193. *The Reactions of Some Cyclic Tertiary Amines with N-Halogeno-compounds.*

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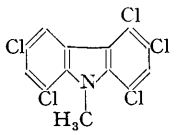
A number of cyclic tertiary amines have been chlorinated with *N* : 2′ : 4′ : 6′-tetrachlorobenzanilide and brominated with *N*-bromosuccinimide. Dealkylation occurs to a slight extent, but in general the halogenation is facile, extensive, and not selective with regard to position in the molecule. Often it is accompanied by dehydrogenation to a ring system of aromatic type. This accords with the view that the *N*-halogeno-compounds exhibit chemical reactivities of homolytic type.

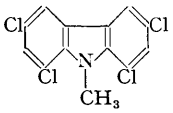
The discovery by Crane, Forrest, Stephenson, and Waters (*J.*, 1946, 827) that tertiary aliphatic amines, such as methyldi-(2-chloroethyl)amine, could be dealkylated upon chlorination with substituted *N*-chlorobenzanilides in a non-ionising solvent seemed to us to offer a new route for the controlled degradation of cyclic amines such as *N*-methylpiperidine, nicotine, and other alkaloids, but the following work shows that this method of degradation of amines is of little practical value.

Although a certain amount of dealkylation occurs when the cyclic *N*-methylamines, *N*-methylpiperidine, *N* : 6 : 8-trimethyl-1 : 2 : 3 : 4-tetrahydroquinoline, nicotine, narcotine, and ergotoxine are treated with *N* : 2′ : 4′ : 6′-tetrachlorobenzanilide in cold carbon tetrachloride or benzene solutions, the amount of formaldehyde which is liberated corresponds to only 1—2% of the *N*-methyl content of the amine taken. Furthermore, even in the simplest cases we were unable to establish the production of the corresponding demethylated secondary cyclic amine (*e.g.*, piperidine), or of any of the amino-aldehydes which could have been formed by the rupture of the heterocyclic ring at a N–C link. Similarly, *N*-benzylpiperidine gave only a very small yield of benzaldehyde, though dimethylaniline was extensively demethylated. Even when one or two molecular equivalents of *N*-chloro-imide were employed the reaction produced much hydrogen chloride, and an examination of the basic material in the reaction product always showed that a small part of the amine had been extensively chlorinated, though the majority of it could be recovered unchanged. From the large amount of active chlorine which could be taken up it appeared that the saturated ring system of *N*-methylpiperidine and its analogues had suffered chlorination in all possible positions, and that the chlorinated reaction product then lost hydrogen chloride very easily, possibly to yield bases of the pyridine type, traces of which could indeed be detected by smell.

Attention was then directed to the chlorination of *N*-methyltetrahydrocarbazole, in which chlorination in an allyl position was envisaged as a possibility (compare Ziegler *et al.*, *Annalen*,

1942, **551**, 80). With this substance we were able to establish that, in benzene solution, nuclear substitution and elimination of hydrogen chloride from the aliphatic ring proceeded simultaneously since a pentachloro-*N*-methylcarbazole (possibly I) was isolated as a reaction product. Under the most drastic conditions, *N*-methylcarbazole yielded only a tetrachloro-derivative (probably II), so that the extra chlorine atom of (I) must have been introduced into the *cyclo*hexene ring of the starting product before dehydrogenation to the benzenoid ring was complete. In support of this view of the reaction, we then found that *N*-methyldihydro-acridine gave acridine methochloride, evidently by substitution at the central methylene group followed by elimination of hydrogen chloride.

(I.) 

 (II.)

N-Bromosuccinimide reacted throughout in a very similar manner. Thus in carbon tetrachloride suspension *N*-methylpiperidine yielded a little formaldehyde, *N*-benzylpiperidine gave a little benzaldehyde, and dimethylaniline gave some formaldehyde. Just as triethylamine gives acetaldehyde, glyoxal, and diethylamine on chlorination with *N*-chloro-imides (Waters *et al.*, *loc. cit.*), so these same products were identified as resulting from the reaction between triethylamine and *N*-bromosuccinimide in carbon tetrachloride suspension. The bromination of *N*-methyltetrahydrocarbazole does not proceed well except in the presence of a little benzoyl peroxide (compare Schmidt and Karrer, *Helv. Chim. Acta*, 1946, **29**, 573; Schmidt and Leutersegger, *ibid.*, 1947, **30**, 1965), and appears to give at most a tetrabromo-*N*-methyl-carbazole, whilst *N*-methylcarbazole gives no more than a tribromo-compound. A corresponding dehydrogenation of an alicyclic ring system by *N*-bromosuccinimide has recently been noted by Barnes (*J. Amer. Chem. Soc.*, 1948, **70**, 145). Bromine reacts quite differently with these tertiary amines: it first forms red perbromides, and does not effect any detectable dealkylation.

The foregoing reactions of the *N*-chloro- and *N*-bromo-compounds accord with the hypothesis of substitution *via* homolytic bond fission (compare Robertson and Waters, *J.*, 1947, 492) since this would not be expected to be noticeably selective with respect to the attack on any one particular C–H bond.

In contrast to the saturated amines which have already been mentioned, pyridine, α-picoline, and quinoline were not substituted either by *N* : 2′ : 4′ : 6′-tetrachlorobenzanilide or by *N*-bromosuccinimide, though they promoted a slight evolution of free chlorine from the *N*-chloro-imide in boiling dry carbon tetrachloride solution. Evidently the methyl group of α-picoline does not show marked allylic reactivity.

Experimental.

Reaction between N-*Methylpiperidine and* N : 2′ : 4′ : 6′-*Tetrachlorobenzanilide in Benzene.*—*N*-Methyl-piperidine (8·6 ml.) in dry benzene (100 ml.) was slowly treated, with mechanical stirring, with 24 g. (1 equiv.) of the chloro-imide in 75 ml. of benzene, the mixture being kept cool with iced water. On the following day 50 ml. of dilute hydrochloric acid were added, solid trichlorobenzanilide was removed by filtration, and the two liquid layers were separated. The benzene layer contained only a little trichloro-benzanilide, whilst the aqueous layer yielded, on distillation, a little formaldehyde, which was characterised as its dimedone derivative, m. p. and mixed m. p. 191°. On neutralisation *N*-methyl-piperidine was recovered from the aqueous layer in about 50% yield: besides this there was only a small dark residue from which positive tests for secondary bases could not be obtained. When excess of *N*-chloro-imide was used this dark residue smelt distinctly of pyridine, but this, if present, was insufficient in quantity for definite characterisation. A quantitative experiment indicated that the yield of formaldehyde was about 1 mol. per 80 mols. of tertiary base.

The chlorination proceeded similarly in dry carbon tetrachloride solution, but it was found that, on long standing, *N*-methylpiperidine reacted with carbon tetrachloride with deposition of *N*-methyl-piperidine hydrochloride.

N-Benzylpiperidine (Wallach, *Annalen*, 1905, **343**, 74) reacted with the *N*-chloro-imide in a similar way, but gave no characterisable reaction products, other than a very small percentage of benzaldehyde. The following figures illustrate the outcome of the chlorination in benzene at 18°:

Base taken, mol.	0·01	0·01	0·01	0·005
Chloro-imide taken, mol.	0·01	0·02	0·03	0·035
Chloro-imide reacted, %	98·6	99·7	99·8	86·9
Chlorine converted into Cl^-, %	30·5	29·9	27·2	14·1

This indicates that there is extensive chlorination of a small fraction of the original base.

N : 6 : 8-*Trimethyl*-1 : 2 : **3** : 4-*tetrahydroquinoline* was prepared in the hope that it might give more

recognisable basic products after chlorination in a similar manner, but again the only product which could definitely be characterised was formaldehyde. This base, m. p. 48·5°, b. p. 127°/16 mm., was prepared by methylating 6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoline (Ewins, *J.*, 1913, **103**, 102) with formaldehyde and formic acid (compare *J. Amer. Chem. Soc.*, 1933, **55**, 5476) (Found : C, 81·6; H, 9·7; N, 8·1. $C_{12}H_{17}N$ requires C, 82·3; H, 9·7; N, 8·0%). Its *picrate* had m. p. 143° (Found : C, 53·4; H, 5·06. $C_{18}H_{20}O_7N_4$ requires C, 53·5; H, 4·95%).

The alkaloids nicotine, narcotine, and ergotoxine were also chlorinated by the *N*-chloro-imide in benzene solution. Each yielded a small quantity of formaldehyde, owing to fission of the molecule at an *N*-methyl group. Dimethylaniline gave formaldehyde (weighed as its dimedone derivative) corresponding to 1 CH_2O per 1·6 NMe_2 groups (*i.e.*, very much more than from the saturated heterocyclic compounds).

Brominations with N-*Bromosuccinimide.*—1·94 G. of *N*-methylpiperidine in 25 ml. of dry chloroform were mixed with 10·5 g. (3 equivs.) of *N*-bromosuccinimide in the same solvent. Rapid reaction set in after 1 minute, but was controlled by cooling in ice-water. After 12 hours water was added, and after filtration the two liquid layers were separated. The aqueous layer, on distillation, yielded a little formaldehyde (dimedone derivative separated), but no sign of a salt of a secondary base. No other derivatives of the original base, except its hydrobromide, could be isolated from the remaining portions of the reaction mixture.

The quantitative bromination of *N*-benzylpiperidine in carbon tetrachloride gave the following results, indicating again the extensive bromination of a small fraction of the base :

Base taken, mol.	0·0063	0·0063	0·0063
Bromo-imide taken, mol.	0·0059	0·0118	0·0177
Bromo-imide reacted, %	99·3	99·3	99·2
Bromine converted into Br^-, %	51·7	39·3	18·6

Benzaldehyde and *N*-benzylpiperidine (separated as the picrate) were the only identifiable reaction products.

N-Bromosuccinimide under carbon tetrachloride reacted with dimethylaniline slowly, after an induction period of several minutes, and gave an appreciable percentage of formaldehyde. The *N*-bromo-imide reacted immediately with triethylamine in dry carbon tetrachloride and gave a red gum. This was treated with dilute hydrochloric acid, and the aqueous solution was separated. It gave a positive colour reaction for acetaldehyde with sodium nitroprusside and piperidine; when treated with dimedone it yielded the anhydride of the glyoxal derivative (m. p. 215°, *ex* alcohol) and with 2 : 4-dinitrophenylhydrazine the derivatives of both acetaldehyde (m. p. 155°) and glyoxal (m. p. 327°). From this aqueous solution there were also obtained both unchanged triethylamine (as the picrate) and diethylamine (as the toluene-*p*-sulphonamide, m. p. and mixed m. p. 60°).

N-Bromosuccinimide did not react with either pyridine or α-picoline in dry carbon tetrachloride solution. When each of these bases was refluxed with *N* : 2′ : 4′ : 6′-tetrachlorobenzanilide in dry benzene solution a small amount of free chlorine was slowly evolved, even when precautions were taken to maintain anhydrous conditions by passing a slow current of thoroughly dried air through the boiling solutions. No chlorination of either base could be detected however.

N-Methylpiperidine in dry carbon tetrachloride reacted immediately with bromine in the same solvent to give a deep red solution and eventually a red gum. This gum proved to be a perbromide, readily converted into *N*-methylpiperidine hydrobromide, but after decomposition with water the product gave no aldehydic reactions, and no tests for secondary bases.

Halogenation of N-*Methyl*-1 : 2 : 3 : 4-*tetrahydrocarbazole.*—(*a*) **3·7** G. of base (Plant and Perkin, *J.*, 1921, **119**, 1831) and 47 g. (7 equivs.) of *N* : 2′ : 4′ : 6′-tetrachlorobenzanilide were allowed to react in 130 ml. of dry benzene. The mixture became warm and evolved hydrogen chloride. After 6 hours, 50 ml. of water were added, solid trichlorobenzanilide was filtered off, and the liquid layers were separated. The aqueous layer on treatment with dimedone yielded only 1 mg. of the formaldehyde derivative, m. p. 191°. The benzene layer on evaporation gave a brown paste, from which by repeated crystallisation from alcohol there was obtained a *pentachloro*-N-*methylcarbazole* (possibly I), m. p. 196·5° (Found : C, 44·0; H, 1·48; C, 50·9. $C_{13}H_6NCl_5$ requires C, 44·2; H, 1·7; Cl, 50·2%). This showed a very weak violet fluorescence in ultra-violet light, with a weak afterglow. Dehalogenation could not be effected by heating either with magnesium turnings in dry ether or with amalgamated zinc in hydrochloric acid.

(*b*) 3·7 G. of base and 25 g. (7 equivs.) of *N*-bromosuccinimide were suspended in 100 ml. of dry carbon tetrachloride. Reaction set in, with evolution of hydrogen bromide after an induction period of 5 minutes. After 48 hours water was added, and the layers were separated as in (*a*). The carbon tetrachloride layer yielded a brown solid which by repeated crystallisation, using alternately ethanol and light petroleum, gave a microcrystalline *tetrabromo*-N-*methylcarbazole*, m. p. 85° (Found : C, 30·4; H, 1·99; Br, 63·9. $C_{13}H_7NBr_4$ requires C, 31·3; H, 1·4; Br, 63·9%).

Halogenation of N-*Methylcarbazole.*—(*a*) 3 G. of base (compare Ehrenreich, *Monatsh.*, 1911, **32**, 1104) and 28 g. (5 equivs.) of chloro-imide were mixed in 80 ml. of dry benzene. There was no rapid reaction, but trichlorobenzanilide slowly separated. After 12 hours water was added and the liquid layers were separated. The aqueous portion gave no aldehydic reactions. The benzene layer yielded, after repeated crystallisations from ethanol, a *tetrachloro*-N-*methylcarbazole* (possibly II), m. p. 161° (Found : C, 49·1; H, 2·10; Cl, 44·8. $C_{13}H_7NCl_4$ requires C, 48·9; H, 2·19; Cl, 44·5%), together with a less pure *trichloro*-N-*methylcarbazole*, m. p. 113° (Found : Cl, 39·1. $C_{13}H_8NCl_3$ requires Cl, 37·4%), which on further treatment with the *N*-chloro-imide in benzene yielded the tetrachloro-*N*-methylcarbazole of m. p. 161°. When the latter was kept with excess of *N*-chloro-imide no further chlorination occurred, and the initial material could be recovered unchanged.

(*b*) 2 G. of base, 7·9 g. (4 equivs.) of *N*-bromosuccinimide, and 0·2 g. of benzoyl peroxide were refluxed together in 40 ml. of dry carbon tetrachloride. The liquid portion of the product left a green gummy

residue on evaporation, from which by repeated crystallisation from alcohol there were obtained a *tribromo-N-methylcarbazole*, m. p. 186° (Found: C, 37·7; H, 2·0; Br, 56·1. $C_{13}H_8NBr_3$ requires C, 37·9; H, 1·9; Br, 57·4%), and a less pure *dibromo-N-methylcarbazole*, m. p. 141° (Found: Br, 51·8. $C_{13}H_9NBr_2$ requires Br, 47·2%).

Chlorination of N-*Methyl*-9 : 10-*dihydroacridine*.—1 G. of base (Decker and Dunant, *Ber.*, 1906, **39**, 2721) in 10 ml. of dry benzene was treated with 3·44 g. (2 equivs.) of the *N*-chloro-imide in 20 ml. of benzene and reacted immediately. After 24 hours the yellow solid was filtered off and extracted four times with hot dilute hydrochloric acid, and this extract was evaporated on the water-bath. It left a yellow residue with a strong green fluorescence in alcoholic solution, and, when treated with alcoholic sodium picrate, yielded the picrate of *N*-methylacridine, m. p. 186° (Found: C, 56·1; H, 3·3; N, 12·5. Calc. for $C_{20}H_{15}O_7N_4$: C, 56·9; H, 3·3; N, 13·3%). For confirmation, the same product was prepared by methylating acridine with methyl sulphate and converting the product into its picrate.

The non-basic residue from the chlorination reaction was warmed with alkali and then recrystallised from alcohol. It gave *N*-methylacridone, m. p. and mixed m. p. 202°. There was no experimental evidence of the production of formaldehyde.

The analyses were carried out microchemically by Drs. Weiler and Strauss. All m. p.s are corrected.

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