Investigation of the Reaction Products of 5-Amino-1,3-disubstituted-pyrazoles with Aromatic Aldehydes. Synthesis of New Fluorinated 1,3,4-Trisubstituted-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7-ones

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The condensation products of 5-amino-1,3-disubstituted-pyrazoles with aromatic aldehydes were identified as 2,4-dihydro-2,5-diphenyl-4-(phenylmethylene)-3*H*-pyrazol-5-imine derivatives Treatment of these products with mercaptoacetic acid gave new fluorine containing 1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7-ones.

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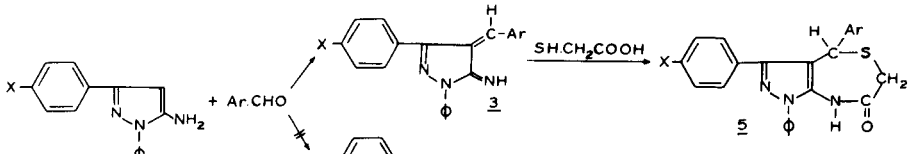
The biological activity of pyrazole and its derivatives is well known (1-3), but the chemistry and biological activities of pyrazolo[3,4-*e*][1,4]thiazepine have received little attention. Only a few references can be found in the literature concerning the antiinflammatory activity of pyrazolothiazepines (4,5). The behavior of 5-amino-pyrazole towards condensation with aldehydes and ketones (6,7) resembles that of 2-aminoindole; the resulting condensation products could be valuable intermediates for the synthesis of pyrazolo[3,4-*e*][1,4]thiazepines. Reaction of 5-aminopyrazole with aldehydes can lead to the formation of either intermediates **3** or **4**. Swett, *et al.* (8), have synthesized pyrazolo[3,4-*e*][1,4]thiazepines starting with 5-amino-1,3-dimethylpyrazole, and have further suggested a structure of type **3** as the most likely for the intermediates formed in this reaction. However, since they were unable to either purify or characterize these intermediates, they could not rule out the possibility of intermediate Schiff bases of type **4**, which could rearrange to **3**. They assigned the structure of the final pyrazolothiazepines on the basis of some reductive experiments. We have further investigated the condensation reaction of 5-amino-1,3-diphenylpyrazoles with aromatic aldehydes and have shown that only the intermediates **3** are formed.

The condensation products were purified by recrystallization from ethanol and gave a single spot on tlc in both benzene-ethyl acetate (50:50) and benzene-petroleum ether (50:50). These products were identified by ir and pmr spectral data. The pmr spectra of these products in deuteriochloroform exhibit a broad resonance signal for =NH at δ 8.85 ppm (1H, showing a beautiful quadrupole splitting pattern which confirms that this proton is attached to a nitrogen atom. The resonance signal at δ 6.75 ppm is due to a methine proton (=CH-). This is in conformity with the structure **3**. The methine resonance signal of the alternative structure **4** would have been observed at δ 8.5 ppm (9). Both the absence of the $-NH_2$ signal from the region of δ 3.4 ppm and the disappearance of the original (=CH-) resonance signal of **1** at δ 6.1 ppm provide additional support for the complete condensation of **1** with **2**. The condensation thus appears to take place at the 4-position of the 5-amino-1,3-diphenylpyrazoles, due to maximum electron density at the 4-position (10).

Compounds **3** were found to be very reactive, and readily condense with mercaptoacetic acid in dry toluene giving 1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7-ones (**5**). The structure **5** was confirmed by ir and pmr spectral analysis. In the ir spectrum, appearance of a new absorption band at 1680



1 a; $\phi = C_6H_5$, X = F
1 b; $\phi = C_6F_5$, X = F
1 c; ϕ = p-Cl C_6H_4, X = F
1 d; ϕ = p-F·C_6H_4, X = H
1 e; ϕ = p-F·$C_6H_4SO_2$-, X = F
1 f; ϕ = p-CH_3·$C_6H_4SO_2$-, X = F

2 a; Ar = C_6F_5
2 b; Ar = p-Cl·C_6H_4
2 c; Ar = m-Cl·C_6H_4
2 d; Ar = p-F·C_6H_4
2 e; Ar = o-O_2N·C_6H_4

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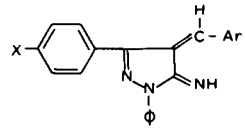
Table I

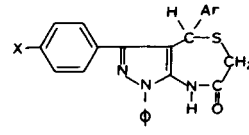
Analytical Data for 2,4-Dihydro-2,5-diphenyl-4-(phenylmethylene)-3*H*-pyrazol-3-imines



Compound No.	X-⟨⟩	∅	Ar	Yield %	M.p. °C	Formula	Analysis Calcd. C	H	N	Found C	H	N
1	*p*-F-C_6H_4	C_6H_5	*p*-Cl-C_6H_4	85	148	$C_{22}H_{15}ClFN_3$	70.30	3.99	11.18	70.20	3.89	11.19
2	*p*-F-C_6H_4	C_6H_5	*m*-Cl-C_6H_4	80	152	$C_{22}H_{15}ClFN_3$	70.30	3.99	11.18	70.15	3.78	10.99
3	*p*-F-C_6H_4	C_6H_5	*o*-NO_2-C_6H_4	78	142	$C_{22}H_{15}FN_4O_2$	68.39	3.88	14.50	68.22	3.70	14.39
4	*p*-F-C_6H_4	*p*-Cl-C_6H_4	*p*-F-C_6H_4	83	155	$C_{22}H_{14}ClF_2N_3$	67.09	3.55	10.67	66.89	3.42	10.52
5	C_6H_5	*p*-F-C_6H_4	C_6F_5	85	215	$C_{22}H_{11}F_6N_3$	61.22	2.55	9.74	61.11	2.45	9.64
6	*p*-F-C_6H_4	C_6F_5	*p*-F-C_6H_4	74	200	$C_{22}H_{10}F_7N_3$	58.79	2.22	9.35	58.68	2.11	9.28
7	*p*-F-C_6H_4	C_6F_5	*p*-Cl-C_6H_4	80	210	$C_{22}H_{10}ClF_6N_3$	56.71	2.14	9.02	56.69	2.11	8.89
8	*p*-F-C_6H_4	C_6F_5	C_6F_5	84	213	$C_{22}H_5F_{11}N_3$	50.67	1.15	8.06	50.51	1.11	7.88
9	*p*-F-C_6H_4	*p*-CH_3-$C_6H_4SO_2$-	*p*-F-C_6H_4	80	145	$C_{23}H_{17}F_2N_3O_2S$	63.15	3.89	9.61	63.11	3.71	9.59
10	*p*-F-C_6H_4	*p*-CH_3-$C_6H_4SO_2$-	C_6F_5	70	180	$C_{23}H_{13}F_6N_3O_2S$	54.22	2.55	8.25	54.11	2.41	8.21
11	*p*-F-C_6H_4	*p*-F-$C_6H_4SO_2$-	C_6F_5	85	223	$C_{22}H_{10}F_7N_3O_2S$	51.46	1.94	8.18	51.34	1.81	8.11

Table II

Analytical Data for 1*H*-Pyrazolo[3,4-*e*][1,4]thiazepin-7-ones



Compound No.	X-⟨⟩	∅	Ar	Yield %	M.p. °C	Formula	Analysis Calcd. C	H	N	S	Found C	H	N	S
1	*p*-F-C_6H_4	C_6H_5	*p*-Cl-C_6H_4	75	172	$C_{24}H_{17}ClFN_3OS$	64.07	3.78	9.34	7.11	63.89	3.62	9.12	7.01
2	*p*-F-C_6H_4	C_6H_5	*m*-Cl-C_6H_4	70	201	$C_{24}H_{17}ClFN_3OS$	64.07	3.78	9.34	7.11	63.81	3.60	9.21	6.98
3	*p*-F-C_6H_4	C_6H_5	*o*-NO_2-C_6H_4	80	207	$C_{24}H_{17}FN_4O_3S$	62.60	3.69	12.17	6.95	62.49	3.59	12.11	6.85
4	*p*-F-C_6H_4	*p*-Cl-C_6H_4	*p*-F-C_6H_4	85	165	$C_{24}H_{16}ClF_2N_3OS$	61.60	3.42	8.98	6.84	61.54	3.29	8.73	6.68
5	C_6H_5	*p*-F-C_6H_4	C_6F_5	78	240	$C_{24}H_{13}F_6N_3OS$	57.02	2.57	8.31	6.33	56.89	2.39	8.14	6.22
6	*p*-F-C_6H_4	C_6F_5	*p*-F-C_6H_4	82	160	$C_{24}H_{12}F_7N_3OS$	55.06	2.29	8.03	6.11	54.88	2.21	7.89	6.09
7	*p*-F-C_6H_4	C_6F_5	*p*-Cl-C_6H_4	84	162	$C_{24}H_{12}ClF_6N_3OS$	53.36	2.22	7.78	5.93	53.14	2.10	7.69	5.82
8	*p*-F-C_6H_4	C_6F_5	C_6F_5	85	240	$C_{24}H_8F_{11}N_3OS$	48.40	1.34	7.05	5.37	48.29	1.22	6.89	5.29
9	*p*-F-C_6H_4	*p*-$CH_3C_6H_4SO_2$-	*p*-F-C_6H_4	75	163	$C_{25}H_{19}F_2N_3O_3S_2$	58.70	3.71	8.21	12.52	58.51	3.62	8.11	12.40
10	*p*-F-C_6H_4	*p*-$CH_3C_6H_4SO_2$-	C_6F_5	78	190	$C_{25}H_{15}F_6N_3O_3S_2$	51.45	2.57	7.20	10.96	51.30	2.39	7.11	10.85
11	*p*-F-C_6H_4	*p*-F-$C_6H_4SO_2$-	C_6F_5	70	243	$C_{24}H_{12}F_7N_3O_3S_2$	49.06	2.04	7.16	10.90	48.90	1.98	7.00	10.83

cm^{-1} demonstrates the presence of the carbonyl group. The pmr spectrum in trifluoroacetic acid also exhibits one additional peak at δ 3.4 ppm, due to the presence of the $-CH_2$ group.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded using a Perkin Elmer Model 337 spectrophotometer. Proton magnetic resonance spectra and fluorine 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. The chemical shifts are reported in ten parts per million and hundred parts per million, respectively.

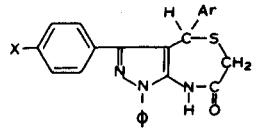
1-(*p*-Fluorophenyl)-3-phenyl-5-aminopyrazole, 3-(*p*-fluorophenyl)-1-phenyl-5-aminopyrazole, 1-(*p*-chlorophenyl)-3-(*p*-fluorophenyl)-5-aminopyrazole, 3-(*p*-fluorophenyl)-1-pentafluorophenyl-5-aminopyrazole, 3-(*p*-fluorophenyl)-1-(*p*-methylphenylsulfonyl)-5-aminopyrazole and 3-(*p*-fluorophenyl)-1-(*p*-fluorophenylsulfonyl)-5-aminopyrazole were reported by Joshi, *et al.* (11).

2,4-Dihydro-2,5-diphenyl-4-(phenylmethylene)-3*H*-pyrazol-3-imines (**3**).

The appropriate 1,3-disubstituted-5-aminopyrazoles (0.1 mole) and arylaldehyde (0.1 mole) were heated under reflux in dry toluene (100 ml.) for 3 to 5 hours; water was removed with the help of a Dean-Stark water separator. Excess solvent was removed from the reaction mixture and the residue was poured into ether. The resulting solid material was filtered, washed with ether and then recrystallized from ethanol. Analytical data for all of the compounds which were synthesized are recorded in Table I.

Table III

Pmr and ^{19}F Nmr Data for the Pyrazolothiazepine Derivatives



Compound		→	Ar	Chemical Shift (Ppm, δ)							
				Pmr Spectral Data					^{19}F Nmr Spectral Data		
				NH	CH	CH_2	Aromatic Protons	Solvent	Ar-F	C_6F_5	Solvent
1	*p*-F-C_6H_4	C_6H_5	*p*-Cl-C_6H_4	8.0	5.3	3.2	6.1 to 7.8	TFA	34	—	DMF
2	*p*-F-C_6H_4	C_6H_5	*m*-Cl-C_6H_4	7.9	5.2	3.4	6.5 to 7.4	TFA	36	—	DMSO
3	*p*-F-C_6H_4	C_6H_5	*o*-NO_2-C_6H_4	7.9	5.1	3.2	6.6 to 7.4	TFA	32	—	DMSO
4	*p*-F-C_6H_4	*p*-Cl-C_6H_4	*p*-F-C_6H_4	7.8	5.3	3.1	6.3 to 7.8	TFA	33 37	—	DMSO
7	*p*-F-C_6H_4	C_6F_5	*p*-Cl-C_6H_4	7.9	5.1	3.4	6.4 to 7.5	TFA	35	65 79 86	DMF
8	*p*-F-C_6H_4	C_6F_5	C_6F_5	7.8	5.0	3.1	6.5 to 7.3	TFA	—	—	—
9	*p*-F-C_6H_4	*p*-CH_3-$C_6H_4SO_2$-	*p*-F-C_6H_4	7.8	5.8	3.6	6.8 to 7.6	TFA	32 38	—	DMF
10	*p*-F-C_6H_4	*p*-CH_3-$C_6H_4SO_2$-	C_6F_5	8.0	5.4	3.3	6.6 to 7.5	TFA	37	64 80 89	DMSO
11	*p*-F-C_6H_4	*p*-F-$C_6H_4SO_2$-	C_6F_5	7.9	5.2	3.2	6.5 to 7.3	TFA	—	—	—

1,3,4-Trisubstituted-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7-ones (**5**).

A mixture of the appropriate 2,4-dihydro-2,5-diphenyl-4-(phenylmethylene)-3*H*-pyrazol-3-imine (0.1 mole) and mercaptoacetic acid (0.1 mole) was refluxed 8 to 10 hours in dry toluene (100 ml.). The reaction mixture was then cooled, excess solvent was removed under reduced pressure and the residue was washed with ether several times. Crystallization from ethanol, afforded **5** in good yield. Compounds **5** are listed in Table II. Pmr and ^{19}F nmr spectral data are given in Table III.

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