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Fluorine containing Bioactive Heterocycles†

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In recent decades, there has been considerable interest in medical applications and biochemistry of organic compounds containing fluorine. The discovery of 5-fluorouracil in the fifties is a classical example of a heterocyclic compound where the replacement of even one hydrogen by a fluorine atom led to great modification in biological activity of the parent non-fluorinated heterocycle. This presentation gives a background to this exciting new area in organic chemistry and briefly describes some of the recent work in the author's laboratory.

ALTHOUGH fluorine was discovered by Moissan in 1886, the biochemical aspects of compounds containing carbon-fluorine bond received greater attention only since the late 1940s when Rudolph Peters elucidated the mechanism of the toxic action of fluoro acetate and established the concept of 'lethal synthesis'[1]. However, during the decades since the 1950s, a tremendous development has taken place in the clinical applications of fluorinated compounds and many new heterocycles are in actual use in clinical medicine and as agricultural chemicals. This remarkable progress is due to several characteristic features of the fluorocarbon chemistry system[2]. Fluorine does not behave as a 'true halogen' due to its position in the Periodic Table. The nine protons in the nucleus of the element strongly interact with a similar number of electrons since all of them occupy inner shells. Thus, the Van der Waal's radius of fluorine (1.35 Å) is contracted to such an extent that it closely resembles that of a hydrogen atom (1.2 Å). It is the only element which can replace hydrogen without notable steric consequences and is also the most electronegative element. This close resemblance with bioactive hydrogen analogs with respect to steric requirements at enzyme receptor sites may lead to pitfalls such as a 'lethal synthesis'.

TABLE 1

	Covalent radii Å	Bond lengths Å	Van der Waal's radii Å
H	0.37	H_3C—H 1.11	H 1.2
F	0 72	H_3C—F 1.39	F 1.35
Cl	0.98	H_3C—Cl 1.78	Cl 1.8

For similar reasons, there are several interesting features of a carbon-fluorine bond, *viz.* (i) the C—F bond distance is less than C—C bond distance (1.54 Å), (ii) the C—F bond strength increases ; chemically, it leads to the fact that a CF_3 group is unusually stable and will remain unchanged under very rigorous reaction conditions, and (iii) the ionic character of the bond increases with fluorination (C—F, 43 ; C—Cl, 12 ; C—Br, 7 ; C—I, 2%).

The accumulation of fluorine on carbon leads to increased oxidative and thermal stability, and many organofluorine compounds are thus useful due to their being metabolically non-degradable (*viz.* inhalation anesthetics, synthetic blood *etc.*).

TABLE 2—COMPARATIVE BOND ENERGIES

Bond	Energy kcal mol^{-1}
C—H	98
C—F	108 - 116
C—Cl	81
C—Br	68
C—I	57

Yet another important feature of these compounds is that incorporation of fluorine may lead to increased lipid solubility, thereby enhancing rates of absorption and transport of drugs *in vivo*. In fact, the CF_3 group is one of the most lipophilic of all substituents. This explains the introduction of CF_3 (and $SO_2.CF_3$) in many heterocycles used as drugs, dyes, herbicides *etc.*

This change in properties may confer on the molecule unusual physical and biological properties, and this knowledge has been quickly translated into useful applications in the field of medicinal chemistry. The similarity of steric bulk and the dissimilarity of chemical behaviour enable many fluorinated compounds to act as antimetabolites with respect to their corresponding halogen-free compounds. A typical example is that of fluoroacetic acid. Thousands of cattle die every year mainly in South Africa, Australia and other parts of Southern Hemisphere after eating plants like gifblaar (*Dichapotalum cynosum*), box poison (*Oxylo-*

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bium perviflroum) and heart lead poison (*Gastrolobium bilobum*). The toxicity of these plants is due to the presence of fluoroacetic acid whose concentration may exceed 1% of the dry weight of leaves or seeds. When fluoroacetic acid (or a precursor) is ingested, it mimics acetic acid so well that it can intrude into the tricarboxylic acid cycle (Krebs-Martius-Knoop cycle), and replaces the natural metabolite and combines with the oxalylacetic acid to give α-fluorocitric acid. The metabolic cycle is then blocked, the fluorocitric acid can neither be eliminated, nor 'digested' and the biomolecular key-units are paralysed by this 'lethal synthesis'[1].

Once the principle of 'antimetabolite formation by introduction of fluorine' was recognised, it was tempting to apply it to chemotherapy, and during recent decades, some notable successes have been achieved in heterocyclic chemistry. It will suffice here just to give one well known example which shows how even the replacement of one hydrogen by a fluorine atom can greatly modify the biological activity of the parent non-fluorinated compound. This is the monofluorination of uracil to give 5-fluorouracil (5-FU) which was synthesised by Heidelberger *et al.*[3,4] with this idea in mind. 5-Fluorouracil, a potent anticancer drug, and its derivatives have been the subject of many recent publications. It was found to be incorporated in place of uracil into RNA of bacterial and mammalian cells as well as that of some viruses. Subsequently, it was revealed that 5-fluoro-2′-deoxyuridine (5-FUDR) is even more effective and less toxic than 5-FU itself. Both of these substances are anabolised to 5-fluoro-2′-deoxyuridylic acid (5-FUDRP), a potent competitive inhibitor of thymidylate synthetase, the enzyme which normally converts 2′-deoxyuridylic acid to thimidylic acid, an essential component of DNA. This is due to the presence, at the critical C-5 position, of fluorine which blocks the essential addition of formate. Since 5-FU and its anabolites are concentrated in cancer cells, this enzymetic blockade inhibits tumour growth by causing 'thymineless death' of neoplastic cells[5].

New fluorine containing heterocycles :

During the last two decades, the research group of the author has given considerable attention to the synthesis of fluorine containing bioactive molecules. Recently, fluorinated 1,3-diketones have been employed as reaction intermediates for synthesis of different types of bioactive heterocycles. Thus, we have been able to incorporate perfluoroalkyl groups, like CF_3, C_2F_5 into heterocycles by indirect methods. Such compounds include the various pyrazoles[6], isoxazoles[7], pyrazolo[1,5-*a*]pyrimidines[8], 1,2,4-triazolo[4,3-*b*]pyridazines[9], 1*H*-pyrazolo[3,4-*b*]pyridines[10], various 1,4-diazepines[11], 1,5-benzodiazepines[12], pyrazolo[5, 1-*c*]1, 2, 4-triazines[13], *etc.* Some of these compounds have shown promising CNS depressant, antiobesity and anticholinergic activites.

Our more recent interest has been in fluorine containing indoles[14] and particularly spiroindoles[15] and a number of novel heterocyclic systems have been reported. It is not possible to review all the work done but some of our recent work in the field of pyrazole and indole chemistry are briefly narrated here.

Fluorine containing pyrazoles and their derivatives :

The pyrazolopyridine nucleus has aroused great interest in recent years due to a wide variety of biological activities associated with it. Antiinflammatory, antipyretic, analgesic, bactericidal, vasodilating, respiration stimulating, bronchodilating and hypotensive activities of this system have been reported in the literature. The first synthesis of 1*H*-pyrazolo[3,4-*b*]pyridine nucleus was reported by Bulow[16]. However, its fluorine containing derivatives have not received attention. We have employed fluorinated 1,3-diketones, prepared by us earlier, to introduce fluorinated moieties into the system. A number of new 1*H*-pyrazolo[3,4-*b*]pyridines have been reported[10]. An interesting observation was the fact that when instead of 1-(4′-fluorophenyl)-4,4,4-trifluorobutane-1,3-dione, 1-(4′-fluorophenyl)butane-1,3-dione was used, two isomeric products were obtained which could be separated by column chromatography and the second product was identified as pyrazolo[1,5-*a*]-pyrimidine.

The chemistry and biological activities of pyrazolo[3,4-*e*][1,4]thiazepines have received little attention. Only a few references can be found in the literature concerning the antiinflammatory activity of pyrazolothiazepines. We have reinvestigated the reaction of 5-aminopyrazole with aldehydes and characterised the identity of the intermediate leading to pyrazolo[3,4-*e*][1,4]thiazepines about which there was some ambiguity in the literature[17].

In view of the interesting psychopharmacological properties associated with previous compounds, the system has been further investigated[18]. The pyrazolothiazepin-7-ones have been reduced by $LiAlH_4$ to pyrazolo[3,4 *e*][1,4]thiazepines and converted into pyrazolo[3,4-*e*][1,4]thiazepin-7-thiones by phosphorus pentasulphide, and such conversions are being reported for the first time in such systems Very recently[19], we have employed α-ketohydrazonyl halides (1) as versatile reaction intermediates for synthesis of various categories of heterocycles

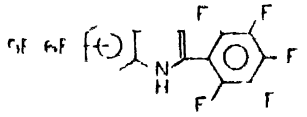
$$\mathrm{Ar.CO.\underset{\displaystyle Br}{\underset{|}{C}} = N.NH.Ar'}$$

(1)

including pyrazolo[5,1-*a*]imidazoles[20] and 3-aroyl-4-acetyl/benzoyl-5-methyl-1-phenylpyrazoles[21].

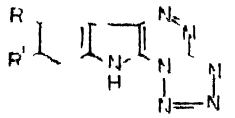
Fluorine containing indoles :

The indole nucleus is well known for its psychopharmacological activity. Oxypertine and diindolylmethane derivatives are potent CNS depressants. Medmain and methylmedmain have shown antiserotonin and hypotensive activities. Introduction of substituents at 5- or 6-position of the indole ring is expected to prevent enzymatic hydroxylation and conjugation It has been observed that incorporation of fluorine atom into the indole ring would tend to increase drug persistence by increasing its solubility in lipid material and fat deposits in the body. Encouraged by these observations, we have undertaken a comprehensive programme for developing new fluorine containing indoles as possible psychopharmacological agents. Amongst the types investigated are 5/6-substituted-2-aryl-indoles and bisindolylmethanes[23,28] as possible antidepressants and antifertility agents, indolyl glyoxamides and tryptamines[24,25], indole-2,3-dione derivatives[26] *etc.* Only two compounds are mentioned here. We have recently reported the synthesis of 2-pentafluorophenyl-5/6-fluoroindoles (2) and their various derivatives which are likely to possess novel biological properties[27].



(2)

Another novel heterocyclic system synthesised by us is 10*H*-tetrazolo[5′,1′ : 3,4][1,2,4]triazino-[5,6-*b*]indole (3) which we could obtain while investigating the reactions of 3-hydrazino-1,2,4-triazino[5,6-*b*]indole[28].



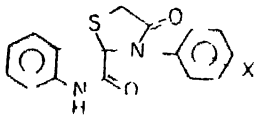
(3)

Various fluorinated derivatives obtained from 3-hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indole have also been prepared[29].

Indoles with C-3 as spiro atom :

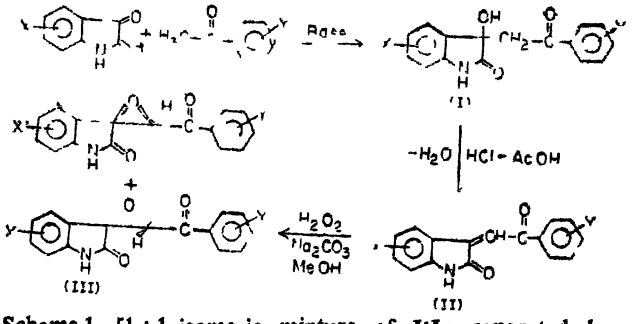
More recently, spiro-indoles have been associated with various biological activities[15]. While exploring the subject, we found the lack of literature on their fluoroanalogs, synthetic and spectral details *etc.* We have, therefore, given a good deal of attention to fluoro-analogs of indoles with C-3 as spiro atom and incidentally synthesised some new heterocyclic systems.

The first system investigated was spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones (4) which was prepared by a modified convenient synthesis[30] without isolating the intermediate isatin-3-anils. There were only two references in the literature for such compounds of which one was a patent and other did not report any yields or spectral data.



(4)

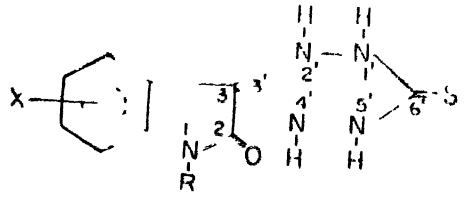
In another study, fluorinated isatins have been subjected to different reactions which include their conversion to 3-aroylmethyleneindol-2-ones and the reactions of the latter with hydrazine yielding spiro-[indole-3,3′-pyrazol]-2-ones[31]. Further, the reaction of 3-aroylmethyleneindol-2-ones with hydrogen peroxide has been reinvestigated as it was felt that theoretically, the product should exist in the form of two isomers differing in the stereochemical arrangement of the hydrogen atom of oxirane ring. No such report was cited in the literature. Also, the mass fragmentation studies of such compounds have not been reported earlier. We have been able to isolate the two geometrical isomers by preparative tlc over silica gel G using benzene-ethyl acetate (1 : 1) under ultraviolet lamp[32]. The two compounds were found to give identical mass spectrum, although in the pmr spectrum, the peak due to C*H* was at a slightly different position in the two cases (Scheme 1).



Scheme 1. [1 : 1 isomeric mixture of III ; separated by preparative tlc over silica gel G using benzene-ethyl acetate (1 . 1)]. Identical ir and mass spectra ; in pmr, peaks due to C*H* slightly different δ 5.1 (IIIa) and 5.2 (IIIb). Epoxidation : Disappearance of II (C*H*) resonance signal at δ 7.15 ; ir 1 050 cm^{-1} (oxirane ring).

We have also investigated the reactions of fluorinated isatins and *N*-acetylisatins with thiocarbohydrazide[33,34]. A literature survey revealed various interesting reactions of thiocarbohydrazide with cyclic ketones, cyclic *ortho*-diketones and isatin. On reinvestigating the reaction, we found that isatin, when treated with thiocarbohydrazide in aqueous ethanolic medium, gave a novel spiro compound 2-oxo-1′,2′,4′,5′-tetrahydrospiro[3*H*-indole-3,3′-1,2,4,5-tetrazine]-6′-thione (5) in 65-70% yield whereas

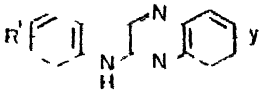
N-acetylisatin on similar treatment, afforded only a thiocarbohydrazone.



(5)

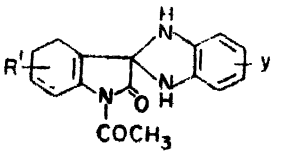
ir 1 700 (C=O) (isatin : 1 730 and 1 680) and –NH peaks 3 400, 3 280, 3 200, 3 100 cm^{-1} (NH), pmr $N^1'H$ and $N^{4'}H$ (2H, δ 11.1), $N^4'H$ (1H, δ 14.15, downfield due to H bonding), N^3H (δ 12.45) and NH of indole (δ 8.3) ; mass (R = H) M^+ *m/e* 235 (65%), and M^+-CO 207 (100%)

Earlier, we also investigated the reactions of isatin and *N*-acetylisatin with fluorinated 1,2-phenylene diamines and 2,3-diaminopyridine[35] in different media. The reactions are solvent dependent and while in glacial acetic acid, indole-2,3-diones afford exclusively indolo[2,3-*b*]quinoxalines (6) ; the same



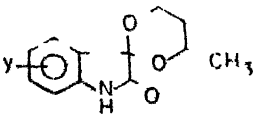
(6)

reactants, with 1-acetylindole-2,3-diones gave a spiro derivative, which was characterized as 1'-acetyl-1,3-dihydrospiro[2*H*-benzimidazole-2,3'-[3*H*]indol]-2' (1'*H*)-ones (7).



(7)

Yet another new spiro system bearing an indolone moiety was obtained during the oxalic acid-catalysed ketalisation of fluorinated indole-2,3-diones with alkanediols[36]. Butan-1,3-diol, under such conditions, yielded 4-methylspiro[1,3-dioxane-2,3'-[3*H*]indole-2'(1'*H*)one (8).



(8)

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