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Synthesis of Fluorine Containing Tetracyclic Ring Systems: 1,2,4-triazino [3′,4′,3,4] [1,2,4] triazino [5,6-b] Indole and 1,2-4-triazino [4′,3′:2,3] [1,2,4] triazino [5,6-b] Indole

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Tetracyclic ring systems *viz.* 2-methyl-1-oxo-11H-1,2,4-triazino [3′,4′:3,4] [1,2,4] triazino [5,6-b] indole (V) and 3-methyl-4-oxo-11H-1,2,4-triazino [4′,3′:2,3] [1,2,4] triazino [5,6-b] indole (VI) were synthesized by the cyclization of 2-oxo-propionic acid [5H-1,2,4-triazino] [5,6-b] indole-3-yl hydroazone (IV). Cyclization of (IVb) (X = 7-F) and (IVc) (X = 8-F) afforded the angular product (V) exclusively, while cyclization of IVa (no F) and IVd (X = 9-CF_3) gave a mixture of angular (V) and linear products (VI) in the ratio 3 : 1. Compound (IV) was prepared from III on heating with sodium hydroxide in ethanol-water (50 : 50) while the hydrazide (III) was itself obtained by the condensation of 3-hydrazino dervatives (II) with ethyl pyruvate in absolute ethanol. The synthesised compounds may prove to be effective pesticides also.

INTRODUCTION

1,2,4-Triazino [5,6-b] indole derivatives find useful applications in medicinal chemistry[1–3]. Various 3-substituted triazino [5,6-b] indoles have exhibited antiviral and antibacterial activities[4, 5]. Recently, semicarbazones and thiosemicarbazones of triazino indoles were reported as active anti-inflammatory agents[6]. 8-Fluoro and 8-trifluoromethyl analogues of triazino [5,6-b] indoles have been claimed to have antiviral activity.[7]

3-Hydrazino-1,2,4-triazino indoles can undergo cyclization reactions with various reagents leading to the formation of novel tetracyclic ring systems. Earlier, we have studied some of its cyclization reactions[8–10]. However, the reaction of 3-hydrazino-1,2,4-triazino indole with ethyl pyruvate has not been studied so far, though other heterocyclic hydrazines[11, 12] react with it yielding various interesting products. Further, there is some controversy about the structures of the final product when hydrazone of 1,2,4-triazino [5,6-b] indoles are cyclized because the chances of cyclization are equal both at N-2[13] and N-4[14, 15].

Considering all these observations, we have now investigated the novel reaction of 3-hydrazino-1,2,4-triazino [5,6-b] indoles with ethyl pyruvate and report the formation of fluorine containing heterocyclic stystems, 2-methyl-1-oxo-11H-1,2,4-triazino [3′,4′:3,4] [1,2,4] triazino [5,6-b] indole (V) and 3-methyl-4-oxo-11H-1,2,4-triazino [4′,3′: 2,3] [1,2,4] triazino [5,6-b] indole(VI) for the first time. It is interesting to note that mode of cyclization depends on the substituent at indole ring and fluorine again plays a critical role[16–22]. Cyclization of IV with fluorine at 7 or 8 position gives exclusively angular product (V) while cyclization of IV without F substituent or trifluoromethyl group at 9 position gives a mixtures of linear (IV) and angular product (V).

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 577 spectrophotometer (ν_{max} in cm^{-1}). PMR spectra in TFA on a Jeol FX90Q spectrometer at 89.5 MHz using TMS as internal reference and 19_F NMR spectra in TFA on a Jeol FX90Q spectrometer at 84.25 MHz using hexafluorobenzene as an external standard (Chemical Shifts in δ, ppm). Mass spectra were recorded on an MS-50 Kratos mass spectrometer at 70 eV. Purity of the compounds was checked by TLC on silica gel plates.

Ethyl-2-oxo propionate-[5H-1,2,4-triazino [5,6-b] indole-3-yl]-hydrazone (IIIa)

A mixture of 3-hydrazino-5H-1,2,4-triazino [5,6-b] indole (0.01 mole) and ethylpyruvate (0.011 mole) was refluxed in absolute ethanol (50 mL) for 5–6 h. The reaction mixture was cooled, filtered and recrystallized from ethanol to yield yellow crystals (m.p. 360°C; yield 95%).

2-Oxopropionic acid-[5H-1,2,4-triazino [5,6-b] indole-3-yl]-hydrazone(IVa)

IIIa (0.01 mole) and NaOH (0.8 g) was refluxed in water-ethanol mixture (50 mL : 50 mL) for 4 h. On cooling, the solution was acidified with conc. hydrochloric acid and precipitate filtered, recrystallized from ethanol to give the desired compound (m.p. > 360°C; yield 90%).

2-Methyl-1-oxo-11H-1,2,4-triazino [3′,4′: 3,4] [1,2,4] triazino [5,6-b] indole (Va) and 3-Methyl-4-oxo-11H-1,2-4-triazino [4′,3′: 2,3] [1,2,4] triazino [5,6-b] indole (VIa)

A solution of IVa (0.01 mole) in glacial acetic acid was refluxed for 60 h. The reaction mixture was then cooled and filtered. The precipitate obtained was crystallized from acetic acid to give Va (m.p. > 360°C; yield 66%). The volume of filtrate was reduced and on concentration gave orange coloured compound VIa (m.p. 345°C; yield 19%).

RESULTS AND DISCUSSION

Fluorine containing 1,2,4-triazino [5,6-b] indole-3-thione(I) on refluxing with hydrazine hydrate, afforded 3-hydrazino derivative (II). 3-Hydrazino-5H-1,2,4-

triazino [5,6-b] indole (II) was condensed with ethyl pyruvate 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 III or the ester part condensing with heteryl hydrazine giving intermediate III′. It has been found that condensation follows the first route affording ethyl-2-oxopropionate-[5H-1,2,4-triazino [5,6-b] indole-3-yl] hydrazone (III). This agrees with structural assignments. In the IR spectra, additional absorption bands in the region 3480–3250 (>NH) and 1705 (>C═O) cm^{-1} are observed.

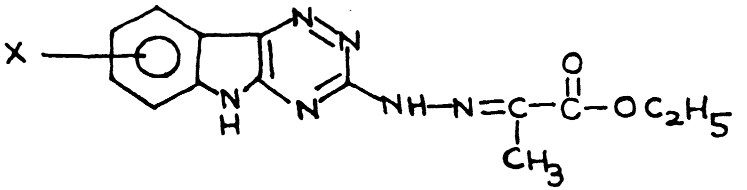
The PMR spectra showed signals at δ 0.6–0.9 (t, 3H, —CH_3), 1.9 (s, 3H, N═C—CH_3), 3.8–4.1 (q, 2H, —CH_2), 7.0–7.6 (m, 4H, Ar-H) and 10.1 (br, s, 1H, NH). Compound III on heating with sodium hydroxide in ethanol-water undergoes hydrolysis to afford 2-oxopropionic acid-[5H-1,2,4-triazino [5,6-b] indole-3-yl] hydrazone (IV) in 90% yield. This compound could be directly prepared by the reaction of II and pyruvic acid; however, former reaction had a better yield. Hydrolysis of compound III was confirmed on the basis of appearance —OH absorption in IR spectrum at 3150–2950 along with NH absorption and disappearance of PMR signals at δ 0.6–0.9 (—CH_3) and 3.8–4.1 (—CH_2).

Refluxing a solution of IV in glacial acetic acid, *via* dehydrocyclization reaction, gave the cyclized compounds V and VI involving the cyclization at N-4 to produce V or at N-2 to produce VI depending upon the substituents in the indole ring. In our experiments, we have observed that cyclization of IVb and IVc (with fluorine at 7 and 8 position) gives exclusively angular product (V), while cyclization of IVa and IVd (with no fluorine and trifluoro-methyl group at 9-position) gives a mixture of angular (V) and linear (VI) product in the ratio 3:1. The two isomers are separated by fractional crystallization.

The compounds isolated from the reaction of IVb, IVc and from the acetic acid insoluble portion in case of Va and Vd showed characteristic absorption in the IR spectra at 3330–3150 (NH), 1630 (C═O) cm^{-1}. The shifting of carbonyl and the NH absorption to lower wave number indicates the formation of hydrogen bonded cyclic structure (V) involving the cyclization at N-4[10]. The PMR spectra exhibit resonance signals at δ 2.45 (s, 3H, —CH_3), 7.0–8.1 (m, Ar-H), 10.4 (b, s, 1H, NH). The mass spectrum of product where X═H has M^+ at m/z 252 (25%) and base peak at 224 (M^+—CO) (100%). In view of the stability of the benzenoid structures, cyclization at N-4 is presumed to be favoured and compounds have been assigned the angular structure (V).

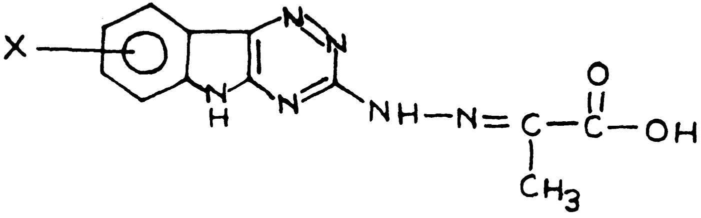
The acid soluble portion in case of IVa and VId yielded orange compound in low yield. This compound shows IR absorptions at 3440–3380 ν(NH) and 1730 ν(C═O) cm^{-1}. The PMR spectra showed characteristic signals at δ 2.1 (s, 3H, —CH_3), 6.5–8.1 (m, Ar—H), 10.38 (br s, 1H, NH). The mass spectrum of product X═H has M^+ at m/z 252 (96.1%). It is well known from the literature[19] that formation of a more benzenoid structure is favoured and on this basis, formation of VIa and VId as the minor products are supported.

TABLE-1



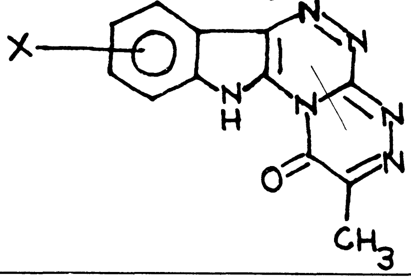
S. No.	Substituent X	Chemical name	Physical characteristics			IR Spectral data (cm^{-1})		PMR Spectral data				
			Nature	m.p. (°C)	(%) yield	ν(N—H)	ν(C=O)	—CH$_3$	N=C—CH$_3$	—OCH$_2$	Aromatic protons	—NH
IIIa	H	Ethyl-2-oxopropionate-[5H-1,2,4-triazino [5,6-b] indole-3-yl]-hydrazone.	Yellow crystals	360	95	3480–3250	1705	0.6–0.9 3-H (t)	1.9 3-H (s)	3.8–4.1 2-H (q)	7.0–7.6 4-H (m)	10.1 2-H (br, s)
IIIb	7-F	Ethyl-2-oxopropionate-[7-fluoro-5H-1,2,4-triazino [5,6-b] indole-3-yl]-hydrazone	Yellow crystals	260	85	3460–3240	1700	0.65–0.90 3-H (t)	1.8 3-H (s)	3.7–4.1 2-H (q)	7.2–7.7 4-H (m)	10.2 2-H (br, s)
IIIc	8-F	Ethyl-2-oxopropionate-[8-fluoro-5H-1,2,4-triazino [5,6-b] indole-3-yl]-hydrazone	Dark yellow crystals	285	90	3480–3300	1690	0.5–0.85 3-H (t)	1.85 3-H (s)	3.9–4.2 2-H (q)	7.4–7.8 4-H (m)	9.95 2-H (br, s)
IIId	9-CF$_3$	Ethyl-2-oxopropionate-[9-trifluoro methyl-5H-1,2,4-triazino [5,6-b] indole-3-yl]-hydrazone	Yellow crystals	239	80	3450–3220	1710	0.6–0.85 3-H (t)	2.1 3-H (s)	3.5–4.0 2-H (q)	7.1–7.7 4-H (m)	10.0 2-H (br, s)

TABLE-2



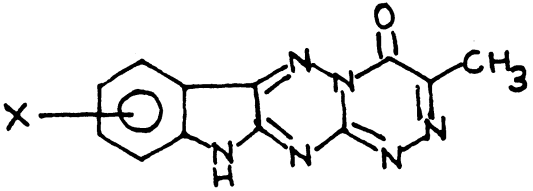
S. No.	Substituent X	Chemical name	Physical characteristics			IR spectral data (cm^{-1})	PMR Spectral data		
			Nature	m.p. (°C)	(%) yield	ν(OH) and ν(N-H)	N=C—CH$_3$	Aromatic protons	—NH
IVa	H	2-Oxopropionic acid-[5H-1,2,4-triazino-[5,6-b] indole-3-yl]-hydrazone	orange	360	90	3150–2950	2.0 3-H (s)	7.0–7.6 4-H (m)	9.8–10.1 2-H (br, s)
IVb	7-F	2-Oxopropionic acid-[7-fluoro-5H-1,2,4-triazino [5,6-b] indole-3-yl]-hydrazone	Light orange	329	80	3260–2900	1.8 3-H (s)	7.2–7.5 4-H (m)	10.0–10.2 2-H (br, s)
IVc	8-F	2-Oxopropionic acid-[8-fluoro-5H-1,2,4-triazino [5,6-b] indole-3-yl]-hydrazone	orange	280	87	3200–2950	2.2 3-H (s)	7.1–7.8 4-H (m)	9.6–9.9 2-H (br, s)
IVd	9-CF$_3$	2-Oxopropionic acid-[9]-trifluoromethyl-5H-1,2,4-triazino [5,6-b] indole-3-yl]-hydrazone	orange	330	78	3250–3000	2.1 3-H (s)	7.0–7.4 4-H (m)	9.9–10.2 2-H (br, s)

TABLE-3



S. No.	Substituent X	Chemical name	Physical characteristics			IR spectral data (cm^{-1})		PMR spectral data		
			Nature	m.p. (°C)	(%) yield	ν(NH)	ν(C=O)	—CH_3	Aromatic protions	—NH
Va	H	2-Methyl-1-oxo-11H-1,2,4-triazino [3′,4′ : 3,4] [1,2,4]-triazino [5,6-b] indole	Yellow	> 360	66	3250–3150	1630	2.45 3-H (s)	7.0–8.1 4-H (m)	10.4 1-H (br, s)
Vb	7-F	7-Fluoro-2-methyl-1-oxo-11H-1,2,4-triazino [3′,4′ : 3,4] [1,2,4]-triazino [5,6-b] indole	Yellow	360	75	3100–2950	1645	2.39 3-H (s)	7.2–8.2 4-H (m)	10.2 1-H (br, s)
Vc	8-F	8-Fluoro-2-methyl-1-oxo-11H-1,2,4-triazino [3′,4′ : 3,4] [1,2,4]-triazino [5,6-b] indole	Light yellow	360	78	3300–3200	1660	2.40 3-H (s)	7.1–7.9 4-H (m)	9.9 1-H (br, s)
Vd	9-CF_3	9-Trifluoromethyl-2-methyl-1-oxo-11H-1,2,4-triazino [3′,4′ : 3,4] [1,2,4]-triazino [5, 6-b] indole	Yellow	260	65	3280–3000	1650	2.42 3-H (s)	7.3–8.4 4-H (m)	10.0 1-H (br, s)

TABLE-4



S. No.	Substituent X	Chemical name	Physical characteristic			IR spectral data (cm^{-1})		PMR spectral data		
			Nature	m.p. (°C)	(%) yield	ν(N—H)	ν(C═O)	—CH_3	Aromatic protons	—NH
VIa	H	3-Methyl-4-oxo-11H-1,2,4-triazino [4',3' : 2,3] [1,2,4] triazino [5,6-b] indole	Orange	345	19	3440–3380	1730	2.1 3-H (s)	6.5–8.1 4-H (m)	10.38 1-H (br, s)
VIb	9-CF_3	9-Trifluoromethyl-3-methyl-4-oxo-11H-1,2,4-triazino [4',3' : 2,3] [1,2,4] triazino [5,6-b] indole	Orange	340	20	3420–3400	1720	2.0 3-H (s)	6.7–8.2 4-H (m)	10.25 1-H (br, s)

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