

STUDIES ON IMIDAZOLE DERIVATIVES AND RELATED COMPOUNDS. SYNTHESIS OF
5-OXO-5H-IMIDAZO[2,1-b]PYRIDO[3,2-e][1,3]THIAZINE, A NEW RING SYSTEM

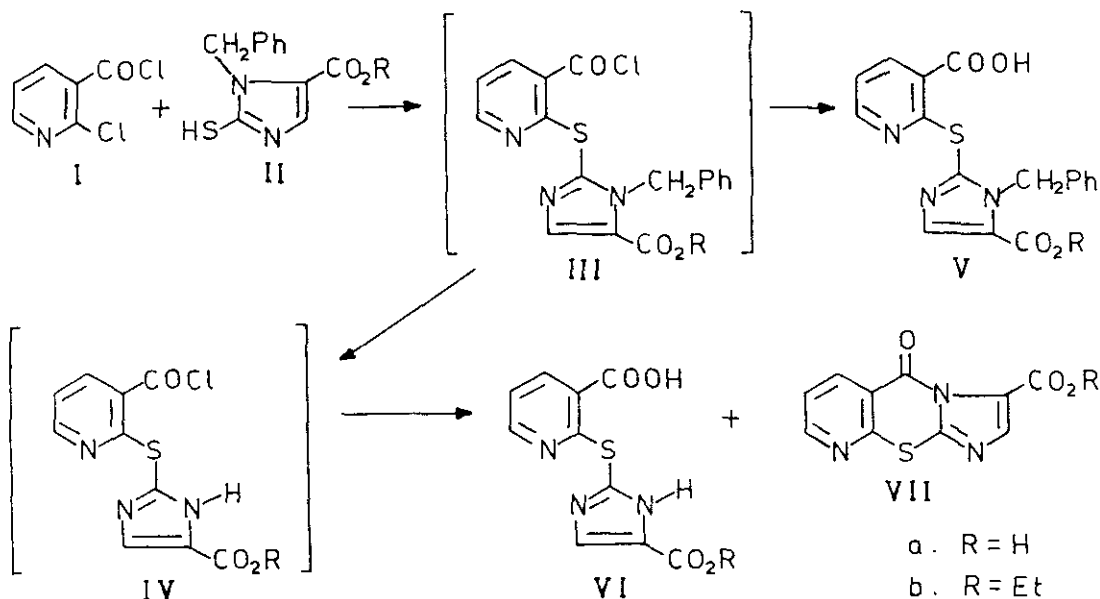
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Abstract- The reaction between 2-chloronicotinic acid chloride (I) and 1-benzyl-2-mercapto-1H-imidazole-5-carboxylic acid (IIa) or its ethyl ester (IIb) led to the formation of 5-oxo-5H-imidazo[2,1-b]pyrido[3,2-e][1,3]thiazine-3-carboxylic acid (VIIa) or its ethyl carboxylate (VIIb) respectively. This new ring system undergoes ring-opening reactions by nucleophiles giving 2-(2-imidazolylthio)pyridine derivatives.

Recently, some imidazolylheteroaryl sulphides have been extensively explored because of the variety of uses for this biologically important class of compounds.¹⁻⁷ In the light of these data and in connection with our continuing studies on the synthesis of imidazole derivatives with potential biological activity,⁸⁻¹⁰ our particular interest has now been focused on the preparation of some 2-(2-imidazolylthio)pyridine derivatives. These compounds were prepared by reaction between 1-alkyl-2-mercapto-1H-imidazole-5-carboxylic acids or their ethyl esters and 2-chloropyridine derivatives. The present paper deals with the synthesis and properties of the hitherto unknown highly reactive 5-oxo-5H-imidazo[2,1-b]pyrido[3,2-e][1,3]thiazine ring system, which was formed from the reaction between 2-chloronicotinic acid chloride (I) and 1-benzyl-2-mercapto-1H-imidazole-5-carboxylic acid (IIa) or its ethyl ester (IIb). Considering the synthesis some remarks may be made. At first, the reaction of I with an equimolar amount of II in refluxing benzene for two hours afforded a mixture of compounds V, VI, and VII (see Scheme 1). In these conditions 5-oxo-5H-imidazo[2,1-b]pyrido[3,2-e][1,3]thiazine-3-carboxylic acid (VIIa), or the corresponding ethyl carboxylate (VIIb), were the major products, certainly resulting from a ring-closure reaction at the nitrogen atom next to the COOR group of the debenzylated intermediate IV. The formation of the acid V as a minor product is probably due to the partial hydrolysis of the intermediate III. In fact, the yield of V drastically decreased when the reaction was carried out in anhydrous benzene. An incomplete ring-closure reaction after two hours of the intermediate IV, which undergoes hydrolysis during the separation of the reaction products, can explain the formation of VI.¹¹

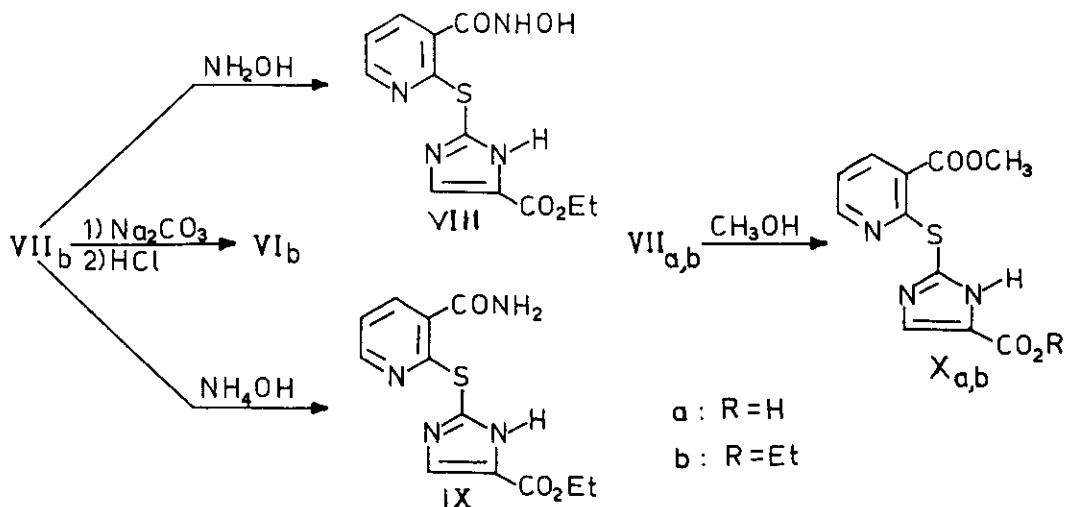
Scheme 1



It is interesting to note that the formation of VI and VII greatly depends on reaction times. In fact, when the reaction between I and II was carried out in the same conditions for eighteen hours, the products V and VII only were obtained. On the contrary, it must be emphasized that the yield of V is independent on reaction times. Moreover, when the reaction was performed with an equimolar amount of triethylamine, the sole V was obtained; then the presence of hydrochloric acid in the reaction mixture accounted for the formation of intermediate IV by debenzilation of III. When after refluxing for thirty minutes, gaseous ammonia was bubbled in the mixture of the reaction between I and IIb, only 2-(1-benzyl-5-ethoxycarbonyl-2-imidazolylthio)pyridine-3-carboxamide was produced (mp 175-176 °C from acetonitrile/water, y 97%; uv (methanol): 254(4.32), 290sh(3.70); $^1\text{H-nmr}$ (DMSO- d_6) δ : 7.93 (s, 1H, H-4 imidazole), 7.80 (broad s, 2H, NH_2), 5.60 (s, 2H, N- CH_2); ir (KBr): 3320, 3160, 1725, 1675 cm^{-1}). An explanation of this result was rapidly found. Evidently the assumed intermediate III was indeed formed but it readily converted to the corresponding carboxamide. On the other hand, addition of thionyl chloride to a mixture during the reaction, resulted in recovery of VIIb only (y 98%). Most likely under these conditions the acid Vb was converted to the acid chloride IIIb which undergoes a ring-closure reaction to give VIIb. Thus, all the above products led us to conclude that in the synthesis the essential point is the nucleophilic attack of the mercapto group of II at highly electron-deficient C-2 atom of I. In fact, it must be noted that several attempts to obtain V, starting from II and 2-chloropyridine at different conditions, failed. Of course, as expected, in no case 2-chloropyridine reacted with II. Our interest in compound VII was also stimulated by the possibility of employing it as potential synthon for novel 2-(2-imidazolylthio)pyridine derivatives. In fact compound VIIb readily undergoes a ring-opening reaction by nucleophiles in polar solvents. For instance, as reported in Scheme 2, the reaction of VIIb with hot 5% sodium carbonate

solution afforded VIb in good yield. Moreover when compound VIIb was treated with free base hydroxylamine in methanol or 30% ammonia, sizable amounts of 2-(5-ethoxycarbonyl-2-imidazolylthio)pyridine-3-carbohydroxamic acid (VIII) or the 3-carboxamide analog (IX) respectively were obtained.¹²

Scheme 2



A very important behaviour of VIIa,b was discovered during the study of their uv spectra in methanol solution; both the compounds undergo ring-opening reaction to give Xa,b, methyl carboxylate of VIa,b.¹³ The degradation rate of VIIb was so high that, also performing the spectrum immediately, a mixture was always revealed; otherwise it was possible to determine the spectrum of VIIa. The maxima and the molar absorptivities of the longest wavelength bands of VIIb were obtained examining its stable solution in CHCl_3 . The rate constants for a pseudo-first order reaction were calculated on the bands at 340 nm, unaffected by the absorption of the resulting Xa,b; at 20 °C the rate constant of VIIb was about 150 times greater than that of VIIa ($k = 3.8 \cdot 10^{-2} \text{ min}^{-1}$ and $2.5 \cdot 10^{-4} \text{ min}^{-1}$ respectively). The identity of the uv spectra of compounds X, and VI, with those of unambiguous compounds V provides evidence of an identical structure. Accordingly, it is reasonable to presume the COOR group in the fused ring compounds VII be in the position 3. In addition, the structure of compounds VI was determined on the basis of ¹H-nmr studies. The spectra show a broad signal due to the NH proton and a sharp singlet due to the H-4 proton of the imidazole nucleus; of course, on exchange with D_2O , the NH signal disappears whereas the H-4 singlet remains unaltered. With regard to compounds VII, the presence of some fragment ions in their mass spectra agrees with the assigned structure only.¹¹

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REFERENCES AND NOTES

All compounds gave correct microanalyses. Melting points are uncorrected. Ir spectra (cm^{-1}) were measured from potassium bromide discs with a Perkin-Elmer 283 spectrometer; uv spectra were recorded with a Beckman DU-8B spectrophotometer (solvent: methanol, λ max nm, Log ϵ) and ^1H -nmr spectra (ppm δ from TMS) with a Perkin-Elmer R32 instrument for DMSO-d_6 solutions. The mass spectra were recorded by FAB method on a VG Micromass 70-70 E2 spectrometer.

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- 11 A solution of equimolar amounts of I and II in benzene was refluxed for two hours. After cooling the solid which separated was filtered and washed with cold 5% sodium carbonate solution to give VII. Acidification of the alkaline solution with dilute hydrochloric acid (pH 4) gave a precipitate which was collected and suspended in boiling acetonitrile. Compound VI was collected by filtration of the hot suspension; the filtrate was cooled and V separated out.
 Va : mp 200-201 °C from DMF/ H_2O (y 10%); ir: 1690, 1620; uv: 207(4.52), 253(4.41), 295sh(3.69); ^1H -nmr: 7.91(s, 1H, H-4 imidazole), 5.60(s, 2H, N- CH_2). Vb : mp 208-209 °C from EtOH (y 8%); ir: 1720; uv: 206(4.43), 254(4.32), 295sh(3.61); ^1H -nmr: 7.96(s, 1H, H-4 imidazole), 5.60(s, 2H, N- CH_2).
 VIa : mp 264-265 °C from DMF/ H_2O (y 15%); ir: 1700; uv: 209(4.27), 254(4.22), 295sh(3.63); ^1H -nmr: 13.20-12.90(broad, 1H, NH imidazole), 8.03(s, 1H, H-4 imidazole). VIb : mp 213-214 °C from EtOH (y 20%); ir: 1730, 1680; uv: 208(4.31), 254(4.28), 295sh(3.61); ^1H -nmr: 13.25-13.00(broad, 1H, NH imidazole), 8.08(s, 1H, H-4 imidazole). VIIa : mp 272-273 °C from DMF/ H_2O (y 65%); ir: 1750, 1720; uv: 209(4.29), 229(4.32), 270(3.98), 340(3.30); ^1H -nmr: 9.08-8.75(m, 2H, H-6+H-8), 8.60(s, 1H, H-2), 7.85-7.65(m, 1H, H-7); mass spectrum: m/z 246(100%) $|\text{M-H}|^-$, m/z 248(100%) $|\text{M+H}|^+$, the m/z 338(45%) and m/z 340(92%) were assumed to be entirely due to $|\text{M+glycerol-H}|^-$ and $|\text{M+glycerol+H}|^+$ respectively. VIIb : mp 196-197 °C from EtOH (y 60%); ir: 1735, 1705; uv(CHCl_3): 274(4.15), 350(3.52); ^1H -nmr: 8.90-8.82(m, 2H, H-6+H-8), 8.70(s, 1H, H-2), 7.70-7.52(m, 1H, H-7), 4.65-4.35(q, 2H, CH_2), 1.60-1.38(t, 3H, CH_3); mass spectrum: m/z 366(28%) $|\text{M+glycerol-H}|^-$, m/z 380(100%) $|\text{M+glycerol+H}|^+$, m/z 295(55%) $|\text{PyCONCCO}_2\text{Et+glycerol-H}|^-$, m/z 297(20%) $|\text{PyCONCCO}_2\text{Et+glycerol+H}|^+$, m/z 250(45%) $|\text{PyCONCCO+glycerol-H}|^-$, m/z 252(15%) $|\text{PyCONCCO+glycerol+H}|^+$.
- 12 VIII : mp 182 °C (dec.) from DMF/ H_2O (y 96%); ir: 3300, 1695, 1645; uv: 203(4.21), 254(4.26), 290sh(3.67); ^1H -nmr: 13.40-13.00(broad, 1H, NH imidazole), 11.70-11.30(broad, 1H, NHOH), 9.50-9.30

(broad, 1H, NHOH), 8.20(s, 1H, H-4 imidazole). IX : mp 197-198 °C from EtOH/ H_2O (y 96%); ir: 3380, 3280, 1690, 1610; uv: 204(4.26), 254(4.27), 290sh(3.66); $^1\text{H-nmr}$: 13.25-13.00(broad, 1H, NH imidazole), 8.23(s, 1H, H-4 imidazole), 7.90-7.70(broad, 2H, NH_2).

- 13 Xa : during the determination of mp over 266-267 °C the compound eliminates MeOH to give VIIa. Ir: 1740, 1710; uv: 210(4.29), 255(4.23), 295sh(3.53); $^1\text{H-nmr}$: 13.20-12.90(broad, 1H, NH imidazole), 7.92(s, 1H, H-4 imidazole), 3.92(s, 3H, CH_3). Xb : the compound behaves as Xa and over 98-99 °C gives VIb. Ir: 1720; uv: 209(4.27), 255(4.24), 295sh(3.58); $^1\text{H-nmr}$: 13.40-13.10(broad, 1H, NH imidazole), 8.05(s, 1H, H-4 imidazole), 4.40-4.25(q, 2H, CH_2CH_3), 3.95(s, 3H, CH_3), 1.38-1.22(t, 3H, CH_2CH_3).

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