Journal of Medicinal and Pharmaceutical Chemistry

VOL. 1 No. 2 (1959)

Review

The Trifluoromethyl Group in Medicinal Chemistry[1]

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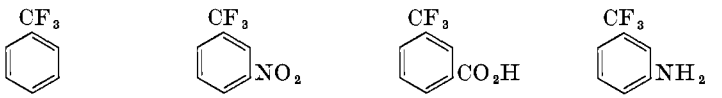
One of the procedures often employed by the medicinal chemist in searching for new drugs is the synthesis of structural modifications of prototype compounds which are known to possess significant activity in the test tube, pharmacological activity in the laboratory animal or practical utility in man. During the past 15 years a substantial effort has been devoted to the incorporation of the trifluoromethyl group into such prototype molecules, in some instances in place of a methyl group, in other instances in place of a chlorine atom. There are a number of reasons for the selection of the trifluoromethyl group for this purpose. First, it could be anticipated that the new compounds and the prototypes would have similar physical properties, and secondly, the new compounds would be acceptable as medicinal agents in view of the known unique chemical and physiological stability of the trifluoromethyl group.[2]

The first report of the pharmacological evaluation of compounds containing the trifluoromethyl group was that of Lehmann[3] in 1928: it is important only from an historical point of view. He found that benzotrifluoride (I), *m*-nitrobenzotrifluoride (II), *m*-trifluoromethylbenzoic acid (III) and *m*-aminobenzotrifluoride (IV) affected the central nervous system of frogs; *m*-nitrobenzotrifluoride and *m*-trifluoromethylbenzoic acid were potent stimulants



I II III IV

while *m*-aminobenzotrifluoride was found to be a depressant with narcotic effects characterized by a quick onset and long duration of activity.

The significance of Lehmann's findings can be minimized because they were perhaps incomplete and inconclusive. Their importance, however, becomes more apparent in view of the recent appearance of a number of new anaesthetic, ataractic, antiemetic and diuretic agents which contain the trifluoromethyl group.

1. Fluorinated Hydrocarbons as Inhalation Anaesthetics

A number of these new compounds containing the trifluoromethyl group were found by way of their being evaluated as inhalation anaesthetics. Krantz and his co-workers[4, 5] examined a group of 18 fluorinated as well as fluorinated and halogenated hydrocarbons and seven fluorinated ethers and from this study two interesting compounds have emerged; these are 2,2,2-trifluoroethyl vinyl ether (V) and bis-(2,2,2-trifluoroethyl) ether (VI). In the dog and in the monkey, 2,2,2-trifluoroethyl vinyl

$CF_3CH_2OCH{=}CH_2$ V

$(CF_3CH_2)_2O$ VI

ether had an induction period longer than that of its non-fluorinated analogue, ethyl vinyl ether, but comparable to ethyl ether. The quantity of 2,2,2-trifluoroethyl vinyl ether used was about equal to the quantity of ethyl ether required to produce a comparable anaesthesia. In the clinical evaluation of this substance as an inhalation anaesthetic, Dornette[6] found in 80 cases that it gave a rapid induction, a labile but usually smooth maintenance and rapid recovery. Muscular relaxation, however, was not complete and delayed recovery from anaesthesia followed attempts to produce relaxation by deepening too greatly the level of anaesthesia. It was also noted that 2,2,2-trifluoroethyl vinyl ether, with a boiling point of 42·7°, was difficult to administer smoothly by the open technique, so that in 68 of the 80 cases use was made of a closed system employing a partial re-breathing technique.

The lower flammability limit for 2,2,2-trifluoroethyl vinyl ether in oxygen was 3 per cent; this was to be compared with 2·1 per

cent for ethyl vinyl ether and 1·9 per cent for ethyl ether. Krantz indicated, however, that 3 per cent is below the concentration required to maintain anaesthesia with 2,2,2-trifluoroethyl vinyl ether.

When Krantz[7a] found that perfluoroethyl ether (VII) was completely devoid of any anaesthetic or pharmacological activity even in concentrations of 75 per cent in the inspired air, he turned to bis-(2,2,2-trifluoroethyl) ether (VI). Surprisingly, this compound elicited violent convulsions upon inhalation; for example,

$(CF_3CF_2)_2O$

VII

in concentrations as low as 30 parts per million, white mice convulsed violently within 30 sec. The convulsions stopped promptly when the agent was removed from the inspired air. Repeated exposures on subsequent days evoked similar convulsions but did not appear to produce injury to the animals as shown by studies of blood chemistry or histological examination of lungs, brain, kidney and bone marrow. The convulsive seizures were readily prevented by sodium pentothal, ethyl ether, or 2,2,2-trifluoroethyl vinyl ether, but not by mephenesin. The electroencephalogram showed marked cortical disrhythmia; the spikings were reminiscent of those observed subsequent to pentylenetetrazol injections or in the myoclonic type of petit mal epilepsy. As a consequence, four human mentally disturbed patients for whom electroshock therapy was indicated were subjected to this agent; volumes of 1 to 3 ml dispersed on cotton in the ordinary nasal decongestant inhaler were used. The patients were not anaesthetized, and the inhaler was placed in one of the nostrils. Convulsive seizures began within 1 to 3 min. and continued from 2 to 4 min. when the inhaler was withdrawn. The seizure episode resembled that of electroshock therapy. The patients became unconscious for periods of from 5 to 17 min. following the convulsions; the recovery was uneventful and two of the patients who had previously been combative assumed a more cooperative attitude. A recent brief clinical paper by Krantz[7b] has indicated that further work with this compound as a substitute for electroshock or pentylenetetrazol therapy in psychotic patients is in progress.

In 1946, Robbins[8] reported on the anaesthetic activity in mice and dogs of 46 fluorinated as well as fluorinated and halogenated hydrocarbons. Of these compounds 14 contained the trifluoromethyl group, and all of them possessed anaesthetic activity. From the 46 compounds, Robbins selected four outstanding compounds (VIII–XI) and these are shown below. It is interesting that three of the four compounds so selected contained the

$CF_3CHBrCH_3$ VIII

$CF_3CHClCH_2Cl$ X

CF_3CHBr_2 IX

$CHF_2CHClCH_3$ XI

CF_3CHCl_2 XII

trifluoromethyl group. While he also tested 2,2-dichloro-1,1,1-trifluoroethane (XII), he did not select this compound as one of the outstanding candidates. Robbins stated that he felt that further clinical investigations of the above four compounds as possible anaesthetic agents was indicated; however, no reports of clinical trials with these compounds are to be found. Furthermore, as mentioned previously, Krantz[5] had reported in 1953 that he had evaluated some 18 fluorinated as well as fluorinated and halogenated hydrocarbons as inhalation anaesthetics and had concluded that while several of them elicited anaesthetic action, their toxicity, especially to the myocardium, obviated their clinical use.

Independently, however, beginning in 1951, Suckling and his co-workers[9] in England synthesized a series of Arctons (Freons) and from these compounds, Raventós,[10] on the basis of his pharmacological results, selected 2-bromo-2-chloro-1,1,1-trifluoroethane (XIII) (halothane) for clinical trial. One cannot

$CF_3CHBrCl$ XIII

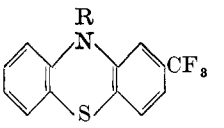
help being impressed by Robbins' foresight. The clinical experience with halothane now includes some 20,000 cases. At concentrations of 0·5 to 3·5 per cent there is obtained a smooth, easy and rapid induction; maintenance of surgical anaesthesia with

adequate muscular relaxation is obtained in a concentration of 0·4 to 1·6 per cent. Recovery is complete and uneventful within 3 to 6 min after anaesthesia. Halothane is non-inflammable and its vapours mixed with oxygen in proportions of 0·5 to 50 per cent are not explosive. As with all medicinal products this agent has some failings; for example, it produces little analgesia before loss of consciousness, it depresses respiration, and, finally, while its potency permits an exact control of anaesthesia it does not permit a wide margin of error and it can be used safely only in the control of a trained anaesthetist using equipment allowing minute accuracy. For example, continuous supervision is required to prevent overdosage since this can lead to a profound hypotension with cardiac arrest. In view of its boiling point of 50·2°, the non-rebreathing technique in a closed system is the preferred method of administration with halothane. There have been two reports[11] of deaths following halothane anaesthesia; in one, the cause of death was cardiac arrest; in the second, yellow atrophy of the liver and acute pancreatitis, findings consistent with what would have been expected with a delayed, chloroform type of poisoning.

Several recent papers[12, 13] have reported on 1088 human cases using an azeotrope of halothane and ethyl ether (68·3 per cent halothane and 31·7 per cent ethyl ether) and of a 1 : 1 molar mixture of halothane and ethyl ether in an effort to circumvent the undesirable aspects of halothane anaesthesia. The lower limit of explosiveness of the azeotrope with oxygen is 10·7 per cent.

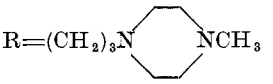
2. 2-Trifluoromethylphenothiazine Derivatives as Ataractic and Antiemetic Agents

To this point, the discussion has been concerned with comparatively simple organic compounds with a narrow range of pharmacodynamic activity. The 2-trifluoromethylphenothiazines carrying a 3-dimethylaminopropyl (XIV) or a 3-(4-methyl-1-piperazinyl) propyl (XV) side chain in the 10-position represent, structurally, a more complex series of organic compounds. Taken collectively these compounds, *in vitro*, have shown antihistaminic, anticholinergic and smooth muscle relaxant properties; in



$R=(CH_2)_3N(CH_3)_2$

XIV



XV

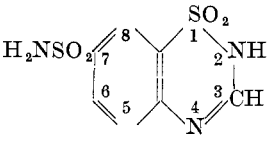
laboratory animals they have shown central nervous system depressant activity, now commonly referred to as tranquillization or ataraxia, reduction in body temperature, hypnosis, lessening of locomotor activity, antiemetic, anti-strychnine and anti-nicotine activities as well as a variety of effects on both the sympathetic and parasympathetic nervous systems.[14]

By far the largest body of clinical data available is concerned with trifluprομazine (XIV).[15] In the psychotic patient, trifluprομazine has been found effective in modifying aggressive and hostile behaviour, in alleviating delusions and hallucinations as well as in controlling the restlessness, anxiety, insomnia and other emotional disturbances which are commonly associated with alcohol withdrawal in the alcoholic patient; it has sometimes been dramatic in improving selected dermatoses of psychogenic or emotional origin; and, it holds promise as an adjunct to local anaesthetics.

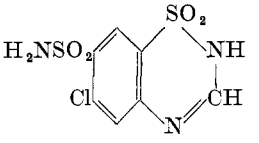
A recent monograph[16] on trifluoperazine (XV) has described it as possessing value for psychotic patients who have not been aided by other therapies. The several contributors to the monograph emphasize that this drug, because of its potency, must be used both with skill and with judgment. An interesting observation evolving from these early clinical studies is that while trifluoperazine is an effective agent in calming the aggressive patient, it may, paradoxically, also function as a euphoriant, to stimulate the lethargic patient into what appears to be a more cheerful and productive mental state. However, since the type of patient who responds to the drug's stimulating effects describes the experience as 'not an increase in drive but a disturbing sensation of being driven',[17] there is some question as to whether this property of the drug can serve as a therapeutic advantage.

3. 6-Trifluoromethyl-1,4,2-benzothiadiazine 1,1-dioxides as Diuretic Agents

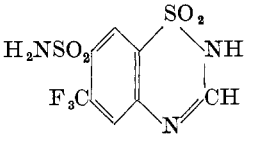
Several other interesting compounds containing the trifluoromethyl group are to be found amongst the substituted 1,2,4-benzothiadiazine 1,1-dioxides. Thus, while 7-sulphamyl-1,2,4-benzothiadiazine 1,1-dioxide (XVI) demonstrated essentially no diuretic activity,[18] the introduction of a chlorine atom (XVII)[19] or a trifluoromethyl group (XVIII)[20, 21] into the 6-position led to



XVI

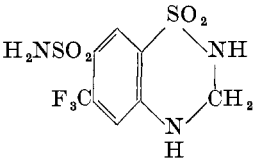


XVII



XVIII

new types of potent diuretic agents. It was also of interest that even greater potency was found with the corresponding 3,4-dihydro derivative (XIX).[22-25]



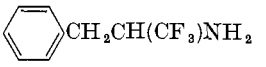
XIX

4. Miscellaneous Compounds Containing the Trifluoromethyl Group

This completes the discussion of compounds containing the trifluoromethyl group where clinical utility has been established for representative compounds. The remainder of the discussion will be concerned with a diverse group of compounds containing the trifluoromethyl group which were subjected to a stylized pharmacological or chemotherapeutic screening; as far as is known, none of these compounds has been evaluated clinically.

In laboratory animals, α-trifluoromethylphenethylamine (XX)[26] afforded a protective action against aerosolized histamine; 1,1,1-trifluoro-2-amino-3-*cyclo*hexylpropane (XXI) while ineffective against the same agent, was moderately effective as an

anti-asthmatic. The latter compound demonstrated no pressor effects. 5-Trifluoromethyl-5-benzylhydantoin (XXII) was found to be ineffective in protecting laboratory animals against electro-shock induced convulsions.



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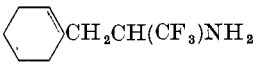
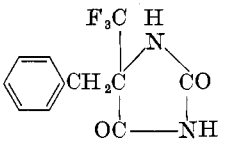
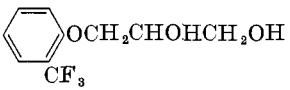


XXI

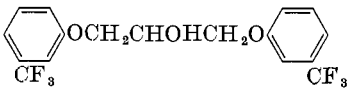


XXII

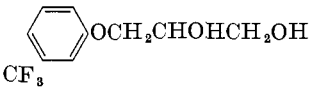
Three glyceryl ethers (XXIII–XXV)[27] were compared with mephenesin (XXVI) for their ability to cause loss of righting



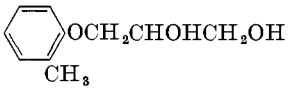
XXIII



XXV

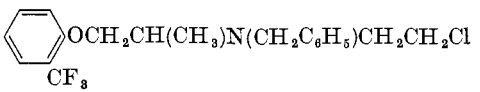


XXIV

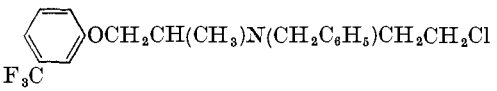


XXVI

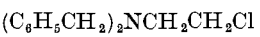
reflex in mice. The first two compounds were somewhat less potent than mephenesin, the third compound was inactive. Two derivatives (XXVII, XXVIII)[28] possessing some structural



XXVII



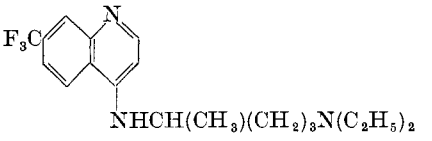
XXVIII



XXIX

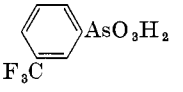
similarity to Dibenamine (XXIX) were evaluated for their adrenergic blocking action; neither was found to be of interest. The

trifluoromethyl analogue of chloroquine (XXX)[29] was evaluated in the laboratory against experimentally induced malaria and

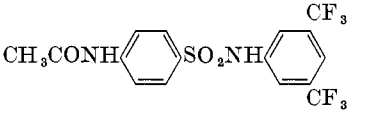


XXX

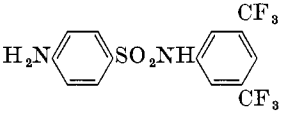
found to possess no apparent advantage over chloroquine, one of the established therapeutic agents in this field; similarly, only one compound, *m*-(trifluoromethyl)benzenearsonic acid (XXXI), out of a large heterogeneous group of compounds containing the trifluoromethyl group, was reported by Gilman and his co-workers[30] to be active in experimentally induced malaria; however, while this arsonic acid was somewhat active, the specific contribution of the trifluoromethyl group to this activity was uncertain. Two sulphanilamide derivatives (XXXII, XXXIII)[32] have been described but no data are available on their chemotherapeutic



XXXI

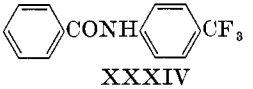


XXXII

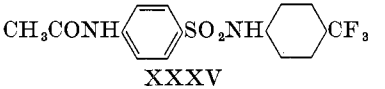


XXXIII

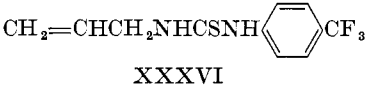
activity. Several acyl and arylsulphonyl derivatives of *p*-aminobenzotrifluoride (for example XXXIV–XXXVI) were inactive in



XXXIV

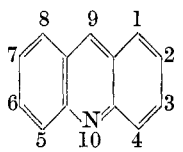


XXXV



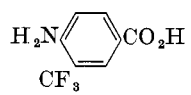
XXXVI

experimental amebiasis and against *Mycobacterium tuberculosis* in the presence of serum.[31] Five acridine derivatives (XXXVII–XLI) containing the trifluoromethyl group were tested against *Staphylococcus aureus, Bacillus coli* and *Pseudomonas pyocyanea*; none was as effective as 9-aminoacridine, which was used as the



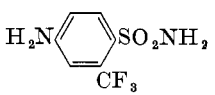
XXXVII	9-$[CH_3CO]_2N$	3-CF_3
XXXVIII	9(10H)-O	3-CF_3
XXXIX	9-H_2N	3-CF_3
XL	9-H_2N	1-CF_3
XLI	9(10H)-O	1-CF_3

standard.[33] Several trifluoromethyl derivatives of *p*-aminobenzoic acid, sulphanilamide and *p,p'*-diaminodiphenyl sulphone (XLII–XLIV)[34] were generally ineffective *in vitro* against a large number of pathogenic and non-pathogenic organisms; *in vivo* they were ineffective in mice against influenza and MM virus, *Streptococcus hemolyticus* and *Elbertella typhosa*. 5,5,5-Trifluoronorvaline (XLV), 6,6,6-trifluoronorleucine (XLVI) and 5-methyl-6,6,6-



XLII

XLIII



XLIV

$CF_3(CH_2)_2CH(NH_2)CO_2H$

XLV

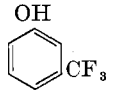
$CF_3(CH_2)_3CH(NH_2)CO_2H$

XLVI

trifluoronorleucine (XLVII)[35] did not inhibit the growth of *Saccharomyces cerevisiae* at concentrations up to 100 μg. The growth of *B. coli* was 50 per cent inhibited by $1 \cdot 7$ μg of 5,5,5-trifluoronorvaline; the other two were ineffective; the inhibition was completely reversed by methionine, leucine and valine and partially reversed by glutamic acid, isoleucine, tryptophan and homocystine. Of a large series of fluorinated compounds tested for their ascaricidal activity, *m*-trifluoromethylphenol (XLVIII) was found to be the most active; the next most active compound was 1,1,1,7,7,7-hexafluoro-4-(trifluoromethyl)-4-heptanol

$CF_3CHCH_3(CH_2)_2CH(NH_2)CO_2H$

XXLVII

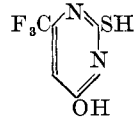


XLVIII

$(CF_3CH_2CH_2)_2C(CF_3)OH$

XLIX

(XLIX).[36] Finally, 6-(trifluoromethyl)-2-thiouracil (L) was found to have less than one one-hundredth the antithyroid activity of 2-thiouracil.[37]



L

In conclusion, it may be said that a relatively large number of compounds containing the trifluoromethyl group has been screened for pharmacological and chemotherapeutic activity; that, of these, a number were found to be sufficiently active to merit a trial in man; and, finally, from these latter studies, have come a few useful pharmaceutical agents in the fields of inhalation anaesthetics, ataractic agents, antiemetic agents, and diuretic agents.

Summary. During the past fifteen years a substantial effort has been devoted to the incorporation of the trifluoromethyl group into prototype molecules which are known to have pharmacological activity in the laboratory animal or practical utility in man. In most instances, the trifluoromethyl group has been used to replace a methyl group or a chlorine atom. From this relatively large number of compounds which were screened for pharmacological and chemotherapeutic activity, a small number were found to be useful as pharmaceutical agents in the fields of inhalation anaesthetics, ataractic agents, antiemetic agents, and diuretic agents.

(*Revised manuscript received 5 January, 1959*)

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