**Acknowledgment.**—We wish to express our thanks to the Buffalo Electro-Chemical Company for donation of the hydrogen peroxide used in this work.

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## Catalytic Dehydrogenation of Primary and Secondary Alcohols with Platinum and Oxygen: Selective Dehydrogenation in the Steroid Series[1]

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RECEIVED JULY 19, 1954

Dehydrogenation of primary and of secondary alcohols to aldehydes and ketones, respectively, over metal surfaces at elevated temperature is a well-known and extensively documented procedure.[2] Copper and nickel have been employed most commonly as catalysts in this connection, although the use of silver, ruthenium, platinum, palladium and other elements occasionally has been reported.

In 1855, Strecker[3] noted that cinnamyl alcohol can be converted into cinnamic aldehyde by the action of platinum and oxygen at *room temperature*. Some years later Grimaux[4] observed the conversion of glycerol into glyceraldehyde under similar conditions. The reaction of primary alcohols with platinum and with palladium in the presence of oxygen and of other hydrogen acceptors[5] was studied in greater detail by Wieland, who established that the aldehydes formed initially are subject to further oxidation resulting in the formation of carboxylic acids and of peroxyacids.[6] Despite the obvious potentialities of this procedure, particularly as regards secondary alcohols, applications of the method have been few.[7]

In 1942, Mannich and Siewert[8] attempted catalytic dehydrogenation of the cardiac glycoside, ouabain, and obtained in poor yield two crystalline products, which, however, were incompletely characterized. More recently Heyns and his associates have oxidized successfully a number of sugars to the corresponding sugar acids[9] and have demonstrated the usefulness of the method in connection with oxidations of inositol[10] and of kojic acid.[11]

Our interest in platinum–oxygen dehydrogenation was aroused by the remarkable selective conversion of the $C_3$-hydroxyl group of dihydroouabagenin into a keto group as described in the preceding paper.[12] We have therefore investigated the action of platinum and oxygen on a variety of other alcohols with a view toward establishing the scope and limitations of the method.

The general procedure adopted in this work was as follows. A suspension of platinum oxide was first reduced to platinum in an atmosphere of hydrogen, and the hydrogen carefully replaced with air by repeated evacuation. The system was then filled with oxygen, and the catalyst suspension was stirred until the uptake of oxygen ceased. A solution of the sample was added through a dropping funnel, and stirring was continued until no further absorption of oxygen was observed. The reaction time in our experiments varied from 7 to about 24 hours. It was subsequently found that air can be substituted for oxygen without any adverse effect upon the reaction rate or upon the yield of oxidation product.

The solvents we have found most satisfactory are ethyl acetate, water, and dilute acetone. Poor yields of impure materials were obtained when acetic acid or dimethylformamide were employed.

Our results are listed in Table I. Contrary to the experience of Wieland,[5] we obtained benzaldehyde in good yield by dehydrogenation of benzyl alcohol. In the steroids we have investigated thus far only the $C_3$-hydroxyl group has proved susceptible to dehydrogenation by this method. The yields obtained are superior to those of partial Oppenauer oxidation,[13–15] and the specificity of

TABLE I

DEHYDROGENATION OF VARIOUS ALCOHOLS WITH PLATINUM AND OXYGEN

| No. | Compound | Product | Yield, % |
|---|---|---|---|
| 1 | *n*-Octyl alcohol | *n*-Octyl aldehyde | 21[a] |
| 2 | Benzyl alcohol | Benzaldehyde | 72[a] |
| 3 | Cyclohexanol | Cyclohexanone | 68[a] |
| 4 | 2-Methylcyclohexanol | 2-Methylcyclohexanone | 50 |
| 5 | Cholestan-3$\beta$-ol | Cholestan-3-one | 72 |
| 6 | Cholestan-3$\alpha$-ol | Cholestan-3-one | 50 |
| 7 | Methyl 3$\alpha$-hydroxycholanate | Methyl 3-ketocholanate | 73 |
| 8 | Methyl 3$\alpha$,6$\alpha$-dihydroxycholanate | Methyl 3-keto-6$\alpha$-hydroxycholanate | 75[b] |
| 9 | Methyl 3$\alpha$,12$\alpha$-dihydroxycholanate | Methyl 3-keto-12$\alpha$-hydroxycholanate | 70 |
| 10 | Methyl 3$\alpha$,7$\alpha$,12$\alpha$-trihydroxycholanate | Methyl 3-keto-7$\alpha$,12$\alpha$-dihydroxycholanate | 70 |

[a] Isolated as the 2,4-dinitrophenylhydrazone. [b] Isolated as the free acid.

(1) This investigation was supported by a research grant, H-1084, from the National Heart Institute, of the National Institutes of Health, Public Health Service.

(2) J. Houben, "Die Methoden der Organischen Chemie," 3rd. Ed., Vol. II, Georg Thieme, Leipzig (1925), p. 23; A. Mailhe, *Chem. Zeit.*, **29**, No. 34, 462 (1905); R. Delaby and J. Dumoulin, *Compt. rend.*, **180**, 1277 (1925); R. Delaby, *ibid.*, **182**, 140 (1926); W. Triebs and H. Schmidt, *Ber.*, **60**, 2335 (1927); A. Halasz, *Ann. Chim.*, **14**, 318 (1940); R. Paul, *Bull. soc. chim.*, **5**, 1592 (1938); **8**, 507 (1941).

(3) A. Strecker, *Ann.*, **93**, 370 (1855).

(4) Grimaux, *Bull. soc. chim.*, [2] **45**, 481 (1886).

(5) The use of cyclohexanone as a hydrogen acceptor has been shown by E. C. Kleiderer and E. C. Kornfeld, *J. Org. Chem.*, **13**, 455 (1948), to facilitate nickel-catalyzed dehydrogenations of a variety of secondary alcohols including cholesterol, cholestanol, epicoprostanol, benzhydrol and fluorenol.

(6) H. Wieland, *Ber.*, **45**, 484, 2606 (1912); **46**, 3327 (1913); **54**, 2353 (1921).

(7) In this connection it should be noted that catalytic *oxygenation* of tetrahydrocarbazole over platinum has been employed as a preparative procedure by B. Witkop and J. Patrick, THIS JOURNAL, **73**, 2188 (1951).

(8) C. Mannich and G. Siewert, *Ber.*, **75**, 750 (1942).

(9) K. Heyns, *Ann.*, **558**, 177 (1947); K. Heyns and R. Heinemann, *ibid.*, **558**, 187 (1947); K. Heyns and O. Stöckel, *ibid.*, **558**, 192 (1947).

(10) K. Heyns and H. Paulsen, *Ber.*, **86**, 833 (1953).

(11) K. Heyns and G. Vogelsang, *ibid.*, **87**, 13 (1954).

(12) R. P. A. Sneeden and R. B. Turner, THIS JOURNAL, **77**, 130 (1955).

(13) J. von Euw, A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **27**, 1287 (1944).

(14) T. F. Gallagher and J. R. Xenos, *J. Biol. Chem.*, **165**, 365 (1946).

(15) S. Kuwada and S. Morimoto, *Bull. chem. soc., Japan*, **17**, 147 (1942).

attack at $C_3$ in the bile esters, no. 8, 9 and 10, contrasts with preferential attack at other positions when chromic acid[16] and N-bromosuccinimide[17] are used. Oxidation of both cholestan-3$\beta$-ol and cholestan-3$\alpha$-ol (no. 5 and 6, respectively) to cholestan-3-one suggests that orientation of the hydroxyl group is not a determining factor, at least as far as $C_3$ is concerned.

Our attempts to oxidize cholesterol by the above procedure have met with conspicuous failure.[18] Whether the presence of a double bond at the 5,6-position imposes a structural limitation on the method, or whether our cholesterol contained traces of a poison has not been ascertained as yet.

### Experimental[19]

Oxidation of *n*-Octyl Alcohol.—A suspension of 250 mg. of platinum oxide in 5 ml. of ethyl acetate was stirred magnetically in an atmosphere of hydrogen until reduction to platinum was complete. The hydrogen in the system was then replaced with air by careful and repeated evacuation.[20] Oxygen was admitted and stirring continued until no further oxygen was absorbed. A solution of 580 mg. of redistilled *n*-octyl alcohol in 10 ml. of ethyl acetate was then added through an attached dropping funnel, and the mixture was stirred for 20 hours, at the end of which time the uptake of oxygen had ceased. The catalyst was removed by filtration and, after distillation of the bulk of the solvent, the residual material was treated with a solution of 1.2 g. of 2,4-dinitrophenylhydrazine in methanolic sulfuric acid. Three hundred mg. of *n*-octyl aldehyde 2,4-dinitrophenylhydrazone, m.p. 100–101°, was obtained in this way, corresponding to an over-all yield from *n*-octyl alcohol of 21%.

Oxidation of Benzyl Alcohol.—A solution of 627 mg. of redistilled benzyl alcohol in 10 ml. of ethyl acetate was added to a suspension of platinum (prepared from 250 mg. of platinum oxide as described in the preceding experiment) in 5 ml. of ethyl acetate under an atmosphere of oxygen. After stirring for 24 hours the absorption of oxygen had ceased. The reaction product, isolated as described above, furnished 1.18 g. of benzaldehyde 2,4-dinitrophenylhydrazone, m.p. 227–228° dec.; yield 72% based on benzyl alcohol.

Oxidation of Cyclohexanol.—Cyclohexanol (577 mg.), was treated as described in the preceding experiment. Oxidation was complete in 18 hours. Isolation of the product in the usual way furnished 1.05 g. of the 2,4-dinitrophenylhydrazone of cyclohexanone as yellow plates, m.p. 160°; yield, 68% based upon cyclohexanol.

In a second experiment 962 mg. of cyclohexanol in 100 ml. of water was oxidized as previously described with the exception that air was used in place of oxygen. After 24 hours the reaction mixture was continuously extracted with ether, and the ether was finally removed by distillation through a short column. The residual material furnished 1.98 g. (74%) of cyclohexanone 2,4-dinitrophenylhydrazone, m.p. 159–160°.

Oxidation of 2-Methylcyclohexanol.—The 2-methylcyclohexanol employed in this experiment was a redistilled sample of commercial material which must be presumed to contain both *cis* and *trans* isomers. Oxidation of 414 mg. of alcohol by the standard procedure, furnished, after distillation from a Hickman flask, 220 mg. (50%) of 2-methylcyclohexanone, identified by its quantitative conversion into the corresponding 2,4-dinitrophenylhydrazone, m.p. 230–232°.

Oxidation of Cholestan-3$\beta$-ol.—A solution of 600 mg. of cholestan-3$\beta$-ol in 45 ml. of ethyl acetate was added to a suspension of platinum (from 200 mg. of platinum oxide) in 10 ml. of ethyl acetate. The mixture was stirred in an atmosphere of oxygen; after 7 hours the oxidation was complete. The yield of cholestan-3-one, m.p. 128–129°, was 435 mg. (72%).

Oxidation of Cholestan-3$\alpha$-ol.—Cholestan-3$\alpha$-ol (160 mg., m.p. 182–184°) in 15 ml. of ethyl acetate was oxidized as described above with platinum derived from 100 mg. of platinum oxide. Crystallization of the reaction product from acetone furnished 80 mg. (50%) of cholestan-3-one, m.p. 128–130°.

Oxidation of Methyl 3$\alpha$-Hydroxycholanate.—Methyl 3$\alpha$-hydroxycholanate (450 mg., m.p. 126–127°) and platinum from 200 mg. of platinum oxide in 20 ml. of ethyl acetate were stirred under oxygen according to the usual procedure. Crystallization of the crude product from methanol gave 330 mg. (73%) of methyl 3-ketocholanate, m.p. 118–120°.

Oxidation of Methyl 3$\alpha$,6$\alpha$-Dihydroxycholanate.—Methyl 3$\alpha$,6$\alpha$-dihydroxycholanate (500 mg., m.p. 86–89°) was treated as described in the preceding experiments. The product was an oil, which failed to crystallize. The material was accordingly saponified for 0.5 hour with 100 mg. of sodium hydroxide in 10 ml. of methanol containing 2 ml. of water. Crystallization of the free acid from acetone–petroleum ether furnished 279 mg. of material, m.p. 199–201°, $[\alpha]_D$ +14.2° (methanol), that did not depress the melting point of an authentic sample of methyl 3-keto-6$\alpha$-hydroxycholanate supplied through the courtesy of Dr. T. F. Gallagher. A second crop, 80 mg., m.p. 197–200°, was obtained from the mother liquors making a total yield of 75%.

Oxidation of Methyl 3$\alpha$,12$\alpha$-Dihydroxycholanate.—Oxidation of methyl 3$\alpha$,12$\alpha$-dihydroxycholanate (500 mg.) in ethyl acetate solution was carried out in the usual way. The product, 350 mg. (70%), crystallized from aqueous methanol and melted at 142–144°. The substance was identified as methyl 3-keto-12$\alpha$-hydroxycholanate by a mixed melting point determination with an authentic sample.

Oxidation of Methyl 3$\alpha$,7$\alpha$,12$\alpha$-Trihydroxycholanate.—Methyl 3$\alpha$,7$\alpha$,12$\alpha$-trihydroxycholanate (410 mg., m.p. 151–153°) was oxidized in 25 ml. of ethyl acetate. Absorption of oxygen ceased after 16 hours. Crystallization of the crude reaction product from dilute ethanol furnished 290 mg. (70%) of methyl 3-keto-7$\alpha$,12$\alpha$-dihydroxycholanate, m.p. 173–175° (lit.[21] 171–172°). The diacetate prepared as a derivative melted at 192–194° (lit.[21] 190–191°).

(16) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publishing Corp., New York, N.Y., 1949, p. 126.

(17) L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **71**, 3935 (1949).

(18) The capricious behavior of cholesterol in catalytic *hydrogenation* is well known. *Cf.* E. B. Hershberg, E. Oliveto, M. Rubin, H. Staeudle and L. Kuhlen, THIS JOURNAL, **73**, 1144 (1951); H. R. Nace, *ibid.*, **73**, 2379 (1951).

(19) All melting points are corrected.

(20) In the course of this work we experienced one fire, which was traceable to incomplete removal of hydrogen at this stage. Care should be exercised to wash all catalyst from the walls of the vessel by gentle swirling prior to admitting oxygen.

(21) A. S. Jones, M. Webb and F. Smith, *J. Chem. Soc.*, 2164 (1949).

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## Alkyl Derivatives of Iminodiacetic Acid

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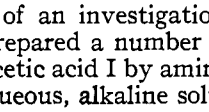
RECEIVED JUNE 8, 1954

Replacement of amino hydrogen atoms by carboxymethyl groups has been shown to produce compounds which form highly stable chelates with alkaline earth and transition group metals. This augmented tendency to combine with metal ions has been ascribed both to the increased ionic charge of the donor molecule and to the well-known stabilizing effect of added rings within a chelate structure.[1]

In the course of an investigation of the above effect we have prepared a number of alkyl derivatives of iminodiacetic acid I by amination of chloroacetic acid in aqueous, alkaline solution (Table I).

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(1) P. Pfeiffer and H. Simons, *Ber.*, **76B**, 847 (1943).