxylation were oils, one of these was converted, *via* the free acid and acid chloride, to its crystalline amide, thus affording certainty as to the identity of the optically active products.

The optical rotatory power of the dehydroxylated products obtained was found to vary with the duration of exposure to the reaction environment, and to diminish the longer the reaction was allowed to proceed. This suggested, and further experiment showed, that optically active derivatives of 2-phenylpropionic acid are slowly racemized by Raney nickel in refluxing ethanol, a phenomenon previously thought not to occur.[4]

An attempt was made to follow the rate of dehydroxylation by studying the disappearance of optical activity when ethyl D(−)-mandelate was refluxed with Raney nickel in ethanol. In one experiment the reaction mixture lost 93% of its activity on refluxing for only 20 minutes, suggesting that dehydroxylation occurs quite rapidly in comparison with the gradual racemization of the product noted above.

It is possible to deduce the stereochemical course of the present reaction with some certainty. D(−)-Atrolactic acid (I) has been related[6] to D(−)-mandelic acid (II) by means of the displacement rule.[7] II has been related[8] to D(−)-1-phenylethanol (III) which in turn is related[9] to D(−)-1-phenylethylamine (IV). IV has been produced[10] without inversion from D(+)-2-phenylpropionic acid (V). Eliel has recently offered[11] further stereochemical evidence correlating the configurations of (−)I and (+)V. A change in the sign of rotation in the present dehydroxylation, then, indicates that the transformation I → V here occurs with practically complete retention of configuration. This conclusion is opposite to that tentatively reached regarding sulfone desulfuration,[4] and suggests that the two processes proceed *via* different mechanisms. The present results are reminiscent of those obtained by Ott and Krämer[12] in their study of the optical consequences of catalytic hydrogenolysis of a carbon–chlorine bond. These investigators prepared optically active 2-chloro-2-phenylpropionic acid by action of thionyl chloride on active atrolactic acid, the two acids presumably being configurationally similar. Reduction of the former acid with palladium–charcoal catalyst in acetic acid or ether led to a 2-phenylpropionic acid of opposite rotation and presumably therefore of identical configuration. Reduction with zinc in acetic acid, however, proceeded with apparent inversion. Further investigations of hydrogenolysis phenomena with Raney nickel are currently in progress.



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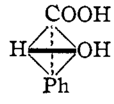

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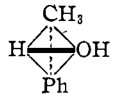

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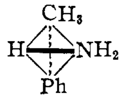

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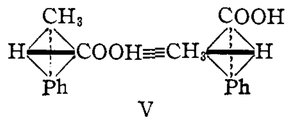

V

Experimental

Dehydroxylation of Methyl Atrolactate.—Atrolactic acid[13] was converted to its methyl ester, b.p. 127.5° (18 mm.), by ordinary Fischer esterification. The ester (5 g.) was heated with Raney nickel (*ca.* 36 g.) in refluxing absolute ethanol (60 ml.) for four hours. The mixture was filtered (Celite) and the cake rinsed with ether (200 ml.) and ethanol (50 ml.). Removal of solvents led to 3.4 g. (75%) of oily methyl 2-phenylpropionate. The latter ester (2.5 g.) was hydrolyzed by heating in water (30 ml.) containing sulfuric acid (1.5 ml.) for five hours. The cooled, salted mixture was extracted with ether, and the solvent removed from the dried extract. There remained 1.8 g. of oil which was refluxed for 30 minutes with thionyl chloride (15 ml.), cooled, and poured into chilled ammonium hydroxide. The resulting oil was extracted into ether, the extract decolorized through Norit, and the solvent distilled. The 0.8 g. of oily product rapidly crystallized, and was recrystallized from a mixture of benzene and ligroin to give shining platelets, m.p. 91°. These gave no mixed m.p. depression with authentic 2-phenylpropionamide.

Dehydroxylation of Mandelamide.—Mandelamide (1.0 g.), Raney nickel (*ca.* 9 g.) and ethanol (50 ml.) were heated under reflux for five hours. Filtration and solvent evaporation led to 0.72 g. (80%) of crude phenylacetamide. Recrystallization from a 1:7 mixture of ethanol and ligroin gave a product m.p. 152–153° which showed no mixed m.p. depression with authentic phenylacetamide.

The experiment was duplicated exactly, except that the alcohol solvent was replaced with benzene. Residual alcohol in the Raney nickel remaining after quick suction filtration was removed by distilling 15 ml. of the benzene solvent prior to addition of the mandelamide. A 40% yield of phenylacetamide was obtained, m.p. and mixed m.p. with an authentic sample after recrystallization as above, 158–159°.

Resolution of Atrolactic Acid.—The racemic acid was resolved using *d*- and *l*-1-phenylethylamine after the procedure of Smith.[5] The L(+)-atrolactic acid had m.p. 114.5° and $[\alpha]^{25}D$ 37.7° (*c* 3.5, ethanol), while the D(−)-isomer had

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[5] L. Smith, *J. prakt. Chem.*, [2] **84**, 743 (1911).

[6] K. Freudenberg, J. Todd and R. Seidler, *Ann.*, **501**, 199 (1933).

[7] K. Freudenberg, "Stereochemie," F. Deuticke, Leipzig and Vienna, 1933, p. 695 ff.

[8] K. Mislow, THIS JOURNAL, **73**, 3954 (1951).

[9] H. R. Snyder and J. H. Brewster, *ibid.*, **71**, 291 (1949). Other references given here.

[10] H. I. Bernstein and F. C. Whitmore, *ibid.*, **61**, 1324 (1939).

[11] E. L. Eliel and J. P. Freeman, *ibid.*, **74**, 923 (1952).

[12] E. Ott and K. Krämer, *Ber.*, **68B**, 1655 (1935).

[13] E. L. Eliel and J. P. Fereman, procedure submitted for publication in "Organic Syntheses."

m.p. 115° and $[\alpha]^{25}\mathrm{D}$ −35.4° (*c* 3.5, ethanol). The recorded constants[14] are m.p. 116–117° and $[\alpha]^{14}\mathrm{D}$ ±37.7°.

Methyl D(−)- and L(+)-Atrolactates.—Five parts resolved atrolactic acid, fifty parts methanol, and one part by weight of sulfuric acid were refluxed four hours, cooled, and poured into water. The esters were isolated by ether extraction in about 68% yield. Methyl D(−)-atrolactate had $[\alpha]^{25}\mathrm{D}$ −5.0° (*c* 4.9, ethanol), while the L(+)-isomer had $[\alpha]^{25}\mathrm{D}$ 5.0° (*c* 5.2, ethanol). The oils were used without further purification.

Ethyl D(−)- and L(+)-Atrolactates.—The corresponding ethyl esters were prepared in the general manner described above. The D(−)-ester was made from an acid sample only 87% resolved, and had $[\alpha]^{25}\mathrm{D}$ −20.0° (no solvent). The L(+)-antipode had $[\alpha]^{24}\mathrm{D}$ 26.1°. The value reported[15] for optically pure ethyl D(−)-atrolactate is $[\alpha]^{13}\mathrm{D}$ −26.7°.

Raney Nickel with Active Methyl Atrolactates.—Methyl D(−)-atrolactate (2.8 g.), ethanol (50 ml.) and Raney nickel (*ca.* 20 g.) were heated under reflux for four hours. The mixture was cooled, filtered, and the solvent evaporated from the filtrate, leaving 1.9 g. (75%) of crude methyl D(+)-2-phenylpropionate, $[\alpha]^{25}\mathrm{D}$ 86.0° (*c* 5.4, ethanol). The product was distilled prior to analysis, b.p. 130–140° (75 mm.), d^{25}_{25} 1.0362, $n^{25}\mathrm{D}$ 1.4494.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.19; H, 7.37; mol. refr., 46.44. Found: C, 72.24, 72.27; H, 7.39, 7.52; mol. refr., 46.58.

Raney Nickel with Active Ethyl Atrolactates.—Ethyl D-(−)-atrolactate (2.14 g., $[\alpha]^{25}\mathrm{D}$ −20.0° (no solvent), 87% optically pure) was refluxed in absolute ethanol (60 ml.) containing Raney nickel (*ca.* 18 g.) for three hours. Customary processing led to 1.73 g. (88%) of oily ethyl D(+)-2-phenylpropionate having $[\alpha]^{23}\mathrm{D}$ 45.5° (*c* 2.9, ether). Levene and co-workers report[16] $[\alpha]\mathrm{D}$ −51.0° for the pure enantiomorphic ester. The present sample is thus about 94% optically pure. Since the starting material appeared only about 87% optically pure, it is obvious that little if any racemization attended the present dehydroxylation. No attempts were made to purify the small quantities of intermediate products obtained in these experiments, and the varying "optical purity" obtained in each case probably is due to variable traces of residual solvents or other impurities.

The above product (1.50 g.) was hydrolyzed on refluxing in water (30 ml.) containing sulfuric acid (1 ml.) for 4.5 hours. Customary isolation led to 1.38 g. (94%) of oily D(+)-2-phenylpropionic acid, $[\alpha]^{20}\mathrm{D}$ 51.0° (*c* 3.3, abs. ethanol), corresponding to 94% optical purity.[4]

The free acid was treated as before with thionyl chloride to produce a 73% yield of D(+)-2-phenylpropionyl chloride having $[\alpha]^{20}\mathrm{D}$ 50.5° (*c* 2.5, ether) and corresponding to 86% optical purity. An ether solution of this acid chloride was slowly added to chilled ammonium hydroxide, and the amide isolated in the usual way. Recrystallization from a 1:5 mixture of benzene and ligroin gave pure D(+)-2-phenylpropionamide, m.p. 94°, $[\alpha]^{20}\mathrm{D}$ 27.8° (*c* 2.0, 75% ethanol). The material obtained appeared to be 99% optically homogeneous.[4]

Ethyl L(+)-atrolactate (1.67 g., $[\alpha]^{23}\mathrm{D}$ 26.1° (no solvent)) was refluxed in absolute ethanol (75 ml.) with Raney nickel (*ca.* 12 g.) for three hours. The oily ethyl L(−)-2-phenylpropionate, isolated in 64% yield in the usual way, had $[\alpha]^{20}\mathrm{D}$ −34.7° (*c* 1.7, ether). Vacuum distillation, b.p. 58° (2 mm.), gave a colorless product, $[\alpha]^{24}\mathrm{D}$ −35.7° (*c* 3.1, ether).

This product (0.71 g.) was refluxed an additional hour in ethanol containing Raney nickel (3 g.). The product (0.62 g.) was recovered as usual and had $[\alpha]^{23}\mathrm{D}$ −30.2° (*c* 3.0, ether). The material was treated with Raney nickel (10 g.) in the same manner for an additional 16 hours, after which the 0.33 g. of oil isolated had $[\alpha]^{23}\mathrm{D}$ −25.0° (*c* 1.8, ether). Thus the original ethyl L(−)-2-phenylpropionate of about 86% optical purity appeared to be converted to a sample of only 75% optical purity on treatment with Raney nickel during a 17-hour period.

Examinations of the rotations of the crude original dehydroxylation products in the several experiments above show an apparent variation in the extent of racemization obtained from one experiment to another. This is due in all probability to factors not yet fully appreciated or controlled. Thus the conditions for the dehydroxylations above were not standardized with regard to concentration or ratio of reactants, and several different catalyst samples of varying pyrophoric activity were employed. The effect of such factors on the stereochemical consequences of Raney nickel catalysis is under present investigation.

Racemization of L(−)-2-Phenylpropionamide with Raney Nickel.—Optically pure L(−)-2-phenylpropionamide (0.10 g., $[\alpha]^{20}\mathrm{D}$ −28.5° (75% ethanol)) was refluxed with absolute ethanol (40 ml.) and Raney nickel (4 g.) for 24 hours. Customary isolation gave 0.047 g. of solid having $[\alpha]^{21}\mathrm{D}$ −16.5° (*c* 1.6, 75% ethanol). The amide was thus racemized to the extent of about 20% during this period.

Raney Nickel with Ethyl L(+)-Mandelate.—Ethyl L(+)-mandelate of $[\alpha]^{25}\mathrm{D}$ 122° (chloroform) (1.15 g.) was placed in absolute ethanol (50 ml.) containing Raney nickel (8 g.). A portion of the mixture was removed, centrifuged, and the supernatant liquid found to have a rotation of 1.50° per dm. The aliquot was returned to the original bulk, and the mixture refluxed for 20 minutes, quickly chilled, and another aliquot removed and centrifuged. The supernatant now had a rotation of 0.10° per dm. Ethyl mandelate thus appeared to be 93% dehydroxylated during the course of 20 minutes. The aliquot was returned to the bulk and the mixture allowed to stand at room temperature overnight. At this time an aliquot proved optically inactive.

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[14] A. McKenzie and G. W. Clough, *J. Chem. Soc.*, **97**, 1020 (1910).

[15] A. McKenzie and G. W. Clough, *ibid.*, **97**, 2569 (1910).

[16] P. A. Levene, L. A. Mikeska and K. Passoth, *J. Biol. Chem.*, **88**, 27 (1930).