[CONTRIBUTION FROM THE RADIATION LABORATORY AND DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY[1]]

Hydrogenation of Fatty Acids to Alcohols

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A procedure for converting fatty acids to the corresponding alcohols by high pressure hydrogenation of the mixed Cd–Ni salts of the acid in the presence of copper chromite is described. Reductions were made on the normal and branched chain C_1- to C_5-acids with yields of 70–95%. The preparation was applied to the small scale synthesis of a number of C^{14}-labeled alcohols and these were converted to the corresponding halides for use as synthetic intermediates. This reduction method was used to convert $C^{14}O_2$ to methanol-C^{14} and methyl-C^{14} iodide by going through the intermediate, formic acid. The procedure was reliable and capable of good yields on a small scale.

Although many methods for the reduction of fatty acids to their corresponding alcohols have been described, most of these present certain disadvantages when applied to small scale syntheses with isotopic materials.

Thus, reduction of fatty acids with lithium aluminum hydride,[2] while very satisfactory on a large scale, often introduces small amounts of contaminating alcohols by splitting of the ether solvents used in the reduction.[3a,b]

By esterification of fatty acids and hydrogenation in the presence of copper chromite[4,5,6] alcohols can be prepared in excellent yields, but the product is either diluted with the esterifying alcohol if it is the same as that produced by the reduction, or contaminated with another alcohol if they are different. Other methods present comparable difficulties.

Reduction of Cd–Ni Salts of Fatty Acids.—A recent series of patents describes the high pressure hydrogenation of a number of high molecular weight unsaturated fatty acids to a series of products in most cases mixtures of the corresponding alcohols and esters.[7] A study has been made of the adaptability of this method to the reduction of propionic acid.

When a mixture of 90% Cd and 10% Ni propionate was subjected to the conditions described for the reduction of Cd–Ni oleate by Richardson and Taylor,[7] that is, 133 atmospheres hydrogen pressure at 340° for 3 hours, the principal product was found to be propyl propionate. To continue the reduction of the ester to the alcohol in a one-step process, copper chromite catalyst[8] was added to the reaction mixture but the product consisted chiefly of a low boiling hydrocarbon, presumably propane or propylene. In a series of experiments it was found that by increasing the pressure and decreasing the temperature the reduction could be controlled to produce almost exclusively the alcohol (see Table I).

TABLE I

REDUCTION OF Cd–Ni PROPIONATE IN THE PRESENCE OF COPPER CHROMITE[a]

Hydrogen pressure atm., cold	Temp., °C.	Time of heating, hr.	Product, % "Propane"	Propanol
133	340	0.5	12	60
133	340	3	68	15
150	320	1	17	57
150	280	9	2	47
200	270	9	59	30
200	240	9	2	74
235	240	9	<1	92

[a] Reductions were made in a 115-cc. stainless steel reaction vessel. The reduction mixture consisted of 20 millimoles of 90% Cd–10% Ni propionate mixed with 1.5 g. of copper chromite.

Path of the Reduction.—From a study of Richardson and Taylor's patents and our experiments, it is felt that there are probably two paths for the reduction of the acid to the alcohol operating under the conditions of this reaction. In one, the mixed metal salt of the acid is reduced directly to the alcohol. In the other, alcohol produced by reduction in the bomb reacts with the metal salts of the fatty acid to produce the ester, which is then reduced by the copper chromite.

If copper chromite is not added to the reaction mixture most of the reaction will stop at the ester stage. It is not surprising, either, that propane is the principal product from the reduction at 340° for this is far above the normal temperature that can be used in copper chromite reductions.[4]

In the work presented in this paper this procedure was extended to C_1- through C_5-fatty acids, but no attempt was made to determine the optimum conditions of temperature, pressure, time and metal salt composition for the reduction of any acids other than propionate. More work on these reductions would probably give superior yields to those reported (70–95%). This method of reduction is a general one and can probably be extended to other acids with little modification.

The question of possible cracking or polymerization of the alcohols or acids under the conditions of the reduction was investigated by mass spectrographic analyses of the C_1- and C_3-reductions. The halides produced from these preparations showed no contamination. Since copper chromite does not normally produce isomerization or crack-

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[2] R. F. Nystrom, W. H. Yanko and W. G. Brown, THIS JOURNAL, **70**, 411 (1948).

[3] (a) J. D. Cox, H. S. Turner and R. J. Warne, *J. Chem. Soc.*, 3167, 3176 (1950). (b) R. Ostwald, P. T. Adams and B. M. Tolbert, "Synthesis of Several C^{14}-labeled DL Alanines," University of California Radiation Laboratory Report 962 (1950).

[4] H. Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937.

[5] B. M. Tolbert, F. C. Christenson, F. N. H. Chang and P. P. T. Sah, *J. Org. Chem.*, **14**, 525 (1949).

[6] H. Hauptmann, P. T. Adams and B. M. Tolbert, "The Synthesis of Leucine and Several Branched Chain Fatty Acids," University of California Radiation Laboratory Heport No. 935 (1950).

[7] A. S. Richardson and J. E. Taylor, U. S. Patents 2,340,344 and 2,340,687 to 2,340,691.

[8] H. Adkins, "Organic Syntheses," Vol. II, John Wiley and Sons, Inc., New York, N. Y. 1943, p. 144.

TABLE II

HYDROGENATION OF ACIDS TO ALCOHOLS AND THEIR CONVERSION TO HALIDES

Starting material Sodium salt	Amt., g.	Halide produced	Amt., g.	Sp. act. of prod. μc./mg.	Calcd. % yield of alcohol	Yield of halide, %
Formate-C^{14}	1.39	Methyl-C^{14} iodide	1.93	8.8	85	80[a]
Acetate-1-C^{14}	1.645	Ethyl-1-C^{14} iodide	2.66	9.1	95	85
Butyrate-1-C^{14}	2.202	Butyl-1-C^{14} bromide	1.47	0.09	75	54
Isobutyrate-1-C^{14}	2.20	Isobutyl-1-C^{14} iodide	2.4	0.08	80	65
Valerate-1-C^{14}	2.56	Amyl-1-C^{14} bromide	1.77	12.6	80	57
Isovalerate-1-C^{14}	2.48	Isoamyl-1-C^{14} bromide	1.51	0.01	70	50

[a] The yields of methyl iodide on other runs varied from 70–90%.

ing and the Cd–Ni salts were successfully used under more severe conditions to hydrogenate large unsaturated fatty acids, this result is not unexpected.

In this process for preparing alcohols the very difficult problem of fractionating a product on small scale is avoided, since no contaminating organic materials are introduced during the synthesis. In both test and radioactive preparations the alcohols were usually converted directly to their iodides or bromides in order to avoid the difficult process of separating the alcohol–water mixture.

Conversion of Carbon Dioxide to Methanol.—The reduction of labeled carbon dioxide to methanol has been described by various methods.[3a,9,10,11] Most of these methods present the same difficulties discussed in the reduction of fatty acids and the direct hydrogenation of carbon dioxide requires a special catalyst that is difficult to prepare.

The conversion of carbon dioxide to formic acid and the direct reduction of Cd–Ni formate was studied as an alternate method and shown to be very satisfactory for the preparation of labeled methanol and methyl iodide. A simplified modification of the procedure of Melville, *et al.*,[9] for the hydrogenation of potassium bicarbonate was developed. It was found that carbon dioxide could be routinely reduced to formate in 85–90% yield and this could be converted to methanol in 85–90% yield to give an over-all yield of labeled methanol of 70–80% based on carbon dioxide.

Experimental

Sodium Formate-C^{14}.—Potassium bicarbonate (20 millimoles) was reduced with hydrogen and palladium black catalyst as described by Melville, *et al.*[9] At the completion of the reduction the reaction mixture was filtered and the filtrate stirred with 10 ml. of wet packed Dowex 50 ion exchange resin in the acid form. The resin was filtered off and washed 3–4 times with water. The filtrate was titrated with sodium hydroxide and evaporated to dryness. The yield was 85–90%.

Carboxyl-labeled Fatty Acids.—The various carboxyl-labeled fatty acids were prepared by carbonation of the corresponding Grignard reagents.[12] Yields varied from 95–98% on a 20 millimole scale.

Propanol-1-C^{14}.—Sodium propionate-1-C^{14} (1.44 g., 15.0 millimoles, 5.5 × 10^4 dis./min./mg.) was dissolved in 5 ml. of water and treated with 15 ml. of wet packed Dowex 50 cation exchange resin (250–500 mesh) to convert the salt to the free acid. The mixture was thoroughly stirred, filtered, and the filtrate plus washings added to a wet Cd–Ni hydroxide slurry prepared as follows: In a 50-ml. centrifuge tube 1.70 g. of cadmium chloride·$2.5H_2O$ (7.43 millimoles) and 0.24 g. of nickel nitrate hexahydrate (0.83 millimole) were dissolved in 10 ml. of water. Excess sodium hydroxide was added and the precipitate collected by centrifugation and washed 3–4 times with water.

The resulting solution of Cd–Ni propionate was evaporated to dryness on a steam-bath using an air stream. (Note: In a test reaction, acidification of the Cd–Ni propionate followed by steam distillation of the acid showed that the conversion of sodium propionate to the dry Cd–Ni salt was quantitative.) The dry mixture was transferred to a 115-ml. stainless steel reaction vessel[13] containing 1.5 g. of copper chromite catalyst.[14] The vessel was evacuated and maintained at a pressue of 50 microns for 4–8 hours to remove final traces of water. It was observed that the presence of moisture at this point markedly reduced yields.

The reaction vessel was filled to a pressure of 235 atmospheres with electrolytic hydrogen and heated at 240° with shaking for nine hours. When cooled, the vessel was transferred to a vacuum line and the hydrogen released through a liquid nitrogen-cooled spiral trap containing a sintered glass disk.[15] After evacuation, the reaction vessel was held at reduced pressure for five hours while warmed to approximately 80° with an infrared lamp and the distillate collected in the cold trap. The product consisted of 1.14 g. of a solution of 74% propanol in water (94% yield). The sample was oxidized to carbon dioxide and converted to barium carbonate for radioactivity measurements[12]: calcd. specific activity, 8.9 × 10^3 dis./min./mg. $BaCO_3$; found, 8.5 × 10^3 dis./min./mg. $BaCO_3$.

Propyl-1-C^{14} Bromide.—The propanol–water mixture from the reduction was converted to the bromide using 4 ml. of phosphorus tribromide, washed with water and dried over phosphorus pentoxide.[15] The yield was 1.26 g. or 73% from propanol.

Propyl-1-C^{14} Iodide.—A propanol–water mixture prepared as described above was treated with 10 g. of iodine, 0.62 g. of red phosphorus and 3 ml. of water.[10] The propyl iodide was washed with water and dried over phosphorus pentoxide. The yield was 86% from the alcohol.

C_1–C_5-Alcohols and Halides.—Using the same experimental procedure as outlined above, a number of aliphatic acids were reduced to the corresponding alcohols and converted to the iodide or bromide. The data on these reductions and conversions are listed in Table II. The yields of the alcohols are calculated from experimental data on the efficiency of conversion of the alcohol to the halide under the conditions of the reaction.

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[10] B. M. Tolbert, THIS JOURNAL, **69**, 1529 (1947).

[11] D. Harmon, T. D. Stewart and S. Ruben, *ibid.*, **64**, 2293 (1942).

[12] M. Calvin, *et al.*, "Isotopic Carbon," John Wiley and Sons, Inc., New York, N. Y., 1949.

[13] Micro Series Reaction Vessel. American Instrument Company, Silver Springs, Maryland.

[14] The procedure of Adkins[8] was followed with the exception that the final acid wash was carried out with dilute (5%) nitric acid instead of acetic acid in order to eliminate trace contamination of the reduction products with ethanol.

[15] B. M. Tolbert, *et al.*, *J. Org. Chem.*, **14**, 527 (1949).