fine crystals. These crystals were especially evident under polarized light. In glyceryl adipate they were small aggregates of needles; in glyceryl sebacate spheroid clusters.

Summary

1. The changes in acid number and water evolved as the glyceryl adipate (acid) reaction proceeds at 190° have been measured. No temperature increase was observed on initial mixing and an appreciable time was required to reach 50% esterification. The reaction appears to be only interesterification. Gelation occurs when approximately 30 mole per cent. of tetramer or higher polymer has been formed. There is evidence that, at gelation, a small amount of the initially formed acid esters is still present.

2. The glyceryl sebacate reaction has been studied at 190°. It apparently progresses like the glyceryl adipate reaction but there is some evidence that, in this case, a small amount of intraesterification as well as interesterification has occurred. Gelation takes place at a slightly lower degree of molecular complexity than in the case of glyceryl adipate. The initially formed acid esters indicated as present in glyceryl adipate at gelation also appear to be present in glyceryl sebacate.

3. Data comparing the effect of increasing the chain length in the polybasic acid portion of glyceryl polyester reactions are presented. As the chain length increases, the time to attain gelation increases, the average molecular weight and area per average molecule increases, the average basicity at gelation decreases, the molecular complexity at gelation decreases.

BOUND BROOK, NEW JERSEY

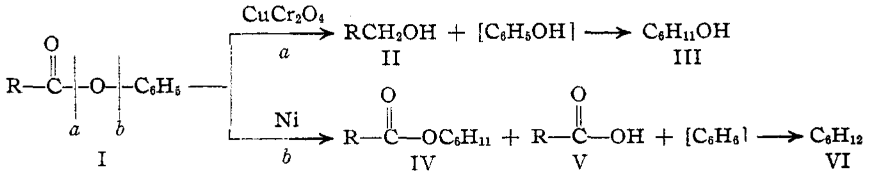
RECEIVED OCTOBER 16, 1940

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING AT THE UNIVERSITY OF PENNSYLVANIA]

The Hydrogenation of Aryl Esters[1]

BY WM. R. McCLELLAN AND RALPH CONNOR

The formation of hexahydrochroman[2] by the hydrogenation of coumarin over Raney nickel suggested that the formation of ethers might be characteristic either of lactones or of aryl esters (I). Since the latter had apparently not been hydrogenated over either nickel or copper chromite, their behavior over each catalyst was investigated. The main reactions are shown in the flow diagram.



Over copper chromite the esters (I) of phenol gave results similar to those observed with esters of alcohols. The details are given in Table I. Without considering the specific mechanism, the net result was hydrogenolysis of the ester grouping with cleavage between oxygen and acyl (*a*), giving alcohols (II) and phenol. The latter was converted to cyclohexanol (III).[3,4] Hydrogenation of the lactone (VII) of *o*-hydroxyphenoxyacetic acid gave β-(*o*-hydroxyphenoxy)-ethyl alcohol (VIII) without any apparent attack of the aromatic ring over copper chromite. The formation of toluene from phenyl benzoate and of methanol and cyclohexanol from phenyl carbonate are the expected results of the continued hydrogenolysis and hydrogenation of the initial products.

The details of the results using Raney nickle as a catalyst are given in Table I. No ethers were isolated. Excepting the hydrogenations of phenyl carbonate, phenyl benzoate and the lactone of *o*-hydroxyphenoxyacetic acid (VII), two major competitive reactions were observed over Raney nickel. One of these was the hydrogenation of

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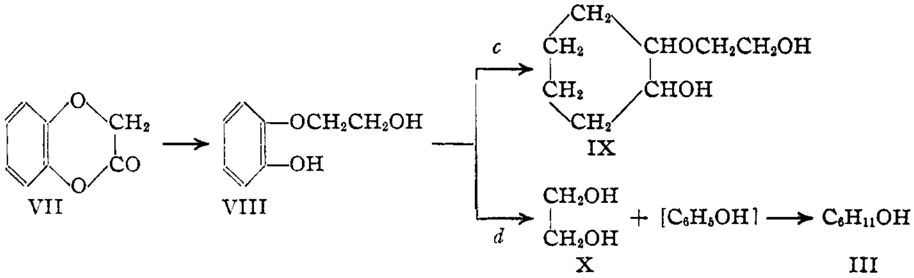
[1] This communication is constructed from a thesis submitted by Wm. R. McClellan in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Pennsylvania in June, 1940.

[2] De Benneville and Connor, THIS JOURNAL, **62**, 283 (1940).

[3] The presence of a phenolic group has been reported to labilize aromatic nuclei to hydrogenation over copper chromite.[4]

[4] Adkins, "Reactions of Hydrogen, etc.," University of Wisconsin Press, Madison, Wisconsin, 1937, p. 61.

the aromatic nucleus, giving the cyclohexyl ester (IV) in yields of 20–50%. A more novel reaction was the hydrogenolysis (20–60%) of the ester with cleavage between the oxygen and aryl group[5,6] (*b*), giving an acid (V) and benzene, which was converted to cyclohexane (VI). This reaction is specific for aryl esters, for neither cyclohexyl *n*-butyrate nor ethyl cinnamate (Table I) underwent hydrogenolysis over Raney nickel under these conditions.



The behavior of phenyl carbonate over Raney nickel differed from that of the typical esters in that hydrogenation occurred at lower temperatures. Furthermore, cleavage (*b*) occurred so readily that this constituted the sole reaction and the cyclohexyl ester (IV) was not obtained. The products were cyclohexane and cyclohexanol, the latter being the product expected from the decarboxylation and hydrogenation of the acid (C_6H_5-OCOOH) which would be the initial product of cleavage (*b*). The cyclohexane was not formed by the hydrogenolysis of cyclohexanol, for the latter was unchanged (Table I) after treatment at 200° over Raney nickel.[7]

Hydrogenation of phenyl benzoate gave the products which would be expected from the reactions shown in the flow sheet: cyclohexyl hexahydrobenzoate, hexahydrobenzoic acid and cyclohexane. However, in this case the major reaction (45%) was the formation of methylcyclohexane and cyclohexanol.[7] While these products would be formed[5] if phenyl benzoate were converted to phenyl benzyl ether, it seems more plausible[8] to assume that the ester reacts over Raney nickel as it does over copper chromite (cleavage at *a*).

An additional example of the hydrogenolysis of esters over nickel by cleavage *a* was found in the case of the lactone of *o*-hydroxyphenoxyacetic acid (VII). This compound underwent neither of the reactions mentioned above as characteristic of esters of phenols over Raney nickel. Instead, β-(2-hydroxycyclohexyloxy)-ethyl alcohol (IX), ethylene glycol (X) and cyclohexanol (III) were formed. The same products were obtained by the hydrogenation of β-(*o*-hydroxyphenyl)-ethyl alcohol (VIII), which appears to be the initial product from the hydrogenation of VII. Nuclear hydrogenation (*c*) of VIII gives IX, while hydrogenolysis (*d*) similar to that observed with other alkyl aryl ethers[5] is responsible for the formation of III and X. The ease of formation of VIII from VII under these conditions is different from the behavior of esters in general,[9] but it is in line with the results obtained with coumarins.[2,10]

Some of the by-products noted in Table I may require explanation. Small amounts (less than 10%) of *n*-propyl propionate, *n*-butyl *n*-butyrate and isobutyl isobutyrate were obtained from the hydrogenations of phenyl propionate, phenyl *n*-butyrate and *p*-tolyl isobutyrate, respectively. It therefore appears[11] that such aryl esters may also undergo reaction over Raney nickel according to scheme *a* and the alcohols (II) thus formed undergo ester interchange[12] (with I or IV). The slight extent to which this reaction occurs, compared to the results with VII and coumarins,[2,10] makes it unlikely that the behavior of the latter can be attributed solely to their character as aryl esters.

Ethyl esters were obtained when the Raney nickel catalyst had been stored under alcohol.

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[5] While the hydrogenolysis of aryl alkyl ethers is relatively difficult, over Raney nickel they are also cleaved between oxygen and the aromatic ring. The exceptions are benzyl aryl ethers which give the cyclohexanol and toluene (ref. 4, p. 73).

[6] Indications were noted[2] that a similar reaction, formation of β-cyclohexylpropionic acid, occurred in the hydrogenation of coumarin.

[7] The yields of products in some of the reactions carried out at 250° suggest that a small amount of cyclohexanol is converted to cyclohexane, as would be expected at this temperature (ref. 4, p. 80).

[8] No evidence has been obtained for the formation of ethers, while examples of the hydrogenation of esters to alcohols over nickel are known.[9]

[9] Folkers and Adkins, This Journal, **53**, 1097 (1931); Palfray and Sabetay, *Chemie et Industrie, numéro special* (Congres de Bruxelles), 1935, p. 746; *Bull. Soc. Chim.*, **3**, 682 (1936); **5**, 1424 (1938); Rainey and Adkins, This Journal, **61**, 1107 (1939); Ovakimian, Kuna and Levene, *ibid.*, **62**, 667 (1940); de Benneville and Connor, ref. 10.

[10] De Benneville and Connor, *ibid.*, **62**, 3067 (1940).

[11] While the formation of the alcohols could occur if ethers were initial products of the hydrogenation, this does not seem an attractive mechanism for the reasons already noted.[8]

[12] The conditions are favorable for ester interchange [Connor and Adkins, This Journal, **54**, 4681 (1932)].

TABLE I

HYDROGENATION DATA[a]

								Products, molar % of theoretical				
No.	Compound	Mole	Time, hr.	Temp., °C.	Catalyst	II	III	IV	V	VI	$RCOOCH_2R$[b]	$RCOOC_2H_5$[c]
1	Phenyl propionate	0.25	19	250	9 g. $CuCr_2O_4$[d]	82	86	..	..	..	..	..
2	Phenyl *n*-butyrate	.20	15	250	8 g. $CuCr_2O_4$[d]	81	98	..	..	..	..	..
3	Phenyl cinnamate	.15	11	250	6 g. $CuCr_2O_4$	81[e]	82	..	..	..	..	..
4	Phenyl carbonate	.15	10	250	5 g. $CuCr_2O_4$	75[f]	82	..	..	..	..	..
5	Phenyl benzoate	.20	18	250	9 g. $CuCr_2O_4$[d]	(69)[g]	87	..	..	..	..	..
6	VII	.13	3.5	250	6 g. $CuCr_2O_4$	77[h]	..	..	..	..	..	..
7	Phenyl propionate	.40	2.5	250	6 g. Ni	...	..	20	48	42	10	..
8	Phenyl propionate	.40	5	200	7 g. Ni	...	..	27	39	55	5	7
9	Phenyl *n*-butyrate	.30	2.5	250	7 g. Ni	...	..	32	12	46	8	9
10	Phenyl *n*-butyrate	.30	2.5	200	7 g. Ni	...	..	23	29	52	10	12
11	Phenyl cinnamate	.10	3	250	5 g. Ni	...	8	35[i]	25[j]	[k]	..	24
12	Phenyl cinnamate	.15	4	200	7 g. Ni	...	13	49[i]	17[j]	[k]	..	16[l]
13	Phenyl carbonate	.20	3.5	185	6 g. Ni	...	97	..	..	72	..	..
14	Phenyl carbonate	.20	1.5	190	6 g. Ni	...	93	..	..	80	..	..
15	Phenyl benzoate	.30	4	250	6 g. Ni	(44)[m]	37	21	20	27	..	..
16	Phenyl benzoate	.30	6	200	6 g. Ni	(42)[m]	48	21	20	25	..	..
17	*p*-Tolyl isobutyrate	.35	6	250	6 g. Ni	...	..	38[n]	15	25[o]	4	..
18	*p*-Tolyl isobutyrate	.34	13.5	200	9 g. Ni	...	..	57[n]	19	30[o]	3	..
19	VII	.15	5	200	6 g. Ni	60[p]	25[q]	..	..	..	..	..
20	Cyclohexyl *n*-butyrate	.23	6.5	250	6 g. Ni	...	10[r]	85	2[r]	..	..	..
21	Ethyl cinnamate	.25	12	250	5 g. Ni	...	..	..	..	..	..	88[s]
22	Cyclohexanol	.40	7	200	6 g. Ni	...	91	..	..	..	..	..
23	VIII	.10	1.5	180	5 g. Ni	40[p]	50[q]	..	..	..	..	..

[a] The hydrogenations were carried out at 100–200 atm. No solvent was used except in experiments 11 (25 ml. of methylcyclohexane), 12 (50 ml. of methylcyclohexane) and 23 (30 ml. of ethanol). Two to three milliliters of solvent was used to keep the catalyst moist in experiments 13, 14 (methylcyclohexane), 15 and 16 (*n*-amyl ether). [b] This column contains the yields of *n*-propyl propionate, *n*-butyl *n*-butyrate and isobutyl isobutyrate from phenyl propionate, phenyl *n*-butyrate and *p*-tolyl isobutyrate, respectively. [c] The results noted in this column were obtained when the catalyst was not completely free of alcohol (see experimental part). [d] In these runs the rate of hydrogenation became very slow and they were interrupted to allow the introduction of 3 g. of fresh catalyst. This amount is included in the figures given in the table. [e] $R = C_6H_5CH_2CH_2—$. [f] Methanol. [g] This figure is for toluene, formed by hydrogenolysis of benzyl alcohol. [h] β-(*o*-Hydroxyphenoxy)-ethyl alcohol[14] (VIII). [i] Cyclohexyl β-cyclohexylpropionate, b. p. 135–136° (4 mm.); $n^{33}{}_D$ 1.4715; $d^{30}{}_4$ 0.968; *M*D calcd., 68.73; *M*D found, 68.77. *Anal.* Calcd. for $C_{15}H_{26}O_2$: C, 75.56; H, 11.00; sapon. no. 238. Found: C, 75.49, 75.40; H, 10.70, 10.90; sapon. no. 240. [j] $R = C_6H_{11}CH_2CH_2—$. [k] No attempt was made to separate VI from the methylcyclohexane used as a solvent. [l] Ethyl β-cyclohexylpropionate (3 parts) and ethyl β-phenylpropionate (2 parts). [m] These figures are the yields of methylcyclohexane isolated. Under these conditions II (benzyl alcohol) would be converted to toluene, then methylcyclohexane. [n] 4-Methylcyclohexyl isobutyrate. [o] Methylcyclohexane. [p] β-(2-Hydroxycyclohexyloxy)-ethyl alcohol (IX), b. p. 175–176° (36 mm.); $n^{30}{}_D$ 1.4772; $d^{30}{}_4$ 1.089; *M*D calcd., 41.64; *M*D found, 41.61. *Anal.* Calcd. for $C_8H_{16}O_3$: C, 59.95; H, 10.07. Found: C, 59.96, 60.10; H, 10.02, 10.08. [q] Approximately an equivalent amount of ethylene glycol was also obtained (20% in experiment 19, 53% in experiment 23). [r] Since there was no appreciable hydrogen absorption, these products must be the result of hydrolysis[13] rather than hydrogenolysis. [s] The product was ethyl β-cyclohexylpropionate.[2]

It was observed that 6 g. of the catalyst retained about 1 g. of alcohol which could not readily be removed by washing with ether or methylcyclohexane; this alcohol formed ethyl esters by ester interchange.[12] Formation of this by-product was avoided by treatment of the catalyst as described in the experimental part.

The difficulty of attaining completely anhydrous conditions in the hydrogenation apparatus has been pointed out previously.[13] Hydrolysis was probably responsible for a few results in which the amount of cyclohexanol formed was greater than could be accounted for by alcoholysis and by cleavage *a*.

Unlike the case of coumarin, the temperature had no important influence upon the products from the hydrogenation of aryl esters. Data in Table I include results at both 200 and 250°.

Experimental Part

In order to avoid the formation of ethyl esters (Table I), the Raney nickel catalyst was freed from alcohol, except in experiments 8–12, inclusive. This was accomplished by allowing the catalyst to stand under ether for several hours and decanting. This was repeated several times and the catalyst stored under ether.

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(13) Connor and Adkins, THIS JOURNAL, **54**, 3423 (1932).

(14) Read and Miller, *ibid.*, **54**, 1195 (1932).

For economy of space in publication, the details of the isolation and identification of the hydrogenation products have not been submitted. A brief outline of the method follows.

When nickel was used for the hydrogenation of aryl esters, part of the acid formed reacted with nickel and was recovered from the salt by alkaline extraction, followed by acidification.

The hydrogenation products were separated with a Widmer column containing a glass helix 11 cm. in length with nine turns. Small fractions were in some cases further purified by redistillation through a column 19 cm. long with an inside diameter of 0.5 cm. and with a nichrome wire helix (two turns per cm.) fitted snugly inside the column. Both columns were jacketed.

All of the products except esters and saturated hydrocarbons were identified by the preparation of known solid derivatives and the determination of mixed melting points with authentic samples. The saturated hydrocarbons were identified by boiling points, densities and refractive indices. The esters were identified by saponification equivalents, densities, refractive indices and the preparation of known solid derivatives of the hydrolytic products.

The yields quoted in Table I include not only the pure product isolated, but also the amount present in intermediate fractions. For example, in a fraction containing acid and ester, the identity of the components was shown by the preparation of solid derivatives of the hydrolytic products. The amounts of acid and ester were then determined by neutralization and saponification equivalents and these data included in calculating the total yield. These results were usually checked by refractive indices, which were also useful in the examination of the hydrocarbon fractions.

Summary

The esters of phenol ($RCOOC_6H_5$) are converted to alcohols (RCH_2OH) and cyclohexanol over copper chromite. Over nickel, three reactions may occur: (1) formation of cyclohexyl esters ($RCOOC_6H_{11}$), (2) cleavage in a different manner than that observed over copper chromite, giving an acid (RCOOH) and cyclohexane, and (3) cleavage similar to that obtained over copper chromite. Of these, the last was unimportant except in the case of a lactone and of phenyl benzoate. The formation of cyclic ethers from coumarins previously reported cannot be attributed to the character of coumarins as aryl esters.

PHILADELPHIA, PENNA. RECEIVED NOVEMBER 12, 1940

[CONTRIBUTION FROM THE PEDIATRIC RESEARCH LABORATORY OF THE JEWISH HOSPITAL OF BROOKLYN]

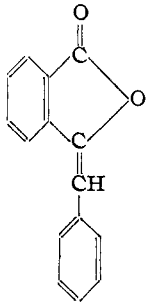
Synthesis of Derivatives of Symmetrical Diphenylethane Related to Materials Occuring Naturally. III. The Relationship between Benzalphthalide and the Benzylisoquinoline Alkaloids

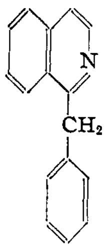
BY SAMUEL NATELSON AND SIDNEY P. GOTTFRIED

While studying the structure of benzalphthalide in the further attempt to use it as a starting material in the synthesis of biologically important compounds, it became apparent that certain derivatives of benzalphthalide, in addition to being related to the sterols, are also structurally linked to the benzylisoquinoline alkaloids. With this relationship in view, it was decided to attempt to prepare various derivatives of benzylisoquinoline, and eventually papaverine itself.

An examination of the structure of benzalphthalide shows that its conversion to a benzylisoquinoline derivative involves adding one more carbon to the five-membered heterocycle and replacing the oxygen by nitrogen.

This can be accomplished in two ways: first by building up the carbon chain and replacing the oxygen by nitrogen, second by replacing the oxygen by nitrogen and then building up the carbon chain. Both methods were attempted.


Benzalphthalide


Benzylisoquinoline

In the first method, the benzalphthalide was converted to 2-stilbene carboxylic acid by reduction and dehydration, applying and improving the method of Gabriel.[1] This procedure was described in the first paper of this series.[2] The method of Sonn and Müller[3] which was used to prepare *o*-β-phenethylbenzaldehyde (2) was found

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[1] Gabriel and Posner, *Ber.*, **27**, 2506 (1894).

[2] Natelson and Gottfried, THIS JOURNAL, **58**, 1432 (1936).

[3] Sonn and Müller, *Ber.*, **52**, 1927 (1919).