INTRAMOLECULAR WEAK HYDROGEN BONDS IN SUBSTITUTED 4-ARYLTHIAZOLES

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Abstract: We have synthesized new polysubstituted 4-arylthiazoles with a substitution pattern able to form intramolecular weak hydrogen bonds as secondary structure, and besides, displaying in the aromatic region of their ^{1}H-NMR spectra an ABX spin system and only one singlet (the thiazolic proton), thus permitting us to make doubtless assignments. These results confirmed previous assignments made by us in other thiazole-derivatives prepared by the first time. The spectroscopic data (IR, ^{1}H-NMR and MS) of these thiazoles, as well as of the required intermediates, are discussed.

Introduction

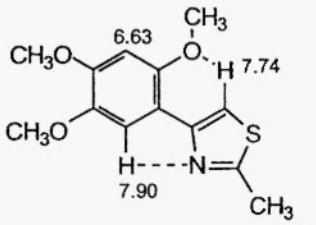
In a previous communication (1) we have given account of our novel findings in the ^{1}H-NMR spectra of fifteen thiazole derivatives recently prepared in our laboratory (2-4) and not previously described. We observed unquestionable paramagnetic shifts in some of the proton magnetic resonance spectra of these polysubstituted 4-phenylthiazoles. In order to explain the unexpected paramagnetic shifts encountered for some hydrogens in the aromatic region, we provided the theory that they were due to intramolecular weak hydrogen bonding.

Now we wish to confirm our theory with data obtained from four new compounds specially prepared since they arise easy to assign peaks in their spectra, and besides, three of them are able to form intramolecular weak hydrogen bonds as secondary structure.

Results and Discussion

The ^{1}H-NMR spectrum of 2-methyl-4-(2,4,5-trimethoxyphenyl)thiazole, **1**, shows paramagnetic shifts for H-6 (benzene) and the thiazolic proton, if these shifts are compared to the corresponding ones observed in the spectrum of the methylarylderivative **2**. These variances were attributed to hydrogen bonding of the type C-H---O and C-H---N. However, since three aromatic singlets are found in the spectra of both 4-arylthiazoles, it is difficult to make the assignments only with 1D ^{1}H-NMR spectra and deduce the secondary structure, if present. We have found that the thiazolic signal shows *ringing* in the spectra at 90 MHz (1). However, this *ringing* is not observed in the spectra obtained in pulse instruments.

As the case of the other previously prepared thiazole derivatives was similar to the preceding one, we prepared the following thiazoles in order to obtain ^{1}H-NMR spectra in which we could make doubtless assignments, having in the aromatic region an ABX spin system and only one singlet.



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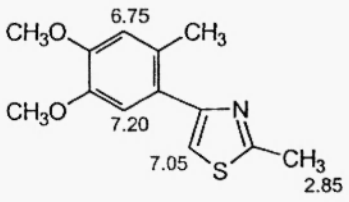

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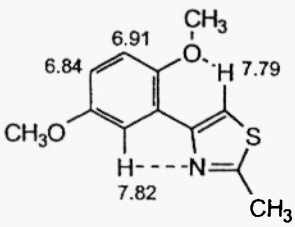
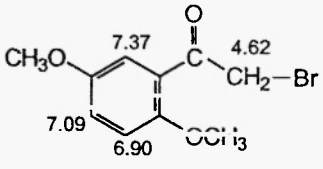


3

We now prepared 2-methyl-4-(2,5-dimethoxyphenyl)thiazole, **3**. Included in the formula are the ^{1}H-NMR data ($CDCl_3$, 300 MHz), and we can see that the chemical shifts for H-6 and the thiazolic proton are close to those observed in the spectrum of compound **1**, thus confirming the assignments made previously (1).

The 4-arylthiazole **3** was obtained by reaction of α-bromo-2,5-dimethoxyacetophenone, **4**, with thioacetamide. The IR spectrum of **3** shows absorption at 3149 cm^{-1} (C–H in thiazole).

The required α-bromoketone **4**, was obtained by bromination of **5**, with $CuBr_2$ in $CHCl_3$/AcOEt. Cf. (5). By this method the resulting bromoketone is quite stable since there are no bromine free radicals.



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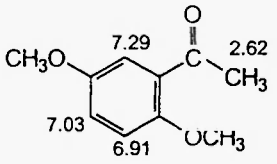

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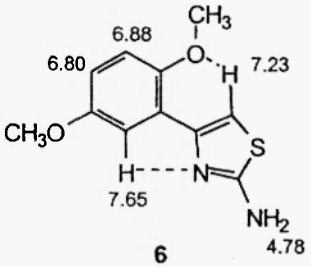
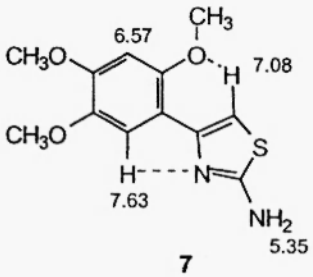


6

Other compound now prepared is 2-amino-4-(2,5-dimethoxyphenyl)thiazole, **6**, in order to compare it with the trimethoxyphenyl-thiazole, **7**, which presents three aromatic singlets in its ^{1}H-NMR spectrum. Cf. (1). As we can see from the resonance data in formula **6**, these are in good agreement with the previous assignments made for structure **7**. The amino-thiazole **6** was obtained by reaction of α-bromo-2,5-dimethoxyacetophenone, with thiourea.



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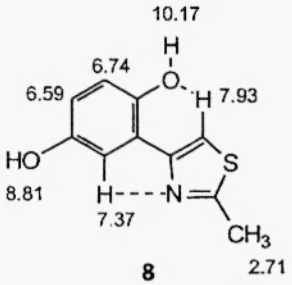

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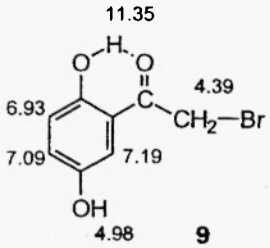
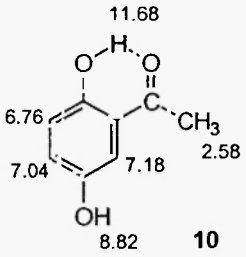


9

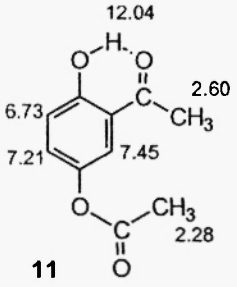
The next compound prepared was 2-methyl-4-(2,5-dihydroxyphenyl)thiazole, **8**. Due to its low solubility in $CDCl_3$, its ^{1}H-NMR spectrum was determined in DMSO-d_6. The rotamery was confirmed as indicated below (after compound **12**). This thiazole, **8**, was obtained by reaction of α-bromo-2,5-dihydroxyacetophenone, **9**, with thioacetamide. The bromination was made with $CuBr_2$ in $CHCl_3$/AcOEt to avoid ring bromination. This synthetic route is better that the one in five steps that starts from gentisic acid (6).

The required quinacetophenone, **10**, was obtained from *p*-diacetoxybenzene by a Fries transposition, as described in Organic Syntheses (7). Notwithstanding we obtained the stated yield, as well as the green colour and the reported melting point, the ^{1}H-NMR spectrum indicates it is a mixture of two products (two ABX systems are present). The more soluble compound was isolated by

chromatography and it is 5-O-acetyl-quinacetophenone (IR and ^{1}H-NMR), **11**. The less soluble compound (quinacetophenone, **10**), was isolated by fractional crystallization from acetone after decolorization.



10



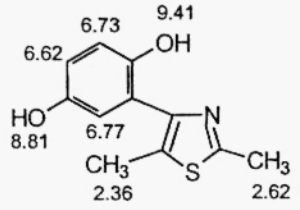
11

Both ketones, **10** and **11**, are yellow; so, there is an additional green component, in small amount, which is retained in the adsorbents.

Finally, we prepared 2,5-dimethyl-4-(2,5-dihydroxyphenyl)thiazole, **12**. A different rotamer is expected for this compound since in a rotamer of type **8**, there would be steric hindrance between the thiazolic methyl at C-5 and the phenolic hydroxyl at C-2, as is shown in molecular models. The ^{1}H-NMR spectrum of **12** (also in DMSO-d_6), showed an up-field shift of 0.6 ppm for H-6, thus confirming the absence of weak hydrogen bonds in this compound. This way we can conclude that the rotamery showed in formulas **8** and **12** is correct.

The dimethyl-dihydroxyphenyl-thiazole **12** was obtained by reaction of α-bromo-2,5-dihydroxypropiophenone, **13**, with thioacetamide. The IR spectrum (KBr wafer) of thiazole **12** indicates an amphoteric-ion structure, **12 a**. There are bands at 3266 (OH, polymer), 2765 and 2556 cm^{-1} (ammonium salt). *In chloroform solution* the phenolic band is shifted to 3600 cm^{-1} (free OH) *and there is no NH+ absorption.*

Since compound **12** gave negative test with 2% $AgNO_3$ in ethanol (8), it was discarded the presence of the precursor hydrobromide, which also gives IR ammonium bands.



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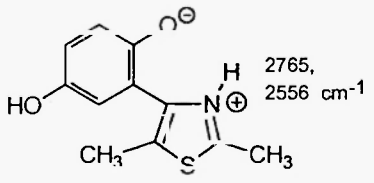
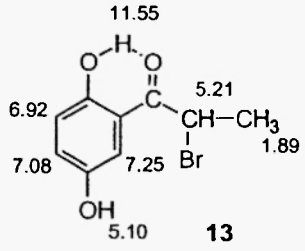


12 a

The 2,5-dihydroxypropiophenone, **14**, required to obtain **13**, was obtained with good yield, in two steps. The first, a Fries transposition of 1,4-dipropionoxybenzene, gave ketone **14** and its 5-propionate, **15**. We used a different method since the reported (9) gave very bad yields. The second step was acid solvolysis (HCl/MeOH) of the above mixture in order to obtain compound **14**. Cf. (10).

The 2,5-dihydroxypropiophenone, **14**, as the methylketone **10**, is yellow, and not white as stated (9). Its ^{1}H-NMR spectrum, as indicated in formula **14**, agrees with this structure. It presents IR bands at 3469 (OH, dimer) and 1640 cm^{-1} (chelated CO). The IR spectrum of 2,5-dihydroxypropiophenone-5-propionate, **15**, as in the case of compound **11**, doesn't show OH absorption. There are carbonyl bands at 1752 (phenolic ester) and 1641 cm^{-1} (chelated ketone).



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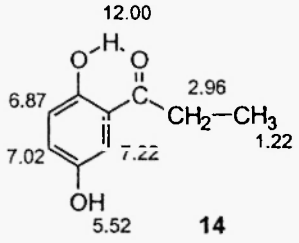

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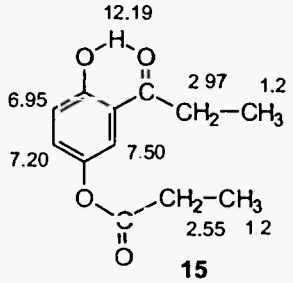

15

In conclusion, the ^{1}H-NMR spectra of the new thiazole derivatives described in this paper permitted us to make doubtless assignments for all the hydrogens, specially in the case of those which present paramagnetic shifts due to weak hydrogen bonding. Moreover, the assignments made previously (1) for other 4-arylthiazoles were confirmed. Experiments "at infinite dilution" corroborated that the observed hydrogen bonding was intramolecular.

EXPERIMENTAL

The IR spectra were recorded in a Perkin-Elmer FTIR-1600 spectrophotometer. The ^{1}H-NMR spectra were obtained in a Varian Inova 300 spectrometer and TMS as internal standard. The EI-MS data were acquired using a JEOL JMS-SX 102 A double-focusing instrument and a Finnigan Mat GCQ ion trap, with electron energy 70 eV.

α-Bromo-2,5-dimethoxyacetophenone, **4**.- To a solution of 2,5-dimethoxyacetophenone (11) (1.8 g, 10 mmoles) in chloroform (20 ml), were added finely pulverized $CuBr_2$ (4.46 g, 20 mmoles) and ethyl acetate (20 ml). The reaction mixture was refluxed for 1:30 h, with magnetic stirring. A current of N_2 was passed (30 min) to eliminate HBr, and the white solid (CuBr) was filtered. The solvents were evaporated *in vacuo*, MeOH added and concentrated. The bromo-compound crystallized (2.05 g, 79%) as a grayish-white solid, m.p. 84-86°C. A recrystallization from ethanol gave hard, long needles, m.p. 85-87°C (1.72g, 66%). IR (KBr) 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.80, s (OCH_3); 3.91, s (OCH_3); 4.62, s (CH_2); 6.90, d, J=9Hz (H-3); 7.09, dd, J=9 and 3 Hz (H-4) and 7.37 ppm, d, J=3 Hz (H-6). M.W. calc. for $C_{10}H_{11}BrO_3$, 259. MS (ei): M_1^+ 258, 16%; $M_2^{\cdot+}$ 260, 16%; m/z 165, 100% (ArCO+).

2-Methyl-4-(2,5-dimethoxyphenyl)thiazole, **3**.- A mixture of **4** (0.26 g, 1 mmol), thioacetamide (0.15 g, 2 mmoles), $CaCO_3$ (0.10 g) and dioxane (3 ml) was refluxed for 30 min, with magnetic stirring. The reaction mixture was filtered, concentrated and water was added. Ethanol was added to dissolve a separated oil and left at room temperature some days until crystallization. Plane prisms (some hexagonal) were obtained (200 mg, 87%). M.p. 55-57°C. IR (KBr) 3149 (C–H in thiazole ring), 891, 806 and 735 cm^{-1} (asym. trisubstituted benzene). Cf. (12). ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.79, s (CH_3); 3.85, s (OCH_3); 3.88, s (OCH_3); 6.84, dd, J=9 and 3 Hz (H-4); 6.91, d, J= 9 Hz (H-3); 7.79, s (thiazole H); and 7. 82 ppm, d, J=3 Hz (H-6). M.W. calc. for $C_{12}H_{13}NO_2S$, 235. MS (ei): $M^{\cdot+}$ 235, 100%.

2-Amino-4-(2,5-dimethoxyphenyl)thiazole, 6.- To a solution of **4** (0.26 g, 1 mmol) in dioxane (1 ml), thiourea was added (0.15 g, 2 mmoles). The flask was stoppered and heated at 50°C (oven) during 30 min. After cooling, the reaction mixture was filtered. The pale yellow solid (hydrobromide) was washed with ether and dissolved in hot water. After cooling, dilute (1:3) NH_4OH was added to precipitate the amino-thiazole. The solid was triturated, filtered and washed with water. Round clusters of needles were formed from

EtOH (0.14 g, 61 %). M.p. 122.5-123.5°C. IR (KBr): 3377 and 3274 (NH_2), 3128 cm^{-1} (thiazolic C–H). ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.82, s (OCH_3); 3.87, s (OCH_3); 6.80, dd, J=9 and 3 Hz (H-4); 6.88, d, J=9 Hz (H-3); 7.23, s (thiazolic H) and 7.65 ppm, d, J= 3 Hz (H-6). M.W. calc. for $C_{11}H_{12}N_2O_2S$, 236. MS (ei): $M^{\cdot+}$ 236, 100%.

Quinacetophenone, **10**.- It was prepared as described (7). 12.7 g from the main fraction from ethanol were dissolved in acetone (500 ml). The black solution was decolorized with charcoal and Tonsil. The yellow solution was evaporated and yielded 8.52 g of hard, yellow crystals. M.p. 203.5-204°C. IR (KBr): 3244 (OH, polymer), 1641 (chelated CO) and 1300 cm^{-1} (C–C stretching in C–(CO)–C). Cf. (13). ^{1}H-NMR ($CDCl_3$/DMSO-d_6, 90 MHz): 2.58, s (CH_3CO); 6.76, d, J=9 Hz (H-3); 7.04, dd, J=9 and 3 Hz (H-4); 7.18, d, J=3 Hz (H-6); 8.82, s (OH-5) and 11.68 ppm, s (OH-2). *Quinacetophenone-5-acetate*, **11**, was isolated from the solid obtained from the mother liquor of the crystallization from ethanol: 1.47 g were dissolved partially in a mixture of CH_2Cl_2-$CHCl_3$ (1:1, 40 ml). A greenish residue was filtered and the solution chromatographed in alumina (15 g), developing with CH_2Cl_2. The first two yellow coloured fractions were evaporated and crystallized from hexane (0.23 g, m.p. 91°C; and 0.33 g, m.p. 88-91°C). IR (KBr): 1757 (CO, phenolic ester) and 1642 cm^{-1} (chelated CO). ^{1}H-NMR ($CDCl_3$, 90 MHz): 2.28, s (Ar–$OCOCH_3$); 2.60, s (Ar–CO–CH_3); 6.73, d, J=9 Hz (H-3); 7.21, dd, J=9 and 3 Hz (H-4); 7.45, d, J=3 Hz (H-6) and 12.04 ppm, s (OH).

α-Bromoquinacetophenone, 9.- Prepared as 4. Reflux time 5 h. M.p. 114-116°C (from ethanol-benzene). IR (KBr) 3340 (OH) and 1644 cm^{-1} (chelated CO). ^{1}H-NMR ($CDCl_3$, 300 MHz): 4.39, s (CH_2); 4.98, s (OH-5); 6.93, d, J=9 Hz (H-3); 7.09, dd, J=9 and 3 Hz (H-4); 7.19, d, J=3 Hz (H-6) and 11.35 ppm, s (OH-2). M.W. calc. for $C_8H_7BrO_3$, 231. MS (ei): $M_1^{\cdot+}$ 230, 67%; $M_2^{\cdot+}$ 232, 65%; m/z 137, 100% (Ar–CO+).

2-Methyl-4-(2,5-dihydroxyphenyl)thiazole, 8.- To a solution of thioacetamide (0.22 g, 3 mmoles) in ethanol (2 ml), a solution of α-bromoquinacetophenone (0.34 g, 1.5 mmoles) in ethanol (1.5 ml) was added. The mixture was concentrated almost to dryness (H_2S is evolved from excess thioacetamide). Water was added and a slightly yellow solid was separated (hydrobromide). It was suspended in water and dilute (1:3) NH_4OH was added. The solid was filtered (190 mg, 63%), m.p. 185°C. IR (KBr) 3298 (OH) and 3123 cm^{-1} (thiazolic C–H). ^{1}H-NMR (DMSO-d_6, 300 MHz): 2.71, s (CH_3); 6.59, dd, J=9 and 3 Hz (H-4); 6.74, d, J=9 Hz (H-3); 7.37, d, J=3 Hz (H-6); 7.93, s (thiazolic H); 8.81, s (OH-5) and 10.17 ppm, s (OH-2). M.W. calc. for $C_{10}H_9NO_2S$, 207. MS (ei): $M^{\cdot+}$ 207, 100%.

2,5-Dihydroxypropiophenone, 14.- Was prepared as described for **10** (10). After acid solvolysis the grayish solid obtained melted at 77-79°C (small needles). It was dissolved in ether and diluted with hexane; a black solid was separated and filtered. Upon dilution with hexane and concentration, yellow prisms crystallized. M.p. 80-82°C. An ethanolic solution gave dark green colour with aqueous $FeCl_3$ solution. IR (KBr): 3469 (OH, dimer) and 1640 cm^{-1} (chelated CO). ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.22, t, J=7.2 Hz (CH_3); 2.96, q, J=7.2 Hz (CH_2); 5.52, s (OH-5); 6.87, d, J=9 Hz (H-3); 7.02, dd, J=9 and 3 Hz (H-4); 7.22, d, J=3 Hz (H-6) and 12.00 ppm, s (OH-2).

2,5-Dihydroxypropiophenone-5-propionate, **15**.- It was isolated from the mixture obtained from the above reaction, by chromatography in alumina (with some Tonsil at the top) dissolving and eluting with AcOEt. M.p. 71-73°C, small needles from ethanol. Its ethanolic solution gave purple colour with aqueous $FeCl_3$, and wine red colour in the hydroxamate test for esters (14,15). IR (KBr): 1752 (CO, phenolic ester), 1641 (chelated CO) and 1136 cm^{-1} (C–O–C stretching). ^{1}H-NMR ($CDCl_3$, 90 MHz): 2 superposed triplets about 1.25 ppm (2 CH_3); 2.55, q, J=7.5 Hz ($OCOCH_2$); 2.97, q, J=7.5 Hz ($COCH_2$); 6.95, d, J=9 Hz (H-3); 7.20, dd, J=9 and 3 Hz (H-4); 7.50, d, J=3 Hz (H-6) and 12.19 ppm, s (chelated OH).

α-Bromo-2,5-dihydroxypropiophenone, **13**.- Prepared as compound **9**. M.p. 106-107°C (from benzene-heptane). IR (KBr): 3419 (OH, polymer) and 1634 cm^{-1} (chelated CO). ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.89, d, J=6.6 Hz (CH_3); 5.10, s (OH-5); 5.21, q, J=6.6 Hz (CH); 6.92, d, J=9 Hz (H-3); 7.08, dd, J=9 and 3 Hz (H-4); 7.25, d, J=3 Hz (H-6) and 11.55 ppm, s (OH-2). M.W. calc. for $C_9H_9BrO_3$, 245. MS (ei): $M_1^{\cdot+}$ 244, 17%; $M_2^{\cdot+}$ 246, 17%; m/z 137, 100% (ArCO+).

2,5-Dimethyl-4-(2,5-dihydroxyphenyl)thiazole, **12**.- Prepared as thiazole **8**. The cement coloured crude product, m.p. 188-192°C, was dissolved in Et_2O-MeOH and decolorized with Tonsil/charcoal. Upon concentration and crystallization from MeOH-Et_2O, a white solid was obtained (0.2 g, 60 %). M.p. 191-192°C. It gave negative test with 2 % $AgNO_3$ in ethanol (no presence of hydrobromide). IR (KBr): 3266 (OH, polymer), 2765 and 2556 cm^{-1} (ammonium salt, **12 a**). IR ($CHCl_3$): 3600 (free OH) and there is not NH+ absorption. ^{1}H-NMR (DMSO-d_6, 300 MHz): 2.36, s (CH_3-5); 2.62, s (CH_3-2); 6.62, dd, J=8.7 and 3 Hz (H-4); 6.73, d, J=8.4 Hz (H-3); 6.77, d, J=3 Hz (H-6); 8.81, s (OH-5) and 9.41 ppm, s (OH-2). M.W. calc. for $C_{11}H_{11}NO_2S$, 221. MS (ei): $M^{\cdot+}$ 221, 100%.

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