

THE MANUFACTURE OF SYNTHETIC DRUGS AND FINE CHEMICALS*

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RECENT articles in some of the daily papers might have given the impression that there has been a phenomenal advance in the matter of drugs and fine chemicals, and that scores of these are now being manufactured in the country. Names and quantities are usually not mentioned, and

* A symposium on this subject was opened by the writer at the Baroda Session of the Indian Science Congress on the 5th January 1942. In the October issue of the *Journal of the Society of Dyers and Colourists* (1941, 57, 305), just come to hand, Bruce has presented an elaborate account of "Vital developments from the dyestuff industry" in which he has clearly demonstrated its fundamental importance as a key industry. On account of its striking application to our own problems, an extract will be of interest.

"It surely is apparent now that any nation which, for the maintenance of its population has to keep its position as an industrial power, must, for its continued existence, maintain and control supply and be self-sufficient for every vital manufacture. . . . Industrial development has been so rapid and technical advance so prolific and important that, to-day, a nation might be rendered completely powerless in an international struggle because of the lack of some vital manufacture, apart from weapons, even while her rulers and general body of her industrialists were unaware of the product's existence. . . . Arising from the dye industry as a basis, almost any organic substance can, if necessary, be made in great quantities. . . . It is this wider aspect of the subject which must be appreciated to envisage the developments possible from dyes as a basis, for it is undoubtedly on that foundation that the enormous edifice of the synthetic chemical industry has been built. . . . The most important of these facts is that this country is largely dependent in almost all its present-day industries on synthetic organic products. Their key importance is such that the country's strength in this field must be a measure of its greatness as an industrial country. . . . Again, those countries exploiting the synthetic organic chemical industry with energy gain a lead and an advantage transcending that of geographical position and even of many rich natural resources, if these are not also industrially exploited, because high quality manufacture gives greater return for

one has merely to make enquiries for some of the commonest medicinal chemicals from the trade to realise that no undue optimism would be justified. There has undoubtedly been much progress in the production of tinctures, extracts, galenicals, etc., but little or none in the manufacture of synthetic medicinal and allied chemicals, the variety and scope of which can be gauged from the Directory of the Association of British Chemical Manufacturers, which contains over 4,000 items, including synthetic drugs, disinfectants, anæsthetics, analytical reagents, and photographic chemicals. It is probable that, among the necessarily narrow range of chemicals required for the army, which must take precedence at the present time, many are being made. For essential war requirements, price and other factors normally governing the production of commodities would be minor considerations, but if a real synthetic drug industry is to develop, one has to examine carefully the foundations on which it is built and the chances it has of survival after the war. The few medicinal chemicals we are producing—ether, chloroform, chloral hydrate, ethyl chloride, etc.—are in inadequate quantities and at more or less noncompetitive prices; or in the alternative, as in the case of sulphanilamide, the synthesis has been based on imported chemicals—aniline,

effort, needs skilled labour and altogether means greater prosperity than abundance of raw material and agricultural produce can bring. Another fact that emerges is that the most important organic chemical industries are fundamentally dependent on coal, lime, salt (with water and air), i.e., raw materials within easy reach. . . . The national failing in buying for immediate expedience, in place of making for permanent assurance of supply, is surely a bitter regret to-day. We have always too readily assumed that we could not compete with certain manufacturers without making the attempt. . . . A most important fact is that the manufacture of synthetic organic products has already developed at a much greater rate than any other established industrial activity and appears to have still greater potentialities of further increase than any other class of manufacture."

acetic acid, chlorsulphonic acid, etc.—which may no longer be available. The writer was at one time associated with a factory manufacturing aspirin from imported salicylic acid and acetic anhydride, and when a rise in price of the latter removed the small margin of profit the project had to be abandoned, the manufacture of acetic anhydride being outside the programme and beyond the resources of the firm concerned. The first and most urgent problem, therefore, is the manufacture of the essential inorganic and organic raw materials, intermediates and solvents; since many of the newer pharmaceuticals are based on coal tar products, this would be contingent on the development of a dye industry, for which more or less the same basic chemicals would be required on such a scale that their economic preparation, at prices comparable with those prevailing in Europe and America in normal times, would become inevitable. Bayer, Ciba, and Sandoz have had their success as producers of synthetic drugs on account of their being primarily dye manufacturers. Apart from many dyes themselves, which are used as antiseptics, biological stains, etc., the range of medicinal chemicals derived from coal tar hydrocarbons and dye intermediates is too numerous to be listed and a few common examples must suffice, such as phenol, resorcinol, sodium salicylate, aspirin, benzoic acid, saccharin, sulphanilamide, sulphathiazole, salvarsan and other arsenicals, atebriin and stilboestrol. As an instance of the dependence of drug production on the availability of coal tar intermediates and the relevant inorganic heavy chemicals, one might refer to sulphathiazole, the value of which against plague and as a bactericide of wide utility has been demonstrated in the Haffkine Institute; it is in great demand and the price of the imported substance is prohibitive. In the absence of the basic chemicals which are unavailable in the country, the production of sulphathiazole on a large scale has been impossible.

It is well known that the difficulty in the manufacture of dyes, excepting perhaps the complicated antraquinonoid vat colours in which unusual condensations requiring prolonged and careful study of the experimental conditions are involved, is not in the final stages of the conversion of intermediates into dyes, but in the manufacture of the intermediates themselves. The fundamental

organic raw materials, benzene, toluene, naphthalene and anthracene, and the necessary inorganic chemicals—acids, alkalis, metals and salts of which there are over 80 required—should be produced in adequate quantities, and at prices that would not rule out a given dye or drug right at the start. Two outstanding features of the modern dyestuff industry, which would apply even more forcibly to synthetic drugs, are that raw materials of the utmost purity are employed and the final marketed product should be, if not chemically pure, of a standardised quality in which there is no variation from bulk to bulk. Benzene, for instance, has to conform to a very exacting and rigid specification, but has at the same time to be produced at less than a quarter of the price quoted by the firm which seems to be the only one in India now in a position to produce benzene of the requisite purity. These problems concerning raw materials, as well as those related to the production of the bulk intermediates, such as nitrobenzene, aniline, phenol, resorcinol, β -naphthol, and salicylic acid, can only be solved by the biggest of our tar distilleries and chemical companies with the active and single-minded assistance of Government. The preparation of such intermediates in university laboratories is a very useful exercise for technical chemists or chemical engineers under training, but no more. Many of us have been attempting to utilise whatever facilities we have for the production of a few lbs. of one or other of these. While this has been unavoidable in the present emergency, it has little bearing on the ultimate possibility of their manufacture. These are all chemicals for which the methods of manufacture, the plant and procedures are known. In a country in which the chemical industries are largely undeveloped, Government must take the initiative for ensuring that the establishment and continued progress of such vitally important industries as dyes and drugs are made possible by every assistance for production in the first instance of the essential raw materials and intermediates. The position at the moment is obviously a difficult one, but some attempt must be made to import the necessary plant on the basis of a plan, which would include as many of the inorganic and organic chemicals as possible. The plant is the one obstacle in our way. One cannot go into details in

this note, but it is obvious that, in addition to the very specialised experience that is necessary for their fabrication, particularly of high pressure autoclaves provided with agitators and having to withstand stringent conditions of temperature and corrosion, our engineering firms are handicapped by the lack of the special constructional materials—alloys, stainless steels, facilities for acid-proof and other linings and so on. We cannot afford to wait for these to be made by natural processes of trial, error and evolution; and in the initial stages the plant must be imported, although one realises that in the long run a stable chemical industry must be self-contained for its supply of chemical plant, of which the varied types demanded by modern chemical operations must be fabricated in the country.¹ There is all the difference between the construction of chemical plant and their operation. Many years must elapse before we are in a position to construct the chemical plant required for a full-fledged chemical industry, embracing both heavy chemicals and organic fine chemicals; Great Britain has had to turn to Germany and America for many years, even after the experience of the last War, for certain plant units.² We have, however, chemists and chemical engineers sufficient in number and ability to operate plant of the most complicated character. Our cotton industry has existed on imported machinery; it is our premier industry and it occupies a not inconsiderable place in the cotton industry of the world. With a given range and size of plant, production for a long period becomes possible and, during the interval, there is nothing to prevent a determined and organised effort being made to develop plant fabrication.

The expansion and modernisation of our ordnance factories are helpful. After the war, the plant, processes and technical personnel would all be useful for the fine chemical industry.

¹ Cf. Morgan and Pratt, *Rise and Development of British Chemical Industry*.

² Cf. Bruce, *loc. cit.* "In the chemical industry such plants are available in only one or two of the biggest industrial countries in the whole world, and they cannot be improvised to function in an emergency. Some of them take years to build and almost as long a period elapses before their functions are being discharged with high efficiency."

One aspect of the production of drugs and fine chemicals, which needs attention, is the scale on which production should be undertaken. The manufacture of a chemical in several small factories is usually much less efficient and economical than centralised production. Naturally the question has to be considered in all its bearings, but a much closer scrutiny must be made of what the economic units are in each case. One has only to think of the research that is continually necessary to improve quality and yield, the advantages of setting apart units of equipment for the preparation of a single chemical, and the tremendous spadework that has to be done to inspire confidence in the purity of pharmacologically potent drugs, to be convinced of the need for carefully co-ordinated schemes of production.

A survey of our synthetic drug and fine chemical requirements must be undertaken on the same lines as the survey now in progress regarding dyes. The Chemicals Sub-Committee of the National Planning Committee collected data and prepared reports on these subjects, and it is to be greatly regretted that these reports on many problems of immediate practical importance have perforce gone into cold storage. Whatever organisation might now undertake the work, it is necessary to have accurate data on our requirements of the major synthetic drugs as early as possible. The survey must take into account the points of view of the pharmaceutical chemist, public health authorities dealing with diseases, such as cholera, typhoid, malaria, etc., hospitals, private practitioners, and the men carrying out medical and pharmacological research. A drug may have to find a place in the programme of manufacture because it is used in large quantities or it is a vital requirement as a specific for a certain disease. Having prepared a list of drugs and the quantity in each case for a 10 or 15 year plan, the raw materials and intermediates could be calculated, so that the whole scheme may be linked up with that of the dyestuff industry and provision made for the chemicals (e.g., ethyl chlorocarbonate, the alkylamines, cyanacetic acid, etc.) for which the latter industry, as outlined at present, has no need. Only thus could we visualise the establishment of a synthetic drug industry of some magnitude within a reasonable time.