Synthesis and Reactions of some 6-(3-methyl-4-chlorophenyl)-4-(5-barbiturate),2,3,,4,5-tetrahydropyridazin-3-ones

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Summary: Some new pyridazinone derivatives (3) were synthesized through the addition of barbituric acid to β-aroylacrylic acid (1) followed by cyclization of the adducts. Reactions of (3) with anisaldehyde, bromine-acetic acid mixture and $POCl_3$ gave the 4,5,6-trisubstituted pyridazinone (4), the 5-bromopyridazinone (5) and the tetrachloro derivative (6), respectively. The latter reacts with hydrazine hydrate to give tetrahydrazino derivative (7). Reaction of (3) with phosphorus pentasulfide in one instance namely at short time and less amount of P_2S_5 gave the monothio derivative (8), in the second instance at long times and excess P_2S_5 gave the tetrathioderivative (9). Compound (2,3a) and (6) possess moderate activity against Gram-positive. Compound (2) possesses also moderate activity against Gram-negative and slight activity against fungi.

Introduction

A large number of pyridazinones are reported to exhibit insecticidal [1-3], herbicidal [4-6], allergenic [7], antihypertensive [8-10], analgesic [11], antiinflammatory [11] and bactericidal [12] activities. Several substituted pyridazinones have been synthesized through the addition of hydrocarbons [13], indole [14], 3,5-dimethylpyrazole [12] to β-aroylacrylic acids followed by cyclization of the adducts with hydrazines to the corresponding pyridazinones.

The biological activity of substituted pyridazinones prompted us to synthesize a new class of pyridazinones through the addition of barbituric acid to α-aroylacrylic acid followed by cyclization of the adduct to the corresponding pyridazinones. The various compounds prepared are outlined in Scheme-1.

The reaction of 3-methyl-4-chloro-β-benzoylacrylic acid (1) with barbituric acid in absolute ethanol gave β-(3-methyl-4-chlorobenzoyl)- α-(5-barbiturate) propionic acid 2. The structure of (2) was derived from its IR (ν_{max} in cm^{-1}) spectrum showed νC=O (acid) at 1705, νC=O at 1665, and νNH at 3420. The ^{1}H-NMR (DMSO-d_6) spectrum of (2) exhibited signals at δ 7.98 - 7.53 (3H, m, Ar-H), 4.20 - 3.70 (4H, m, CH_2-CH and -C-CH-C-) and 2.40 (3H, s, CH_3).

The reaction of (2) with hydrazine hydrate, phenylhydrazine and/or semicarbazide in boiling ethanol gave the pyridazinone derivatives (3a-c). The identities of compounds (3a-c) were determined by their C,H,N analysis and IR spectra. The IR spectra showed νC=O at 1650-1660, νC=N at 1590-1595 and νNH at 3400-3460.

Compound (3a) was subjected to further studies. Thus, condensation of (3a) with anisaldehyde in the presence of ethanolic KOH took place at the 5-position to give 4,5,6-trisubstituted pyridazin-3-one (4). The IR spectrum of (4) showed νC=O at 1670, νC=N at 1600 and νNH at 3460.

In the present investigation, it was found that treatment of (3a) with bromine-acetic acid mixture afforded compound (5). The formation of this compound can be mechanistically explained on the basis that the first step is dehydrogenation, followed by addition of bromine on the formed double bond and the elimination of hydrogen bromide in a similar manner to that observed in the bromination of pyrazolines [15]. The infrared spectrum showed νC=O at 1665, νC=N at 1590 and νNH at 3240.

Pyridazinone (3a) react with electrophilic reagents like phosphorus oxychloride to give the

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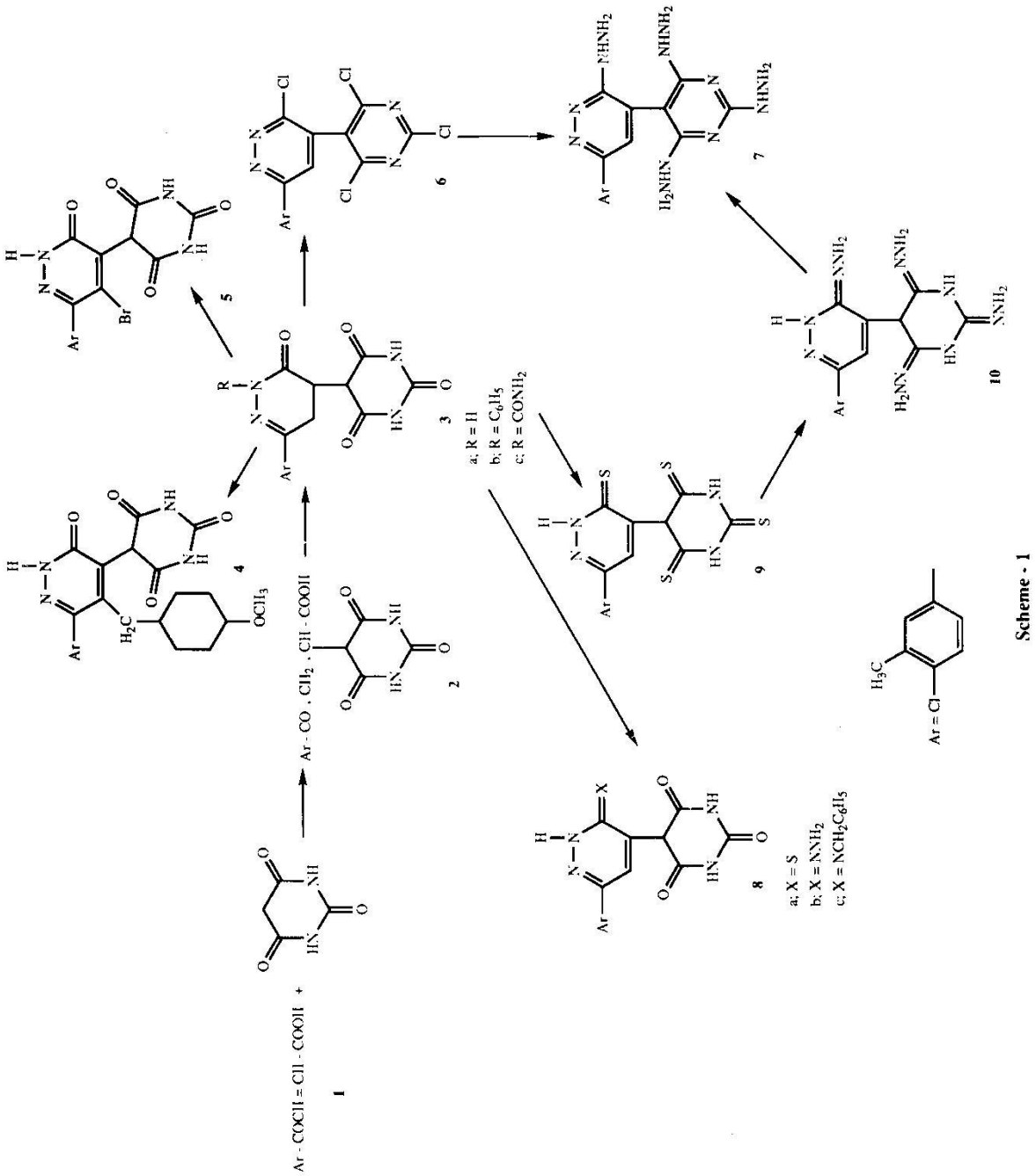

Scheme - 1

tetrachloroderivative (**6**) by substitution of the hydroxyl groups of enol with chlorine together with dehydrogenation. The phenomenon of dehydrogenation is not new since it is observed in the reactions of pyridazinones with P_2S_5 [16] and Grignard reagents [17].

The structure of (6) was derived from its IR spectrum showed νC=N at 1590, νC-Cl at 680 and was devoid of νC=O. The ^{1}H-NMR (DMSO-d_6) spectrum of (**6**) exhibited signals at δ 8.40-7.60 (4H, m, Ar-H) and 240 (3H, s, CH_3).

Reaction of (6) with hydrazine hydrate in ethanol gave the tetrahydrazinoderivative (7). Its infrared spectrum showed νC=N at 1600 and νNH at 3400.

In the present investigation, it has been observed that two different products could be obtained in the reaction of pyridazinone (**3a**) with phophorus pentasulfide in dry xylene. The nature of the products seemed to depend on time of reaction and amount of phosphorus pentasulfide.

a) In one instance, namely at short time and less amount of phosphorus pentasulfide, the reaction of (**3a**) with 0.02 moles phosphorus pentasulfide for half an hour stopped at formation of monothione (**8a**) with dehydrogenation.

The structure of (**8a**) was confirmed by its IR spectrum showed νC=O at 1660, νC=N at 1610, νC=S at 1380 and νNH at 3340. Structure of (**8a**) was further established by its reaction with hydrazine hydrate and benzylamine to give the hydrazone derivative (**8b**) and Schiff base (**8c**), respectively. The IR spectra of (**8b**) and (**8c**) exhibited characteristic absorption bands for νC=O at 1660-1680, νC=N at 1590 and νNH at 3240-3440.

(b) In the second instance, at long times and excess of phosphorus pentasulfide the reaction of (3a) with 0.06 moles phosphorus pentasulfide for 6 hours gave the tetrathione derivative (**9**) with dehydrogenation. The IR spectrum of (**9**) showed νC=N at 1600, νC=S at 1375 and νNH at 3450 and was devoid of νC=O. Structure of (**9**) was further established by its reaction with hydrazine hydrate to give one and the same compound (**7**), presumably though the conversion of the hydrazone derivative formed to the hydrazine derivative (**7**).

The similarity of these compounds were identified by IR spectra and by mixed melting points determination with the sample prepared above.

Screening for antibacterial activity

In this study, the activity of the prepared compounds (**2**), (**3a**) and (**6**) was tested by the disk diffusion method [18]. Watmann No. 1 filter paper disks were sterilized by autoclaving for one hour at 140°C. The sterile disks were impregnated with different compounds (125 mg/disk)., Agar plates were surface inoculated uniformaly from fresh broth culture of *Staphylococcus aureus* (as strains Gram positive), *Escherichia coli* (as strains Gram negative), *Aspergillus fumgytus* (as fungi). The impregnated disks were placed on the medium suitably spaced apart and the plates were incubated at 5°C for 1 hour to permit good diffusion and transferred to an incubator at 28°C for 24 hours. The zones of inhibition were then measured. The results are listed in Table 1.

Table 1:

Compound No.	*Staphylococus aureus*	*Escherichia coli*	*Aspergillus fumgytus*
2	++	++	+
3a	++	+	-
6	++	+	-

++Fairly sensitive (inhibition zone 9-12 mm)
+slight sensitivie (inhibition zone 6-9 mm)
- Not sensitivie

From table 1, it is clear that compounds (**2**), (**3a**) and (**6**) possess moderate activity against Gram-positive. Compound (**2**) possesses moderate activity, the other compounds possess slight activity against Gram negative. Compound (**2**) possesses slight activity while the other compounds are not sensitive against fungi.

Experimental

Unless specifide, standard laboratory grade solvents and reagents were employed. Melting points were determined on a Buchi melting point apparatus and are uncorrected. IR spectra in KBr were recorded on a Unicam SP 1200 spectrophotometer, ^{1}H-NMR on a Varian VN 1009

(5-60 T) instrument using TMS as internal standard.

Reaction of (1) with barbituric acid: Formation of (2)

To a solution of (1) (0.01 mol) in absolute ethanol (20 ml), barbituric acid (0.01 mol) was added and the reaction mixture refluxed for 10 hr. The solid that separated on cooling was crystallized from benzene to give (2), m.p. 210° yield (49%) (Found: C, 51.4; H, 3.7; N, 7.7; $C_{15}H_{13}ClN_2O_6$ requires C, 51.07; H, 3.68; N, 7.94%) M^+ 352.

Reaction of (2), (6), (8a) and (9) with hydrazine hydrate, phenylhydrazine, semicarbazide, benzylamine: Formation of (3a-c), (7), (8b) and (8c).

To a solution of (2), (6), (8a) or (9) (0.01 mol) in ethanol (20 ml), hydrazine hydrate, phenylhydrazine, semicarbazide or benzylamine (0.01 mol or 0.04 mol) was added and the reaction mixture refluxed for 10 hr. The solid that separated on cooling was crystallized from ethanol. (3a): m.p. 195°, yield 34% (Found: C, 51.3; H, 3.8; N, 16; $C_{15}H_{13}ClN_4O_4$ requires: C, 51.65, H, 3.72, N, 16.06% M^+ 348. (3b) m.p. 178°C, yield 30% (Found: C, 59.6; H, 4.2; N, 12.9; $C_{21}H_{17}ClN_4O_4$ requires: C.59.36; H, 4.03; N, 13.18%) M^+ 424. (3c) m.p. 220°, yield 25% (Found: C.48.8; H, 3.5; N, 17.5; $C_{16}H_{14}ClN_5O_5$ requires: C, 49.04; H, 3.60; N, 17.87%) M^+ 391. (7): m.p. 148°, yield 40% (Found: C, 44.9; H, 4.8; N, 42.0; $C_{15}H_{19}ClN_{12}$ requires: C, 44.71; H, 4.75; N, 41.75%) M^+ 402. (8b): m.p. 210°, yield 46% (Found: C,49.7; H, 3.8; N, 23.4) $C_{15}H_{13}ClN_6O_3$ requires C, 49.93; H, 3.63, N, 23.29%M^+ 360. (8c): m.p. 225°, yield 37% (Found: C, 60.5; H, 4.1; N, 16.3; $C_{22}H_{18}ClN_5O_3$ requires: C, 60.62; H, 4.16; N, 16.06%) M^+ 435.

Condensation of anisaldehyde with (3a): Formation of (4)

A warm solution of (3a) (0.01 mol) in ethanol (20 ml) was treated with ethanolic KOH solution (25 ml; 4%) and then anisaldehyde (0.01 mol) added dropwsie with continuous shaking. The reaction mixture was refluxed for 2 hr, cooled, poured into cold water and the solid obtained crystallized from ethanol to give (4), m.p. 183°, yield 43% (Found C, 59.3; H, 3.8; N, 12.2 $C_{23}H_{19}ClN_4O_5$, requires: C, 59.16; H, 4.10; N, 12.00%) M^+ 466.

Action of bromine-acetic acid mixture on (3a): Formation of (5)

The solution of (3a) (0.01 mol) in glacial acetic acid (20 ml) was stirred and treated portionwise with bromine at 60-70°. The solution was further stirred for 2 hr, then cooled in ice. The precipitated product was filtered off, washed with light petroleum (40-60°C), stirred with conc. ammonium hydroxide for 15 minutes. The solid product was crystallized from acetic acid to give (5), m.p. 270°C, yield 70% (Found: C, 42.4; H, 2.5; N, 13.2 $C_{15}H_{10}BrClN_4O_4$ requires: C, 42.32; H, 2.36; N, 13.16%) M^+ 425.

Reaction of (3a) with $POCl_3$: Formation of (6)

A mixture of (3a) (0.03 mol) and $POCl_3$ (20 ml) was gently refluxed for 30 minutes, cooled, treated with crushed ice and the precipitated solid filtered and crystallized from ethanol to give (6), m.p. 165°, yield 55% (Found: C, 42.6; H, 1.6; N, 13.5 $C_{15}H_7C_{15}N_4$ requires C, 42.84; H, 1.67; N, 13.32%) M^+ 420.

Action of P_2S_5 on (3a): Formation of (8a) and (9)

A solution of (3a) (0.01 mol), P_2S_5 (0.02 mol or 0.06 mol) and dry xylene (50 ml) was boiled under refex for 1/2 hr, or 6 hr. The reaction mixture was filtered while hot and then concentrated, the produc which separated on cooling was crystallized from ethanol to give (8a) or (9).

(8a) m.p. 190°, yield 45% (Found C, 49.8; H, 3.1; N, 15.5%; $C_{15}H_{11}ClN_4O_3S$ requires C, 49.65; H, 3.05; N, 15.44%) M^+ 362. (8b): m.p. 220°, yield 48% (Found: C, 44.1; H, 2.8; N, 13.5; $C_{15}H_{11}ClN_4S_4$ requires: C, 43.83; H, 2.69; N, 13.63%) M^+410.

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