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CARCINOGENIC AND
CHRONIC TOXIC HAZARDS
OF AROMATIC AMINES

BY

T. S. SCOTT



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Preface

It is more than a hundred years since aromatic amines were first discovered and introduced into industry. For the first 75 years ignorance, disbelief or disregard of the consequences of their expanding use and distribution restricted understanding of the hazards and delayed progress in their control in all but a few countries. During the last twenty-five years knowledge of their long-term effects has grown and has been disseminated. Action in most countries was undoubtedly delayed by the Second World War and it is only in the last decade that there has been reliable statistical evidence and experimental proof to confirm the opinion of those who had tried to make their warnings heard and believed. The blame for half a century of inaction does not lie entirely with the industrialist. The leaders of the world's chemical industry are essentially scientists and cannot be expected, in the absence of adequate scientific proof, to accept unreservedly opinions based on probabilities and hypotheses or on the enthusiasms of doctors.

The probabilities and hypotheses have now been converted into fact by the evidence which has been adduced by statisticians, experimental pathologists and industrial physicians. The days of waiting for evidence on which to act are past. In most countries the trend of industrial and commercial practice is pointed in the right direction and action has been taken to eliminate unsafe working practice. That some nations still lag behind is to be deplored. Their failure to observe the necessary

standard of working practice can no longer be ascribed to ignorance; one can only conclude that it is deliberate and all reasonable people must condemn it. Free exchange, between the nations of the world, of all data concerning the safeguarding of the health of workers in dangerous materials, is imperative. There can be no justification for withholding vital information of this nature or of failing to apply it.

A great fund of technical and medical knowledge exists, the application of which can almost certainly protect workers against the known hazards of today. In this monograph an account is given of the available knowledge concerning those aromatic amines in use in industry which have potential chronic toxic or carcinogenic effects and the measures which may be taken to prevent these hazards are described. Some oversimplification of complex medical, chemical and industrial matters has been made in an attempt to make them comprehensible to a variety of readers, so that the chemist may understand the medicine, the doctor the chemistry and the administrator or interested lay reader the principles behind the technicalities which he may not understand in detail.

Many new compounds will be introduced into industry. Other compounds, already manufactured on a scale too small to have been revealed as dangerous substances, may come to be in greater demand and extension of their manufacture may eventually reveal unsuspected toxicity or carcinogenicity. New methods of manufacture and new processes may result in the formation of carcinogens or toxic chemicals as by-products or impurities. As industry expands and as the advances of scientific knowledge make its technology more complex, the lessons of the past must not be forgotten. In the future, research into methods of combating old and new dangers and in preventing new outbreaks of disease must be promoted and pursued as vigorously as the search for new and better products.

Acknowledgements

It is with pleasure that I express my thanks to the Clayton Aniline Company Limited for permission to publish this monograph and my gratitude to the management and members of the Company for their enlightened attitude to the prevention of industrial hazards before and during my long association with them.

I could never have attempted the work described in this book nor could I have completed the preparation of the manuscript without the valuable advice and criticism I have received from many of my chemical, technical and administrative colleagues at Clayton and from many people outside the Company. My debt to them all is great but if I name only one, I know the others will understand why I do so.

Dr. M. H. C. Williams, whose recent death in a road accident is such a tragic loss to industrial medicine and to the cause of cancer prevention, gave me much encouragement in the early stages of preparation. He was my co-author in a work detailing a code of industrial practice for the control of industrial bladder tumours which was published in 1957. A good deal of the material on prevention in Chapters 12, 13 and 14 is adapted from that article, by permission of the editor of the British Journal of Industrial Medicine.

PART I.

SURVEY OF THE GENERAL
PROBLEM OF TOXICITY OF
AROMATIC AMINES

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Introduction

ORIGIN OF AROMATIC AMINES

Although aromatic amines do not occur naturally they constitute a highly important series of compounds which are now used on a large scale in many industries. A little over a century ago they were great rarities even to the research chemist. They are synthetic compounds engineered by the chemist's art from aromatic hydrocarbons, which are ring compounds many of which, like benzene, toluene and xylene, have a distinctive aroma. The aromatic hydrocarbons were originally obtained almost exclusively from coal-tar but in recent years an increasing proportion of the world's supply has been obtained from crude petroleum and it is now estimated that about half of it comes from this source. Venkataraman (1952) lists 215 aromatic compounds in coal-tar in order of their boiling points (from 80.1° to 519° C). The most important of the hydrocarbons are benzene, toluene, naphthalene and anthracene, all of which are starting points in the synthesis of a large number of aromatic amines. Amines are also present in the coal-tar but in insufficient quantities to make their recovery rewarding.

Aromatic amines all contain nitrogen (in the ' NH_2 group'), usually introduced by the action of nitric acid or less commonly by ammonia. The simplest and best known of them is aniline, which has been made in vast quantities throughout the world for the last hundred years. Before that aniline was a rare chem-

ical which had been discovered in 1826 by Unverdorben, who obtained it by distilling the vegetable dye indigo. The name was given to it by Fritzsche in 1841, who derived it from *anil*, the Portuguese word for indigo. In 1842, Zinin devised a synthetic process which yielded workable amounts. This method is, in principle, the same as that which is generally used today, nitration of benzene to give nitrobenzene by the action of nitric acid and subsequent reduction of the resulting nitrobenzene to aniline (Fig. 1). Most other aromatic amines are derived in a

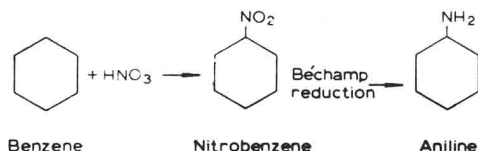


Fig. 1.

similar way; for example, toluidines from toluene. An important alternative method for the manufacture of some compounds is by the action of ammonia on a phenol, naphthol or appropriate halogen compound, for example, beta-naphthylamine from beta-naphthol (Fig. 2).

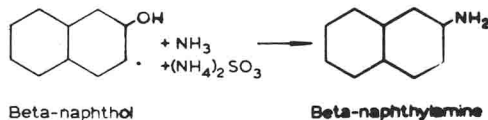


Fig. 2.

Aromatic amines are used in chemical, textile, dyeing, rubber, pigment, paper and some other industries. Their principal use is in the manufacture of synthetic dyestuffs and colouring material, but they are also widely used as chemicals for rubber. Their other uses are generally on a smaller scale than in these industries. They are nearly all colourless themselves; they are the plain bricks which the chemist builds into the architecture of the molecules of a wide range of colours. Because of their origin,

these colours were often referred to as coal-tar colours or as aniline dyes. Neither coal-tar nor aniline is a dyestuff; their main virtue in this respect is as raw materials for the colours. Many people may have associated coal-tar with colour not because of the chemical uses of its constituents, but because of the spectrum of colour produced on wet coal-tar by the refraction of light. In the early days of synthetic colours the expression 'aniline dyes' was used as an assurance of their quality when compared with inferior vegetable dyes and this name has also persisted. It is not difficult, therefore, to understand how the names of these raw materials came to be associated so inseparably in the minds of the public with the finished products.

Coal-tar is a by-product of the manufacture of coal-gas by the distillation of coal. The gas was first made commercially in 1807, when it was used to light the street Pall Mall in London. Its manufacture soon became a large industry. At first there was no use for the coal-tar, of which an embarrassing amount was produced, and it was burned as a fuel to get rid of it. In 1845 Hofmann, the first superintendent of the Royal College of Chemistry, isolated benzene and toluene from coal-tar and proceeded to carry out extensive research on these compounds and on aniline. A serious danger of handling benzene, apart from its toxicity, was manifested in these early days with tragic emphasis when C. B. Mansfield, Hofmann's pupil, was burned to death while distilling benzene from coal-tar for presentation at the Great Exhibition of 1851. Another pupil of Hofmann was W. H. Perkin, who was to become famous when five years later he made, from these coal-tar products, the first synthetic dyestuff, a discovery which was the forerunner of the vast range of colours which came to be manufactured from them.

Chemists in these early days were beginning to explore what Wöhler in 1828 called the trackless jungle of chemistry. Molecular structure was not understood and much of the organic chemistry was empirical, without any plan, order or scientific principle to guide the chemists through the maze of their new discoveries.

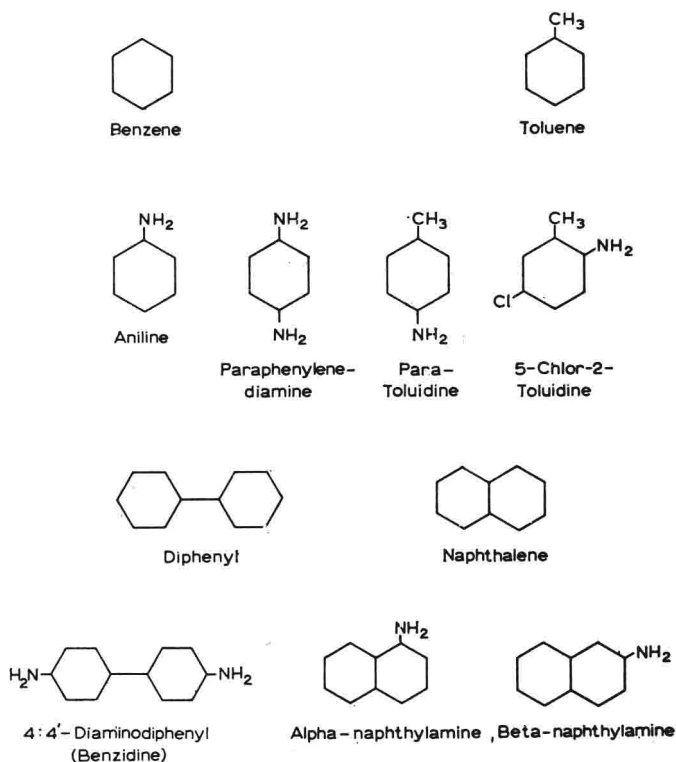
When Michael Faraday discovered benzene in 1825 there was no real science of chemistry and even though Liebig, who was Hofmann's teacher, cast a gleam of light on its structure in 1832, no real pattern was apparent. It was not until 1858 that order began to be possible and that the synthesis of an ever-increasing number of organic chemical compounds became practicable. In that year Kekulé and Couper independently propounded a theory of organic molecular structure, postulating that carbon was quadrivalent and that carbon atoms could link together to form molecular chains. It was another seven years before Kekulé hit upon the idea that a closed ring of six carbon atoms forms the molecule of benzene; it is related that as he dozed by the fire the idea came as an image of a snake swallowing its own tail. As Levinstein (1938) wrote many years later, he realised that six is the carbon number Nature likes best and the benzene ring is the most stable way of arranging six carbon atoms. This important hypothesis was the key to the synthesis of a large number of compounds and a new conception of organic chemistry was born.

STRUCTURE OF AROMATIC AMINES

Primary aromatic amines are compounds composed of one or more benzene rings to which the NH_2 group is attached. This group is introduced by the replacement of one or more of the hydrogen atoms by one or more NH_2 groups. The benzene ring may be substituted as in toluene, where a methyl group replaces a hydrogen atom, conjoined as in diphenyl, or condensed as in naphthalene or anthracene (Fig. 3).

The NH_2 group, in turn, may be substituted by alkyl or aryl groups. When one of its hydrogen atoms is replaced the resultant compound is a secondary amine and in a tertiary amine two hydrogen atoms are replaced. A great number of compounds is thus possible and as the amines may react with other amines or other compounds the permutations and combinations are, in

theory, infinite and in practice enormous. Fig. 4 shows some of the more commonly used and simple of these aromatic amines. It can be appreciated that many variations on the simple theme



Note

Not all the amines shown are manufactured direct from the parent hydrocarbon.

Fig. 3.

are possible; for example, by the substitution in various positions in the ring of further NH_2 groups, by the substitution of a

halogen, carboxyl or other group elsewhere in the ring, or the introduction of an alkyl or aryl group in the NH_2 group itself.

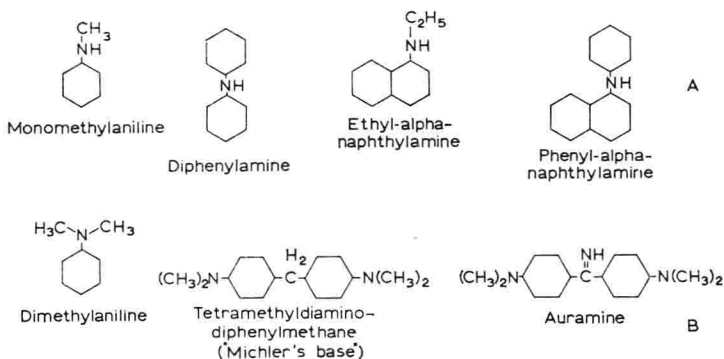


Fig. 4. A. secondary amines. B. tertiary amines.

TOXICITY OF AROMATIC AMINES

It was soon manifest to the early workers that many aromatic amines are acutely toxic and the well-known clinical picture of 'anilism', or methaemoglobinaemia, which can be caused by many amines, became familiar to them as soon as aniline was discovered. It was not difficult for them to associate the cause with the effect or to appreciate that the compounds could be absorbed by inhaling their vapour or by skin contamination. Acute cystitis, often accompanied by severe haematuria (blood in the urine), was another dramatic sequel of massive exposure which was readily related to the causal chemical. Some of these compounds are powerful skin sensitizers and the cause of the acute dermatitis was easily recognisable. All these manifestations usually cleared up quickly and readily on removal from exposure to the offending chemical.

The more serious long-term effects of certain aromatic amines, particularly some double-ring compounds, could not have been

foreseen. These effects are the initiation of neoplastic growth in the urinary tract, usually in the bladder but sometimes in the uréter, the pelvis of the kidney or the urethra. When they did eventually arise they could not be diagnosed in their early stages, they could not easily be related to their chemical cause and they did not clear up spontaneously on removal from exposure – in fact, in many instances the sequelae did not appear until many years after exposure had ceased.

Acute poisoning is characterised by methaemoglobinaemia, which produces cyanosis of a distinctive type manifested by a peculiar bluish-grey colour of the skin and mucous membranes. If the exposure is massive or if it is continued for long periods, a secondary anaemia may result from the consequent haemolysis (breaking down of the blood). If there is concomitant cystitis with bleeding from the bladder, the anaemia is aggravated by the loss of blood. The resulting condition is not a true chronic poisoning but is merely the continued summation of the acute effects and, in fact, can be produced as an acute reaction by a large single exposure or dose.

Apart from neoplastic disease few reports of chronic poisoning have been traced and none has proved authentic. For example, H. M. Chief Inspector of Factories in his report for 1955 (Barnett, 1955) suggested that aniline may have been a factor in some cases of toxic anaemia, a serious form of delayed poisoning often associated with some hydrocarbons*, but benzene was admitted to be the main factor in some of the cases and aniline was not the only toxic agent present in any of them. Oberst, Heckler and Comstock (1956) found no evidence of chronic poisoning by aniline vapour after six months of exposure of experimental animals. The only relevant finding was one which could have been expected, and that was an increase in metabolites in the urine as the amount of amine absorbed increased.

* Gerarde (1960) has described the toxicity of the aromatic hydrocarbons at length.