SYNTHESIS AND STRUCTURE OF SOME 1-(2-THIENYLMETHYL)-1*H*-IMIDAZOLE DERIVATIVES AS POTENTIAL ANTIMICROBIAL AGENTS

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Abstract- A series of 1-(2-thienylmethyl)-1*H*-imidazole derivatives were synthesized starting from 2-thienylmethylamine (I) and ethyl chloroacetate. The structure of all the new compounds were determined by uv, ir, and ^{1}H-nmr spectroscopy. Preliminary tests of biological activity on these compounds showed that 1-(2-thienylmethyl)-1*H*-imidazole-5-carbohydroxamic acid (XII) is fairly active against *Escherichia Coli* and *Bacillus Subtilis*.

In previous reports [1,2] we described the preparation of a number of imidazole derivatives with biological interest. We also showed that imidazoles which possess a carbohydroxamic group at C-5, together with an sp^{3}-hybridized exocyclic atom in position 1, are apt to be antimicrobial agents. In any case we found that 5-substituted imidazoles are more biologically active than the corresponding 4-substituted isomers. In the literature [3-7] some interesting imidazole derivatives with heterocyclic substituents at the side-chain attached in position 1 have been reported. In the light of these data our particular interest has now been focused on the synthesis of a series of 1-(2-thienylmethyl)-1*H*-imidazole derivatives which combine all the above-mentioned features. These compounds were prepared according to the synthetic route outlined in the Scheme [8]. The mps and spectral data of the imidazoles are assembled in the Table. Considering the synthesis some remarks may be made. In order to obtain IV, if the Claisen reaction is performed with sodium methoxide in THF better yields are obtained, but a transesterification, revealed by ^{1}H-nmr spectra of the subsequent products, occurs. Subsequently compound IV, which separated as a very hygroscopic solid, was converted directly to ethyl 2-mercapto-1-(2-thienylmethyl)-1*H*-imidazole-5-carboxylate (V) by a ring-closure reaction with potassium thiocyanate in acidic medium followed by hydrolysis to the corresponding acid VI. Several studies [9-11] on thione - thiol tautomerism of 2-mercaptoimidazoles indicated, from spectroscopic evidence, the predominance of the thione form. In compound V the presence of a strongly electron-withdrawing group in position 5 alters the equilibrium in favour of a partially ionized thiol form stabilized by resonance effect. Its uv spectrum, in methanol solution, exhibits, together with the band at 235 nm of the 2-thienylmethyl group, a lower-intensity band at 262 nm due to the thione, and a higher one at 298 nm due to the thiol form. In agreement with this attribution, in alkaline solution the sole band of the thiol form, which shows the expected intensity increase and a bathochromic shift of

about 10 nm due to full ionization, appears. The long-wavelength band of the 2-methylthio derivative XIII occurs at a shorter wavelength as compared to the one of compound V owing to the lower stabilization of the excited state by charge delocalization. The carboxylic acid VI and its 2-methylthio derivative XV behave similarly. The ir spectra of 2-mercaptoimidazoles V and VI, in the solid state, show a characteristic SH-stretching band at about 2560 cm^{-1} that remains unchanged also in dilute carbon tetrachloride solution. Of course in the spectra of 2-methylthio derivatives XIII and XV no absorption in the region of SH-stretching is detectable, whereas a well-defined band at about 1530 cm^{-1} appears. Moreover the ^{1}H-nmr spectra of compounds V and VI show a broad singlet at about δ 12.90 due to the mercapto group, while in the spectra of all the 2-methylthio derivatives a sharp singlet at δ 2.65 is detectable.

Scheme :

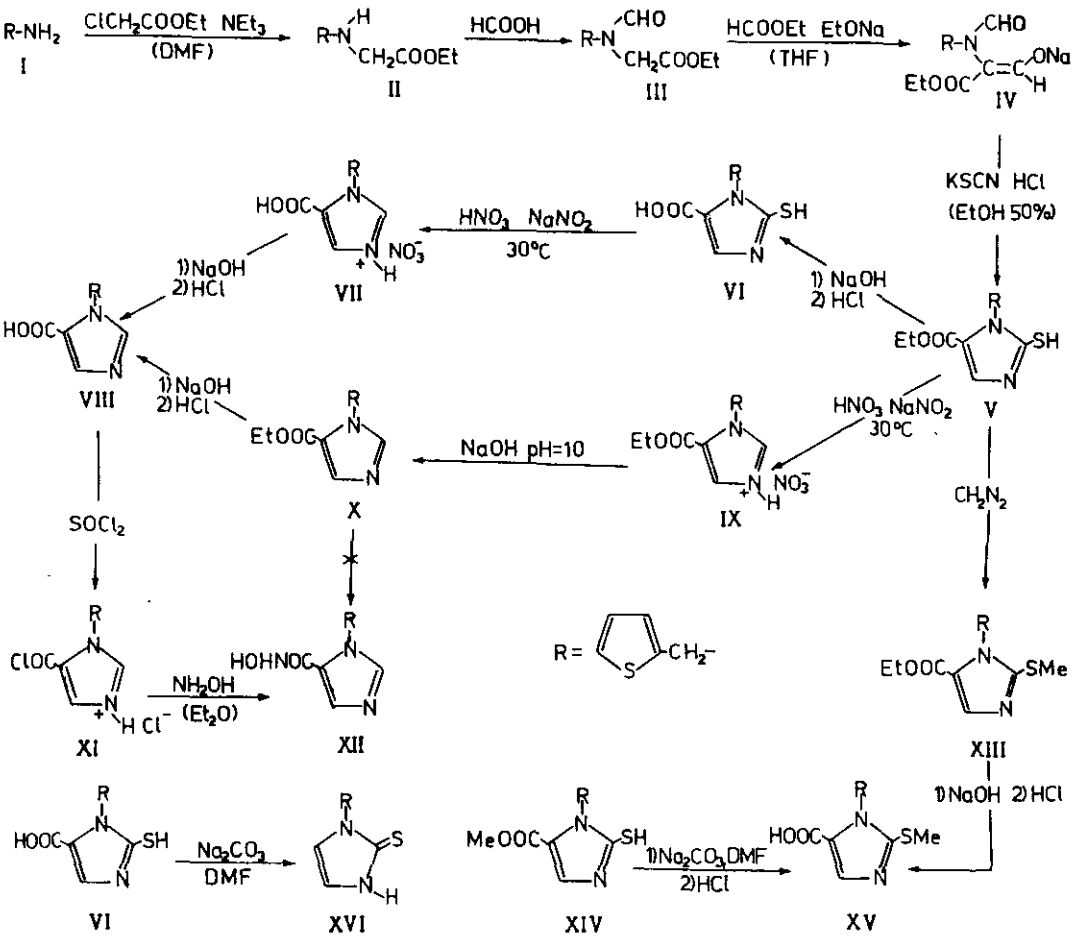

Table: 1-(2-Thienylmethyl)-1*H*-imidazole Derivatives

No (*a*)	Mp ^{0}C(*b*) Solvent	Yield %	Formula	Ir (*c*) ν max cm^{-1}	^{1}H-Nmr (*d*) δ, ppm	Uv λ max nm(Log ε)
V	157-158 EtOH/H_2O	63	$C_{11}H_{12}N_2O_2S_2$	1720,2560	12.92(br s,1H,SH),7.78(s,1H,H-4), 5.83(s,2H,NCH_2)	202(4.05),235(4.07),262(3.95),298(4.00) (*e*); 232(4.16),308(4.15) (*f*); 236(4.09),292(4.04) (*g*)
VI	216-218 ethanol	98	$C_9H_8N_2O_2S_2$	1675,2565	12.80(br s,1H,SH),7.80(s,1H,H-4), 5.54(s,2H,CH_2)	236(4.11),263(3.98),290(4.01) (*e*); 235sh(4.18), 287(4.11) (*f*); 236(4.12),257sh(3.98),289(4.05) (*g*)
VII	159-160 ethanol	96	$C_9H_9N_3O_5S$	1730	9.30(s,1H,H-2),8.28(s,1H,H-4), 5.92(s,2H,CH_2)	
VIII	233 dec ethanol	98(*h*)	$C_9H_8N_2O_2S$	1690	8.10(s,1H,H-2),7.63(s,1H,H-4), 5.76(s,2H,CH_2)	233(4.24) (*e*)
IX	173 dec methanol	97	$C_{11}H_{13}N_3O_5S$	1730	9.37(s,1H,H-2),8.37(s,1H,H-4), 5.91(s,2H,NCH_2)	
X	68-69 EtOH/H_2O	80	$C_{11}H_{12}N_2O_2S$	1710	8.20(s,1H,H-2),7.73(s,1H,H-4), 5.74(s,2H,NCH_2)	235(4.26) (*e*)
XI	179 dec ether	82	$C_9H_8Cl_2N_2OS$	1755	9.80(s,1H,H-2),8.40(s,1H,H-4), 6.10(s,2H,CH_2)	
XII	161-162 water	46	$C_9H_9N_3O_2S$	3270,1670	10.97(s,1H,OH),9.07(s,1H,NH), 7.98(s,1H,H-2),7.47(s,1H,H-4), 5.76(s,2H,CH_2)	233(4.22) (*e*)
XIII	34-35 hexane	97	$C_{12}H_{14}N_2O_2S_2$	1710,1530	7.75(s,1H,H-4),5.65(s,2H,NCH_2), 2.65(s,3H,SCH_3)	201(3.98),236(4.08),272(4.15) (*e*); 225(4.22), 231(4.21),264(4.11) (*f*); 235(4.13),263(4.05) (*g*)
XIV	145-146 EtOH/H_2O	75	$C_{10}H_{10}N_2O_2S_2$	1715,2560	12.95(br s,1H,SH),7.85(s,1H,H-4), 5.75(s,2H,CH_2),3.80(s,3H,CH_3)	235(4.10),262(3.97),298(4.02) (*e*); 236(4.14), 307(4.16) (*f*)
XV	188-189 ethanol	86(*i*)	$C_{10}H_{10}N_2O_2S_2$	1690,1520	7.76(s,1H,H-4),5.66(s,2H,CH_2), 2.65(s,3H,CH_3)	236(4.09),270(4.09) (*e*); 235(4.13),263(4.01) (*f*); 233(4.14),259(4.01) (*g*)
XVI	129-130 EtOH/H_2O	98	$C_8H_8N_2S_2$	1580,1480	11.95(br,1H,NH),6.76-6.66(m,2H, H-4 + H-5),5.40(s,2H,CH_2) (*j*)	235(4.17),265(4.11) (*e*); 237(4.24) (*f*); 237(4.13),260(4.05) (*g*)

(*a*)-All compounds gave correct microanalyses; (*b*)-Uncorrected; (*c*)-KBr; (*d*)-99.9% DMSO-d_6 solution, TMS as internal reference; H-2,H-4, and H-5 refer to the imidazole ring; (*e*)-Solvent: MeOH; (*f*)-Solvent: 0.5*N* NaOH; (*g*)-Solvent: 0.5*N* HCl; (*h*)-Value referred to step VII ⟶ VIII; (*i*)-Value referred to step XIII ⟶ XV; (*j*)-Solvent: $CDCl_3$.

Several attempts to obtain 5-carbohydroxamic acids with a mercapto group at position 2, starting from compounds V and VI, failed. In fact from the reaction of compound V either with hydroxylamine hydrochloride in methanol at *p*H = 9 or with the free base in anhydrous ether, the starting product was recovered. Unfortunately, using the acid VI the reaction also did not occur because, in no case, the intermediate acid chloride was obtained. Instead the 1-(2-thienylmethyl)-1*H*-imidazole-5-carbohydroxamic acid (XII) was prepared in good yield from compound VIII, through the corresponding acid chloride hydrochloride XI, by the reaction with free base hydroxylamine in anhydrous ether. Attempts to synthesize compound XII directly from the ester X were unsuccessful. 2-Methylthio-1-(2-thienylmethyl)-1*H*-imidazole-5-carboxylic acid (XV), which was obtained in very good yield by alkaline hydrolysis of XIII, was also isolated when compound XIV was heated in DMF in presence of sodium carbonate. Probably in this reaction the sulfur atom at position 2 is alkylated by the ester group. It must be underlined that attempts to isomerize the corresponding ethyl ester V under the same reaction conditions were ineffective. Previously Jones [12] reported that a similar conversion occurs when methyl (or ethyl) 2-mercaptoimidazole-4(5)-carboxylate is heated up to the melting point. Nevertheless, in this case, a subsequent decarboxylation occurs. On the other hand 2-mercapto-1-(2-thienylmethyl)-1*H*-imidazole-5-carboxylic acid (VI), by heating in DMF and in the presence of sodium carbonate, undergoes decarboxylation giving the pure 1,3-dihydro-1-(2-thienylmethyl)-2*H*-imidazole-2-thione (XVI). In the latter compound, which lacks an electron-withdrawing substituent at position 5 of the imidazole ring, it is not surprising that the thione - thiol equilibrium entirely favours the former structure. In fact, in agreement with this attribution, the uv spectrum of XVI, in methanol solution, exhibits a band at 265 nm, while in the ir spectrum the $\nu_{C=S}$ band is detectable at 1580 cm^{-1}. Moreover the ^{1}H-nmr spectrum shows a broad signal at δ 11.95 due to the NH proton and a multiplet at δ 6.76-6.66 due to the protons of the imidazole nucleus; of course on exchange with D_2O the NH signal disappears whereas the H-4 and H-5 protons give two doublets with J = 2 Hz. In addition it must be noted that compound XVI, contrary to all 2-mercaptoimidazoles reported above, is insoluble in dilute sodium carbonate solution and also remains unaltered by treatment with diazomethane.

For the evaluation of the possible effect that an asymmetric carbon atom connected to position 1 may have on biological activity, we tried to make some 1-[phenyl(2-thienyl)methyl]imidazole derivatives applying the same procedure reported in the Scheme. Unfortunately, under the conditions involved in the ring-closure step, the side-chain immediately detached and ethyl 2-mercaptoimidazole-5(4)-carboxylate was obtained [13]. The title compounds have been tested against a number of microorganisms. Preliminary *in vitro* experiments have shown that compound XII appears to be the most interesting member of this series; in fact, its minimal inhibitory concentration against *Escherichia Coli 120* and *Bacillus Subtilis ATCC 9466* on BHI agar + 10% serum medium is 0.5 µg/ml and 1.5 µg/ml respectively.

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8 Compounds II - V were prepared according to the literature 1. Compound II: yield 65%, bp 122-123 ^{0}C/0.4 mm, ir: 3320,1740 cm^{-1}. Compound III: yield 87%, bp 128-129 ^{0}C/0.05 mm, ir: 1740,1675 cm^{-1}.

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