

Investigation of the Reactions of Fluorine Containing 3-Hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indoles with Ethyl Acetoacetate. Synthesis of some Novel Tetracyclic Ring Systems

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Novel tetracyclic ring systems *viz.* 3-methyl-1-oxo-12*H*-1,2,4-triazepino[3',4':3,4][1,2,4]triazino[5,6-*b*]indole (4a) and 3-methyl-5-oxo-12*H*-1,2,4-triazepino[4',3':2,3][1,2,4]triazino[5,6-*b*]indole (5a), having angular and linear structures respectively, were synthesized by the cyclization of 3-oxobutanoic acid [5*H*-1,2,4-triazino[5,6-*b*]indole-3-yl]hydrazone (3a). However, cyclization of 3b (R = CH₃, R¹ = R² = H) afforded the angular product 4b exclusively. Moreover, cyclization of 3c (R = R² = H, R¹ = F) yielded 7-fluoro-1-oxo-10*H*-1,3-imidazo[2',3':3,4][1,2,4]triazino[5,6-*b*]indole (6c) and 7-fluoro-3-oxo-10*H*-1,3-imidazo[3',2':2,3][1,2,4]triazino[5,6-*b*]indole (7c) instead of the expected triazepinone derivatives. Compound 3d (R = R¹ = H, R² = CF₃) also gave an imidazole derivative but only one angular product was obtained. In all these reactions, formation of the angular product involving cyclization at N-4 is favoured. Characterization of these products have been done by elemental analyses, ir, pmr, ¹⁹F nmr and mass spectral studies.

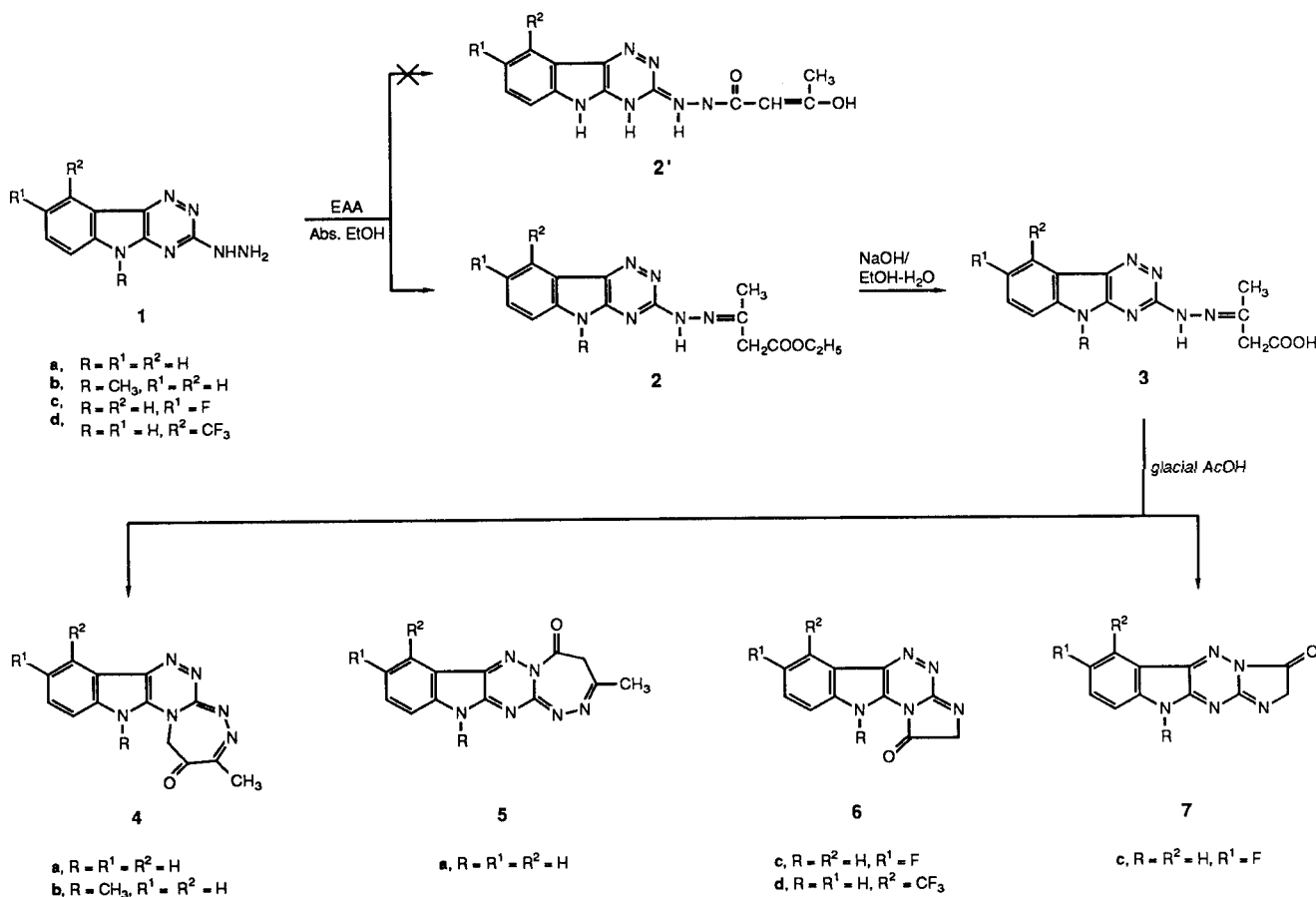
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1,2,4-Triazino[5,6-*b*]indole derivatives find useful applications in medicinal chemistry [1-3]. Recently, semicarbazones and thiosemicarbazones of triazinoindoles

were reported as active antiinflammatory agents [4].

3-Hydrazino-1,2,4-triazinoindoles can undergo cyclization reactions with various reagents leading to the forma-

Scheme 1



tion of novel tetracyclic ring systems. Earlier, we have reported some of its cyclization reactions [5,6]. However, the reaction of 3-hydrazino-1,2,4-triazinoindole with ethyl acetoacetate has not been studied so far, though other heterocyclic hydrazines react with it yielding different interesting products.

The hydrazinopyridazines and quinolines [7,8] undergo cyclocondensation with ethyl acetoacetate in ethanol to afford the corresponding pyrazolone derivatives. Hydrazinopyridazines have also been reported [9] to give condensed triazolopyridazine. However, a number of reports record the formation of hydrazones under identical conditions with other heterocyclic hydrazines [10-14]. The cyclization of these hydrazones in ethanol in presence of sodium ethoxide [10] or on heating at their melting points has been reported to yield pyrazolones [11], whereas hydrolysis of the hydrazones followed by cyclization in glacial acetic acid afforded triazepinones [12-14] exclusively. However, when we investigated the cyclization reaction of hydrazone of 1,2,4-triazino[5,6-*b*]indole, we obtained two different products for which there is a distinct possibility as the chances of cyclization are equal both at N-2 [15] and N-4 [16,17].

Considering all these observations, we have now investigated the reaction of 3-hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indoles with ethyl acetoacetate and report the formation of a novel heterocyclic system (Scheme I).

3-Hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indoles **1** were condensed with ethyl acetoacetate in absolute ethanol. From the spectral data, the product was found to be a hydrazone and not a pyrazolone. This hydrazone may be formed either with the carbonyl group of the ester molecule condensing with hydrazine giving the intermediate **2** or the ester part condensing with heteryl hydrazine giving intermediate **2'**. It has been found that condensation follows

the first route affording ethyl-3-oxobutanoate [5*H*-1,2,4-triazino[5,6-*b*]indole-3-yl]hydrazone (**2**) in 90-95% yield. This agrees with structural assignments. In the ir spectra, additional absorption bands in the region 3480-3250 (>NH) and 1710 (>C=O) cm^{-1} are observed. In the pmr spectra signals at δ 1.1-1.3 (t, 3H, $\text{CH}_2\text{-CH}_3$), 2.2 (s, 3H, N=C-CH_3), 3.4 (s, 2H, $\text{N=CH}_2\text{-C=O}$), 4.2-4.4 (q, 2H, $\text{-CH}_2\text{-CH}_3$), 6.9-7.6 (m, 4H, aromatic protons) and 10.1 (b, 1H, NH) ppm are observed. In the mass spectrum of **2a**, the molecular ion peak was observed at m/z 312 and in **2c** at m/z 330, corresponding to their molecular weight.

Compound **2** on alkaline hydrolysis afforded the corresponding acid **3** in 80-84% yield. This was supported by the appearance of hydroxyl absorption in the ir spectra at 3080-2800 cm^{-1} along with NH absorption and disappearance of a quartet and a triplet in pmr spectra.

On refluxing a solution of **3** in glacial acetic acid, a dehydrocyclization reaction yielded a variety of products depending upon the substituents in the indole ring. Cyclization of **3a** ($\text{R} = \text{R}^1 = \text{R}^2 = \text{H}$) furnished two products in a 3:1 ratio. The major compound obtained from glacial acetic acid-insoluble portion displayed characteristic ir absorptions in the region 3330-3150 (>NH) and 1630 (>C=O) cm^{-1} and pmr resonance signals at δ 2.38 (s, 3H, -CH_3) and at δ 3.05 (s, 2H, -CH_2) ppm. The NH proton was observed as a broad signal at δ 10.85 ppm. In mass spectrum, M^+ appears at m/z 266 (100%). On the basis of these spectral data, the compound is identified as a triazepinone derivative. The structure of the compound may be either angular **4a** involving cyclization at N-4 or linear **5a** due to cyclization at N-2. However the position of the carbonyl and the NH absorption at a lower wave number indicated the formation of hydrogen bonded cyclic structure and cyclization at N-4, leading to the formation of 3-methyl-1-oxo-12*H*-1,2,4-triazepino[3',4':3,4][1,2,4]triazino[5,6-*b*]indole (**4a**).

Table I
Analytical Data of 1,2,4-Triazino[5,6-*b*]indole Derivatives

Compound No.	R	R ¹	R ²	MP °C	Yield %	Formula	Analysis %					
							C	H	N	C	H	N
							Calcd.	Found				
2a	H	H	H	186	92	C ₁₅ H ₁₆ N ₆ O ₂	57.69	5.12	26.92	57.65	5.15	26.90
2b	CH ₃	H	H	142	93	C ₁₆ H ₁₈ N ₆ O ₂	58.89	5.52	25.76	58.81	5.56	25.78
2c	H	F	H	275	95	C ₁₅ H ₁₅ FN ₆ O ₂	54.54	4.54	25.45	54.50	4.59	25.42
2d	H	H	CF ₃	224	91	C ₁₆ H ₁₅ F ₃ N ₆ O ₂	50.52	3.94	22.10	50.55	3.90	22.16
3a	H	H	H	268	82	C ₁₃ H ₁₂ N ₆ O ₂	54.92	4.22	29.57	54.95	4.26	29.55
3b	CH ₃	H	H	242	84	C ₁₄ H ₁₄ N ₆ O ₂	56.37	4.69	28.18	56.35	4.66	28.16
3c	H	F	H	294	85	C ₁₃ H ₁₁ FN ₆ O ₂	51.65	3.64	27.81	51.60	3.62	27.87
3d	H	H	CF ₃	286	80	C ₁₄ H ₁₁ F ₃ N ₆ O ₂	47.72	3.12	23.86	47.74	3.10	23.85
4a	H	H	H	282	66	C ₁₃ H ₁₀ N ₆ O	58.64	3.75	31.57	58.60	3.72	31.59
4b	CH ₃	H	H	302	76	C ₁₄ H ₁₂ N ₆ O	60.00	4.28	30.00	60.05	4.25	30.02
5a	H	H	H	298	18	C ₁₃ H ₁₀ N ₆ O	58.64	3.75	31.57	58.62	3.78	31.61
6c	H	F	H	300	62	C ₁₁ H ₈ FN ₅ O	54.32	2.46	28.80	54.36	2.48	28.77
6d	H	H	CF ₃	298	72	C ₁₂ H ₈ F ₃ N ₅ O	49.14	2.04	23.89	49.17	2.08	23.86
7c	H	F	H	300	24	C ₁₁ H ₈ FN ₅ O	54.32	2.46	28.80	54.34	2.40	28.84

The acid-soluble portion yielded a yellow compound in low yield. This compound shows an ir absorption at 3440-3380 (>NH) and 1710 (>C=O) cm^{-1} . In the pmr spectrum, characteristic signals are observed at δ 2.22 (s, 3H, $-\text{CH}_3$), 2.84 (s, 2H, $-\text{CH}_2$) and at 10.38 (b, 1H, NH) ppm. In the mass spectrum, M^+ appears at m/z 266 (4%) corresponding to the molecular weight of the cyclized triazepinone derivatives, but the fragmentation pattern is different from **4a**. Thus it may be inferred that these two compounds are isomeric triazepinones, differing in the position of cyclization. From these observations, the acid soluble compound is identified as 3-methyl-5-oxo-12*H*-1,2,4-triazepino[4',3':2,3][1,2,4]triazino[5,6-*b*]indole (**5a**) with cyclization at N-2. It is well known from the literature [16,18] that formation of a more benzenoid structure is favoured and on this basis, formation of **4a** as the major product is supported.

Cyclization of **3b** ($\text{R} = \text{CH}_3$, $\text{R}^1 = \text{R}^2 = \text{H}$) afforded a single product **4b** in 76% yield. This compound was also found to be a triazepinone derivative as confirmed by mass spectrum and elemental analyses. In view of the stability of the benzenoid structure, cyclization at N-4 is presumed to be favoured and compound has been tentatively assigned the angular structure **4b**.

Cyclization of **3c** gave two compounds in the acid soluble portion, and unchanged **3c** was recovered from the insoluble portion. Compound **7c** obtained in 24% yield shows characteristic ir absorption bands at 3440-3380 cm^{-1} (>NH) and 1700 (>C=O) and pmr signals at δ 2.82 (s, 2H, $-\text{CH}_2$) and 9.85 (NH) ppm. Surprisingly, the methyl protons did not appear in pmr. The molecular ion peak of this compound appears at m/z 243 (4%). On the basis of these spectral data along with the elemental analyses the product is proposed to be imidazo derivative **6**, **7** instead of expected triazepinone **4**, **5**. Further the presence of free carbonyl and NH absorption in the ir and the low yield suggest the linear structure involving the cyclization at N-2 and has been identified as 7-fluoro-3-oxo-10*H*-1,3-imidazo[3',2':2,3][1,2,4]triazino[5,6-*b*]indole (**7c**).

Compound **6c** obtained in 62% yield exhibits an ir absorption band at 3320-3130 cm^{-1} (>NH) and a hydrogen

bonded carbonyl absorption at 1635 cm^{-1} . The pmr spectrum displays a singlet at δ 3.02 ppm corresponding to methylene proton and no methyl signal was observed in this case also. The NH signal was observed at δ 10.25 ppm. The molecular ion peak was observed at m/z 243 (18%), corresponding to the molecular weight of the imidazolo-triazinoindole derivative. From these data the compound is identified as 7-fluoro-1-oxo-10*H*-1,3-imidazo[2',3':3,4]-[1,2,4]triazino[5,6-*b*]indole (**6c**) having an angular structure.

Further more, the cyclization of **3d** afforded a single product in 72% yield. This has also been identified as an imidazolotriazinoindole. It shows ir absorption at 3330-3160 (>NH) and 1630 (>C=O) cm^{-1} . In the pmr spectrum in addition to aromatic protons, signals are observed at δ 2.86 (s, 2H, $-\text{CH}_2$) and at δ 10.30 ppm due to NH proton. The M^+ appears at m/z 293 (18%). The hydrogen bonded carbonyl and NH absorption and its exclusive formation suggest the angular structure in view of stability and has been identified as 6-trifluoromethyl-1-oxo-12*H*-1,2,4-imidazo[3',4':3,4][1,2,4]triazino[5,6-*b*]indole (**6d**).

The presence and position of fluorine was confirmed by ^{19}F nmr. Fluorine attached to an indole ring was observed as a doublet at δ -115.147 and -115.49 ($^{\text{HF}} = 25.5$ Hz) and the trifluoromethyl group as singlet at -62.968 ppm.

Characteristic ir, pmr and mass spectral data of triazepinotriazinoindole and imidazolotriazinoindole derivatives are given in the Table II and Table III. In the

Table II
Characteristic IR and PMR Spectral Data of
Triazepinotriazinoindole and Imidazolotriazinoindole Derivatives

Compound No.	IR		PMR (ppm, δ)			
	CO	NH	CH_3	CH_2	aromatic	NH
4a	1630	3300-3150	2.38	3.05	6.8-7.6	10.85
4b [a]	1670	-	-	-	-	-
5a	1710	3440-3380	2.22	2.22	6.85-7.7	10.38
6c	1635	3320-3130	-	3.02	6.75-7.75	10.25
6d	1630	3330-3160	-	2.86	6.8-7.8	10.30
7c	1700	3440-3380	-	2.82	6.7-7.6	9.85

[a] The pmr spectrum could not be taken due to very low solubility.

Table III
Mass Fragments of Triazepinotriazinoindole and
Imidazolotriazinoindole Derivatives

Compound No.	m/z (%)							
	266	254	225	186	179	143	128	103
4a	266 (100)	254 (18)	225 (22)	186 (16)	179 (16)	143 (22)	128 (22)	103 (22)
4b	280 (40)	238 (22)	200 (100)	144 (32)	116 (30)	102 (36)	76 (30)	
5a	266 (4)	224 (100)	186 (44)	155 (22)	135 (21)	128 (34)	103 (54)	
6c	243 (18)	242 (5)	204 (100)	175 (24)	161 (16)	148 (32)	121 (42)	78 (30)
6d	293 (18)	292 (100)	254 (9.4)	223 (55)	177 (24)	171 (30)	151 (28)	
7c	243 (4)	242 (22.2)	218 (3)	204 (100)	175 (25.5)	161 (18)	148 (26)	121 (46)

pmr, the presence and position of the *NH* proton has been confirmed by deuterium exchange experiments.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 557 spectrophotometer. The pmr spectra were recorded on a Jeol (model FX 90 Q) at 89.55 MHz using TMS as the external reference and TFA as the solvent. The ¹⁹F nmr spectra were recorded on a Jeol (model FX 90 Q) and taken in DMSO-d₆ at 84.25 MHz. Hexafluorobenzene (at δ -162.9 ppm) was used as the external reference. All chemical shifts are in δ ppm. The mass spectra were recorded on MS-30 and MS-50 Kratos mass spectrometer operating at an ionization potential of 70 eV.

3-Hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indoles **1a-d**.

These were prepared following the method of Joshi *et al.* [5]. Analytical data of new hydrazino derivatives are as follows:

Compound **1b** had mp 211°, yield 78%.

Anal. Calcd. for C₁₀H₁₀N₆: C, 56.07; H, 4.67; N, 39.25. Found: C, 56.02; H, 4.71; N, 39.28.

Compound **1d** had mp 232°, yield 64%.

Anal. Calcd. for C₁₀H₇F₃N₆: C, 44.77; H, 2.61; N, 31.34. Found: C, 44.72; H, 2.66; N, 31.30.

Ethyl 3-Oxobutanoate[5*H*-1,2,4-Triazino[5,6-*b*]indole-3-yl]hydrazones **2a-d**.

3-Hydrazino-5*H*-1,2,4-triazino[5,6-*b*]indole (0.01 mole) was refluxed with ethyl acetoacetate (0.01 mole) in absolute ethanol (50 ml) for 5 hours. The reaction mixture was concentrated. On cooling, a cream coloured compound separated which was filtered, dried and recrystallized from ethanol.

3-Oxobutanoic Acid [5*H*-1,2,4-Triazino[5,6-*b*]indole-3-yl]hydrazones **3a-d**.

A solution of ethyl 3-oxobutanoate[5*H*-1,2,4-triazino[5,6-*b*]indole-3-yl]hydrazone (0.01 mole) and sodium hydroxide (0.02 mole) in ethanol:water (1:1), 50 ml, was refluxed for 4 hours and filtered. The filtrate was acidified with dilute hydrochloric acid to give a solid compound which was filtered, dried and recrystallized from ethanol to give the desired compound.

Synthesis of 3-Methyl-1-oxo-12*H*-1,2,4-triazepino[3',4':3,4][1,2,4]-triazino[5,6-*b*]indole (**4a**) and 3-Methyl-5-oxo-12*H*-1,2,4-triazepino[4',3':2,3][1,2,4]triazino[5,6-*b*]indole (**5a**).

A solution of **3a** (0.01 mole) in glacial acetic acid (50 ml) was refluxed for 44 hours. The solution was cooled to 0°. On cooling, a brown coloured compound separated which was filtered, dried and recrystallized from ethanol. This compound has been identified as **4a**, mp 282°, yield 66%.

The filtrate from the above reaction was concentrated and poured into water. The precipitated compound was filtered, dried and purified by column chromatography using silica gel as adsorbent. The yellow coloured compound was obtained in the fraction benzene:ethyl acetate (1:4) and is referred to as **5a**, mp 298°, yield 18%.

Compound **4b** has been synthesized similarly by refluxing **3b** in glacial acetic acid for 52 hours. On cooling a solid compound separated which was filtered and purified by column chromatography. Only one product was obtained in the fraction

benzene:ethyl acetate (1:1) as a yellow coloured compound and is identified as 3,12-dimethyl-1-oxo-12*H*-1,2,4-triazepino[3',4':3,4]-[1,2,4]triazino[5,6-*b*]indole (**4b**), mp 302°, yield 76%.

Synthesis of 7-Fluoro-3-oxo-10*H*-1,3-imidazo[3',2':2,3][1,2,4]-triazino[5,6-*b*]indole (**7c**) and 7-Fluoro-1-oxo-10*H*-1,3-imidazo[2',3':3,4][1,2,4]triazino[5,6-*b*]indole (**6c**).

A solution of **3c** (0.01 mole) in glacial acetic acid was refluxed for 46 hours. The solution was concentrated, cooled and poured into water. The separated compound was filtered and dried. The crude compound gave two spots on tlc, which were separated by column chromatography. The first component was obtained in the fraction benzene:ethyl acetate (4:1) as a brownish yellow coloured compound and referred to as **7c**, mp above 300°, yield 24%.

The second component obtained in the fraction benzene:ethyl acetate (1:4) as a brown coloured amorphous compound is referred to as **6c**, mp above 300°, yield 62%.

Compound **7d** has been synthesized as the sole product in the cyclization of **3d** as above. This is purified by column chromatography and obtained in the fraction benzene:ethyl acetate (1:1), mp 298°, yield 72%.

Analytical data of all 1,2,4-triazino[5,6-*b*]indole derivatives which were synthesized are recorded in the Table 1.

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