In the case of the series of esters of the primary alcohols a zig-zag graph is obtained when adjacent points are joined by straight lines. The esters of the alcohols containing an even number of carbon atoms have melting points which lie above a smooth curve approximating the points, whereas those esters of alcohols containing an odd number of carbons lie below this curve. This type of graph is not unusual, for similar step-like arrangements are observed when the melting points are graphed against the number of carbons in various series of hydrocarbons, acids, aldehydes, amines and esters of monobasic and dibasic acids.

Several unsuccessful attempts were made to prepare the α-hexabromostearic acid esters of the following alcohols: dimethylpropylcarbinol, diphenylcarbinol, triphenylcarbinol and myricyl alcohol. The crude products obtained in these cases resembled the above esters; however, due to difficulty in extracting them, they could not be obtained in the pure state.

Summary

Thirteen new esters of α-hexabromostearic acid were prepared and their melting points determined. These white, wax-like solids have definite melting points and are generally soluble in hot organic solvents. The esters of the tertiary alcohols seem to deviate considerably from those of the primary and secondary alcohols in that they have abnormally high melting points and are much less soluble in hot organic solvents. The melting points of the esters decrease with the increase in the number of carbons in the alcohol. A graph of the melting points against the number of carbons in the alcohol indicates a step-like arrangement in which the esters of the alcohols having an even number of carbons lie above a smooth curve approximating the points.

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[CONTRIBUTION FROM THE EXPERIMENTAL RESEARCH LABORATORIES, BURROUGHS WELLCOME AND COMPANY]

MIXED BENZOINS. IX. MESO CHLORO DERIVATIVES

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The original purpose of this work was to seek a route for the conversion of a mixed benzoin into its isomer. Four benzoins were investigated—benzoin (as check), 4′-methoxybenzoin[1] (benzanisoin), 2-chloro-4′-methoxybenzoin (*o*-chlorobenzanisoin) and 2-chloro-3′,4′-dimethoxybenzoin (*o*-chlorobenzveratroin). The first steps were the conversion of the benzoin into the corresponding benzil, and this in turn into the phenyl α,α-dichlorobenzyl ketone. On the basis of data in the literature, it was believed that the chlorine atoms might be sufficiently firmly attached to withstand catalytic reduction, while the CO group was reduced to CHOH. The chlorine atoms could then be removed. Assuming that the chlorine atoms attached themselves to the carbon atom which originally carried

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[1] Nomenclature of Buck and Ide, THIS JOURNAL, 54, 3302 (1932).

the OH group in the benzoin (as would seem probable from the fact that the original benzoin and not its isomer is formed on catalytically reducing the benzil), then the isomeric benzoin would be produced according to the scheme

$$\mathrm{RCHOHCOR'} \longrightarrow \mathrm{RCOCOR'} \longrightarrow \mathrm{RCCl_2COR'} \longrightarrow (\mathrm{RCCl_2CHOHR'}) \longrightarrow \mathrm{RCOCHOHR'}$$

Unfortunately the reaction did not take this course, the phenyl α,α-dichlorobenzyl ketone being reduced first to the phenyl α-chlorobenzyl ketone (desyl chloride) and then to the desoxy compound. The phenyl α-chlorobenzyl ketone, if treated with sodium ethylate, rapidly regenerated the original benzoin, a result in line with the work of Ward.[2] The series of reactions

$$\begin{tikzcd}
 & & \mathrm{RCHOHCOR'} \\
\mathrm{RCCl_2COR'} \arrow[r] & \mathrm{RCHClCOR'} \arrow[ur] \arrow[dr] & \\
 & & \mathrm{RCH_2COR'}
\end{tikzcd}$$

fixes the position of the chlorine atoms in the dichloro and monochloro compounds since the positions of the CHOH and CH_2 groups are known.[3,4]

An attempt was next made to convert the dichloro compound into the diethyl acetal, with the object of reducing this. The compound, however, immediately broke up into a mixture of the corresponding benzoic ester and the benzal chloride, according to the equation

$$\mathrm{RCCl_2COR'} + \mathrm{EtOH} = \mathrm{RCHCl_2} + \mathrm{R'COOEt}$$

Smaller amounts of a benzaldehyde diethylacetal are also produced as follows

$$\mathrm{RCCl_2COR'} + \mathrm{EtOH} + 2\mathrm{NaOEt} = \mathrm{RCH(OEt)_2} + \mathrm{R'COOEt} + 2\mathrm{NaCl}$$

These reactions independently establish the position of the chlorine atoms in the dichloro compounds, and, incidentally, offer a new method for determining the structures of benzoins, since benzoins are derived, in a direct manner, from the dichloro compounds.

Zinin[5] has noted the production of benzaldehyde and potassium benzoate by the action of alcoholic potassium hydroxide on "chlorobenzil" (phenyl α,α-dichlorobenzyl ketone), the reaction taking place slowly in the cold, and quickly on heating. The fission by the action of sodium ethylate, on the contrary, takes place almost immediately at room temperature.

Redsko[6] reported the production of phenyl α,α-dichlorobenzyl ketone[5] by the action of phosphorus pentachloride on benzoin. Evidently its production is a side reaction and not the main reaction. The present authors confirm the production of this compound under modified condi-

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[2] Ward, *J. Chem. Soc.*, 1541 (1929).

[3] Buck and Ide, THIS JOURNAL, **53**, 1536 (1931).

[4] Buck and Ide, *ibid.*, **53**, 1912 (1931).

[5] Zinin, *Ann.*, **119**, 177 (1861).

[6] Redsko, *J. Russ. Phys.-Chem. Soc.*, **21**, [1] 421 (1889); *Ber.*, Ref. **22**, 760 (1889).

tions. The reaction appears to be general, as the corresponding dichloro compounds are produced from the mixed benzoins examined, although only in poor yield. Benzoin itself and the mixed benzoins examined were found to give, in benzene solution and at room temperature, relatively large amounts of the corresponding benzil, when treated with phosphorus pentachloride. The phenyl α-chlorobenzyl ketones (desyl chlorides), which might have been expected, were not found. Under suitable conditions the yield of the benzil is surprisingly large. Once the benzil is formed, the production of the dichloro compound would follow naturally, on raising the temperature. Since the benzil is an intermediate, this method of formation of the dichloro compound is valueless as an indication of the position of the chlorine atoms.

Zinin did not observe the formation of tolane tetrachloride in the reaction between benzil and phosphorus pentachloride, although later Eiloart[7] obtained it by using excess of pentachloride on benzil. The present authors always found tolane tetrachloride, to the extent of about 10%, to be formed. Smaller amounts of *p*-methoxytolane tetrachloride are formed from 4-methoxybenzil. With the other mixed benzoins examined, the corresponding tolane tetrachlorides are produced in very small amounts and are inseparable by fractional crystallization. They remain as small residues when the phenyl α,α-dichlorobenzyl ketones are removed in a reaction (*e. g.*, catalytic reduction).

The three unsymmetrical benzils were reduced catalytically. Up to the present only the original benzoins and none of the isomeric benzoins have been obtained. This fact, together with the formation in each case of only one phenyl α,α-dichlorobenzyl ketone, brings out the marked difference of reactivity between the two carbonyl groups of the benzils. In the cases of the *o*-chlorobenzils examined, it was thought that the ortho chlorine atom might have some steric effect, tending to cause the carbonyl groups remote from it to react with the phosphorus pentachloride. As a matter of fact, the contrary effect was observed, the phenyl α,α-dichlorobenzyl ketone being formed with greater ease in the cases of the *o*-chlorobenzils, the group attacked being the carbonyl adjacent to the ortho chlorine atom.

The high degree of reactivity of the meso chlorine atoms (toward sodium ethylate and catalytic reduction) is noteworthy, particularly in view of the alleged stability of α,α-dichlorobenzyl ketone toward silver salts, etc.[5]

A point of interest is that if the phenyl α-chlorobenzyl ketone from 4′-methoxybenzoin is reduced catalytically, there is obtained benzyl 4-methoxyphenyl ketone, and not 4-methoxybenzyl phenyl ketone, which is produced on the reduction of 4′-methoxybenzoin by tin and

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[7] Eiloart, *Am. Chem. J.*, **12**, 231 (1890).

hydrochloric acid.[3] The other chloro compounds give the usual desoxy compounds on catalytic reduction, as would be expected.

The experimental work presents some unusual difficulties. Most of the compounds show marked supercooling effects, so that it is very difficult, in the absence of seeding crystals, to obtain crystalline products. The separation of the tolane tetrachlorides from the phenyl α,α-dichlorobenzyl ketones by fractional crystallization is difficult, and, indeed, in some cases impossible. The uncontrollable nature of catalytic reduction, when applied to mixed benzoin work, is also brought out. Thus (adding hydrogen in the proportion of two atoms for each molecule of ketone), an unsymmetrical benzil gives the benzoin, together with the unchanged benzil and the hydro compound. Similarly, with the dichloro compounds, unchanged material and the desoxy compounds are usually present in the reduction mixtures.

Experimental

The mixed benzoins used were prepared as described elsewhere.[8,9]

Phenyl α,α-Dichlorobenzyl Ketone (*ms-ms*-Dichlorodesoxybenzoin, Chlorobenzil).—The method of Zinin[5] was used. It is very difficult to separate completely the product from the tolane tetrachloride simultaneously formed.

Substituted Phenyl α,α-Dichlorobenzyl Ketones.—The method of Zinin was found to be unsuitable for substituted benzils. The general method used consisted of dissolving the substituted benzil (0.03 mole) in benzene (100 cc.), adding the phosphorus pentachloride (0.09 mole), and refluxing the solution. The benzene was evaporated under reduced pressure (stopping the operation as soon as phosphorus pentachloride is seen to sublime), the flask cooled, and the contents rapidly and cautiously treated with cold water (about 25 times the weight of the benzil used, the water added in one lot). When the resulting reaction is over, the milky emulsion is extracted with ether (if solid is present this is removed before extraction), the extract washed with water, the ether evaporated, and the resulting oil, together with any solid material removed, dissolved in warm alcohol. On seeding and standing, the product crystallized out. From the dichloro compound from 4-methoxybenzil, a little *p*-methoxytolane tetrachloride can be separated by fractional crystallization, but in the other cases the amount of the tolane tetrachloride formed is insignificant. The results are given in Table I. The time of refluxing is rather critical. Yields are given for a good grade of product, not necessarily analytically pure. Alcohol is the best solvent for recrystallization. The compounds are very soluble in ether and benzene, moderately soluble in alcohol, and sparingly soluble in petroleum ether.

TABLE I

PHENYL α,α-DICHLOROBENZYL KETONES

	Compound -chlorobenzyl ketone	Hours refluxed	Yield, %	M. p., °C.	Formula	Analyses Calcd. C	Analyses Calcd. H	Analyses Found C	Analyses Found H
1	4-Methoxyphenyl α,α-di-	4.5	67	81	$C_{15}H_{12}O_2Cl_2$	61.01	4.10	60.89	4.41
2	4-Methoxyphenyl α,α-2-tri-	2.2	97	109	$C_{15}H_{11}O_2Cl_3$	54.63	3.37	54.93	3.59
3	3,4-Dimethoxyphenyl α,α-2-tri-	1.8	82	120	$C_{16}H_{13}O_3Cl_3$	53.41	3.63	53.73	3.77

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[8] Buck and Ide, THIS JOURNAL, **52,** 4107 (1930).

[9] Kinney, *ibid.*, **51,** 1592 (1929) (omitting the steam distillation).

***p*-Methoxytolane tetrachloride,** recrystallized from alcohol in which it is sparingly soluble, forms bundles of slender, tiny needles, melting at 153°.

Analysis. Calcd. for $C_{15}H_{12}OCl_4$: C, 51.44; H, 3.46. Found: C, 51.65; H, 3.72.

Phenyl α-Chlorobenzyl Ketones.—The general method used was to dissolve 0.02 mole of the phenyl α,α-dichlorobenzyl ketone in 50 cc. of absolute alcohol, and to reduce this catalytically, as slowly as possible, using slow shaking and very little (10–20 mg.) platinum oxide. Hydrogen was added in the proportion of two atoms for each molecule of ketone. The solution was filtered and concentrated on the steam-bath. On seeding and standing the product crystallized out. Results are given in Table II.

The corresponding desoxy compounds were isolated, as side products, in three of the four cases, none being found in the reduction of 4-methoxyphenyl α,α-2-trichlorobenzyl ketone.

The compounds are rather soluble in alcohol, very soluble in ether and benzene and moderately or sparingly soluble in petroleum ether.

Table II

Phenyl α-Chlorobenzyl Ketones

Compound, -chlorobenzyl ketone	Yield, %	M. p., °C.	Formula	Analyses Calcd. C	H	Found C	H
Phenyl α-	65	68	$C_{14}H_{11}OCl$	72.87	4.81	72.78	4.86
4-Methoxyphenyl α-2-di-	81	75	$C_{15}H_{12}O_2Cl_2$	61.22	4.12	61.53	4.55
3,4-Dimethoxyphenyl α-2-di-	70	99	$C_{16}H_{14}O_3Cl_2$	59.07	4.34	59.05	4.37

4-Methoxyphenyl α-chlorobenzyl ketone was only obtained as a thick oil, doubtless owing to the presence of unchanged material and the desoxy compound. By pouring an alcoholic solution into water and extracting with petroleum ether, benzyl 4-methoxyphenyl ketone was obtained in about 10% yield on concentrating the extract. It was identified by comparison and by mixed melting point determinations with an authentic specimen, prepared by the Friedel–Crafts method.[6] After extraction with petroleum ether, the emulsion was extracted with ether. The oil obtained on evaporating the ether gave 4′-methoxybenzoin in good yield on treatment with sodium ethylate (see later), proving that the oil was mainly the 4-methoxyphenyl α-chlorobenzyl ketone.

Conversion of Phenyl α-Chlorobenzyl Ketones into Benzoins.—The method used was to dissolve about 5 g. of the phenyl α-chlorobenzyl ketone in absolute alcohol (*ca.* 50 cc.), cool the solution, and add to it a cold solution of three molecules of sodium ethylate in the minimum amount of absolute alcohol. The mixture was kept at about 40° for fifteen minutes, during which time sodium chloride separated out. The whole was then poured into cold water (500 cc.) containing 20 cc. of concd. hydrochloric acid. The oil which separated soon solidified on standing in a cold place and the solid was then filtered off and recrystallized from alcohol. The benzoin was identified by analysis and by comparison and mixed melting point determinations with authentic specimens. The yield of the pure benzoin is very good and the structure of the product agrees in each case with the assumption that the chlorine atom is directly replaced by the hydroxyl group.

Reduction of Phenyl α-Chlorobenzyl Ketones to Phenyl Benzyl Ketones (Desoxy Compounds).—0.01 mole of the phenyl α-chlorobenzyl ketone, dissolved in 50 cc. of alcohol, was reduced with platinum oxide, two atoms of hydrogen being added per molecule of ketone. After filtration and concentration on the steam-bath, the solution deposited crystals on standing. The product was identified by comparison and by mixed melting point determinations with authentic specimens. The yields are very good, averaging about 80% of the theoretical for the pure product. In each case the structure of the desoxy compound formed is that which would be expected if the chlorine atom were directly replaced by a hydrogen atom.

Benzils from Benzoins by the Action of Phosphorus Pentachloride.—The benzoin (about 10 g.) was dissolved in 100 cc. of benzene, the solution cooled if necessary, and one mole of phosphorus pentachloride added cautiously, in one lot. Hydrogen chloride was evolved briskly, but there was only a slight heat effect. The reaction was soon completed, and the solution was then allowed to stand at room temperature. After standing it was poured into ice water (700 cc.), the benzene layer separated and the liquors extracted with ether. The total extracts were evaporated under reduced pressure and the residue dissolved in alcohol. On standing the benzil crystallized out and was identified by comparison and mixed melting point determinations with an authentic specimen.

Similar experiments were carried out using three times the amount of phosphorus pentachloride (3 moles), adding the chloride rapidly in small portions, and so regulating the addition that violent frothing did not occur. The best results, excepting in the case of 4'-methoxybenzoin, are obtained by using 3 moles of phosphorus pentachloride and allowing the solution to stand for only ten minutes. Under these conditions the yields were, for benzil, 72%; for 2-chloro-4'-methoxybenzil, 90% and for 2-chloro-3'-4'-dimethoxybenzil, 50%. From 4'-methoxybenzoin, after standing for four hours with 3 moles of phosphorus pentachloride, a yield of 42% was isolated while under other conditions only oils were obtained.

If the solutions (3 moles of phosphorus pentachloride) be refluxed for four hours and then worked up as above, it is possible to isolate the corresponding phenyl α,α-dichlorobenzyl ketones, but only after laborious fractional crystallization. The yield is best in the case of benzoin itself (about 30%) but in the other cases it was no more than 10%.

Fission of Phenyl α,α-Dichlorobenzyl Ketones.—About 10 g. of the phenyl α,α-dichlorobenzyl ketone was dissolved in the minimum amount of absolute alcohol (50 to 100 cc.) and the solution cooled. To this solution was added a cold solution of two molecular proportions of sodium ethylate. A slight rise in temperature took place and some sodium chloride usually separated out. After standing at room temperature for twenty minutes, the mixture was poured into 700 cc. of water and extracted three times with ether. The ether was evaporated and the residual oil distilled under reduced pressure, separating it into two fractions as far as possible. The fractions were then further distilled at ordinary pressure, until approximately pure. The higher fraction was identified by its boiling point and by its saponification (alcoholic potash) to the acid. The lower fraction was hydrolyzed by heating with hydrochloric acid (four hours at 150° with 10% hydrochloric acid for the benzaldehyde fraction, seven hours at 175° with 35% hydrochloric acid for the *o*-chlorobenzaldehyde fraction. There was considerable destruction of material in the latter case). The benzaldehyde formed was identified as the phenylhydrazone, and the *o*-chlorobenzaldehyde as 2-chloro-benz-anti-aldoxime. Mixed melting point determinations were carried out in each case with authentic specimens. Allowing for fractionation losses, the yields approached the theoretical. Usually a small residue (5 to 10%) remained after the first distillation. The absence of free aldehydes in the lower-boiling fractions was verified by means of sodium bisulfite, etc.

Analytical results not given here (C, H, Cl) indicate clearly that the lower-boiling fractions consist chiefly, to the extent of about 90%, of the benzal chloride. From the separation of sodium chloride in the reaction it is assumed that the contaminant is the diethylacetal. With the amounts of material available, it was not possible to separate the components by fractional distillation.

Ethyl anisate and benzal chloride were obtained from 4-methoxyphenyl α,α-dichlorobenzyl ketone; ethyl anisate and *o*-chlorobenzal chloride from 4-methoxyphenyl α,α-2-trichlorobenzyl ketone and ethyl veratrate, and *o*-chlorobenzal chloride from 3,4-dimethoxyphenyl α,α-2-trichlorobenzyl ketone. The reaction mixture from phenyl α,α-dichlorobenzyl ketone proved to be inseparable by fractional distillation; it was therefore heated for four hours at 150° with hydrochloric acid (1:2) and the product separated into benzaldehyde and benzoic acid.

Summary

1. The phenyl α,α-dichlorobenzyl ketones from three representative mixed benzoins have been prepared and examined. They have been reduced catalytically to the phenyl α-chlorobenzyl ketones, and these in turn to the desoxy compounds. The conversion of the phenyl α-chlorobenzyl ketones to the parent benzoins was also carried out.
2. It has been found that phosphorus pentachloride in the cold behaves chiefly as an oxidizing agent toward benzoins, good yields of the benzils being obtained.
3. The phenyl α,α-dichlorobenzyl ketones, when treated with alcoholic sodium ethylate in the cold, rapidly break up into a mixture of the corresponding benzoic ester and the benzal chloride. Small amounts of the diethylacetal are also formed.
4. Parallel experiments on benzoin were carried out as a check.

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THE SYNTHESIS OF BETA-ETHOXYAMINES[1]

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The method of preparation of β-ethoxyamines described in this paper was evolved with the idea that it might be possible to synthesize numerous substituted derivatives, in the manner that Boord[2] and his co-workers have used in the preparation of isomeric olefins. It was further felt that these ethoxyamines might be more easily resolved than the corresponding alcohols and the active ethers might then be split to yield various optically active β-hydroxyamines which should be of interest from a pharmaceutical point of view. A second point of interest concerning these ethoxyamines was their possible use as basic resolving agents. In this respect they form a continuation of a study by Brode and Littman[3] on the synthesis and resolution of a quite different type of asymmetric amine. The method of

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[1] Presented at the Mid-West regional meeting of the American Chemical Society, St. Louis, Mo., April 5, 1932.

[2] Boord and co-workers, This Journal, **52,** 651, 3396 (1930); **53,** 1505 (1931); **54,** 751 (1932).

[3] Brode and Littman, *ibid.*, **52,** 1655, 5056 (1930); **53,** 1531 (1931).