

mental, the success achieved had stimulated a vigorous demand among farmers for preparations for field use.

Answering questions, Mr. Heath said that spraying did not wet the fleece, but jetting at 150 lb. pressure did. The main growth of new fleece occurred after the tick season. The effect of D.D.T. on keds was even more spectacular than on ticks. Mr. Bracey wondered what retention of D.D.T. there was in the short hair of the face. If large crystals were deposited from a spray they might easily be rubbed off, so the problem might resolve itself into getting a deposit of the smallest possible crystals. [See also p. 311 of this issue.]

H. SHAW.

¹ *Soap*, 21, No. 4, 139 (1945).

² *The Grower*, 23, 430 (1945).

³ *Nature*, 155, 394 (1945).

ALKYL FLUOROPHOSPHONATES : PREPARATION AND PHYSIOLOGICAL PROPERTIES

By DR. H. McCOMBIE and DR. B. C. SAUNDERS
University Chemical Laboratory, Cambridge

THIS article gives a very brief preliminary account of some of the work initiated and carried out on toxic fluorophosphonates during the War at Cambridge by an extra-mural Ministry of Supply research team working under our direction. For security reasons during the War, this work has not hitherto been published, though secret reports (which were also made available to American workers almost from the inception of the investigations) have from time to time been submitted to the Ministry of Supply. More detailed accounts of these investigations and a fuller bibliography will be published in due course in the appropriate journals.

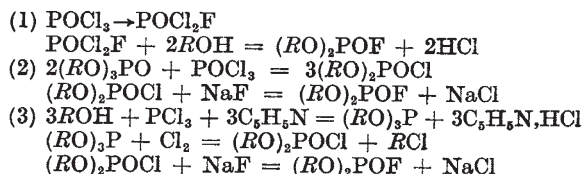
Until this work began in Cambridge in 1941, the alkyl fluorophosphonates had received practically no attention. Lange¹ gave a tedious and laborious method for preparing dimethyl and diethyl fluorophosphonates in very poor yield as follows. Phosphorus pentoxide was fused with ammonium fluoride, a mixture of ammonium monofluorophosphonate and ammonium difluorophosphonate being produced. The monofluorophosphonate was converted into the silver salt which was then heated with the alkyl iodide, the overall yield being less than 4 per cent. Passing reference was made to an effect on the vision, but no record was made of the toxicity of these two compounds. No other fluorophosphonates were recorded. During 1941, we prepared several alkyl fluorophosphonates R_2PO_2F ($R = \text{Me, Et, } n\text{-Pr, iso-Pr, and } n\text{-Bu}$) and one of us made a preliminary report² to the effect that :

(1) These substances have high toxicity as lethal inhalants. Death takes place rapidly (for example, a concentration of 1 : 10,000 of the di-*iso*-propyl ester killed 6/6 rats, 10/10 mice and 2/3 rabbits within 25 minutes from the beginning of exposure of 10 minutes). Such rapid effect and quick knock-out action is shown by few other gases or vapours.

(2) At lower and non-fatal concentrations, a peculiar effect is produced on the eyes, quite distinct from lachrymation. The material causes the pupils to become acutely constricted, and the effect may last for several days. In addition there is interference with visual accommodation. There is no tear forma-

tion and little or no irritation produced in the eyes. Reading is rendered difficult and vision at night is seriously affected.

Synthetic Methods. It then became obvious that practicable methods of synthesizing fluorophosphonates must be devised, and in Report No. 2 on Fluorophosphonates³ we proposed the following methods :

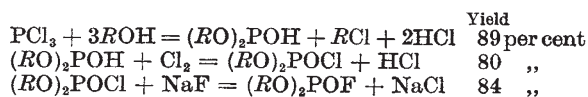


Method 1 and a modification of method 3 were destined to play a very important part in subsequent researches. In our next report⁴ we showed that method 1 could be employed in the case of ethyl alcohol and phosphorus oxydichlorofluoride giving a 93 per cent yield of diethyl fluorophosphonate. (See also British Secret Patent⁵.) In preparing the trialkyl phosphite (method 3), the use of pyridine imposed a severe restriction for large-scale preparation, and it was soon found that the cheaper and more readily available dimethylaniline could be used in its place^{4,6}.

Although substitution of dimethylaniline for pyridine provided an important modification in the preparation of alkyl phosphites, the method was still not sufficiently cheap for large-scale work. It was decided then to try the effect of eliminating the tertiary base altogether. The result of the action of phosphorus trichloride on ethyl alcohol was *diethylhydrogen phosphite* in high yield. It seemed at first that this modification was useless, as the required triethyl phosphite was not produced. We decided nevertheless to try the effect of chlorine on the hydrogen phosphite and found that the essential *chlorophosphonate* was produced in 80 per cent yield^{6,7}.

As subsequent reports will show, it may be said that this discovery altered the whole course of fluorophosphonate chemistry. It now became possible to prepare the fluorophosphonates in excellent yield⁸ and from cheap and readily accessible materials, in particular no tertiary base being required.

The synthesis may then be represented as follows :



Semi-Technical Scale. Further modifications were then made in this 'hydrogen-phosphite' method of preparing diisopropyl fluorophosphonate (the most toxic of the series) in order to put it on a semi-technical scale.

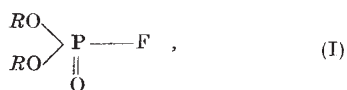
After a large number of experiments, we found that the preparation could be run virtually as a *one-stage process*⁹. Other simplifications were introduced, and the whole process now consists simply in adding phosphorus trichloride to isopropyl alcohol, dissolved in carbon tetrachloride, without external cooling. The crude product (still in carbon tetrachloride) is chlorinated and then heated with sodium fluoride. After filtration, the carbon tetrachloride is distilled off and the pure diisopropyl fluorophosphonate distilled^{10,11}.

This process formed the basis of the method employed both in Great Britain and afterwards in America for the production of this and similar compounds.

Although the action of POCl_2F on an alcohol cannot compete with the 'hydrogen phosphite' method for large-scale work, the former was found extremely valuable for exploratory purposes. In particular, it was found possible to prepare diaryl fluorophosphonates [for example, $(\text{C}_2\text{H}_5\text{O})_2\text{POF}$] and diethyl dithiofluorophosphonate [$(\text{C}_2\text{H}_5\text{S})_2\text{POF}$] by the action of phosphorus oxydichlorofluoride on the appropriate phenol or mercaptan¹².

Toxicity and Miosis

Employing the methods mentioned above, numerous fluorophosphonates and related compounds were prepared in Cambridge. The eye-effect was tested out on ourselves and members of the team. Toxicity tests by inhalation were carried out by Prof. E. D. Adrian¹³ and his team (see below). The constricting effect on the pupil of the eye (miotic effect) and high toxicity by inhalation usually went together. By September 1942 we had established the fact¹³ that



if R is *iso*-propyl or *sec.* butyl (Formula I) the toxicity was of a high order and higher than with a primary group (for example, R = ethyl, *n*-propyl, *n*-amyl, *iso*amyl). The lethal concentration (L.C.₅₀) for mice (10 minutes exposure) for *isopropyl* fluorophosphonate was 0.44 gm./m.³ for deaths within 2 hours. Most of the deaths actually occurred within half an hour.

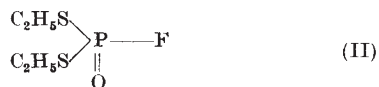
The toxicity of *sec.*-butyl fluorophosphonate was of a similar order.

Diisopropyl fluorophosphonate has very little odour. When human observers were exposed to a concentration of 1 part in a million of the vapour for 5 minutes, severe miosis started a few minutes after leaving the chamber. The pupil constriction and reduction in the powers of visual accommodation persisted for several days. Significant miosis can be produced by exposures sufficiently low as to give no sensory warning and to be undetectable chemically. This has been abundantly proved in this laboratory by workers who have taken great precautions when dealing with the substance (use of fume-cupboards, respirators, etc.) and yet vision has been blurred for several days. This observation has been confirmed by American workers.

Relationship Between Structure and Physiological Action

In Report No. 6¹², we also reported that miotic effect and toxicity became negligible when the fluorine atom in diethyl fluorophosphonate was replaced by the following atoms or groups: —H, —OH, —Cl, —C₂H₅, —OC₂H₅, —SCN, —NH₂, —NHCH₃, —NHC₂H₅, —OCH₂CH₂Cl, —SH.

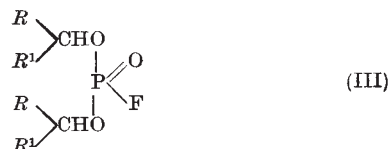
These physiological effects also disappeared when oxygen atoms were replaced by sulphur as in II.



We also showed that ethyl difluorophosphonate $(\text{C}_2\text{H}_5\text{O})_2\text{POF}_2$ has neither miotic nor toxic action.

Early in 1943, we reported the preparation of *dicyclohexyl* fluorophosphonate by the action of

phosphorus oxydichlorofluoride on *cyclohexanol*^{14,15}. This liquid had the high toxicity expected of it, and intense pupil-constricting effect was observed with animals and human beings. *Di-sec.*-hexyl fluorophosphonate¹⁶ also possessed high toxicity and miotic action.



From the examination of a large number of compounds, a striking correlation between physiological action and chemical constitution thus became clear, namely, that a secondary grouping increases potency; and furthermore, our results showed that for non-cyclic compounds, R and R^1 (Formula III) must, for the maximum results, be unsubstituted alkyl radicals. For example, *di-α*-carbethoxy-ethyl fluorophosphonate is scarcely toxic (R = —COOC₂H₅, R^1 = CH₃).

A few of the toxicities¹³ for 10 minutes exposures (deaths within 2 hours) are summarized in the accompanying table. More precise figures and full details of the technique used will be given later.

Ester	L.C./50 in gm./m. ³	Remarks
<i>Diisopropyl</i> fluorophosphonate	0.36 (rats) 0.44 (mice)	More toxic than phosgene. Quick knock-out action comparable with hydrogen cyanide. Strong miotic action
<i>Di-sec.</i> -butyl fluorophosphonate	0.6 (mice)	Strong miotic action
<i>Dicyclohexyl</i> fluorophosphonate	0.11-0.14 (mice, rats and rabbits)	10-day observation: strong miotic action.

Summary

Numerous dialkyl fluorophosphonates have been synthesized by several methods in this laboratory, two of which proved to be particularly useful, namely, (1) the action of phosphorus oxydichlorofluoride on an alcohol, (2) the chlorination of a dialkyl hydrogen phosphite followed by fluorination. Both processes have been patented. The production of the dialkyl fluorophosphonate from phosphorus trichloride utilizing the second method has been reduced to a 'one-stage operation' and has been developed on a semi-technical scale.

The fluorophosphonates are stable liquids and in general are highly toxic by inhalation, having a quick knock-out action and possessing powerful miotic action. A strict correlation between chemical constitution and physiological action has been brought to light, and the fluorophosphonic esters of secondary alcohols are the most potent.

The use of some of the less toxic of these compounds as insecticides has been suggested by us¹⁰. We also claimed that some of these compounds might be useful as fungicides, bactericides and disinfectants, and may have clinical application⁵.

We are indebted to the Chief Scientific Officer of the Ministry of Supply for permission to publish the above. We are grateful to Mr. Davidson Pratt for the interest that he has shown in this work, and to the staffs of the Chemical Defence Research Department, Ministry of Supply, in London, Sutton Oak and

Porton, with whom we have kept in close contact during the years 1939-45.

The following have taken part in these investigations at Cambridge:

H. McCombie ; B. C. Saunders.	
F. J. Buckle.	G. J. Stacey.
N. B. Chapman.	F. E. Smith.
H. G. Cook.	F. Wild (part-time).
R. Heap.	I. G. E. Wilding.
J. D. Hlett.	S. J. Woodcock.
F. L. M. Pattison.	

The physiological action on animals of most of the compounds described above were examined at the Cambridge Extra Mural Testing Station by:

E. D. Adrian.	B. A. Kilby.
K. J. Carpenter.	M. Kilby.

- ¹ Lange, *Ber.*, 65, 1598 (1932).
² Saunders, B. C., Ministry of Supply Meeting (London, Dec. 11, 1941). See also Report No. 1 on Fluorophosphonates to Min. of Supply by McCombie, H., and Saunders, B. C. (Dec. 18, 1941).
³ McCombie, H., and Saunders, B. C., Report No. 2 on Fluorophosphonates to Min. of Supply (Feb. 27, 1942).
⁴ McCombie, H., and Saunders, B. C., Report No. 3 on Fluorophosphonates to Min. of Supply (March 28, 1942).
⁵ British Secret Patent. Min. of Supply. H. McCombie, B. C. Saunders, N. B. Chapman and R. Heap (April 17, 1944).
⁶ McCombie, H., Saunders, B. C., and Stacey, G. J., *J. Chem. Soc.*, 380 (1945). Cook, H. G., McCombie, H., and Saunders, B. C., *ibid.*, 873 (1945).
⁷ McCombie, H., and Saunders, B. C., Report No. 4 on Fluorophosphonates to Min. of Supply (May 20, 1942).
⁸ McCombie, H., and Saunders, B. C., Report No. 7 on Fluorophosphonates to Min. of Supply (Jan. 16, 1943).
⁹ McCombie, H., and Saunders, B. C., Report No. 8 on Fluorophosphonates to Min. of Supply (March 1, 1943).
¹⁰ British Secret Patent. Ministry of Supply, H. McCombie, B. C. Saunders (Sept. 15, 1943).
¹¹ Sutton Oak Report at Ministry of Supply Meeting (London, March 22, 1944).
¹² McCombie, H., and Saunders, B. C., Report No. 6 on Fluorophosphonates to Min. of Supply (Sept. 30, 1942).
¹³ Reports to Min. of Supply from Cambridge University Extra Mural Testing Station, by E. D. Adrian, B. A. Kilby *et al.* (1941 onwards).
¹⁴ McCombie, H., and Saunders, B. C., Report No. 9 on Fluorophosphonates to Min. of Supply (April, 1943).
¹⁵ XL Report to Min. of Supply (Jan. 7, 1943).
¹⁶ McCombie, H., and Saunders, B. C., Report No. 11 on Fluorophosphonates to Min. of Supply (May 27, 1943).

GEOLOGICAL STUDIES IN GREECE

By PROF. G. GEORGALAS

Department of Mineralogy and Petrology, University of Athens

IN geological research Greece has lagged behind the rest of Europe. This is mainly because, since its liberation in 1830, little attention has been paid to the exploitation of its natural resources. The opinion which persisted for nearly a century that the subsoil of Greece did not contain mineral wealth contributed to a great extent to the belief that the geological study of the country was valueless.

The few geological studies of particular regions which had been written up to 1910 came mainly from foreign men of science, and only a very few, principally by C. Mitzopoulos, Socrates Papavasiliou and Th. Skouphos, from Greeks. Many of the trunk roads and railways were projected without any previous geological survey to determine the nature of the rock to be cut, the possibility of landslides, etc. In the Corinth Canal, for example, there are frequent falls of great masses of rock from the sides, which are nearly vertical. The geological composition of

the region was not studied beforehand in order to determine the proper inclination of the banks.

The compilation of a detailed geological map of Greece has not yet been begun. There are only geological maps, drawn to large scale (mainly 1:300,000) of some areas of Greece, made mainly by foreign scientific workers, particularly by the German, Prof. A. Philippson.

Greater interest in geological research in Greece began after 1910, inspired by my predecessor, Prof. C. A. Ktenas. Up to 1935, when he died, Ktenas had surveyed several regions of Greece, investigating the possibilities of exploiting industrial minerals, and also from a purely scientific point of view.

Both Ktenas and his predecessor, Prof. Mitzopoulos, had many years previously stressed the need for setting up a Geological Survey in Greece. Thanks to the persistent efforts of Ktenas and myself, it became possible for me to establish, in 1919, the present Geological Survey of Greece, which I directed until 1936. The Survey has experienced great difficulties. It began its work with a very small number of scientific workers and the sums provided by the State were always very meagre. Nevertheless, to date many serious studies have been made which have contributed to a fuller knowledge of some of the sources of natural wealth of the country. The following notes refer to some of the principal investigations which have been made.

I studied for the first time and announced the existence of deposits of bauxite in Greece. Up to 1922, these deposits were regarded—owing to incorrect chemical analysis—as deposits of iron ore rich in quartz (SiO₂) and therefore unsuitable for exploitation. The announcement was followed by the discovery by others of deposits of bauxite in various regions of Greece. It is at present known that there are deposits of bauxite in Phthiotis-Phokis (massif of Parnassos-Ghiona), the Island of Amorgos, near the town of Eleusis and elsewhere. The reserves of bauxite in Greece are estimated to be of the order of hundreds of millions of tons. In Phthiotis-Phokis alone it is estimated that there are more than fifty million tons of bauxite. The fact that these particular deposits are found near the falls of the River Acheloös, which could generate enormous electric power, promises the possibility of developing an aluminium industry in Greece.

I also studied the lignite deposits in Greece. The existing reserves are estimated to be of the order of several million tons. Research has still to be carried out on how and where Greek lignite could be used.

I have also investigated the outcrops of petroleum which occur in many places in Greece, especially in the region of Jannina (Epirus) and in western Thrace. Prospecting carried out at the expense of the National Bank of Greece in western Thrace did not give satisfactory results. The War unfortunately prevented prospecting in the Jannina region.

The personnel of the Geological Survey recently began to study the beds of kaolin on the Island of Melos in the Cyclades, but this work was also interrupted by the War. The quality of the kaolin is excellent and it only remains to determine the potential amounts available for exploitation.

The Geological Survey, both through myself and its other geologists, has assisted many small towns and villages in Greece on the question of a supply of drinking water. Assistance has also been given to the State services when measures had to be taken to rebuild inhabited areas devastated by earthquake, as