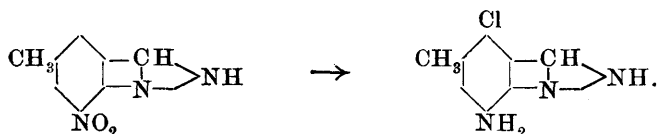


CIV.—*The Formation of Chlorinated Amines by the Reduction of Nitro-compounds.*

By WINIFRED GRACE HURST and JOCELYN FIELD THORPE.

THE first reference to the fact that the reduction of aromatic nitro-compounds to the corresponding amino-derivatives through the agency of tin and hydrochloric acid often leads to the production of by-products containing chlorine seems to have been made by Fittig (*Ber.*, 1875, **8**, 15), who was able to isolate some chlorobromoaniline by the reduction of *p*-bromonitrobenzene. Subsequently, Kock (*Ber.*, 1887, **20**, 1569) obtained considerable quantities of *p*-chloroaniline by the reduction of nitrobenzene under similar experimental conditions.

No one who has used this method of reduction can have failed to notice the production of these halogenated by-products, although very few attempts seem to have been made either to identify them or to work out an experimental basis for their formation. That, under certain conditions, they may constitute the main product of the reaction, has been shown by Gabriel and Stelzner (*Ber.*, 1896, **29**, 305), who, by the reduction of nitromethylindazole, obtained only the chloroaminomethylindazole:

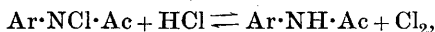


Gabriel and Stelzner consider that the reaction is due to the formation of the intermediate hydroxylamine derivative, which, in the presence of the halogen acid, passes into the halogen substituted amine in accordance with the observation of Bamberger (*Ber.*, 1895, **28**, 251). They also observe that if the para-position is occupied, the halogen enters the ortho-position, as, for example, in the production of chlorobromoaniline in the manner described by Fittig (*loc. cit.*).

During the autumn months, the staff and research students of this laboratory have been engaged in the preparation of considerable quantities of phenacetin, and, in the first instance, this substance was prepared by the method recommended by Hinsberg (*Annalen*, 1899, **305**, 278), in which tin and concentrated hydrochloric acid are used as the reducing agents, and the product is directly acetylated by acetic anhydride:

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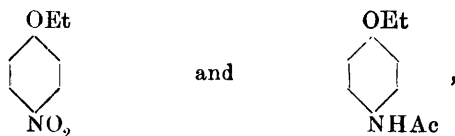
King (T., 1911, **99**, 1190), and were formed by taking advantage of the equilibrium existing between chloroamines, hydrogen chloride, anilides, and chlorine,



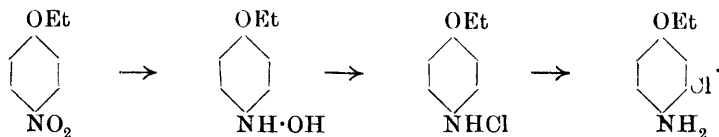
which was discovered by Orton and Jones (T., 1909, **95**, 1456). The chlorophenacetin, prepared by the action of this reagent on phenacetin, melted at 128—129°, and the corresponding base at 64—65°.

It will be noticed that the melting points of the compounds prepared by Reverdin and Düring, and by Orton and King, lie very close together, and it seemed likely that the substances might be identical. This proved to be the case, because a specimen of chlorophenacetin prepared in accordance with the instructions given by Orton and King was shown, by direct comparison, to be identical with the compound formed by the chlorination, reduction, and acetylation of *p*-nitrophenetole, as well as by the methods described by Reverdin and Düring.

It follows, therefore, that the chlorination of the compounds

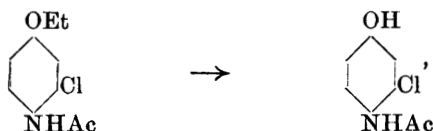


leads to the formation of chlorine derivatives having the halogen in the ortho-position with respect to the ethoxyl group, and that the ortho-position with respect to the basic group can only be filled when the nitro-group is reduced in the manner described in this communication. The view of Gabriel and Stelzner as to the cause of this reaction is, therefore, in all probability the correct one, although it is likely, owing to the ease with which chloroamines pass into aminochloro-derivatives (Chattaway and Orton, T., 1899, **75**, 1046), that the course of the reaction may be represented by the expression:



It also follows that the chlorination of an amine of this type cannot be preceded by the formation of the chloroamine in accordance with the view of Chattaway and Orton (*loc. cit.*, p. 1048), because the chlorination of phenacetin and similar substances leads to the production of halogen derivatives having the halogen in the meta-position with respect to the basic group.

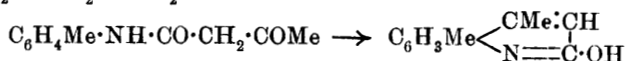
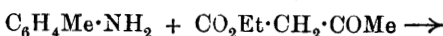
During the course of these experiments, we discovered the curious fact that, whereas a practically quantitative yield of the phenol can be obtained from chlorophenacetin by treatment in benzene solution with aluminium chloride,



the phenol cannot be prepared from the corresponding methyl ether in this way.

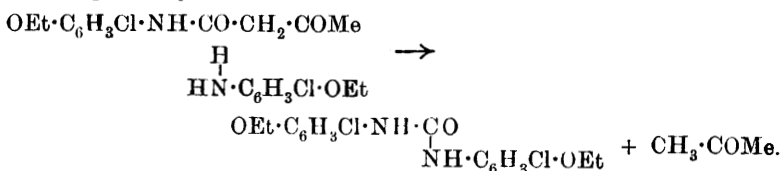
With the object of characterising the new chlorinated bases by the formation of typical derivatives, we studied the action of ethyl acetoacetate on them in the hope of preparing the corresponding hydroxyquinolines.


This reaction has been used by Knorr (*Ber.*, 1884, **17**, 542), by Conrad and Limbach (*Ber.*, 1888, **21**, 525), and, more recently, by Ewins and King (*T.*, 1913, **103**, 104). The last-named authors were able to show that the formation of the quinoline derivative depended on the intermediate production of the corresponding amide of acetoacetic acid, thus:



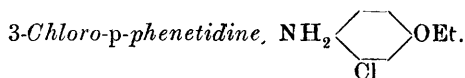
and that the amides of this type can be readily prepared by merely boiling a mixture of equimolecular quantities of the base and acetoacetic ester.

On applying the conditions described by Ewins and King to the chlorinated bases, described in this paper, we obtained a crystalline substance, but investigation showed that it was not the corresponding amide of acetoacetic acid, but a derivative of carbamide, which must have been formed by the interaction of the base and the amide, probably in accordance with the scheme:



A similar substance is obtained by the action of ethyl acetoacetate on the chloro-base, NH_2  OEt , and the reaction seems, therefore, to be a general one for compounds of this type.

EXPERIMENTAL.



The reduction of *p*-nitrophenetole was effected by tin and hydrochloric acid, 100 grams of the nitro-compound being used with 200 grams of tin and 500 c.c. of concentrated hydrochloric acid. Under these conditions, a yield of about 50 per cent. of the chlorophenetin is produced if the reaction is moderated by cooling under running water, but the yield is increased to 90 per cent. if the reaction is carried out in a large flask fitted with a double surface condenser, and allowed to proceed without cooling. The separation of the chloro-compound from the normal product of reduction can be readily effected by taking advantage of the fact that the acetate of the chlorinated base is completely dissociated by water, and that the base can therefore be extracted by ether from an acetic acid solution containing the unchlorinated base in the form of its undissociated acetate. The method adopted was as follows.

The product of reduction was mixed with an excess of freshly slaked lime and distilled in a current of steam, the distillate being collected in a known quantity of dilute hydrochloric acid, since the basic mixture is rapidly coloured by exposure to air. When all oil had distilled over, excess of sodium acetate solution was added, and the liquid extracted by ether.

In order to remove the last traces of the unchlorinated base, the ethereal solution was shaken with a little dilute acetic acid, and then with dilute hydrochloric acid. The hydrochloric acid extract, when mixed with an equal volume of concentrated hydrochloric acid, deposited the whole of the chlorinated base as its crystalline hydrochloride.

The base isolated from this hydrochloride is a colourless liquid, which boils at $161.5^\circ/33$ mm. It solidifies when cooled by ice, and can be obtained in colourless needles, melting at 24° , by cooling a solution in light petroleum (b. p. $60-70^\circ$). (Found, $N=8.27$; $Cl=20.69$. $\text{C}_8\text{H}_{10}\text{ONCl}$ requires $Cl=20.7$; $N=8.2$ per cent.)

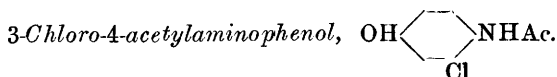
The *hydrochloride* crystallises from 20 per cent. hydrochloric acid in small needles, which melt and decompose at 225° .



The chloro-base is acetylated with remarkable ease, and the acetyl derivative is best prepared by dissolving the hydrochloride

of the base in water, adding rather more than the theoretical quantity of sodium acetate, and shaking the milky solution with a slight excess of acetic anhydride until precipitation is complete. It forms well-defined prisms from benzene, and melts at 97° . (Found, N=6.62; Cl=16.57. $C_{10}H_{12}O_2NCl$ requires N=6.56; Cl=16.6 per cent.)

When hydrolysed by dilute sulphuric acid, the acetyl derivative is converted into the base from which it was derived. A specimen of this chlorophenacetin was examined by Professor A. R. Cushny, F.R.S., and was found to be non-toxic; its physiological action has not yet been investigated.

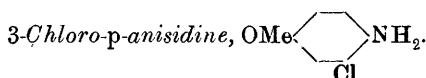


The hydrolysis of the ethoxy-group was effected in the following manner. Five grams of 3-chloroaceto-*p*-phenetidide were dissolved in 15 c.c. of dry benzene contained in a flask fitted with a good reflux condenser. Five grams of aluminium chloride were added, and the violent reaction was allowed to proceed without cooling. The cooled liquid was then diluted with water and extracted with ether. The residue was purified by treatment with dry ether, and, after crystallisation from chloroform, yielded long prisms, melting at 121° :

0.2800 gave 19.0 c.c. N_2 at 22° and 751 mm. N=7.59.

0.3004 „ 0.2285 AgCl. Cl=18.82.

$C_8H_8O_2NCl$ requires N=7.54; Cl=19.1 per cent.



This base is prepared in the same way as the corresponding ethoxy-derivative. The hydrochloride is, however, less readily soluble in dilute hydrochloric acid, and is completely precipitated from an aqueous solution containing 6 per cent. of the acid. It is a colourless, highly refractive liquid, which boils at $156^{\circ}/31$ mm.:

0.1447 gave 11.4 c.c. N_2 at 20° and 768 mm. N=9.1.

C_7H_8ONCl requires N=8.9 per cent.

The *acetyl* derivative is precipitated when the base, dissolved in dilute hydrochloric acid, is treated with excess of sodium acetate solution, and then shaken with rather more than the requisite quantity of acetic anhydride. It crystallises from benzene in prisms, which melt at 114° :

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0.3542 gave 22.2 c.c. N_2 at 22° and 748.5 mm. $N = 6.99$.

0.3162 „ 0.2246 AgCl. $Cl = 17.58$.

$C_9H_{10}O_2NCl$ requires $N = 7.0$; $Cl = 17.8$ per cent.

2-Chloro-4-ethoxybenzeneazo- β -naphthol, $OEt \begin{array}{c} \diagup \\ \diagdown \end{array} \begin{array}{c} Cl \\ \diagdown \\ \diagup \end{array} N:N \cdot C_{10}H_6 \cdot OH$.

Five grams of 3-chloro-*p*-phenetidine were dissolved in dilute hydrochloric acid, and diazotised in the usual manner. The diazotised solution was then poured into an alkaline solution of β -naphthol, when the azo-compound separated as dark red crystals. When recrystallised from acetic acid it forms brilliant red needles which melt at 140° :

0.3391 gave 25.2 c.c. N_2 at 19.5° and 770 mm. $N = 8.63$.

0.1914 „ 0.0841 AgCl $Cl = 10.88$.

$C_{18}H_{15}O_2N_2Cl$ requires $N = 8.6$; $Cl = 10.9$ per cent.

s-Di-2-chloro-4-ethoxyphenylcarbamide,
 $OEt \cdot C_6H_3Cl \cdot NH \cdot CO \cdot NH \cdot C_6H_3Cl \cdot OEt$.

Fifteen grams of 3-chloro-*p*-phenetidine were mixed with 5 grams of ethyl acetoacetate, and heated rapidly to 200 — 210° , with constant shaking. After a few minutes, colourless crystals separated on the cooler portions of the containing vessel, and, on cooling, the whole mass solidified. The substance was purified by first removing coloured impurities by means of alcohol, and then recrystallising from xylene. It forms slender needles, which melt at 235° and boil at 287° under ordinary atmospheric pressure without decomposition. It is sparingly soluble in all organic solvents:

0.1116 gave 0.2275 CO_2 and 0.0483 H_2O . $C = 55.60$; $H = 4.81$.

0.1131 „ 8 c.c. N_2 at 28.5° and 767 mm. $N = 7.8$.

0.2364 „ 0.1807 AgCl. $Cl = 18.93$.

$C_{17}H_{18}O_3N_2Cl_2$ requires $C = 55.3$; $H = 4.9$; $N = 7.6$; $Cl = 19.2$ per cent.

s-Di-2-chloro-4-hydroxyphenylcarbamide,
 $OH \cdot C_6H_3Cl \cdot NH \cdot CO \cdot NH \cdot C_6H_3Cl \cdot OH$.

s-Di-2-chloro-4-ethoxyphenylcarbamide was dissolved in xylene, and an equal weight of aluminium chloride added. A vigorous reaction set in on warming, and a crystalline solid slowly separated. When the reaction had ceased, the mixture was diluted with water, and the precipitated phenol separated by filtration. It was purified by dissolving in aqueous sodium hydroxide, extracting the solution with ether to remove soluble impurities, and then

precipitating the phenol by means of carbon dioxide. It crystallises from alcohol in microscopic needles, which melt at 251° :

0.1710 gave 0.3150 CO_2 and 0.0492 H_2O . $\text{C}=50.23$; $\text{H}=3.20$.

0.2884 ,, 22.2 c.c. N_2 at 19° and 765 mm. $\text{N}=8.91$.

0.0991 ,, 0.0904 AgCl . $\text{Cl}=22.56$.

$\text{C}_{13}\text{H}_{10}\text{O}_3\text{N}_2\text{Cl}_2$ requires $\text{C}=49.84$; $\text{H}=3.2$; $\text{N}=8.9$; $\text{Cl}=22.6$ per cent.

The *diacetyl* derivative is formed when the above phenol is boiled with acetic anhydride until a crystalline precipitate begins to separate. It crystallises from absolute alcohol in prisms, melting at 227° :

0.1227 gave 7.8 c.c. N_2 at 20.5° and 760 mm. $\text{N}=7.25$.

$\text{C}_{17}\text{H}_{14}\text{O}_5\text{N}_2\text{Cl}_2$ requires $\text{N}=7.1$ per cent.

The structure of the substances described above was proved by their formation from the carbamide derivative, prepared by the direct condensation of carbamide with 3-chloro-*p*-phenetidine. The mixed bases were heated at 170° until ammonia ceased to be evolved, when the mass, which solidified on cooling, was rubbed with dilute hydrochloric acid, and then with water, to remove excess of base and unchanged carbamide. When the residue was treated with alcohol, a colourless substance remained undissolved, which melted at 235° , and yielded the same phenol and acetyl derivative as those described above. The yield of the carbamide derivative by this method is, however, very small.

s-Di-3-chloro-4-ethoxyphenylcarbamide,

$\text{OEt}\cdot\text{C}_6\text{H}_3\text{Cl}\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}\cdot\text{C}_6\text{H}_3\text{Cl}\cdot\text{OEt}$.

This compound was formed by the action of ethyl acetoacetate on 2-chloro-*p*-phenetidine, a substance which was produced by the chlorination of *p*-nitrophenetole by potassium chlorate and hydrochloric acid, and subsequent reduction. The condensation was carried out in the same way as with the isomeric chloro-derivative, only in this case the product does not solidify until it is treated with dilute hydrochloric acid. It crystallises from alcohol in slender needles, melting at 211° :

0.0984 gave 6.5 c.c. N_2 at 15.5° and 762.5 mm. $\text{N}=7.74$.

0.1300 ,, $\text{HCl}=6.95$ c.c. $\text{N}/10\text{-AgNO}_3$ (Robertson's method).
 $\text{Cl}=19.0$.

$\text{C}_{17}\text{H}_{18}\text{O}_3\text{N}_2\text{Cl}_2$ requires $\text{N}=7.6$; $\text{Cl}=19.2$ per cent.

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