41. *A New Method of Nuclear Methylation of Aromatic Amines.*

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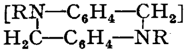
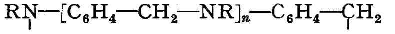
A method of nuclear methylation of aromatic amines is described consisting in the heating to temperatures above 300° (*e.g.*, dry distillation) of the so-called anhydro-4-aminobenzyl alcohols (I or II). It is assumed that the reaction starts with the formation of radicals (III), which subsequently undergo disproportionation with formation of nuclear methylated amines (cf. IV) and unidentified oxidised resinous substances. Addition of an alkaline reagent is essential to obtain good yields. It prevents the condensation of anhydro-4-aminobenzyl alcohols to substances containing methylene linkages between several aromatic groups, which under such conditions decompose mainly with formation of the original amines.

In an attempt to obtain *p*-toluidine by a method which did not involve toluene as starting material, the possibility of nuclear methylation of aniline and other aromatic amines was examined. The Hofmann reaction, consisting in the treatment of an aromatic amine with methyl alcohol and acid at high temperatures under pressure, fulfils this purpose, but it possesses certain disadvantages, *e.g.*, the necessity of working under high pressure, and in the case of the preparation of only partially nuclear methylated amines, such as *p*-toluidine, the formation of several products.

Aromatic primary and secondary amines with a free *p*-position react in presence of mineral acids with formaldehyde, forming anhydro-4-aminoaryl alcohols (Kålle and Co., B.P. 1895, 1963). These are polymers and should possess a ring or long-chain structure consisting of two or more molecules (I or II). In the latter case the free valencies of the terminal atoms would be saturated by the addition of a water or an aniline molecule. The same substances can also be obtained by other methods, *e.g.*, dehydration of 4-amino-aryl alcohols by heat or by a treatment with acids. We have now attempted to convert these substances into the corresponding nuclear methylated aromatic amines. 4-Aminobenzyl alcohol and its anhydrides yield *p*-toluidine when reduced by zinc and mineral acid (D.R.P. 83,544), but the yields are unsatisfactory.

(I.)


$[RN—C_6H_4—CH_2]_n$
$H_2C—C_6H_4—NR$



$RN—[C_6H_4—CH_2—NR]_n—C_6H_4—CH_2$ (II.)

Hydrazobenzene when heated to high temperatures decomposes with formation of aniline and azobenzene (Hofmann, *Proc. Roy. Soc.*, 1863, **12**, 576), and it is likely that this reaction starts with the cleavage of the NH–NH linkage, forming free radicals Ar·NH·, which become stabilised by disproportionation involving undissociated hydrazobenzene :

$$NHPh{\cdot}NHPh \longrightarrow 2NHPh{\cdot} \qquad 2NHPh{\cdot} + NHPh{\cdot}NHPh \longrightarrow 2NH_2Ph + NPh{:}NPh$$

Hydrocarbons possessing aliphatic C–C linkages also decompose at high temperatures, starting with a cleavage of such a link and the formation of radicals, which become stabilised by disproportionation with other undissociated hydrocarbons, thus forming saturated hydrocarbons of smaller carbon content in addition to unsaturated hydrocarbons (cf. Rice and Rice, "The Aliphatic Free Radicals," Baltimore, 1935, pp. 91, 142). The stabilisation of free radicals by disproportionation appears to be a general phenomenon, probably first observed in the formation of triphenylmethane by heating of hexaphenylethane (Gomberg and Cone, *Ber.*, 1904, **37**, 2037; cf., *e.g.*, Marvel *et al.*, *J. Amer. Chem. Soc.*, 1939, **61**, 2769, 2771; Treckel and Selwood, *ibid.*, 1941, **63**, 3397) :

$$CH_2R{\cdot}CH_2R \longrightarrow 2CH_2R{\cdot} \qquad 2CH_2R{\cdot} + CH_2R{\cdot}CH_2R \longrightarrow 2CH_3R + CHR{:}CHR$$

We considered that, since the polymerised anhydro-4-aminobenzyl alcohols (I or II) contain CH_2–NH linkages which are intermediate between NH–NH and CH_2–CH_2 linkages, they might behave similarly, and form when heated to high temperatures in the first place radicals of the type (III; $n = 0, 1, 2. \ldots.$), which in turn would undergo disproportionation with formation of *p*-toluidine (IV; $n = 0$) or substances (IV; $n = 1, 2 \ldots.$) from which *p*-toluidine could be easily obtained during the heating.

$$\text{(III.)}\quad {\cdot}NH—[C_6H_4{\cdot}CH_2{\cdot}NH]_n—C_6H_4{\cdot}CH_2{\cdot} \longrightarrow NH_2—[C_6H_4{\cdot}CH_2{\cdot}NH]_n—C_6H_4{\cdot}CH_3 \text{ (IV.)}$$
$$\longrightarrow {\cdot}NH–[C_6H_4{\cdot}CH_2{\cdot}NH]_{n-1}—C_6H_4{\cdot}CH_2{\cdot} + NH_2{\cdot}C_6H_4{\cdot}CH_3$$

Indeed, anhydro-4-aminobenzyl alcohol, when heated to a high temperature under pressure or, more conveniently, when dry distilled, decomposes with formation of a mixture of almost equal parts of aniline and *p*-toluidine; in addition, small amounts of *N*-methyl-*p*-toluidine, high-boiling amines, and volatile amines (especially ammonia) are formed. The yield of the aniline–*p*-toluidine mixture is, however, less than 25%.

The formation of aniline from anhydro-4-aminobenzyl alcohol might be unexpected, and might lead to doubts about the structure of this substance prepared from aniline, mineral acid, and formaldehyde. However, 4-aminobenzyl alcohol, prepared by reduction of 4-nitrobenzyl alcohol, and the anhydro-4-aminobenzyl alcohol obtained from it, the structures of which are beyond doubt, behave in the same way.

Following up certain considerations to be discussed below, we have found that heating (dry distillation) of anhydro-4-aminobenzyl alcohol in an alkaline medium yields 35—40% of *p*-toluidine, accompanied by only negligible amounts of by-products. The improvement can be obtained in presence of alkaline substances such as sodium acetate, sodium bicarbonate, sodium borate, but the use of sodium carbonate or calcium hydroxide is preferable. Neutral diluents such as fuller's earth, kieselguhr, or sand have little or no effect on the yield and quality of the amines formed.

Anhydro-4-aminobenzyl alcohol obtained by dehydration of 4-aminobenzyl alcohol, and this alcohol itself give the same result. Other substances, which at the temperature required in these experiments decompose with formation of anhydro-4-aminobenzyl alcohol, and, consequently, behave similarly, are 4-aminobenzylaniline and similar derivatives.

Anhydro-4-aminobenzyl alcohol was prepared under different conditions, *i.e.* with variation in the amount of formaldehyde or acid and in the temperature. The best results were obtained by first condensing 1 mol. of aniline hydrochloride with 1·2—1·5 mols. of formaldehyde below 20°. If this temperature or the acid concentration is increased, the anhydro-4-aminobenzyl alcohol is accompanied by increasing amounts of resins. Such products are also formed when anhydroaminobenzyl alcohol, obtained by dehydration of 4-aminobenzyl alcohol or by condensation of aniline, formaldehyde, and mineral acid below 20°, is treated with mineral acid on the water-bath. In this case, formaldehyde is split off, indicating the formation of CH_2 linkages between different aromatic groups completely analogous to those existing in phenol–formaldehyde resins.

Aromatic amines connected by methylene linkages, when heated above 400°, decompose with formation of aniline or its derivatives. The simplest representative, 4 : 4′-diaminodiphenylmethane (heated under pressure, since its b. p. lies below the decomposition temperature), yields a small amount of aniline and *p*-toluidine. Similarly, when the more complicated resinous methylene derivatives obtained from anhydro-4-aminobenzyl alcohol are heated above 400°, they decompose with formation of a negligible amount of *p*-toluidine and a small yield of aniline.

The formation and subsequent decomposition of such resinous products, when anhydro-4-aminobenzyl alcohol is heated in absence of alkaline substances to the high temperature required, explains the formation of aniline and a reduced total yield of amines. The function of these alkalis is to prevent formation of such products detrimental to the yield of *p*-toluidine. This is confirmed by the fact that distillation in the presence of alkalis of the above-mentioned condensation products, *e.g.*, obtained by treatment of anhydro-4-aminobenzyl alcohol with mineral acids at water-bath temperature, does not give the improved yield of *p*-toluidine.

This convenient and economical method of nuclear methylation can be applied to other aromatic amines with a free *p*-position, and in many cases is much superior to the existing methods. An alkaline medium is always required to give satisfactory yields (20—40%) of the desired methylated amines, for in its absence a mixture of the methylated aromatic amine with the original amine in a smaller total yield is obtained. In addition, varying amounts of by-products similar to those obtained in the case of anhydro-4-aminobenzyl alcohol, especially higher-boiling amines of the 4 : 4′-diaminodiphenylmethane type, are obtained. Typical examples are given later, but it should be realised that the amount of methylated amines may vary with the type and amount of the added alkaline substances.

Anhydro-4-amino-3-methylbenzyl alcohol (from *o*-toluidine) gives in presence of calcium hydroxide a good yield of *m*-4-xylidine in addition to some 4 : 4′-diamino-3 : 3′-dimethyldiphenylmethane, and the 2-methyl analogue (from *m*-toluidine) decomposes similarly with formation of *o*-4-xylidine. Anhydro-4-amino-2 : 5-dimethylbenzyl alcohol (from *p*-xylidine) yields in addition to *ψ*-cumidine some 4 : 4′-diamino-2 : 2′ : 5 : 5′-tetramethyldiphenylmethane. This method also allows the preparation of the hitherto unknown 4-*amino*-1 : 2 : 3-*trimethylbenzene* (m. p. 24°) from anhydro-4-amino-2 : 3-dimethylbenzyl alcohol (from *o*-3-xylidine), the Hofmann reaction apparently leading to the formation of 1-amino-2 : 5 : 6-trimethylbenzene (Noelting and Forel, *Ber.*, 1885, **18**, 2680). Anhydro-4-amino-3-methoxybenzyl alcohol (from *o*-anisidine) gives only a moderate yield of 4-amino-3-methoxytoluene, whereas anhydro-4-amino-1-hydroxymethylnaphthalene (from α-naphthylamine) yields a mixture of similar amounts of α-naphthylamine and 4-methyl-1-naphthylamine, which can be separated by means of their picrates.

This reaction can be extended to the anhydro-4-aminoaryl alcohols derived from secondary amines. Dry distillation of anhydro-4-monomethylaminobenzyl alcohol (from monomethylaniline) in presence of calcium hydroxide yields *N*-methyl-*p*-toluidine and some *p*-toluidine. It appears that the methyl group attached to the nitrogen atom is liable to split off at the high temperature of the reaction, *viz.*, > 300° and generally 400—500°.

The fate of the oxidised part of the starting material, which serves as the source of hydrogen for the disproportionation, has not been investigated, for the resins produced are intractable.

EXPERIMENTAL.

Destructive Distillation of 4-*Aminobenzyl Alcohol.*—(i) 4-Aminobenzyl alcohol (37 g.; Fischer and Fischer, *Ber.*, 1895, **28**, 880) is heated under reflux on an air-bath for 30 mins., and then dry distilled. Fractions: < 200°, 3 g. (m. p. 15°); 200—210°, 5 g. (m. p. 10°); > 210°, 2 g. (oil). All fractions are mixtures of aniline and *p*-toluidine, identified in the usual manner. The approximate proportions may be indicated by the m. p.'s, if the small amounts of by-products are neglected: a mixture of equal parts of aniline and *p*-toluidine (m. p. 44°) melts at 14°. (ii) 4-Aminobenzyl alcohol (75 g.) and anhydrous sodium carbonate (75 g.) are thoroughly mixed, heated under reflux, and dry distilled as above; yield, 42 g. Fractions: 195—200°, 10 g. (m. p. 15°); 200—205°, 17 g. (m. p. 34°). These fractions contain only a small amount of aniline and consist mainly of *p*-toluidine. A small amount of a high-boiling viscous oil is also obtained. (iii) 4-Aminobenzyl alcohol (0·953 g. or 0·743 g.) is slowly heated with 5% sulphuric acid. Water containing formaldehyde (0·045 g. or 0·036 g.) is collected.

Anhydro-4-*aminobenzyl Alcohol.*—*Preparation.* Aniline hydrochloride (130 g., 1 mol.) is dissolved in water (600 g.) and a 37·5% aqueous formaldehyde solution (120 c.c., 1·5 mols.) added, the mixture being stirred and cooled. After 30 mins., water (720 c.c.) is added to the dark red, gelatinous product, and the mixture made alkaline with sodium carbonate. The colourless precipitate is filtered off and washed until free from alkali.

Dry distillation. (i) Anhydro-4-aminobenzyl alcohol (500 g.) yields 140 g. of a mixture of oil and solid. Fractions: 193—195°, 22 g. (m. p. 17°); 195—200°, 50 g. (m. p. 19°); 200—205°, 24 g. (m. p. 19°); 205—210°, 11 g. (m. p. 17°); 250—400°, 24 g. (thick oil). The lower-boiling fractions consist of aniline and *p*-toluidine, and contain small amounts of *N*-methyl-*p*-toluidine, identified by its nitroso-derivative. During the distillation, volatile amines, especially ammonia, are also formed. (ii) Anhydro-4-aminobenzyl alcohol (500 g.) is mixed with anhydrous sodium carbonate (500 g.) and dry distilled. Yield, 250 g. of a semi-solid mixture. Fractions: < 195°, 20 g. (m. p. 19°); 195—200°, 167 g. (m. p. 35°); 200—205°, 15 g. (m. p. 29°); 205—210°, 8 g. (m. p. 20°); 210—270°, 15 g. (thick oil); residue, 14 g. The fractions, b. p. 195—205°, consist almost entirely of *p*-toluidine; the first fraction contains also an appreciable amount of aniline, and those above 205° some *N*-methyl-*p*-toluidine. (iii) The alcohol (500 g.) is mixed with calcium hydroxide (500 g.) and dry distilled. Yield, 283 g. of a semi-solid mixture. Fractions: 198—200°, 138 g. (m. p. 25°); 200—205°, 52 g. (m. p. 37°); 205—220°, 20 g. (m. p. 28°); high-boiling residue, 60 g. (thick oil). The first fraction contains in addition to *p*-toluidine a small amount of aniline, the third some *N*-methyl-*p*-toluidine. (iv) Dry distillation in presence of zinc, copper, iron, kieselguhr, sand, fuller's earth and similar neutral substances, or in presence of acids, does not give better yields of *p*-toluidine than method (i). (v) Anhydro-4-aminobenzyl alcohol (100 g.) is heated with concentrated hydrochloric acid (100 c.c.) and water (500 c.c.) at 70° for 3 hours. The mixture is then neutralised, and the precipitate filtered off, washed, and dried. A portion of this substance (84 g.) is mixed with sodium carbonate (83 g.) and dry distilled. Yield, 31 g. Fractions: < 180°, 3 g. (oil); 180—200°, 5 g. (m. p. 16°); 200—204°, 6 g. (m. p. 12°); high-boiling fraction, 16 g. (vi) Quantities as in (v) are heated at 100° for 1 hour, and the product treated as in (v). A portion (85 g.) and sodium carbonate (85 g.) are dry distilled. Yield, 38 g. Fractions: < 180°, 3 g. (oil); 180—195°, 6 g. (m. p. 10°); 195—202°, 10 g. (m. p. 13°); high-boiling fraction, 18 g. (vii) Aniline hydrochloride (130 g.), water (600 c.c.), and 37·5% aqueous formaldehyde solution (80 c.c.) are heated at 70° for 30 mins.; the mixture is made alkaline, and the precipitate filtered off, washed, and dried. A portion (138 g.) and calcium hydroxide (138 g.) are distilled. Yield, 43 g. Fractions: < 190°, 8 g. (oil); 190—198°, 9 g. (m. p. 16°); 198—204°, 12 g. (m. p. 26°); high-boiling fraction, 9 g.

Dry Distillation of 4-*Aminobenzylaniline.*—4-Aminobenzylaniline (50 g.; Paal and Sprenger, *Ber.*, 1897, **30**, 70) is mixed with calcium hydroxide (50 g.) and dry distilled. Yield 38 g. (oil). Fractions: < 192°, 18·5 g. (m. p. 4°); 192—205°, 9 g. (m. p. 8°); *i.e.*., a mixture of aniline and *p*-toluidine.

Decomposition of 4 : 4′-*Diaminodiphenylmethane.*—This substance (25 g.) is heated under pressure at 400° for 18 hours. The product is steam-distilled, and the distillate extracted with ether and redistilled Yield, 4 g. of a mixture consisting of aniline and *p*-toluidine.

Anhydro-4-*amino*-3-*methylbenzyl Alcohol.*—*Preparation.* *o*-Toluidine hydrochloride (143·5 g., 1 mol.) is dissolved in water (1 l.) and 37·5% aqueous formaldehyde (120 c.c., 1·5 mol.) added, the mixture being stirred and cooled. After 30 mins., the mixture is made alkaline with sodium hydroxide, and the white precipitate filtered off, washed, and dried.

Dry distillation. (i) Anhydro-4-amino-3-methylbenzyl alcohol (440 g.) afforded 155 g. of an oil. Fractions: 200—205°, 20 g.; 205—210°, 76 g.; 210—220°, 38 g.; 220—245°, 6 g. The first three fractions are a mixture of *o*-toluidine (b. p. 197°) and *m*-4-xylidine (b. p. 212°; benzoyl derivative, m. p. and mixed m. p. 192°). (ii) The alcohol obtained from *o*-toluidine (436 g.) is mixed with calcium hydroxide (500 g.) and dry distilled. Yield, 270 g. (oil). Fractions: < 211°, 34 g.; 211—214°, 134 g.; high-boiling fraction, 87 g. The fractions below 215° consist of *m*-4-xylidine and a very small amount of *o*-toluidine; from the high-boiling fraction, 4 : 4′-diamino-3 : 3′-dimethyldiphenylmethane (72 g.) is isolated; m. p. and mixed m. p. 153°.

Anhydro-4-*amino*-2-*methylbenzyl Alcohol.*—*m*-Toluidine hydrochloride (430·5 g., 3 mols.) is dissolved in water (3 l.), and 37·5% aqueous formaldehyde solution (360 c.c., 4·5 mols.) added. After being stirred at 12° for 30 mins., the mixture is made alkaline. The precipitate is filtered off, washed, dried, thoroughly mixed with calcium hydroxide (450 g.), and dry distilled. Yield, 180 g. (oil). Fractions: < 220°, 13 g.; 220—229°, 110 g.; high-boiling product, 44 g. The fractions below 229° consist almost entirely of *o*-4-xylidine (m. p. 48°, after one recrystallisation from light petroleum; pure *o*-4-xylidine, b. p. 224°; m. p. 48°).

Dry Distillation of Anhydro-4-*amino*-2 : 5-*dimethylbenzyl Alcohol.*—(i) The alcohol, prepared from *p*-xylidine (1 mol.), hydrochloric acid (1 mol.), and 37·5% aqueous formaldehyde solution (1·1—1·5 mols.), affords 73 g. of distillate. Fractions: 212—225°, 35 g.; 225—250°, 19 g.; 250—270°, 11 g. The first two fractions contain about equal amounts of *p*-xylidine (b. p. 215°) and ψ-cumidine (b. p. 234°; m. p. 68°). (ii) The alcohol (obtained from *p*-xylidine, 385 g.) is thoroughly mixed with calcium hydroxide (400 g.) and dry distilled. Yield, 203 g. of a semi-solid mixture. Fractions: < 230°, 12 g.; 230—240°, 76 g.; 240—250°, 15 g.; high-boiling fraction, 61 g. The first fraction contains *p*-xylidine and mainly ψ-cumidine, the second and third almost pure ψ-cumidine [m. p. 66°, after one recrystallisation from light petroleum (b. p. 60—80°)], and the last consists mostly of 4 : 4′-diamino-2 : 5 : 2′ : 5′-tetramethyldiphenylmethane (after one crystallisation from light petroleum, m. p. and mixed m. p. with an authentic specimen, 139°).

Dry Distillation of Anhydro-4-*amino*-2 : 3-*dimethylbenzyl Alcohol.*—This substance is obtained as usual from *o*-3-xylidine hydrochloride (315 g.) and 37·5% aqueous formaldehyde solution (250 c.c.) as a white powder. It is mixed with calcium hydroxide (350 g.) and dry distilled. Yield, 127 g. (oil). Fractions: < 230°, 12 g.; 230—240°, 45 g.; 240—250°, 36 g.; high-boiling fraction, 18 g. The lower-boiling fractions contain a little *o*-3-xylidine (b. p. 222°), but mostly 4-*amino*-1 : 2 : 3-*trimethylbenzene* (b. p. 238—240°; m. p. 24°) (Found: N, 10·6. $C_9H_{13}N$ requires N, 10·4%); *acetyl* derivative, m. p. 140° (Found: N, 8·2. $C_{11}H_{15}ON$ requires N, 7·9%).

Dry Distillation of Anhydro-4-*amino*-3-*methoxybenzyl Alcohol.*—A sample obtained from *o*-anisidine (123 g.) is mixed with calcium hydroxide (150 g.) and dry distilled. Fractions: < 225°, 5 g.; 225—235°, 17 g., mostly 3-methoxy-*p*-toluidine (b. p. 238°), identified by its acetyl derivative (m. p. 129°).

Anhydro-4-*amino*-1-*hydroxymethylnaphthalene.*—α-Naphthylamine (1400 g.), concentrated hydrochloric acid (1126 g.), water (12 l.), and 37·5% aqueous formaldehyde solution (1176 c.c.) are stirred together for 20 hours below 20°. The mixture is made alkaline, and the anhydro-4-amino-compound, a reddish powder, is filtered off, washed, dried, mixed with calcium hydroxide (1600 g.), and dry distilled. Yield, 735 g. (oil). Fractions : $<$ 300°, 34 g.; 300—305°, 116 g.; 305—310°, 199 g.; 310—315°, 106 g.; 315—320°, 14 g.; 320—340°, 45 g. These fractions consist mainly of α-naphthylamine (b. p. 300°) and 4-methyl-1-naphthylamine (b. p. 309—310°). They are separable by means of their picrates. The oil is dissolved in a minimum amount of boiling alcohol, and a slight excess of picric acid in boiling alcohol added. On cooling, the less soluble 4-methyl-1-naphthylamine picrate separates; it is recrystallised from alcohol to constant m. p., 205° (decomp.). The picrate is decomposed by hot sodium carbonate solution, and pure 4-methyl-1-naphthylamine is obtained (m. p. 49°).

Dry Distillation of Anhydro-4-methylaminobenzyl Alcohol.—This substance (45 g.) and calcium hydroxide (45 g.) on distillation afford 27 g. of oil. Fractions: 208—211°, 15 g.; 211—220°, 3 g. The fractions contain some *p*-toluidine (b. p. 200°) but mainly *N*-methyl-*p*-toluidine (b. p. 212°), identified by its nitroso-derivative (m. p. 49°).

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