[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

ORGANIC REACTIONS WITH BORON FLUORIDE. XVII.* REARRANGEMENT OF ALKYL SALICYLATES AND THE REACTION OF ALCOHOLS WITH SALICYLIC ACID

W. J. CROXALL, F. J. SOWA, AND J. A. NIEUWLAND

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The rearrangement of esters of the phenyl acetate type to hydroxyacetophenone has been frequently studied. Although, aluminum chloride[1] is most commonly used for this purpose, boron fluoride[2,3] has likewise proved to be an efficient rearranging agent.

The purpose of this investigation was to study the rearrangement of esters of salicylic acid both in the presence and absence of foreign bodies such as benzene and diphenyl oxide. A second part of this work was devoted to the reaction of alcohols with salicylic acid. Both parts were accomplished in the presence of boron fluoride.

EXPERIMENTAL

Preparation of alkyl salicylates.—Three moles of salicylic acid and six moles of the various alcohols were weighed in a three-necked flask fitted with a mechanical stirrer, dropping funnel, and reflux condenser. While the acid-alcohol solution was stirred, 100 cc. of concentrated sulfuric acid was slowly added and the contents were refluxed for two and one half hours. The ester was purified in the usual manner. The physical properties of the esters are listed in Table I. The yields were about 60% of the theoretical in all cases.

Rearrangement of alkyl salicylates.—The procedure for the rearrangement of *n*-propyl, isopropyl, *n*-butyl and isobutyl salicylates was quite uniform and will therefore be described by a general example with only a few comments in particular cases.

One mole (68 g.) of boron fluoride was passed into one mole of the alkyl salicylate contained in a 500 cc. flask connected to a reflux condenser. The solution became warm during the addition of boron fluoride. The resulting product was then heated to 130–140° on an oil bath for two hours; during this time some boron fluoride was evolved. When cooled the solution was treated with a sodium carbonate solution, and the dissolved acids were reprecipitated by the addition of hydrochloric acid. The oily mixture of acids that separated was extracted with carbon tetrachloride. The extract was then placed in a two-liter three-necked flask equipped with a

* For previous paper see, O'CONNER AND SOWA, *J. Am. Chem. Soc.*, **59**, (1937).

[1] FRIES AND FINCK, *Ber.*, **41**, 4371 (1908).

[2] MEERWEIN, *ibid.*, 411 (1933).

[3] SMITH AND HALLER, *J. Am. Chem. Soc.*, **56**, 237 (1934).

mechanical stirrer and condenser. The carbon tetrachloride was practically all removed by distillation in order to dry the acids. Two moles of methyl alcohol and 20 cc. of concentrated sulfuric acid were added to the acids and refluxed for two hours

TABLE I

PHYSICAL PROPERTIES OF COMPOUNDS PREPARED

NAME OF COMPOUND	B.P., °C. (UNCORR.)	n_D^{25}	SP. GR. (25°)
Isopropyl salicylate	118/17 mm.	1.5090	1.0781
n-Propyl salicylate	236–40/745 mm.	1.5100	1.005
n-Butyl salicylate	146/20 mm.	1.5095	1.0681
Isobutyl salicylate	135/17 mm.	1.5075	1.0681
Methyl salicylate	79/6 mm.	1.5350	1.1750
Methyl 2-hydroxy-3-isopropylbenzoate	110/6 mm.	1.5125	1.0799
Methyl 2-hydroxy-5-isopropylbenzoate	130/6 mm.	1.5131	1.0625
Methyl 2-hydroxy-3-*sec.*-butylbenzoate	116/5 mm.	1.5200	1.0765
Methyl 2-hydroxy-5-*sec.*-butylbenzoate	138/5 mm.	1.5107	1.0113
Methyl 2-hydroxy-5-*tert.*-butylbenzoate	125/7 mm.	1.5140	1.0399
Salicylic acid	153 (m. p.)		
2-Hydroxy-3-isopropylbenzoic acid[4]	70–72 (m. p.)		
2-Hydroxy-5-isopropylbenzoic acid[5]	120 (m. p.)		
2-Hydroxy-5-*tert.*-butylbenzoic acid[7]	150 (m. p.)		
2-Isopropylphenol[12]	212–14	1.5261	0.9930
4-Isopropylphenol[12]	225–27	1.5227	0.9825
2,4-Diisopropylphenol[12]	248	1.5118	0.9497
2-*sec.*-Butylphenol[6]	228–31	1.5200	0.9747
4-*sec.*-Butylphenol[6]	239–42	1.5150	0.9659
2,4-di-*sec.*-Butylphenol	265–67	1.5072	0.9341
4-*tert.*-Butylphenol[11]	232–35, 98 (m. p.)		
Isopropylbenzene	152	1.4883	0.8580
tert.-Butylbenzene[10]	167	1.4905	0.8623
2-Isopropyldiphenyl oxide[8]	262	1.5677	1.0521
4-Isopropyldiphenyl oxide[8]	287	1.5599	1.0398
2-*sec.*-Butyldiphenyl oxide	285–88	1.5535	1.0095
4-*sec.*-Butyldiphenyl oxide	302	1.5502	1.0013

to form the methyl esters. The product was then washed successively with water and a sodium carbonate solution to remove the sulfuric and unesterified acids.

The esters were fractionated under reduced pressure through a column† one meter

[4] FILETI, *Gazz. chim. ital.*, **16**, 113 (1886).

[5] PATERNO AND MAZZARA, *ibid.*, **8**, 389 (1878).

[6] READ, HEWITT, AND PIKE, *J. Am. Chem. Soc.*, **54**, 1194 (1932).

[7] DOBRUZYCKI, *J. prakt. Chem.*, [2], **36**, 389 (1887).

[8] SMITH, *J. Am. Chem. Soc.*, **56**, 718 (1934).

[9] SARTORETTO AND SOWA, *ibid.*, **59**, 603 (1937).

[10] SENKOWSKI, *Ber.*, **23**, 2413 (1890).

[11] SMITH, *J. Am. Chem. Soc.*, **55**, 3718 (1933).

[12] SOWA, HINTON, AND NIEUWLAND, *ibid.*, **55**, 3402 (1933).

† The authors wish to thank C. A. Young for designing and building this column.

long, packed with single-turn glass helices, insulated with asbestos, and equipped with a variable resistance heating coil wound about the inside jacket. A total reflux, partial take-off head equipped with a dephlegmator was used. In all cases distillation curves were plotted to show the composition of the mixture.

The extract with sodium carbonate solution was acidified with hydrochloric acid to give the unesterified acids. This product was proved, by decarboxylation, to be a mixture of acids. The order of decreasing rate of esterification seemed to be salicylic acid, 2-hydroxy-3-alkylbenzoic acid, 2-hydroxy-5-alkylbenzoic acid, 2-hydroxy-3,5-dialkylbenzoic acid. All the salicylic acid was converted to the methyl ester and only a very small quantity of methyl 2-hydroxy-3,5-dialkylbenzoate was formed.

Rearrangement of isopropyl salicylate.—Following the procedure outlined above one mole of isopropyl salicylate and 38.5 g. of boron fluoride gave, after rearrangement and esterification with methyl alcohol, methyl salicylate (20.0 g.); methyl 2-hydroxy-3-isopropylbenzoate (39 g.) and methyl 2-hydroxy-5-isopropylbenzoate (16 g.). The higher-boiling residue (18 g.) was not fractionated.

The unesterified acids gave the following phenols; 2-isopropylphenol (5 g.), 4-isopropylphenol (16 g.), 2,4-diisopropylphenol (19 g.), and 4 g. of residue.

The methyl esters were saponified by alcoholic caustic soda and the following acids were obtained: salicylic acid (m. p. 153°), 2-hydroxy-3-isopropylbenzoic acid[4] (m. p. 70–71°), and 2-hydroxy-5-isopropylbenzoic acid[5] (m. p. 120°). These acids gave the following phenols upon decarboxylation: phenol, 2-isopropylphenol, and 4-isopropylphenol, respectively.

Rearrangement of n-*propyl salicylate.*—By rearranging one mole of *n*-propyl salicylate with 58 g. of boron fluoride the following methyl esters were obtained from the rearrangement products after esterification with methyl alcohol: methyl salicylate (26 g.), methyl 2-hydroxy-3-isopropylbenzoate (60 g.), and methyl 2-hydroxy-5-isopropylbenzoate. An unidentified residue (13 g.) remained. This was probably methyl 2-hydroxy-3,5-diisopropylbenzoate.

The unesterified acids yielded upon decarboxylation 2-isopropylphenol (2 g.), 4-isopropylphenol (5 g.), 2,4-diisopropylphenol (7 g.) and 3 g. of residue.

The boiling points of all the methyl esters obtained from the *n*-propyl were identical with those from the rearrangement of isopropylsalicylate, and the acids obtained upon saponification of the corresponding methyl esters had the same melting points as listed above under the rearrangements of isopropyl salicylate. The phenols obtained upon decarboxylation of the acids also corresponded with the isopropylphenols.

Rearrangement of n-*butyl salicylate.*—One mole of *n*-butyl salicylate and one mole of boron fluoride yielded the following methyl esters after esterification of the rearrangement product with methyl alcohol: methyl salicylate (21 g.), methyl 2-hydroxy-3-*sec.*-butyl salicylate (76 g.), and methyl 2-hydroxy-5-*sec.*-butyl salicylate (13 g.).

By decarboxylation of the unesterified acids the phenols, 2-*sec.*-butylphenol (9 g.), 4-*sec.*-butylphenol (5 g.), and 2,4-di-*sec.*-butylphenol (30 g.) were obtained.

The methyl esters referred to were saponified and decarboxylated. The products corresponded with phenols, 2-*sec.*-butylphenol[6] and 4-*sec.*-butylphenol[6].

Rearrangement of isobutyl salicylate.—One mole of isobutyl salicylate and one mole of boron fluoride reacted violently. In this case carbon tetrachloride was used as a solvent and the reflux period was reduced to one hour. Methyl salicylate (22 g.) and methyl 2-hydroxy-5-*tert.*-butylsalicylate (87 g.) were separated after esterification of the rearrangement product with methyl alcohol. After decarboxylation of the unesterified acids only 4-*tert.*-butylphenol (25 g.) was found.

The methyl 2-hydroxy-5-*tert.*-butylbenzoate was saponified to 2-hydroxy-5-*tert.*-butylbenzoic acid[7] (m. p. 150°). This acid yielded 4-*tert.*-butylphenol upon decarboxylation.

Migration of alkyl groups to foreign bodies.—One mole of isopropyl salicylate, one mole of boron fluoride and 550 g. of benzene were refluxed for one and one-half hours. The products were then washed with water and a solution of sodium carbonate to remove acids.

The benzene layer upon fractionation yielded unchanged benzene (460 g.), isopropylbenzene (74 g.), and a small quantity of unchanged ester.

The solution in sodium carbonate upon acidification gave acids (81 g.), the greater part of which was salicylic except for about 5 g. of 3-isopropyl-2-hydroxybenzoic.

n-Propyl and *n*-butyl salicylates required a higher temperature to rearrange, and the operation was therefore carried out in diphenyl oxide solution instead of benzene. Both the propyl and butyl groups transferred to a great extent to the diphenyl oxide nucleus and are found as isopropyl and *sec.*-butyl radicals substituted in the 2 and 4 positions in diphenyl ether. The isopropyl diphenyl ether was identical with that previously reported[8]. The butyl diphenyl ethers were cleaved with sodium in liquid ammonia[9] to *sec.*-butylphenols. Salicylic acid and a small quantity of alkylsalicylic acids were also formed.

One mole of isobutyl salicylate and one mole of boron fluoride refluxed for four hours and treated as above gave 165 g. of benzene, 27 g. of *tert.*-butylbenzene[10] and 110 g. of unchanged ester.

From the sodium carbonate solution there was 74 g. of acid, which proved to be a mixture of 69 g. of salicylic acid, and 5 g. of 2-hydroxy-5-*tert.*-butylsalicylic acid, which upon decarboxylation gave 4-*tert.*-butyphenol.

Reaction of alcohols with salicylic acid.—The procedure was quite uniform and only one general description will be given with a few comments in each case.

One mole of salicylic acid (138 g.) and two moles of an alcohol were weighed in a two-liter, three-necked flask equipped with a stirrer and refluxed condenser. Various quantities of boron fluoride were added (see below) and refluxed about two hours. Two layers usually appeared.

The contents were then washed with a solution of sodium carbonate, extracted with ether, and dried over anhydrous potassium carbonate and fractionated.

The sodium carbonate wash solution was acidified, the acids were dried by the distillation from a carbon tetrachloride solution and then converted to the corresponding methyl esters as described under the rearrangement of alkyl salicylates.

Isopropyl alcohol.—Employing the procedure mentioned above, with isopropyl alcohol and 38 g. of boron fluoride, a yield of 76 g. of isopropyl salicylate was obtained. Practically no nuclear substitution took place, since the acid portion gave only methyl salicylate after treatment with methyl alcohol and sulfuric acid.

Upon repetition of the experiment with isopropyl alcohol, with the addition in this case of 80 g. of boron fluoride instead of 38 g., a vigorous reaction took place and two layers separated. The contents were refluxed for one-half hour.

After the formation of the methyl esters of the products of the reaction the following compounds were isolated: methyl salicylate (27 g.), methyl 2-hydroxy-3-isopropyl benzoate (92 g.), and methyl 2-hydroxy-5-isopropylbenzoate (43 g.).

The unesterified acids gave the following phenols upon decarboxylation: 2-isopropylphenol (2 g.), 4-isopropylphenol (12 g.), and 14 g. of 2,4-diisopropylphenol.

sec.-*Butyl alcohol.*—Treatment of salicylic acid with *sec.*-butyl alcohol according

to the general procedure with 34 g. of boron fluoride and esterification of the resulting products with methyl alcohol the following methyl esters were isolated: methyl salicylate (102 g.), methyl 2-hydroxy-3-*sec.*-butyl salicylate (14 g.), and a quantity of 2-hydroxy-5-*sec.*-butyl salicylate. A small quantity of 2-*sec.*-butylphenol and 4-*sec.*-butylphenol was obtained by the decomposition of the unesterified acids. No *sec.*-butylsalicylate was isolated.

Isobutyl alcohol.—Isobutyl alcohol and salicylic acid with 34 g. of boron fluoride gave 142 g. of isobutyl salicylate, 20 g. of salicylic acid and 22 g. of 2-hydroxy-5-*tert.*-butyl benzoic acid. This upon decarboxylation gave 4-tert.-butylphenol[11].

tert.-*Butyl alcohol.*—By the treatment of *tert.*-butyl alcohol as above with 34 g. of boron fluoride, 33 g. of salicylic acid and 50 g. of 2-hydroxy-5-*tert.*-butyl benzoic acid was formed. A higher-boiling fraction of 4 g. was not identified.

DISCUSSION

Both *n*-propyl and isopropyl salicylates yielded identical rearrangement products, namely, 2-hydroxy-3-isopropylbenzoic, 2-hydroxy-5-isopropylbenzoic, and 2-hydroxy-3,5-diïsopropylbenzoic acids. In the *n*-butyl salicylate rearrangement the *n*-butyl group isomerized to a *sec.*-butyl radical and was found as a substitution product in the aromatic nucleus, as in 2-hydroxy-3-*sec.*-butylbenzoic, 2-hydroxy-5-*sec.*-butylbenzoic, and 2-hydroxy-3,5-di-*sec.*-butylbenzoic acids. The isobutyl radical in isobutyl salicylate was transformed to a *tert.*-butyl group and isolated as a substitution product in the aromatic nucleus. Salicylic acid was also formed in each arrangement.

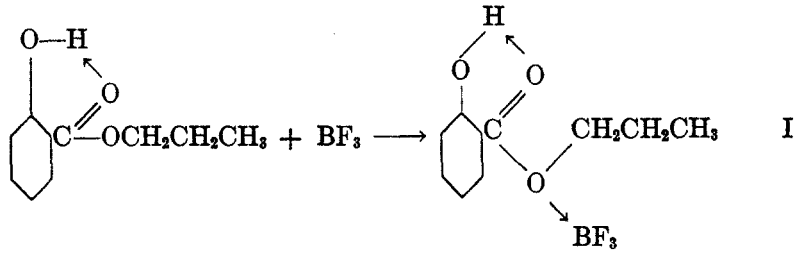
Substitution took place ortho and para to the hydroxyl group and meta to the carboxyl as would be expected. The ortho substitution products predominated when isopropyl and *sec.*-butyl groups were introduced, while the *tert.*-butyl group entered the para position almost exclusively.

All products isolated were phenolic, thus showing the absence of any condensation on the hydroxyl group as was characteristic in olefin-phenol condensations[12]. The propylene salicylic acid condensation[13] takes place on the carboxyl group with subsequent rearrangements into the nucleus and with no intermediate etherification. The rearrangement of alkyl salicylates should be a convenient method for obtaining pure alklyl phenols. The deactivation of the phenolic group affords additional chemical evidence of the existence of a chelated ring in salicylic acid.

Since the *n*-propyl, *n*-butyl and isobutyl esters rearranged to isopropyl, *sec.*-butyl, and *tert.*-butyl substituted acids respectively, the migration might be considered as taking place through the intermediate olefin stage with subsequent condensation of the activated olefin into an activated position in the aromatic nucleus. The products seemed to indicate

[13] CROXALL, SOWA, AND NIEUWLAND, *ibid.*, **56**, 2054 (1934).

that the rearrangement is inter- as well as intra-molecular. The reactions may be illustrated as follows:



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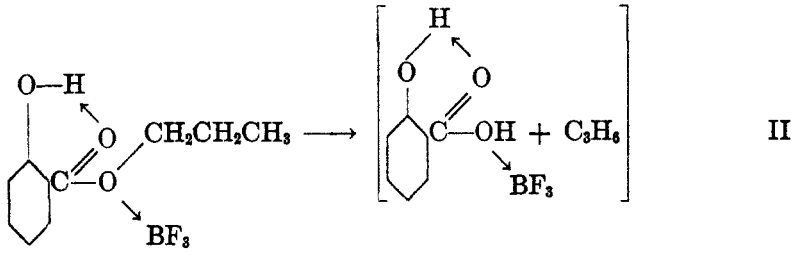

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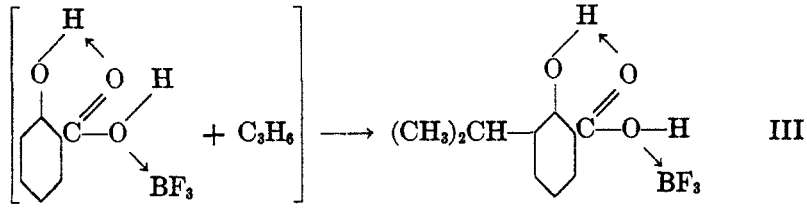

III

Further condensation of C_3H_6 formed in equation II can take place by addition at the five position in the product of equation III. The product would then be a dialkylsalicylic acid. The olefin stage was further verified by rearranging the esters in the presence of foreign bodies such as benzene and diphenyl oxide. In the latter case most of the alkyl migration took place to the foreign body, where the substituent was present as the isomerized alkyl group.

Salicylic acid reacted with isopropyl, isobutyl and *tert.*-butyl alcohols to give the corresponding isopropyl, isobutyl and *tert.*-butyl salicylates.

Although smaller quantities of boron fluoride led to the formation of esters from alcohols and salicylic acid, greater quantities did not give esters, but resulted in nuclear-substituted salicylic acids The products were the same as those isolated by the rearrangement of the corresponding esters. The *n*-butyl and isobutyl groups from the alcohol or ester were found as a substituted isomerized radical. It seemed that although in

the alkylation of phenols, the reaction proceeded through the etherification stage, the reaction took place in the case of hydroxyaromatic acids, through the ester stage. Direct nuclear condensation of the olefin through the dehydration of the alcohol was not eliminated as a possible course in considering the formation of nuclear-substituted products. The esters of benzoic acid did not rearrange to give nuclear-substituted acids. This shows that the hydroxyl group exerted an activating influence upon the benzene nucleus.

The substituted salicylic acids were separated by preparing the methyl esters and fractionating these. The fractionation curves showed no other compounds besides those reported.

SUMMARY

The rearrangement of the isopropyl, *n*-propyl, isobutyl and *n*-butyl esters of salicylic acid has been studied with boron fluoride.

Isopropyl and *n*-propyl salicylate gave the same rearrangement products. Isobutyl salicylate rearranged to *tert.*-butyl salicylic acid derivatives.

The rearrangements have also been carried out in the presence of foreign bodies such as benzene and diphenyl oxide.

Additional evidence of chelation in salicylic acid was presented. Substitution took place ortho and para to the hydroxyl, and meta to the carboxyl group as expected.

The alcohols, isopropyl, isobutyl, *sec.*-butyl and *tert.*-butyl, reacted with salicylic acid to form the corresponding esters, while with *sec.*-butyl and *tert.*-butyl alcohol nuclear substitution resulted. Use of an excess of boron fluoride caused the formation of alkyl-substituted salicylic acids which corresponded to the compounds formed by the rearrangement of the esters.

The course of the reactions has been discussed.