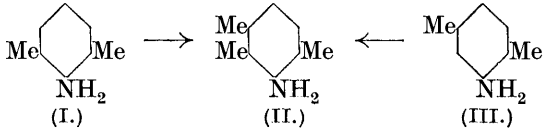
CCXVII.—*The Nuclear Alkylation of Aromatic Bases. Part I. The Action of Methyl Alcohol on the Hydrochlorides of* o- *and* p-*Toluidine, Mesidine, and Dimethylmesidine.*

By Donald Holroyde Hey.

Hofmann and Martius showed that nuclear methylation of aromatic amines can be effected (*a*) by heating the amine hydrochloride with methyl alcohol at 280—300° (*Ber.*, 1871, **4**, 742) and

(*b*) by heating the quaternary iodide, *e.g.*, phenyltrimethylammonium iodide, at 220—230° or higher (*Ber.*, 1872, **5**, 704). The essential reaction whereby nuclear methylation is effected is probably the same in both cases, since the primary action of the alcohol on the amine hydrochloride is to produce some secondary and then some tertiary base. It was later shown that nuclear methylation could also be effected by heating the hydrochlorides of either secondary or tertiary alkylarylamines and by heating alkylarylamines with metallic salts such as the chlorides of zinc, cobalt, and cadmium (Calm, *Ber.*, 1882, **15**, 1642; Benz, *ibid.*, p. 1646; Reilly and Hickinbottom, J., 1920, **117**, 103). These reactions formed the subject of a number of subsequent investigations by Hofmann (*Ber.*, 1872, **5**, 720; 1875, **8**, 61; 1880, **13**, 1729; 1882, **15**, 2895; 1884, **17**, 1913; 1885, **18**, 1821), and also by Eisenberg (*Ber.*, 1882, **15**, 1011), Nölting and Baumann (*Ber.*, 1885, **18**, 1145), Nölting and Forel (*Ber.*, 1885, **18**, 2668), and Limpach (*Ber.*, 1888, **21**, 640, 643). The extension of the reaction to include alcohols other than methyl alcohol was investigated by Hofmann (*Ber.*, 1874, **7**, 526; 1877, **10**, 528), Calm (*loc. cit.*), Benz (*loc. cit.*), Effront (*Ber.*, 1884, **17**, 419, 2324), and Hodgkinson and Limpach (J., 1892, **61**, 420). The primary object of the present investigation was to ascertain the extent to which nuclear alkylation can proceed in these reactions.

The view seems to be prevalent that the *p*- and *o*-positions in the benzene nucleus are attacked by the entering alkyl groups in the Hofmann–Martius reaction, and when these positions are occupied nuclear alkylation ceases. In most current text-books the possibility of *m*-alkylation is definitely denied. It is sometimes mentioned that pentamethylaniline can be prepared by the Hofmann–Martius reaction, but, since the initial material is not stated, this need not involve *m*-alkylation, for *s*-*m*-xylidine, as Limpach (*loc. cit.*) and Dimroth, Leichtlin, and Friedemann (*Ber.*, 1917, **50**, 1534) have shown, can readily be converted into pentamethylaniline. One or two cases are recorded which apparently involve a methyl group entering the *m*-position with respect to the amino-group. For example, Nölting and Baumann (*loc. cit.*) claimed that on heating the hydrochloride of mesidine (I) with methyl alcohol at 200—300° they obtained *iso*duridine (II), identical with the base formed on heating the hydrochloride of ψ-cumidine (III) with methyl alcohol.



(I.) (II.) (III.)

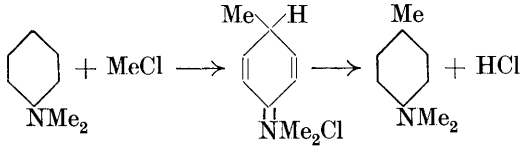
But Limpach (*loc. cit.*), with the object of studying the laws governing the nuclear alkylation, repeated the experiment of Nölting and Baumann on mesidine and isolated only mesidine itself, the initial material. He therefore concluded that an alkyl group is not substituted for hydrogen in the *m*-position with regard to the amino-group.

In reviewing the work done at this time and earlier, ambiguous cases will necessarily be encountered, since some of the work was done at a time when the structure of benzene and the isomerism of its derivatives were imperfectly understood, and several of the earlier experimental examples are of little value, since the particular xylidine, or mixture of xylidines, used as initial material was not specified. More recently, Liebermann and Kardos (*Ber.*, 1914, **47**, 1563), in studying certain by-products in the Hofmann–Martius reaction, claimed to have obtained from *m*-4-xylidine *iso*duridine (II) probably contaminated with mesidine. On the other hand, these authors found that *iso*duridine (II) (obtained from ψ-cumidine, III) could not be further methylated, and Hofmann (*Ber.*, 1884, **17**, 1913) came to a similar conclusion.

It appears, therefore, that up to the present there has been little justification for supposing that an alkyl group can enter the *m*-position in the Hofmann–Martius reaction and so give rise to complete nuclear alkylation. It is now shown, however, that alkylation can be effected at the *m*-position, and the statement that alkylation ceases after the *p*- and *o*-positions have been filled is therefore incorrect.

From the theoretical aspect, alkylation at the *m*-position would appear to be by no means improbable. The mechanism of the Hofmann–Martius " rearrangement " has been studied by Beckmann and Correns (*Ber.*, 1922, **55**, 852), who support the theory that alkylation is effected by means of alkyl halide, and also by Howard and Derick (*J. Amer. Chem. Soc.*, 1924, **46**, 166), who state that there is no indication of the synthesis of *m*-compounds by the Hofmann–Martius " rearrangement " and regard the quaternary halide as the essential compound which undergoes " molecular rearrangement." Both these investigations dealt with the action of heat on methylaniline hydrochloride. With regard to the " rearrangement " of free alkylarylamines in the presence of dry metallic salts, evidence has been obtained (Hickinbottom, J., 1927, 64; Hickinbottom and Waine, J., 1930, 1558; Hickinbottom and Preston, J., 1930, 1566) which indicates that the mechanism here involved is one of true isomerisation, and further, that this rearrangement is distinct from that obtaining when an alkylarylamine hydrochloride is heated. In *o,p*-alkylation in the ordinary Hof-

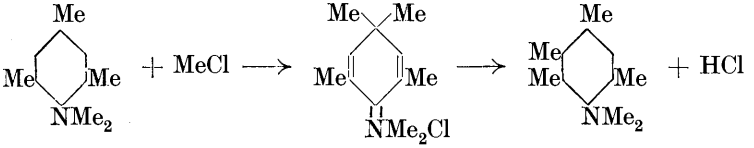
mann–Martius reaction, it is now generally held, in accordance with the views of Hofmann and of Beckmann and Correns (*loc. cit.*), that nuclear alkylation does not of necessity involve true intramolecular migration, but is more probably the result of ordinary intermolecular action, as indicated below (compare Orton and Jones, *Brit. Assoc. Reports*, 1910, 85; Robinson and Robinson, J., 1917, **111**, 965) :



In the above example the tertiary base only is represented, but any particular tertiary base, under the experimental conditions, will be in equilibrium with the corresponding secondary and primary bases, thus :

$$R{\cdot}NMe_2,HCl \underset{MeOH}{\overset{H_2O}{\rightleftharpoons}} R{\cdot}NHMe,HCl \underset{MeOH}{\overset{H_2O}{\rightleftharpoons}} R{\cdot}NH_2,HCl$$

If then, as seems most probable, alkylation at the *p*- and *o*-positions proceeds in this manner, there would appear to be no very cogent reason why alkylation should not proceed until every nuclear hydrogen is displaced, but, after the *p*- and *o*-positions have been substituted, further alkylation would involve an intermediate quinonoid form containing two alkyl groups at one nuclear carbon atom and subsequent true intramolecular migration, as shown below :



(IV.) (V.) (VI.)

Several cases are recorded by Bamberger and his collaborators of the transformation of quinonoid systems into hydroxy-benzenoid compounds, involving the migration of a methyl group (*e.g.*, Bamberger, *Ber.*, 1900, **33**, 3600; Bamberger and Rising, *ibid.*, pp. 3623, 3636, etc.), and it is also well known that hydroaromatic systems containing the *gem*-dimethyl group can be readily transformed into derivatives of *o*-xylene (Crossley and Le Sueur, J., 1903, **83**, 110; Crossley, J., 1904, **85**, 264, etc.).* On these grounds there would

* The conversion of santonin into *desmotropo*santonin in the presence of hydrochloric acid, which has long been known as the transformation of a quinonoid into a hydroxy-benzenoid system, has recently been shown to involve at the same time the migration of a methyl group (Clemo, Haworth, and Walton, J., 1929, 2368; 1930, 1110; Clemo and Haworth, J., 1930, 2579; Ruzicka and Eichenberger, *Helv. Chim. Acta*, 1930, **13**, 1117).

appear to be little objection to complete nuclear alkylation as envisaged above, even though it involves a mechanism, namely, true intramolecular migration, which may not be brought into play in the well-established cases of *p*- and *o*-alkylation. In brief, complete alkylation, on this basis, does not necessitate *m*-migration.

In addition to the mechanism outlined above, two other possibilities by means of which alkylation could proceed at the *m*-position should also be mentioned, (*a*) by *m*-migration of the alkyl group, and (*b*) by direct substitution of alkyl chloride at the *m*-position. The former suggestion is regarded as highly improbable, involving, as it does, a mechanism of which there appears as yet to be no proven example (*Ann. Reports*, 1927, 154; Baker and Ingold, J., 1929, 423). The second possibility, involving direct substitution at the *m*-position, cannot similarly be regarded as altogether improbable when the *o*- and *p*-positions are already substituted (especially when the substituents are methyl groups), and, in the absence of the further evidence obtained in this investigation, would have to be regarded as a likely alternative mechanism.

In the present investigation, originally undertaken to find definite proof whether alkylation can be effected in the *m*-position, the hydrochlorides of a number of bases were heated with an excess of the alcohol in an autoclave at 250—300°.

The action of methyl alcohol on *o*-toluidine hydrochloride under these conditions gave rise to a high yield of primary methylated bases, mainly mesidine (I), and a smaller quantity of *iso*duridine (II), thus suggesting that some alkylation at the *m*-position had taken place. The amount of *m*-toluidine present, after two distillations, in the *o*-toluidine used was estimated bromometrically (Callan and Henderson, *J. Soc. Chem. Ind.*, 1922, **41**, 161T) to be less than 2%, and the quantity of *iso*duridine formed in the above experiment gave indications of being considerably more than could arise from this proportion of *m*-toluidine in the initial material.

This indication that *m*-alkylation occurs after the *p*- and *o*-positions have been filled was confirmed by the action of methyl alcohol on the hydrochloride of *p*-toluidine (which can be obtained effectively free from *m*-toluidine) and of mesidine: *iso*duridine was obtained in both cases, in the latter in considerable amount. In an attempt to effect complete nuclear methylation, by the action of methyl alcohol on dimethylmesidine hydrochloride, five methyl groups were introduced into the nucleus, but the product was not pentamethylaniline but pentamethylphenol.

Some of the by-products obtained in these reactions may throw light on the mechanism by which the nuclear alkylation is effected.

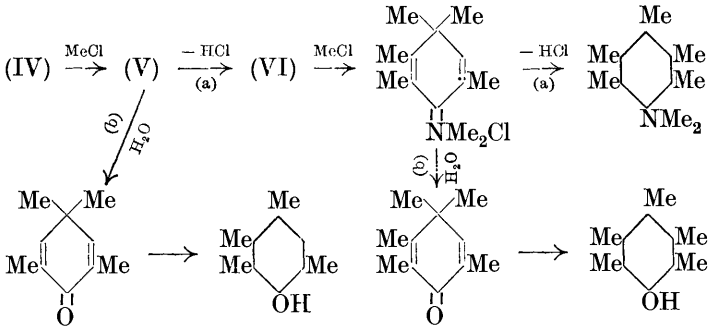
Three types have been encountered: (*a*) hydrocarbons, (*b*) derivatives of acridine, and (*c*) phenols.

(*a*) A small quantity of hexamethylbenzene was obtained from the methylation of mesidine, its formation being favoured by a slightly higher temperature and a longer period of heating (compare Hofmann, *Ber.*, 1872, **5**, 704, 720; 1880, **13**, 1729; Dimroth, Leichtlin, and Friedemann, *loc. cit.*).

(*b*) The production of acridine derivatives has been extensively investigated by Liebermann and Kardos (*Ber.*, 1913, **46**, 208; 1914, **47**, 1563), who obtained a variety of methylated acridines by heating the hydrochlorides of a number of aromatic amines with methyl alcohol at 250—260°. The products obtained from aniline, *o*-toluidine and *p*-toluidine were not separated and identified, the authors concluding that in these cases other side reactions largely intervened. It is now shown that *o*- and *p*-toluidine both give rise, under the experimental conditions here specified, almost exclusively to one acridine derivative only, namely, 1 : 3 : 7 : 9-tetramethylacridine. This particular derivative was never encountered, at least in the pure state, by Liebermann and Kardos (*loc. cit.*), though they obtained from the methylation of *m*-4-xylidine, in addition to two hexamethyl derivatives, a tetramethylacridine, m. p. 93—99°, which they regarded as being 1 : 3 : 7 : 9-tetramethylacridine. The compound here obtained from *o*- and *p*-toluidine melts at 121°, which agrees with the melting point recorded by Senier and Compton (J., 1907, **91**, 1927), who obtained the base by a synthetic method. Further agreement is shown in the melting point of the picrate. Moreover the fact that the same tetramethylacridine is obtained from both *o*- and *p*-toluidine further indicates that the compound has the constitution cited above.

(*c*) There appears to be no previous record of the formation of alkylated phenols during the Hofmann–Martius reaction. This is somewhat surprising, since the quantities formed are in many cases considerable and they are easily detected and isolated. For example, when *o*-toluidine hydrochloride was heated with methyl alcohol at 260—280° in an autoclave, in addition to the methylated bases already mentioned, there was also isolated, by distillation with steam from acid solution, a phenolic solid, which consisted mainly of mesitol together with a small proportion of *iso*durenol. Further, when dimethylmesidine hydrochloride was heated with methyl alcohol in the same way, the phenolic product consisted almost exclusively of pentamethylphenol. No pentamethylaniline and no acridine derivatives could be isolated in this experiment, the basic product consisting mainly of *iso*duridine, together with some mesidine. This may possibly be due in part to the fact that a

larger quantity of water was present in this reaction (see experimental part), and also to the smaller scale on which it was carried out, since the acridine by-products, for example, under most favourable conditions, only constitute 5—6% of the reaction product. The fact that, although pentamethylphenol was formed, no pentamethylaniline was isolated seems to indicate that with progressive methylation of the nucleus the replacement of the amino-group by hydroxyl is facilitated. It is well known that, in general, the successive introduction of methyl groups into the nucleus of a phenol decreases progressively the acidic strength (*e.g.*, Boyd, J., 1915, **107**, 1540, 1546), until in pentamethylphenol a compound is obtained which does not dissolve in cold aqueous alkali and readily separates from hot alkaline solution as free phenol: Dimroth, Leichtlin, and Friedemann (*loc. cit.*) even considered its existence as a quinonoid ketone. The formation of phenols in the Hofmann–Martius reaction is here considered to involve the intermediate formation of such a quinonoid ketone, produced by hydrolysis of a quinoneimine derivative:



This is in entire agreement with, and is regarded as giving support to, the mechanism of *m*-alkylation outlined on p. 1584. Indeed, if the mechanism of nuclear methylation is here correctly represented as involving the intermediate formation of quinoneimine forms, it would be surprising if phenols were not formed at the same time by hydrolysis. With progressive methylation, the tendency for reaction (b), *i.e.*, phenol formation, to take place at the expense of reaction (a) appears to become greater, so that when conditions are favourable to the formation of a pentamethylated derivative the product consists almost solely of the phenol. The reaction appears to be somewhat similar to the formation of trimethyl-ψ-quinol and cumoquinol from β-mesitylhydroxylamine, as shown by Bamberger and Rising (*Ber.*, 1900, **33**, 3636). Incidentally, the nuclear methylation at the *m*-position in mesidine does not appear to be in agree-

ment with the theory put forward by Howard and Derick (*loc. cit.*) for the mechanism of the Hofmann "rearrangement" of methylaniline hydrochloride, which essentially involves the formation of a quaternary halide, since mesidine has long been known to be incapable of forming such a compound. The two cases may not be strictly comparable, however, since Howard and Derick only studied the action of heat on the dry hydrochloride of methylaniline.

In view of the fact that alkylated phenols had never before been encountered as products of the Hofmann–Martius reaction, it seemed desirable to look closely into experimental conditions. This question is discussed in the experimental part. Previous workers have observed the liberation of volatile bases on adding alkali to their reaction product, but this fact would not necessarily indicate that some phenol formation had taken place, since the formation of acridine derivatives also involves the separation of a nitrogen atom from the benzene nucleus.

EXPERIMENTAL.

Apparatus and Experimental Conditions.—The amine hydrochloride and methyl alcohol were heated in electrically heated steel autoclaves, of about 250 and 1400 c.c. capacity. The product always contained iron in solution which was precipitated on the addition of alkali, and in order to minimise this the reactants were usually contained in an open Pyrex vessel, fitting loosely within the autoclave. At the conclusion of each reaction the tube and its contents were withdrawn and the inside of the autoclave was washed out with dilute acid and finally with aqueous alkali, the washings being added to the main reaction product.

As the formation of phenols in the Hofmann–Martius reaction had not been previously recorded, it seemed necessary to find whether the iron took any essential part in their formation, as previous workers had often carried out their experiments in sealed glass tubes. Some reactions were therefore carried out in a Pyrex vessel, fitted with a loosely fitting cover, inside an enamel-lined autoclave, both with and without the addition of metallic iron. In the former case some iron had been acted upon during the reaction (2 g.), whereas in the latter the product was entirely free from iron, but in both experiments phenol formation took place to approximately the same extent. It was therefore concluded that the presence of the iron did not materially affect the course of the reaction.

Gokhlé and Mason (J., 1930, 1757), in carrying out the *N*-methylation of α-naphthylamine by heating the sulphate with methyl alcohol in a steel autoclave at 180°, found that the walls of the autoclave

were not attacked. Our experiments, however, were effected at rather higher temperatures. These workers observed the formation of some α-naphthol in their experiment, which, unlike the formation of the phenols in the present investigation, would not be entirely unexpected on account of the ready interchange between amino- and hydroxyl groups that is known to take place in the naphthalene series.

The thermometer pocket of the autoclave must reach below the surface of the reactants, otherwise the temperatures recorded may be 30—50° too low. The temperatures given by previous workers vary somewhat, which may in part be due to an underestimation of the autoclave temperature, as instanced above, or to the difficulty of ascertaining correctly the temperature inside a sealed tube. In agreement with Howard and Derick (*loc. cit.*), it was found that the main factor for nuclear methylation was temperature, the most suitable range in the examples studied being 260—280°. Six hours' heating at this temperature was often sufficient, and prolonging the action to 40 hours did not materially affect the product, apart from slightly increasing the yield of by-products. Under the conditions of time, temperature, and concentration here adopted for the methylation of the toluidines, the product consisted of a high percentage of primary bases, substantially free from secondary and tertiary bases. On the other hand, in an experiment on the action of methyl alcohol on *o*-toluidine hydrochloride at 200—230°, the product consisted almost wholly of the tertiary base dimethyl-*o*-toluidine; at 230—250° some mesidine was also formed.

The Action of Methyl Alcohol on o-*Toluidine Hydrochloride.*—380 G. of the hydrochloride of redistilled " pure " *o*-toluidine (containing less than 2% *m*-toluidine) (1 mol.) and 200 g. (*ca.* 2½ mols.) of dry methyl alcohol were heated in the autoclave at 260—280° for 10 hours. The reaction product was made strongly acid with sulphuric acid (to prevent distillation of appreciable quantities of the bases) and distilled with steam. An almost colourless oil, with a phenolic odour, solidified (36 g.; A) in the receiver. The residue was made alkaline with sodium hydroxide (a strongly ammoniacal and fishy odour was produced, and iron precipitated as hydroxide) and subjected to prolonged distillation with steam; a slightly yellow, basic oil in the distillate was extracted with benzene and recovered (170 g.; B). The liquid containing the less volatile products was filtered from the ferric hydroxide and extracted with benzene, the ferric hydroxide also being washed with hot benzene; evaporation of the solvent left a dark oil (100 g.; C).

Treatment of the distillate from acid solution (*A*). On distillation of the solid, the greater portion was collected at 220—222° as a

colourless oil with a characteristic odour, which solidified on cooling. Recrystallisation from dilute methyl alcohol gave mesitol (25 g.), m. p. 70—71°. Its feebly acidic properties were confirmed, it being to a large extent extracted from alkaline solution by organic solvents. Its identity was confirmed (*a*) by preparation of bromomesitol (Biedermann and Ledoux, *Ber.*, 1875, **8**, 250; Jacobsen, *Annalen*, 1879, **195**, 270), m. p. 79—80° (Found : Br, 37·0. Calc. for $C_9H_{11}OBr$: Br, 37·2%); (*b*) by preparation of mesityl phenylurethane (Auwers, *Ber.*, 1899, **32**, 19), m. p. 141—142° (Found : C, 75·1; H, 6·7. Calc. for $C_{16}H_{17}O_2N$: C, 75·3; H, 6·7%); and (*c*) by comparison and mixed melting point with mesitol prepared from mesidine by means of the diazo-reaction. A smaller quantity of a higher-boiling fraction was also collected (b. p. 230—250°), and after successive distillations the main fraction, which solidified on cooling, was recrystallised twice from light petroleum (b. p. 80—100°), *iso*durenol being obtained, m. p. 79—81°. Its identity was confirmed (*a*) by brominating the phenol in glacial acetic acid, keeping the solution at room temperature and finally pouring it into water, and recrystallising the precipitated solid from aqueous alcohol, *bromoisodurenol* separating in long white needles, m. p. 135° (Found : C, 52·5; H, 5·7. $C_{10}H_{13}OBr$ requires C, 52·4; H, 5·7%); (*b*) by acetylating the bromo-derivative with warm acetic anhydride and a few drops of concentrated sulphuric acid, pouring the solution into water, and recrystallising the precipitated solid from aqueous alcohol, *bromoisodurenyl acetate* separating in tufts of white needles, m. p. 98° (Found : C, 53·0; H, 5·3. $C_{12}H_{15}O_2Br$ requires C, 53·1; H, 5·5%); (*c*) by heating a slight excess of the phenol with phenyl *iso*cyanate at 90—100° for 3—4 hours, washing the solid product with sodium hydroxide solution, and recrystallising it from aqueous alcohol, iso*durenyl phenylurethane* being obtained in small white prisms, m. p. 178—179° (Found : C, 75·9; H, 7·2. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1%); (*d*) by benzoylation of the phenol by the Schotten–Baumann method, iso*durenyl benzoate* being obtained in white plates, m. p. 71—72°, from aqueous alcohol (Found : C, 80·5; H, 7·2. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%); and (*e*) by comparison and mixed melting point with *iso*durenol prepared from *iso*duridine by means of the diazo-reaction.

Treatment of the distillate from alkaline solution (*B*). Practically the whole of the liquid distilled as an almost colourless oil between 229° and 236°. Redistillation gave pure mesidine (approximately 160 g.) (b. p. 232—233°), and acetylation of a small portion in the usual manner gave acetomesidide, m. p. 216° (Found : C, 74·4; H, 8·4. Calc. for $C_{11}H_{15}ON$: C, 74·6; H, 8·5%). The p-*toluenesulphonyl* derivative, obtained by shaking the base with *p*-toluene-

sulphonyl chloride in the presence of alkali, separated as a solid (it being insoluble in aqueous alkali), and crystallised from alcohol in white needles, m. p. 167° (Found : C, 66·6; H, 6·4. $C_{16}H_{19}O_2NS$ requires C, 66·4; H, 6·6%). The *picrate* of mesidine, prepared in the usual manner, crystallised from alcohol–light petroleum (b. p. 80—100°) in yellow prisms, m. p. 189—191° (decomp.) (Found : N, 15·4. $C_{15}H_{16}O_7N_4$ requires N, 15·4%). A small quantity of higher-boiling material from B was added to the less volatile bases C.

Treatment of the non-volatile residue (*C*). The residual oil, together with the small quantity of higher-boiling material from the alkaline steam distillate (B), was distilled and three fractions were collected, (i) b. p. 240—280° (30 g.), (ii) b. p. 280—350° (22 g.), and (iii) b. p. 350—365° (35 g.). A small quantity of black tarry matter remained. Fraction (i) on redistillation gave mainly mesidine (20 g.), together with a small quantity of *iso*duridine; fraction (ii) gave a further quantity of *iso*duridine. The *iso*duridine, when pure, boiled at 258—260°, solidified when cooled to 10°, and gave an acetyl derivative, m. p. 217·5°, after crystallisation from alcohol (Found : C, 75·2; H, 8·8; N, 7·5. Calc. for $C_{12}H_{17}ON$: C, 75·4; H, 8·9; N, 7·3%). (Nölting and Baumann, *loc. cit.*, and Limpach, *loc. cit.*, give 210—211° and 215°, respectively, as the m. p. of aceto*iso*-duridide.) On admixture with acetomesidide (m. p. 216°), the melting point was depressed to 195—200°. The *picrate* of *iso*-duridine, formed in the usual manner, crystallised from alcohol in yellow prisms, m. p. 199—200° (decomp.) (Found : N, 14·6. $C_{16}H_{18}O_7N_4$ requires N, 14·8%). Fraction (iii), which partly solidified, gave on trituration with alcohol 1 : 3 : 7 : 9-tetramethylacridine (18 g.), which crystallised from alcohol in fine long yellow needles, m. p. 120—121° (Found : C, 86·8; H, 7·3; N, 5·8. Calc. for $C_{17}H_{17}N$: C, 86·8; H, 7·2; N, 5·95%). Its picrate melted at 210—211° (compare Senier and Compton, J., 1907, **91**, 1927). Concentration of the alcoholic mother-liquors gave further quantities of this tetramethylacridine, and finally a small quantity of a second acridine derivative was obtained, m. p. 73—74°, which may possibly be 1 : 3-dimethylacridine, for which Kaufmann (*Annalen*, 1894, **279**, 286) gives m. p. 71°. The total yield (about 180 g.) of mesidine in this experiment, from B and C, was more than 50%, calculated on the weight of *o*-toluidine hydrochloride taken.

The Action of Methyl Alcohol on p-*Toluidine Hydrochloride.*—The *p*-toluidine hydrochloride was made from " pure " *p*-toluidine, previously recrystallised from aqueous alcohol in the form of its hydrate, which melted finally at 43° 40 G. of *p*-toluidine hydrochloride were heated in the autoclave with 25 g. of dry methyl alcohol (nearly 3 mols.) for 12 hours at 250—275°. Steam-distillation of

the product from strongly acid solution gave a phenolic distillate, which solidified (2 g.) and was almost wholly mesitol, identical with that obtained from the methylation of *o*-toluidine. When the residue was made alkaline, a strong ammoniacal smell was observed and ferric hydroxide was precipitated, and on distillation with steam a basic oil was obtained; this on redistillation was collected between 230° and 240° (20·5 g.) and consisted of almost pure mesidine. The residue from the second steam distillation was filtered from the ferric hydroxide and extracted with benzene, the ferric hydroxide also being washed with hot benzene. After removal of the benzene the residual oil was distilled, and two fractions were collected, (i) b. p. 250—340° (2 g.) and (ii) b. p. 340—360° (2 g.). The former was acetylated and after successive crystallisations aceto*iso*duridide was obtained, identical with that obtained in the previous experiment. The higher fraction partly solidified; the solid material was removed, drained, and crystallised twice from alcohol, 1 : 3 : 7 : 9-tetramethylacridine being obtained.

The Action of Methyl Alcohol on Mesidine Hydrochloride.—50 G. of mesidine hydrochloride and 25 g. of dry methyl alcohol (approximately 2·7 mols.) were heated in the autoclave for 12 hours at 240—270°. The product was diluted with water and made alkaline with sodium hydroxide solution; ammoniacal odours were evolved and the precipitated metallic hydroxide was filtered off. The filtrate was extracted with benzene, and on distillation of the extract three fractions were collected, (i) b. p. 235—250° (20 g.), (ii) b. p. 250—300° (7·5 g.), and (iii) b. p. 300—350° (5 g.). The aqueous alkaline layer was heated to remove benzene and when cold was acidified; mesitol slowly separated in white needles. Fraction (i), treated with an excess of dilute sulphuric acid, left a small crystalline residue of hexamethylbenzene, m. p. 165°, after two crystallisations from alcohol (Found : C, 89·1; H, 11·2. Calc. for $C_{12}H_{18}$: C, 88·9; H, 11·1%). Steam-distillation of the acid solution gave a further small quantity of mesitol, and when the residual acid solution was made alkaline a basic oil was liberated consisting of mesidine and *iso*duridine. The two bases were readily separated and identified by redistillation, followed by acetylation and successive recrystallisations. Fraction (ii) was completely acetylated, the product consisting mainly of aceto*iso*duridide. Fraction (iii) contained tarry matter, probably together with some acridine derivatives, as indicated by the formation of a fluorescent solution on the addition of hydrochloric acid, but this was not further treated.

The above method of working up the product is inferior to that adopted in the former two examples, since direct extraction of the product, made alkaline, with an organic solvent always removes, in

addition to the bases, a large proportion of the phenols which are present, owing to the feeble acidity of the latter. The better method is to remove the phenols first by distillation with steam from strongly acid solution.

Preparation of N-*Methyl- and* N-*Dimethyl-mesidine.*—*N*-Dimethylmesidine, prepared by the method of Bamberger and Rudolf (*Ber.*, 1906, **39**, 4289), was obtained as a colourless oil, b. p. 213—215°, which formed a *picrate* in the usual manner, obtained from hot alcohol in fine yellow needles, m. p. 182° (decomp.) (Found: N, 13·9. $C_{17}H_{20}O_7N_4$ requires N, 14·3%). A little monomethylmesidine was also isolated (compare Bamberger and Rudolf, *loc. cit.*). With a reduced amount of methyl sulphate, the product was mainly the secondary base. The monomethylmesidine thus obtained was a colourless oil, b. p. 220—221°, which formed a *picrate* in the usual manner. Crystallisation from alcohol, in which it was more soluble than the picrate of the tertiary base, gave *monomethylmesidine picrate* in yellow rhombic prisms, m. p. 179° (Found: N, 15·3. $C_{16}H_{18}O_7N_4$ requires N, 14·8%). On admixture with the picrate of dimethylmesidine (m. p. 182°) the melting point was depressed to 155—160°. By treating monomethylmesidine with *p*-toluenesulphonyl chloride in the presence of alkali, the p-*toluenesulphonyl* derivative was obtained, which crystallised from alcohol in white needles, m. p. 145—146° (Found: C, 67·2; H, 7·2. $C_{17}H_{21}O_2NS$ requires C, 67·3; H, 6·9%).

The Action of Methyl Alcohol on Dimethylmesidine Hydrochloride.—37 G. of dimethylmesidine (1 mol.), 15 g. of methyl alcohol (2 mols.), and 38 c.c. of concentrated hydrochloric acid (approximately 12 g. of hydrogen chloride, *i.e.*, 1½ mols.) were heated in the autoclave for 12 hours at 230—250°. The product was treated with sulphuric acid and subjected to distillation with steam; the oil in the distillate was filtered off after solidifying (4 g.), and the filtrate extracted with ether, evaporation of which left a small quantity of a phenolic residue consisting mainly of mesitol. The solid was distilled, b. p. 260—265°, and then crystallised from light petroleum (b. p. 80—100°), pentamethylphenol being obtained in white needles, m. p. 126° (Found: C, 80·1; H, 9·4. Calc. for $C_{11}H_{16}O$: C, 80·5; H, 9·75%). By heating the phenol in slight excess with phenyl *iso*cyanate and washing the product with warm sodium hydroxide solution, *pentamethylphenyl phenylurethane* was obtained; it crystallised from alcohol–light petroleum (b. p. 80—100°) in small white needles, m. p. 215° (Found: C, 76·6; H, 7·3; N, 5·1. $C_{18}H_{21}O_2N$ requires C, 76·3; H, 7·4; N, 4·95%). Preparation of the benzoyl derivative by the Schotten–Baumann method gave *pentamethylphenyl benzoate*, which crystallised from 95% alcohol in white

rhombic plates, m. p. 127° (Found: C, 80·35; H, 7·5. $C_{18}H_{20}O_2$ requires C, 80·6; H, 7·5%).

The residue from the acid steam-distillation was made alkaline by the addition of sodium hydroxide; a strongly ammoniacal and fishy odour was observed, and iron precipitated. The alkaline mixture was distilled with steam and the first distillate, collected in dilute hydrochloric acid, was shown to contain methylamines; subsequently mesidine (6 g.) was collected. The residue was extracted with benzene, and after evaporation of the solvent the residual oil was distilled and three fractions were collected, (i) b. p. 200—250° (3 g.), (ii) b. p. 250—300° (5 g.), and (iii) above 300° (2 g.). Fraction (i) consisted mainly of mesidine, and fraction (ii) mainly of *iso*duridine, both bases being identified with the previous authentic specimens by acetylation, followed by fractional crystallisation. Fraction (iii) consisted of a dark viscous mass containing much tarry matter. It could not be acetylated and no acridine derivatives could be isolated from it.

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