Journal of Fluorine Chemistry, 38 (1988) 153–161

Received: March 24, 1987; accepted: November 19, 1987

SYNTHESIS AND MASS SPECTRAL STUDIES OF FLUORINE CONTAINING 5a, 7b, 12a, 14b-TETRAHYDROBISINDOLO [2,3-b:2',3'-b'] BENZO [1,2-d:4,5-d'] DIFURANS

KRISHNA C. JOSHI, VIJAY N. PATHAK AND RAGINI GUPTA

Department of Chemistry, University of Rajasthan,
Jaipur-302004 (India)

SUMMARY

2:1 Cycloadducts ($-H_2$) are formed when various fluorinated 2-arylindoles are stirred with p-benzoquinone in acidic medium and are identified as dimers of the type 5a, 7b, 12a, 14b-tetrahydrobisindolo [2,3-b:2',3'-b'] benzo [1,2-d:4,5-d'] difurans. All the synthesized compounds have been characterized by their analytical and spectral (IR, PMR, ^{19}F NMR and Mass) data.

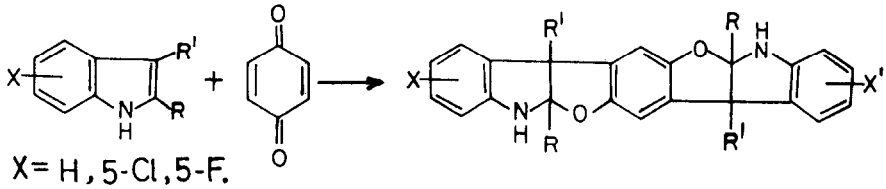
INTRODUCTION

The role of fluorine and perfluoro groups in indole chemistry is noteworthy. Introduction of fluorine at 5-/6-positions of the indole nucleus prevents enzymatic hydroxylation and conjugation [1] . In continuation to our recent work on fluorine containing indole derivatives [2-5] , we now report for the first time , the synthesis of several fluorinated Noland type 2:1 adducts viz: 5a, 7b, 12a, 14b-tetrahydrobisindolo [2,3-b:2',3'-b'] benzo [1,2-d:4,5-d'] difurans. These compounds have been obtained from indoles, having appropriate fluorinated aryl groups at the 2-position.

Abstract: Symposium International "Centenaire de la Decouverte du Fluor", Paris, Aug. 1986, p.65 .

0022-1139/88/$3.50

On treatment with p-benzoquinone in acetic acid medium, 2:1 cycloadducts ($-H_2$) are formed (Scheme 1). The compounds may possess novel physical and biological properties and the mass fragmentation studies of such systems are being reported [6,7].



X= H, 5-Cl, 5-F.

1 2 3

X = H , 2- Cl , 2- F ; X'=H, 9-Cl, 9-F.

R = CH_3 , 4 - FC_6H_4 , 3 - CH_3-4-FC_6H_3 ,
3 - Cl - 4 - FC_6H_3 , 2,5 - $F_2C_6H_3$,
2 , 3 , 4 , 5 , 6 - C_6F_5 .

R'= H , CH_3.

Scheme 1.

RESULTS AND DISCUSSION

Stirring of the appropriate fluorinated indole (1) with p-benzoquinone (2) was done at room temperature in glacial acetic acid medium for about fifty hours. In the IR spectra of compounds (3a-3i), $>$NH absorptions appeared at 3350-3450cm^{-1} and the absence of $>$C=O peaks in the region 1720-1620 cm^{-1} confirmed that ketonic groups were not present. None of the adducts show peaks in the hydroxyl region. Consequently, the two oxygen atoms of the adducts must be present as ether linkages. In the ^1H NMR of compounds (3a,3b) the two methyls originally present in (1a,1b) at δ 2.37 and δ 2.24 ppm now appear as sharp singlets at δ 1.5 (2-CH_3) and δ 1.64 ppm (3-CH_3). In compounds (3c-3i), the disappearance of the signals at δ 6.4 ppm in (1c-1i) and appearance of sharp singlets at δ 3.65 ppm due to -CH protons at the C-3 positions of the indole

nuclei support the formation of dimers. In ^{19}F NMR of compound (3d), a singlet appears at δ -111.08 ppm and in compound (3h), a doublet at δ -138.59 ppm, a triplet at δ -152.55 ppm and another triplet at δ -158.3 ppm due to $-C_6F_5$ at 2-position of indole nucleus showing that both the indole units are chemically equivalent. Additional support was obtained by mass spectra as molecular ion peaks M^+ at 396 (3a), 492 (3c), 528 (3d) and 564 (3g) correspond to their molecular masses (Table I).

Compound (3d) under electron impact provides a molecular ion, M^+, I (m/z 528,64.4%) (Scheme 2) which eliminates a $C_{15}H_{10}FNO$ moiety to generate cation radical II (m/z 289, 15%). Compounds having furan moiety are characterized by elimination of CO and HCO moieties followed by ring expansion to form a stable 2 π-electron aromatic system (cation VIII m/z 236, 100%). This suggests that there is an initial breakage of C-O bond. Cation VIII forms the base peak and ring expansion results in the formation of stable azatropolium cation which is a 6 π-electron system and retains aromaticity.

Further, the fragmentation pathway is supported by the formation of fluorene type of compounds [8] formed by loss of HCN from the 2-phenylindole fragment indicating that the bond at 2-position of the indole ring is considerably stronger due to high degree of conjugation between indole of 2-phenyl ring and is therefore not easily broken. It may be concluded that 2-fluoroaryl group is an additive part of indole nucleus instead of a simple substituent as in case of the adduct of 2,3-dimethyl substituted indole, where there is an initial loss of methyl radical.

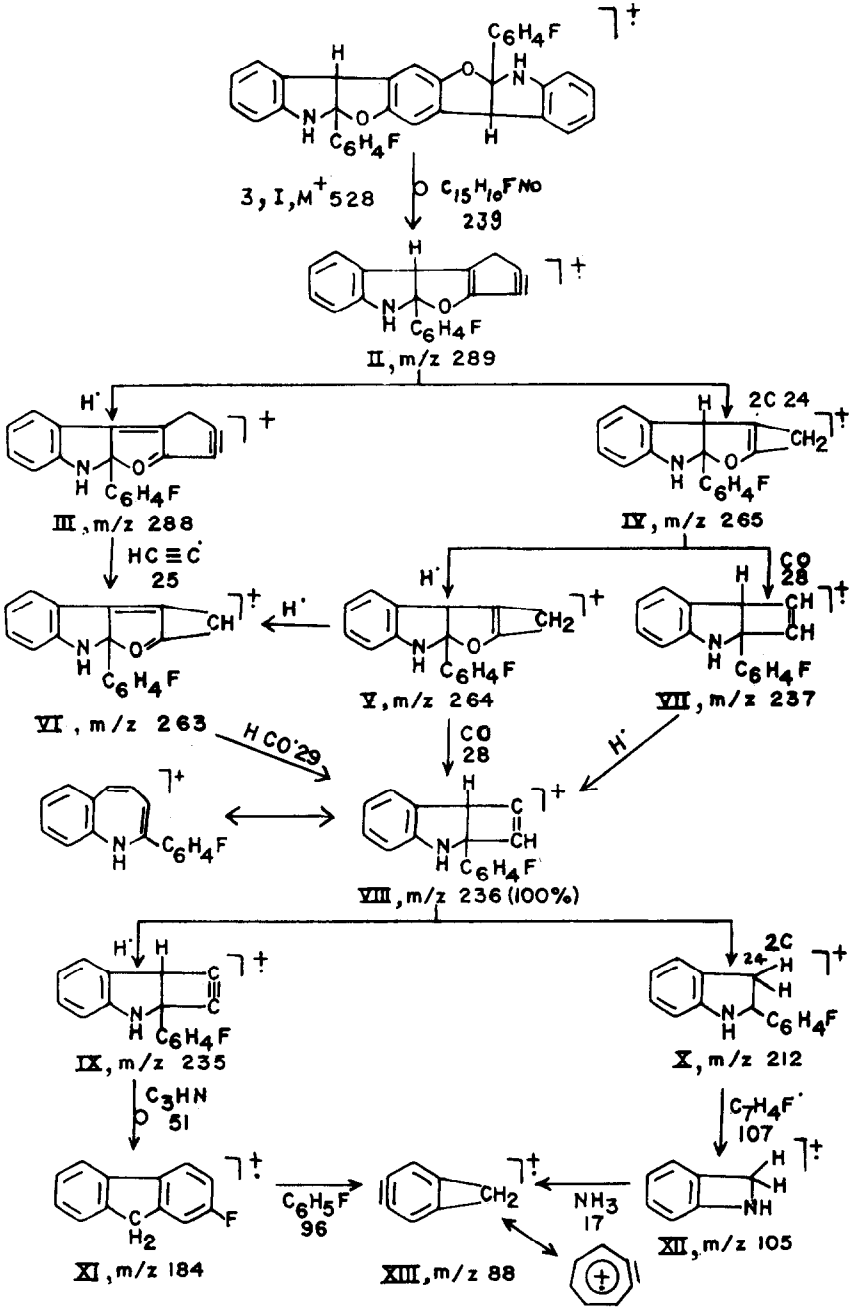
EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on Perkin Elmer (Model 557) in KBr. ^1H and ^{19}F NMR were recorded on Jeol (Model FX-90Q) using $CDCl_3$ as solvent, TMS as internal standard for ^1H NMR at 89.55 MHz and C_6F_6 as external standard for ^{19}F NMR at 84.25 MHz. Mass spectra were recorded on Kratos 30 and 50 mass spectrometer. All compounds are homogeneous on TLC in various solvent systems.

TABLE I

Major mass fragments of new compounds prepared

Fragment No.	Compound No.3a		Compound No.3c		Compound No.3d		Compound No.3g	
	m/z	Relative intensity %	m/z	Relative intensity %	m/z	Relative intensity %	m/z	Relative intensity %
I	M^+ 396	100	M^+ 492	38.6	M^+ 528	64.4	M^+ 564	82.1
II	381	30.0	491	34.4	289	15.0	338	22.8
III	366	12.5	490	85.4	288	52.1	337	100
IV	155	27.2	269	63.9	265	19.4	335	52.3
V	144	22.8	245	23.4	264	15.4	307	21.0
VI	130	8.8	244	30.5	263	25.0	282	18.0
VII	77	31.0	218	38.5	237	36.7	253	54.1
VIII	-	-	217	100	236	100	232	25.4
IX	-	-	216	51.9	235	54.8	229	15.5
X	-	-	193	31.9	212	40.8	201	5.0
XI	-	-	88	7.5	184	5.0	112	7.5
XII	-	-	-	-	105	15.0	78	12.5
XIII	-	-	-	-	88	7.5	-	-



Scheme 2. Mass fragmentation pattern of 5a,12a-di(4-fluorophenyl)-5a,7b,12a,14b-tetrahydrobisindolo[2,3-b:2',3'-b'] benzo [1,2-d:4,5-d']difuran.

5-Fluoro-2,3-dimethylindole

5-Fluoro-2,3-dimethylindole was prepared by the method of Dave [9] . Ethyl methyl ketone (0.05 mole) and 4-fluorophenylhydrazine hydrochloride (0.04 mole) were treated in glacial acetic acid (30 ml) at 90°C on an oil bath. After 25 minutes, the liquid started to bubble and at this stage, the flask was removed from the hot bath. Within a few minutes a rapid reaction started followed by vigorous refluxing of acetic acid. The exothermic reaction subsided in about 10 minutes and the reaction mixture was further heated at 90°C for an additional 2.5 hours. It was then cooled to room temperature and poured into ice. The compound was filtered, dried and recrystallized from light petroleum (b.p. 60-80). Product m.p. = 85°C, yield 80%.

2-Substituted fluoroaryl indoles (1)

2-Substituted fluoroaryl indoles were prepared by the method of Joshi et al. [10] . An appropriate phenylhydrazine (1.02 mole) was treated with fluorinated acetophenone (1.0 mole) and phenylhydrazone so formed was cyclized with P.P.A. (480 g) on an oil bath at 125-150°C. The resultant mass was cooled and poured into crushed ice to give the desired indole. It was filtered, dried and recrystallized from ethanol. It gave a single spot on TLC.

5a, 7b, 12a, 14b-Tetrahydrobisindolo [2,3-b:2',3'-b'] benzo [1,2-d:4,5-d'] difurans (3)

A mixture of the appropriate indole (0.01 mole) and p-benzoquinone (0.01 mole) in glacial acetic acid (30 ml) was stirred at room temperature for about fifty hours. The solid so obtained was filtered and washed with a little acetic acid, dried and recrystallized from dioxan. All the synthesized compounds were homogeneous on TLC. The analytical and spectral data of all compounds are listed in Tables II and III respectively.

TABLE II

Analytical data of new compounds prepared.

Compound No.	X	X'	R	R'	M.P. °C	Molecular formula	Yield %	Elemental analysis Calc/Found		
								C	H	N
3a	H	H	CH_3	CH_3	>300	$C_{26}H_{24}N_2O_2$	15	78.8/78.7	6.1/6.0	7.1/7.0
3b	2-F	9-F	CH_3	CH_3	285	$C_{26}H_{22}F_2N_2O_2$	17	72.2/72.0	5.1/5.0	6.5/6.4
3c	H	H	C_6H_5	H	>300	$C_{34}H_{24}N_2O_2$	14	82.9/82.8	4.9/4.9	5.7/5.4
3d	H	H	4-FC_6H_4	H	>300	$C_{34}H_{22}F_2N_2O_2$	14	77.3/77.1	4.2/4.1	5.3/5.3
3e	H	H	3-CH_3,4-FC_6H_3	H	224	$C_{36}H_{26}F_2N_2O_2$	12	77.7/77.6	4.7/4.4	5.0/5.0
3f	H	H	3-Cl,4-FC_6H_3	H	>300	$C_{34}H_{20}Cl_2F_2N_2O_2$	12	68.3/68.2	3.4/3.2	4.7/4.6
3g	H	H	2,5-$F_2C_6H_3$	H	275	$C_{34}H_{20}F_4N_2O_2$	11	72.3/72.3	3.5/3.1	5.0/4.8
3h	H	H	2,3,4,5,6-C_6F_5	H	182	$C_{34}H_{14}F_{10}N_2O_2$	8	60.7/60.5	2.1/2.0	4.2/4.1
3i	2-Cl	9-Cl	4-FC_6H_4	H	>300	$C_{34}H_{20}Cl_2F_2N_2O_2$	12	68.3/68.2	3.4/3.2	4.7/4.6

TABLE III

Spectral data of new compounds prepared

Compound No.	X	X'	R	R'	IR (cm^{-1})			^1H NMR (δ ppm)				
					N-H (s)	C-O-C	C=C	2-CH_3	3-CH_3	C-H	Ar-H + N-H	CH_3
3a	H	H	CH_3	CH_3	3350-3450	1020	1600	1.49	1.62	-	6.86-7.62	-
3b	2-F	9-F	CH_3	CH_3	3350-3450	1030	1590	1.5	1.64	-	6.89-7.60	-
3c	H	H	C_6H_5	H	3335-3440	1040	1600	-	-	3.65	6.87-7.49	-
3d	H	H	4-F C_6H_4	H	3340-3450	1040	1600	-	-	3.64	6.87-7.49	-
3e	H	H	3-CH_3 4-FC_6H_3 3-Cl	H	3340-3430	1035	1610	-	-	3.62	6.84-7.60	2.2
3f	H	H	4-FC_6H_3	H	3350-3440	1030	1600	-	-	3.64	6.88-7.72	-
3g	H	H	2,5-F_2 C_6H_3	H	3340-3430	1020	1610	-	-	3.64	6.87-7.53	-
3h	H	H	2,3,4, 5,6-C_6F_5	H	3330-3440	1035	1605	-	-	3.65	6.83-7.61	-
3i	2-Cl	9-Cl	4-FC_6H_4	H	3340-3430	1040	1590	-	-	3.62	6.82-7.66	-

ACKNOWLEDGEMENT

The authors are thankful to Ministry of Defence, New Delhi (India) for financial support.

REFERENCES

1 B.A. Whittle and E.H.P. Young, J. Med. Chem., 6 (1963) 378.

2 K.C. Joshi, V.N. Pathak and P. Chand, Agric. Biol. Chem., 42 (9) (1978) 1723.

3 K.C. Joshi, V.N. Pathak and P. Chand, J.F. Prakt. Chemie., Band 322, 2 (1980) 314.

4 K.C. Joshi, A. Dandia and N. Ahmed, Heterocycles, 24 (1986) 2479.

5 K.C. Joshi, J. Indian Chem. Soc., 63 (1985) 187.

6 W.E. Noland and F.J. Baude, J. Org. Chem., 31 (1966) 3321.

7 W.E. Noland and C. Reich, J. Org. Chem., 32, (1967) 828.

8 J.H. Beynon and A.E. Williams, Appl. Spectrosc., 14 (1960) 156.

9 V. Dave, Org. Preparation Procedure Int., 8 (1) (1976) 41.

10 K.C. Joshi, V.N. Pathak and P. Chand, J.F. Prakt.Chemie., Band 320, 4 (1978) 701.