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ERNEST FOURNEAU

1872—1949

BY
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ERNEST FOURNEAU.

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ERNEST FRANÇOIS AUGUSTE FOURNEAU was born on October 4th, 1872, at Biarritz, which was also the natal city of the brothers Moureu, with whom he maintained a life-long friendship and by whom he was probably considerably influenced in the choice of a career. On leaving school in 1889 he was apprenticed in the pharmacy of Felix Moureu in Biarritz where he remained for nearly three years. Compulsory military service followed in 1892—1893, after which he proceeded to the École de Pharmacie in Paris, where he had among his fellow students Blaise and Valeur. In 1898 he obtained his diploma as a pharmacien, and then spent a year with Charles Moureu "passing in review most of the methods of organic chemistry." He completed his training with three years of research in Germany under Emil Fischer, Curtius, Gattermann, and finally Willstätter. In those days the production of pharmaceutical chemicals in Britain and France was virtually limited to the few alkaloids and glucosides in use in medicine and Germany was almost the sole source of supply of synthetic drugs. Fourneau returned to France determined to do his utmost to bring his country to the front in this branch of the fine chemical industry. He got the necessary opportunity in the research laboratories of Les Établissements Poulenc Frères, of which he was made Director in 1903 and where he remained until 1911 when Dr. Roux offered him a post as principal of a laboratory of therapeutic chemistry at the Pasteur Institute and in this congenial environment Fourneau passed the remainder of his working life.

While in Germany he published three papers: one with Emil Fischer describing the preparation of molecular anhydrides of amino-acids, such as glycylglycine hydrochloride (*Ber.*, 1901, 34, 2868), and another with Willstätter on lupinine, in which the simpler empirical formula, $C_{10}H_{19}ON$, was adopted for the alkaloid and a beginning was made in the determination of its structure, which it was suggested consisted of a bicyclic system (*ibid.*, 1902, 35, 1910) similar to that postulated for cinchonine, then under investigation by Königs and others; the third paper was by Fourneau alone on 9-phenyladenine, prepared by the general method of treating the appropriate trichloropurine with ammonia and reducing with hydriodic acid the resulting 6-amino-2:8-dichloro-9-phenylpurine (*ibid.*, 1901, 34, 112).

In attempting an appreciation of Fourneau's work it must be remembered that he had a remarkable flair for envisaging the kind of molecular structure which would produce a particular pharmacological effect, that for him chemistry was applicable to a wide range of therapeutics, and that he was gifted with a notable capacity for taking pains to bring his ideas to practical fruition.

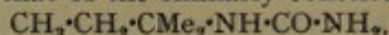
According to his own statement (*J. Pharm. Chim.*, 1910, [vii], 2, 56) his work on amino-alcohols and their derivatives with therapeutic properties arose from the consideration that the two natural local anæsthetics, cocaine and tropacocaine, are *o*-benzoyl derivatives of the methyl ester of an amino-hydroxy-acid (ecgonine) and of an amino-alcohol (*pseudotropine*) respectively. He thought it might be possible to accommodate these functions on a simpler nucleus to produce a substance having at least qualitatively a similar pharmacological effect. He also suggested that a simple nucleus might be devised on which a series of derivatives could be constructed with various therapeutic properties, *e.g.*, hypnotics, sedatives, antipyretics, etc.

The first series of amino-alcohols, represented by the general formula, $HO \cdot CMeR \cdot CH_2 \cdot NMe_2$, prepared by Fourneau (*Compt. rend.*, 1904, 138, 766) included six members in which R was represented by Me, Et, Pr^a , *isoamyl*, Ph, and $Ph \cdot CH_2$. In each case the benzoyl derivative formed a hydrochloride having local anæsthetic action. In the best of the series R was ethyl, and this compound on benzylation and conversion into the hydrochloride became the well-known local anæsthetic stovaine, $Ph \cdot CO \cdot O \cdot CMeEt \cdot CH_2 \cdot NMe_2 \cdot HCl$. Later, with Ribas (*Anal. Fts. Quim.*, 1927, 25, 401) the amino-alcohol (stovaine base) was resolved into (+)- and (-)-forms and these were converted into (+)- and (-)-stovaines of which the former was the more potent local anæsthetic. Stovaine base was also condensed with anhydrous chloral, producing the semi-acetal $Me_2N \cdot CH_2 \cdot CMeEt \cdot O \cdot CH(OH) \cdot CCl_3$, which as the benzoate hydrochloride proved to be a potent local anæsthetic, although its salts were acid and too irritant for practical use (with Mlle. Brydona, *Bull. Soc. chim.*, 1928, [iv], 43, 1023). An intensely active local anæsthetic was also obtained when benzoyl was replaced by *p*-aminobenzoyl in stovaine, as was done in preparing a series of homologues of novocaine $Et_2N \cdot CH_2 \cdot CH_2 \cdot O \cdot CO \cdot C_6H_4 \cdot NH_2$ (with Puyal, *ibid.*, 1922, [iv], 31, 424).

The second idea, that the pharmacological action might be varied by change in substituents,

was also realised to some extent in this series, *e.g.*, the valeryl esters of the amino-alcohols were sedative and some of the esters with aromatic acids were antipyretics (*J. Pharm. Chim.*, 1910, [vii], 2, 57) but these activities were either not well-developed or the derivative was toxic.

A later series (*ibid.*, pp. 337, 397) provided further evidence; it included derivatives of the simple aminomethylethylmethylcarbinol, $\text{HO}\cdot\text{CMeEt}\cdot\text{CH}_2\cdot\text{NH}_2$, corresponding to the stovaine base. This gave with valeryl chloride an amide $\text{HO}\cdot\text{CMeEt}\cdot\text{CH}_2\cdot\text{NH}\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CHMe}_2$, with ethyl chloroformate a urethane $\text{HO}\cdot\text{CMeEt}\cdot\text{CH}_2\cdot\text{NH}\cdot\text{CO}_2\text{Et}$, and with propyl chloroformate the corresponding propyl ester. With potassium cyanate the same alcohol furnished the substituted urea $\text{HO}\cdot\text{CMeEt}\cdot\text{CH}_2\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2$. The urethanes were hypnotic in action when given in large doses, *e.g.*, 0.4 g. per kg. of body weight in rabbits. It was suggested that their lower potency, compared with that of the similarly constituted amylurea



is a result of their greater solubility in water owing to the presence of the alcoholic hydroxyl group.

At first, these amino-alcohols were obtained by treating with ammonia or amines the appropriate chlorohydrins prepared by Tiffeneau's method, the action of alkylmagnesium halides on chloro-ketones (*Compt. rend.*, 1902, 134, 774), but later other methods were added; stovaine base, for example, was also made by the action of ethylmagnesium bromide on dimethyl-aminoacetone or by treating 2-ethyl-2-methylethylene oxide with dimethylamine (*J. Pharm. Chim.*, 1910, [vii], 2, 109).

Ethylene oxides first became available with the preparation of β -methylstyrene oxide in 1905 (Klages, *Ber.*, 1905, 38, 1969; Tiffeneau, *Compt. rend.*, 1905, 140, 1458), and the study of their preparation, constitution, and reactions was continued by Fourneau and Tiffeneau and later by Fourneau and Ribas in a series of papers published from 1905 to 1927. When phenol is heated with epichlorohydrin in a closed tube, at least four products are formed, two of which are interconvertible, *viz.*, the oxide, phenylglycide ether $\text{PhO}\cdot\text{CH}_2\cdot\text{CH}\begin{smallmatrix} \diagup \text{CH}_2 \\ \diagdown \text{O} \end{smallmatrix}$ and the chloro-

hydrin $\text{PhO}\cdot\text{CH}_2\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\text{Cl}$. Similar glycide ethers from *p*-cresol and α -naphthol were described by Lindemann (*Ber.*, 1891, 24, 2145). They all react with amines to form compounds of the type 3-dimethylamino-1-phenoxypropan-2-ol $\text{PhO}\cdot\text{CH}_2\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{NMe}_2$, and Fourneau prepared a series (*J. Pharm. Chim.*, 1910, [vii], 1, 55, 97) in which the phenoxy-group was replaced by *p*-tolylxy, guaiacyl, thymyloxy, etc. All of them had antipyretic and analgesic properties but owing to their cardiac action they proved unsuitable for therapeutic use. This work was later (with Billeter and Bovet, *ibid.*, 1934, [viii], 19, 49) extended to glycidic esters $\text{CRR}'\cdot\text{CH}\cdot\text{CO}_2\text{Et}$, which with ammonia or primary amines in aqueous alcohol gave quantitative

yields of the corresponding amides $\text{CRR}'\cdot\text{CH}\cdot\text{CO}\cdot\text{NR}''\text{R}'''$. These, in experiments on rabbits,

mice, and fish, showed a rapid narcotic action of short duration. The study was continued (with Billeter, *Bull. Soc. chim.*, 1940, [v], 7, 593) as a detailed examination of the more complex action of ammonia, aliphatic amines, or arylamines on phenylglycidic esters.

Fourneau also prepared several series of amino-alcohols to ascertain the effect of changes in structure on pharmacological action, *e.g.*, the group of $\alpha\gamma$ -amino-alcohols, such as 1-dimethyl-aminohexan-3-ol, obtained by the action of dimethylamine on the chlorohydrins resulting from the interaction of chloropropaldehyde and the appropriate alkylmagnesium bromides. The hydrochlorides of the benzoates of these secondary alcohols showed anæsthetic action less durable than that of stovaine (with Mme. Ramart-Lucas, *ibid.*, 1919, [iv], 25, 363; 1920, [iv], 27, 386, 550).

Most of the amino-alcohols so far mentioned contain either a secondary or a tertiary alcohol group, and in 1930 in association with Mlle. Benoit and Firmenich (*ibid.*, 1930, [iv], 47, 858) the investigation of this type of variation was completed with a series containing primary alcohol groups obtained by the action of methyl- or dimethyl-amine on the bromoacetins $\text{R}^1\text{R}^2\text{C}(\text{CH}_2\text{Br})\cdot\text{CH}_2\cdot\text{O}\cdot\text{CO}\cdot\text{CH}_3$ resulting from the action of hydrobromic acid on diprimary glycols in acetic acid. The benzoates of these compounds were local anæsthetics but seemed to present no practical advantage over cocaine or stovaine with which they were compared.

The ephedrines, which Fourneau regarded as amino-alcohols rather than as alkaloids, occupied his attention at intervals from 1904 to 1945. Of the nine papers published on this subject several describe syntheses of ephedrines, and one (with Kanao, *ibid.*, 1924, [iv], 35, 614) is of general interest as it included a useful bibliography of this subject up to that date, described and discussed the reactions used in the various syntheses of the ephedrines, cleared up possible

confusion between ephedrine and the *pseudo*- and *iso*-forms, and indicated which was formed in the various syntheses recorded. Later, with Barrelet (*Anal. Fis. Quím.*, 1929, 27, 500) he synthesised three homologues of ephedrine and in 1945 (with Mlle. Benoit, *Bull. Soc. chim.*, 1945, [v], 12, 985) described the interesting results of a study of the action of methylamine on the mixture of *cis*- and *trans*-forms of β -methylstyrene oxide formed when β -methylstyrene is treated with benzoyl peroxide. *iso*Ephedrine is usually the predominant product; ephedrine and *pseudo*ephedrine are also formed, but little or no *iso*- ψ -ephedrine.

Among other types of local anæsthetics may be mentioned a series derived from piperazine and made by the interaction of piperazine hydrate and ethylene oxides—for example, 1-(2-hydroxy-2-methyl-*n*-butyl)piperazine $\text{HO}\cdot\text{CMeEt}\cdot\text{CH}_2\cdot\text{N}<[\text{CH}_2]_4>\text{NH}$ and the disubstituted bis-compound $\text{HO}\cdot\text{CMeEt}\cdot\text{CH}_2\cdot\text{N}<[\text{CH}_2]_4>\text{N}\cdot\text{CH}_2\cdot\text{CMeEt}\cdot\text{OH}$, both made from ethylmethyl-ethylene oxide (with Barrelet, *ibid.*, 1929, [iv], 45, 1172) and of which a higher homologous series was made (with Samdahl, *ibid.*, 1930, [iv], 47, 1003). These substances from the butyl derivatives upwards were definitely local anæsthetics but some of them proved irritant to the mucous membrane and the cornea. Finally it was found that phenanthrols are converted by 2-diethylaminoethyl chloride into amino-ether oxides (with Matti, *ibid.*, 1940, [v], 7, 615; 1942, [v], 9, 633), of which the 1-, 2-, 3-, 4-, and 9-2'-diethylaminoethoxyphenanthrenes were prepared and also the 9:10-disubstituted product. The mono-series proved to be local anæsthetics but none was analgesic; the disubstituted substance produced intense anæsthesia when applied to the tongue. The more interesting observation was also recorded that while the monosubstituted products were cardiac sedatives and lowered excitability of the myocardium, the single disubstituted product obtained, viz., 9:10-bis(diethylaminoethoxy)phenanthrene dihydrochloride, was very toxic.

Of the two bases, ψ -tropine and ecgonine, which Fourneau had in mind as models when the work on local anæsthetics was started, all products so far described are based on the ψ -tropine or amino-alcohol type. Work on the ecgonine or amino-hydroxy-acid type was much less fruitful. The first acid used was phenyl-lactic acid (*ibid.*, 1907, [iv], 1, 549); "the benzoyl derivatives of ethyl phenyldimethylaminolactate $\text{Me}_2\text{N}\cdot\text{CH}(\text{CO}_2\text{Et})\cdot\text{CHPh}\cdot\text{O}\cdot\text{COPh}$ " was an effective local anæsthetic but too acid for practical use. Attention was then given to hydroxy-*isobutyric* acid: the propyl ester of the derived chloro-derivative was converted into propyl β -dimethylamino- α -hydroxyisobutyrate of which the valerate $\text{Me}_2\text{N}\cdot\text{CH}_2\cdot\text{CMe}(\text{CO}\cdot\text{OC}_3\text{H}_7)\cdot\text{O}\cdot\text{CO}\cdot\text{C}_4\text{H}_9$ as the hydrobromide had some success as a hypnotic under the name "Quietol" although the benzoyl derivative of the ethyl ester, which had intense anæsthetic properties when applied to the tongue, like the previous compound, was too acid for use (*J. Pharm. Chim.*, 1908, [vi], 27, 513; *Bull. Soc. chim.*, 1909, [iv], 5, 229); and the insertion of a second dimethylamino-group failed to overcome this difficulty (*ibid.*, 1921, [iv], 29, 413).

Apart from the hypnotics arising out of the work described above, Fourneau also investigated certain other series providing such drugs, notably the ureides of bromovaleric acids on which three comprehensive papers were published (with Florence, *ibid.*, 1927, [iv], 41, 1518; 1928, [iv], 43, 211, 1027), dealing especially with the interrelations of chemical structure and hypnotic action. It was found in a comparative study using the known α -bromoisovalerylurea, $\text{CHMe}_2\cdot\text{CHBr}\cdot\text{CO}\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2$, and α -bromo- α -ethylbutyrylurea, $\text{CEt}_2\text{Br}\cdot\text{CO}\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2$, as reference standards, that the effect of displacement of the bromine atom in the chain, and accumulation of bromine atoms, confirmed the relation already observed by Overton between the partition coefficient in oil and water and the hypnotic properties, and supported Tiffeneau's statement that the relation holds only within the same series. Migration of the bromine atom from the α - to the β -position reduced the hypnotic action, the partition coefficient, and the solubility in water, but it was concluded later that the α -position of the bromine atom is not specific, active ureides with the bromine in β - and γ -positions being also found. Branching in the chain produced a marked increase in solubility in water and in the partition coefficient, and in this series the partition coefficient and hypnotic action were closely parallel.

Among other series of pharmacologically active compounds prepared and investigated by Fourneau, were derivatives of benzodioxan and aminocoumarans, which simulate the sympatholytic action of yohimbine and ergotamine (with Maderni and Mme. de Lestrangé, *J. Pharm. Chim.*, 1933, [viii], 18, 185), of which the most interesting appeared to be 3-diethylaminomethylbenzodioxan which suppresses and reverses the vasoconstrictive action of adrenaline and induces lowering of body temperature in rabbits (with Bovet, *Compt. rend. Soc. Biol.*, 1933, 113, 388). Attention was also directed to the intense acetylcholine type of activity shown in a series of amino-acetals of polyhydric alcohols, which is at its peak in 2:3-ethylidenedioxypropyltrimethylammonium iodide (I; $\text{R} = \text{H}$, $\text{R}' = \text{Me}$) (with D. Bovet, F. Bovet, and

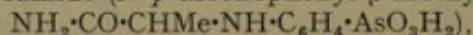
Montézin, *Bull. Soc. Chim. biol.*, 1944, 26, 516). This line of work was then extended to the examination of muscarine-like action in amino-acetals of the general types (I) and (II). All the examples examined showed this type of action, which reached a maximum in type (I) with $R = H$ and $R' = Me$, and in type (II) with $R = H$, but fell off when R or R' was increased and disappeared when $R = R' = Ph$. It was also reduced by the insertion of a hydroxyl group (with Bovet, Montézin, J. P. Fourneau, and Mlle. Chantalou, *Ann. Pharm. Franç.*, 1944, 2, 120; 1945, 3, 114). This was followed by a paper dealing with the complex reactions, simulating those of nicotine, muscarine, and curare, shown by a series of halogenated derivatives of alkyltrimethylammonium salts (with D. Bovet and F. Bovet, *ibid.*, 1946, 4, 166).



The work so far mentioned relates almost wholly to symptomatic drugs, but Fourneau also made notable contributions to chemotherapy proper. In the early years of this century great interest was aroused by Thomas's successful treatment of trypanosomiasis in animals with atoxyl (*Proc. Roy. Soc.*, 1905, B, 76, 589) which was shown by Ehrlich and Bertheim to be sodium hydrogen *p*-aminophenylarsonate, $p\text{-NH}_2 \cdot C_6H_4 \cdot AsO(OH) \cdot ONa$ (*Ber.*, 1907, 40, 3292), and they in common with Fourneau (*J. Pharm. Chim.*, 1907, [vi], 25, 332, 528) agreed that it was first made by Béchamp in 1863. This inaugurated a period of great activity, during which the important drug "Salvarsan" was discovered in Germany, and Ehrlich and Hata published their conclusions on the therapeutic superiority of organic arsenical compounds containing arsenic in the tervalent form over the phenylarsonic acid series in which arsenic is quinquevalent (*Die experimentelle Chemotherapie der Spirilloosen*, Berlin, 1911). Fourneau gave reasons for disagreement with these views and promised further work on the subject (*Ann. Inst. Pasteur*, 1921, 35, 571). The results were published in two remarkable papers (*ibid.*, 1923, 37, 551; 1926, 40, 933) in which he had as colleagues M. Navarro-Martin, M. and Mme. Tréfouel, and Mme. de Lestrangle-Trévisse. The preparation of a large number of arsenical compounds, many of them already known, was described and there was recorded for each the maximum tolerated dose and the effective curative dose in animals infected with trypanosomes or spirochaetes. The effects, on efficiency against each type of infection, of the nature and orientation of each substituent alone or in conjunction were discussed in detail. Among the points stressed by Ehrlich and Hata against quinquevalent arsenic compounds was their liability to cause nervous disorders including ocular trouble, and Fourneau was at pains to point out that as a number of his compounds did not produce these effects in the experimental animals this kind of action could not be attributed to the arsonic acid group. Among the compounds dealt with were the ten isomeric aminohydroxyphenylarsonic acids, which were fully described later, with a comparison of their pharmacological constants (with M. and Mme. Tréfouel and Mlle. Benoit, *Bull. Soc. chim.*, 1927, [iv], 41, 499), and one of these in the form of its *N*-acetyl derivative, viz., 3-acetamido-4-hydroxyphenylarsonic acid, is the well-known drug "Stovarsol" which was adopted in the British Pharmacopœia in 1936 under the name acetarsol. The drug now seems to be used principally for the treatment of amœbiasis and *Trichomonas vaginalis* and for congenital syphilis in young children because it can be administered orally.

It should be noted that 3-amino-4-hydroxyphenylarsonic acid had already been made by Ehrlich and Bertheim (*Ber.*, 1912, 45, 756) during their preparation of "Salvarsan," but its recognition as the basis of a useful drug was undoubtedly the result of the careful work of Fourneau and his colleagues on its preparation and pharmacological action. The series also included "Orsanine," 4-acetamido-2-hydroxyphenylarsonic acid, which was rather more toxic than "Stovarsol" and unlike the latter is an effective trypanocide (cf. Walls, *Chem. and Ind.*, 1951, 607).

Among other arsenic compounds prepared by Fourneau may be mentioned the optically active forms of methyltryparsamide (*N*-*p*-arsonophenyl-β-methylglycine amide,



obtained by the use of quinine, which were used for the resolution of synthetic (±)-ephedrine (with Nicolitch, *Bull. Soc. chim.*, 1928, [iv], 43, 1232).

Special interest also attaches to the series of diarsonic acid derivatives of various aryl nuclei, which exhibited a reversal of the trypanocidal action of the monoarsonic acids, being active against *T. congolense* but inactive towards *T. brucei* (with M. and Mme. Tréfouel, Bovet, and Koetschet, *Compt. rend.*, 1933, 196, 1173) and to the so-called "alcoholic arsonic acids," such as 4-amino-3-hydroxymethylphenylarsonic acid, $NH_2 \cdot C_6H_3(CH_2 \cdot OH) \cdot AsO_3H_2$, which in

pharmacological tests in mice proved 3—4 times as active as atoxyl, indicating that the $\text{CH}_2\cdot\text{OH}$ group had a favourable influence on trypanocidal action (with Mme. de Lestrang, *Bull. Soc. chim.*, 1933, [iv], 53, 330).

Fourneau also published five papers on organic mercury compounds of which two with K. I. Melville (*J. Pharm. exp. Ther.*, 1931, 41, 21, 47) deal with mercurial chemotherapy, the first being a study of the evaluation and mechanism of mercurial toxicity in rabbits and the correlation of the various types of this action with chemical structure in the four groups of compounds tested. In the second paper a method is developed for the quantitative determination of the diuretic activity of mercurial compounds by intravenous injection into rabbits, the results being expressed in the form of a chemotherapeutic coefficient. All the soluble mercury compounds tested were active, but no well-defined relation between degree of activity and chemical structure was found.

Fourneau and his colleagues, M. and Mme. Tréfouel, also made important contributions to the chemotherapy of malaria. They first examined the biological method of estimating the efficacy of an antimalarial drug, involving the use of canaries experimentally infected with avian malaria (*Plasmodium relictum*), and, having developed a standard method (with Stefanopoulo, Mlle. Benoit, Mme. de Lestrang, and K. Melville, *Ann. Inst. Pasteur*, 1930, 44, 503), tried it out on a few known antimalarial drugs including plasmoquin, which had become available in 1926, and then proceeded to apply the test to well over 100 substances of varied types, including complex amino-alcohols, several kinds of quinoline derivatives, and organic compounds of antimony, arsenic, lead, and mercury. The preparation of these compounds was described separately (with Mlle. Benoit, *ibid.*, p. 719; with Wancolle, *Bull. Soc. chim.*, 1930, [iv], 47, 738). This investigation may be regarded as a preliminary screening test and it afforded no positive results of importance. In two further papers (with Bovet and Mlle. Benoit, *Ann. Inst. Pasteur*, 1931, 46, 514; 1933, 50, 731) a series of substituted quinolines of the plasmoquin type were used in biological tests on the Java sparrow or rice finch (*Orizolis orizivora*), which always carries a natural infection of *Hæmoproteus orizivora* similar in type to the malaria parasite. The substances used were mainly 6-alkoxy-8-aminoquinolines derivable from the general formula $\text{RO}\cdot\text{Q}\cdot\text{NH}\cdot[\text{CH}_2]_n\cdot\text{NR}'_2$. $[\text{CH}_2]_n$ was also in many cases changed to a branched chain or a branched oxygenated chain, either of which had a dystherapeutic effect. Among a number of promising compounds final choice was made of 8-3'-diethylaminopropylamino-6-methoxyquinoline which had a chemotherapeutic index of 1:100 compared with 1:40 recorded for plasmoquin (side-chain $\cdot\text{NH}\cdot\text{CHMe}\cdot[\text{CH}_2]_3\cdot\text{NEt}_2$) in the same series of tests. This substance, first distinguished as F710, was subsequently named "Rhodoquine" in France and later "Plasmocide" in Russia.

Two other drugs of German origin also attracted Fourneau's attention. In 1921 biological and clinical reports began to appear about a new and effective trypanocide, Bayer 205, the chemical structure of which was not disclosed. It aroused intense curiosity and was investigated by Fourneau and his colleagues, who assigned to the drug the now well-known formula and described the preparation of F309, which was soon generally accepted as identical with Bayer 205 (with M. and Mme. Tréfouel and Vallée, *Compt. rend.*, 1924, 178, 675). A full account of the drug including a review of the already extensive literature was given as an introduction to a description of their own researches on ureas of aminobenzamidonaphthalenesulphonic acids, for which the results of biological tests with comments on the variation of these with changes in chemical structure were recorded, the most interesting feature being in some cases the large effect on trypanocidal action induced by a small deviation in structure (*Ann. Inst. Pasteur*, 1924, 38, 81). The second drug was "Prontosil," 2:4-diamino-4'-sulphamylazo-benzene hydrochloride, to which attention was first called by Domagk's paper (*Deut. med. Woch.*, 1935, 61, 250) describing its action on mice infected with hæmolytic streptococci. After it had been shown (M. and Mme. Tréfouel, Nitti, and Bovet, *Compt. rend. Soc. Biol.*, 1935, 120, 756) that the antibacterial action of this drug was probably due to its breakdown in the body into sulphanilamide, which they found to be active against streptococci in the mouse and rabbit (cf. Buttle, Gray, and Stephenson, *Lancet*, 1936, 230, 1286), considerable interest was aroused in the investigation of the range of activity of sulphanilamide and its analogues and derivatives, to which Fourneau and his group made two important contributions (*Compt. rend. Soc. Biol.*, 1936, 122, 258, 652). In the first they dealt with the action of 130 compounds, all related to or analogous with sulphanilamide, and showed that changes in the character, or orientation of the two substituents, or addition of a third, usually reduced or even abolished streptococidal action, which however was retained after diazotisation and coupling. The second paper dealt with the inhibition of moulds which was found to run parallel with the action on streptococci.

The same group of workers then began work on other sulphur compounds (*Compt. rend.*, 1937, 204, 1763; 205, 299) and recorded that in the 4 : 4'-dinitrodiphenyl series the sulphide and disulphide were active but inferior to sulphanilamide, whereas the sulphone was more active than the latter against streptococcal infection in mice. It was also active, in higher doses, against pneumococcal septicæmia. About the same time the dinitro- and the diamino-sulphones were under examination in England by Buttle, Stephenson, Smith, Dewing, and Foster (*Lancet*, 1937, 232, 1331). Their results were in general agreement with the French findings for the dinitro-compound, but they were much more concerned with the more toxic diamino-derivative, which proved to be 100 times as active as sulphanilamide against streptococcal infections and was also effective in prolonging the lives of mice infected with pneumococcus. The obstacle to therapeutic use of this new and potent antibacterial agent was its toxicity and this was overcome when the French group investigated the diacetyl derivative, di-(*p*-acetamidophenyl) sulphone, which they found to be 10 times as active as sulphanilamide against either streptococcal or pneumococcal infections in mice; it was also much less toxic than the parent diamino-compound.

As every chemist knows, there have been enormous developments from these early observations and to-day there is almost a special section of therapeutics based on what are colloquially called "sulpha" and "sulphone" drugs.

In addition to the work on ephedrine already referred to, Fournéau was concerned with two other alkaloids, Hesse's quebrachine, which was identified as yohimbine (with Page, *Bull. Sci. Pharmacol.*, 1914, 21, 7), and corynanthine; the latter he isolated from *Pseudocinchona africana*, and showed that it was isomeric with yohimbine (*Compt. rend.*, 1909, 148, 1770; with Fiore, *Bull. Soc. chim.*, 1911, [iv], 9, 1037) and yielded on acid hydrolysis corynanthic acid. On alkaline hydrolysis an acid of lower rotation was produced, which on methylation did not reproduce corynanthine, but according to some authorities a mixture of corynanthine and yohimbine (*Compt. rend.*, 1910, 150, 976; with Mlle. Benoit, *Bull. Soc. chim.*, 1945, [v], 12, 934).

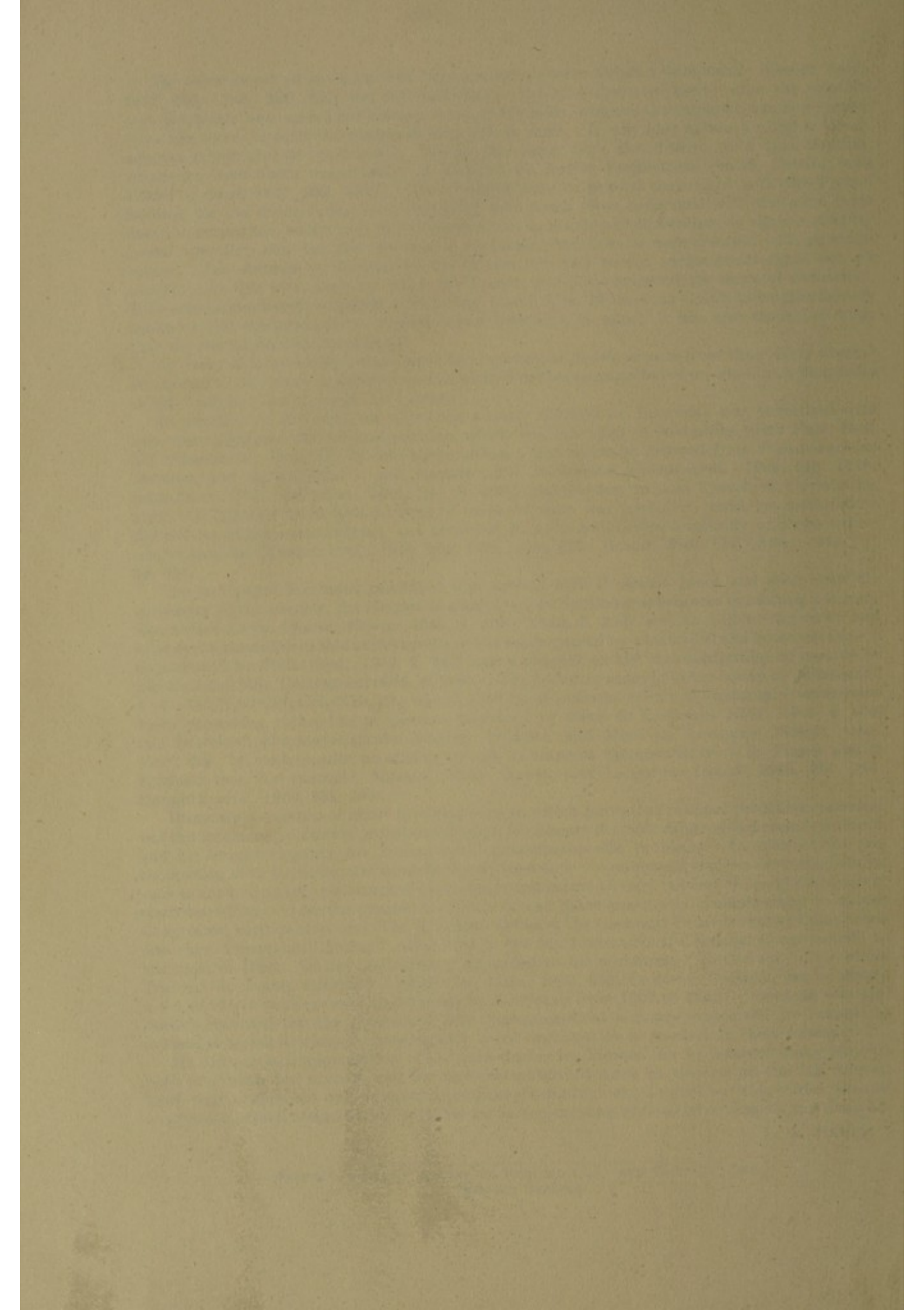
The last paper Fournéau published was written with Professor Janot and dealt with the chemistry of the curares, the *Erythrina* alkaloids, and synthetic substances exhibiting a curare-like action (*Ann. Pharm. Franç.*, 1948, 6, 406; 1949, 7, 353), and to add to the value and exhaustive character of this useful review it was accompanied by a historical and botanical section contributed by Paris (*ibid.*, 1949, 7, 346) and a chapter on the standardisation of curares by Cheymol and Mlle. Corteggiani (*ibid.*, p. 368). It included an account of the action of "Flaxedil," 1 : 2 : 3-C₆H₃(O·CH₂·CH₂·NEt₃)₃I₃, one of a series of phenolic ethers of quaternary ammonium bases possessing curare-like properties, described by Mme. de Lestrangé (*ibid.*, 1948, 6, 450) and examined pharmacologically (Bovet, Depierre, and Mme. de Lestrangé, *Compt. rend.*, 1947, 225, 74) with results promising enough to warrant therapeutic trials in France and in England (see, for example, Mushin, Wien, Mason, and Langston, *Lancet*, 1949, 256, 726; Doughty, *ibid.*, 1950, 258, 899).

There are a number of other investigations to which limitation of space precludes reference, but the foregoing account is probably sufficient to indicate the wide range of Fournéau's interests and his unique capacity for dealing with chemotherapeutic problems. In spite of his pre-occupation with experimental work he found time to write numerous reviews on special drugs, such as the two on organic arsenical compounds and curare already referred to, and he frequently contributed reports on the current prospects of and developments in chemotherapy to special Congresses, such as that on "The Relations between the Chemical Constitution of Compounds and their Therapeutic Action" submitted to the 6th International Chemical Congress held at Bucarest in 1925. In the bibliography appended to his admirable "Notice sur la Vie et les Travaux de Ernest Fournéau" (*Bull. Soc. chim.*, 1950, 953) Professor Delépine has published a list of thirty such reviews contributed by Fournéau from 1902 to 1949. Fournéau was also much concerned for the progress of the pharmaceutical industry, especially in France, as evidenced by his writings on patents and on the organisation of research in chemotherapy.

He did not lack appreciation of his work during his lifetime, for he received many honours both in France and abroad, and the memoirs published since his decease on the 5th August, 1949, bear witness not only to great achievements in his chosen subject but also to the personal inspiration, which attracted and retained for so long a group of devoted colleagues and disciples.

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