SYNTHESIS OF SOME NEW FLUORINE CONTAINING 1,3,4-TRISUBSTITUTED 4,8-DIHYDRO-1H-PYRAZOLO [3,4-α] [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-α] [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-α] [1,4] thiazepin-7-ones have been reported by us earlier¹,². 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

\[
\text{R}_2^1 \text{N} = \text{C} = \text{C} \text{R}_3^1 + \text{Ar} - \text{C} - \text{R}_3^0 \xrightarrow{\text{Dry Toluene}} \left[ \begin{array}{c} \text{Ar} \\ \text{R}_2^1 \\ \text{N} = \text{C} \text{R}_3^1 \\ \text{C} = \text{R}_3^0 \\ \text{N} = \text{C} \text{R}_3^1 \\ \text{R}_2^1 \\ \text{N} = \text{C} \text{R}_3^1 \end{array} \right]
\]

\[a, \text{R}_1^1 = \text{C}_6\text{H}_5, \text{R}_2^1 = 4-\text{F}\cdot\text{C}_6\text{H}_4
\]

\[b, \text{R}_1^1 = \text{C}_6\text{F}_5, \text{R}_2^1 = 4-\text{F}\cdot\text{C}_6\text{H}_4
\]

\[
\text{HS} \cdot \text{CH}_2 \text{COOH} \xrightarrow{\text{LiAlH}_4} \left[ \begin{array}{c} \text{Ar} \\ \text{R}_2^1 \\ \text{N} = \text{C} \text{R}_3^1 \\ \text{C} = \text{S} \\ \text{N} = \text{C} \text{R}_3^1 \\ \text{Ar} \\ \text{R}_2^1 \\ \text{N} = \text{C} \text{R}_3^1 \end{array} \right]
\]

\[\text{R}_3^1 = \text{H}, \text{CH}_3
\]

\[\text{Ar} = \text{C}_6\text{H}_5, 3-\text{F}\cdot\text{C}_6\text{H}_4, 4-\text{F}\cdot\text{C}_6\text{H}_4,
\]

\[3,4-\text{F}_2\cdot\text{C}_6\text{H}_3, \text{C}_6\text{F}_5
\]

\[\text{SCHEM}E-I
\]
fluorine containing 1,3,4-trisubstituted 4,8-dihydro-1H-pyrazolo[3,4-a] 
[1,4] thiazepin-7(6H)-ones (II), their corresponding 7-thione derivatives (III) 
and reduction products of II (IV) [vide Scheme 1]. 
Compounds II were obtained by the condensation of fluorine containing 5-amino-
1,3-disubstituted pyrazoles(1) 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 -CH₂-(1500 cm⁻¹) absorptions in IR spectra corro-
boration the formation of II, which was further confirmed by ¹H NMR and ¹⁹F NMR. 
In ¹H NMR spectra, all the aromatic protons resonate at 66.9-7.7 ppm. The >NH 
signals are observed downfield at 69.0 ppm due to deshielding by C=O. Other 
significant resonance signals were obtained at 6 3.3-3.75 (2H, S-CH₂), 5.4-5.6 
(1H, CH -Ar) and 2.4-2.6 (3H, CH₃). 
The position of fluorine in aromatic ring (Ar-F) was observed by ¹⁹F NMR at 639.4 
and the resonance signals of 4-F, 2,6-F and 3,5-F of perfluorophenyl group were 
observed at 6 80.0, 72.0 and 83.2 ppm, respectively with respect to TFA. 
Compounds II, on treatment with P₂S₅ 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 
进一步 support from ¹H NMR spectra. Due to high electronegativity of sulphur, 
protons of -CH₂ will be deshielded and shift to downfield region (63.8-3.9). 
Reduction of compounds II was carried out by LiAlH₄, in dry solvent ether, leading 
to the formation of compounds IV, 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 CDCl₃ using tetramethylsilane (TMS) as 
internal reference standard and ¹⁹F NMR at 56.4 MHz using trifluoroacetic acid 
(TFA) as external standard. The chemical shifts are expressed in δ(ppm) down-
field 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
5-Amino-3-(4-fluorophenyl)-1-phenyl pyrazole (Ia) - It was prepared according to literature method\(^5\) 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 15.8 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-g][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 mercaptoaetic 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. 185 °C, yield 3.6 g (85%).

(Found: N, 9.43; S, 7.73; C\(_{24}\)H\(_{17}\)F\(_2\)N\(_3\)S requires N, 9.69; S, 7.39%). \(\nu_{\text{max}}\) cm\(^{-1}\) 3060 (NH), 1680 (C=O), 1600 (C=N), 1420 (C-N), 1000-1100 (C-F). \(^1\)H NMR: \(\delta\) 3.3 (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-4H-pyrazolo[3,4-g][1,4]thiazepin-7(6H)-thione (IIa) - Compound II (R\(_1\) = Ar = C\(_6\)H\(_5\), R\(_2\) = 4-FC\(_6\)H\(_4\), R\(_3\) = H; 4.15 g, 0.01 mole), P\(_2\)S\(_2\) (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\(_{18}\)F\(_2\)N\(_3\)S requires N, 9.74; S, 14.94%). \(\nu_{\text{max}}\) cm\(^{-1}\) 3060 (NH), 1600 (C=O), 1500 (C=N), 1000-1100 (C-F). \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 3.75-4.0 (2H, CH\(_2\)),

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

\(^{-73-}\)
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][1,2]4,6,7,8-tetrahydrothiazepine (IVa) - Compound II (4.15 g, 0.01 mole) was added portion-wise to a suspension of LiAlH₄ (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, C₂₄H₂₀FN₂S requires N, 10.47; S, 7.98). \[\text{cm}^{-1}\text{max}\] 3160 (NH), 1600 (C=N), 1520 (C-N). \[\text{H NMR (CDCl₃)}: 63.5 (4H, CH₂CH₂), 5.6 (1H, CH) 6.9-7.7 (14H, aromatic protons).

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

Acknowledgements - We are thankful to the Indian Council of Medical Research, New Delhi, for the award of a Research Associateship (K.D.) and to the Council of Scientific and Industrial Research, New Delhi, for award of a J.R.F. (A.D.).
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References


Received, 30th August, 1980