Fluorine Containing Bioactive Heterocycles. Part II. Synthesis of Some New Fluorine Containing Arylglyoxals, Their Hydrates and 1,5-Disubstituted Hydantoins

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Eight new fluorine containing arylglyoxals have been synthesized by the oxidation of the active methyl group of fluorinated acetophenones by selenium dioxide in dioxan-water medium. The corresponding hydrates were obtained by dissolving arylglyoxals in minimum amounts of benzene and adding hot water. Seventeen new fluorine containing 1,5-disubstituted hydantoins were subsequently prepared by the condensation of these arylglyoxals with arylureas in ethanol and characterized by ir, pmr and mass spectral studies. Representative compounds have been screened for their possible anticonvulsant and analgesic activities. None of the compounds show significant analgesic acitivity.

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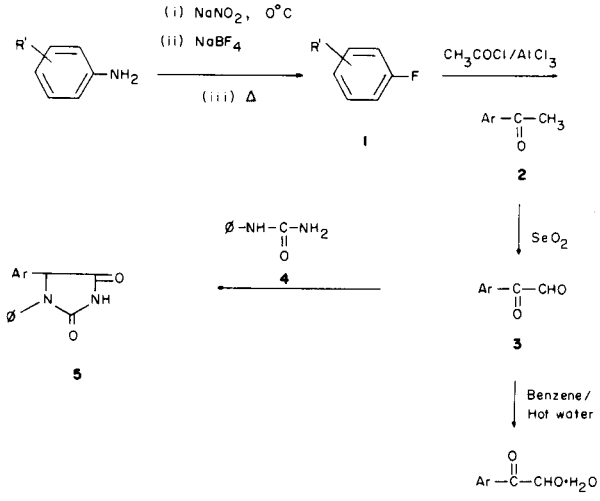
The biological activity of aliphatic and aromatic gyloxals and their derivatives is well known (1,2), but the chemistry and biological activities of fluorinated arylglyoxals have recieved little attention. Arylglyoxals have been used as antiviral agents (3,4), for inactivation of pig liver prenyltransferase enzyme (5), antileukemic activity (6) and inhibition of spore germination (7). Surprisingly, there is scanty information on the synthesis and biological activity of such compounds in the literature. Only *p*-fluorophenylglyoxal has been reported thus far (8). Since the introduction of a fluorine atom usually imparts characteristic biological properties to be of medicinal interest. Detailed spectral studies of these glyoxals have been made by ir, pmr and mass spectrum.

The hydantoin nucleus, containing an active urea moiety, is well known for its diverse biological activities such as lowering blood sugar level in mammals (9), aldose reductase (10-12), antiarrhythmic (13,14), antitubercular (15), antiinflammatory (16), antitumor (17,18), anticonvulsant activities (19,20) and as fungicides (21). Further, no experimental details except patents (22) are available in literature for preparation of 1,5-disubstituted hydantoins from arylglyoxals and arylureas. It was, therefore, thought worthwhile to synthesize new fluorine containing 1,5-disubstituted hydantoins from arylglyoxals prepared by us (Scheme I).

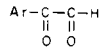
Scheme I



Formation of arylglyoxals and their hydrates of type **3** from corresponding aryl ketones **2** was confirmed by ir, pmr and mass spectral studies. Appearance of two sharp peaks in the region 1850-1590 cm^{-1} corresponds to two carbonyl groups of the arylglyoxal. In case of their hydrates, a broad absorption is noticed at 3570-3450 cm^{-1} due to hydroxyl group of water. Generally, formation of hydrates of organic compounds depends upon the polarity of the molecule (23,24) and this may possibly explain the non-formation of hydrates of compounds **3h**, **3i** and **3j**. The pmr spectra showed a singlet at δ 7.9-8.1 ppm of (1H, CH) in case of arylglyoxal and at δ 3.2-3.4 ppm (2H, water) in hydrates. Further, formation of these derivatives is confirmed by mass spectra, *e.g.*, the molecular ion peak of **3c** was observed at 186.5 and of **3e** at 166. Base peaks of these compounds were observed at (M^+ -29) by the loss of the aldehyde (-CHO) moiety from the molecular ion. Formation of monohydrate derivatives was confirmed by the mass spectra of these compounds (**3c**, m^+ 204.5; **3e**, m^+ 184) and base peaks were observed at (M^+ -47) by the loss of hydrated aldehyde (CHO) moiety. These arylglyoxals on treatment with arylures in absolute ethanol, afford hydantoins of type **5**. These compounds show >NH absorption in ir at 3200-3100 cm^{-1} and two sharp carbonyl peaks at 1800-1700 cm^{-1}. The pmr spectrum showed a signal at δ

Table 1

Analytical Data for Fluorinated Phenylglyoxals and their Hydrates

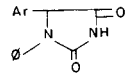


					Analysis					Hydrate of Phenylglyoxals	Analysis			
					Calcd.		Found				Calcd.		Found	
Compound	Ar	Yield %	bp °C	Formula	C	H	C	H	Formula	Mp °C	C	H	C	H
3a (b)	C_6H_5	80	95-97/25mm	$C_8H_6O_2$	71.64	4.47	71.32	4.41	$C_8H_6O_2 \cdot H_2O$	71	63.15	5.26	63.06	5.18
3b (b)	4-F-C_6H_4	78	65-67/5mm	$C_8H_5FO_2$	63.15	3.28	63.21	3.30	$C_8H_5FO_2 \cdot H_2O$	79	56.47	4.11	56.31	4.06
3c	2-Cl,4-F-C_6H_3	76	80-85/5mm	$C_8H_4ClFO_2$	51.47	2.14	51.28	2.21	$C_8H_4ClFO_2 \cdot H_2O$	68	46.94	2.93	46.78	2.91
3d	3-Cl,4-F-C_6H_3	72	60-65/8mm	$C_8H_4ClFO_2$	51.47	2.14	51.50	2.18	$C_8H_4ClFO_2 \cdot H_2O$	74	46.94	2.93	46.84	2.89
3e	2-F,5-CH_3-C_6H_3	74	100-105/8mm	$C_9H_7FO_2$	65.06	4.21	64.90	4.18	$C_9H_7FO_2 \cdot H_2O$	88	58.69	4.89	58.42	4.79
3f	4-F,3-CH_3-C_6H_3	77	80-85/5mm	$C_9H_7FO_2$	65.06	4.21	65.20	4.19	$C_9H_7FO_2 \cdot H_2O$	83	58.69	4.89	58.39	4.81
3g	3-F,4-OCH_3-C_6H_3	69	140-145/6mm	$C_9H_7FO_3$	59.34	3.84	59.18	3.78	$C_9H_7FO_3 \cdot H_2O$	95	54.00	4.50	53.91	4.41
3h	2,4-DiF-C_6H_3	75	60-65/4mm	$C_8H_4F_2O_2$	56.47	2.35	56.28	2.18	(a)					
3i	2,5-DiF-C_6H_3	70	90-95/5mm	$C_8H_4F_2O_2$	56.47	2.35	56.50	2.21	(a)					
3j	C_6F_5	59	70-75/8mm	$C_8HF_5O_2$	42.85	0.44	42.71	0.31	(a)					

(a) No hydrate formation (27,28). (b) Reported in the literature (8).

Table 2

Analytical Data for 1,5-Disubstituted Hydantoins



						Analysis					
						Calcd.			Found		
Compound	Ar	∅	Yield%	Mp °C	Formula	C	H	N	C	H	N
5a	C_6H_5	C_6H_5	72	195	$C_{15}H_{12}N_2O_2$	71.42	4.76	11.11	71.32	4.97	11.07
5b	4-F-C_6H_4	C_6H_5	68	180	$C_{15}H_{11}FN_2O_2$	66.66	4.07	10.37	66.62	4.18	10.48
5c	2-Cl,4-F-C_6H_3	C_6H_5	78	169	$C_{15}H_{10}ClFN_2O_2$	59.11	3.28	9.19	59.31	3.21	9.18
5d	3-Cl,4-F-C_6H_3	C_6H_5	76	176	$C_{15}H_{10}ClFN_2O_2$	59.11	3.28	9.19	59.27	3.38	9.16
5e	2-F,5-CH_3-C_6H_3	C_6H_5	70	220	$C_{16}H_{13}FN_2O_2$	67.60	4.57	9.85	67.42	4.52	9.78
5f	4-F,3-CH_3-C_6H_3	C_6H_5	65	185	$C_{16}H_{13}FN_2O_2$	67.60	4.57	9.85	67.50	4.41	9.55
5g	3-F,4-OCH_3-C_6H_3	C_6H_3	68	95	$C_{16}H_{13}FN_2O_3$	64.00	4.33	9.33	63.81	4.31	9.31
5h	2,4-DiF-C_6H_3	C_6H_5	78	175	$C_{15}H_{10}F_2N_2O_2$	62.50	3.47	9.72	62.41	3.37	9.81
5i	C_6F_5	C_6H_5	82	127	$C_{15}H_7F_5N_2O_2$	52.63	2.04	8.18	52.58	2.02	8.28
5j	4-F-C_6H_4	4-CH_3-C_6H_4	85	195	$C_{16}H_{13}FN_2O_2$	67.60	4.57	9.85	67.51	4.77	9.65
5k	4-F-C_6H_4	4-Cl-C_6H_4	70	191	$C_{15}H_{10}ClFN_2O_2$	59.11	3.28	9.19	59.28	3.38	9.28
5l	3-Cl,4-F-C_6H_3	4-Cl-C_6H_4	74	194	$C_{15}H_9Cl_2FN_2O_2$	53.09	2.65	8.25	53.21	2.48	8.45
5m	3-Cl,4-F-C_6H_3	4-CH_3-C_6H_4	59	187	$C_{16}H_{12}ClFN_2O_2$	60.28	3.76	8.79	60.37	3.88	8.67
5n	2-Cl,4-F-C_6H_3	H	72	168	$C_9H_6ClFN_2O_2$	47.26	2.62	12.25	47.18	2.51	12.18
5o	3-Cl,4-F-C_6H_3	H	70	173	$C_9H_6ClFN_2O_2$	47.26	2.62	12.25	47.38	2.71	12.20
5p	2-F,5-CH_3-C_6H_3	H	64	174	$C_{10}H_9FN_2O_2$	57.69	4.32	13.46	57.38	4.42	13.31
5q	4-F,3-CH_3-C_6H_3	H	66	330	$C_{10}H_9FN_2O_2$	57.69	4.32	13.46	57.61	4.52	13.56

Scheme I

1a, R′ = H
1b, R′ = 2-Cl
1c, R′ = 3-Cl
1d, R′ = 2-CH_3
1e, R′ = 4-CH_3
1f, R′ = 2-OCH_3

2a, Ar = C_6H_5
2b, Ar = 4-F-C_6H_4
2c, Ar = 2-Cl,4-F-C_6H_3
2d, Ar = 3-Cl,4-F-C_6H_3
2e, Ar = 2-F,5-CH_3-C_6H_3
2f, Ar = 4-F,3-CH_3-C_6H_3
2g, Ar = 3-F,4-OCH_3-C_6H_3
2h, Ar = 2-4-DiF-C_6H_3
2i, Ar = 2-5-DiF-C_6H_3
2j, Ar = C_6F_5

4a, ∅ = H
4b, ∅ = C_6H_5
4c, ∅ = 4-$CH_3C_6H_4$
4d, ∅ = 4-Cl-C_6H_4

9.05 ppm corresponding to the position of >NH and another signal at δ 5.25 ppm due to the -CH proton. Mass spectral studies agree with their molecular weights, *viz.*, M^+ of **5c** and **5k** at 304.5 and for **5e** M^+ and base peak at 284. The anticonvulsant activities of some representative compounds (**5b** to **5f** and **5l**) were evaluated in albino mice against supramaximal electroshock seizure pattern. The anticonvulsant ability of these hydantoins were found to be in the range of 50-95%. The maximum anticonvulsant activity (95%) was exhibited by **5b** to **5d**. Compounds **5e**, **5f** and **5l** show only 50% anticonvulsant activity. Toxicity studies reveal that the latter compound possess low toxicity and the approximate LD_{50} values were in the range of 450->1000 mg/kg. None of the compounds show analgesic activity in mice by the mouse tail pinch method (29).

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded using a Perkin Elmer Model 337 spectrophotometer. Proton magnetic resonance spectra were recorded on a Perkin Elmer Model RB-12 spectrometer using tetramethylsilane (TMS) and trifluoroacetic acid (TFA) as internal and external standards, respectively.

Preparation of Fluorinated Arylhydrocarbons **1**.

Fluorobenzene, *o*-chlorofluorobenzene, *m*-chlorofluorobenzene, *o*-fluorotoluene, *p*-fluorotoluene and *o*-fluoroanisole were prepared from corresponding amines by the Balz Schiemann reaction (25).

Preparation of Fluorinated Aryl Ketones **2**.

4-Fluoroacetophenone, 3-chloro-4-fluoroacetophenone, 2-chloro-4-fluoroacetophenone, 4-fluoro-3-methylacetophenone, 2-fluoro-5-methylacetophenone, 3-fluoro-4-methoxyacetophenone, 2,4-difluoroacetophenone and 2,5-difluoroacetophenone were prepared by the method of Buu-Hoi *et al.*, (26).

Preparation of Fluorinated Arylglyoxals and Their Hydrates **3**.

These glyoxals were prepared by the oxidation of the active methyl group by selenium dioxide in dioxane and water as solvent (8). The appropriate ketone (0.1 mole), selenium dioxide (0.1 mole), dioxane (60 ml) and water (2 ml) were refluxed in a three-necked flask, with stirring for about 4 hours at 50-55°. Dioxane and water were removed by distillation and the residual arylglyoxal distilled under reduced pressure. The hydrates of these glyoxals were prepared by dissolving them in a minimum quantity of benzene and adding hot water. The compounds prepared are listed in Table 1.

Preparation of Substituted Arylureas **4**.

Phenylurea, 4-chlorophenylurea, 4-methylphenylurea and 4-methoxyphenylurea were prepared by the sodium cyanate method (27,28) by dissolving the appropriate arylamine (0.1 mole) in glacial acetic acid and water, adding sodium cyanate (0.1 mole in 50 ml of warm water) with stirring.

Preparation of 1,5-Disubstituted Hydantoins **5**.

These were prepared by condensing an appropriate arylurea (0.25 mole) with arylglyoxal (0.30 mole) in the presence of concentrated hydrochloric acid and glacial acetic acid as a catalyst in absolute ethanol (22). On refluxing for about 4 hours, a solid mass was obtained which was filtered and recrystallized from a benzene-petroleum ether mixture.

The compounds prepared are listed in Table 2.

Pharmacological Studies.

The anticonvulsant activities of **5b** to **5f** and **5l** were determined by observing complete protection against supramaximal electroshock induced convulsions in albino mice. A 2% aqueous suspension of gum acacia and the compound under study at a dose of 150 mg/kg was orally administered to a group of 5 mice each of either sex weighing 15-25 g. Complete protection within 4 hours against tonic extension was taken as an evidence of anticonvulsant activity.

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