REACTIONS OF 3-HYDRAZINO-5H-1,2,4-TRIAZINO [5,6-b] INDOLES WITH TRIFLUOROACETIC ANHYDRIDE, ACETYLACETONE, HEXAFLUOROACETYLACETONE AND ACETOPHENONE

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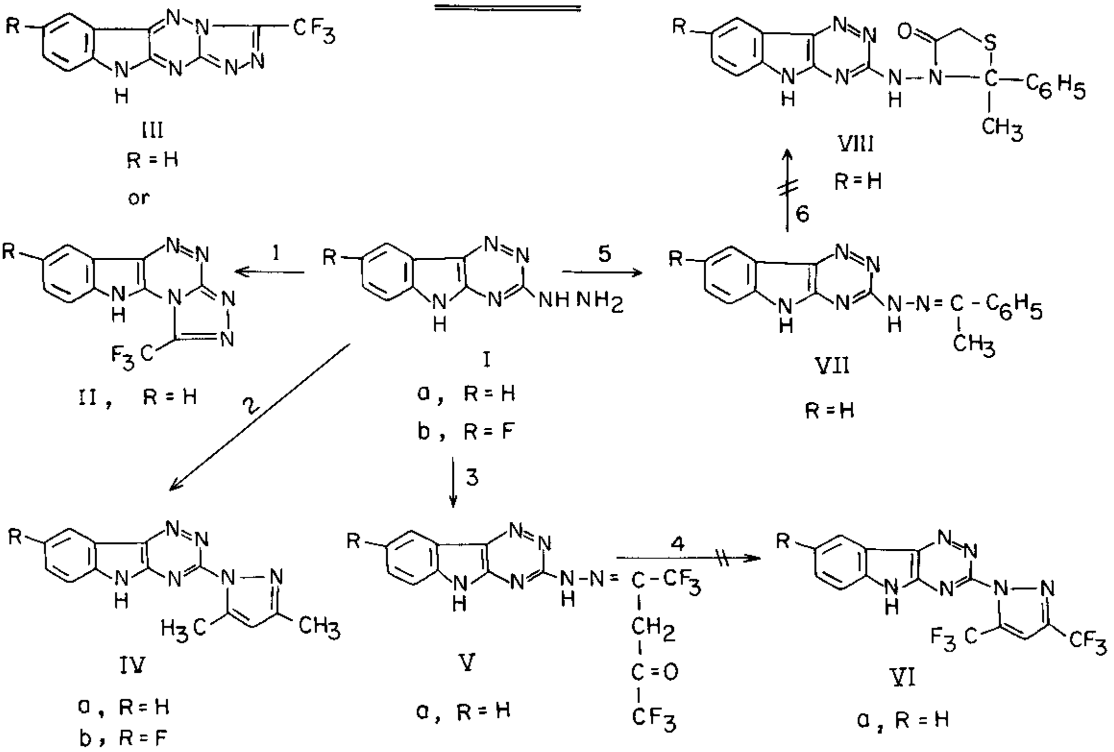
Abstract - 3-Hydrazino-5H-1,2,4-triazino [5,6-b] indole affords a tetracyclic ring system containing compound: 3-trifluoromethyl-10H-1,2,4-triazolo [4',3':2,3] [1,2,4] triazino [5,6-b] indole with trifluoroacetic anhydride. 3-Hydrazino derivatives, react with acetylacetone, in absolute ethanol giving rise to 3- [1-(3,5-dimethylpyrazolyl)] -5H-1,2,4-triazino [5,6-b] indoles while the reaction with hexafluoroacetylacetone gives corresponding hydrazone instead of expected 3- [1-(3,5-bis(trifluoromethyl)pyrazolyl)] -5H-1,2,4-triazino [5,6-b] indole. 3-Hydrazino derivatives also condense with acetophenone but the resulting hydrazone does not produce thiazolidinone with mercaptoacetic acid. All the synthesized compounds have been characterized on the basis of elemental analyses and ir, pmr, ^{19}F nmr and mass spectral studies.

Therapeutic importance of 1,2,4-triazino [5,6-b] indole derivatives has been studied by several investigators[1-4]. Various 3-substituted triazino [5,6-b] indoles have exhibited antiviral and antibacterial activities[5,6]. Some 5-substituted 3-hydrazino-1,2,4-triazino [5,6-b] indoles are effective in hypertension[7] while some others have been used as anesthetic and analgesic[8].

These observations prompted us to synthesize various novel derivatives of 1,2,4-triazino [5,6-b] indole (SCHEME-I). The synthesis of 3-hydrazino-5H-1,2,4-triazino [5,6-b] indoles has recently been reported by us[9,10]. 3-Hydrazino-5H-1,2,4-triazino [5,6-b] indole (Ia) was treated with trifluoroacetic anhydride in DMF and the resultant product, on being refluxed in glacial acetic acid, afforded

SCHEME - I



1. $(CF_3CO)_2O$; 2. $CH_3COCH_2COCH_3$; 3. $CF_3COCH_2COCF_3$; 4. PPA ;
5. $C_6H_5COCH_3$; 6. $HSCH_2COOH$

a compound which shows characteristic absorption bands in ir spectrum at 3200-3250 (broad), 1600-1640 cm^{-1} and M+ at m/e 278. Pmr spectrum could not be detected due to its insolubility in all common organic solvents. On the basis of these observations, the compound may be either 3-trifluoromethyl-10H-1,2,4-triazolo [4',3':2,3] [1,2,4] triazino [5,6-b] indole (III) or 1-trifluoromethyl-10H-1,2,4-triazolo [3',4':3,4] [1,2,4] triazino [5,6-b] indole (II), but the chances of cyclization are more at N-2 because of higher nucleophilicity of N-2 than that of N-4. Therefore, the cyclization is likely to take place at N-2 suggesting structure III for the desired compound.

Further, the reaction of 3-hydrazino-5H-1,2,4-triazino [5,6-b] indole was investigated with 1,3-diketones. When 3-hydrazino derivative (Ia) was treated with acetylacetone in absolute ethanol, a compound having characteristic ir absorption bands at 3250-3300, 2960, 1600-1640 cm^{-1} and pmr signals at δ8.4, 7.7, 6.53, 2.53 and 2.91 ppm was obtained. On the basis of characteristic pyrazolyl methine resonance signal at δ 6.53 ppm and other spectral data, it has been identified as 3-[1-(3,5-dimethylpyrazolyl)]-5H-1,2,4-triazino [5,6-b] indole(IVa). A similar reaction took place with 8-fluoro-3-hydrazino-5H-1,2,4-triazino [5,6-b] indole. But when hexafluoroacetylacetone was used as condensing agent, instead of acetylacetone with Ia, the resultant product does not show characteristic pyrazolyl methine resonance signal and has M^+ at m/e 390. Therefore, it is not the expected 3-[1-(3,5-bis(trifluoromethyl)pyrazolyl)]-5H-1,2,4-triazino [5,6-b] indole (VIa) but a hydrazone of hexafluoroacetylacetone and 3-hydrazino derivative (Va) as confirmed by ir, pmr and mass spectral data. Further, an attempted cyclization of this hydrazone with PPA failed.

3-Hydrazino-5H-1,2,4-triazino [5,6-b] indole also condenses with acetophenone giving rise to the corresponding hydrazone (VII). Shafie[11] has reported the cyclization of hydrazones with mercaptoacetic acid to yield thiazolidone derivatives, this hydrazone was, therefore, further refluxed with mercaptoacetic acid, in toluene, expecting a thiazolidinone derivative (VIII), but the experiment was unsuccessful.

Experimental Procedure - All melting points are uncorrected. Ir spectra were recorded on Perkin-Elmer (model-557) in KBr pellets. Pmr (60MHz) and ^{19}F nmr (56.4 MHz) spectra were recorded on Perkin-Elmer (model-RB.12) using TMS and TFA as external references, respectively. The purity of all compounds was checked by tlc done on silica gel plates.

3-Hydrazino-5H-1,2,4-triazino [5,6-b] indoles (Ia,b) - Either of the 1,2,4-triazino [5,6-b] indole-3-thione (2.0 g) was refluxed with hydrazine hydrate (15 ml) for 4-5 hr. On cooling, crystals separated out, which were filtered and washed with ethanol to afford the desired compound.

Ia ; mp 276-77° (lit.[7] mp 278-79°)
Ib ; mp 295-97° (lit.[10] mp 295-97°)

3-Trifluoromethyl-10H-1,2,4-triazolo [4',3':2,3] [1,2,4] triazino [5,6-b] indole(III)-

To a solution of 3-hydrazino-5H-1,2,4-triazino [5,6-b] indole (2.0 g, 0.01 mole) in DMF (30 ml), trifluoroacetic anhydride (2.5 g, 0.012 mole) was added with stirring at 15-20°. The solid obtained was filtered and refluxed with glacial acetic acid

(15 ml) for 5 hr. On cooling, it afforded the desired compound which was recrystallized from DMF, mp 343°, yield 1.4g (50%)(Found: N, 30.32, $C_{11}H_5F_3N_6$ requires N, 30.21%). $\nu_{max}^{cm^{-1}}$ 3200-3250(NH broad),1600-1640(C=N,N=N),1000-1400(CF_3);M^+at m/e 278.

3-[1-(3,5-Dimethylpyrazolyl)]-5H-1,2,4-triazino[5,6-b]indole(IVa)- 3-Hydrazino-5H-1,2,4-triazino[5,6-b]indole (2.0g, 0.01 mole) was refluxed with acetylacetone (1.0g, 0.01 mole) in absolute ethanol (40 ml) for 5 hr. The solution, on cooling, gave a white compound. It was filtered and recrystallized from ethanol, mp 304°, yield 1.72g (65%)(Found: N, 31.46, $C_{14}H_{12}N_6$ requires N, 31.43%). $\nu_{max}^{cm^{-1}}$ 3250-3300 (NH), 1600-1640 (C=N, N=N); pmr (TFA): δ8.4(NH), 6.53 (pyrazolyl CH), 7.7 (aromatic) and 2.53, 2.91 ppm (both CH_3).

8-Fluoro-3-[1-(3,5-dimethylpyrazolyl)]-5H-1,2,4-triazino[5,6-b]indole(IVb)- It was obtained by the reaction of Ib with acetylacetone following the procedure as in IVa, mp 320°, yield (68%)(Found: N, 29.34, $C_{14}H_{11}FN_6$ requires N, 29.78%). $\nu_{max}^{cm^{-1}}$ 3240-3300(NH), 1600-1640 (C=N, N=N); pmr (TFA): δ8.2(NH), 6.4 (pyrazolyl CH) 7.6 (aromatic) and 2.5, 2.9 ppm (both CH_3).

Hydrazone of 3-hydrazino-5H-1,2,4-triazino[5,6-b]indole and hexafluoroacetylacetone(V) - A mixture of 3-hydrazino-5H-1,2,4-triazino[5,6-b]indole (2.0 g, 0.01 mole) and hexafluoroacetylacetone (2.08g, 0.01 mole) was refluxed in absolute ethanol for 5 hr. On cooling, yellow flakes were obtained, which were filtered and recrystallized from ethanol, mp 248°, yield 2.73 g (70%)(Found: N, 21.24, $C_{14}H_8F_6N_6O$ requires N, 21.53%). $\nu_{max}^{cm^{-1}}$ 3250, 3080-3160 (both NH), 1640(C=O),1600-1620(C=N, N=N), 1000-1400(CF_3); pmr (TFA): δ 3.65(CH_2), 7.52(aromatic), 8.04 and 9.12 (both NH); M^+ at m/e 390; ^{19}F nmr (TFA): δ-10.0 ($-\overset{O}{\overset{\|}{C}}-CF_3$) and 1.2 ppm($-\overset{N}{\overset{\|}{C}}-CF_3$). Further, this hydrazone was heated for 8 hr with PPA and poured into water and the original compound was again recovered.

Hydrazone of 3-hydrazino-5H-1,2,4-triazino[5,6-b]indole and acetophenone (VII) - A mixture of Ia and acetophenone was refluxed in ethanol in molar ratio for 4 hr, cooled and filtered, mp 311°, yield(80%)(Found: N, 27.42, $C_{17}H_{14}N_6$ requires N,27.81%). $\nu_{max}^{cm^{-1}}$ 3400, 3100(both NH), 1600-1640(C=N, N=N). The hydrazone VII was further refluxed for 15 hr with mercaptoacetic acid in dry toluene, but on workup the hydrazone was obtained as such.

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