Equilibria in Hydrogenation of Esters and of Indoles

By Homer Adkins and Robert E. Burks, Jr.[1]

Esters and Alcohols

The hydrogenation of esters to alcohols over copper chromium oxide is a reversible reaction.[2] The published data show that the concentration of esters at equilibrium is about 1% with diethyl adipate, diethyl glutarate, methyl myristate and ethyl laurate at 240–260° under 200–300 atm. of hydrogen. The determination of the extent of hydrogenation of the laurate and the myristate is complicated by the fact that each equilibrium mixture would contain four esters and two alcohols. The mixtures from the adipate or the glutarate are much more complex since the esters might be derived from three acids and three alcohols, three of the alcohols and acids being bifunctional. In a further study of ester–alcohol equilibria in the pressure range below 300 atm., it seemed advisable to use an ester such as n-octyl caprylate, from which only a single alcohol and ester could be formed, e.g.

$$C_7H_{15}CO_2C_8H_{17} + 2H_2 \rightleftarrows 2C_8H_{17}OH$$
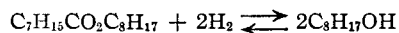
The data showing the effect of pressure upon the extent of hydrogenation of n-octyl caprylate are summarized in Table I. When the concentration of ester is plotted against the pressure of hydrogen the data lie upon a smooth curve from values of 1% of ester at 4000 p.s.i. to 80% ester at 140 p.s.i. Thus the hydrogenation of esters to alcohols is of preparational value under pressures of 200–300 atm., while the reverse reaction, of, for example, the dehydrogenation of 1-octanol to n-octyl caprylate, is a practical process at 10 atm. or less. The data in Table II on equilibria for 2-ethyl-1-butanol and neopentyl alcohol show variations in concentration of ester at equilibrium similar to those given in Table I for 1-octanol. The reactions proceed more slowly with the branched alcohols than with 1-octanol, but the concentrations of ester at equilibrium for a given pressure of hydrogen are similar for the three alcohols.

The % of ester (Tables I and II) or indoline (Table III), after equilibrium was established, is given in terms of the maximum amount possible. The amounts of reactants present in the steel vessel at the beginning of each experiment are given in the footnotes to the tables. The pressures recorded in the tables are those observed after equilibrium had been established and while the reaction mixture was at the indicated temperature. The pressures at the beginning of the experiments were higher or lower than these values depending upon whether hydrogenation or dehydrogenation occurred. The time intervals were those elapsing from the time the reaction mixture reached the indicated temperature until there was no observable increase or decrease in pressure. Reaction mixtures were usually allowed to stand a few hours at the indicated temperature after reaction was apparently complete.

A thermodynamically significant equilibrium constant for the alcohol–ester–hydrogen reaction cannot be calculated from the data available. However, the values calculated from the data in Table I through the expression, g. ester/g. alcohol × the square of the pressure of hydrogen in p.s.i. are reasonably constant, i. e., 2850, 2730, 2760, 2780, 3020, 3280, 3200, 4010, 4380 and 2570. Since the alcohol and ester exert a pressure of about 60 p.s.i. at 260° allowance is made for this in calculating the values given above.

The dehydrogenation of alcohols to esters in a closed reaction vessel has some preparational value. Neopentyl trimethylacetate and 2-ethylbutyl 2-ethylbutyrate were most conveniently made directly from the corresponding alcohols by this procedure. Tetradecyl myristate was also made from 1-tetradecanol by heating the alcohol, in a flask under reflux, with copper chromium oxide at 230–270°. The dehydrogenation of 1-octanol to the ester took place without any detectable amount of other reactions. However, the dehydrogenation of 2-ethyl-1-butanol at 290° over copper chromium oxide at a gage pressure of 400 p.s.i. gave significant amounts of products boiling higher than the desired ester.

The use of W-4 Raney nickel[3] in attempts to dehydrogenate 1-tetradecanol and 1-octanol resulted in the formation of tridecane and heptane in 64–75% yields. The conversion of an alcohol to a hydrocarbon with one less carbon atom is similar to that previously reported at a somewhat higher temperature.[4] It seems possible that the reaction proceeds through dehydrogenation of the alcohol to an aldehyde and the loss of carbon monoxide.

Indoles and Indolines

Coonradt[5] observed that the hydrogenation of indole (I) to indoline (II) proceeded to the extent of only 70–80% over copper chromium oxide at 170–190° and 250 atm. of hydrogen. The effect
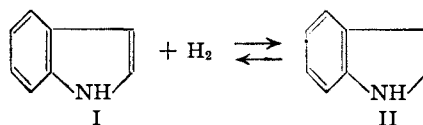

of pressure of hydrogen upon the extent of hydrogenation has been determined not only for indole

(1) Eastman Kodak Co. Fellow in 1946 and 1947.
(2) Burks and Adkins, This Journal, 62, 3300 (1940).
(3) Adkins and Pavlic, ibid., 69, 3039 (1947).
(4) Wojcik and Adkins, ibid., 55, 1293 (1933).
(5) Adkins and Coonradt, ibid., 63, 1563 (1941).

but also for 1-methylindole, 2,3-dimethylindole and 3,3-dimethylpseudoindole. The last compound was investigated because it cannot have a double bond in the position represented in I but must have the structure III.

III
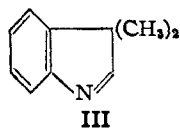
Copper chromium oxide is quite inactive for the hydrogenation of the benzenoid ring of indolines to octahydroindole. The conversion of indolines to octahydroindoles is a very slow and essentially irreversible reaction under the conditions used in these studies. At 150° the amount of octahydroindole produced during the establishment of equilibrium between indole and indoline averaged only about 1% of the indole submitted to hydrogenation. Even at 170° the conversion of indole to octahydroindole was 1 to 2% except for one run. With 1-methylindole the conversion to 1-methyloctahydroindole averaged about 2.6% at 170°. Hydrogenation and dehydrogenation in the system involving 2,3-dimethylindole proceeded much more slowly than in the cases of indole and 1-methylindole, so that the conversion to octahydro-2,3-dimethylindole averaged 4.6% at 170°. As would be expected, more octahydroindoles were produced in those runs starting with indolines than those proceeding from indoles. The reaction mixtures apparently contained only the indoles, indolines and octahydro-indoles. The data presented in Table III and discussed below have to do with the ratio of indoles and indolines in the reaction mixtures.

The extent of hydrogenation of indole to indoline at equilibrium is quite markedly affected by the pressure of hydrogen. When plotted the per cent. conversions to indoline at 170° are found to lie within experimental error upon a smooth curve from values of 50% indoline at 475 p.s.i. to 91% at 5100 p.s.i. At 150° the extent of conversion to indoline is somewhat higher for a given pressure than at 170°. At either temperature the values calculated from the expression g. indole × p.s.i. of H_2/g. indoline are reasonably constant. At 170° the values average 442 for the seven experiments reported in Table III. The individual figures being 416, 536, 408, 437, 428, 406 and 461. At 150° the average value is 337 for five runs having the values 353, 379, 397, 282 and 307.

The concentrations of 1-methylindole and 1-methylindoline at equilibrium for various pressures of hydrogen were quite similar to those for indole and indoline. However, the conversion of 2,3-dimethylindole to 2,3-dimethylindoline was much less for a given pressure of hydrogen than for the two indoles having hydrogens in the 2,3-positions. Hydrogenation and dehydrogenation proceeded so slowly in the 2,3-dimethylindole system at 170° that the values for concentrations at

equilibrium were not determined precisely nor over a wide range of hydrogen pressures. At an average pressure of 3650 p.s.i. the conversion to 2,3-dimethylindoline averaged 35% for four hydrogenations starting with 2,3-dimethylindole. Four dehydrogenations starting with 2,3-dimethylindoline or mixtures containing it showed after reaction an average of 47% of the indoline at an average pressure of about 2900 p.s.i. It thus appears that at equilibrium at 2900 to 3700 p.s.i. the conversion of 2,3-dimethylindole to 2,3-dimethylindoline is of the order of 40%. This value is approximately half that for the hydrogenation of indole itself under similar conditions.

The hydrogenation of 3,3-dimethylpseudoindole (III) and its trimer proceeded to completion in twenty to thirty minutes over copper chromium oxide at 500–600 p.s.i. of hydrogen. The product of hydrogenation, 3,3-dimethylindoline, did not undergo dehydrogenation over copper chromium oxide, as the indoline was recovered after four hours at 170° and 500 p.s.i. of hydrogen. Therefore it may be concluded that the low oxidation potential of a double bond in indoles is not concerned with a carbon to nitrogen double bond but with a carbon to carbon linkage.

Kistiakowsky[6] and his associates, in measuring heats of hydrogenation, have shown that the substitution of an alkyl group for hydrogen on the carbons of a double bond or the introduction of other double bonds in conjugation decreases the numerical value for ΔH. Thus while the value of ΔH for ethylene is −32.82 kcal., it is −27.95 for 2-butene, while for the hydrogenation of the first double bond in benzene the value is +5.6 kcal. On the basis of Kistiakowsky's results one would expect that the hydrogenation of a completely substituted double bond, as in 2,3-dimethylindole, would evolve even less heat than that from an unsubstituted indole. Thus, as reported here, the hydrogenation of 2,3-dimethylindole would be even less complete than that of indole or of 1-methylindole.

TABLE I

EQUILIBRIA OF n-OCTYL CAPRYLATE, n-OCTANOL AND HYDROGEN AT 260°[e]

Ester at equil., %	Pressure, p. s. i.	Time, hr.	Ester at equil., %	Pressure, p. s. i.	Time, hr.
0.9[a]	3980	0.7	15.8[a]	930	5.0
1.9[a,d]	2700	1.1	16.0[a,d]	915	4.0
2.4[a]	2450	1.7	41.8[b]	470	48.0
5.5[a]	1580	2.8	57.7[c]	325	8.8
9.7[b]	1200	11.0	80.3[a]	140	10.0

[a] 50 g. (0.195 mole) of ester at beginning of reaction. [b] 50.75 g. (0.39 mole) of n-octanol at beginning of reaction. [c] 20 g. (0.078 mole) of ester and 30.45 g. (0.234 mole) of alcohol at beginning of reaction. [d] 15 g. of catalyst used in this experiment instead of 5 g. as in the others. [e] At 290° the concentrations of ester at equilibrium were 2.5, 14.5, 39.2 and 63.8% at pressures of 2940, 1380, 550 and 200 p.s.i., respectively.

(6) For references see Kistiakowsky, Conn and Smith, THIS JOURNAL, 61, 1868 (1939).

TABLE II

EQUILIBRIA OF 2-ETHYLBUTYL 2-ETHYLBUTYRATE, 2-ETHYL-1-BUTANOL AND HYDROGEN AND OF NEOPENTYL TRIMETHYLACETATE, NEOPENTYL ALCOHOL AND HYDROGEN AT 260°

Ester at equil., %	Pressure, p. s. i.	Time, hr.	Ester at equil., %	Pressure, p. s. i.	Time, hr.
5.2[a,c]	2660	20	79.5[a,d]	295	28
15.9[a,c]	1090	31	62.9[a,f]	240	35
24.5[a,c]	450	31	7.6[b,e]	1390	15
30.5[a,c]	360	30	44.4[b,g]	380	50

[a] 2-Ethylbutyl 2-ethylbutyrate. [b] Neopentyl trimethylacetate. [c] 51 g. (0.5 mole) of 2-ethyl-1-butanol at beginning of reaction. [d] 30.85 g. (0.154 mole) of 2-ethylbutyl 2-ethylbutyrate at beginning of reaction. [e] 35 g. (0.4 mole) of neopentyl alcohol at beginning of reaction. [f] 35.9 g. (0.35 mole) of 2-ethyl-1-butanol at beginning of reaction.

TABLE III

EQUILIBRIA BETWEEN INDOLES, INDOLINES AND HYDROGEN

% Indoline	Pressure, p. s. i.	Time, hr.	% Indoline	Pressure, p. s. i.	Time, hr.
Indole
92.5[d]	5100	2.4[a]	87.0[d]	2360	5.0[b]
90.2[e]	4900	4.5[a]	86.1[f]	2350	4.0[b]
87.0[e]	2725	1.2[a]	85.1[f]	2270	4.0[b]
85.9[e]	2660	2.0[a]	80.0[e]	1220	3.0[b]
72.7[d]	1140	1.0[a]	81.2[d]	1200	4.7[b]
54.9[e]	495	1.0[a]	72.2[d]	800	6.0[b]
50.8[d]	475	4.0[a]			
2,3-Dimethylindole
37.8[g]	4500	10[e]	39.8[l]	3560	7[a]
34.8[l]	3720	24[a]	45.7[m]	3520	20[a]
28.6[g]	3650	9[a]	39.1[n]	2230	9[a]
35.3[g]	3630	6[a]	52.5[i]	2180	17[a]
44.3[h]	3610	46[a]			
1-Methylindole
89.4[j]	3250[a]	8.0[a]	61.1[k]	530	5.5[a]
75.1[j]	1120[a]	8.7[a]			

[a] 170°. [b] 150°. [c] 200°. [d] From 15 g. of indole. [e] From 15.3 of indoline. [f] From 10 g. of indole. [g] From 15 g. of 2,3-dimethylindole. [h] From 11.5 g. of a mixture containing 5.7 g. of 2,3-dimethylindole and 5.8 g. of 2,3-dimethylindoline. [i] From 11.9 g. of 2,3-dimethylindoline. [j] From 13.1 g. of 1-methylindole. [k] From 13.3 g. of 1-methylindoline. [l] From 11.3 g. of 2,3-dimethylindole. [m] From 11.1 g. of a mixture containing 5.2 g. of 2,3-dimethylindole and 5.9 g. of 2,3-dimethylindoline. [n] From 10.8 g. of a mixture containing 5.9 g. of 2,3-dimethylindole and 4.9 g. of 2,3-dimethylindoline.

Experimental Part

The hydrogenations and dehydrogenations were in general carried out in a steel reaction vessel having a total void of 270 ml. The gages were of the standard commercial type and were checked for accuracy up to 1000 p.s.i. by comparison with a dead weight gage. The catalyst, copper chromium oxide, was made by both of the methods described in "Organic Syntheses."[7] There was little if any difference in the activities of the catalysts so prepared. Five grams of catalyst was normally used with the esters and alcohols and 2 g. with the indoles and indolines.

The ester content of the reaction mixtures was deter-

mined by saponification in 0.5 N potassium hydroxide in alcohol or ethylene glycol. A high boiling medium is required for the saponification of the branched chain esters. Hydroxyl values were determined by the use of acetic anhydride in pyridine.

Reaction mixtures containing indoles, indolines and octahydroindoles were made up to a volume of 250 ml. with dioxane purified over sodium, after the catalyst had been removed and washed with dioxane. A 10-ml. aliquot of the solution of the reaction mixture was made up with 40 ml. of water and enough dioxane (10–20 ml.) to give a homogeneous solution. The solution was then titrated with 0.3 N hydrochloric acid. The progress of neutralization was followed with a glass electrode and a Beckman pH meter. The octahydroindole showed a break at pH 7 to 9 while the indolines showed a break at about pH 3. The end-point for the octahydroindole could be determined within 0.05 ml. of acid and the indoline within 0.10 ml. The indole present was determined by difference. The fractionation of certain reaction mixtures, through a Fenske column 1.3 cm. inside diameter and 18 cm. in length with a total-reflux partial-take-off head, gave amounts of product in good agreement with those estimated by electrometric titration.

n-Octyl caprylate and caprylic acid were made by oxidation of 1-octanol b. p. 83–84° (6 mm.) with chromic acid in sulfuric acid. The ester was obtained directly in 43% yield and additional amounts were obtained by the esterification of the 36% yield of caprylic acid obtained from the oxidation. The ester was also isolated from the dehydrogenation of 1-octanol in the equilibrium studies. The ester had b. p. 108–109° (0.4 mm.), 124–125° (0.8 mm.), $n^{25}D$ 1.4338, and a molecular weight by saponification of 258 (calcd. 256.3).

2-Ethylbutyl 2-ethylbutyrate was isolated by fractionation of the runs on the dehydrogenation of 2-ethyl-1-butanol. The ester had a b. p. 86–88° (6 mm.), $n^{25}D$ 1.4222. The alcohol had b. p. 147–148°, $n^{25}D$ 1.4209, and a molecular weight based upon its hydroxyl value of 104.3 (calcd. 102.1).

Neopentyl alcohol (b. p. 110–111°) was prepared by the catalytic hydrogenation of ethyl trimethylacetate. Ethyl trimethylacetate (b. p. 114–117°) was prepared by heating trimethylacetic acid (41 g.) and dry ethyl alcohol (122 g.) in a steel reaction vessel for seven and one-half hours at 225°. The water and alcohol were distilled out after 180 ml. of benzene was added to the reaction mixture. The desired ester (30.8 g.) was then distilled. An additional 7.3 g. of ester was obtained, after addition of 100 ml. of benzene, by refractionation of the alcohol–benzene–water fraction. The neopentyl trimethylacetate (b. p. 163–165°, $n^{25}D$ 1.4020) was prepared by the dehydrogenation of neopentyl alcohol. 1-Tetradecanol, b. p. 111–113° (0.1 mm.), m. p. 38°, molecular weight based upon hydroxyl value of 216.8 (calcd. 214.3), was dehydrogenated over copper chromium oxide in a flask at 230–270° for five hours to n-tetradecyl myristate, m. p. 42–43°, molecular weight based upon saponification 437 (calcd. 424), in a yield of about 55%.

1-Tetradecanol when heated at 175–250° over Raney nickel was converted in 75% yield to tridecane, $n^{25}D$ 1.4239, d^{20}_4 0.7569, m. p. −6°. 1-Octanol, at 200° under hydrogen at 1350 p.s.i. over Raney nickel, was converted in 64% yield to n-heptane, b. p. 95–97°, $n^{25}D$ 1.3854, d^{20}_4 0.6813.

Indole[8] (b. p. 141–142° (22 mm.), m. p. 52.3°), 1-methylindole[9] (b. p. 102–104° (6 mm.), $n^{25}D$ 1.6021, picrate m. p. 149–151°), 2,3-dimethylindole[10] (b. p. 153–155° (11 mm.), m. p. 106–107°, picrate m. p. 155–156°) and 3,3-dimethylpseudoindole[11] (b. p. 90–94° (7 mm.), m. p. of trimer 217–222°) were made by methods described in the literature.

(7) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., pp. 325, 1842.

(8) Tyson, "Organic Syntheses," Vol. XXIII, John Wiley and Sons, New York, N. Y., (1942), p. 42.

(9) Weissgerber, Ber., 43, 3522 (1910).

(10) Snyder and Smith, THIS JOURNAL, 65, 2452 (1943).

(11) Brunner. Monatsh., 16, 849 (1895).

Tyson's procedure was modified in that a temperature of 325° rather than of 350–360° was found sufficient. The yield of crude 1-methylindole obtained from the reaction of methyl iodide with the potassium salt of indole was 77% of the theoretical. The products from several runs for each indole were combined, refluxed with Raney nickel and then distilled. Since 3,3-dimethylpseudoindole trimerizes, even at room temperature, it was prepared and hydrogenated immediately. The trimer, m. p. 217–222°, was also hydrogenated and found to give the same product as the monomer. The crude 2,3-dimethylindole was purified by shaking it with Raney nickel in dioxane for five hours at room temperature under 415 p.s.i. of hydrogen. The final yield (22.6 g.) of pure 2,3-dimethylindole, b. p. 164–167° (20 mm.), m. p. 106–107°, was 61% of the theoretical.

The indolines were obtained by fractionation, through a Fenske column, of the reaction mixtures from hydrogenation. Indoline distilled at 119° (24 mm.), n^{25}D 1.5883, and had a neut. equiv. of 119 (calcd. 119). 1-Methylindoline distilled at 82–83° (6 mm.), n^{25}D 1.5670, picrate m. p. 163–164°. 3,3-Dimethylindoline showed m. p. 31–33°, b. p. 105–106° (12 mm.), n^{25}D 1.5513; benzene sulfonamide, m. p. 102–102.5°, neut. equiv. 151.7 (calcd. 147). 2,3-Dimethylindoline had b. p. 110–112°, n^{25}D 1.5524, m. p. acid oxalate 134–136°.

Summary

The extent of the hydrogenation of an ester of the type of n-octyl caprylate to 1-octanol over copper chromium oxide at 260° increases from 20% at 10 atm. to 99% at 250 atm. of hydrogen. Thus the process may be used for the conversion of an alcohol, RCH_2OH, to the corresponding ester, RCO_2CH_2R, as well as the hydrogenation of an ester to alcohol.

The extent of the hydrogenation of indole and of 1-methylindole to the corresponding indolines, over copper chromium oxide at 150–170°, increases from 50% at 30 atm. to 90% at 400 atm. of hydrogen. The equilibrium between 2,3-dimethylindole and the corresponding indoline is even more unfavorable to complete hydrogenation, the ratio of the indole to the indoline at equilibrium being about 3 to 2 at 250 atm. of hydrogen. In contrast, the hydrogenation of 3,3-dimethyl-pseudoindole, with the double bond in the 1,2 rather than in the 2,3 position as with the other indoles studied, goes to completion under 35 atm. of hydrogen.


Organolithium Compounds with Hydroxyl, Nitrilo and Sulfonamido Groups

BY HENRY GILMAN AND DONALD S. MELSTROM

The halogen–metal interconversion reaction is particularly suitable, in connection with studies concerned with physiological action, for the preparation of organolithium compounds containing a functional group which under ordinary conditions reacts with RLi compounds. Some of the functional groups present in molecules which have been prepared in accordance with the reaction

$$RX + n\text{-}C_4H_9Li \longrightarrow RLi + n\text{-}C_4H_9X$$
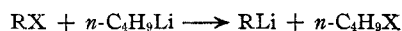
are amino,[1a] azomethylene,[1b] phenolic hydroxyl[1c] and carboxyl.[1c]

We are now reporting the preparation of RLi compounds from bromophenyl alcohols like m- and p-bromobenzyl alcohols, p-bromophenethyl alcohol and p-bromo-α-methylbenzyl alcohol. The yields of interconversion products, as determined by carbonation and isolation of the corresponding carboxylic acids, range from 18 to 52%. However, the actual yields of RLi compounds are greater, since the interconversion products when treated in another study with triphenyllead chloride instead of with carbon dioxide were converted into the expected unsymmetrical organolead compounds in yields of 41 to 63%. Also, the halogen–metal interconversion product of o-bro-

mobenzyl alcohol, although not studied by carbonation of the reaction product, gave a 70% yield of triphenyl-o-hydroxymethylphenyllead by reaction with triphenyllead chloride. Incidentally, improved directions are given for the preparation of p-bromobenzyl alcohol.

The isolation of terephthalic acid by carbonation of the interconversion product of p-bromobenzonitrile and n-butyllithium indicates that p-carboxybenzonitrile was formed and underwent hydrolysis incidental to working up the reaction products. Carbonation of the interconversion product from p-bromobenzenesulfonamide and n-butyllithium gave p-carboxybenzenesulfonamide which was slightly contaminated with what may be a reduction product. It is interesting to note in this connection that carbonation of the interconversion product from p-iodo-N,N-diethylbenzenesulfonamide gave directly a 72% yield of p-carboxy - N,N - diethylbenzenesulfonamide, the melting point of which was unchanged after crystallization.[1c]

Experimental

Preparation of p-Bromobenzyl Alcohol.—Ziegler and Tiemann[2] prepared this alcohol from p-bromophenyl-magnesium bromide and formaldehyde. They obtained a 61% yield of product distilling over the range 125–140° (11 mm.), but their yield of pure compound (crystallized from ethanol) is not reported. We tried this method, patterning the procedure after that described for cyclo-

(1) (a) Gilman and Stuckwisch, THIS JOURNAL, 63, 2844 (1941), and 64, 1007 (1942); (b) Gilman and Spatz, ibid., 62, 446 (1940), and 63, 1553 (1941); (c) Gilman and Arntzen, ibid., 69, 1537 (1947). For general references, see pp. 538–539 of Gilman, "Organic Chemistry," Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943.

(2) Ziegler and Tiemann, Ber., 55, 3406 (1922).