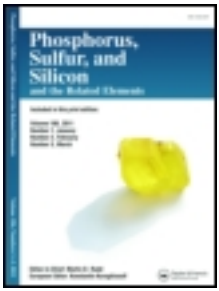

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SYNTHESIS OF CERTAIN 6-(ARYLTHIO)URACILS AS POTENTIAL ANTIVIRAL AGENTS

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SYNTHESIS OF CERTAIN 6-(ARYLTHIO)URACILS AS POTENTIAL ANTIVIRAL AGENTS

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A series of 6-(Arylthio)uracils have been prepared *via* condensation of 6-chlorouracil or 5-ethyl-6-chlorouracil with the corresponding thiophenol derivatives in pyridine or ethanolic potassium hydroxide. The synthesized compounds were tested for their antiviral activity. Some of the 5-ethyl-6-(arylthio)uracil derivatives **10**a-g showed moderate activities against hepatitis B Virus (HBV) and HIV-1 virus.

Keywords: 6-(arylthio)uracils; antiviral activity; HBV; HIV-1

INTRODUCTION

Retroviruses are the causative agents of fatal diseases like acquired immunity deficiency syndrome (AIDS) and infective hepatitis B. Retroviral chemotherapy is currently receiving the attention of many scientists. As a result of extensive search, a large number of nucleoside analogues have been synthesized and investigated for their antiviral activities. Among these, 3′-azido-3′-deoxythymidine (AZT, **I**)[1,2], The serious side effects, suppression of bone marrow cell growth[3], combined with the appearance of AZT-resistant HIV variants[4] give an incentive to search for other promising candidates having a higher selectivity against retroviruses. A series

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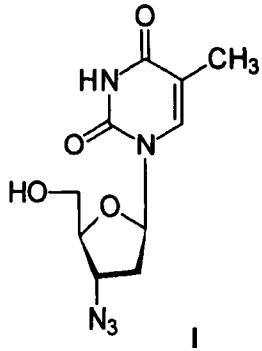
of 6-substituted acyclouridines have been reported to possess marked selectivity towards HIV-1, among these derivatives 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT, **II**)[5–12]. In continuation to our researches in the field of 6-(arylthio)uracils and related derivatives[13–15], we rationalized to synthesize some series of 6-(arylthio)uracils, structurally-related to HEPT, as potential antiviral agents.



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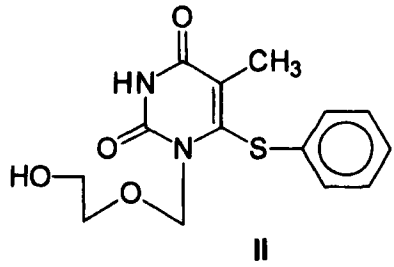
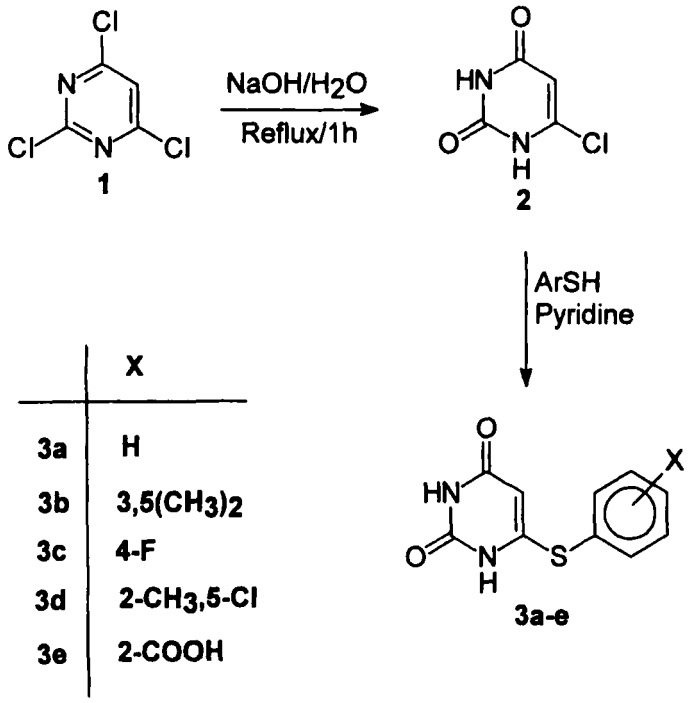


II

RESULTS AND DISCUSSION

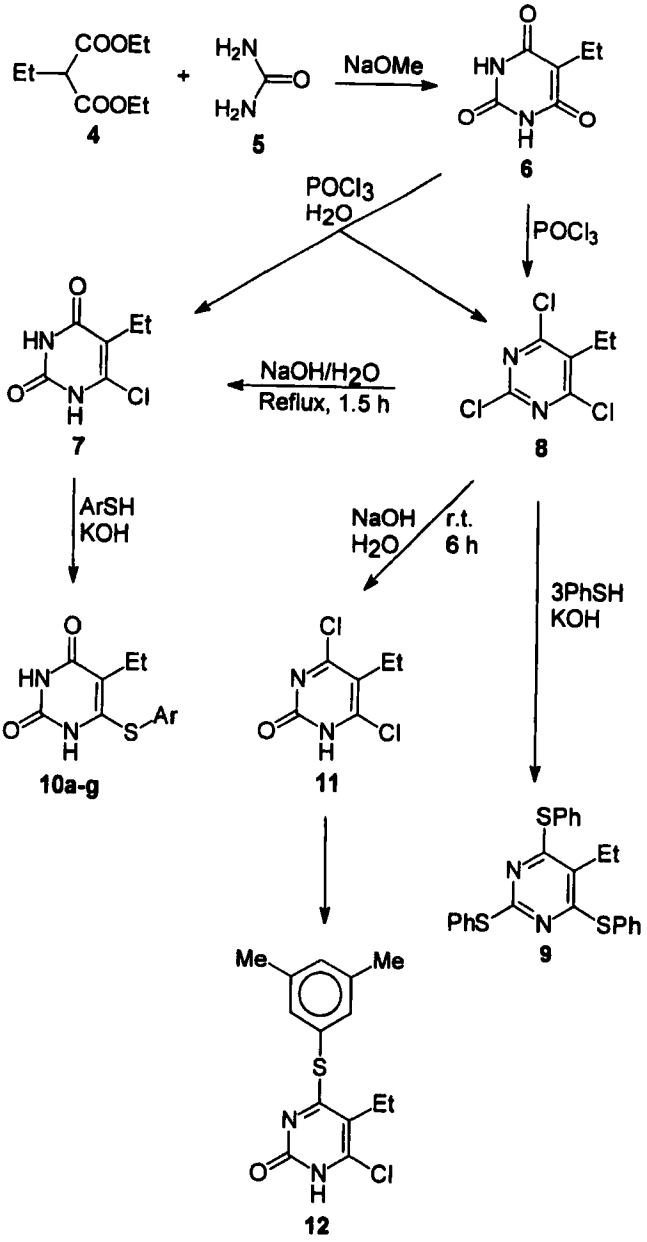
The starting material 2,4,6-trichloropyrimidine **1** was prepared from barbituric acid *via* the action of phosphorus oxychloride and *N,N*-dimethylaniline[16]. Treatment of **1** with aqueous sodium hydroxide afforded 6-chlorouracil **2**[17], which was allowed to react with certain thiophenols in boiling pyridine to yield the corresponding 6-(arylthio)uracils **3**a-e (Scheme 1).

5-Ethylbarbituric acid **6** was prepared *via* the condensation of diethyl ethylmalonate **4** and urea **5** in the presence of sodium methylate[18]. Kaul *et al*[19] reported the reaction of 5-ethylbarbituric acid with phosphorus oxychloride in the presence of catalytic amounts of water to yield 5-ethyl-6-chlorouracil **7**. Attempted preparation of **7** *via* application of this method yielded 2,4,6-trichloro-5-ethylpyrimidine **8** as the major product in addition to the target compound **7** as minor product, the separation of compounds **7** & **8** was successfully achieved by column chromatography. Compound **7** was successfully prepared in good overall yield from 5-ethylbarbituric acid *via* heating with phosphorus oxychloride for 2 hours



SCHEME 1

to yield **8**, which was selectively hydrolyzed to **7** by refluxing with 10% aqueous sodium hydroxide for 1.5 hours. Treatment of compound 8 with three equivalents of thiophenol in ethanolic potassium hydroxide yielded 2,4,6-*tris*(phenylthio)-5-ethylpyrimidine **9**. The reaction of **7** with equimolecular amount of thiophenol or substituted thiophenols in ethanolic potassium hydroxide yielded the corresponding 5-ethyl-6-(arylthio)uracils **10**a-g. A more selective hydrolysis of compound **8** was also achieved by stirring with 10% aqueous sodium hydroxide solution at room temperature to furnish the dichloro derivative **11**, which was subsequently reacted with 3,5-dimethylthiophenol in ethanolic sodium hydroxide to afford 4-(3,5-dimethylphenylthio)-5-ethyl-6-chloro-1,2-dihydropyrimidine-2-one **12** (Scheme 2).



SCHEME 2

ANTIVIRAL TESTING

Six representative compounds (**3b**, **3c**, **10b**, **10e**, **10f** and **10g**) were selected for evaluation of their activity against hepatitis B virus (HBV) and human immunodeficieny virus (HIV-1). The potential antiviral effect against HBV was tested on HEP G2 2.15 as described earlier[20]. In brief: Quantitation of HBV-DNA in culture supernatant was done using DIG labeling of PCR product followed by solid phase hybridization whereas the cytotoxicity of the compounds were assessed by MTT-assay. The antiviral activity against HIV-1 in MT-4 cells was carried out following the previously described method[21]. The results are summarized in table I. The compounds **10e** and **10g** showed only moderate activity against HBV whereas compounds **10b** and **10f** displayed moderate activity against HIV-1. The compounds **3b** and **3c** were found to be completely inactive, this indicates that the presence of an alkyl group at position 5 is essential for antiviral activity.

TABLE I Antiviral activity of compounds **3b**, **3c**, **10b**, **10e**, **10f** and **10g** against HEP G2 2.15 and HIV-1 in MT-4 cells

Compound No.	*HBV (HEP G2 2.15): μM*		*HIV-1 (MT-4): μM*	
	IC_{50}[a]	CC_{50}[b]	IC_{50}[a]	CC_{50}[b]
3b	>100	>100	>100	>100
3c	>100	>100	>100	>100
10b	>100	>100	77	>100
10e	52	92	>10	>10
10f	>100	>100	3	72
10g	38	>100	70	>100

a. Effective dose of compound achieving 50% inhibition.
b. Cytotoxic dose of compound required to reduce proliferation of normal cells by 50%.

EXPERIMENTAL

Melting points (°C, uncorrected) were recorded on a Fisher-Johns apparatus. Most of the NMR spectra were recorded on a Bruker 250 FT NMR

spectrophotometer at 250 MHz for ^1H and 62.9 MHz for ^{13}C using TMS as an internal standard and DMSO-d_6 as solvent (chemical shift in δ, ppm). Mass spectra were recorded on a Varian MAT 311A spectrophotometer at 70 eV.

6-(Arylthio)uracils 3a-e

A mixture of 6-chlorouracil **2** (1.47 g, 0.01 mol) and the appropriate thiophenol (0.01 mol), in pyridine (20 ml) was heated under reflux for 1.5 h. Pyridine was then distilled *in vacuo*and the residue was treated with water (50 ml). The separated solid was filtered, washed with water and crystallized from ethanol.

3a: mp 275[22].

3b: mp 251–3[13].

3c: mp 256–8, Yield 1.9 g (80%), Anal. $C_{10}H_7FN_2O_2S$ %Calc.(Found): C 50.42(50.33), H 2.96(2.94), N 11.75(11.58). Ms m/z(rel. int.): 238(M^+, 82), 239(M^++1, 13), 240(M^++2, 7), 128(39), 68(100). ^1H NMR: 4.57(d,1H,5-H,J=1.6Hz), 7.40–7.73(m,4H, Ar-H), 10.97(s,1H,NH) and 11.55(s,1H,NH). ^{13}C NMR: 95.74(C-5), 117.19, 117.54, 121.71, 121.77, 138.06, 138.20, 162.01, 162.12(Ar-C), 156.60(C-2), 156.38(C-6) and 161.49(C-4).

3d: mp 242–4, Yield 2.0 g (74%), Anal. $C_{11}H_9ClN_2O_2S$ %Calc.(Found): C 49.16(49.28), H 3.38(3.36), N 10.43(10.29). Ms m/z(rel. int.): 268(M^+, 100), 269(M^++1, 16), 270(M^++2, 42), 235(23), 208(49), 68(76). ^1H NMR: 2.38(s,3H,CH3), 4.54(d,1H,5-H, J=1.6Hz),7.51–7.58(m,2H,Ar-H), 7.68(s,1H,Ar-H), 11.01(s,1H,NH) and 11.59(s,1H, NH). ^{13}C NMR: 19.44(CH_3), 95.64(C-5), 127.57, 131.00, 131.25, 132.78, 135.34, 141.43(Ar-C), 150.79(C-2), 154.44(C-6) and 162.18(C-4).

3e: mp 279–81(dec.), Yield 1.74 g (66%), Anal. $C_{11}H_8N_2O_4S$ %Calc.(Found): C 49.99(49.71), H 3.05(3.21), N 10.60(10.62). ^1H NMR: 4.58(d,1H,5-H,J=1.5Hz), 7.43–8.20(m,4H,Ar-H), 10.91(s,1H,NH), 11.59(s,1H,NH) and 12.84(s,1H,COOH).

2,4,6-Trichloro-5-ethylpyrimidine 8

5-Ethylbarbituric acid (15.6 g, 0.1 mol) was added portionwise to phosphorus oxychloride (50 ml) and the mixture was heated under reflux for 2

h. On cooling, the mixture was poured cautiously to crushed ice (400 g) with vigorous stirring, extracted with ether (300 ml), the ether extract was dried over anhydrous sodium sulfate, evaporated to yield 17 g (80%) of **8**. mp 74–6 (Lit.[22], mp 76–9 and Lit.[23], mp 75–7).

5-Ethyl-6-chlorouracil 7

2,4,6-Trichloro-5-ethylpyrimidine **8** (21 g, 0.1 mol) was added to 10% sodium hydroxide solution (250 ml) and the mixture was heated under reflux for 90 min. On cooling, the mixture was acidified with conc. HCl to pH 2–3 and kept in refrigerator for 3 h. The precipitated solid was filtered, washed with cold water, dried and crystallized from water to yield 13.8 g (79%) of **7**. mp 215–7, Anal. $C_6H_7ClN_2O_2$%Calc.(Found): C 41.27(40.90), H 4.04(4.17), N 16.05(15.92). Ms m/z(rel. int.): 175(44), 176(8), 177(13), 160(7), 154(100), 136(82). ^{1}H NMR: 0.96(t,3H,CH_3,J=8.0Hz), 2.27(q,2H,CH_2, J=7.0Hz), 11.32(s,1H,NH) and 11.82(s,1H,NH). ^{13}C NMR: 12.54(CH_3), 18.58(CH_2), 111.39(C-5), 140.54(C-6), 149.59(C-2) and 162.67(C-4).

5-Ethyl-6-arylthiouracils 10a-g

Compound **7** (1.75 g, 0.01 mol) and the appropriate thiophenol (0.01 mol) were added to a solution of potassium hydroxide (0.6 g) in ethanol (50 ml) and the mixture was heated under reflux for 4 h. The solvent was evaporated *in vacuo* and the residue was treated with water (100 ml), filtered, washed with water, dried and crystallized from ethanol (**10**a,b,f,g) or aqueous-ethanol (**10**c,d,e) to yield **10**a-g in 75–80% yields. **10a**: Ar=C_6H_5, mp 210–2, Anal. $C_{12}H_{12}N_2O_2S$ %Calc.(Found): C 58.04(58.31), H 4.87(4.94), N 11.28(11.27). Ms m/z(rel. int.): 248(M^+, 100), 249(M^++1, 18), 250(M^++2, 9), 233(94), 171(34), 123(25), 109(24). ^{1}H NMR: 0.92(t,3H,CH3,J=7.4Hz), 2.44(q,2H,CH2,J=7.5Hz), 7.33–7.41 (m,5H,Ar-H), 10.87(s,1H,NH) and 11.21(s,1H,NH). ^{13}C NMR: 13.57(CH_3). 19.70(CH_2), 118.91(C-5), 127.54, 129.48, 129.60, 131.60(Ar-C), 142.52(C-2), 150.42(C-6) and 162.99(C-4).

10b: Ar=4-FC_6H_4, mp 260–2, Anal. $C_{12}H_{11}FN_2O_2S$ %Calc.(Found): C 54.12(54.10), H 4.17(4.09), N 10.52(10.61). Ms m/z(rel. int.): 266(M^+, 97), 267(M^++1, 16), 268(M^++2, 5), 251(100), 208(17), 171(38), 141(44). ^{1}H NMR: 0.93(t,3H,CH3,J=7.5Hz), 2.47(q,2H,CH_2,J=7.0Hz),

7.24(d,2H,Ar-H,J=8.0Hz), 7.48(d,2H,Ar-H,J=7.0Hz), 10.83(s, 1H,NH) and 11.24(s,1H,NH). ^{13}C NMR: 13.66(CH_3). 19.71(CH_2), 118.28(C-5), 116.43, 116.79, 126.56, 126.61, 133.05, 133.18, 163.02, 163.96(Ar-H), 143.18(C-2), 150.55(C-6) and 160.05(C-4).

10c: Ar=2-$CH_3C_6H_4$, mp 212–4, Anal. $C_{13}H_{14}N_2O_2S$ %Calc.(Found): C 59.52(59.41), H 5.38(5.50), N 10.68(10.54). ^{1}H NMR: 0.94(t,3H,$CH_2C\underline{H}_3$,J=7.2), 2.34(s,3H,CH_3), 2.44(q,2H,CH2,J=7.4), 7.23–7.48(m,4H,Ar-H), 10.82(s,1H,NH) and 11.22(s,1H,NH). ^{13}C NMR: 13.45($CH_2\underline{C}H_3$), 19.58(CH_2), 19.92(CH_3), 118.26(C-5), 127.01, 127.70, 129.90, 130.11, 130.56, 137.91(Ar-C), 142.94(C-2), 150.45(C-6) and 162.84(C-4).

10d: Ar=3-$CH_3C_6H_4$, mp 179–81, Anal. $C_{13}H_{14}N_2O_2S$ %Calc.(Found): C 59.52(59.49), H 5.38(5.52), N 10.68(10.80). ^{1}H NMR: 0.95(t,3H,$CH_2C\underline{H}_3$,J=7.4.0Hz), 2.31(s,3H, CH_3), 2.45(q,2H,CH_2,J=8.0Hz), 7.23–7.48(m,4H,Ar-H), 10.82(s,1H,NH) and 11.22(s, 1H,NH). ^{13}C NMR: 13.61($CH_2\underline{C}H_3$), 19.74(CH_2), 20.73(CH_3), 118.63(C-5), 126,97, 127.52, 128.20, 129.16, 130.66, 138.82(Ar-C), 142.83(C-2), 150.48(C-6) and 163.03(C-4).

10e: Ar=4-$CH_3C_6H_4$, mp 177–9, Anal. $C_{13}H_{14}N_2O_2S$ %Calc.(Found): C 59.52(59.40), H 5.38(5.43), N 10.68(10.59). Ms m/z(rel. int.): 262(M^+, 100), 263(M^++1, 18), 264(M^++2, 7), 247(97), 204(9), 171(24), 141(44). ^{1}H NMR: 0.94(t,3H,$CH_2C\underline{H}_3$,J=7.3Hz), 2.31(s,3H,CH_3), 2.46(q,2H,CH2,J=7.2Hz), 7.21(d,2H,Ar-H,J=8.0Hz), 7.31(d,2H,Ar-H, J=8.0Hz), 10.70(s,1H,NH) and 11.22(s,1H,NH). ^{13}C NMR: 13.63($CH_2\underline{C}H_3$), 19.69(CH_2), 20.58(CH_3), 118.07(C-5), 127.50, 130.17, 130.73, 137.80(Ar-C), 143.52(C-2), 150.49(C-6) and 163.03(C-4).

10f: Ar=3,5(CH_3)$_2C_6H_3$, mp 239–41, Anal. $C_{14}H_{16}N_2O_2S$ %Calc.(Found): C 60.84(60.77), H 5.84(5.91), N 10.14(10.08). Ms m/z(rel. int.): 276(M^+, 100), 277(M^++1, 17), 278(M^++2, 5), 261(78), 218(8), 171(18). ^{1}H NMR: 0.94(t,3H,$CH_2C\underline{H}_3$,J=7.2Hz), 2.27(s,6H,CH_3), 2.48(q,2H,CH2,J=7.3Hz), 6.97(s,1H,Ar-H), 7.03(s,2H,Ar-H), 10.72(s,1H,NH) and 11.21(s,1H,NH). ^{13}C NMR: 13.64($CH_2\underline{C}H_3$), 19.75(CH_2), 20.67(2xCH_3), 118.34(C-5), 127.73, 129.48, 130.64, 138.83(Ar-C), 143.09(C-2), 150.49(C-6) and 163.03(C-4).

10g: Ar=2(CH_3),5-ClC_6H_3, mp 253–5, Anal. $C_{13}H_{13}ClN_2O_2S$ %Calc.(Found): C 52.61(52.42), H 4.41(4.60), N 9.44(9.37). Ms m/z(rel. int.): 296(M^+, 83), 297(M^++1, 14), 298(M^++2, 30), 281(98), 263(21), 238(10), 171(100), 157(42). ^{1}H NMR: 0.93(t,3H,$CH_2C\underline{H}_3$,J=7.3Hz),

2.31(s,6H,CH_3), 2.42(q,2H,CH2,J=7.3Hz), 7.27(s,1H,Ar-H), 7.33(s,2H,Ar-H), 10.82(s,1H,NH) and 11.24(s,1H,NH). ^{13}C NMR: 13.55($CH_2\underline{C}H_3$), 19.34(CH_2), 19.69(CH_3), 118.63(C-5), 127.67, 129.16, 130.36, 131.03, 132.07, 137.92(Ar-C), 141.96(C-2), 150.52(C-6) and 162.82(C-4).

2,4,6-Tris(phenylthio)-5-ethylpyrimidine 9

2,4,6-Trichloro-2-ethylpyrimidine **8** (2.1 g, 0.01 mol) and thiophenol (3.3 g, 0.03 mol) were added to a solution of potassium hydroxide (1.7 g. 0.03 mol) in ethanol (50 ml) and the mixture was heated under reflux for 4 h. The solvent was evaporated *in vacuo* and the residue was treated with water (100 ml), filtered, washed with water, dried and crystallized from ethanol yield 2.8 g (65%) of **9**. mp 119–21. Anal. $C_{24}H_{20}N_2S_3$ %Calc.(Found): C 66.63(66.52), H 4.66(4.80), N 6.48(6.39). Ms m/z(rel. int.): 432(M^+, 74),433(M^++1, 26), 444(M^++2, 8), 355(7), 323(8), 307(24), 154(100). ^1H NMR: 1.23(t,3H,CH_3,J=8.8), 2.72(q,2H,CH_2,J=7.4Hz), 7.12–7.44(m,15H,Ar-H). ^{13}C NMR: 11.32(CH_3), 21.21(CH_2), 124.51(C-5), 127.12, 128.52, 128.83, 129.14, 129.28, 133.57, 134.89(Ar-C), 165.72(C-2) and 173.88(C-4,6).

4,6-Dichloro-5-ethyl-1,2-dihydropyrimidine-2-one 11

Compound **8** (21 g, 0.1 mol) was added to 10% sodium hydroxide solution (250 ml) and the mixture was stirred at room temperature for 6 h. The mixture was then acidified with conc. HCl to pH 2–3 and allowed to stand for 1 h. The separated solid was filtered, washed with water, dried and crystallized from aqueous ethanol to yield 11.6 g (60%) of **11**. mp 198–200. Anal. $C_6H_6Cl_2N_2O$ %Calc.(Found): C 37.33(36.92), H 3.13(3.36), N 14.52(14.28).

4-(3,5-Dimethylphenylthio)-5-ethyl-6-chloro-1,2-dihydropyrimidine-2-one 12

Compound **11** (1.9 g, 0.01 mol) and 3,5-dimethylthiophenol (1.4 g, 0.01 mol) were added to a solution of potassium hydroxide (0.56 g. 0.01 mol) in ethanol (30 ml) and the mixture was heated under reflux for 4 h.

The solvent was evaporated *in vacuo* and the residue was treated with water (100 ml), filtered, washed with water, dried and crystallized from ethanol yield 1.7 g (58%) of **11**. mp 171–3. Anal. $C_{14}H_{15}ClN_2OS$ %Calc.(Found): C 57.03(57.17), H 5.13(5.24), N 9.51(9.37). Ms m/z(rel. int.): 294(M^+, 100), 295(M^++1, 23), 296(M^++2, 37), 279(38), 259(10), 200(26), 138(19). ^{1}H NMR: 0.97(t,3H,$CH_2C\underline{H}_3$,J=7.4Hz), 2.30(s,6H,CH_3), 2.49(q,2H,CH_2,J=7.4Hz), 7.12(s,1H,Ar-H), 7.21(s,2H,Ar-H). ^{13}C NMR: 11.64($CH_2\underline{C}H_3$), 19.32(CH_2), 20.49(2xCH_3), 120.83(C-5), 125.65, 131.44, 132.10, 138.52(Ar-C), 141.52(C-6), 149.28(C-4) and 154.39(C-2).

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