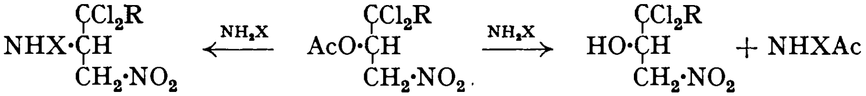
183. *The Action of Amines upon Esters. Part I.*

By Harry Irving.

Chattaway has shown (this vol., p. 355) that the action of ammonia, *p*-toluidine, or an arylhydrazine upon certain acetic esters (I; R = Cl or $CH_3{\cdot}CHCl$) does not proceed normally with the formation of acetamide, aceto-*p*-toluidide, or a β-acetylarylhydrazine and the liberation of the parent alcohol (II). On the contrary, the ammonia or substituted amine appears to displace the acetoxy-group with the formation of a primary amine, *N*-alkyl-*p*-toluidine, or β-alkylarylhydrazine (III). Thus:



$$\begin{array}{ccccc} CCl_2R & & CCl_2R & & CCl_2R \\ NHX{\cdot}CH & \xleftarrow{NH_2X} & AcO{\cdot}CH & \xrightarrow{NH_2X} & HO{\cdot}CH \quad + NHXAc \\ CH_2{\cdot}NO_2 & & CH_2{\cdot}NO_2 & & CH_2{\cdot}NO_2 \\ \text{(III.)} & & \text{(I.)} & & \text{(II.)} \end{array}$$

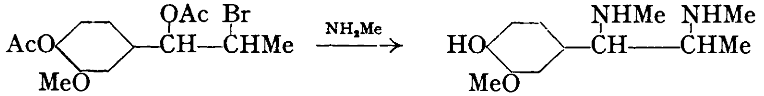
(R = Cl, or $CH_3{\cdot}CHCl$; X = H, *p*-$CH_3{\cdot}C_6H_4$, or $C_6H_5{\cdot}NH$.)

The unexpected course of these reactions is attributed to the presence of the electron-restraining (CCl_2R and NO_2) groups which, it is suggested, render the β-carbon atom in the alkyl group of the ester so kationoid that donor molecules (*i.e.*, ammonia, aniline, or hydrazine) attack the ester to a greater extent at this point than at the ketonic carbon atom of the acyl group.

Should this explanation be correct, any ester of any alcohol in which the carbon atom of the carbinol group is made sufficiently kationoid should show abnormal reactions of this novel and interesting type. In the present paper these implications have been examined and an attempt has been made to realise further examples.

A survey of the literature does not reveal many cases of reactions which belong indubitably to the abnormal type under consideration. Solomon and Sharp (J., 1931, 1468), however, record that the action of dry alcoholic methylamine above 100° upon the acetoxy-bromide (IV) unexpectedly yielded the diamine (V), both the β-bromine atom and

(IV.)



(V.)

the α-acetoxy-group having been replaced by methylamino-groups although the *p*-acetoxy-group was deacetylated in the normal manner.

The authors correlated this type of behaviour with the presence of a *p*-acetoxy-group in the aryl residue, but did not discuss in any further detail the mechanism of the amination.

The formation of methyl β-aminocrotonate and butyramide by the action of dry ammonia upon the *O*-butyrate of methyl β-hydroxycrotonate, $Me{\cdot}C(O{\cdot}CHO{\cdot}C_3H_7){:}C{\cdot}CO_2Me$, was studied by Bouveault and Bongert (*Bull. Soc. chim.*, 1902, **27**, 1051), who remarked " La formation d'une amide au moyen d'un éther dans les conditions où nous avons opéré, constitue un phénomène assez rarement observé." The formation of butyramide showed that the probable course of the reaction was simply normal amide formation, followed by the further and well-established action of ammonia upon the methyl acetoacetate thereby liberated. Methyl β-butyroxycrotonate and phenylhydrazine gave similarly β-butyrylphenylhydrazine and phenylmethylpyrazolone.

Chattaway's results are not, however, amenable to explanation in such a simple manner, for it has now been found that γγγ-trichloro-α-nitro-β-hydroxypropane (II; R = Cl), from which the reactive acetate (I; R = Cl) is derived, will not react either with phenylhydrazine or with ammonia.

On the other hand, the β-chloro-derivative, $CCl_3{\cdot}CHCl{\cdot}CH_2{\cdot}NO_2$, obtained by the action of phosphorous pentachloride upon this alcohol is extremely reactive. When it is treated with dry ammonia, *p*-toluidine, or phenylhydrazine in dry ethereal or alcoholic solution, much heat is evolved and the products are identical with those obtained from the same amines and the acetoxy-compound (I; R = Cl) itself.

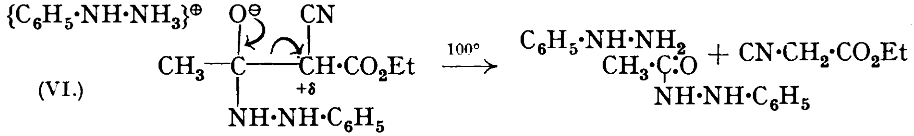
Now since this reactive chlorine atom is attached to a carbon atom bearing electron-restraining (CCl_3,$CH_2{\cdot}NO_2$) groups, its ease of anionisation will be reduced. Its observed reactivity is therefore analogous to the well-established kationoid activity of picryl chloride, Pic·Cl (Pic = 2 : 4 : 6-trinitrophenyl), which with ammonia, anilines, and hydrazines yields picramide, *N*-picrylanilines, and β-picrylhydrazines respectively (cf. " Organische Chemie," Beilstein, 4th ed., vol. V, p. 274). The analogous behaviour of the two chloro-compounds suggested that picryl acetate, AcO·Pic, in which the 1-carbon atom is undoubtedly kationoid, should undergo amination reactions similar to those shown by Chattaway's acetate (I). This expectation has not, however, been realised, for the action of dry ammonia upon a solution of picryl acetate in dry ether or in dry alcohol gave only ammonium acetate and ammonium picrate, no trace of picramide being formed. Further the action of phenylhydrazine gave no β-picrylphenylhydrazine.

These results are difficult to reconcile with Chattaway's hypothesis, especially when it is recalled that the glycollic ester $Pic{\cdot}O{\cdot}CH_2{\cdot}CO_2Et$ readily yields 2 : 4 : 6-trinitrophenylhydrazine, $Pic{\cdot}NH{\cdot}NH_2$, on treatment with hydrazine (Buchner, *Ber.*, 1894, **27**, 3250), and that trinitroanisole, Pic·OMe, reacts with an alcoholic solution of phenylhydrazine to give β-picrylphenylhydrazine, $Pic{\cdot}NH{\cdot}NH{\cdot}C_6H_5$, even below 35° (Giua and Cherchi, *Gazzetta*, 1919, **49**, II, 156).

Since the anomalous reactions of the acetate (I) did not appear to be paralleled by those of phenolic esters, a series of aliphatic analogues of the general type AcO·CHRR′ were examined in order to determine (a) the number and (b) the type of electron-restraining groups which would suffice to induce abnormal amination reactions.

The CCl_3 group alone does not appear to confer a sufficiently kationoid character upon an attached carbon atom, for the esters βββ-trichloro-α-acetoxypropionamide, $CCl_3{\cdot}CH(OAc){\cdot}CO{\cdot}NH_2$ (Pinner and Fuchs, *Ber.*, 1877, **10**, 1061), γγγ-trichloro-α-acetamido-β-acetoxypropane, $CCl_3{\cdot}CH(OAc){\cdot}CH_2{\cdot}NHAc$ (Chattaway and Witherington, J., 1935, 1623), γγγ-trichloro-β-acetoxypropane, $CCl_3{\cdot}CH(OAc){\cdot}CH_3$ (isopral), and βββ-trichloro-α-acetoxy-α-phenylethane, $CCl_3{\cdot}CH(OAc){\cdot}C_6H_5$ (Jozitsch, *Centr.*, 1897, I, 1014), do not appear to react readily with phenylhydrazine or ammonia. βββ-Trichloro-α-acetoxy-α-methoxyethane (*O*-acetylchloral methyl alcoholate), $CCl_3{\cdot}CH(OAc){\cdot}O{\cdot}CH_3$, and chloral diacetate, $CCl_3{\cdot}CH(OAc)_2$, are similarly inert under conditions which would suffice to initiate a reaction in the case of the acetate (I). Under more drastic conditions, phenylhydrazine yields a black coked mass : the vigorous exothermic reaction resembles closely the action of phenylhydrazine upon chloral itself and the isolation of small amounts of β-acetylphenylhydrazine from the reaction products suggests that the detachment of the acetyl groups is a primary stage.

Esters of the type $CCl_3{\cdot}CH(OAc)X$ were next considered, in which the second electron-restraining group X was introduced to reinforce the effect of the CCl_3 group. Here X could be $CH_2{\cdot}NO_2$, as in the ester (I) originally investigated, or CN, CO_2H, CO_2R, or $>C:O$. Of these possibilities, compounds of the type $CCl_3{\cdot}CH(OAc){\cdot}CO{\cdot}C_6H_5$ were not examined, since the introduction of a keto-group would undoubtedly mask the effect sought for by providing an alternative and more powerfully directing centre to which donor molecules would be attracted. This contention is supported by the action of phenylhydrazine upon ethyl acetoacetate, whereby the β-phenylhydrazone, and not the phenylhydrazide, of acetoacetic ester is formed (Nef, *Annalen*, 1891, **266**, 71; compare Knorr, *ibid.*, 1887, **238**, 146). Furthermore, the action of phenylhydrazine upon ethyl α-cyanoacetoacetate also yields no hydrazide and, despite the presence of an undoubtedly strongly kationoid α-carbon atom, the phenylhydrazine does not attack at this point either. In the cold, however, an addition compound, probably to be formulated as (VI), results. At 100° this decomposes smoothly to give ethyl cyanoacetate and β-acetylphenylhydrazine (Haller, *Compt. rend.*, 1895, **120**, 1193).


(VI.)

$$\{C_6H_5{\cdot}NH{\cdot}NH_3\}^{\oplus}\quad CH_3{-}\overset{O^{\ominus}}{\underset{NH{\cdot}NH{\cdot}C_6H_5}{C}}{-}\overset{CN}{\underset{+\delta}{C}}H{\cdot}CO_2Et \xrightarrow{100^\circ} \overset{C_6H_5{\cdot}NH{\cdot}NH_2}{CH_3{\cdot}\underset{NH{\cdot}NH{\cdot}C_6H_5}{C}{:}O} + CN{\cdot}CH_2{\cdot}CO_2Et$$

None of the compounds $CCl_3{\cdot}CH(OAc){\cdot}CN$, $CCl_3{\cdot}CH(OAc){\cdot}CO_2H$, and $CCl_3{\cdot}CH(OAc){\cdot}CO_2Et$ reacts simply with amines in a manner similar to that observed by Chattaway. Here, however, the problem is complicated by the fact that, at some stage, intramolecular elimination of hydrogen chloride takes place in every case: the unsaturated compound thereby produced may react further with the amine and then undergo a rearrangement. Chloral acetylcyanohydrin, $CCl_3{\cdot}CH(OAc){\cdot}CN$, for example, reacts with aniline (3 mols.) in alcoholic or ethereal solution to give a mixture of aniline hydrochloride, acetanilide, and dichloroacetanilide: *p*-toluidine yields similarly a mixture of its hydrochloride, aceto-*p*-toluidide and dichloroaceto-*p*-toluidide, hydrogen cyanide being liberated in each case.

Since these reactions do not proceed quantitatively, they cannot be said definitely to prove that at least a partial replacement of the acetoxy-group by amine does not take place as Chattaway's theory would predict, although, as Lapworth pointed out with reference to the analogous reactions of amines upon chloral cyanohydrin itself (J., 1931, 1387), such a direct replacement is exceedingly improbable. Further it is difficult to see how a primary reaction product such as $CCl_3{\cdot}CH(CN){\cdot}NH{\cdot}C_6H_5$ could be resolved into the products actually isolated when the reaction is carried out in the absence of water.

O-Acetyltrichlorolactic acid, $CCl_3{\cdot}CH(OAc){\cdot}CO_2H$, like trichlorolactic acid itself, was found to yield glyoxal phenylosazone, carbon dioxide, and phenylhydrazine hydrochloride when heated with an alcoholic solution of phenylhydrazine: with ammonia, apart from ammonium chloride, no definite products could be isolated (cf. Pinner and Fuchs, *loc. cit.*). Ethyl trichlorolactate, $CCl_3{\cdot}CH(OH){\cdot}CO_2Et$, and phenylhydrazine in alcoholic solution gave a good yield of the yellow osazone of dichloropyruvic ester (carbethoxyglyoxal phenylosazone). These reactions are being submitted to a more detailed investigation.

A final attempt to realise an example of abnormal ester behaviour led to the examination of the dimeride of acetyl cyanide, *O*-acetylmethyltartrononitrile (VII). Despite the presence of two such powerfully electron-restraining groups as the cyano-group, this ester appeared to react normally with amines, giving with an excess of aniline, dissolved in dry ether, a 75% yield of acetanilide, with dry ammonia an 87% yield of acetamide, and, as Brunner found (*Sitzungsber. Akad. Wiss. Wien*, 1894, **103**, 661), an 83% yield of β-acetylphenylhydrazine with excess of phenylhydrazine in dry ether. The course of these reactions may be represented as follows :

$$\text{(VII.)}\quad CH_3{\cdot}C(CN)_2{\cdot}O{\cdot}CO{\cdot}CH_3 \xrightarrow{NH_2X} CH_3{\cdot}CO{\cdot}NHX + CH_3{\cdot}C(CN)_2{\cdot}OH \longrightarrow$$

$$HCN + CH_3{\cdot}CO{\cdot}CN \xrightarrow{NH_2X} CH_3{\cdot}CO{\cdot}NHX + HCN$$

$$(X = H,\ C_6H_5,\ \text{or}\ NH{\cdot}C_6H_5)$$

The primary formation of such a compound as $CH_3{\cdot}C(CN)_2{\cdot}NHX$ predicted by the application of Chattaway's theory, apart from its inherent improbability in this reaction (cf. p. 799), is here excluded on the grounds that (a) in the absence of water such a compound could not rearrange to give $CH_3{\cdot}CO{\cdot}NHX$, and (b) the maximum yield of amide (anilide or hydrazide) on this hypothesis would be 50%, *i.e.*, less than that actually observed in three different reactions.

So far, therefore, it has not been found possible to adduce one additional and unambiguous example of the abnormal behaviour of esters recorded by Chattaway. Excluding methyl β-butyroxycrotonate, picryl acetate, and the dimeride of acetyl cyanide—all of which react " normally "—the esters discussed above are all acetates of the type $CH_3{\cdot}CO{\cdot}O{\cdot}CHRR'$ and may be classified in two categories : (a) those which are unreactive ($R = CCl_3$; $R' = CH_3$, $CH_2{\cdot}NHAc$, C_6H_5, $O{\cdot}CH_3$, OAc, or $CO{\cdot}NHAc$) and (b) those in which the β-hydrogen atom is very readily detached, thereby initiating an intramolecular elimination of hydrogen chloride ($R = CCl_3$; $R' = CN$, CO_2H, or CO_2Et).

The anomalous nitro-esters ($R = CCl_3$ or $CH_3{\cdot}CHCl{\cdot}CCl_2$; $R' = CH_2{\cdot}NO_2$) would appear, therefore, to belong to some intermediate category in which the β-carbon atom is sufficiently kationoid to attract donor molecules, but insufficiently so to promote a facile elimination of hydrogen chloride. The validity of Chattaway's explanation is thus seen to be dependent upon an (unlikely) very special adjustment of the electron-restraint of the attached groups R and R'.

Now the " abnormal " reactions seem to occur only when R' contains a readily ionisable hydrogen atom, and it appears from preliminary work that, under the influence of proton acceptors (ammonia, aniline, or arylhydrazine), such esters (I) readily lose acetic acid to form nitro-olefins (VIII) (compare Schmidt and Rutz, *Ber.*, 1928, **61**, 2142) to which the ammonia, aniline, or arylhydrazine then adds on (compare Wieland and Sakellarios, *Ber.*, 1919, **52**, 901). Thus :

$$\text{(I)} \xrightarrow{NH_2X} NH_3X{\cdot}OAc + CCl_2R{\cdot}CH{:}CH{\cdot}NO_2\ \text{(VIII)} \xrightarrow{NH_2X} \text{(III)}$$

The enhanced reactivity of the tetrachloronitroparaffin $CCl_3{\cdot}CHCl{\cdot}CH_2{\cdot}NO_2$, and the inertness of the parent nitro-alcohol (II) now become readily explicable. In this connection the strikingly analogous action of potassium cyanide upon α-chloro-β-benzoyl-α-phenylethane, $C_6H_5{\cdot}CHCl{\cdot}CH_2{\cdot}CO{\cdot}C_6H_5$, may be recalled, for here, as Rupe and Schneide found (*Ber.*, 1895, **28**, 960 ; compare Lapworth, J., 1904, **85**, 1355), the ultimate product, α-cyano-β-benzoyl-α-phenylethane, $C_6H_5{\cdot}CH(CN){\cdot}CH_2{\cdot}CO{\cdot}C_6H_5$ is obtained, not by the direct replacement of Cl by CN, but by elimination of hydrogen chloride, followed by the addition of hydrogen cyanide to the benzylideneacetophenone, $C_6H_5{\cdot}CH{:}CH{\cdot}CO{\cdot}C_6H_5$, so formed.

EXPERIMENTAL.

The Reactions of βγγγ-*Tetrachloro*-α-*nitropropane with Phenylhydrazine*, p-*Toluidine, and Ammonia*.—7·0 G. of tetrachloro-α-nitropropane (Henry, *Bull. Acad. roy. Belge*, 1897, **34**, 568) were added slowly to 6·5 g. of phenylhydrazine in 15 c.c. of dry alcohol. Much heat was evolved and γγγ-trichloro-α-nitro-β-phenylhydrazinopropane separated. After being washed with water, it crystallised from boiling alcohol in almost colourless, six-sided prisms, with domed ends (8·8 g. ; theo., 9·1 g.), m. p. 120—122° (decomp.) alone or mixed with an authentic specimen (Found : Cl, 35·4. Calc. for $C_9H_{10}O_2N_3Cl_3$: Cl, 35·6%).

γγγ-Trichloro-α-nitro-β-*p*-toluidinopropane (3·0 g.), similarly prepared by the interaction of *p*-toluidine (1·2 g.) and the nitroparaffin (2·5 g.) in 10 c.c. of dry alcohol, formed pale yellow, compact crystals, from light petroleum, m. p. and mixed m. p. 60—61° (Found : Cl, 35·9. Calc. for $C_{10}H_{11}O_2N_2Cl_3$: Cl, 35·8%).

When dry ammonia gas was passed into a cooled solution of βγγγ-tetrachloro-α-nitropropane (10 g.) in 20 c.c. of anhydrous ether (or 15 c.c. of dry alcohol), much heat was evolved and from the resulting mixture of ammonium chloride and γγγ-trichloro-α-nitro-β-aminopropane hydrochloride, the free base was isolated from the latter as described by Chattaway (*loc. cit.*), and characterised as its *N*-acetyl derivative, which formed colourless prisms from alcohol, m. p. and mixed m. p. 137° (Found : Cl, 42·8. Calc. for $C_5H_7O_3N_2Cl_3$: Cl, 42·7%).

The Interaction of Aniline and O-Acetylchloralcyanohydrin in Dry Alcohol or Ether.—Aniline (3 mols., 13·0 g.) in 10 c.c. of dry alcohol was added to chloral acetylcyanohydrin (1 mol., 10·0 g.) in 20 c.c. of alcohol. The temperature rose gradually from 12° to 52° but there was no marked evolution of hydrogen cyanide. The reaction was completed by gentle boiling for 5 minutes and after distillation of half of the alcohol under reduced pressure the product was worked up by one or other of the following procedures :

(a) More alcohol was removed until a crystalline mass (19 g., m. p. 80—100°) separated, which after five recrystallisations from absolute alcohol gave dichloroacetanilide (6·5 g.; theo., 9·5 g.) in colourless prisms, m. p. 118° alone or mixed with an authentic specimen (compare Pinner, *Ber.*, 1877, **10**, 1061; Cech, *Ber.*, 1876, **9**, 337). Since only catalytically small amounts of water could have been present throughout, the formation of dichloroacetanilide, $CHCl_2 \cdot CO \cdot NH \cdot C_6H_5$, in this yield (70%) shows that the substance $CCl_3 \cdot CH(CN) \cdot NH \cdot C_6H_5$ could not have been formed intermediately.

(b) The concentrated alcoholic solution was poured into 100 c.c. of water; an oil then separated which almost immediately solidified to a mass of colourless crystals (14·6 g., m. p. 76—85°; theo., for dichloroacetanilide 9·5 g. and acetanilide 6·2 g. = 15·7 g.). This solid (A) was collected, and the aqueous-alcoholic filtrate evaporated to small bulk; the pale yellow solid which then separated was collected and crystallised four times from boiling water (charcoal), acetanilide (1·2 g.), m. p. and mixed m. p. 114°, being obtained. The solid (A) was crystallised four times from alcohol and gave 7·1 g. of dichloroacetanilide, m. p. 118°; the more soluble fraction from the alcoholic mother-liquors melted at about 80° and contained chlorine (19·5 and 23·4% in different preparations). It appears to be identical with the substance which Pinner (*loc. cit.*) identified tentatively with monochloroacetanilide, but which appears from the work of Kötz (*J. pr. Chem.*, 1921, **103**, 231) to be a mixture of acetanilide and dichloroacetanilide.

The Action of Phenylhydrazine upon O-Acetyltrichlorolactic Acid.—*O*-Acetyltrichlorolactic acid (2·4 g.) and phenylhydrazine (5 mols., 5·4 g.) were boiled with 15 c.c. of alcohol until the evolution of carbon dioxide ceased. The cooled solution was poured into dilute hydrochloric acid and the viscous solid which then separated was extracted with ether and dried over anhydrous sodium sulphate. Glyoxalphenylosazone (1·4 g.), left on removal of the solvent, formed yellow silky leaflets, m. p. 169—170° after two recrystallisations from alcohol (Found : N, 23·2. Calc. for $C_{14}H_{14}N_4$: N, 23·5%).

The Action of Phenylhydrazine upon Ethyl Trichlorolactate.—4·4 G. of ethyl trichlorolactate and 6·5 g. (3 mols.) of phenylhydrazine were refluxed gently with 30 c.c. of alcohol for 2 hours. The soft yellow powder (5·9 g., m. p. 220°) which separated on cooling was collected and crystallised twice from boiling alcohol and then from benzene–light petroleum, from which carbethoxyglyoxalphenylosazone separated in yellow leaflets, m. p. 225—227° (decomp.) (Found : C, 66·1; H, 5·8; N, 18·0. Calc. for $C_{17}H_{18}O_2N_4$: C, 65·8; H, 5·8; N, 18·1%). The identity of this osazone with that described by Fenton (J., 1902, **81**, 431) and Will (*Ber.*, 1891, **24**, 3833) was established by warming with aqueous-alcoholic potash for 2 hours. On acidification carboxyglyoxalphenylosazone separated; it gave bright yellow, slender prisms, m. p. 220—224° (decomp.), from boiling chloroform (Fenton, *loc. cit.*, gives m. p. 222—224°) (Found : N, 19·8. Calc. for $C_{15}H_{14}O_2N_4$: N, 19·9%).

The Action of Dry Ammonia and Aniline upon the Dimeride of Acetyl Cyanide.—Dry ammonia gas was passed into a solution of dimolecular acetyl cyanide (VII) (1·52 g.) in 10 c.c. of dry alcohol until saturated and the whole was maintained at 25° for 12 hours. The solution was then distilled rapidly until the temperature reached 150° and the residue of acetamide was collected and crystallised from benzene (1·13 g.; theo., 1·3 g.; m. p. 80°).

1·7 G. (slight excess) of redistilled aniline and 1·24 g. of dimolecular acetyl cyanide were refluxed gently with 25 c.c. of anhydrous ether for 2 hours. The solvent was then distilled off and acetanilide remained (1·83 g.; theo., 2·43 g.), m. p. 114·5° (from water).

THE OLD CHEMISTRY DEPARTMENT, OXFORD.

[*Received, March* 30*th*, 1936.]