

V.—*The Action of Halogens on Compounds containing the Carbonyl Group.*

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THE question of the nature of the mechanism of substitution in carbon compounds has attracted much attention during recent years, more especially in certain cases where the compounds are benzenoid in character and in which the process of substitution in the aromatic nucleus appears to involve the initial formation of an additive product of the compounds with the agent used or of an intermediate substitution product in which the substituting atom or group is not found in its final position of attachment.

Considerably less is known of the mode in which substitution occurs in fatty compounds; and in what is possibly the simplest case of all, namely, that of direct substitution such as occurs among the paraffins, it may be said that there is no evidence which affords any real assistance in arriving at conclusions as to the mechanism of the process, and generally these cases have been avoided as being the most difficult to solve.

The case of substitution in the group of compounds containing the complex $\text{:CH}\cdot\text{CO}$, such as ketones, aldehydes, carboxylic acids and their derivatives, is one of considerable interest, and in certain aspects has aroused much discussion, for there is here a possibility that the characteristic replaceability of the α -hydrogen atom may be not a direct process, but one due to the initial formation of the enolic form $\text{:C:C(OH)}\cdot$, and this view has appeared more probable since it has been shown that the nitro-paraffins, which in many respects resemble carbonyl compounds, are apparently not capable of being brominated directly, but are easily converted into monobromo-derivatives if they are first transformed into the *isonitro*-form which corresponds with the enolic forms of carbonyl compounds. It is a general rule, too, that those carbonyl compounds are the most easily attacked which are known to be capable of conversion into their enolic forms or one of the corresponding metallic derivatives.

The difficulty with which the paraffins are attacked by halogens renders this question of the mechanism of their substitution most difficult to investigate in a satisfactory way, and it seems desirable, therefore, that search should be made for some other class of more easily substituted compounds in which the process is direct, at least in the same sense as it probably is in the paraffin series, and the work described in the present paper was commenced in the hope that, after all, the bromination of simple ketones might prove to be mainly the

result of "direct" substitution. The results obtained, however, can only be interpreted on the opposite assumption; briefly stated, they were as follows.

The action of bromine on acetone in dilute aqueous solution is exceedingly slow, but becomes more rapid in presence of acids, the resulting accelerations being of the same order in the case of the more powerful mineral acids (sulphuric, hydrochloric, and nitric acids), and less obvious in the case of the weaker ones, such as acetic acid. The influence of hydrochloric acid on the velocity was not appreciably affected by the presence of an equivalent amount of potassium chloride or bromide. Neutral salts of strong bases and acids in general did not produce any marked influence on the speed of reaction. It was noticed, too, that the velocity observed in diffused daylight was not appreciably different from that in darkness.

The effect of the three mineral acids was nearly proportional to the amounts used, but in the case of sulphuric acid, between the concentrations 0.04- and 0.40-normal, the effect was proportionately slightly greater as the dilution increased. The velocity was nearly proportional to the concentration of acetone, but was practically independent of the concentration of the bromine.

Discussing these points in the reverse order, it may be observed that the independence of the velocity of reaction on the concentration of bromine shows clearly, first, that the reaction proceeds in at least two stages, in one or more of which the bromine is not involved, and, secondly, that in the stage or stages in which the bromine takes part, the velocity of reaction is so great that the time occupied is not measurable.

The approximate proportionality of the velocity to the concentration of the acetone indicates that in the reaction representing that stage, the velocity of which is measured, only one molecule of acetone takes part, whilst the observations as to the influence of acids of different concentration are best explained on the supposition that in this reaction one hydrogen ion is involved.

The increasing degree of dissociation of sulphuric acid due to dilution becomes apparent in the slight increase of the velocity constants representing the speed of absorption of bromine per equivalent of acid per litre.

The effects produced by sulphuric, nitric, and hydrochloric acids at the concentrations 0.40-normal were represented approximately by the numbers 1.19, 1.20, 1.36. These numbers, although of the same order of magnitude, are not proportional to the respective concentrations of the hydrogen ions. This discrepancy, however, is not without parallel, and does not militate seriously against the foregoing general conclusion.

It seems probable, then, that the bromination of acetone under the

conditions maintained is best regarded as the result of a slow, reversible change effected in the acetone by the hydrogen ions, followed by an almost instantaneous bromination of the product, a change which is not appreciably reversible. This intermediate product is perhaps the enolic form of the ketone, as it has been already shown that in many cases the rapid attainment of equilibrium between the tautomeric forms of carbonyl compounds is brought about by acids (Trans., 1902, 81, 1503, and 1903, 83, 1121), whilst there is ample reason for believing that the enolic forms are the more rapidly attacked by substituting agents.

It is clear, also, that the independence of the speed of reaction on the concentration of bromine shows that the velocity with which the second form of the acetone is brominated must be incomparably greater than that of the reverse change of the labile to the normal form, so that the observed velocity is a fairly precise measure of the speed with which acetone is converted from the normal into the less stable form.

In the case of the interaction of chlorine and acetone, the speed of reaction is more obviously dependent on the concentration of the halogen, but as that concentration diminishes, the velocity decreases until it approximates very nearly to that observed when bromine is used under similar conditions. This difference might be explained in at least two ways : (1) that chlorine acts directly on acetone, or (2) that the halogen is capable of existing in the initial change in the ketone which precedes the actual substitution. Of these, however, the first possibility is apparently disposed of by experiments on the action of chlorine on neutral solutions of acetone, as in this case the initial velocity of reaction is far too small to account for the difference in the speeds with which chlorine and bromine are absorbed by acetone in presence of acid : in both cases, the speed increases with lapse of time, owing, doubtless, to the increasing amount of acid present.

The last part of the paper contains an account of some experiments which were made for the purpose of ascertaining whether the action of chlorine and bromine on other carbonyl compounds is accelerated by acids, and the results show beyond question that the effect is a fairly general one and is well marked in the case of acetone and other ketones in solvents other than water, and also in those of carboxylic acids and their anhydrides and esters.

The ease with which dry acetic acid may be brominated in presence of halogen hydrides leads to a simple explanation of the part played by small quantities of phosphorus in promoting the action of halogens on carboxylic acids. The phosphorus chlorides and bromides which are produced in the first instance, will react so as to remove the water present, supplying at the same time the requisite hydrogen chloride or bromine ; in the absence of water, the halogen hydrides

will be produced by the interaction of the phosphorus halogen compounds with some of the carboxylic acid itself. The usual explanation, namely, that the halogen only attacks the acid chloride or bromide is no longer necessary since it has been shown that the accelerating effect of powerful acids is not confined to substitutive changes in the series of carboxylic acids.

EXPERIMENTAL.

Bromination of Acetone.

The action of bromine on acetone, either undiluted or dissolved in organic solvents, is difficult to control, and dilute aqueous solutions of the ketone were therefore employed, the experiments being made with the object of ascertaining, first, the effect of varying concentrations of acetone and bromine, and, secondly, the effects produced by foreign substances which might reasonably be expected to alter the velocity of reaction, either by their influence on the state of dissociation of the reacting substances or by retarding or accelerating the changes of structure which the ketone might undergo.

In the preliminary experiments, a dilute aqueous solution of acetone was rendered yellow by the addition of bromine water and then divided between a number of stoppered bottles, to each of which was then added varying quantities of a number of electrolytes. The results showed clearly that the effect of neutral salts, such as sodium sulphate, potassium bromide, &c., was very slight, but that acids caused a very marked increase in the speed with which the colour of the bromine disappeared, so that, instead of occupying some days or even weeks, the action was at an end in a few hours or minutes, according to the affinity and the amount of acid present. Thus with equivalent amounts of sulphuric acid, hydrochloric acid, and acetic acid, the first two acted very rapidly, and the last caused a marked acceleration; with acetic acid in presence of an excess of sodium acetate,* the change was almost as slow as in the absence of acids.

In order to ascertain whether the product of the action of bromine on acetone in presence of dilute mineral acid was a simple substitution product, 30 grams of acetone were dissolved in a mixture of 200 c.c. of water and 50 c.c. of ordinary hydrochloric acid, the whole being allowed to remain for several weeks in a stoppered vessel with one molecular proportion of bromine. After the colour of the solution had entirely disappeared, the solution was filtered from a very small

* In this instance it was found necessary to submit the sodium acetate to a preliminary treatment with a small quantity of bromine, the excess of which was afterwards removed by a stream of air, as the salt invariably absorbed a small quantity of halogen even after repeated crystallisation.

quantity of crystalline matter, cooled in ice, and saturated with calcium chloride, the oil which separated being removed, dried, and fractionally distilled.

The crystalline material was insoluble in water and crystallised from ethyl acetate in fine needles melting at 75°.

0.3112 gave 0.6483 AgBr. Br = 88.6.

C_3H_5OBr requires Br = 88.5 per cent.

The compound appeared to agree in all its properties with the penta-bromoacetone melting at 76°.

The liquid portion of the product had the characteristic pungent odour of bromoacetone, and, when rapidly distilled under atmospheric pressure, passed over for the most part between 130° and 142°, a certain amount of a dark brown residue remaining in the flask. The fraction boiling at 130—142° was washed with dilute sodium carbonate solution to remove the hydrogen bromide liberated during the distillation, dried over anhydrous sodium sulphate, and analysed.

0.1685 gave 0.2338 AgBr. Br = 59.0.

C_3H_5OBr requires Br = 58.4 per cent.

There is therefore no reason to suppose that the reaction between acetone and bromine in presence of dilute acids is in any way abnormal. It may be mentioned that in the quantitative experiments described below the products invariably had the pungent odour of bromoacetone.

A series of quantitative experiments was made with a dilute aqueous solution of acetone at a constant temperature, the concentration of the bromine being determined from time to time by withdrawing aliquot portions of the solution by means of a pipette, and running these directly into a solution of potassium iodide; the amount of iodine liberated was ascertained by titration with a 0.05-normal solution of sodium thiosulphate, the exact value of which was checked from time to time.

The concentration of the acetone was kept somewhat low in order that its condition of hydration might be as nearly as possible the same in different experiments, which will only be the case in dilute solution. Moreover, the relative amount of bromine employed at first was always considerably less than one molecular proportion, so that the concentration of the unsubstituted portion of the acetone should not vary too widely; it was found, as a matter of fact, that within the limits adopted the relative initial concentrations of the bromine and acetone did not appreciably affect the nature of the results.

In every case in which a flask had to be opened several times during an operation, so that a measurable quantity of volatile materials might

have escaped, a second flask was prepared simultaneously, in precisely the same way, and opened for titration only at the beginning and at the end of the experiment; in the few cases in which the titres did not correspond, the results were rejected. Further, in order that the results should have at least a comparative value, the correct working of the thermostat and the concentration of the solutions were tested by another determination of the velocity of reaction in a solution of standard concentration, so that any material variation in the conditions could be readily detected and the necessary allowance made. These measurements were, however, made with the object of ascertaining the general character of the influence of the materials employed, and are to be regarded as approximations only, but it is probably safe to suppose them comparable.

The speed of removal of bromine by a dilute aqueous solution of acetone in the absence of free acid or alkali is very small; thus, in a solution containing 40 grams of acetone per litre, the free bromine at the commencement of the experiment corresponded with 9.25 c.c. of $N/20$ thiosulphate per 25 c.c. of the solution, whilst at the end of three days, during which time it remained at the temperature of the laboratory, the titre had only diminished to 9.05, and at the end of a week it was 8.70.

In the presence of acid, the speed of disappearance of the bromine was nearly constant. The numbers obtained in the following experiments, in which the concentration of acetone and sulphuric acid, as well as the temperature, are those which were adopted throughout as the standard for comparison, prove clearly that the speed at the end of the operation is practically identical with that at the commencement. The temperature throughout the series of experiments was 20.3° , except where a statement to the contrary occurs. The titres are those for 25 c.c. of solution, and are given in terms of $N/20$ thiosulphate; the initial and final numbers are expressed in the same terms, but were always determined by the titration of 50 c.c. of the solution, so that the numbers in these cases are one-half of those actually obtained, and were used throughout for the determination of the approximate value of the constant k , this term being found by the aid of the formula:

$$k = 10^4 \times V/c_1c_2,$$

where V is the velocity of disappearance of free bromine in gram-molecules per litre, and c_1 and c_2 are the concentrations of the ketone in gram-molecules, and of the acid in gram-equivalents per litre respectively.

The numbers in the third column of the following table are those calculated on the assumption that the reaction may be represented by a straight line between the initial and final points.

Experiment A.

Quantities employed : acetone = 40 grams ; normal H_2SO_4 = 400 c.c. per litre.

Time.	Titre.	Calculated.
0	19.25	—
10 minutes	17.05	16.95
20 „	14.80	14.60
60 „	5.00	5.30
67 „	3.50	3.65
70 „	3.00	3.05
75 „	1.60	1.90
80 „	0.65	0.75
83 „	0.05	—

$$k = 8.38$$

Two other experiments with the same concentrations of acid and ketone gave $k = 8.52$ and 8.57 .

As these experiments indicated that the velocity of bromination was nearly independent of the amount of bromine present, two other experiments were made with small quantities of the halogens and these confirmed this conclusion, the same rectilinear character being evident and the constants found being (*B*) 8.40 and (*C*) 8.55 .

In Fig. I (p. 37), the results of the last two experiments are compared with those given in the foregoing table.

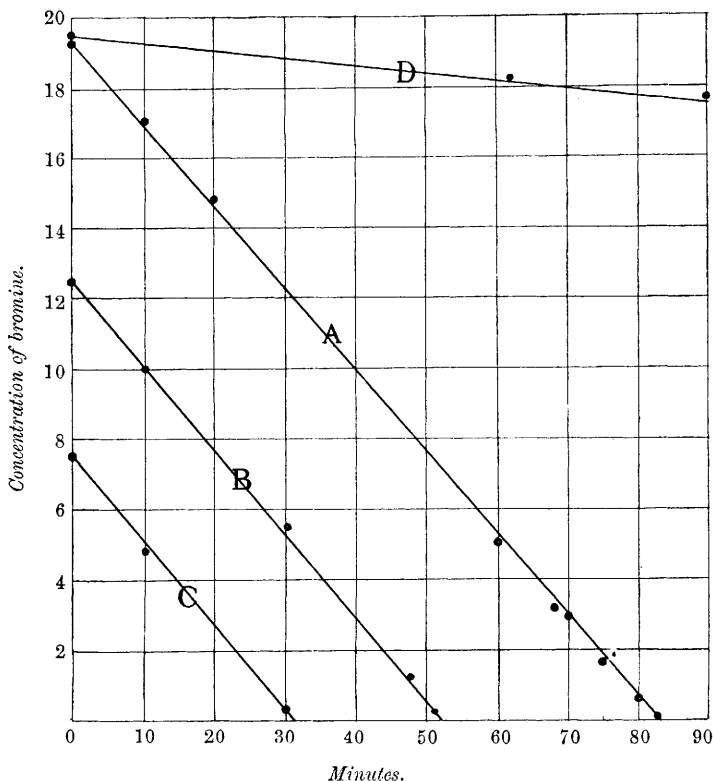
In order to determine whether the initial change produced in the ketone by the acid was a reversible one, a solution containing 40 grams of acetone and 400 c.c. of normal sulphuric acid was prepared and allowed to remain for four days, when a measured bulk of bromine water was added and the whole at once diluted to one litre with water at 20.3° , an exactly similar solution being made simultaneously in which the ketone and acid were brought into contact only at the last moment. It was found that the titres of 25 c.c. of these solutions, five minutes after making up, were 17.2 and 17.4 respectively, whilst the corresponding velocity constants were $k = 8.31$ and 8.43 respectively ; it seems clear, therefore, that the initial change occurs only to a very minute extent and is of a reversible character.

Effect of the Concentration of Ketone and Acid.—The line *D* in Fig. I represents a portion of a line joining the points corresponding with the initial and final titres obtained in an experiment in which the concentration of the acetone is only one-tenth of that present in *A*, *B*, and *C* ; the reaction velocity was somewhat less than a tenth of that observed in the other three cases.

The mean results obtained in a number of experiments at 20.3° are given in the following table, and represent the variation of $k = 10^4 \times V/c_1c_2$ with the concentration of ketone and acid.

Sulphuric acid. gram-mols. per litre	Acetone (grams per litre)			
	4	10	20	40
0.40	8.07	8.24	8.38	8.49
0.20	—	8.53	8.59	8.71
0.10	—	—	8.81	8.93
0.04	—	—	—	9.68

FIG. 1.



With hydrochloric and nitric acids at a concentration of 0.40 gram-molecules per litre and 40 grams of acetone per litre, the reaction was also rectilinear, the constants found being 11.56 and 10.21 respectively. In presence of potassium chloride and bromide with hydrochloric acid of the above concentration, the constants (k) were 11.69 and 11.54 respectively, in both cases, an amount of

the salt equivalent to the acid present being employed. The results obtained with 0.40-normal acetic acid were very inconsistent, a rapid fall in the bromine concentration being observed at first and due perhaps to some impurity in the acetic acid, which was not readily removed, even by distillation over sodium acetate. With acetic acid in the presence of two equivalents of sodium acetate which had been purified by a preliminary treatment with bromine, a rapid initial fall in the titre from 16.80 to 14.25 occurred in the course of a quarter of an hour, whilst subsequently the action became so slow that after an additional period of five days the titre had fallen only to 13.90.

Chlorine and Acetone.

On the whole, it was found that when chlorine was allowed to act on acetone in dilute aqueous solution in presence of mineral acids, this halogen invariably disappeared somewhat more rapidly than bromine. The following details of two simultaneous series of measurements made with two solutions of identical concentration as to acetone and acid will serve to show what was the general nature of the difference observed in the two cases.

Quantities employed: acetone = 20 grams per litre; normal H_2SO_4 = 400 c.c. per litre.

A. Bromine.		B. Chlorine.	
Time.	Titre.	Time.	Titre.
0	9.20 c.c.	0	(?)
12.5 minutes	7.75 "	11.0 minutes	11.00 c.c.
34.0 "	5.45 "	19.0 "	8.90 "
65.5 "	1.80 "	26.0 "	7.70 "
71.5 "	1.15 "	38.5 "	5.65 "
77.5 "	0.40 "	47.0 "	4.50 "
		55.5 "	3.40 "
		64.0 "	2.25 "
		74.0 "	1.10 "
		81.0 "	0.35 "

It will be noticed that the chlorine at first disappears with considerably the greater speed, but, as the concentration of the halogen diminishes, the velocity of chlorination approaches very nearly to that of bromination, so that it appears that the velocity of substitution is not so nearly independent of the concentration of the halogen in the former as in the latter case.

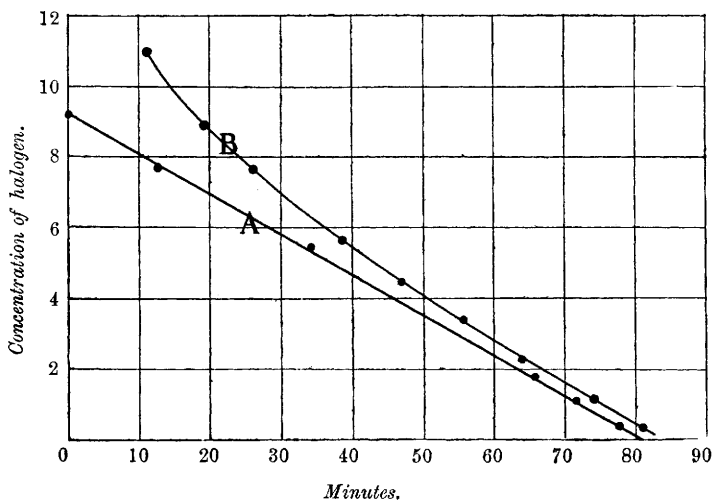
To test the question as to whether chlorine exerts an independent or direct influence on the speed of substitution, the effects of the two halogens on dilute, initially neutral, aqueous solutions of acetone were

directly compared and the following results obtained, the concentration of the acetone being 40 grams per litre.

A. Bromine.			B. Chlorine.		
Time.	Titre.		Time.	Titre.	
0	10.70	c.c.	0	9.95	c.c.
4 hrs. 5'	10.45	"	3 hrs. 6'	9.85	"
23 " 53'	10.70	"	23 " 6'	9.55	"
87 " 3'	10.30	"	87 " 0'	7.60	"
168 " 0'	9.10	"	168 " 0'	2.40	"

Thus the action of chlorine alone on acetone is very slow indeed and does not account for the very considerable difference between the initial velocities of chlorination and bromination in the presence of acid.

FIG. 2.



Bromination of Acetone in Solvents other than Water.

Specimens of purified light petroleum, benzene, and chloroform were allowed to remain in contact with bromine for some hours and were then washed repeatedly with dilute alkali and water and finally dried. This treatment was found to be necessary, as almost all specimens of these liquids were found to decolorise a small quantity of bromine, and the subsequent action of bromine on acetone dissolved in them was much too rapid for comparative experiments, owing, probably, to the production of free hydrogen bromide.

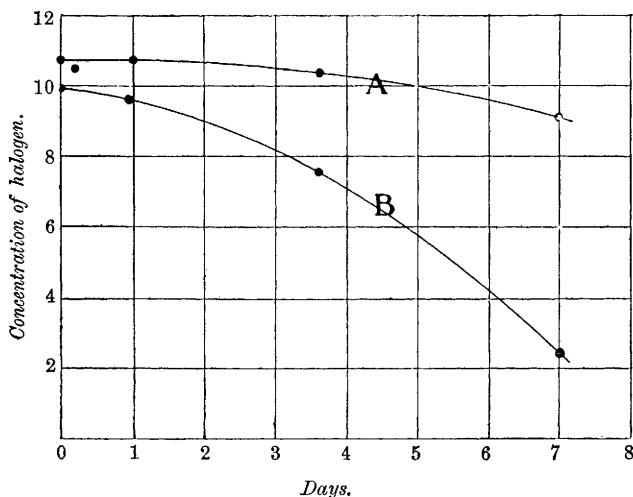
Highly dilute solutions of acetone, hydrogen chloride, and bromine

in the purified solvents were then prepared, and it was found on mixing the solutions of acetone and bromine that the disappearance of the colour of the latter was conveniently slow at first and that addition of the hydrogen chloride solution produced a very marked acceleration. It was also observed that, when no hydrogen chloride was added, the disappearance of successive small quantities of bromine occurred with increasing rapidity, owing, no doubt, to the hydrogen bromide formed.

Effect of Acids on the Speed of Bromination and Chlorination of other Carbonyl Compounds.

Many ketones are not, at first, easily attacked by bromine, but when once the reaction has begun it proceeds rapidly. This effect

FIG. 3.



may be noticed when, for example, methyl isopropyl ketone is treated with bromine in the cold or when α -bromocamphor is prepared by adding bromine to camphor which is being heated on the water-bath.

Acetic anhydride, when mixed with bromine at the ordinary temperature, is only very slowly affected, but, if previously saturated with hydrogen chloride or if mixed with a few drops of sulphuric acid and subsequently cooled, is so readily attacked that on the addition of bromine the temperature rises appreciably and in the course of a few minutes the colour of the halogen may disappear.

Diethyl malonate was examined as a type of ester which is comparatively easily brominated. When this substance is mixed with purified bromine at the ordinary temperature, no marked effect is noticeable, often during the course of some hours; in presence of a small quantity of hydrogen chloride, however, the action proceeds very rapidly, even if the temperature is kept low. A striking experiment may be made by mixing a few grams of the ester with an approximately equal bulk of bromine in the cold; a few drops of the mixture are warmed in a test-tube over a Bunsen burner, and when the resulting action is complete the fuming product is cooled and added to the bulk of the mixture; a violent reaction soon occurs, hydrogen bromide is evolved in large quantities, and the colour of the liquid changes from a deep brown to a very pale yellow, the change being usually complete in less than a minute.

Acetic acid was chosen to illustrate the case of acids. As is well known, bromine scarcely acts on acetic acid even at its boiling point, and it was found that, even when saturated with hydrogen chloride or bromide, this acid, when containing 1 or 2 per cent. of water, is only slowly attacked by the halogen at the temperature of the water-bath. If, however, it is repeatedly purified by freezing, it becomes easy to prepare bromoacetic acid, first by saturating the dry product with hydrogen chloride, and then by warming it at 80—90° with a slight excess of bromine: thus, from 33 grams of 99 per cent. acetic acid saturated with hydrogen chloride, a yield of 54 grams of bromoacetic acid or 71 per cent. of the calculated amount was obtained after 9 hours' heating with bromine on the water-bath.

In another experiment, 100 grams of the acid containing 95 per cent. of pure acetic acid were mixed with 22 grams of acetyl chloride for the purpose of removing water and affording simultaneously the requisite hydrogen chloride. After 42 grams of this mixture had been heated for 5 hours on the water-bath, the product was treated with successive quantities of bromine and distilled at the end of 6 hours; a yield of 83 grams of crystalline bromoacetic acid was thus obtained corresponding with about 85 per cent. of the calculated amount.

The effect of chlorine on dry acetic acid is similar; in diffused daylight, acetic acid saturated with hydrogen chloride was only slowly chlorinated at 100°, but this is also the case when phosphorus is employed, and the speed in the two cases appears to be very similar. It is probable, therefore, that in direct sunlight the yield by this process might be as good and the action as rapid as in the ordinary method, but no opportunity was obtained of trying the reaction under these conditions.

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