

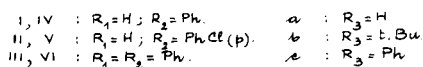
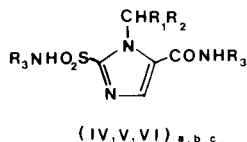
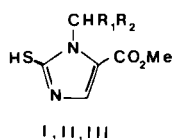
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Received July 30, 1981

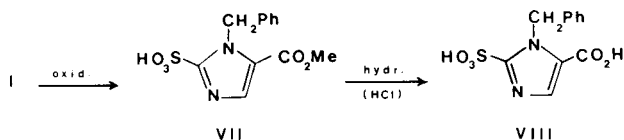
1-Alkylaryl-2-sulfamoylimidazole-5-carboxamides IV, V and VI were prepared starting from methyl 1-alkylaryl-2-mercaptoimidazole-5-carboxylates I, II and III. Many interesting reaction intermediates such as the 1-alkylaryl-2-sulfamoylimidazole-5-carboxylic acids (XVII, XX and XXI) were isolated. The structures of all of the compounds were determined by ir and nmr spectroscopy. Diuretic activity tests were also carried out on these compounds. In addition, 1-alkylaryl-2-sulfamoylimidazole-5-carboxamides XXVII, XXVIII and XXIX were also prepared and tested for biological activity.

J. Heterocyclic Chem., **19**, 561 (1982).

In our previous paper (1) we reported the preparation of a series of 1-alkylaryl-2-mercaptoimidazole-5-carboxylic acids. When tested on bacteria and fungi the 5-carboxylic acids showed lower minimal inhibitory concentrations compared to the 4 isomers. Many compounds with sulfamoyl group show diuretic activity while heterocyclic sulfonamides are used as antibacterial and antiepileptic drugs (2-7). We therefore decided to investigate the reactions of methyl 1-alkylaryl-2-mercaptoimidazole-5-carboxylates I, II and III, intermediates for the synthesis of the 5-carboxylic acids, and their conversion to 1-alkylaryl-2-sulfamoylimidazole-5-carboxamides (IV, V and VI).

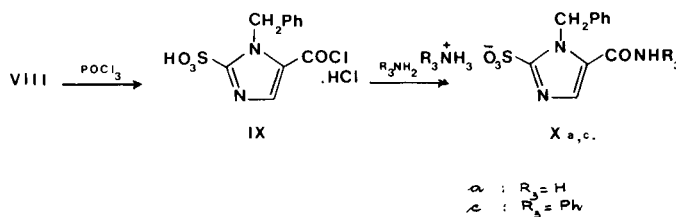


Compound I was converted to 1-benzyl-5-methoxycarbonylimidazole-2-sulfonic acid (VII) by oxidation with hydrogen peroxide followed by hydrolysis to 1-benzyl-2-sulfoimidazole-5-carboxylic acid VIII.

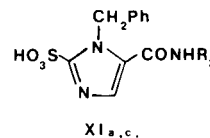


The structure of the compound VIII was confirmed by pmr spectroscopy. It gave a signal at δ 12.90 due to the hydrogens of the two acid groups, another signal at δ 7.30 attributed to the aromatic multiplet and two other singlets at δ 8.28 and 6.00 due to the H(4) and the methylene group, respectively. Chlorination of VIII with phosphoryl chloride gave the acid chloride, IX, but due to its instability, the crude product was converted directly to the related

diamide by reaction with amines. It was only by rationalizing the latter product that we obtained an indication of the formation of the chloro intermediate IX. This product has a carboxamyl group and is the sulfonic acid salt of the amine. The formation of compounds X led us to conclude that chlorination occurred only at the carboxyl group while the sulfo group did not react with the phosphoryl chloride as reported in the literature for the 4-imidazole-sulfonic acid (8).

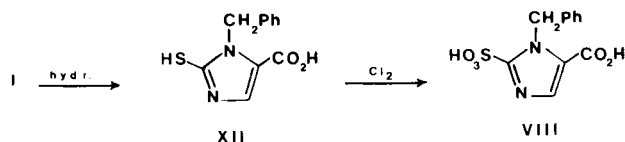


Evidence for the assigned structures X is provided by the ir spectra which gave amide I bands at about 1670 cm^{-1} and the NH absorption signal at about 3380 cm^{-1} . The signals between 1220 and 1280 cm^{-1} were attributed to the sulfo group vibrations. The pmr spectrum of anilinium 1-benzyl-5-(N-phenylcarboxamyl)imidazole-2-sulfonate Xc, showed a singlet at δ 10.58 due to the hydrogen atom of the CONH group and a multiplet at δ 6.25 due to the protons of the PhNH_3^+ group. Unequivocal evidence for the structures of the compounds X was provided by their chemical reactions. Treatment of X with cold dilute hydrochloric acid led to 1-benzyl-5-carboxamylimidazole-2-sulfonic acids, XI.

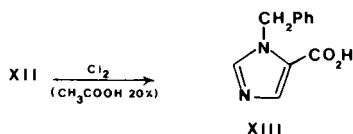


Owing to the difficulty in chlorinating the sulfo group, we therefore decided to oxidize the mercapto group with chlorine. We anticipate that with such oxidizing agents, the sulfochloride will be formed according to a mechanism

reported by some authors (9-13). The starting material for this reaction, 1-benzyl-2-mercaptoimidazole-5-carboxylic acid (XII), was obtained by the hydrolysis of the corresponding methyl carboxylate I. Chlorination of XII at 0-4° in water, 15% acetic acid or 3*N* hydrochloric acid led to the sulfo derivative VIII.



On the other hand, desulfonation occurred if the reaction were carried out in 20% acetic acid. The product was identified as 1-benzylimidazole-5-carboxylic acid XIII.



In concentrated hydrochloric acid no reaction occurred at -3° and the starting material XII, was recovered.

Finally by chlorinating XII with chlorine in 50% acetic acid at 5-7° followed by the action of the amines, two products, XVI and IV, were obtained. It was proposed that these compounds were formed *via* the intermediates XIV and XV, respectively.

Since only small quantities of IV were obtained by this method, we were able to obtain better yields by reacting XVII with thionyl chloride and converting the resulting acid chloride to the required amides IV by the action of the appropriate amines. This method led to improved yields of IV.

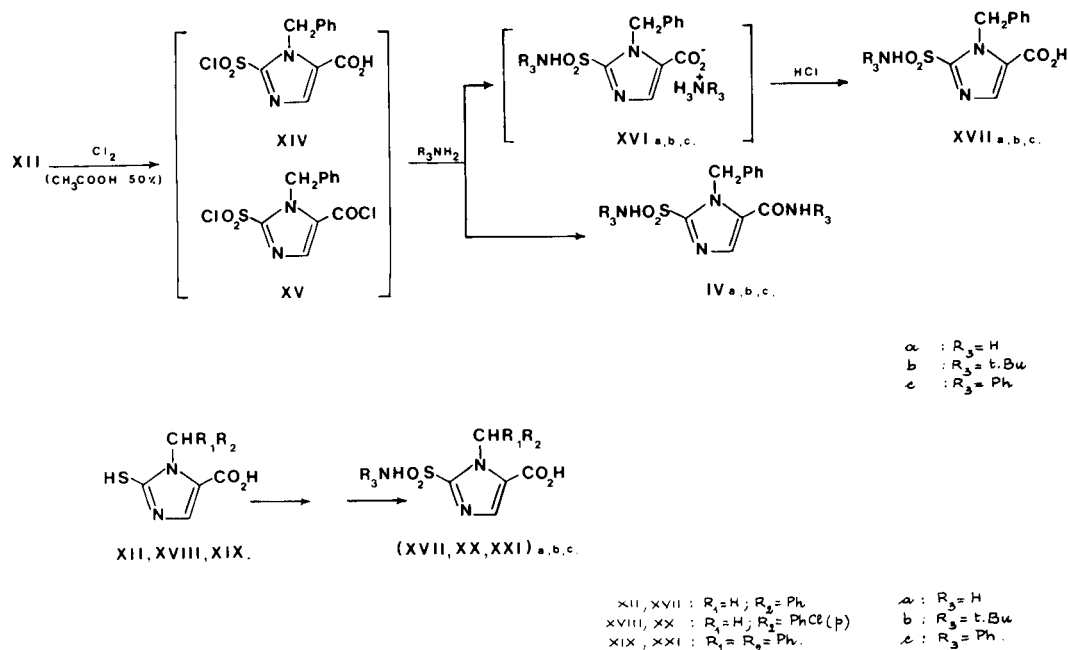
Starting from compounds II and III, the main products obtained *via* the corresponding mercaptocarboxylic acids XVIII and XIX were the 1-alkylaryl-2-sulfamoylimidazole-5-carboxylic acids (XX and XXI). From these compounds the final products V and VI were prepared as described above.

Table 1

Analytical and Spectral Data of 1-Alkylaryl-2-sulfamoylimidazole-5-carboxamides (IV, V, VI)

Compound	Mp°C Solvent	Yield %	Formula	Analysis (a)			Ir, ν max cm ⁻¹ (b)	Pmr, δ , ppm (c)
				C	H	N		
IVa	245-246 Ethanol	15	C ₁₁ H ₁₂ N ₄ O ₃ S	46.97 (47.13)	4.37 4.31	19.76 19.99	3450, 3340, 3300, 3180, 1675, 1185, 1160.	8.10 (s, 2H, SO ₂ NH ₂), 7.70 (s, 1H, H(4)), 7.25 (m, 7H, aromatic + CONH ₂), 5.90 (s, 2H, CH ₂)
IVb	158-159 Ethanol/water	15	C ₁₆ H ₂₈ N ₄ O ₃ S	57.92 (58.16)	7.02 7.18	13.97 14.27	3320, 3140, 1650, 1170, 1150.	8.10 (s, 1H, SO ₂ NH), 7.90 (s, 1H, CONH), 7.50 (s, 1H, H(4)), 7.20 (m, 5H, aromatic), 5.80 (s, 2H, CH ₂), 1.22 (s, 9H, CONH- <i>t</i> -Bu), 1.12 (s, 9H, SO ₂ NH- <i>t</i> -Bu)
IVc	180-181 acetonitrile	10	C ₂₃ H ₂₀ N ₄ O ₃ S	63.56 (63.87)	4.66 4.73	13.13 12.95	3300, 3160, 1660, 1180, 1160.	11.10 (s, 1H, SO ₂ NH), 10.30 (s, 1H, CONH), 7.85 (s, 1H, H(4)), 7.25 (m, 15H, aromatic), 5.90 (s, 2H, CH ₂)
Va	222-224 water	10	C ₁₁ H ₁₁ ClN ₄ O ₃ S	42.14 (41.97)	3.51 3.52	17.53 17.80	3430, 3380, 3300, 3180, 1670, 1180, 1160.	8.15 (s, 1H, SO ₂ NH ₂), 7.15 (s, 1H, H(4)), 7.25 (m, 6H, aromatic + CONH ₂), 5.85 (s, 2H, CH ₂)
Vb	165-166 Ethanol/water	20	C ₁₆ H ₂₇ ClN ₄ O ₃ S	53.44 (53.72)	6.37 6.35	12.78 13.12	3290, 3100, 1640, 1165, 1140.	8.15 (s, 1H, SO ₂ NH), 7.90 (s, 1H, CONH), 7.50 (s, 1H, H(4)), 7.20 (m, 4H, aromatic), 5.79 (s, 2H, CH ₂), 1.21 (s, 9H, CONH- <i>t</i> -Bu), 1.11 (s, 9H, SO ₂ NH- <i>t</i> -Bu)
Vc	201-202 Ethanol	20	C ₂₃ H ₁₉ ClN ₄ O ₃ S	58.89 (59.16)	4.12 4.10	12.05 11.99	3380, 3180, 1650, 1170 1150.	11.10 (s, 1H, SO ₂ NH), 10.30 (s, 1H, CONH), 7.90 (s, 1H, H(4)), 7.25 (m, 14H, aromatic), 5.87 (s, 2H, CH ₂)
VIa	180-181 Ethanol/water	15	C ₁₇ H ₁₆ N ₄ O ₃ S	56.99 (57.28)	4.60 4.52	15.45 15.72	3420, 3390, 3300, 3160, 1670, 1180, 1150.	8.30 (s, 2H, SO ₂ NH ₂), 7.70 (s, 1H, H(4)), 7.65 (s, 1H, methine), 7.30 (m, 12H, aromatic + CONH ₂)
VIb	243-244 Ethanol/water	15	C ₂₆ H ₃₂ N ₄ O ₃ S	63.80 (64.07)	6.87 6.88	12.20 11.95	3390, 3160, 1650, 1160, 1140.	8.30 (s, 1H, SO ₂ NH), 7.60 (s, 1H, H(4)), 7.45 (s, 1H, methine), 7.20 (m, 10H, aromatic), 7.00 (s, 1H, CONH), 1.32 (s, 9H, CONH- <i>t</i> -Bu), 1.08 (s, 9H, SO ₂ NH- <i>t</i> -Bu)
VIc	145-146 Ethanol	15	C ₂₉ H ₂₄ N ₄ O ₃ S	68.70 (68.48)	4.76 4.75	10.95 11.01	3380, 1660, 1170, 1150, 1101)	11.12 (s, 1H, SO ₂ NH), 9.97 (s, 1H, CONH), 7.68 (s, 1H, H(4)), 7.56 (s, 1H, methine), 7.25 (m, 20H, aromatic)

(a) Values in parentheses refer to calculated percentages. (b) Potassium bromide. (c) DMSO-d₆ solution, TMS as internal reference.



The ir spectra of compounds IV, V and VI show well defined bands between 3450 and 3180 cm^{-1} attributable to the ν NH of sulfamoyl and carboxamido groups, at 1180-1140 cm^{-1} to the ν SO_2 modes and at 1675-1670 cm^{-1}

to the ν CO. With regard to the acids XVII, XX and XXI, the ν NH and ν CO of the carboxamido group disappeared as expected while at about 1700 cm^{-1} the band of the carboxyl group was observed. From the pmr spectra it can be

Table 2

Analytical and Spectral Data of 1-Alkylaryl-2-sulfamoylimidazole-5-carboxylic Acids (XVII, XX, XXI)

Compound	Mp $^{\circ}\text{C}$ Solvent	Yield %	Formula	Analysis (a)			Ir, ν max cm^{-1} (b)		Pmr, δ , ppm (c)
				C	H	N			
XVIIa	190-191 acetonitrile	40	$\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_4\text{S}$	46.70 (46.96)	3.99 3.94	14.74 14.52	3360, 3200, 1690, 1170, 1160.	8.21 (s, 2H, NH_2), 7.78 (s, 1H, H(4)), 7.30 (m, 5H, aromatic), 5.88 (s, 2H, CH_2)	
XVIIb	191-192 ethanol	73	$\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_4\text{S}$	53.39 (53.18)	5.71 5.68	12.16 12.45	3210, 1700, 1175, 1140.	8.10 (s, 1H, NH), 7.70 (s, 1H, H(4)), 7.20 (m, 5H, aromatic), 5.80 (s, 2H, CH_2), 1.10 (s, 9H, <i>t</i> -Bu)	
XVIIc	209-210 acetonitrile	60	$\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_4\text{S}$	56.95 (57.13)	4.31 4.23	11.72 11.75	3180, 1700, 1180, 1160.	11.10 (s, 1H, NH), 7.80 (s, 1H, H(4)), 7.15 (m, 10H, aromatic), 5.88 (s, 2H, CH_2)	
XXa	226-227 ethanol	60	$\text{C}_{11}\text{H}_{10}\text{ClN}_3\text{O}_4\text{S}$	42.01 (41.84)	3.24 3.19	13.20 13.31	3380, 1690, 1180, 1160.	8.27 (s, 2H, NH_2), 7.80 (s, 1H, H(4)), 7.25 (m, 4H, aromatic), 5.85 (s, 2H, CH_2)	
XXb	209-210 acetonitrile/water	70	$\text{C}_{15}\text{H}_{18}\text{ClN}_3\text{O}_4\text{S}$	48.19 (48.45)	4.92 4.87	11.50 11.30	3200, 1710, 1165, 1150.	8.20 (s, 1H, NH), 7.75 (s, 1H, H(4)), 7.15 (m, 4H, aromatic), 5.82 (s, 2H, CH_2), 1.10 (s, 9H, <i>t</i> -Bu)	
XXc	198-200 carbon tetrachloride	65	$\text{C}_{17}\text{H}_{14}\text{ClN}_3\text{O}_4\text{S}$	51.92 (52.10)	3.80 3.60	10.61 10.72	3220, 1710, 1185, 1160.	11.10 (s, 1H, NH), 7.80 (s, 1H, H(4)), 7.15 (m, 9H, aromatic), 5.85 (s, 2H, CH_2)	
XXIa	235-237 ethanol	50	$\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_4\text{S}$	57.40 (57.13)	4.35 4.23	11.60 11.75	3320, 3280, 1720, 1180, 1170.	8.35 (s, 2H, NH_2), 7.80 (s, 1H, H(4)), 7.74 (s, 1H, methine), 7.30 (m, 10H, aromatic)	
XXIb	163-164 ethanol	60	$\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_4\text{S}$	61.18 (60.99)	5.68 5.60	10.04 10.16	3230, 1710, 1180, 1160.	8.27 (s, 1H, NH), 7.75 (s, 1H, H(4)), 7.70 (s, 1H, methine), 7.20 (m, 10H, aromatic), 1.08 (s, 9H, <i>t</i> -Bu)	
XXIc	138-140 ethanol	60	$\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}_4\text{S}$	63.59 (63.72)	4.47 4.41	9.80 9.69	3400, 1710, 1180, 1150.	11.15 (s, 1H, NH), 7.78 (s, 2H, H(4) + methine), 7.20 (m, 15H, aromatic)	

(a) Values in parentheses refer to calculated percentates, (b) Potassium bromide. (c) DMSO- d_6 solution, TMS as internal reference.

seen that the presence of the sulfamoyl and carboxamido (or carboxyl) groups in the 2 and 5 positions caused general downfield shifts compared to the signals of the parent imidazoles in which the 2 and 5 positions are unsubstituted. This is due to the electron withdrawing effects of these substituents and the increased conjugation in the imidazole system. In the pmr spectrum of 1-benzylimidazole, for instance, the signals of the imidazole ring protons overlapped those of the phenyl group (δ 7.00-7.40) and the methylene group showed a singlet at δ 5.10. In the case of the compounds IV and XVII, the proton in the 4 position and the methylene group appeared as singlets with chemical shift at δ 7.80 and 5.85, respectively (Tables 1 and 2). Since compounds IV, V, VI, XVII, XX and XXI

have the structural features of diuretic drugs, their pharmacological properties were also studied. Preliminary experiments in mice in which the compounds were administered intraperitoneally show that XXa and XXc exhibit considerable diuretic effect. The activity, however, disappears if $R_3 = t\text{-Bu}$ (XXb). The diuretic activity seems to be related to the presence of a chlorine atom on the substituent in position 1 since none of the compounds, XVII and XXI showed this activity.

Since imidazolecarboxamides are known to exhibit biological activity (14-17) the following new compounds, XXVIIa,b, XXVIIIa,c and XXIX, were therefore prepared according to Scheme 1

Scheme 1

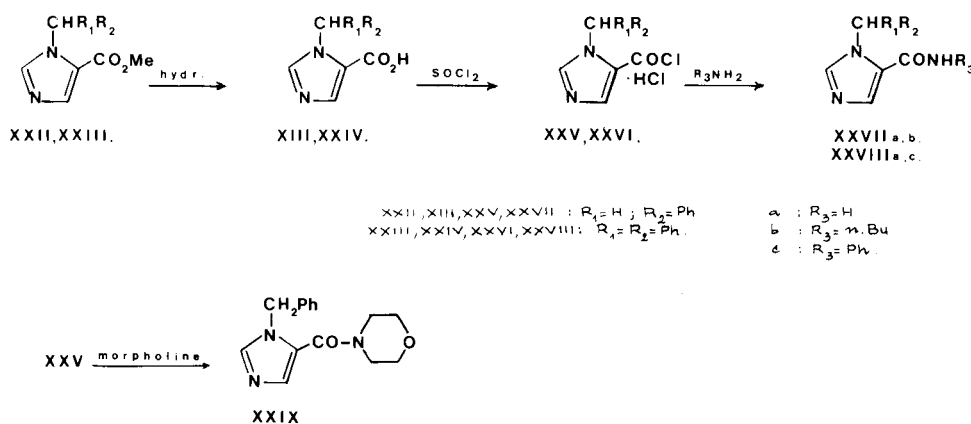


Table 3

Analytical and Spectral Data of 1-Alkylarylimidazole-5-carboxamides (XXVII, XXVIII) and 1-Benzyl-5-morpholinocarbonylimidazole (XXIX)

Compound	Mp°C Solvent	Yield %	Formula	Analysis (a)			Ir, ν max cm^{-1} (b)	Pmr, δ , ppm (c)
				C	H	N		
XXVIIa	184-185 chloroform	80	$\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}$	65.58 (65.67)	5.59 5.47	20.89 20.91	3340, 3310, 1670.	7.92 (s, 1H, H(2)), 7.68 (s, 1H, H(4)), 7.20 (m, 7H, aromatic + NH_2), 5.59 (s, 2H, CH_2)
XXVIIb	92-93 benzene/petroleum ether	85	$\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}$	69.82 (69.64)	7.54 7.40	16.20 16.24	3320, 1635.	8.22 (m, 1H, NH), 7.93 (s, 1H, H(2)), 7.60 (s, 1H, H(4)), 7.25 (m, 5H, aromatic), 5.58 (s, 2H, $\text{CH}_2\text{-Ph}$), 3.15 (m, 2H, N- CH_2), 1.40 (m, 4H, $\text{CH}_2\text{-CH}_2$), 0.93 (m, 3H, CH_3)
XXVIIIa	163-164 water	85	$\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}$	73.36 (73.64)	5.35 5.45	15.03 15.16	3410, 3320, 1650.	7.83 (s, 1H, H(2)), 7.75 (s, 1H, H(4)), 7.45 (s, 1H, methine), 7.30 (m, 7H, aromatic + NH_2), 7.05 (m, 5H, aromatic)
XXVIIIc	115-116 cyclohexane	80	$\text{C}_{23}\text{H}_{14}\text{N}_3\text{O}$	77.97 (78.18)	5.40 5.38	11.88 11.89	3420, 1650.	7.93 (s, 1H, H(2)), 7.68 (s, 1H, H(4)), 7.61 (s, 1H, NH), 7.53 (s, 1H, methine), 7.38 and 7.18 (m, 15H, aromatic)
XXIX	96-97 carbon tetrachloride	80	$\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_2$	66.34 (66.42)	6.43 6.27	15.40 15.40	1630.	8.00 (s, 1H, H(2)), 7.20 (m, 6H, aromatic + H(4)), 5.33 (s, 2H, $\text{CH}_2\text{-Ph}$), 3.35 (m, 8H, morpholine)

(a) Values in parentheses refer to calculated percentages. (b) Potassium bromide. (c) DMSO- d_6 solution, TMS as internal reference.

The ir spectra of the carboxamides, XXVII and XXVIII, showed bands in the region $3420\text{--}3310\text{ cm}^{-1}$ and $1670\text{--}1635\text{ cm}^{-1}$ attributable to the ν NH and ν CO modes, respectively. As expected, the ir spectrum of XXIX gave no ν NH band, but the ν CO appeared at 1630 cm^{-1} . The pmr spectra showed the expected singlets due to the protons in the 2 and 4 positions of the imidazole ring, and the methylene (or methine) group in position 1. As reported for similar compounds (18-20), the lowest-field peak always corresponds to the H(2), and the coupling between H(2) and H(4) is extremely weak ($J_{2,4}$ very small). The aromatic proton signals overlap with the CONH_2 peak in the case of compounds XXVIIa and XXVIIIa, and with the proton in the 4 position in the case of compound XXIX (Table 3).

These compounds were tested *in vitro* for their biological activity against a series of bacteria and fungi on BHI agar + 10% serum medium. None of the 1-alkylarylimidazole-5-carboxamides showed any bacterial activity *in vitro* against the strains tested; the minimal inhibitory concentration was always greater than 100 mcg/ml.

EXPERIMENTAL

The ir spectra were measured with a Perkin-Elmer model 417 spectrophotometer and pmr spectra on a Perkin-Elmer R 32 instrument at a probe temperature of about 38° . Melting points are uncorrected.

1-Benzyl-2-sulfoimidazole-5-carboxylic Acid (VIII).

An 18% aqueous solution of hydrogen peroxide was added gradually to a stirred aqueous suspension of methyl 1-benzyl-2-mercaptoimidazole-5-carboxylate I at 0° . The reaction mixture was treated with sodium hydroxide until the pH was 12. It was allowed to stand at the same temperature for 12 hours. In addition to the oxidation of the mercapto group, hydrolysis of the carboxylate group occurred. On treatment with concentrated hydrochloric acid, compound VIII was separated out, mp $265\text{--}266^\circ$ from water; ir (potassium bromide): $1740, 1300, 1250\text{ cm}^{-1}$.

Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_5\text{S}$: C, 46.80; H, 3.54; N, 9.92. Found: C, 47.02; H, 3.59; N, 9.65.

1-Benzyl-5-chloroformylimidazole-2-sulfonic Acid Hydrochloride (IX).

Compound VIII was refluxed for 6 hours at room temperature with a large excess of phosphoryl chloride. The solid product that separated out was collected and washed several times with anhydrous ether, mp $243\text{--}244^\circ$; ir (potassium bromide): $1770, 1410, 1280\text{ cm}^{-1}$.

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{ClN}_2\text{O}_4\text{S}\cdot\text{HCl}$: C, 39.18; H, 2.98; N, 8.30. Found: C, 38.92; H, 3.00; N, 8.25.

Ammonium 1-Benzyl-5-carboxamylimidazole-2-sulfonate (Xa).

Gaseous ammonia was slowly introduced through a capillary tube for 2 hours into a benzene suspension of IX maintaining the temperature at about 30° . The resulting solid residue was filtered and recrystallized from water, mp $249\text{--}250^\circ$; ir (potassium bromide): $3450, 3350, 1670, 1280, 1220\text{ cm}^{-1}$.

Anal. Calcd. for $\text{C}_{11}\text{H}_{14}\text{N}_4\text{O}_4\text{S}$: C, 44.28; H, 4.73; N, 18.78. Found: C, 44.35; H, 4.65; N, 19.01.

Anilinium 1-Benzyl-5-(*N*-phenylcarboxamyl)imidazole-2-sulfonate (Xc).

A large excess of aniline was slowly added to a benzene suspension of IX. The mixture was allowed to react for 2 hours at 50° . The solid product was filtered and recrystallized from water, mp $265\text{--}266^\circ$; ir (potassium bromide): $3380, 1660, 1280, 1220\text{ cm}^{-1}$.

Anal. Calcd. for $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_4\text{S}$: C, 61.31; H, 4.92; N, 12.43. Found: C, 61.45; H, 5.01; N, 12.60.

1-Benzyl-5-carboxamylimidazole-2-sulfonic Acid (XIa).

A water solution of Xa acidified with cold dilute hydrochloric acid gave XIa, mp $275\text{--}276^\circ$ from ethanol/water; ir (potassium bromide): $3410, 3310, 1700, 1270, 1250\text{ cm}^{-1}$.

Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_4\text{S}$: C, 46.96; H, 3.93; N, 14.94. Found: C, 47.10; H, 3.85; N, 14.73.

1-Benzyl-5-(*N*-phenylcarboxamyl)imidazole-2-sulfonic Acid (XIc).

This compound was prepared as described for XIa, mp $285\text{--}287^\circ$ from water/ethanol; ir (potassium bromide): $3340, 1710, 1290, 1210\text{ cm}^{-1}$.

Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_4\text{S}$: C, 57.13; H, 4.23; N, 11.76. Found: C, 57.25; H, 4.15; N, 11.54.

1-Alkylaryl-2-mercaptoimidazole-5-carboxylic Acids (XII, XVIII and XIX).

A suspension of 1-benzyl (I), 1-*p*-chlorobenzyl (II) or 1-benzhydryl-2-mercaptoimidazole-5-methyl carboxylate (III) in 2*N* sodium hydroxide solution was allowed to react for 2 hours at 60° . After cooling, acidification with dilute hydrochloric acid gave XII, XVIII and XIX, respectively.

1-Benzyl-2-mercaptoimidazole-5-carboxylic Acid (XII).

This compound had mp $221\text{--}222^\circ$ from ethanol; ir (potassium bromide): $3110, 3040, 2940, 2570, 1670\text{ cm}^{-1}$.

Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2\text{S}$: C, 56.39; H, 4.30; N, 11.95. Found: C, 56.12; H, 4.45; N, 12.03.

1-*p*-Chlorobenzyl-2-mercaptoimidazole-5-carboxylic Acid (XVIII).

This compound had mp $247\text{--}248^\circ$ from ethanol; ir (potassium bromide): $3100, 3020, 2920, 2580, 1690\text{ cm}^{-1}$.

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{ClN}_2\text{O}_2\text{S}$: C, 49.16; H, 3.37; N, 10.42. Found: C, 48.93; H, 3.30; N, 10.35.

1-Benzhydryl-2-mercaptoimidazole-5-carboxylic Acid (XIX).

This compound had mp $165\text{--}166^\circ$ from acetonitrile; ir (potassium bromide): $3120, 3040, 2940, 2560, 1700\text{ cm}^{-1}$.

Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: C, 65.78; H, 4.54; N, 9.02. Found: C, 65.60; H, 4.49; N, 9.10.

Chlorination of 1-Alkylaryl-2-mercaptoimidazole-5-carboxylic Acids XII, XVIII and XIX. General Procedure.

Chlorine was introduced through a capillary tube at a moderately rapid rate into a cooled suspension of XII (or XVIII, XIX) in dilute acetic acid while stirring. The crude product was filtered and dried (Table 4).

Table 4

Starting Product	Solvent	Product/ Solvent	time (minutes)	T $^\circ\text{C}$	Yield % (Crude product)
XII	50% acetic acid	1:10	40	5-6	70
XVIII	20% acetic acid	1:15	85	5-6	85
XIX	20% acetic acid	1:15	80	5-6	80

1-Alkylaryl-2-sulfamoylimidazole-5-carboxamides (IV, V and VI)a,b,c (Table 1) and 1-Alkylaryl-2-sulfamoylimidazole-5-carboxylic Acids (XVII, XX and XXI)a,b,c (Table 2). General Procedure.

a) The relative chlorination product of 1-benzyl- or 1-*p*-chlorobenzyl- or 1-benzhydryl-2-mercaptoimidazole-5-carboxylic acid (XII, XVIII and XIX, respectively) was added gradually with swirling to a large excess of liquid ammonia in a Dewar flask. The solution was allowed to stand for a short time, then poured into a beaker for the evaporation of the excess ammonia. On treatment with water, a suspension was formed which after filtration gave IVa (Va or VIa, respectively). Acidification of the aqueous solution with dilute hydrochloric acid gave XVIIa (XXa or XXIa, respectively). b) An excess of *t*-butylamine (4:1) was added dropwise at room temperature to a benzene suspension of each starting product. The reaction mixture was allowed to stand for 3 hours at 60° . After filtration, the solid product was dissolved in water and acidified with dilute hydro-

chloric acid to give XVIIb (XXb or XXIb). The benzene solution, after removal of the solvent gave IVb (Vb or VIb). c) Excess aniline (4:1) was added dropwise at room temperature to a benzene suspension of each starting product. The mixture was allowed to react for 3 hours at boiling temperature. The solid residue was dissolved in water and acidified with dilute hydrochloric acid to give a solid mixture of IVc and XVIIc (Vc and XXc or VIc and XXIc, respectively).

Treatment of this residue with sodium hydrogencarbonate solution gave an insoluble residue identified as compound IVc (Vc or VIc). Acidification with dilute hydrochloric acid yielded XVIIc (XXc or XXIc). From the benzene solution an oily product was obtained after removal of the solvent. Shaking the oil with water and acidifying with dilute hydrochloric acid gave a solid product identical with the mixtures described above.

1-Benzylimidazole-5-carboxylic Acid (XIII).

Methyl 1-benzylimidazole-5-carboxylate (XXII) was added to a 2N sodium hydroxide solution (molar ratio 1:4). The mixture was allowed to react at 60° for 5 hours while stirring. The resulting clear solution was cooled. Acidification with concentrated hydrochloric acid (pH 4) gave a precipitate of XIII which was collected by filtration and recrystallized from water, mp 224-225°; ir (potassium bromide): 1690 cm⁻¹.

Anal. Calcd. for C₁₁H₁₀N₂O₂: C, 65.34; H, 4.98; N, 13.80. Found: C, 64.96; H, 5.07; N, 14.01.

1-Benzhydrylimidazole-5-carboxylic Acid (XXIV).

Methyl 1-benzhydrylimidazole-5-carboxylate (XXIII) was hydrolyzed in a manner similar to XXII. The hydrolysis product was precipitated with acetic acid and recrystallized after filtration from ethanol; mp 214-215°; ir (potassium bromide): 1690 cm⁻¹.

Anal. Calcd. for C₁₇H₁₄N₂O₂: C, 73.38; H, 5.03; N, 10.07. Found: C, 73.51; H, 5.13; N, 10.15.

1-Alkylarylimidazole-5-carbonyl Chloride Hydrochlorides (XXV and XXVI).

Into a cooled and dried flask containing XIII (or XXIV) was added thionyl chloride (molar ratio 1:5). The mixture was refluxed for 0.5 hour. Excess thionyl chloride was slowly removed at reduced pressure. The residue was treated with anhydrous ether and filtered.

1-Benzylimidazole-5-carbonyl Chloride Hydrochloride (XXV).

This compound had mp 205° dec.

Anal. Calcd. for C₁₁H₉ClN₂O.HCl: C, 51.38; H, 3.92; N, 10.89. Found: C, 51.39; H, 4.07; N, 10.95.

1-Benzhydrylimidazole-5-carbonyl Chloride Hydrochloride (XXVI).

The analytical data for this compound could not be determined because of its high hygroscopicity.

1-Alkylarylimidazole-5-carboxamides XXVIIa,b, XXVIIIa,c and 1-Benzyl-5-morpholinocarbonylimidazole XXIX.

The appropriate amine was slowly added to an anhydrous benzene solution of XXV or XXVI. The reaction temperature was maintained at 50°

for 0.5 hour. When gaseous ammonia was used the reaction was maintained at 35° for 2 hours. After removal of the benzene, the resulting residue was recrystallized from the appropriate solvent (Table 3).

Acknowledgement.

We are indebted to Prof. A. Bartolini of Istituto Farmacologia, Università di Firenze, for his useful suggestions and for the pharmacological tests.

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