SYNTHESIS OF SOME NEW FLUORINE CONTAINING 1,3,4-TRISUBSTITUTED 4,8-DIHYDRO-1H-PYRAZOLO [3,4-e] [1,4] THIAZEPIN-7(6H)-ONES AND RELATED COMPOUNDS.

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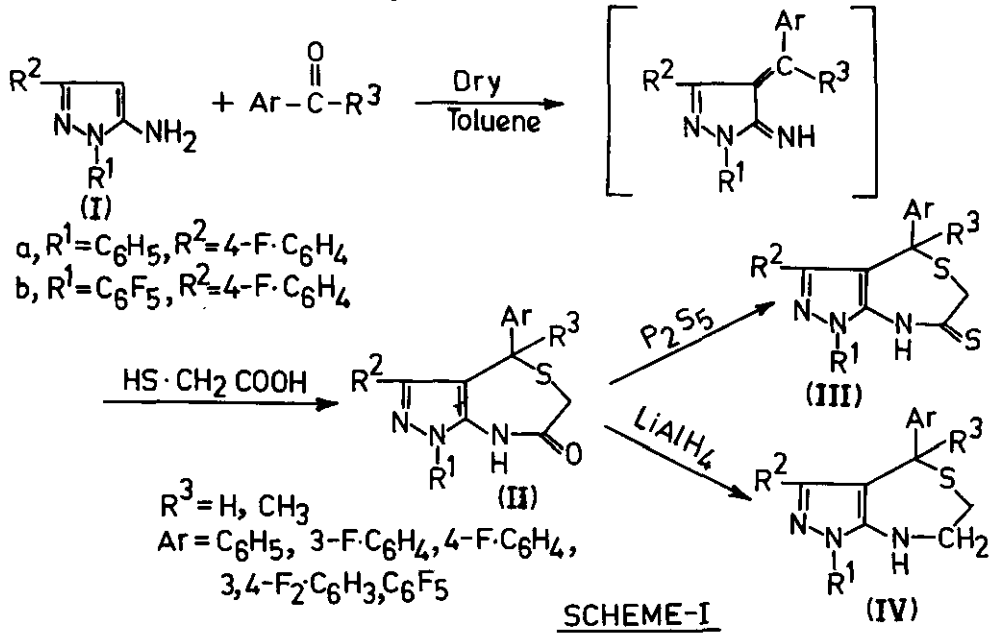
Abstract - A series of new fluorine containing 1,3,4-trisubstituted 4,8-dihydro-1H-pyrazolo [3,4-e] [1,4] thiazepin-7 (6H)-ones have been synthesized by the condensation of fluorine containing 5-amino-1,3-disubstituted pyrazoles with an appropriate aromatic aldehyde/ketone and mercaptoacetic acid in dry toluene. The reduction of 7-oxo group and the conversion of 7-oxo to 7-thione group have been carried out for the first time in such systems by an elegant procedure.

The chemistry and biological activities of some fluorine containing pyrazolo [3,4-e] [1,4] thiazepin-7-ones have been reported by us earlier[1,2]. In view of the interesting psychopharmacological properties associated with such compounds, the system has been further investigated and we now report the synthesis of some new



SCHEME-I

fluorine containing 1,3,4-trisubstituted **4,8-dihydro-1H-pyrazolo [3,4-e] [1,4] thiazepin-7 (6H)-ones** (II), their corresponding 7-thione derivatives (III) and reduction products of II (IV) [vide Scheme I].

Compounds II were obtained by the condensation of fluorine containing 5-amino-1,3-disubstituted pyrazoles(I) with aromatic aldehydes or ketones and mercaptoacetic acid in dry toluene and purified by recrystallization from ethylacetate [single spot in TLC; benzene:ethyl acetate (1:1)]. The appearance of C=O (1680-1720 cm^{-1}) and $-CH_2-$(1500 cm^{-1}) absorptions in IR spectra corroborated the formation of II, which was further confirmed by ^1H NMR and ^{19}F NMR. In ^1H NMR spectra, all the aromatic protons resonate at δ 6.9-7.7 ppm. The >NH signals are observed downfield at δ 9.0 ppm due to deshielding by C=O. Other significant resonance signals were obtained at δ 3.3-3.75 (2H, $S-CH_2$), 5.4-5.6 (1H, CH -Ar) and 2.4-2.6 (3H, CH_3).

The position of fluorine in aromatic ring (Ar-F) was observed by ^{19}F NMR at δ 39.4 and the resonance signals of 4-F, 2,6-F and 3,5-F of perfluorophenyl group were observed at δ 80.0, 72.0 and 83.2 ppm, respectively with respect to TFA.

Compounds II, on treatment with P_2S_5 in dry pyridine, were converted into III and the latter characterized by their IR spectra. The disappearance of C=O absorption band strongly supports the formation of these compounds. This found further support from ^1H NMR spectra. Due to high electronegativity of sulphur, protons of $-CH_2$ will be deshielded and shift to downfield region (δ3.8-3.9).

Reduction of compounds II was carried out by $LiAlH_4$, in dry solvent ether, leading to the formation of compoundsIV, which were characterized by IR and ^1H NMR. The disappearance of C=O band in IR confirmed the formation of IV.

Experimental Procedure - Melting points are uncorrected. All synthesized compounds were routinely checked by elemental analysis. TLC was done on silica gel plates using benzene-ethyl acetate (1:1) as solvent system. IR spectra were recorded on Perkin-Elmer IR-337 spectrophotometer (KBr pellet). The ^1H NMR spectra were recorded at 60 MHz in $CDCl_3$ using tetramethylsilane (TMS) as internal reference standard and ^{19}F NMR at 56.4 MHz using trifluoroacetic acid (TFA) as external standard. The chemical shifts are expressed in δ (ppm) downfield from TMS.

Pentafluorophenyl hydrazine - It was prepared from hexafluorobenzene (18.6 g, 0.1 mole) and hydrazine hydrate (15 g, 0.30 mole) in absolute ethanol, m.p. 75°C

(Lit.[5], m.p. 76°C), yield 5.0 g (85 %).

5-Amino-3-(4-fluorophenyl)-1-phenyl pyrazole (Ia) - It was prepared according to literature method[3] from 4-fluorophenylacetonitrile (16.3 g, 0.1 mole) and phenyl hydrazine (10.8 g, 0.1 mole) in absolute ethanol and recrystallized from methanol, m.p. 140°C (Lit.[3], m.p. 141°C), yield 15.6 g (62 %).

5-Amino-3-(4-fluorophenyl)-1-pentafluorophenyl pyrazole (Ib) - It was prepared from pentafluorophenyl hydrazine and 4-fluorophenylacetonitrile following the above procedure, m.p. 135°C, yield 70 %.

4-Fluoroacetophenone - It was prepared according to the method of Bu Hoi et al.[4] from fluorobenzene (21.1 g, 0.22 mole) and acetyl chloride (17.3 g, 0.22 mole) in the presence of anhydrous $AlCl_3$ (16 g, 0.32 mole), b.p. 195°C, yield 20.3 g (67 %).

3,4-Difluoroacetophenone was similarly obtained.

3-(4-Fluorophenyl)-4-(3-fluorophenyl)-1-phenyl-4,8-dihydro-1H-pyrazolo[3,4-e][1,4] thiazepin-7(6H)-one (IIa) - Equimolar quantities of Ia (2.53 g, 0.01 mole) and 3-fluorobenzaldehyde (1.24 g, 0.01 mole) in dry toluene (20 ml) were refluxed for 1.5 hr. Water was collected azeotropically during reaction time. The mixture was cooled and mercaptoacetic acid (1.01 g, 0.011 mole) was added and it was heated under reflux for 3 hr. The reaction mixture was cooled, excess of solvent was removed under reduced pressure and solvent ether added. The resultant solid was recrystallized from ethyl acetate, m.p. 183°C, yield 3.6 g (85 %). (Found: N, 9.43; S, 7.18, $C_{24}H_{17}F_2N_3OS$ requires N, 9.69; S, 7.39 %). $\nu_{max}^{cm^{-1}}$ 3066 (NH), 1680 (C=O), 1600 (C=N), 1420 (C-N), 1500 ($-CH_2-$) and 1000-1100 (C-F). ^{1}H NMR : δ3.3 (2H, CH_2), 5.4 (1H, CH), 6.9-7.7 (13H, aromatic protons).

All other compounds (IIb-e Table I) were prepared in a similar manner.

3-(4-Fluorophenyl)-1,4-bisphenyl-4,8-dihydro-1H-pyrazolo[3,4-e][1,4] thiazepin-7(6H)-thione (IIIa) - Compound II (R^1 = Ar = C_6H_5, R^2 = 4-FC_6H_4, R^3 = H; 4.15 g, 0.01 mole), P_2S_5 (6.6 g, 0.03 mole) and pyridine (20 ml) were heated together at 170°C for 18 hr. The reaction mixture was concentrated, diluted with water to give a yellow solid, which was recrystallized from benzene-petroleum ether to yield the desired compound; m.p. 165°C, yield 3.4 g (79 %) (Found: N, 9.62; S, 14.80, $C_{24}H_{18}FN_3S_2$ requires N, 9.74; S, 14.84 %). $\nu_{max}^{cm^{-1}}$ 3060 (NH), 1600 (C=N), 1500(C-N), 1000-1100(C-F). ^{1}H NMR ($CDCl_3$): δ3.75-4.0 (2H, CH_2),

5.4(1H, CH), 6.9-7.7 (14H, aromatic protons).

All other compounds (IIIb-e) were prepared in a similar manner.

3-(4-Fluorophenyl)-1,4-bisphenyl-(1H)pyrazolo[3,4-e] [1,4] -4,6,7,8-tetrahydro-thiazepine (IVa) - Compound II (4.15 g, 0.01 mole) was added portion-wise to a suspension of $LiAlH_4$ (0.76 g, 0.02 mole) in dry solvent ether. The reaction mixture was stirred at 60°C for 48 hr on water bath. On completion of reaction, it was cooled in ice and decomposed with 3N NaOH. The ethereal layer separated and after removing the solvent, a sticky mass was obtained. It was recrystallised from petroleum ether, m.p. 80°C, yield 2.8 g (70 %) (Found : N, 10.63 ; S, 7.63, $C_{24}H_{20}FN_3S$ requires N, 10.47 ; S, 7.98). $\nu_{max}^{cm^{-1}}$ 3160 (NH), 1600 (C=N), 1520 (C-N). ^1H NMR ($CDCl_3$): δ3.5 (4H, CH_2CH_2), 5.6 (1H, CH) 6.9-7.7 (14H, aromatic protons).

All other compounds (IVb-d) were prepared in a similar way.

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Table I: Physical data of 1,3,4-trisubstituted 4,8-dihydro-1H-pyrazolo[3,4-e] [1,4] thiazepin-7(6H)-one (II) and related compounds (III and IV)

Compound No.	Ar	R^3	R^2	R^1	Yield %	M.P. °C	Mol. formula	Analysis			
								Calc.		Found	
								N %	S %	N %	S %
IIa	3-F.C_6H_4	H	4-F. C_6H_4	C_6H_5	85	183	$C_{24}H_{17}F_2N_3OS$	9.69	7.39	9.43	7.18
IIb	3,4-F_2.C_6H_3	CH_3	4-F. C_6H_4	C_6H_5	80	159	$C_{25}H_{18}F_3N_3OS$	9.03	6.88	8.98	6.65
IIc	4-F.C_6H_4	CH_3	4-F. C_6H_4	C_6F_5	78	145	$C_{25}H_{14}F_7N_3OS$	7.82	5.95	7.40	5.63
IId	3-F.C_6H_4	H	4-F. C_6H_4	C_6F_5	82	105	$C_{24}H_{12}F_7N_3OS$	8.03	6.11	8.12	6.01
IIe	C_6F_5	CH_3	4-F. C_6H_4	C_6F_5	83	81	$C_{25}H_{10}F_{11}N_3OS$	6.89	5.25	6.58	5.20
IIIa	C_6H_5	H	4-F. C_6H_4	C_6H_5	79	165	$C_{24}H_{18}FN_3S_2$	9.74	14.84	9.62	14.80
IIIb	4-F.C_6H_4	H	4-F. C_6H_4	C_6H_5	75	110	$C_{24}H_{17}F_2N_3S_2$	9.35	14.25	9.10	14.32
IIIc	C_6F_5	H	4-F. C_6H_4	C_6H_5	80	235	$C_{24}H_{13}F_6N_3S_2$	8.06	12.28	8.24	12.08
IIId	C_6F_5	CH_3	4-F. C_6H_4	C_6H_5	78	178	$C_{25}H_{15}F_6N_3S_2$	7.85	11.96	7.57	11.49
IIIe	3-F.C_6H_4	H	4-F.C_6H_4	C_6F_5	81	125	$C_{24}H_{12}F_7N_3S_2$	7.79	11.87	7.48	11.63
IVa	C_6H_5	H	4-F. C_6H_4	C_6H_5	58	80	$C_{24}H_{20}FN_3S$	10.47	7.98	10.63	7.63
IVb	4-F.C_6H_4	CH_3	4-F. C_6H_4	C_6H_5	59	70	$C_{25}H_{21}F_2N_3S$	9.69	7.39	9.48	7.02
IVc	C_6F_5	H	4-F. C_6H_4	C_6H_5	62	180	$C_{24}H_{15}F_6N_3S$	8.55	6.51	8.38	6.47
IVd	3-F.C_6H_4	H	4-F. C_6H_4	C_6F_5	63	105	$C_{24}H_{14}F_7N_3S$	8.25	6.28	8.09	6.13

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