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Note

Aminothiazoles : Part 1—Syntheses and pharmacological evaluation of 4-[isobutylphenyl]-2-substituted-aminothiazoles

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Unreported *p*-isobutyl phenacyl chloride has been prepared by the reaction of chloroacetyl chloride on isobutyl benzene. It is condensed with thiourea and its derivatives to get the title compounds. The products obtained are characterized by their IR, ^{1}H NMR and mass spectral analysis.

The literature survey reveals that 2-substituted-aminothiazoles displayed wide variety of biological activities. The aryl thiazolooxamates have been reported to possess antiallergic activity[1]. The 4-aryl thiazolamides have been reported as herbicides[2]. Thiazolyl ureas[3] have been used in combating unwanted vegetation. Aryl substituted thiazole amines have been reported to be useful as antihypotensives[4]. A few aminothiazole derivatives are used as anaesthestics[5] in fish breeding. Many derivatives of thiazolamine are reported to have cardiotonic[6], fungicidal[7], sedative[8], anaesthetic[9] and bactericidal[10] activities. These reports led us to carry out the synthesis of the title compounds and to evaluate their antibacterial, cardiotonic and anti-inflammatory properties.

Unreported *p*-isobutyl phenacyl chloride **1** was prepared by the action of chloroacetyl chloride on isobutyl benzene. Condensation of **1** with thiourea and its derivatives produced the corresponding 4-[*p*-isobutyl phenyl]-2-substituted-aminothiazoles **2**.

Substituted thioureas were prepared from a known method[11]. The intermediate and final products were characterized by their IR, ^{1}H NMR and mass spectral analyses.

The IR spectra of *p*-isobutyl phenacyl chloride displayed bands around 1705–1680 (C=O) and 1600-1605 cm^{-1} (C=C) apart from other common bands. The IR spectra of the final products exhibited a sharp absorption bands at 3200±15 (NH) and 1580±20 cm^{-1} (C=N and C=C).

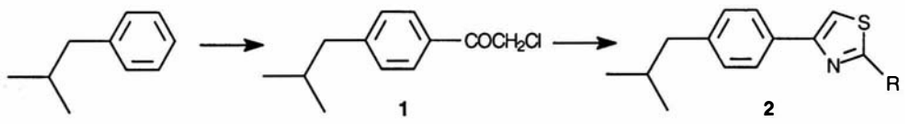
The aromatic protons in the **1** displayed AB pattern of splitting in ^{1}H NMR spectra. The protons of $COCH_2$ - group appeared as a singlet at δ 4.6-4.8. 5H of **2** appeared as a singlet at δ 6.9-7.2 while the other aromatic protons exhibited AB splitting. The molecular ion peak is very weak but conspicuous in the mass spectra of **1**. The base peak is usually formed by the loss of CH_2Cl group. The molecular ion peak of the title compounds is very intense and in some cases they registered a base peak.

Experimental Section

All the melting points are uncorrected. The IR spectra were recorded on a Shimadzu FTIR-8101 M spectrophotometer; ^{1}H NMR spectra on a Varian Gemini FTNMR instrument at 200 MHz using TMS as the internal reference (chemical shifts in δ, ppm); and mass spectra on a Hewlett-Packard MS EM-5989 A spectrometer at 70eV.

***p*-Isobutyl phenacyl chloride 1**. *iso*-Butyl benzene (6.7 g, 0.05 mole) was added to a stirred mixture of anhydrous aluminium chloride (21.2 g, 0.06 mole) and chloroacetyl chloride (11.3 g, 0.1 mole) in 1,2-dichloroethane (125 mL) at 0-5° C. The reaction mass was stirred at 0-5 °C for 3-4 hr. After the reaction was over it was poured into ice-cold water to decompose aluminium chloride. The organic layer was separated and 1,2-dichloroethane was completely distilled off under vaccum to get **1** as a pale yellow viscous liquid, yield 4.58 g (87%) (Found: C, 8.42; H, 7.11; Cl 16.87. $C_{12}H_{15}OCl$ requires C, 68.40; H, 7.12; Cl, 16.86%). IR (KBr, cm^{-1}): 1701-1685(C=O), 1605(C=C); ^{1}H NMR($CDCl_3$, δ ppm): 7.9(d, 2H, Ar-H *ortho* to C=O), 7.3(d, 2H, *meta* to C=O), 4.7(s, 2H, $COCH_2$),2.5-2.6 (d, 2H, benzylic),1.8-2.0(m, 1H, C*H*$(CH_3)_2$, 0.9-1.0 (2s, 6H, CH_3); Mass (m/z) : 210 ($M^{+\cdot}$,3), 167 (M-C_3H_7, 3) 161 (M-CH_2Cl, 100), 133 (161-CO, 10).

2-Amino-4-(*p*-isobutylphenyl) thiazole 2a. Thiourea (0.05 mole, 3.8g) was stirred in water (15 mL) for 15 min at room temperature. Then *p*-isobutyl phenacyl chloride (0.05 mole, 10.5 g) was charged and the reaction mass maintained at reflux for 4-5 hr. Then it was cooled to ambient temperature and



1

2

2a; R = NH_2
2b; R = $NHCH_3$
2c; R = NHPh
2d; R = N = $C(NH_2)_2$

poured into water. The reaction mixture was made alkaline with 10% NaOH solution. The product separated was filtered and washed with water and dried. The product was recrystallised from aqueous methanol, yield 10.5 g (90%), mp 112-16°C (Found: C, 67.25; H, 6.90; N, 12.03; S, 13.76. $C_{13}H_{16}N_2S$ requires C, 67.24; H, 6.89; N, 12.06; S, 13.79%); IR (KBr, cm^{-1}): 3313-3107, 1630,1598 and 1536; ^1H NMR ($CDCl_3$): 7.7(d, 2H, Ar-H *ortho* to thiazole), 7.2 (d, 2H, Ar-H *ortho* to isobutyl), 6.7(s, 1H, thiazole-H), 5.2-5.4 (br s, 2H, NH_2), 2.5(d, 2H, benzylic), 1.8-2.0 [m, 1H, C*H*$(CH_3)_2$], 0.9 (d, 6H, CH_3). Mass (m/z): 232 (M^+, 47), 217(M-CH_3, 3), 203 (M-C_2H_5, 4), 189(M-C_3H_7, 100), 147(189-$NCNH_2$, 13).

2-Methylamino-4-(*p*-isobutylphenyl) thiazole 2b. Thiourea was replaced by methyl thiourea (0.05 mole 4.5 g) in the above procedure described for **2a**. The product were recrystallised from ethyl acetate-*n*-hexane mixture (1:1); yield 9.7 g (78%), m p 118-19°C (Found: C, 68.27; H, 7.33; N, 11.36; S, 13.02. $C_{14}H_{18}N_2S$ requires C, 68.29; H, 7.31; S, 13.00%); IR (KBr, cm^{-1}): 3268, 1581, 1570, 1492 and 1465; ^1H NMR ($CDCl_3$): 7.7(d, 2H, Ar-H *ortho* to thiazole), 7.15(d, 2H, Ar-H *ortho* to isobutyl), 6.65(s, 1H, thiazole-H), 6.0(br s, 1H, NH), 2.95(s, 3H, N-CH_3), 2.5(d, 2H, benzylic), 1.8-2.0 [m, 1H, C*H* $(CH_3)_2$], 0.95(d, 6H, CH_3); Mass (m/z): 246(M^+., 74), 203(M-C_3H_7, 100), 174(M-NCSN, 3), 149(203-$NCNCH_2$, 5).

2-Phenylamino-4-(*p*-isobutylphenyl)thiazole 2c. Phenylthiourea (0.05 mole 7.6 g) was used in place of thiourea in the above procedure described for **2a**. The product was recrystallised from methanol-ethyl acetate mixture (1:1), yield 5.8 g (38%), m p 169-73°C (Found: C, 74.00; H, 6.47; N, 9.10; S, 10.36. $C_{19}H_{20}N_2S$ requires C, 74.02; H, 6.49; N, 9.09; S, 10.38%); IR (KBr, cm^{-1}): 3244-3042, 1623, 1592, 1567 and 1499; ^1H NMR ($CDCl_3$): 7.7 (d, 2H, Ar – H *ortho* to thiazole), 7.18 – 7.2 (d, 2H, Ar – H *ortho* to isobutyl), 6.60 (s, 1H, thiazole–H), 6.67 (br, s, 1H, NH), 7.30–7.50 (s, 1H, -N-Ph), 2.60–2.80 (d, 2H, benzylic), 1.80 – 2.0 [m, 1H, C*H* $(CH_3)_2$], 0.95 (d, 6H, CH_3); Mass (m/z) : 308 (M^+, 100), 251 (M^+ - C_4H_9, 70), 135 (M^+ - C_6H_5 NCN, 7), 101 (M^+ - H_2S, 12).

2-Diaminomethyleneamino-4-(*p*-isobutylphenyl) thiazole 2d. Guanyl thiourea (0.05 mole, 5.9 g) was taken in place of thiourea in the above process. The product obtained was recrystallised from aqueous methanol, yield 4.9 g (36%), m p 238-40°C (Found: C, 61.29; H, 6.56; N, 20.41; S, 11.68. $C_{14}H_{18}N_4S$ requires C, 61.31; N, 20.43; S, 11.67%);. IR (KBr, cm^{-1}) : 3440-3172, 1649,1601, 1536, 1500 and 1460; ^1H NMR (DMSO-d_6): 7.75(d, 2H, Ar-H *ortho* to thiazole), 7.2(d, 2H, Ar-H *ortho* to isobutyl), 7.05(s, 1H, thiazole-H), 6.8-7.0(br, s, 4H, NH_2); Mass (m/z): 274(M^+, 43), 257 (M-NH_3, 17), 232 (M-C_3H_6 or M-$NCNH_2$, 44), 214(257-C_3H_7, 44), 189(232-C_3H_7, 100), 147(189-$NCNH_2$, 19).

Pharmacological evaluation

The 4-substituted aminothiazoles were tested for anti-inflammatory, antibacterial and cardiotonic activities.

Anti-inflammatory activity

The compounds **2b** and **2d** exhibited anti-inflammatory activity by the right paw edema test[12] using carrageenin (1%) on male rats weighing 100-140 g. The test compound vehicle (0.5% carboxymethylcellulose) was administered orally as a garage according to the dose of 10 mL/kg, one hour later 0.1 mL of freshly prepared carrageenin (1%) in normal saline was injected into the plantar aponeurosis of right paw and three hours later the inflammatory response was measured. The percent in inflammation was calculated with respect to vehicle treated control values.

Anti-bacterial activity

The compound **2d** exhibited significant anti-bacterial activity against *Bacillus subtilis*. Anti-bacterial activity was determined by Vincent and Vincent filter paper disc diffusion method[13].

Cardiotonic activity

The compounds of this series could cause cardiac arrest. The compounds that caused diastolic arrest were **2a**, **2c** and **2d**. The effect of test compounds on frog heart were studied in the presence of acetyl choline[14, 15].

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