

LXIV.—*Alkylation by means of Dry Silver Oxide and Alkyl Halides.*

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DRY silver oxide and alkyl iodides have been employed as an alkylating agent, by Purdie and Pitkeathly, in the preparation of alkyloxy- and dialkyloxy-succinic esters from malic and tartaric esters (Trans., 1899, 75, 157), by Purdie and Irvine in the preparation of α -alkyloxypropionic esters from lactic esters (Trans., 1899, 75, 485), and by McKenzie in the preparation of alkyloxyphenylacetic esters from mandelic esters (Trans., 1899, 75, 754).

Apparently, the only prior applications of dry silver oxide as a synthetic agent are its use by Wurtz in the formation of ethyl ether from ethyl iodide (*Ann.Chim. Phys.*, 1856, [iii], 46, 222), and its applications in a similar sense by Erlenmeyer (*Annalen*, 1863, 126, 306), and Linnemann (*Annalen*, 1872, 161, 37).

The object of the present investigation was to ascertain to what

extent the use of dry silver oxide and alkyl halides is applicable to the production of alkyloxy-derivatives directly from hydroxy-compounds, and in general to the production of alkyl derivatives of compounds, of more or less well defined acid character, possessing hydrogen atoms replaceable by alkyl radicles.

The various methods of preparing alkyl derivatives of compounds falling within the assigned limits may be brought under two general headings :

1. The action on a hydroxy-compound of an alcohol, either alone, or in the presence of sulphuric or hydrochloric acid.

2. The action of alkyl halides on metallic derivatives, which, for the purposes of the synthesis, may or may not require to be isolated in the pure state.

To the first general method belong :

The formation of hydrolysable esters from acids by the action of alcohol, with or without the use of a mineral acid.

The formation of fatty ethers from alcohols by the action of alkyl hydrogen sulphates, or alkyl benzenesulphonates.

The formation of ethers of hydroxy-compounds $R \cdot OH$, in which R is not an aliphatic residue. As instances, may be quoted the preparation of benzoin ethers from benzoin, alcohol, and sulphuric acid (Fischer, *Ber.*, 1893, 26, 2412), and the production of glucosides (Fischer, *Ber.*, 1893, 26, 2401). The method does not appear to be applicable to the formation of alkyl derivatives of the simpler types of hydroxy-esters.

The mechanism of the reaction is doubtless the same in all cases, depending upon the formation of esters of the mineral acid containing the alkyl radicle introduced (conceivably also of the complex radicle itself). The general equation would be $ROH + R'X = ROR' + HX$.

To the second general method belong :

The formation of hydrolysable esters of acids by the action of alkyl halides on the sodium or, more usually, silver salts. To the same special case should also be referred the alkylation, through the intermediary of metallic derivatives, of such less distinctly acidic compounds as phenols, amides, imides, lactams, and lactims.

The formation of alkyl derivatives of compounds containing hydrogen atoms (labile or not) replaceable by alkyl groups by the action of alkyl iodides and sodium alkyloxides, represented most simply by ethyl acetoacetate and malonate, benzyl cyanide, and deoxybenzoin.

The formation of alkyl ethers from sodium alkyloxides and alkyl iodides. The cases of the formation of esters of alkyloxy-acids from halogen-substituted esters by the action of alkyloxides, for example, alkyloxypropionates (Schreiner, *Annalen*, 1879, 197, 12), and of alkyloxypropionates from sodiolactates by the action of alkyl iodides

(Wislicenus, *Annalen*, 1863, **125**, 53), may be considered as also illustrating this special case. The general equation for the method would be :



It need scarcely be indicated that the above is not a hard and fast classification, as methods in particular instances may, and do, overlap. It is laid down as presenting a scheme, according to which the study of the action of silver oxide and halides has been directed.

I. Action of Dry Silver Oxide and Ethyl Iodide on 1-Menthol.

The case of menthol is interesting as affording a means of testing the applicability of dry silver oxide and alkyl halides to the etherification of a secondary alcohol, and further, as affording a possible method for the preparation of optically active menthyl ethers.

Menthyl ethyl ether, presumably optically inactive, has been prepared by Brühl (*Ber.*, 1891, **24**, 3376) from sodium menthyloxyde by the action of ethyl iodide. An experiment on a small scale showed that menthol is not etherified, even on prolonged boiling, by alcohol and concentrated sulphuric acid.

The menthol used in the following experiments melted at 42°, boiled at 211—212°, and in a 5.09 per cent. alcoholic solution had $[\alpha]_D^{20} - 49.52^\circ$. For a 5 per cent. alcoholic solution, Arth (*Ann. Chim. Phys.*, 1886, [vi], **7**, 438) gives $[\alpha]_D^{22} - 49.4^\circ$.

A preliminary experiment with dry silver oxide and ethyl iodide showed that interaction had occurred. After three successive treatments with oxide and iodide, the product obtained was an oil of faint ethereal odour, giving $\alpha - 82.33^\circ$ in a 100 mm. tube at 12°.

The preparation was therefore carried out on a larger scale. 111 grams of dry silver oxide ($1\frac{1}{2}$ mols.) were added to the cold solution of 50 grams of menthol (1 mol.) in 150 grams of ethyl iodide (3 mols.). No action occurred in the cold. On warming to the boiling point on a steam-bath, reaction set in, as indicated by ebullition, which continued for one hour after removal from the source of heat. The mixture was subsequently boiled for 6 hours. Some water was formed in the course of the reaction. The solution was filtered, the silver residue washed repeatedly with ether, and, after removal of the ether, the liquid was distilled. The boiling point rose rapidly from 100° to 205°. The product boiling between 208° and 215°, amounting to 52 grams, was collected, and gave $\alpha_D - 72.62^\circ$ in a 100 mm. tube at 11°.

The whole quantity (52 grams), together with 5 grams ($\alpha_D - 82^\circ$)

from the preliminary experiment, was again similarly treated with 74 grams of dry silver oxide and 100 grams of ethyl iodide. The reaction initiated on warming lasted 20 minutes; the boiling was continued for 8 hours. 52 grams of product, boiling between 205° and 215° , separated as above, were obtained, and gave $\alpha_D - 82.22^{\circ}$ in a 100 mm. tube at 11° .

A third treatment with 60 grams of oxide and 80 grams of iodide, in which the initial action was very slight, and the boiling continued for 6 hours, gave 42 grams of substance boiling at $208-213^{\circ}$, which, in a 100 mm. tube at 10.5° , had $\alpha_D - 83.01$. The liquid product from the third treatment was heated on a water-bath before addition of the ethereal washings. The distillation of a small fraction below 40° indicated that in all probability ethyl ether had been formed in the reaction.

The product was fractionated in order to see whether notable increase in rotation could thereby be effected. Three fractions were collected, and the rotations were observed in a 100 mm. tube at 10° :

I. $205-207^{\circ}$, about one-quarter	$\alpha_D - 79.93^{\circ}$.
II. $207-209^{\circ}$, main fraction.....	$\alpha_D - 84.35^{\circ}$.
III. $209-212^{\circ}$, small	$\alpha_D - 84.77^{\circ}$.

Apparently, therefore, the rotation (-84.35° to -84.77°) had reached a maximum. Fractions II and III were united and redistilled, but the lower fraction, $205-207^{\circ}$, was neglected, although nearly pure. Seventeen grams were collected between 207.5° and 209.5° , and taken as pure. The higher fraction was very small. Analysis of the pure product gave figures agreeing with those required for menthyl ethyl ether.

0.1041 gave 0.2978 CO_2 and 0.1220 H_2O . C = 78.02; H = 13.02.

0.1334 ,, 0.3821 CO_2 ,, 0.1576 H_2O . C = 78.11; H = 13.12.

$\text{C}_{12}\text{H}_{24}\text{O}$ requires C = 78.26; H = 13.04 per cent.

The specific rotation of the liquid at 20° was as follows:

$$\alpha_D = -83.94^{\circ}, l = 1, d_{20^{\circ}/4^{\circ}} = 0.8537, [\alpha]_D^{20^{\circ}} = -98.32^{\circ}.$$

II. Attempts to prepare Ethers of Triphenylcarbinol.

The case of triphenylcarbinol may, in many respects, be regarded as crucial. On the one hand, it might be imagined that the presence of the three electronegative phenyl groups might confer fairly well defined acidic properties on the hydroxy-group; on the other, the great stability of the carbinol would no doubt render the substance less susceptible to the action of a reagent such as silver oxide and alkyl halides.

Pure triphenylcarbinol undergoes no change when boiled for 12 hours with dry silver oxide and either ethyl or isopropyl iodide. In the case of ethyl iodide, reaction of any kind is incomplete, although, without doubt, some ethyl ether is produced. Heated in a sealed tube with silver oxide and ethyl iodide at 160° for 4 hours, the carbinol underwent no change, but pure yellow silver iodide was obtained, and, under these conditions, the reaction between the oxide and iodide seems to be complete.

In the case of isopropyl iodide, the interaction at 100° is complete, as indicated by the formation of pure yellow silver iodide, after prolonged boiling with excess of iodide—18 grams of oxide gave 34 grams of iodide; calculated, 36·4 grams—and by the formation of a liquid boiling between 60° and 68° (isopropyl ether boils at 68·5—69°, according to Erlenmeyer, *loc. cit.*).

It is noteworthy that in no other reaction carried out under similar conditions is a pure yellow residue obtained, the residues being invariably dark coloured, brown or greenish-black.

Much delay was caused in the carrying out of the above experiments from the fact that the carbinol was contaminated with triphenylmethane. The recovery of the hydrocarbon indicates, however, that it is not acted upon by silver oxide and iodides, although the presence of three acidic groups united to the :CH residue renders it conceivable that the hydrogen of this radicle might be replaceable by alkyl groups.

III. *Action of Dry Silver Oxide and Alkyl Iodides on Benzoin.*

Benzoin affords an instance of a hydroxy-compound, $\text{R}\cdot\text{OH}$, in which the radicle R is not a hydrocarbon residue. It was therefore of interest to see whether, in this particular case, silver oxide and alkyl iodides would serve as an alkylating agent.

Action of Silver Oxide and Ethyl Iodide on Benzoin.

The ethyl ether of benzoin is described as one of the products of interaction of benzoin, ethyl alcohol, and sodium by Limpricht and Jena (*Annalen*, 1870, 155, 96), who ascribe to it the melting point 95°. It is also described as resulting from the action of ethyl alcohol and concentrated sulphuric acid on benzoin by Fischer (*loc. cit.*), who assigns to it the melting point 62°.

Preliminary experiments on the small scale showed that reaction occurred between benzoin, silver oxide, and ethyl iodide, as the benzoin, which is but sparingly soluble in the hot iodide, eventually dissolved in the mixture. In addition to some unchanged substance,

a solid of lower melting point, contaminated, however, with oily compounds smelling strongly of benzaldehyde, appeared to constitute the main product of the reaction. The following method was finally found most convenient for the isolation of the products.

Finely powdered benzoin (30 grams) was intimately mixed with dry silver oxide (40 grams, 7 grams in excess of the calculated amount) and ethyl iodide (54 grams, an excess of 10 grams) added. No change occurred even on standing one hour in the cold, but on raising to the boiling point, reaction set in, lasting of itself for about half an hour. The mixture was boiled in all for about four hours. During the operation, the benzoin passed into solution and did not crystallise out on cooling. Water was formed in the reaction, and the liquid acquired a distinct odour of benzaldehyde; the silver residue was dark coloured. The products of the reaction were extracted with ether, and after removal of ether on the water-bath, the residual oil was distilled in a vacuum. Two fractions were collected; the first was a liquid, boiling between 95° and 102° under 20—40 mm. pressure; the second an oil which speedily solidified on cooling and stirring, and boiled at 184 — 186° under 12 mm. pressure.

The liquid of low boiling point was redistilled under the ordinary pressure, whereby it was separated into two portions, the first boiling at 190 — 200° , the second at 200 — 207° . The fraction of boiling point 190 — 200° smelt strongly of benzaldehyde and had an acid reaction. A few drops exposed to the air rapidly went semi-solid, yielding an acid dissolved by sodium carbonate solution, from which it was reprecipitated by dilute sulphuric acid. Further evidence of its identity with benzaldehyde was obtained by the preparation of the compound with sodium hydrogen sulphite and of the phenylhydrazone.

The fraction of boiling point 200 — 207° was shaken out repeatedly with concentrated sodium hydrogen sulphite, and from the ethereal solution of the residual oil sodium carbonate solution extracted practically no benzoic acid. On hydrolysing this oil (5.5 grams) with 10 per cent. potassium hydroxide solution, with addition of alcohol, 3.5 grams of benzoic acid were obtained melting at 120° . It is thus evident that one phase of the reaction of dry silver oxide and ethyl iodide on benzoin consists in the partial oxidation of the benzoin, resulting in the formation of benzaldehyde and ethyl benzoate, as may be indicated by the following equations:

- (1) $C_6H_5 \cdot CH(OH) \cdot CO \cdot C_6H_5 + Ag_2O = C_6H_5 \cdot CHO + C_6H_5 \cdot CO_2H + 2Ag.$
- (2) $2C_6H_5 \cdot CO_2H + Ag_2O = 2C_6H_5 \cdot CO_2Ag + H_2O.$
- (3) $C_6H_5 \cdot CO_2Ag + C_2H_5I = C_6H_5 \cdot CO_2C_2H_5 + AgI.$

The residue left in the flask after distillation of the original product in a vacuum was small. On twice recrystallising it from alcohol

a crop of needles melting at 120° to 126° (impure benzoin) was obtained.

The solid substance boiling at 184 — 186° in a vacuum weighed 12 grams. It could be crystallised either from alcohol or light petroleum, and was purified for analysis by recrystallisation from the latter, in which it is easily soluble on boiling. The compound separates, on standing, in warty aggregates of fine needles, and, after recrystallisation, melts at 58 — 58.5° . Analysis gave figures agreeing with those required by the formula $C_6H_5 \cdot CH(OC_2H_5) \cdot CO \cdot C_6H_5$.

0.2285 gave 0.6695 CO_2 and 0.1465 H_2O . C = 79.90; H = 7.12.

0.1683 „ 0.4940 CO_2 „ 0.1030 H_2O . C = 80.04; H = 6.80.

$C_{16}H_{16}O_2$ requires C = 80.00; H = 6.66 per cent.

Action of Isopropyl Iodide and Dry Silver Oxide on Benzoin.

Twenty-two grams of benzoin, 28 grams (5 grams in excess) of dry silver oxide, and 41 grams (7 grams in excess) of isopropyl iodide were used. As the whole of the benzoin did not dissolve in the iodide when heated, 20 grams of benzene were added to nearly complete its solution. On adding half of the oxide to the warm liquid, vigorous action occurred, lasting, however, only a few minutes. After cooling, the remainder of the oxide was added, and a reaction lasting about a quarter of an hour set in. The mixture was subsequently boiled for 2 hours, and, on cooling, needles resembling benzoin in crystalline form were deposited. A further quantity of 10 grams of oxide and 15 grams of iodide was therefore added, which induced further action, lasting 20 minutes. The mixture was finally boiled for 3 hours, the warm liquid filtered, and the residue washed with ether. On cooling the benzene solution, a separation of needles occurred, which, after recrystallisation from alcohol, melted at 128 — 132° , and consisted of unchanged benzoin. The viscid liquid left after distilling off the solvent, was separated as far as possible from deposited benzoin, and distilled in a vacuum. As in the case of the reaction of the oxide and ethyl iodide, a fraction boiling below 100° under about 20 mm. pressure was collected, which proved to be a mixture of benzaldehyde and isopropyl benzoate. From the fraction above 100° , 7 grams of a liquid easily solidifying on cooling and stirring, and fusing below 100° , were obtained, boiling from 175 — 180° under 10 mm. pressure. This was purified by recrystallisation from light petroleum, one volume of the fused substance being easily soluble in about three volumes of the hot solvent and was obtained in aggregates of minute needles melting at 72 — 75° . The melting point was not altered by recrystallisation. The substance reduced Fehling's solution very slightly upon boiling, owing, possibly, to the presence of unchanged benzoin in quantities too

small for detection. Analysis gave figures agreeing with those required for the isopropyl ether of benzoin.

0.1408 gave 0.4132 CO₂ and 0.0912 H₂O. C = 80.03; H = 7.19.

0.1380 „ 0.4056 CO₂ „ 0.0883 H₂O. C = 80.15; H = 7.11.

C₁₇H₁₈O₂ requires C = 80.31; H = 7.08 per cent.

The somewhat greater proportion of benzoin, which escapes reaction in the case of isopropyl iodide, as compared with that of ethyl iodide, may be due to the dilution brought about by the use of benzene, but in greater likelihood is attributable to the superior facility with which isopropyl iodide interacts with silver oxide.

IV. *Action of Dry Silver Oxide and Alkyl Iodides on Amides.*

The alkylation of amides and allied substances presents considerable analogy to the esterification of acids by the action of alkyl halides on metallic salts, as in many instances the silver or other salts can be isolated in a pure state, and submitted to the action of alkyl halides (compare Tafel and Enoch, *Ber.*, 1890, 23, 103). In contradistinction to the comparatively simple case of the metallic salts of carboxylic acids, the metallic salts of amides, &c., may correspond to the labile form of the free compound. In particular does this seem to be the case with the silver salts (Tafel and Enoch, *loc. cit.*).

The object of studying the action of silver oxide and alkyl iodides on amides was to ascertain whether the intermediate step of preparation and isolation of the silver salt could not be obviated, and imino-ethers be prepared directly from amides by the use of this reagent.

Action of Silver Oxide and Ethyl Iodide on Benzamide.

Ethyl benzimino-ether has been prepared from benzonitrile by the action of ethyl alcohol and dry hydrochloric acid (Pinner, *Ber.*, 1883, 16, 1654), and from silver benzamide by the action of ethyl iodide (Tafel and Enoch, *loc. cit.*).

Assuming the reaction to proceed through the formation of silver benzamide, the production of water in the reaction $2C_6H_5 \cdot CO \cdot NH_2 + Ag_2O = 2C_6H_5 \cdot CO \cdot NHAg + H_2O$ would tend to regenerate amide from any imino-ether which might have been formed. It seemed probable, however, that by using a considerable excess of oxide and iodide, the water thus formed might be removed from the sphere of action thus, $Ag_2O + H_2O + 2C_2H_5I = 2AgI + 2C_2H_5 \cdot OH$.

Twelve grams of benzamide, 46 grams of dry silver oxide (calculated 11.6 grams), and 62 grams of ethyl iodide were used. The benzamide was added to the iodide and the liquid warmed, but as solution was incomplete, 20 grams more iodide were added, and, on warming, nearly

the whole of the amide then passed into solution. After addition of the powdered oxide, the liquid was raised to the boiling point when reaction set in, and continued without application of heat for half an hour. After this had subsided, the mixture was boiled for one hour. Water was formed in the reaction, but on continued boiling it disappeared. The silver residue was greenish-yellow. The solution was filtered, and the residue washed with dry ether, the washings being added to the original solution. The liquid had a characteristic odour, and showed no tendency to crystallise on standing. Addition of a slight excess of an ethereal solution of hydrogen chloride caused the precipitation of a crop of fine needles, weighing 7 grams, which melted at 118—120° with evolution of gas, fusing somewhat higher after resolidification. The hydrochloride was further purified by solution in as small a quantity of alcohol as possible, and reprecipitation by dry ether. The chlorine in the air-dried substance was estimated by titration with decinormal silver nitrate solution.

0.2917 required 15.90 c.c. AgNO_3 . Cl = 19.35.

0.3481 „ 18.85 c.c. AgNO_3 . Cl = 19.22.

$\text{C}_6\text{H}_5 \cdot \text{C}(\text{O} \cdot \text{C}_2\text{H}_5) \cdot \text{NH}, \text{HCl}$ requires Cl = 19.13 per cent.

The purified hydrochloride fused at 119—120° with evolution of gas, and after resolidification at 125° (compare Pinner, *loc. cit.*).

Action of Silver Oxide and Ethyl Iodide on Acetanilide.

The examination of the action of the oxide and iodide on acetanilide was undertaken in the hope that it would run a course parallel to that of benzamide, and yield N-phenylacetiminoethyl ether or ethyl isoacetanilide, $\text{C}_6\text{H}_5 \cdot \text{N} : \text{C}(\text{O} \cdot \text{C}_2\text{H}_5) \cdot \text{CH}_3$. Silver formanilide corresponds to the iso-type, yielding iso-ethers by the action of alkyl iodides (Comstock and Kleeberg, *Amer. Chem. J.*, 1879, 12, 498). In contradistinction to sodium acetanilide, $\text{C}_6\text{H}_5 \cdot \text{NNa} \cdot \text{CO} \cdot \text{CH}_3$, silver acetanilide, upon the formation of which the reaction depends, would almost certainly be $\text{C}_6\text{H}_5 \cdot \text{N} : \text{C}(\text{OAg}) \cdot \text{CH}_3$.

Thirteen and a half grams (1 mol.) of acetanilide were dissolved in 47 grams (3 mols.) of hot ethyl iodide, and 35 grams ($1\frac{1}{2}$ mols.) of dry silver oxide were added in small portions to the hot solution. The addition of each portion induced a moderate reaction, which, after all the oxide had been added, lasted half an hour. The mixture was subsequently boiled for one hour, and the product extracted repeatedly by dry ether. After removal of ether on the water-bath, the liquid was left for 24 hours, during which time some unchanged acetanilide was deposited. The remaining liquid was fractionated in a vacuum. The main fraction boiled at 99—100° under 10 mm. pressure, weighed

9 grams, and was a colourless, mobile liquid smelling of geranium; it displayed no tendency to solidify, either upon cooling or after prolonged standing. In addition to this liquid product, a further small quantity of acetanilide was obtained.

The liquid was analysed.

0.2084 gave 0.5600 CO₂ and 0.1510 H₂O. C = 73.28; H = 8.05.

0.1556 „ 0.4192 CO₂ „ 0.1134 H₂O. C = 73.47; H = 8.09.

0.2370 „ 18.0 c.c. moist nitrogen at 5.5° and 733 mm. N = 8.92.

C₆H₅·N:C(O·C₂H₅)·CH₃ requires C = 73.62; H = 7.97; N = 8.59 per cent.

The boiling point of ethyl isoacetanilide under the ordinary pressure is 207—208°. The compound is extremely easily hydrolysed by dilute hydrochloric acid, in which it dissolves rapidly in the cold, and on addition of an excess of platinum chloride to the solution, aniline platinichloride separates in aggregates of blade-like crystals (Pt = 32.60; calculated 32.69 per cent.). This, when shaken with sodium hydroxide solution, gave an oil which coloured calcium hypochlorite solution purple.

On warming a solution of ethyl isoacetanilide for a few moments with concentrated hydrochloric acid, the smell of ethyl acetate was perceptible, and, on cooling, crystals of aniline hydrochloride were deposited.

Like methyl isoformanilide (Comstock and Kleeborg, *loc. cit.*), it yields an amidine by interaction with aniline. Ethyl isoacetanilide (3 grams) was warmed for 5 hours on the water-bath with aniline (2 grams), and the reaction completed by boiling the liquid for a few moments; on cooling, the substance solidified, and was identified as diphenylmethylamidine, melting at 131—132° (Biedermann, *Ber.*, 1874, 7, 540). Four grams of amidine were produced.

0.1910 gave 22.0 c.c. moist nitrogen at 4° and 723 mm. N = 13.43.

C₁₄H₁₄N₂ requires N = 13.33 per cent.

V. *Action of Dry Silver Oxide and Ethyl Iodide on Ethyl Acetoacetate.*

The alkylation of ethyl acetoacetate by the action of silver oxide and alkyl iodides, in addition to serving as an instance of the application of the method to this particular class of compound, is of special interest as affording a possible means for the production of the isomeric ethers in place of the alkyl compounds formed by the action of sodium ethoxide and alkyl iodides. From the fact that silver oxide and iodides effect the direct etherification of the alcoholic hydroxy-group of certain compounds, it seemed quite likely that in the interaction (if any) with ethyl acetoacetate the latter would react

in the enolic form as ethyl β -hydroxycrotonate, and that the product would be ethyl β -ethoxycrotonate. The methoxy-compound has been obtained by the alkylation of ethyl acetoacetate by diazomethane, a reagent which lends itself to the formation of ethers of hydroxy-compounds of acid or feebly acid character (von Pechmann, *Ber.*, 1895, **28**, 1624); the ethoxy-derivative by the action of sodium ethoxide on ethyl β -isochlorocrotonate (Friedrich, *Annalen*, 1883, **219**, 333), and from ethyl acetoacetate by interaction with ethyl orthoformate (Claisen, *Ber.*, 1896, **29**, 1006).

After preliminary experiments with from 20 to 50 grams of ethyl acetoacetate had shown that the product of the interaction with silver oxide and ethyl iodide was mainly ethyl ethylacetoacetate, mixed, however, with a very small proportion of ethyl β -ethoxycrotonate, the following preparation on a large scale was carried out with the object of isolating the latter in a state of purity. Dry silver oxide (174 grams) was added in small portions to a mixture of ethyl acetoacetate (90 grams) and ethyl iodide (237 grams). On warming, after the addition of the first portion of oxide, a vigorous action set in, which was moderated by cooling from time to time with water. After all the oxide had been added and the spontaneous reaction had ceased, the mixture was boiled for 45 minutes. Some water was formed in the reaction. The liquid was filtered, the residue washed four times with ether, and the ethereal solution fractionated after drying over anhydrous sodium sulphate. After removal of ether and excess of iodide, the boiling point rose rapidly to 190° , and 75 grams boiling at 190 – 198° , together with 9 grams boiling at 198 – 205° , were collected. The residue in the distillation flask was small. As both fractions gave a violet colour with alcoholic ferric chloride, they were united, and the ethyl ethylacetoacetate removed by hydrolysis with 60 grams of potassium hydroxide dissolved in 600 c.c. of water. On shaking and warming, nearly all the ester passed into solution, and on further heating a clear, oily layer (ketone) separated. In all, the liquid was heated for less than half an hour. The ketone and unchanged ester were extracted by shaking out twice with ether, and the ethereal solution, after being dried over calcium chloride, was distilled. After removal of the ether on the water-bath, the ketone was distilled off below 110° , a small fraction was collected between 110° and 186° , and the remainder between 186° and 190° . The last fraction gave no coloration with ferric chloride, and on cooling solidified almost completely in tabular crystals, which only partially fused on standing at the temperature of the laboratory. The nearly solid substance was drained as far as possible on the filter pump, and washed with a small quantity of ether. The crystals thus obtained were rather moist, but after pressing on filter paper melted

at 29—30° and were identified as ethyl β -ethoxycrotonate (compare Friedrich, *loc. cit.*). On analysis:

0.1554 gave 0.3461 CO_2 and 0.1256 H_2O . C = 60.74 ; H = 8.98.

$\text{C}_8\text{H}_{14}\text{O}_3$ requires C = 60.76 ; H = 8.86 per cent.

On prolonged standing, the crotonate separated in long, rectangular plates from the impure liquors, removed in the preparation of a pure sample. That the substance was ethyl β -ethoxycrotonate, and not ethyl ethylacetoacetate, was further shown by the facts that it gave no colour with ferric chloride, and that, on hydrolysis with potassium hydroxide, an acid melting and decomposing at 137.5° was obtained.

The alkaline solution, obtained in the removal of the ethyl ethylacetoacetate, upon cautious acidification in the cold with dilute sulphuric acid, yielded a small quantity of β -ethoxycrotonic acid, which separated on spontaneous evaporation of an ethereal solution in well defined, prismatic crystals melting and decomposing at 137.5°. The total quantity of β -ethoxycrotonate formed in the reaction was, as far as could be ascertained, not more than 5 grams, or about 5 per cent. of the whole.

Sodium β -ethoxycrotonate is decomposed on warming in aqueous solution. It is conceivable that any crotonate produced in the alkylation of ethyl acetoacetate by sodium ethoxide might be decomposed in the process of separation, owing to the presence of adventitious traces of hydroxide. The alkylation of ethyl acetoacetate was therefore effected by the aid of potassium ethoxide and ethyl iodide, and the ester examined by the method of hydrolysis described in the case of the silver oxide product. A small quantity of a liquid, which boiled at 210—214°, gave no colour with ferric chloride, and dissolved in potassium hydroxide solution with separation of an oil, was obtained on distilling the methyl propyl ketone and non-hydrolysed oil. This was in all probability ethyl diethylacetoacetate (b. p. 218°). From the alkaline liquor, dilute sulphuric acid precipitated an oily acid, which on long standing partially solidified, the solid melting at 109° without decomposition. It was probably dehydracetic acid (m. p. 108.5—109°), and the quantity was extremely small. No trace of β -ethoxycrotonic acid could be detected.

Modification of the method of carrying out the alkylation of ethyl acetoacetate by means of silver oxide may result in the reaction pursuing a different course, as in the following instance, in which the ethyl iodide was added to the mixture of ester and oxide. The addition of a small quantity of iodide caused a considerable rise in temperature, white fumes appearing in the flask. As it was desired to keep down the temperature, benzene was added, and then the remainder of the iodide was introduced in small quantities. The reaction was

completed by heating for a short time on the steam-bath. More water was formed than in the case of the addition of the oxide to the ester and iodide (p. 739). After removal of benzene and iodide, the ester, which gave a reddish-violet tint with alcoholic ferric chloride, was distilled off. A considerable residue remained in the flask. After standing all night, it partially solidified to needles. In a vacuum, about half of this residue distilled over at approximately 210° under 20 mm. pressure. This distillate was crystallised from light petroleum, from which it separated in fine needles melting at $102-105^{\circ}$. Only 0.7 gram was obtained from 65 grams of ethyl acetoacetate, and after recrystallisation from ether, this gave 0.5 gram, melting at $103-106^{\circ}$. The substance gave a deep blue tint with alcoholic ferric chloride.

Analysis gave figures agreeing best with those required for ethyl diacetylfumarate.

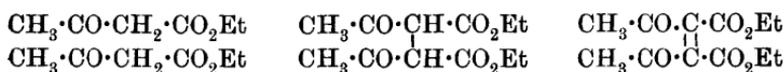
0.1646 gave 0.3420 CO_2 and 0.0912 H_2O . C = 56.66 ; H = 6.15.

0.1578 „ 0.3263 CO_2 „ 0.0840 H_2O . C = 56.39 ; H = 5.91.

$\text{C}_{12}\text{H}_{16}\text{O}_6$ requires C = 56.26 ; H = 6.25 per cent.

No other product could be isolated in a state of purity from the oily residue of high boiling point.

Ethyl diacetylfumarate (m. p. $95.5-96^{\circ}$) has been prepared by the action of iodine on ethyl sodiodiacetylsuccinate (Just, *Ber.*, 1885, 18, 2636), and by the action of finely divided silver on ethyl iodoacetoacetate (Schönbrodt, *Annalen*, 1889, 253, 196). Its formation in the action of silver oxide on ethyl acetoacetate is readily explicable, if it is regarded as produced by oxidation, either directly or through the intermediary of ethyl diacetosuccinate :



Attempts to obtain the acid by hydrolysis with alcoholic potassium hydroxide, resulted only in the production of resinous matter (compare Paal and Härtel, *Ber.*, 1897, 30, 1994).

Action of Silver Oxide and Ethyl Iodide on Ethyl Ethylacetoacetate.

Alkylation of ethyl ethylacetoacetate by silver oxide and ethyl iodide seems to occur, but only to a very slight extent. Forty-eight grams of ethyl ethylacetoacetate (b. p. $193-195^{\circ}$) were boiled with 70 grams of silver oxide and 94 grams of ethyl iodide for 3 hours. The silver residue weighed 112 grams (calculated 142). The ester was separated into three fractions, the first, boiling at $195-198^{\circ}$, constituted the main fraction ; the others were small, and boiled at $198-203^{\circ}$ and $203-214^{\circ}$. All three coloured alcoholic ferric chloride violet. By

partial hydrolysis, a small quantity (about 6 grams) of ester boiling at 204—214° was obtained. It gave no colour with ferric chloride, and on boiling with aqueous potassium hydroxide, gave a non-hydrolysable oil (ketone). No solid acid could be detected among the products of complete hydrolysis. Apparently, the homologue of ethyl β -ethoxycrotonate is not one of the products, or, at any rate, if formed, is produced only in very minute quantities.

VI. *Action of Dry Silver Oxide and Ethyl Iodoacetate on Ethyl Acetoacetate.*

The following experiment was undertaken in order to ascertain whether, in the synthesis of ethyl acetosuccinate from ethyl acetoacetate by the aid of sodium ethoxide and halogen substituted ethyl acetates, silver oxide could be employed in place of sodium ethoxide.

Various experiments had indicated that the use of chloro- or bromo-compounds gives less satisfactory results than that of iodo-derivatives. Ethyl iodoacetate, prepared by the action of potassium iodide on the chloroacetate, was therefore employed in preference to chloroacetate; its boiling point was 170—180°, and it probably contained some chloroacetate. Dry silver oxide (23 grams) was added in two portions to a mixture of 13 grams of ethyl acetoacetate and 21 grams of ethyl iodoacetate. After the reaction had been started on the water-bath, the liquid became very warm, and the flask was therefore cooled to moderate the action. A black deposit, purple by transmitted light, formed on the flask, indicating that metallic silver had in all probability been formed. After the reaction had moderated, benzene was added, and the liquid boiled for some time on the water-bath. Water was formed in the reaction. The solution was filtered, and the residue, which was very dark coloured, was washed with ether. After removal of the solvent, the oily residue was distilled in a vacuum. The main fraction, weighing 8 grams, boiled at 142—144° under 16 mm. pressure, and was an oil of faint, sweetish odour; one drop gave a distinct reddish-violet tint to an alcoholic solution of ferric chloride. As ethyl acetosuccinate gives no coloration with this agent (Conrad, *Annalen*, 1877, 183, 220), it was thought possible that the coloration might be due to the presence of traces of ethyl acetoacetate, but after redistillation in a vacuum, the same tint was given. Analysis gave figures agreeing with those required for ethyl acetosuccinate.

0.1833 gave 0.3715 CO₂ and 0.1231 H₂O. C = 55.27; H = 7.46.

C₁₀H₁₆O₅ requires C = 55.55; H = 7.40 per cent.

On hydrolysis with strong alcoholic potassium hydroxide, the substance gave succinic acid, melting at 179°, which was converted into barium salt. This was dried at 130° and analysed.

0.1265 gave 0.1159 BaSO_4 . Ba = 53.85.

$\text{C}_4\text{H}_4\text{O}_4\text{Ba}$ requires Ba = 54.22 per cent.

A second preparation was undertaken, in order to ascertain whether better yields of the acetosuccinate could be obtained. The silver oxide (46 grams) was added in the cold, and in small portions, to a mixture of 26 grams of ethyl acetoacetate and 43 grams of ethyl iodoacetate. The temperature of the liquid rose considerably on addition of each portion of oxide, and the action was allowed to subside before the next portion was added; 18 grams of acetosuccinate were obtained. The residue in the distillation flask was large. It did not solidify on prolonged standing, and, on attempting to distil it in a vacuum, partial decomposition occurred. A small quantity of a viscid oil distilled over below 210° under 17 mm. pressure, and a thick, tarry residue remained in the flask.

It seemed difficult to account for the fact that the acetosuccinate, prepared as above, gives a distinct coloration with alcoholic ferric chloride. This cannot be due to the presence of traces of oxidation products such as ethyl diacetofumarate, as redistillation does not deprive the compound of this property, and as the coloration is still given after the compound has been dissolved in sodium hydroxide and reprecipitated by acid. The explanation is to be found in the fact that, when prepared by the action of ethyl chloroacetate on ethyl sodioacetoacetate, the acetosuccinate is distinctly acid after distillation in a vacuum, whereas the product as obtained by the silver oxide method is almost exactly neutral. A sample of ethyl acetosuccinate, prepared by the aid of sodium ethoxide and giving no colour with ferric chloride, was shaken with sodium carbonate solution, in which it is insoluble. The neutral ether thus obtained coloured alcoholic ferric chloride in precisely the same way as the silver oxide product. The coloration given by neutral ethyl acetosuccinate is immediately discharged by the addition of a trace of hydrochloric acid; it is reproduced by the addition of a minute quantity of sodium carbonate, but again discharged by an excess of alkali. The coloration given to alcoholic ferric chloride by other substances, such as ethyl acetoacetate and salicylic acid, is similarly destroyed by the presence of free acid or alkali; thus, the red coloration of ethyl acetoacetate is destroyed by a trace of piperidine, reproduced by neutralisation with hydrochloric acid, and destroyed by an excess of hydrochloric acid.

VII. *Action of Silver Oxide and Ethyl Iodide on Ethyl Malonate.*

Ethyl malonate presents an instance of a ketonic compound which might exist in the labile hydroxy-form. That the substance does not

react in the hydroxy-form is shown by the fact that diazomethane is without action on it (von Pechmann, *loc. cit.*, 1628). Claisen (*Ber.*, 1892, 25, 1764) has further pointed out that the replacement of a hydrogen atom of the methyl group of ethyl acetate by the feebly negative carbethoxy-group is likely to lead to the formation of a compound behaving solely in accordance with the ketonic structure. In event of the malonate reacting with the oxide and iodide in the labile form $\begin{matrix} \text{EtO} \\ \text{HO} \end{matrix} > \text{C} : \text{CH} \cdot \text{CO}_2 \text{Et}$, the product would be a β -diethoxyacrylate, which on hydrolysis with potassium hydroxide would in all probability yield β -diethoxyacrylic acid, but under these conditions might also give, by elimination of the ethyl groups attached to oxygen, dihydroxyacrylic, that is, malonic, acid.

Preliminary experiments showed that interaction, if any, was very incomplete, but sufficient indication of the formation of ethyl ethylmalonate was afforded to justify the attempt to isolate it from the product. Sixty-nine grams of dry silver oxide ($1\frac{1}{2}$ mols.) were added to a mixture of 32 grams (1 mol.) of ethyl malonate and 93 grams (3 mols.) of ethyl iodide. Reaction, as indicated by moderate ebullition, was started by warming on the steam-bath, and lasted of itself for half an hour, the mixture being subsequently boiled for 5 hours. No water could be detected in the product, and the silver residue, which was dark brown, weighed 126 grams (calculated 141 grams). By distillation, 28 grams of ester boiling at $192-203^\circ$ were obtained. The residue in the distillation flask was very small, indicating that oxidation had not occurred to any considerable extent. The ester was subjected to partial hydrolysis by boiling with a solution of 15 grams of potassium hydroxide in 60 c.c. of water for 1 hour, and allowing to stand, with frequent shaking, for 24 hours. The non-hydrolysed oil was extracted with ether, and the ethereal solution, after drying with calcium chloride, on distillation gave 2 grams boiling at $195-203^\circ$ (rejected), and 8 grams boiling at $203-206^\circ$. The latter fraction was hydrolysed by boiling with 7 grams of potassium hydroxide dissolved in 20 c.c. of water, sufficient alcohol being added to secure the solution of the oil. The resulting alkaline solution was neutralised by the addition of hydrochloric acid and ammonium hydroxide, and the boiling liquid precipitated by a hot concentrated solution of 8 grams of calcium chloride. The amorphous calcium salt thus obtained was washed with boiling water until free from chloride. A portion dried at 120° was analysed.

0.3738 gave 0.2986 CaSO_4 . Found $\text{Ca} = 23.49$.

$\text{C}_2\text{H}_5 \cdot \text{CH}(\text{CO}_2)_2\text{Ca}$ requires $\text{Ca} = 23.53$ per cent.

That the salt was calcium ethylmalonate was further shown by de-

composing a portion with concentrated hydrochloric acid, and extracting with ether. On evaporation of the ether, a crystalline acid was left, which after drying on a porous tile melted at 111.5° , and commenced to decompose at 160° .

VIII. *Action of Dry Silver Oxide and Methyl Iodide on Salicylic Acid.*

The comparatively strong acidic character of phenolic hydroxyl rendered it practically certain that alkylation of phenols can be effected by means of silver oxide and iodides. Salicylic acid was selected for examination, as containing carboxyl in addition to the phenolic hydroxy-group, and therefore further serving to illustrate the esterification of acids by the use of the reagent. Moreover, the products obtained by the silver oxide method being usually very pure and free from resinous matter, the application of the method to phenolic substances was likely to lead to the formation of compounds free from the resinous matter generally produced by the application of potassium hydroxide and iodides. The interaction of 50 grams of silver oxide and a solution of 20 grams of salicylic acid in 62 grams of methyl iodide and 40 c.c. of benzene was very vigorous, but incomplete. The resulting ester, 17.5 grams, was neutral, and consisted of a mixture of methyl esters of salicylic and methoxybenzoic acids, as shown by the irregularity of the boiling point ($228-240^{\circ}$), and by the production on hydrolysis of an acid which melted at $100-130^{\circ}$, and gave a violet colour with neutral aqueous ferric chloride. 12.5 grams of the mixed esters were therefore again treated with 20 grams of oxide and 25 grams of methyl iodide. No water was formed in the second treatment. By extraction of the oily products with ether and distillation, 12 grams of methyl methoxybenzoate boiling at 245° were obtained, the boiling point being given as 228° by Fölsing (*Ber.*, 1884, 17, 486). Five grams of the ester were hydrolysed by warming with a solution of 5 grams of potassium hydroxide in 20 c.c. of water, until the disappearance of oil. By acidification, 4.5 grams of methoxybenzoic acid, giving no colour with ferric chloride, were obtained. The acid was further purified by solution in a small quantity of warm alcohol and addition of about 3 volumes of water; on cooling, it was deposited in lustrous prisms melting at 99° . The following results were obtained on analysis :

0.1504 gave 0.3470 CO_2 and 0.0721 H_2O . C = 62.92 ; H = 5.32.

$\text{C}_8\text{H}_8\text{O}_3$ requires C = 63.15 ; H = 5.26 per cent.

The production of the pure ester in one operation could apparently have been effected by employment of a larger excess of oxide, in

which case, too, the yield would probably have been better. The use of silver oxide and methyl iodide leads to the formation of a very clean product.

IX. *Action of Silver Oxide and Ethyl Iodide on Benzaldehyde.*

Since the action of silver oxide frequently results in oxidation, the following experiment was carried out in order to see whether it would be possible to effect the oxidation of an aldehyde and esterification of the acid in one operation. Fifteen grams of benzaldehyde, 35 grams of silver oxide, and 48 grams of ethyl iodide were used, and the reaction was very vigorous; the silver residue weighed 50 grams. From the proportions taken, it was to be expected that one-half of the aldehyde would be oxidised and esterified. The product was a mixture of benzaldehyde and ethyl benzoate. After the removal of the greater part of the aldehyde by fractionation, the ester was freed from traces of aldehyde by repeated extraction with sodium hydrogen sulphite solution. Ethyl benzoate boiling at 206° and yielding on hydrolysis benzoic acid melting at 121° was thus obtained.

Discussion of Results.

With respect to the general aspects of the behaviour of silver oxide and alkyl halides as an alkylating agent, it may be remarked that the course of the reaction is usually smooth and rapid. In many instances, complete alkylation is not effected by one treatment, and in others, for example, that of benzoin, the reaction may be slower owing to the insolubility of the substance to be alkylated. The limit of applicability may be regarded as reached in the cases of compounds insoluble in the halide or some neutral solvent. The difficulty of removing inorganic bye-products is reduced to a minimum. In the case of the esterification of acids by the aid of mineral acids, or of acids whose silver salts are unstable, the direct application of silver oxide and alkyl iodides would doubtless secure considerable saving, both in time and material. The possibly prejudicial effect of the water usually formed in the reaction is, to a great extent, mitigated by the practical insolubility of water in the halide, and may, in certain cases, be reduced to a minimum by the employment of a sufficient excess of silver oxide and halide.

It will be seen that the reaction is applicable to the alkylation of typical compounds of all the classes enumerated in the introduction. It is apparently the only reaction whereby direct alkylation of the esters of hydroxy-acids may be brought about.

As regards the suitability of particular halides, iodo-compounds are

found to yield the best results. This is due no doubt in great measure to the inferior stability and consequently readier resolution of iodo- as compared with bromo- and chloro-derivatives. It is possible, however, that a connection may be traced between the fact that the molecular volume of silver iodide is greater than the sum of the atomic volumes of silver and iodine (in other words, there is an expansion in the formation of silver iodide), and the generally observed fact that the elimination of silver iodide in processes of organic synthesis is marked by especial ease. So far as our knowledge of the conditions modifying chemical change goes, it can only be said that this is a coincidence; the two facts may, however, be causally related. In this connection, it is of interest to note that similar volume relations hold for mercuric iodide, and mercuric oxide has been shown to be capable of use instead of silver oxide in the alkylation of ethyl malate (Purdie and Pitkeathly, *loc. cit.*, 157). The tardier action of chloro- and bromo-compounds is, moreover, detrimental, as greater chances are thereby afforded for the occurrence of reactions involving oxidation. Of the alkyl iodides, methyl and ethyl are most suitable, and of these the former lends itself more readily to the reaction than the latter. With isopropyl iodide, the reaction is usually not so complete, for example, in the case of benzoin. This may quite readily be accounted for by the fact that the interaction with silver oxide, with formation of alkyl ethers, is notably less vigorous in the cases of methyl and ethyl than in that of isopropyl iodide.

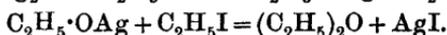
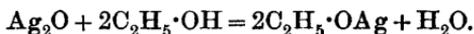
The phenomena of oxidation depend greatly, as was shown in the alkylation of ethyl acetoacetate, upon the conditions under which the experiment is carried out. That oxidation should occur is quite conceivable; in the absence of alkyl iodides, oxidation is extremely vigorous, usually resulting in the production of resinous matter. Oxidation may be almost entirely avoided, either by adding the oxide to a mixture of the compound to be alkylated and the alkyl halide, or by adding the substance to a mixture of oxide and halide.

The simplest explanation of the mechanism of the reaction is that the silver oxide serves merely as a means of removing the elements of hydrogen iodide from the sphere of action. That this view is inadequate is shown by the fact that other oxides, such as those of lead, copper, and zinc, are incapable of replacing oxide of silver in the reaction.

The weight of evidence inclines to the view, that the silver oxide acts in virtue of the production of silver derivatives of greater or less stability, which then, by double decomposition with the alkyl iodide, yield the corresponding ethers. According to this view, all the cases of alkylation by this method fall under the second general heading mentioned in the introduction (p. 730). As to the manner in which

the substitution of silver, and eventually alkyl, for hydrogen is brought about, it may certainly be assumed to occur in cases such as those of esters of hydroxy-acids, in virtue of some such preliminary addition of the elements of silver oxide, as that assumed in Walden's explanation of the optical inversion in the conversion of active chlorosuccinic acids into active malic acids (*Ber.*, 1899, **32**, 1850). In application to a saturated compound like menthol, recourse would have to be made to the theory of the quadrivalency of oxygen. It seems preferable, however, to regard the reaction in every instance as simply one of double decomposition, the hydrogen atom ultimately replaced by alkyls being first replaced by silver. The cycle of changes involved could then be represented by the equations: $2ROH + Ag_2O = 2ROAg + H_2O$; $2ROAg + 2R'I = 2ROR' + 2AgI$; $Ag_2O + H_2O + 2R'I = 2R'OH + 2AgI$.

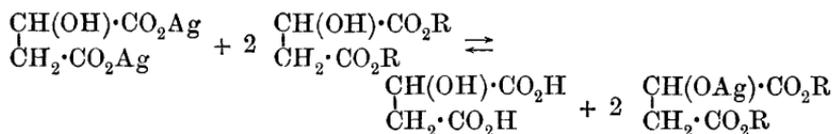
The direct interaction of dry silver oxide and alkyl iodides with formation of ethers represents a process of simple double decomposition, $Ag_2O + 2RI = R_2O + 2AgI$, and is comparable with the production, by the action of basic oxides, of diglycollic acid from chloroacetic acid (Schreiber, *J. pr. Chem.*, 1876, [ii], **13**, 436), and of ether by the action of sodium oxide upon ethyl iodide (Greene, *Bull. Soc. Chim.*, 1878, [ii], **29**, 458). With regard to the cases of ether formation mentioned in the introduction, it must be pointed out that Linne-
mann, in the preparation of propyl ether, employed a mixture of propyl iodide, dry silver oxide, and acetic acid, and that Erlenmeyer, in preparing isopropyl ether, used moist silver oxide. Wurtz (*loc. cit.*) states that interaction of dry silver oxide and ethyl or methyl iodides is very energetic, the substances reacting immediately on one another, with great disengagement of heat. In the author's experience, reaction between thoroughly dried oxide and iodide is very tardy. When 23 grams of dry oxide were added to 32 grams of ethyl iodide, the temperature rose momentarily from 14.5—15°, and then sank steadily, remaining in a corked flask at the temperature of the laboratory for many hours. After standing 3½ days, the liquid was filtered. The liquid consisted mainly of unchanged iodide. The residue, dried at 100°, weighed 29 grams (silver iodide requires 47), indicating that about 25 per cent. of the oxide had entered into reaction. It is probable that interaction with formation of ethers depends upon the presence, or initial formation, of small quantities of alcohol (or water), thus,



The fact that in the presence of a third, more acidic compound the action results in the alkylation of that compound, rather than

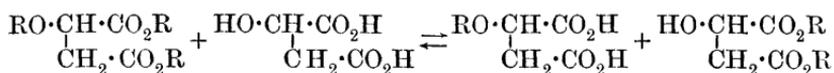
in the production of ether, would follow from the relatively small tendency of the alcohol to form intermediate silver salts.

The formation of unstable silver salts of esters of hydroxy-acids may afford an explanation of the production of esters of alkyloxy-acids in the interaction of silver salts and alkyl iodides (Purdie and Lander, *Trans.*, 1898, **73**, 289). We may imagine in this instance that the ester of the hydroxy-acid, in virtue of its feebly acidic character, enters into double decomposition according to the reversible reaction :



The silver compound of the ester would then undergo further reaction with the alkyl iodide, yielding the alkyloxy-ester. The production of alkyloxy-esters in the interaction of iodides and oxy-silver salts is accompanied in all cases by the production of free organic acid, and the amount of alkyloxy-ester produced varies with the amount of free acid obtained. This fact finds ready explanation by the assumption here made. The explanation, it is true, scarcely covers the fact that free alkyloxy-acid is also found, although in very much smaller proportion, along with free hydroxy-acid.

Free alkyloxy-acid might, however, result from the partition of the ethyl group between the free hydroxy-acid and alkyloxy-ester :



or more simply by the partial hydrolysis possibly effected by the dry potassium carbonate, used in the removal of free acid from the product.

It must be pointed out that the greater production of free acid in the action of isopropyl than in that of ethyl iodide, may be due to the decomposition of the iodide $\text{CH}_3 \cdot \text{CHI} \cdot \text{CH}_3 = \text{HI} + \text{CH}_3 \cdot \text{CH} \cdot \text{CH}_2$. The corresponding reaction with ethyl iodide is not, however, so likely to occur.

If this view of the reactions in question be correct, it might be expected that the formation of esters of alkyloxy-acids could be brought about by the joint action of ethyl iodide and the silver salt of a weak acid on an ester of a hydroxy-acid. As a test case, the action of silver carbonate and ethyl iodide on ethyl tartrate was examined. No action occurred in the cold during one hour with a mixture of 39 grams of silver carbonate, 20 grams of ethyl tartrate, and 44 grams of ethyl iodide. On boiling, a moderately energetic

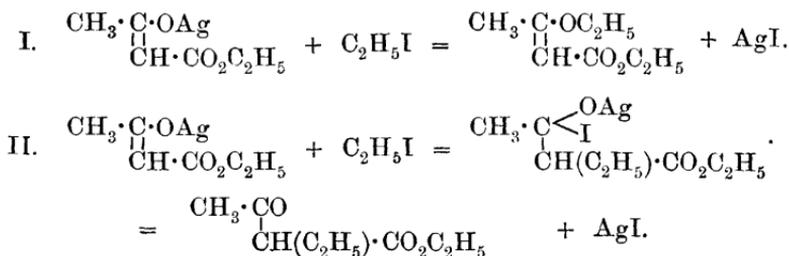
action set in, the yellow silver salt rapidly darkening, and eventually turning black. The product, after 4 hours boiling, was a viscid, neutral liquid. After removal of ethyl carbonate in a vacuum, the bulk of the substance distilled over between 151° and 154° under 11 mm. pressure. In a 100 mm. tube at 20° , the liquid gave $\alpha_D + 32.02^{\circ}$. Ethyl tartrate gives at the same temperature $\alpha_D + 9.13^{\circ}$, and ethyl diethoxysuccinate at 18° , $\alpha_D + 97.52^{\circ}$ (Purdie and Pitkeathly, *loc. cit.*, 159). The notable increase in rotation caused by the action of silver carbonate and ethyl iodide is attributable most simply to the formation of roughly 25 per cent. of dialkyloxy-ester.

A mixture of silver acetate, ethyl tartrate, and excess of ethyl iodide was similarly boiled for 3 hours. Free acid resulted as one of the products, and was removed by potassium carbonate. About one-half of the neutral product consisted of unchanged ethyl tartrate ($\alpha_D^{20} + 9.25^{\circ}$); the remainder was a thick, tarry mass, which could not be distilled in a vacuum. Apart from the small likelihood of partition of silver occurring between a strong acid, such as acetic, and a hydroxy-ester, the fact that the reaction apparently pursued a different course from that anticipated renders the result of the experiment inconclusive.

The results obtained with ethyl acetoacetate are of interest with respect to the question of the probable constitution of this substance. Physical considerations are regarded as proving that ethyl acetoacetate consists mainly of the ketonic form, mixed, however, with a small proportion of the enolic form, the substance presenting an instance of equilibrium of the unimolecular type, as suggested by Traube (*Ber.*, 1896, 29, 1715). The failure of chemical methods of proof of the presence of the two dynamic isomerides in ethyl acetoacetate is attributable in great measure to the fact that a substituting agent usually acts exclusively with one or the other form, as is well shown in the case of diazomethane (von Pechmann, *loc. cit.*). In this particular instance, the equilibrium law would lead us to expect that, as soon as the enolic form has been rendered stable by conversion into methoxycrotonate, more of the enolic form will be produced from the ketonic form, in quantity depending upon the coefficients of velocity of the two isomeric changes, until eventually the whole of the substance has reacted in the enolic form. Such considerations (compare Lowry, *Trans.*, 1899, 75, 241) serve to account for the influence of the so-called ketonising and enolising agents in determining in which form condensation with benzalaniline shall ensue (Schiff, *Ber.*, 1898, 31, 207, 601). Similarly, in the interaction of ethyl acetoacetate with ethyl orthoformate, even although some proportion of the substance were initially present in the hydroxy-form, in so far as the orthoformate appears capable of reaction only with the ketonic form

(Claisen, *Ber.*, 1896, 29, 1005), eventually the whole of the acetoacetate will have reacted in the latter form. Granting that alkylation by means of silver oxide and iodides depends upon the preliminary formation of silver substitution compounds of types corresponding to those of the alkyl derivatives eventually obtained, the simultaneous production from ethyl acetoacetate of both $O \cdot C_2H_5$ and $C \cdot C_2H_5$ homologues, points to the prior formation of the two silver salts, $CH_3 \cdot C(OAg) : CH \cdot CO_2C_2H_5$ and $CH_3 \cdot CO \cdot CHAg \cdot CO_2C_2H_5$, and therefore to the existence of both ketonic and enolic forms in the original substance. If the silver oxide is assumed to act merely by elimination of the elements of hydrogen iodide, the conclusion is more direct, or even unavoidable. The elements of hydrogen iodide would be removed from the ethyl iodide and the replaceable hydrogen atom of the two characteristic groupings $\cdot CO \cdot CH_2 \cdot$ and $\cdot C(OH) : CH \cdot$, and the results obtained would therefore indicate the presence of both these groups in ethyl acetoacetate. As stated above, the view that silver derivatives are actually formed is adopted here.

In cases of syntheses effected by the aid of metallo-derivatives, such as the formation of alkyl homologues from ethyl sodioacetoacetate, in so far as only one type of alkyl homologue is produced, it is possible to explain its formation either by the ONa or CNa constitution for the sodium salt. Where both types of derivative are produced, as, for example, in the action of ethyl chlorocarbonate on ethyl sodioacetoacetate (Claisen, *Ber.*, 1892, 25, 1768), and in the action of acetyl chloride on the sodium and copper compounds (Nef, *Annalen*, 1893, 276, 222), it may be assumed (Nef) that the interaction is of two distinct kinds, namely, double decomposition, and replacement with prior addition. The assumption, certainly by no means improbable, is here made that two definite substances interact, not in one, but in two senses, the course of the reaction of silver oxide and ethyl iodide with ethyl acetoacetate being admittedly susceptible of explanation in the two following ways :



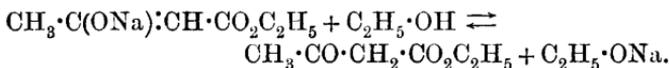
Similar equations would serve to account for the formation of both types of ethyl compound, using the $CH_3 \cdot CO \cdot CHAg \cdot CO_2C_2H_5$ formula, if the elements of C_2H_5I in the indirect action are assumed to be

added on to the CO group. In conformity with the known tendency on the part of silver to form salts corresponding to the enolic or labile form of tautomeric compounds (for example, benzamide, succinimide), it might be expected that the silver salt of ethyl acetoacetate would possess the OAg structure. As such, since interaction with ethyl iodide results in the formation of the $O \cdot C_2H_5$ compound in small proportion, it seems difficult to account for the fact that the $C \cdot C_2H_5$ compound constitutes the main product, unless the simultaneous formation of CAg salt is assumed.

The author has been led to adopt the view that both types of silver salt are capable of formation and interaction simply by double decomposition, not only as affording the simplest explanation of the results obtained, but also because it seems to be in harmony with the state of ethyl acetoacetate as a tautomeric pair in dynamic equilibrium. A somewhat important factor in the consideration of the mechanism of interaction of an agent such as silver oxide and ethyl iodide with a mixture of dynamic isomerides, such as ethyl acetoacetate, is the speed with which the reaction once initiated proceeds. By analogy, it might reasonably be expected that the ease with which oxide of silver interacts with formation of OAg salt would be superior to that with which CAg salt is produced. If the rate of interaction of the ester, oxide, and iodide were slow, time would be allowed for the isomerisation of the ketonic form, so that the reaction would run a course parallel to that with diazomethane. The reaction, on the contrary, is very rapid. Admitting the existence of an affinity between oxide and ether tending to the production of the CAg salt, even were it considerably inferior to that tending to produce the OAg salt, little time is allowed for the ketonic form to undergo the isomerisation necessary for the production of the latter. Traube's observations (*loc. cit.*) of the rate of change of density in solution of ethyl acetoacetate indicate that comparatively large intervals of time are required for the establishment of the condition of equilibrium. That the state of equilibrium is not very greatly affected either by change of temperature or influence of solvent is shown by Perkin's observations of electromagnetic rotation (*Trans.*, 1892, 61, 808), and by Wislicenus' colorimetric results (*Annalen*, 1896, 291, 175; *Ber.*, 1899, 32, 2839).

By inference from the case of silver, provided the view here expressed be accepted, it might be inferred by analogy that the constitution of the sodium, and possibly also potassium, salts of ethyl acetoacetate, should be represented as belonging to the CM type. No stress is laid upon such processes of inference. From the fact that occasionally the sodium salt affords derivatives of both types, it might be argued that sodium salts of both types exist. In the author's opinion, the mode of interaction of the sodio-salt may depend in great

measure upon the mode of its application. Claisen's observation that the interaction of an alcoholic solution of ethyl sodioacetoacetate with ethyl chlorocarbonate leads mainly to the production of ethyl carbonate, suggests the conclusion that the alcoholic solution of sodium salt consists of a mixture in equilibrium of ethyl sodioacetoacetate, alcohol, ethyl acetoacetate, and sodium ethoxide :



In such case, it is not easy to say which form of salt undergoes reaction. Supposing that a CR product should be formed preferentially, temporary formation of CNa salt would account for the ultimate reaction of all the ester in that sense. Nevertheless, it should be mentioned that dry ethyl sodioacetoacetate, although the action of iodine effects the elimination of sodium apparently in the C position, yields both O- and C-derivatives by interaction with ethyl chlorocarbonate, in which case it is also employed in the anhydrous form. A similar case is that of ethyl disodiodiacetosuccinate, which, by the action of iodine on the dry salt, yields ethyl diacetofumarate (Just, *loc. cit.* ; compare Paal and Härtel, *loc. cit.*), and, under similar conditions, gives ethyl bisbenzoyloxycrotonate by the action of benzoyl chloride (Paal and Härtel). The formation of fumarate occurs, however, only to the extent of 5 to 10 per cent. Were a question of constitution under discussion, a complete answer to the question could only be given by accounting for the whole of the sodium salt used.

The author's thanks are due to Prof. Purdie for much valuable advice given during the course of this work.

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