most of the flavonoid material, were finally evaporated *in vacuo* to 25 ml. giving a solution approximately ten times as concentrated as the standard solution.[2] From this solution crude lutonarin was isolated by banding on Whatman #3 filter paper with BAW (see earlier) as the developing solvent and, after elution, was purified from traces of the other flavonoids by rebanding with 30% acetic acid, once for hydrolysis work, twice for spectral work. The color tests, chromatographic data and ultraviolet absorption spectral data obtained from the purified eluate are given in Table I.

Isolation and purification of lutonaretin and lutexin. Lutonarin was hydrolyzed by 1*N* hydrochloric acid as previously described,[2] the reaction being complete in 20–30 hr. At that time the ratio of lutonaretin (the aglycon which formed first) to lutexin was approximately 2:1, but refluxing for 4 days gave a 1:1 ratio. After the methanol had been volatilized, the reaction mixture was neutralized to *p*H 5 with solid sodium acetate. The two aglycons were separated by banding with 15% acetic acid and were eluted with 50% methanol. Each was purified by rebanding with BAW. Chromatographic and spectral data obtained on solutions of these compounds are given in Table I, and the results are compared with results on luteolin obtained simultaneously or recorded in the literature. Co-chromatography with luteolin showed separation of spots in all four solvents.

Interconversion of the aglycons. Solutions of both purified aglycons were subjected to the usual hydrolytic conditions[2] for approximately one day. Paper chromatographic studies of the resulting solutions with four solvents (Table I) showed that each aglycon had been converted in part into the other; the ratio of lutonaretin to lutexin was 1:1 from lutonaretin, 1:2 from lutexin.

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[CONTRIBUTION FROM ORGANIC CHEMICALS DIVISION, MONSANTO CHEMICAL CO.]

Alcoholysis of Alkyl Benzyl Esters of Phthalic Acid[1]

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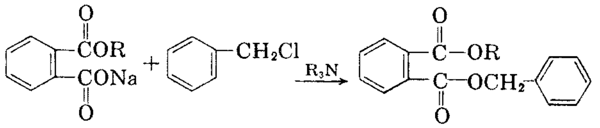
Alkyl benzyl phthalate esters of high purity are not readily prepared by simple conventional methods, especially when the alkyl group contains eight or more carbon atoms. However, a smooth procedure for the preparation of these unsymmetrical esters has been found, involving alcoholysis of the more easily prepared lower alkyl benzyl phthalates with higher molecular weight alcohols. In this alcoholysis reaction the benzyl group exhibits a surprising immobility toward displacement, even if the displacing alcohol has a boiling point higher than that of benzyl alcohol. A mechanistic theory is advanced to explain this immobility.

Methods of preparation of esters date back to the early days of organic chemistry, and one would anticipate little novelty in the reactions of alcohols and acids or in esterification techniques involving alcoholysis or acidolysis. Yet, in our study of the alcoholysis of alkyl benzyl *o*-phthalates, we have observed a behavior anomalous to classical description in that alcoholysis of unsymmetrical diesters does not unequivocally lead to displacement of the lower boiling alcohol by a higher boiling alcohol.

For some time we have been interested in the synthesis of unsymmetrical esters of phthalic acid, particularly those containing a benzyl moiety. These materials have utility in the plasticization of poly(vinyl chloride); this being particularly true of the higher alkyl benzyl phthalates. Preparation of some of these esters by conventional means can be extremely cumbersome. An obvious method of preparation for such esters would involve reaction between the sodium salt of the selected alkyl acid phthalate with benzyl chloride, in the presence of an amine catalyst.[2]



This method is not entirely feasible, however, with the higher alkyl benzyl phthalates, due to the gross insolubility of the sodium alkyl phthalate in many of the common organic solvents. Nonetheless, it is possible to obtain a small (30–40%) yield of the desired unsymmetrical ester if one utilizes the potassium salt of the acid ester and a several-fold excess of the alcohol used in preparation of the alkyl acid phthalate. Preparation of the lower alkyl benzyl phthalates does not result in this low yield, however. Thus, methyl, ethyl, or butyl benzyl phthalates can be prepared smoothly and in excellent yield from the sodium or potassium salt of the acid ester and benzyl chloride. The preparation of the unsymmetrical esters by use of benzyl alcohol and the aliphatic alcohol is also contraindicated, since, assuming equal rates of reaction of the two alcohols, one obtains a statistical mixture of the three possible esters (25% dialkyl phthalate, 50% alkyl benzyl phthalate, and 25% dibenzyl phthalate). Separation of the pure unsymmetrical ester from the other two components is often difficult.

It occurred to us that it should be possible to take advantage of the relative ease of preparation of the lower alkyl benzyl phthalates and utilize these materials as a starting point in the synthesis of the higher alkyl benzyl phthalates. It remained, therefore, only to displace the lower alkyl group, which should be easily carried out by the base-catalyzed alcoholysis with the desired alcohol. In the case of

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(1) Presented in part before the Division of Organic Chemistry at the 134th Meeting of the American Chemical Society, Chicago, Ill., September 1958.

(2) Reid, U. S. Patent 1,554,032 (September 15, 1925).

TABLE I

ALCOHOLYSIS USING ALCOHOLS BOILING LOWER THAN BENZYL ALCOHOL

Exchange Alcohol	Catalyst % Conc. on Ester	Resulting Ester d^{25}_{25}	Resulting Ester Theory yield	% of Theory ROH Removed[c]	ROH Removed d^{25}_{25}	ROH Removed Boiling range
2-Ethylhexanol[a]	NaOH 1.6	1.0066	90%	89	0.8104	115–119
Isooctanol[a]	NaOH 1.2	1.0056	88%	90	0.8111	115–118
p-Methylcyclohexanol[a]	$NaOCH_3$ 0.7	1.1116	85%	94	0.8108	115–117
2(2-Ethylhexoxy) ethanol[a]	$NaOCH_3$ 0.65	1.0630	90%	92	0.8101	112–117
2-Ethylhexanol[b]	$NaOCH_3$ 0.60	1.0055	92%	95	0.776	77–81
2-Octanol[b]	$NaOCH_3$ 0.65	1.0365	93%	94	0.778	77–81

[a] The starting ester in these experiments was benzyl *n*-butyl phthalate. [b] The starting ester in these experiments was benzyl ethyl phthalate. [c] Reaction time in all cases was 3–4 hr., reaction conditions at end of alcoholysis were 160°/25 mm.

TABLE II

ALCOHOLYSIS WITH ALCOHOLS BOILING HIGHER THAN BENZYL ALCOHOL

Exchange Alcohol[c]	Catalyst % Conc. on Ester	Resulting Ester d^{25}_{25}	Resulting Ester Theory yield	% of Theory ROH Removed[d]	ROH Removed d^{25}_{25}	ROH Removed Boiling range
Isodecanol (oxo),[a] b.p. 216–220°	$NaOCH_3$ 0.7	1.0402	93.2%	93	0.8124	115–118
Tridecyl alcohol[a] (oxo), b.p. 262°	NaOH 1.2	1.0238	92%	93	0.8103	115–118
n-Decanol,[a] b.p. 233°	$NaOCH_3$ 0.7	1.0306	94%	93.5	0.8103	115–118
Br. Octadecanol,[a,e] b.p. 200°/15 mm.	$NaOCH_3$ 0.65	0.9940	92%	94	0.8110	115–118
Oleyl alcohol,[b] b.p. 210°/15 mm.	$NaOCH_3$ 0.65	0.9839	85%	91	0.8105	115–111
Isodecanol (oxo)[b]	$NaOCH_3$ 0.8	1.0410	91%	95	0.8100	115–118
Tridecyl alcohol[b] (oxo)	$NaOCH_3$ 0.8	1.0241	89%	93	0.8106	115–188

[a] Concentration of exchange alcohol in these experiments was 1.2 mol./mol. of starting ester. [b] Concentration of exchange alcohol in these experiments was 1.5 mol./mol. of starting ester. [c] Starting ester in all cases was benzyl *n*-butyl phthalate. [d] Reaction time in all cases was 3–4 hr., conditions at end of alcoholysis were 160°/25 mm. Hg in all cases. [e] 2,2,4,9,11,11-Hexamethyl-1-dodecanol.

benzyl *n*-butyl phthalate it was assumed that the butyl group would be replaced preferentially, if the displacing alcohol had a boiling point suitably higher than that of the displaced alcohol, but lower than that of benzyl alcohol, to form little or no symmetrical ester. Consequently, benzyl *n*-butyl phthalate was treated with various commercially available alcohols from C_8 through C_{10} in the presence of a variety of alkaline catalysts. In all cases, the desired alkyl benzyl phthalates were produced smoothly and in good yields (87–95%). The results of these alcoholysis reactions are shown in Table I. During the course of this work certain alcohols with boiling ranges near or higher than the boiling point of benzyl alcohol were utilized. In none of these experiments was there any evidence of even a small portion of the benzyl alcohol having been displaced by alcoholysis. It appeared at this point that the benzyl group exhibited a definite immobility in the reaction. An attempt was made, therefore, to replace both the lower alkyl and benzyl groups in the benzyl alkyl phthalates, by using an exchange alcohol with a boiling point higher than that of benzyl alcohol (b.p. 205°). Five such alcohols were readily available, namely isodecanol (oxo), b.p. 216°, tridecanol (oxo), b.p. 264°, octadecenol (oleyl), b.p. 210°/15 mm., *n*-decanol, b.p. 233°, and a branched octadecanol, b.p. 200°/15 mm. In none of these cases was benzyl alcohol recovered, either with the displaced alcohol or from the reaction mass, as shown in Table II. This immobility of the benzyl group toward displacement by the displacing alcohol persisted despite increased catalyst concentration, higher reaction temperature, or an increase in the molar concentration of the displacing alcohol. The absence of benzyl alcohol in the displaced alcohols was determined by means of the ultraviolet spectra of these materials.

EXPERIMENTAL

The reaction vessel consisted of a 1-l., 3 necked flask fitted with a stirrer, 6-in. Vigreux column, with variable take-off still head, thermometer well, and a Glas-Col mantle for heating. In experiments in which the two alcohols had less than 20° difference in boiling points, a 500 mm. long, 20-mm. diameter glass-helices packed column was used to remove the displaced alcohol. In all cases the alcoholysis of the lower alkyl benzyl phthalates followed a standard reaction scheme, with only minor variations, as dictated by the boiling point and molecular weight of the displacing alcohol. A typical reaction sequence will be described here, involving the alcoholysis of benzyl *n*-butyl phthalate with isodecanol (oxo).

To the reaction vessel, as described above, were charged 312.4 g. (1 mol.) of benzyl *n*-butyl phthalate,[3] 165.9 g. (1.05 mol.) isodecanol, and 2.5 g. (.046 mol.) of sodium methylate. Heat was then applied to the reaction vessel at such a rate that the temperature of the reaction mass was raised to 135–145°, over a period of 30 min. When this temperature was attained, the system was slowly evacuated by means of a water aspirator, until the displaced alcohol began to distill forward at a steady rate (usually 100–200 mm. Hg). As the displaced alcohol removal began to slow, pressure was further reduced so that forward distillation began again. The vapor temperature was controlled by regulation of the reflux ratio, if it became apparent that some exchange alcohol was distilling with the lower molecular weight displaced alcohol. The pressure was gradually reduced, so that the final conditions of 160°/25 mm. were usually obtained about 3 hr. following initial removal of the displaced alcohol. When removal of the displaced alcohol was completed, the reaction mass was cooled under vacuum to room temperature. The system was vented to the atmosphere and 250 cc. water was added. The displaced alcohol was analyzed by examination of its physical properties and ultraviolet spectrum, and found to be pure *n*-butyl alcohol.

The water-oil mixture was heated to 70–75°, with agitation and stirred at this temperature for 15 min. The heterogeneous mixture was allowed to settle into two phases, and the heavier, aqueous, layer was removed from the oil layer. Another 250 cc. portion of water was then added to the oil, and washing as described above was carried out. The aqueous layer from the first wash was acidified to *p*H 2 with 75% sulfuric acid to neutralize the catalyst and recover any acid constituents present in the wash as sodium salt. By this neutralization there was recovered 3.3 g. of *o*-phthalic acid (m.p. 190–193° d., neut. equiv. 82), indicating a small amount of ester hydrolysis had taken place during the removal of the alkaline catalyst.

Following the two washes described above, the oil layer was heated to 135–140° under 75 mm. Hg vacuum, and live steam passed into the mass *via* a subsurface entrance tube. This operation was continued, until the volume of distillate collected equaled the volume of the crude reaction mass. The (upper) organic layer from the steam distillate weighed 11.1 g. after drying over Drierite. Analysis of the ultraviolet spectrum of this material showed it to contain 18.4% benzyl alcohol and 81.6% decyl alcohol. The quantity of benzyl alcohol obtained here corresponds to the quantity of phthalic acid recovered from the acidification of the first water wash. The source of benzyl alcohol here, therefore, is due to hydrolysis rather than alcoholysis. The alcohol-free ester was then further washed first with alkali, then with water, and dried. By this procedure, there was obtained 368.1 g. of neutral ester, specific gravity at 25/25° 1.037, refractive index 1.5135.

Identification of the product of the alcoholysis of benzyl *n*-butyl phthalate was carried out by (1) determination of boiling range to ascertain whether a mixture of esters was present or if a relatively pure benzyl isodecyl phthalate had been prepared and (2) hydrolysis of the finished ester with subsequent qualitative and quantitative identification of the alcohols thus separated.

Distillation was carried out under 0.1-mm. Hg with a short punched column to prevent entrainment. Under these conditions 95% of the material charged boiled between 198° and 203° at 0.1 mm. From these data we conclude that the neutral ester obtained by alcoholysis is not a mixture of a lower with a higher boiling ester.

Hydrolysis of benzyl isodecyl phthalate involved heating the ester at 140–150° at atmospheric pressure with a 200% excess of 50% (aq.) sodium hydroxide. Steam was passed through this mixture until no more alcohol was distilled with the steam distillate, this operation required 12 hr. under these conditions. The steam distillate was saturated with sodium carbonate and the supernatant organic layer separated and dried over Drierite. The remainder of the steam distillate was saturated with sodium carbonate and extracted with ether to remove any alcohol in solution. The ether was evaporated and the residual alcohol added to that separated from the steam distillate. The aqueous solution of the sodium salt of phthalic acid remaining after the hydrolysis was acidified with sulfuric acid to *p*H 2 and the precipitated phthalic acid filtered and dried to constant weight.

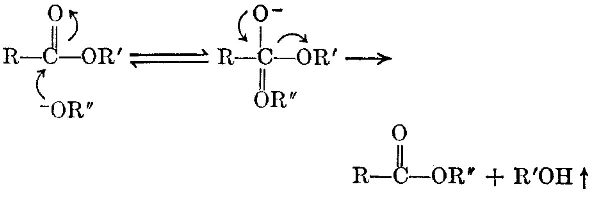
The alcohols were analyzed by ultraviolet spectrophotometry and the spectra compared to synthetic mixtures of benzyl and isodecyl alcohol. The characteristic absorption of benzyl alcohol at 285 mμ was used in this analysis. From these data, the ester before hydrolysis could be shown to contain 51 mol. % isodecyl alcohol and 49 mol. % benzyl alcohol, indicating a relatively pure unsymmetrical ester was formed by the alcoholysis.

In the majority of the experiments, lower alkyl benzyl phthalates were used as the starting esters. It remained to be shown, however, that the immobility of the benzyl group persisted despite an increase in the size of the alkyl chain in the unsymmetrical ester. This was shown to be the case by alcoholysis of benzyl 2-octyl phthalate and benzyl isodecyl phthalate, which were subjected to alcoholysis with tridecyl alcohol (Table III). The displaced alcohol was again identified by its physical properties and found to be free of benzyl alcohol. In the case of alcoholysis of benzyl isodecyl phthalate with tridecyl alcohol, both the alcohol to be displaced and the displacing alcohol had boiling points higher than that of benzyl alcohol. Even under these conditions the alcohol displaced showed no benzyl alcohol to be present, indicating the preferential removal of an aliphatic alcohol although its boiling point is higher than benzyl alcohol.

In experiments in which an attempt was made to remove benzyl alcohol, the charge of the exchange alcohol was increased to 1.5 moles per mole of neutral ester. With this increased charge of alcohol, benzyl n-butyl phthalate was treated with three such alcohols, namely isodecyl (oxo) alcohol, tridecyl (oxo) alcohol, and oleyl alcohol. As shown in Table II the benzyl group exhibited the same immobility despite these more favorable conditions for displacement.

DISCUSSION

The resistance of the benzyl moiety toward displacement by the exchange alcohol is somewhat unexpected and may be due to several factors. Base-catalyzed alcoholyses are considered to proceed through the following sequence[4]:



The driving force in the reaction is, of course, removal of the more volatile alcohol, thereby displacing the equilibrium toward the desired ester.

Several reasons for the lack of activity of the benzyl group in this reaction may be postulated. This lack of activity, for instance, may be due to formation of a stable anion, as follows:

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[3] Trade-name Santicizer 160, Monsanto Chemical Co.

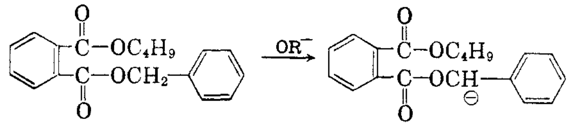
[4] Alexander, *Ionic Organic Reactions*, John Wiley and Sons, New York, 1950, p. 231.

TABLE III

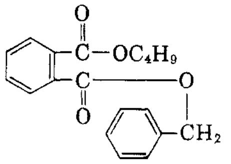
ALCOHOLYSIS OF HIGHER MOLECULAR WEIGHT ALKYL BENZYL PHTHALATES

Starting Ester	Exchange Alcohol[a]	Catalyst % Conc. on Ester	Resulting Ester D_{25}^{25}	Resulting Ester Theory yield	% of Theory ROH Removed[b]	ROH Removed n_D^{25}
Benzyl 2-octyl phthalate	Tridecyl (oxo) alcohol	$NaOCH_3$, 0.8	1.0240	87	88.2	1.4292[c]
Benzyl isodecyl phthalate	Tridecyl (oxo) alcohol	$NaOCH_3$, 0.9	1.0232	81.6	82.8	1.378[d]

[a] Exchange alcohol present in 1.2 mol. concentration per mol. of starting ester. [b] Reaction time in both cases was 4 hr., reaction conditions at end of alcoholysis was 185°/25 mm. in both cases. [c] n_D^{25} pure 2-octanol, 1.4245. [d] n_D^{25} commercial isodecyl(oxo)alcohol, 1.374.



It is entirely conceivable that the contribution of species like the anion shown above is pronounced in the reaction medium. Attack on this species by the alkoxide ion of the exchange alcohol should not result in attack at the carbonyl group of the benzyl ester because the required polarization would be inhibited by the already strong nucleophilic center about the benzyl anion. In addition, this anion derives resonance stabilization from the neighboring phenyl nucleus. This same inhibition to polarization of the carbonyl carbon of the benzyl ester may also be due to an inductive steric effect of the ring:



Thus, in this case the presence of the highly negative aromatic ring may, in part, negate the necessary polarization of the benzyl ester carbonyl carbon. Since this polarization is inhibited by either of the two factors already mentioned, the necessary attack by the alkoxide ion at the carbonyl carbon of the benzyl ester, which is a prerequisite of alcoholysis under these conditions, is inhibited, thereby resulting in the removal of the alkyl group only.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF UTAH]

Compounds Related to Isopimpinellin

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1,2,3,5-Tetramethoxybenzene (III) has been converted to 2,3-dihydroisopimpinellin in a number of steps, two of which employ selective cleavage of a methoxyl group. Acetylation of 4,6,7-trimethoxy-2,3-dihydrocoumarone (VIII) to dihydrokhellinone constitutes an improved method for this compound, an intermediate in the synthesis of khellin. The expected dehydrogenation of 2,3-dihydroisopimpinellin with a number of reagents failed to produce more than spectroscopic amounts of isopimpinellin (I).

The synthesis of furanocoumarins may employ either the appropriate coumarin or a benzofuran. Most of the published work has chosen the coumarin approach[2] due to the activity of the furan ring or the difficulty in dehydrogenation where 2,3-dihydrofuran is used. This latter problem was solved in a synthesis of khellin,[3] a furanochromone, by *N*-bromosuccinimide (NBS) dehydrogenation of an intermediate. Psoralene and related compounds have been produced by dehydrogenation over a palladium-carbon catalyst.[4]

Due to the advantages involved in benzenoid substitution in 2,3-dihydrobenzofuran, we have attempted this approach to isopimpinellin (I).[5] The synthesis was terminated when 2,3-dihydro-I failed to dehydrogenate by any of the variety of methods tried.

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[1] From the Doctoral dissertation of E. G. Paul, National Science Foundation Cooperative Research Fellow, 1959–60.

[2] F. M. Dean, *Progr. in Chem. Org. Nat. Prod.*, **9**, 225 (1952).

[3] T. A. Geissman and T. G. Halsall, *J. Am. Chem. Soc.*, **73**, 1281 (1951).

[4] E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **72**, 1514 (1950).

[5] (a) Isopimpinellin has been obtained recently from xanthotoxin, M. E. Brokke and B. E. Christensen, *J. Org. Chem.*, **24**, 523 (1959), and earlier (b) from bergapten, F. Wessely and F. Kallab, *Monatsh. Chem.*, **59**, 161 (1932).