Synthesis of 6-(P-Halo-Benzyl)-1,2,4-Triazine-3,5(2H,4H) Dithiones Having Potential Antimicrobial Activity

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Summary: Starting from p-halo-benzaldehyde, five-step syntheses of 6-(p-halo-benzyl) 1,2,4 triazine-3,5 (2H,4H) dithiones VI(a-c) have been described according to scheme 1. The spectroscopic data and antimicrobial activity of these compounds have also been reported.

Several 1,2,4-triazines show pronounced antimalarial [1a-c], antimicrobial [2] and antiviral activity [3]. Synthesis of 3,5-diamino-6-(3,4,5-trimethoxy benzyl)-1,2,4 triazine [4] and many 3,5-disubstituted-6-benzyl-1, 2,4-triazines [5] have already been reported. The pharmacological action of several 3-mercapto- and 3,5-dioxo-1,2,4-triazines on central nervous system has been studied [6]. Some of them also exhibit tuberculastic activity [7] as well as antiviral activity [8].

The apparent biological importance of substituted 1,2-dihydro-1,3,5-triazines [1a] and 2,4-dihydro-1,2,4-triazines [9] led us to synthesise 6-(p-halobenzyl)-1,2,4-triazines 3,5 (2H, 4H)-dithiones VI(a-c). Since it is also well established [1c] that electron withdrawing atoms or groups in the 6-phenyl substituent of triazine lead to exhibition of enhanced antimicrobial and antimalarial activity, halogens were selected as substituents at p-position of the 6-benzyl group.

Our initial approach involved the preparation of 4-halo-phenyl pyruvic acids III(a-c) from corresponding 4-halo-benzyldehyde I(a-c) via 2-phenyl-4(4'-halo-benzylidine)-2-oxazoline-5-ones II(a-c). (scheme 1). The procedure used for the preparation of azalactones II(a-c) was similar to that reported by Buck and Ide [10]. The conversion of azalactones to pyruvic acids III(a-c) was accomplished in good yield by base hydrolysis using sodium hydroxide. The resulting keto-acids and benzoic acids were separated by saturation with sulphur dioxide gas as reported in the literature [11].

The reaction of pyruvic acids III (a-c) with thio-semicarbazide in ethanol in the presence of glacial acetic acid afforded thiosemicarbazones IV (a-c) which were further cyclized on refluxing with aqueous potassium carbonate to give 3-thioxo-6(p-halo-benzyl)-1,2,4-triazine (2H,4H)-5-ones V(a-c). The final thiation steps were carried out by treatment of these compounds with phosphorous pentasulphide in pyridine. The percentage yields of 6-(p-halobenzyl)-1,2,4-triazine-3,5-(2H,4H)-dithiones ranged between 53-68%. All the intermediate compounds were identified by spectroscopic methods and comparison with the reported physical data in the case of known compounds. The preparation and spectroscopic data of 3-thioxo-triazine V(a-c) and dithiones IV(a-c) are reported here in detail.

The IR-spectra of V(a-c) in KBr showed weak bands of NH bond at 3320-3460 cm^{-1}, strong C=O absorption in the region 1677-1678 cm^{-1} and C=S

absorption at 1520-1527 cm^{-1}. Lack of OH absorption band near 3600 cm^{-1} and mercapto group (SH) in the region of 2600 cm^{-1} clearly indicated that these compounds exist purely in the keto form, at least in solid state. Attempts were made to run the IR spectra in solution but the compounds were too insoluble in most of the solvents. The ultraviolet spectra in methanol showed absorption maxima ranging from 340-346 nm for different compounds. The spectra in methanol containing 10% hydrochloric acid were identical to that recorded in methanol; however the spectra in methanol containing 10% sodium hydroxide showed shifting of absorption bands. It can be concluded that the compound exist as keto-form in solid state and in neutral and acidic medium but changes over to enolic form in alkaline medium. The results of IR and UV spectra are in accordance to those reported in literature [12]. The NMR spectra were in accordance to the proposed structure. Singlets at 13 15-13 17 ppm showed N_2-H proton and another at 13.28 - 13.30 ppm of N_4-H proton. The mass spectra of all these compounds showed mass peak of 100% intensity. The general fragmentation pattern was also satisfactory.

The IR spectra of 6-(p-halobenzyl) 1,2,4-triazines-3,5(2H,4H) dithiones IV(a-c) showed prominent C=S vibrational frequencies at 1530-1535 cm^{-1}. UV absorption spectra were analogous to V(a-c) showing prominent shifts in alkaline solution confirming the thiolactam structure at least in neutral solution. The NMR spectra also resembled the previously mentioned series V(a-c). The mass spectra of these compounds showed 100% mass peak. Unlike V(a-c) M^+-NH peak was quite prominent.

The antimicrobial activity of dithiones VI(a-c) was tested with 1% solution in nutrient agar media against a number of micro-organisms. The results are summarized in Table 1.

The toxicity tests were carried out on Albino rats under normal light and temperature. 2 mg of each compound was administered per one gram body weight to the animal. After about 1/2 hour the animal became lethargic for one hour or so but resumed normal activity very soon. The dissection of these animals after 48 hours showed no abnormality.

Experimental

The infrared spectra were recorded on a Unicam SP-200 IR spectrophotometer. For ultraviolet spectra, Unicam SP-800 UV spectrophotometer was used. The NMR spectra were recorded on a Jeol-PMX-60 spectrometer and mass spectra were recorded on VG Micromass MM 12 mass spectrometer. The melting points were determined on Thomas-Hoover Unimelt capillary melting point apparatus.

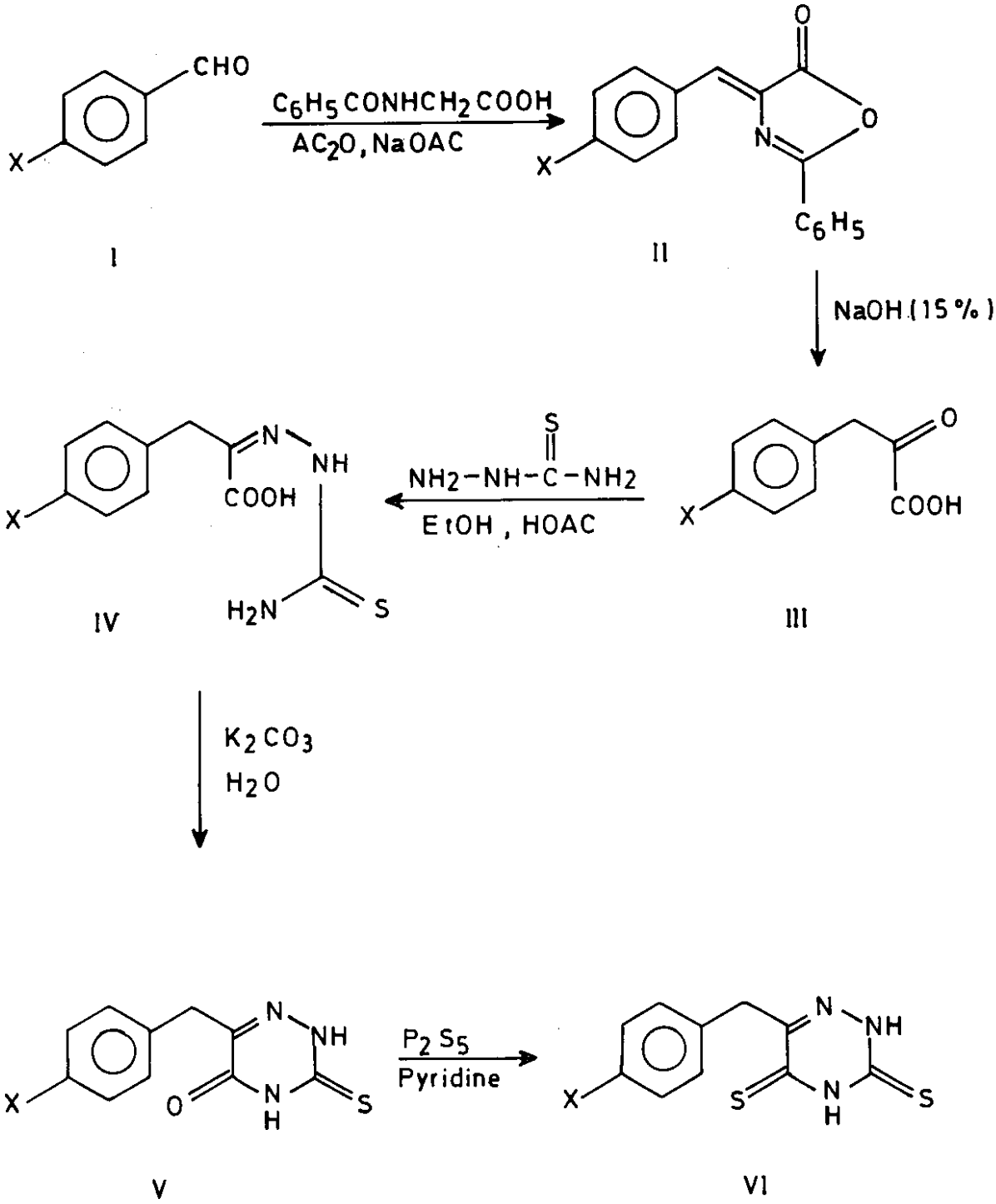
2,4-Dihydro-3-thioxo-6-(p-halo-benzyl)-1,2,4-triazine-5-ones. V(a-c)

General Procedure

A mixture of (4-halo-phenyl)-pyruvic acid-2-thiosemicarbazone (0.1 mole), potassium carbonate (26.6 g) and water (250 ml) was refluxed for two hours. The solution was cooled to room temperature and treated with glacial acetic acid until effervescence seized to occur. The white solid formed was collected by filtration and crystallized from ethanol.

2,4-Dihydro-3-thioxo-6-(p-fluoro-benzyl)1,2,4-triazine-5-one. (Va)

White needles, m.p. 182°C, 90% yield. IR spectrum (KBr) ν cm^{-1} 3390



X = F (a)
= Cl (b)
= Br (c)

SCHEME 1

Table-1

No.	Compound	S.typhi	B.sub	E.coli.	Sh.dy.	Vib.chol.	B.cer.	B.pumi	S.lute
1.	VI(a)	+	++	++	++	+	+	++	++
2.	VI(b)	+	++	++	+	++	+	++	+
3.	VI(c)	+	+	-	-	+	+	++	+

+ = Antimicrobial - = Inactive

Abbreviations	Full name		
1. S.typhi	Solmonella typhi	5. Vib.chol.	Vibrio cholera
2. B.sub.	Bacillus sublillis	6. B.cer.	Bacillus cereus
3. E.coli	Escherichia coli	7. B.pumi	Bacillus pumilus
4. Sh.dy.	Shigella clysenterial	8. S.lute	Sarcina lutea

(NH), 3050, 3250 (C-H), 1678 (C=O), 1592 (C=C, C=N), 1527, 1231 (C=S), 1095 (Ar-F). UV spectrum (CH_3OH) λ_{max} nm (ε), 340 (30121), (10 % HCl in CH_3OH) 342, (10% NaOH in CH_3OH) 350, 310, 295. NMR spectrum (DMSO-d_6) δ(ppm) 3.91 (s, 2H, Ar-CH_2), 7.15 (d, 2H, ArH, J = 10 Hz), 7.33 (d, 2H, Ar-H, J = 10 Hz), 13.17 (s, H, N_2-H), 13.30 (s, H, N_4-H). Mass spectrum m/z (relative intensities) 238 (M^+, 100), 218 (13), 194 (11), 150 (6.2), 135 (45.2), 131 (8), 116(23.7), 109 (64.2), 83 (52.2), 90 (15), 77 (20), 51 (18), 43 (80).

2,4-Dihydro-3-thioxo-6(p-chlorobenzyl)1,2,4-triazine-5-one V (b)

Greenish yellow needles, m.p. 216-7, 71% yield, IR spectrum (KBr) νcm^{-1}; 3380 (NH), 3200-3050 (CH), 1679 (C=O), 1592 (C=C, C=N), 1527, 1231 (Ar-Cl) (C=S), 1090 (Ar-Cl). UV spectrum (CH_3OH) λ_{max} nm (ε), 343 (26533), (10 % HCl in CH_3OH) 342, (10 % NaOH in CH_3OH) 362, 315, 300. NMR spectrum (DMSO-d_6) δ (ppm) 3.90 (s, 2H, Ar-CH_2), 7.25 (d, 2H, Ar-H. J = 8 Hz), 7.38 (d,2H, Ar-H. J = 8-Hz), 13.18 (S,H,N_2-H), 13.35 (S,H,N_4-H). Mass spectrum m/z (relative intensities) 253 (M^+,100), 218 (16.6), 166(6), 151 (26), 131 (10), 116 (35.6), 125 (55.2), 99 (9.1), 90 (20), 77 (21), 51 (19.8), 43 (82).

2,4-Dihydro-3-thioxo-6-(p-bromo-benzyl) 1,2,4-triazine-5-one V(c)

Dirty green needles, m.p. 223-4° C, 84 % yield. IR spectrum (KBr) νcm^{-1} 3400 (NH), 3160-3050 (CH), 2910 (CH), 1677 (C=O), 1590 (C=C, C=N), 1520, 1228 (C=S), 1064 (Ar-Br). UV spectrum (CH_3OH) λ_{max} nm (ε) 346 (19.608), (10 % HCl in CH_3OH) 345, (10 % NaOH in CH_3OH) 351, 310, 298. NMR spectrum (DMSO-d_6) δ (ppm) 3.91 (s,2H, Ar-CH_2), 7.27 (d, 2H, Ar-H. J=7 Hz), 7.54 (d, 2H, Ar-H. J=7 Hz), 13.20 (s,H, N_2-H), 13.38 (s,H, N_4-H). Mass spectrum m/z (relative

intensities), 298 (M^+,100), 218 (15.5), 225(8), 211(7.2), 196 (27.2), 131 (10), 116(36), 170(22), 124 (10.4), 90(22), 77(22), 51(19), 43 (60).

6-(p-Halobenzyl)1,2,4-triazine-3,5 (2H,4H)-dithiones VI(a-c)

General Procedure

A solution of 2,4-dihydro-3-thioxo-6-(p-halobenzyl) 1,2,4-triazine-5-one (0.01 mole) in anhydrous pyridine (20 ml) was rapidly poured in a suspension of phosphorous pentasulphide (2.22 g) in anhydrous boiling pyridine (40 ml). The resulting mixture was refluxed for two hours. The dark red resulting solution was cooled and kept at room temperature for twelve hours. Pyridine was evaporated in vacuum to give a dark brown viscous mass, which was triturated with water (10 ml) and then dissolved in 20% sodium hydroxide (50 ml). The alkaline solution was filtered off with suction over a bed of moist activated charcoal and acidified to pH 3.0 with dropwise addition of concentrated hydrochloric acid. The brownish yellow solid was collected by filtration and recrystallised twice from absolute ethanol to give yellow crystals.

6-(p-Fluorobenzyl) 1,2,4-triazine-3,5 (2H,4H)dithione VI(a)

Brownish needles, m.p. 167°C, 63% yield. IR spectrum (KBr) ν cm^{-1} 3122 (NH), 3040, 2900 (CH), 1585 (C=C, C=N), 1535, 1266 (C=C), 1095 (Ar-F). UV spectrum (CH_3OH) λ_{max} nm (ε) 358 (45678), (10% HCl in CH_3OH) 350, (10 % NaOH in CH_3OH) 370, 310, 295. NMR spectrum (DMSO-d_6) δ (ppm) 3.90 (s, 2H, Ar-CH_2), 7.06 (d, 2H, Ar-H, J = 10 Hz), 7.33 (d, 2H, Ar-H. J = 10 Hz), 13.22 (S, H, N_2-H), 13.63 (S,H,N_4-H). Mass spectrum m/z (relative intensities) 253 (M^+,100), 238 (M-NH, 55), 219 (12), 194 (M-NHCS, 12), 135 (35), 116 (50), 109 (55), 90 (32), 83 (59), 64 (13).

6-(p-Chlorobenzyl) 1,2,4-triazine-3,5 (2H,4H)dithione VI(b)

ellow needles, m.p. 223-4°C, 60% yield. IR spectrum (KBr) νcm^{-1} 3120 (NH), 3038, 2900 (CH), 1581 (C=C, 1581 (C=C, C=N), 1525, 1226 (C=S), 1085 (Ar-Cl). UV spectrum (CH_3OH) λ_{max} nm (ε) 355 (43.863), (10% HCl in CH_3OH) 353, (10 % NaOH in CH_3OH) 370, 310, 296. NMR spectrum (DMSO-d_6) δ (ppm) 3.92 (s,2H, Ar-CH_2), 7.36 (d, 2H, Ar-H. J = 8 Hz), 7.52 (d, 2H, Ar-H, J = 8 Hz), 13.20 (s, H, N_2-H), 13.38 (S,H,N_4-H). Mass spectrum m/z (relative intensities) 269 (M^+, 100), 254 (M-NH, 80), 219 (10), 216 (M-NHCS, 10), 151 (34), 125 (79), 116 (57), 99(52), 90(40), 64 (12).

6-(p-Bromobenzyl) 1,2,4-triazine-3,5 (2H,4H)dithione VI(c)

Yellow needles, m.p. 231-2°C, 58% yield. IR spectrum (KBr) νcm^{-1} 3115 (NH), 3042, 2910 (CH), 1583 (C=C, C=N), 1530, 1230 (C=S), 1065 (Ar-Br). UV spectrum (CH_3OH) λ_{max} nm (ε) 354 (44,444), (10 % HCl in CH_3OH) 353, (10% NaOH in CH_3OH) 360, 310, 295. NMR spectrum (DMSO-d_6) δ(ppm) 3.86 (s, 2H, Ar-CH_2), 7.22 (d, 2H, Ar-H. J = 7 Hz), 7.54 (d, 2H, Ar-H. J = 7 Hz), 13.40 (s, H, N_2-H), 13.60 (s, H, N_4-H). Mass spectrum m/z (relative intensites) 314 (M^+,100), 299 (M-NH, 70), 219 (11), 255 (11), 196 (14), 144 (30), 120 (39), 116 (58), 90(39), 64 (15).

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