[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF SWARTHMORE COLLEGE]

THE MECHANISM AND APPLICATION OF THE FRIES REACTION[1]

BY EDWARD H. COX

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The rearrangement of the phenolic esters to hydroxy aromatic ketones by means of anhydrous aluminum chloride (the Fries reaction) has been observed by many workers.[2] Although aluminum chloride is the most effective reagent used in carrying out these rearrangements, anhydrous ferric chloride and, especially, zinc chloride are only slightly less efficient.[3]

Fries, Witt[4] and recently Auwers[5] have considered the reaction to be intramolecular. Skraup and Poller[6] prepared *o*-acetyl-*m*-cresol by the action of anhydrous zinc chloride on *m*-tolyl acetate and contended that the ester was first decomposed by the zinc chloride into acetyl chloride and *m*-cresol and that the acid chloride then reacted with the cresol to form the ketone. They repeated this reaction but added *m*-chlorobenzoyl chloride and observed that this acid chloride reacted with the cresol at the expense of the more volatile acetyl chloride. Only *m*-chlorobenzoyl-*m*-cresol (2-hydroxy-4-methyl-3′-chlorobenzophenone) was produced; no *o*-acetyl-*m*-cresol was isolated. Auwers and Mauss[7] have contrasted the Fries reaction with that of Friedel–Crafts when applied to phenols, and have drawn a distinction according to whether the acid residue is introduced from without the molecule or is originally present, as is the case in the Fries rearrangements. Since, according to these workers, the Friedel–Crafts reaction when applied to most phenols, in the preparation of aromatic hydroxy ketones, generally gives the *p*-acylphenols,[8] and with a few phenols of certain structure, the meta derivatives, and since on the other hand in the Fries reaction only ortho or para and never *m*-acylphenols are produced, then the Fries displacement according to them is considered to take place within the molecule (intramolecular).

Rosenmund and Schnurr[9] studied the conditions of the Fries transformation in order to improve upon the method. They have discussed

[1] A preliminary report of this work was made at the Richmond, Virginia, meeting of the American Chemical Society, April, 1927, under the title "Mechanism of the Fries Reaction."

[2] Fries and co-workers, *Ber.*, **41**, 4276 (1908); **43**, 214 (1910); **54**, 717 (1921); **56**, 1305 (1923); Auwers, *Ann.*, **421**, 36 (1920); **447**, 162 (1926).

[3] Eijkman, *Chem. Weekblad*, **1**, 455 (1904); Heller, *Ber.*, **42**, 2738 (1909); **45**, 418, 2389 (1912).

[4] Witt and Braun, *ibid.*, **47**, 3219 (1914).

[5] Auwers and Mauss, *Ann.*, **464**, 293 (1928).

[6] Skraup and Poller, *Ber.*, **57**, 2033 (1924).

[7] Auwers and Mauss, *ibid.*, **61**, 1495 (1928).

[8] Auwers and Mauss, *Ann.*, **464**, 295 (1928).

[9] Rosenmund and Schnurr, *ibid.*, **460**, 56 (1928).

their experimental results and have disagreed with Auwers' statement that the reaction is intramolecular. They have found that when a mixture of *o*-chloro-*p*-tolyl acetate (2-chloro-4-methylphenyl acetate) and *p*-tolyl benzoate is acted upon by aluminum chloride, not only 2-acetyl-6-chloro-*p*-cresol (2-hydroxy-3-chloro-5-methylacetophenone) and *o*-benzoyl-*p*-cresol (2-hydroxy-5-methylbenzophenone) are formed, but also 2-benzoyl-6-chloro-*p*-cresol (2-hydroxy-3-chloro-5-methylbenzophenone) and *o*-acetyl-*p*-cresol (2-hydroxy-5-methylacetophenone). They state that if this reaction were strictly intramolecular, the latter two compounds should not have been formed. These authors have also taken exception to Skraup's explanation of the reaction, for they were unable to distil out any free acid chloride, even when working at reduced pressure and in a stream of hydrogen. They have interpreted the mechanism of the Fries change as one involving two molecules of the ester and have likened the reaction to that of Friedel–Crafts where acetic anhydride is the acetylating reagent. The possibility of free radical exchange is also indicated.

The experimental results given in this paper support the contention of Skraup and Poller, *viz.*, that, when phenolic esters are acted upon by anhydrous aluminum or zinc chlorides, the free acid chlorides are produced which then act upon the phenolic group, giving ketones. If the change were intramolecular there should be the possibility of the formation and isolation of some intermediate product. The failure to identify any such product and the results of Rosenmund and Schnurr's work are contrary to the interpretation that the transformation takes place within the ester molecule. That there is no exchange of free radicals is supported by the fact that a catalyst is necessary for the transformation.[10] That the Fries change is comparable to the Friedel–Crafts reaction when acetic anhydride is used is not untenable, since the action of aluminum chloride on acetic anhydride produces acetyl chloride.

In the first part of the experimental work recorded here the Fries reaction is carried out in the relatively inert solvent, diphenyl ether. When anhydrous aluminum or zinc chloride acts upon phenolic esters in the presence of this solvent, the acyl phenols and acyl diphenyl ether are both formed. It is difficult to interpret the formation of the acyl derivative of diphenyl ether other than that it is produced by the medium of the free acid chloride. Some free phenol is invariably recovered from the reaction mixture.

It has also been observed during the course of some experimental work that, if absolute alcohol was added during the reaction of anhydrous aluminum chloride on tolyl acetates, ethyl acetate was distilled from the re-

[10] Skraup [Skraup and co-workers, *Ber.*, **60**, 942, 1070 (1927)] has carried out some pyrolytic reactions on special phenyl esters at high temperatures (350–420°) but the yields of the ketones were very low. When the reactions were carried out in the presence of anhydrous zinc chloride and halogen acids much lower temperatures were required and higher yields of ketones were obtained.

action mixture. Again, in an attempt to rearrange these acetates under pressure, using absolute alcohol containing hydrogen chloride as a solvent, ethyl acetate was found to be one of the reaction products. Finally, it was observed that some acetyl chloride was distilled out when aluminum chloride acted on 2,4,6-trichlorophenyl acetate. These observations support the conclusion that the free acid chloride is an intermediate in the Fries reaction.

That the reaction gives better yields of aromatic hydroxy ketones than are obtained by the Friedel–Crafts method may be explained by the fact that a less amount of aluminum chloride is necessary to effect the transformation and that the progressive splitting and resubstituting of the acyl group give rise to more ideal concentration of the reactants.

In the second part of the experimental work the Fries reaction is applied in the preparation of some acyl derivatives of salicylic acid. The esters of methyl salicylate are prepared by the action of acid chlorides on methyl salicylate, and are transformed by anhydrous aluminum chloride to the acyl salicylates. The acyl esters are then saponified and subsequently reduced to the alkyl salicylic acids by the Clemmensen method. In view of the general interest manifested in the relation of the alkyl phenolic substances to their antiseptic properties and because most of the substances are not given in the literature, it is considered of value to record them.

Experimental. Part I

A general statement of the experimental procedure is as follows: to 40 g. of anhydrous aluminum chloride was added 200 cc. of carbon disulfide. To these was added slowly with heating and stirring a mixture of 50 g. of the phenolic ester and 60 g. of diphenyl ether. After the addition, the reaction mixture was heated for a short time and the carbon disulfide was then distilled off. The temperature was raised from 100–175° for fifteen to forty-five minutes. The reaction melt was decomposed in water and the resulting oily layer separated, treated with a 15% solution of potassium hydroxide and extracted with ether. The aqueous portion was acidified with dilute hydrochloric acid solution and also extracted with ether. Both ether extracts were dried, evaporated and distilled in a vacuum.

Action of Aluminum Chloride on *m*-Tolyl Butyrate in Diphenyl Ether.—The reaction mixture was heated to 100–110° for fifteen to twenty minutes. The alkali-insoluble portion was distilled in a vacuum. Fraction one, boiling from 140–150° at 20 mm., was unchanged diphenyl ether (42 g.); fraction two, boiling from 200–208° at 12 mm., was *p*-butyryl diphenyl ether (24 g.). The second fraction solidified and was crystallized from petroleum ether (m. p. 50°).

Anal. Subs., 0.1336: CO_2, 0.3931; H_2O, 0.0804. Calcd. for $C_{16}H_{16}O_2$: C, 80.00; H, 6.66. Found: C, 80.24; H, 6.73.

Fraction one of the alkali-soluble portion, distilling from 100–135° at 25–30 mm., was *m*-cresol (18 g.) and was identified as the benzoate (m. p. 54–55°). Fraction two, distilling from 175–200° at 15 mm., was *p*-butyryl-*m*-cresol, $C_6H_3(OH)(CH_3)(COC_3H_7)$ (1,3,4). The distillate soon solidified and was crystallized from a mixture of benzene and petroleum ether (m. p. 88°).

Anal. Subs., 0.1632: CO_2, 0.4422; H_2O, 0.1143. Calcd. for $C_{11}H_{14}O_2$: C, 74.15; H, 7.86. Found: C, 73.89; H, 7.84.

Action of Aluminum Chloride on *o*-Tolyl Acetate in Diphenyl Ether.—The reaction mixture was heated for thirty minutes at 175°. The alkali-insoluble portion yielded 54 g. of unchanged diphenyl ether and 14 g. of *p*-acetyl diphenyl ether, distilling from 180–190° at 7 mm. It was crystallized from petroleum ether and melted at 53°.[11]

Anal. Subs., 0.1254: CO_2, 0.3629; H_2O, 0.0764. Calcd. for $C_{14}H_{12}O_2$: C, 79.24; H, 5.66. Found: C, 78.91; H, 6.01.

The alkali-soluble portion yielded 18 g. of *o*-cresol, identified as the *p*-nitrobenzoate (m. p. 90–92°), and 27 g. of *p*-acetyl-*o*-cresol, $C_6H_3(OH)(CH_3)(COCH_3)(1,2,4)$, distilling from 170–175° at 5 mm. It was crystallized from a mixture of benzene and petroleum ether and melted at 110°.[12]

Anal. Subs., 0.2043: CO_2, 0.5380; H_2O, 0.1253. Calcd. for $C_9H_{10}O_2$: C, 72.00; H, 6.66. Found: C, 71.81; H, 6.86.

Action of Aluminum Chloride on *p*-Tolyl Acetate in Diphenyl Ether.—The reaction mixture was heated for fifteen minutes at 160°. The alkali-insoluble portion yielded 46 g. of unchanged diphenyl ether and 11 g. of *p*-acetyl diphenyl ether. The latter compound when mixed with the acetyl diphenyl ether from the above experiments showed a melting point of 52–53°.

The alkali-soluble portion yielded a small amount of *p*-cresol and 15 g. of *o*-acetyl-*p*-cresol, $C_6H_3(OH)(CH_3)(COCH_3)(1,4,2)$, distilling from 120–130° at 7 mm. After crystallization from petroleum ether it melted at 48–49°.[13] An alcoholic solution of the ketone gave a purple color with a few drops of ferric chloride solution.

Anal. Subs., 0.1674: CO_2, 0.4402; H_2O, 0.1025. Calcd. for $C_9H_{10}O_2$: C, 72.00; H, 6.66. Found: C, 71.71; H, 6.85.

Action of Aluminum Chloride on *o*-Tolyl Benzoate in Diphenyl Ether.—The reaction mixture was heated to 170° for thirty minutes. The ether extract from the alkali-insoluble portion was evaporated. The residue was treated with cold petroleum ether, which separated the diphenyl ether from the *p*-benzoyl diphenyl ether (34 g. of the former and 14 g. of the latter were recovered). The ketone was crystallized from ligroin and melted at 71–73°.[11]

Anal. Subs., 0.1192: CO_2, 0.3641; H_2O, 0.0575. Calcd. for $C_{19}H_{14}O_2$: C, 83.21; H, 5.11. Found: C, 83.01; H, 5.03.

The ether extract from the alkali-soluble portion was evaporated and yielded 34 g. of *p*-benzoyl-*o*-cresol, $C_6H_3(OH)(CH_3)(COC_6H_5)(1,2,4)$, and a small amount of *o*-cresol. The ketone was crystallized from benzene and melted at 173°.[14]

Anal. Subs., 0.1708: CO_2, 0.4949; H_2O, 0.0850. Calcd. for $C_{14}H_{12}O_2$: C, 79.24; H, 5.66. Found: C, 79.02; H, 5.57.

Experimental. Part II

All the fatty acid esters of methyl salicylate were made by treating the oil of wintergreen with the respective fatty acid chlorides. The reactions were carried out at about the boiling temperature of the acid chloride and over a period of about two hours, or until all the hydrogen chloride was

[11] Kipper, *Ber.*, **38**, 2491 (1905).

[12] Nencki and Stroeber, *ibid.*, **30**, 1770 (1897).

[13] Auwers, *Ann.*, **364**, 166 (1908).

[14] Heller, *Ber.*, **46**, 1502 (1913).

dispelled. The esters were purified by treatment with dilute sodium bicarbonate solution and distillation in a vacuum. They were considered pure when they showed no blue color with a few drops of ferric chloride solution. The yields averaged about 90%.

Since there were no essential variations in the experimental procedure used for the preparation of the members of these series, but one member of each series will be given in detail, *viz.*, hexylyl and hexylsalicylic acids. The melting points, boiling points and analyses of the different members will be shown in tabular review.

All of the ketones when dissolved in dilute alcohol gave a deep red coloration with a few drops of a solution of ferric chloride, while the reduced products showed a blue color. Reduction of the ketones was considered complete when the ferric chloride test showed a distinct blue color.

Methyl Hexylyl-salicylate, $C_6H_3(OH)(COOCH_3)(COC_6H_{11})(1,2,4)$.—To a suspension of 125 g. of anhydrous aluminum chloride in 200 cc. of boiling carbon disulfide was slowly added with stirring 150 g. of caproate of methylsalicylate (b. p. 204–210° at 20 mm.). After two hours of heating, the carbon disulfide was distilled off and the reaction mixture heated for a few minutes. The mass soon hardened and became impossible to stir (from 90–110°). The melt was decomposed in warm water and the resulting oily layer was washed with hot water, separated and distilled in a vacuum. After distilling off the water, two fractions were separated, one, boiling from 120–170° at 20 mm. (mostly unchanged material) and two, boiling from 210–230° at 20 mm. A small amount of residue remained in the flask. The distillate from fraction two soon solidified. A further recovery from fraction one gave a total yield of 123 g., or 82%. It was crystallized twice from petroleum ether and melted at 50–51°. It formed insoluble sodium and potassium salts. The ketone distilled from 202–205° at 20 mm.

TABLE I

METHYL ACYL-SALICYLATES

			M. p., °C.
1	Methyl propionyl-salicylate	$C_6H_3(OH)(COOCH_3)(COC_2H_5)$	64–65
2	Methyl butyryl-salicylate	$C_6H_3(OH)(COOCH_3)(COC_3H_7)$	73
3	Methyl *iso*-hexylyl-salicylate	$C_6H_3(OH)(COOCH_3)(COC_6H_{11})$	Liquid, b. p. 195–198, 15 mm.
4	Methyl hexylyl-salicylate	$C_6H_3(OH)(COOCH_3)(COC_6H_{11})$	50–51

ANALYSES

	Subs., g.	CO_2, g.	H_2O, g.	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	0.1437	0.3314	0.0797	63.46	5.77	62.89	6.26
2	.2140	.5096	.1244	64.86	6.30	64.94	6.50
3	.1500	.3692	.1013	67.20	7.20	67.12	7.55
4	.1924	.4719	.1287	67.20	7.20	66.89	7.48

Hexylyl Salicylic Acid, $C_6H_3(OH)(COOH)(COC_6H_{11})(1,2,4)$.—Methyl hexylyl-salicylate was hydrolyzed in a boiling 20% solution of potassium

hydroxide. The free acid was precipitated from the potassium salt by hydrochloric acid solution, filtered, dried and crystallized from a mixture of benzene and petroleum ether. After two crystallizations it melted at 117°.

TABLE II

ACYL SALICYLIC ACIDS

			M. p., °C.
1	Propionyl salicylic acid	$C_6H_3(OH)(COOH)(COC_3H_5)$	177–179
2	Butyryl salicylic acid	$C_6H_3(OH)(COOH)(COC_3H_7)$	152–153
3	*Iso*-hexylyl salicylic acid	$C_6H_3(OH)(COOH)(COC_5H_{11})$	132–133.5
4	Hexylyl salicylic acid	$C_6H_3(OH)(COOH)(COC_5H_{11})$	117

ANALYSES

	Subs., g.	CO_2, g.	H_2O, g.	C Calcd., %	H Calcd., %	C Found, %	H Found, %
1	0.1866	0.4217	0.0876	61.85	5.15	61.63	5.31
2	.1688	.3931	.0882	63.46	5.77	63.51	5.84
3	.1582	.3819	.0984	66.10	6.78	65.83	6.96
4	.1499	.3618	.0947	66.10	6.78	65.82	7.06

Hexyl Salicylic Acid,[15] $C_6H_3(OH)(COOH)(C_6H_{13})(1,2,4)$.—Hexylyl salicylic acid was reduced smoothly by zinc amalgam in one to one hydrochloric acid solution. One hundred grams of the ketone was reduced in five hours by 500 g. of zinc amalgam in 800 cc. of dilute acid solution. Reduction was considered complete when a few drops of the oily reaction product dissolved in alcohol showed a dark blue color upon the addition of a few drops of ferric chloride solution. The oily reduced product solidified on cooling. It was washed with hot water, dried and crystallized from ligroin. The acid melted at 83–84°. The crude product weighed 83.5 g., a yield of 88%.

TABLE III

ALKYL SALICYLIC ACIDS

			M. p., °C.
1	Propyl salicylic acid	$C_6H_3(OH)(COOH)(C_3H_7)$	99–100
2	Butyl salicylic acid	$C_6H_3(OH)(COOH)(C_4H_9)$	84–86
3	*Iso*-hexyl salicylic acid	$C_6H_3(OH)(COOH)(C_4H_{13})$	104–105
4	Hexyl salicylic acid	$C_6H_3(OH)(COOH)(C_4H_{13})$	83–84

ANALYSES

	Subs., g.	CO_2, g.	H_2O, g.	C Calcd., %	H Calcd., %	C Found, %	H Found, %
1	0.1441	0.3511	0.0884	66.66	6.66	66.46	6.86
2	.1341	.3326	.0896	68.04	7.21	67.64	7.47
3	.1486	.3810	.1065	70.27	8.10	69.92	8.01
4	. .1400	.3608	.1032	70.27	8.10	70.28	8.24

I wish to express my thanks to Dr. George W. Raiziss of the Dermatological Research Laboratories, Philadelphia, for his part in making the biological tests.

[15] Swiss Patent 127,649 (1927).

Summary

The Fries reaction is discussed and an explanation of the mechanism is given based upon some experimental evidence. The reaction is shown not to be intramolecular. It has been applied to the production of some acyl salicylic esters and acids, many of which are new substances.

The alkyl salicylic acids are produced from the acyl salicylic acids by the Clemmensen reduction method. Although these acids show a higher toxicity than the parent substance, salicylic acid, they also possess by virtue of the alkyl group higher phenol coefficients.

SWARTHMORE, PENNA.

[CONTRIBUTION NO. 54 FROM THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY, RESEARCH LABORATORY OF ORGANIC CHEMISTRY]

THE OXIDATION OF META-XYLORCINOL[1]

BY TENNEY L. DAVIS AND JOSEPH FREDERIC WALKER

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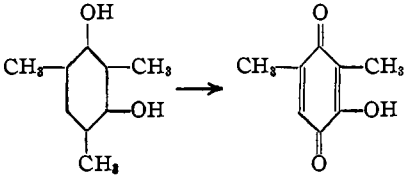
When tribromoresorcinol is oxidized with aqueous chromic acid[2] it does not yield a *m*-quinone, but loses a bromine atom from the position para to one of the hydroxyl groups and yields oxidized and brominated substances which are derivatives of diphenoquinone. We have wished to determine whether a methyl group in the para position would be similarly lost, and have accordingly studied the oxidation of *m*-xylorcinol in which both positions para to hydroxyl are occupied by methyl groups. A similar substance has been studied by Knecht,[3] who found that the action of hot ferric chloride solution on mesorcinol removed a methyl group from the para position and produced a derivative of benzoquinone, thus



It is apparent from Knecht's result that one of the methyl groups is more easily removed by oxidation than is the hydrogen of one of the hydroxyl groups. When tribromoresorcinol is oxidized, the bromine in one of the para positions is similarly removed and one of the hydroxyl groups remains unaffected. *m*-Xylorcinol differs from mesorcinol in having a hydrogen instead of a methyl in the position between the two hydroxyl groups, and it is to be expected that this particular hydrogen atom would be oxi-

[1] A summary of the Doctor's Dissertation of Joseph Frederic Walker, Massachusetts Institute of Technology, June, 1929.

[2] Davis and Hill, THIS JOURNAL, **51**, 493 (1929).

[3] Knecht, *Ann.*, **215**, 96 (1882).