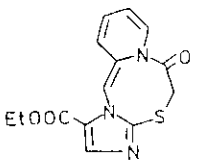
SYNTHESIS AND PROPERTIES OF SOME S-DERIVATIVES OF 1-BENZYL- AND 1-(2-PYRIDYLMETHYL)-5-SUBSTITUTED 2-MERCAPTOIMIDAZOLES[▽]

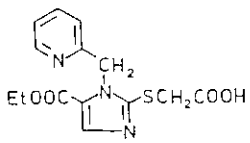
Ricardo Bossio*, Stefano Marcaccini, and Roberto Pepino
C N R, Centro di studio sulla chimica e la struttura dei composti eterociclici e loro applicazioni, Dipartimento di Chimica Organica "Ugo Schiff", Università di Firenze, via G.Capponi 9, 50121 Firenze, Italy

Abstract- The synthesis of imidazol-2-ylthio derivatives IIa-d by reacting 1-benzyl- and 1-(2-pyridylmethyl)-5-substituted 2-mercaptoimidazoles IIIa-d with chloroacetic acid is described. The interesting imidazol-2-ylthio derivatives Va,b,d and VI were obtained on heating IIa-d with acetic anhydride. The reaction between IIIa and 2-chloronicotinic acid chloride was also studied. The structures of all of the compounds were determined by ir and ^{1}H-nmr spectroscopy. Compounds Vb and Vd were also obtained by unequivocal synthesis to support our interpretation.

In a previous paper we reported the cyclization of 2-mercapto-1-(2-pyridylmethyl)-1*H*-imidazole-5-carboxylic acid with acetic anhydride[1].
Continuing our studies concerning the synthesis of novel heterocyclic ring systems having a fused imidazole or benzimidazole ring[1-6], we decided to attempt the synthesis of a fused 1,3,5-thiadiazocine (I) by cyclization of [5-ethoxycarbonyl-1-(2-pyridylmethyl)-1*H*-imidazol-2-ylthio]acetic acid (IIa) with acetic anhydride.



I



IIa

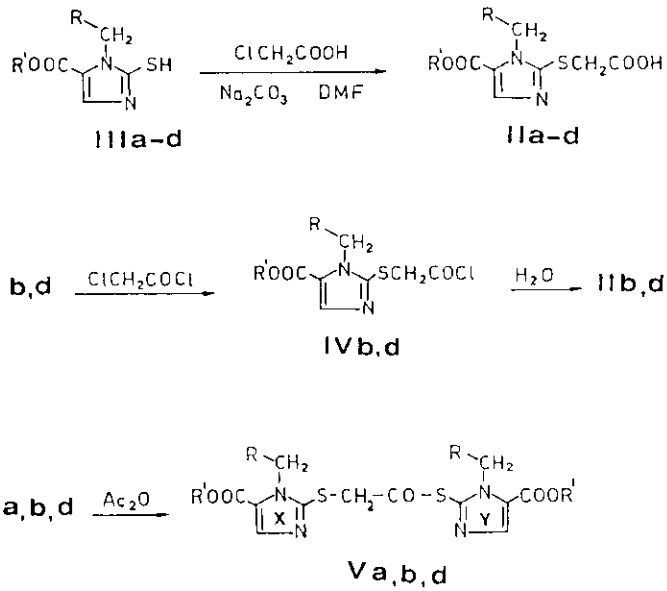
The 5-ethoxycarbonyl derivative IIa was employed to avoid a probable cyclization leading to the formation of 10*H*-10-oxo-imidazo[1,5-a]pyrido[1,2-d]pyrazine ring which was observed by treating several 5-carboxy-1-(2-pyridylmethyl)-1*H*-imidazole derivatives with anhydrides[1]. Although attempts to obtain I were unsuccessful, we

▽ Dedicated to the memory of our co-worker Elena Belgodere

noted an unexpected behaviour of IIa toward acetic anhydride. In fact, on treatment of IIa with acetic anhydride, a condensation involving two molecules of IIa occurred leading to the formation of [5-ethoxycarbonyl-1-(2-pyridylmethyl)-1*H*-imidazol-2-ylthio]ethanethioic acid S-[5-ethoxycarbonyl-1-(2-pyridylmethyl)-1*H*-imidazol-2-yl]ester Va.

In order to evaluate the possibility of extending this very interesting reaction, we prepared some imidazole derivatives structurally analogous to IIa and tested their behaviour toward acetic anhydride. The reactions are summarized in the following scheme.

Scheme 1



On the synthesis of compounds IIa-d some remarks can be made: all of the compounds IIa-d were obtained starting from the corresponding 2-mercapto derivatives IIIa-d on treatment with chloroacetic acid. Compounds IIb,d were prepared in higher yields on treatment of IIIb,d with chloroacetyl chloride followed by hydrolysis of the acid chlorides IVb,d[7]. Treatment of 1-(2-pyridylmethyl)-1*H*-imidazole derivatives IIIa,c with chloroacetyl chloride give only uncrystallizable tars.

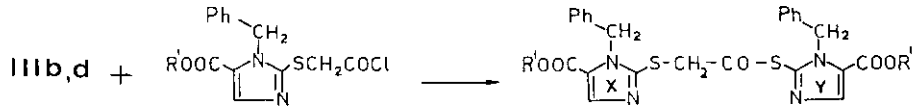
Compounds IIb,d showed a behaviour identical to that of IIa undergoing an analogous condensation.

The structure of compounds Va,b,d was assigned on the basis of their ir and ^{1}H-nmr data. The ir spectra of Va,b showed three CO signals at about 1670, 1720 and 1740 cm^{-1} attributable to the thiolester carbonyl group and to the ester carbonyl groups linked to the nuclei x and y respectively. The ir spectrum of Vd gave no useful informations since only a broad CO signal is detectable. The ^{1}H-nmr spectra of

Va,b,d showed a singlet at δ 4.55-4.98 due to the S-CH_2 group. The singlets at δ 5.50-5.68 and 5.69-5.80 were assigned to the N-CH_2 groups linked to the x and y imidazole nuclei respectively.

In each case the singlet signals due to the H-4 of the y imidazole nucleus were detected at a lower field than the corresponding protons of the x one. This behaviour can be explained by the electron-withdrawing effect of the SCO group.

Further evidence for the structure of compounds Vb,d was provided by their unequivocal synthesis starting from carboxylic acid chlorides IVb,d and mercapto derivatives IIIb,d:

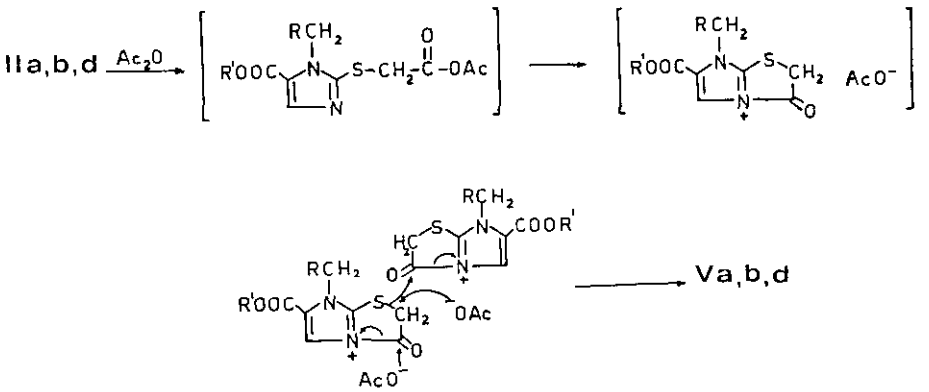


IIIb,d + IVb,d → Vb,d

With regard to the formation of Va,b,d a possible reaction pathway is reported in scheme 2.

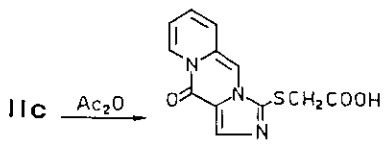
The formation of the intermediate cyclic ion can explain the reactivity of the S-CH_2 bond and the facile nucleophilic attack on the C=O group.

Scheme 2



IIa,b,d $\xrightarrow{Ac_2O}$ [ ] → [ ] → Va,b,d

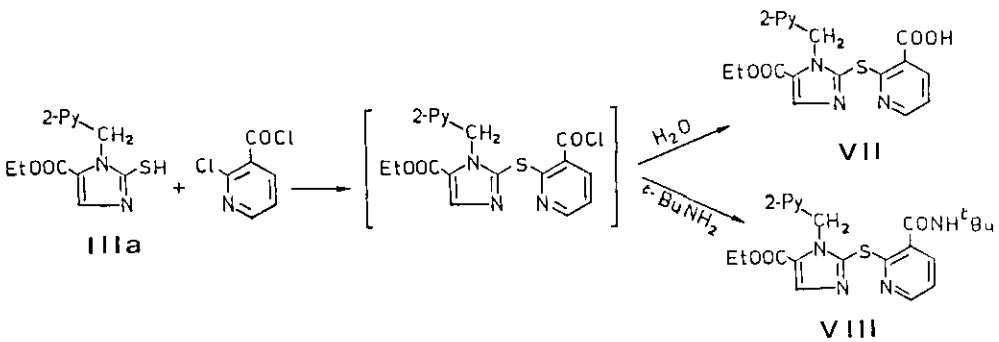
As expected[1], compound IIc gave a ring-closure reaction involving the carboxylic group linked at the 5-position of the imidazole ring and the pyridine nitrogen, giving (10*H*-10-oxo-imidazo[1,5-a]pyrido[1,2-d]pyrazin-2-ylthio)acetic acid (VI). The structure of compound VI was confirmed by means of its ^{1}H-nmr and ir spectral data. In fact in the ^{1}H-nmr spectrum a singlet signal at δ 8.15 due to the H-4 is detectable. Furthermore, in the ir spectrum a peak at 1640 cm^{-1}, due to the N-CO group, appears.



VI

Since we discovered differences in the chemical behaviour of compounds III toward chloroacetyl chloride, we decided to investigate the behaviour of IIIa toward 2-chloronicotinic acid chloride. This choice was made considering the interesting reaction between IIIb and 2-chloronicotinic acid chloride; compound IIIb besides the S-substitution, underwent the detachment of the benzyl group giving 3-ethoxycarbonyl-5*H*-5-oxo-imidazo[2,1-b]pyrido[3,2-e][1,3]thiazine[2] whereas compound IIIa underwent only S-substitution giving 2-[5-ethoxycarbonyl-1*H*-1-(2-pyridylmethyl)imidazol-2-ylthio]nicotinic acid chloride, a very hygroscopic solid which was characterized by conversion into the corresponding carboxylic acid VII and *tert*-butylamide VIII (scheme 3).

Scheme 3



IIIa VII VIII

EXPERIMENTAL

Melting points were obtained in open capillary tubes and are uncorrected. The ir spectra were measured on a Perkin-Elmer 283 spectrophotometer for potassium bromide discs. The ^{1}H-nmr spectra were recorded with a Perkin-Elmer R32 instrument for DMSO-d_6 saturated solutions; chemical shifts are expressed in ppm (δ) from TMS. All of the compounds gave correct microanalyses.

[5-Ethoxycarbonyl-1*H*-1-(2-pyridylmethyl)imidazol-2-ylthio] acetic Acid (IIa)

A suspension of IIIa, $ClCH_2COOH$, and Na_2CO_3 (molar *ratio* 1:1:2) in DMF was refluxed for 2h. Removal of the solvent left a residue which was dissolved in water. On acidification of the above described solution with dil. HCl, compound IIa sepa-

rated out. Mp 144-145 °C from EtOH (yield 70%); ir: 1720 (cm^{-1}); ^{1}H-nmr: 7.78(s, 1H,H-4 imidazole), 5.65(s,2H,NCH_2), 4.00(s,2H,SCH_2).

[5-Carboxy-1*H*-1-(2-pyridylmethyl)imidazol-2-ylthio]acetic Acid (IIc)

This compound (IIc) was obtained as described for IIa except that molar *ratio* IIIc: $ClCH_2COOH$: Na_2CO_3 was 1:1:3 and the reaction time was 1h. Mp 214-215 °C from EtOH (yield 75%); ir: 1700 (cm^{-1}); ^{1}H-nmr: 7.75(s,1H,H-4 imidazole), 5.70(s,2H,NCH_2), 4.00(s,2H,SCH_2).

(5-Ethoxycarbonyl-1*H*-1-benzylimidazol-2-ylthio)acetic Acid (IIb)

This compound (IIb) was obtained starting from IIIb following the procedure described for IIa. Mp 116-117 °C from EtOH (yield 80%); ir: 1720 (cm^{-1}); ^{1}H-nmr: 7.80(s,1H,H-4 imidazole), 5.55(s,2H,NCH_2), 4.09(s,2H,SCH_2).

(5-Carboxy-1*H*-1-benzylimidazol-2-ylthio)acetic Acid (IId)

This compound (IId) was prepared starting from IIId following the procedure described for IIc. Mp 205-206 °C from EtOH (yield 80%); ir: 1710 (cm^{-1}); ^{1}H-nmr: 7.30(s,1H,H-4 imidazole), 5.85(s,2H,NCH_2), 4.05(s,2H,SCH_2).

Alternative Synthesis of IIb and IId- A mixture of IIIb and $ClCH_2COCl$ (molar *ratio* 1:1) in dry benzene was heated at 40 °C for 1h. On cooling a white product separated out which was collected by filtration. The analytical and physical data of this product could not be determined because of its hygroscopicity. The above described product was stirred with water for 15 min and the crude IIb (yield 90%) collected by filtration. In the same manner compound IId was obtained in 92% yield.

[5-Ethoxycarbonyl-1*H*-1-(2-pyridylmethyl)imidazol-2-ylthio]ethanethioic Acid S-[5-Ethoxycarbonyl-1*H*-1-(2-pyridylmethyl)imidazol-2-yl]ester (Va)

A solution of IIa in Ac_2O was refluxed for 10 min. Removal of the solvent under reduced pressure left a residue which was washed with Et_2O/acetone 1:1 to give the crude Va. Mp 190-191 °C from MeCN (yield 90%); ir: 1740 (cm^{-1}), 1720 (cm^{-1}); ^{1}H-nmr: 8.73(s,1H,H-4 imidazole y), 7.90(s,1H,H-4 imidazole x), 5.80(s,2H,NCH_2 y), 5.68(s,2H,NCH_2 x), 4.98(s,2H,SCH_2).

(5-Ethoxycarbonyl-1*H*-1-benzylimidazol-2-ylthio)ethanethioic Acid S-(5-Ethoxycarbonyl-1*H*-1-benzylimidazol-2-yl)ester (Vb)

Method A- A solution of IIb in Ac_2O was heated at 90 °C for 30 min. Removal of the solvent left a residue which was washed with Et_2O to give the crude Vb. Mp 185-186 °C from MeCN (yield 70%); ir: 1740 (cm^{-1}), 1710 (cm^{-1}), 1680 (cm^{-1}); ^{1}H-nmr: 8.68(s,1H,H-4 imidazole y), 7.50(s,1H,H-4 imidazole x), 5.69(s,2H,NCH_2 y), 5.50(s, 2H,NCH_2 x), 4.69(s,2H,SCH_2).

Method B- An equimolecular mixture of IIIb and $ClCH_2COCl$ in dry benzene was heated

at 40 °C for 1h. The calculated amount of IIIb and an excess of NEt_3 were added under stirring to the above described solution. The resulting suspension was refluxed for 30 min, then cooled and filtered. The collected solid product was dried, washed with water and dried again to give the crude Vb (yield 70%).

(5-Carboxy-1*H*-1-benzylimidazol-2-ylthio)ethanethioic Acid S-(5-Carboxy-1*H*-1-benzylimidazol-2-yl)ester (Vd)

Method A- A solution of IId in Ac_2O was heated at 60 °C for 30 min and then cooled in an ice bath. The solid product that separated out was collected and then dissolved in hot AcOH. The above described solution was cooled and the crude Vd separated out. Mp 202-203 °C from DMF/acetone/H_2O (1:1:1) (yield 45%); ir: 1700 (cm^{-1}); ^{1}H-nmr: 8.55(s,1H,H-4 imidazole y), 7.70(s,1H,H-4 imidazole x), 5.70(s,2H,NCH_2 y), 5.55(s,2H,NCH_2 x), 4.55(s,2H,SCH_2).

Method B- An equimolecular mixture of IIId and $ClCH_2COCl$ in dry benzene was heated at 40 °C for 1h. The calculated amount of IIId and an excess of NEt_3 were added under stirring to the above described solution. The collected solid product was dried, washed with water and dried again to give the crude Vd (yield 60%).

(10*H*-10-Oxo-imidazo[1,5-a]pyrido[1,2-d]pyrazin-2-ylthio)acetic Acid (VI)

A solution of IIc in Ac_2O was refluxed for 30 min. On cooling yellow crystals of VI separated out. Mp 205-206 °C from DMF (yield 80%); ir: 1680 (cm^{-1}), 1640 (cm^{-1}); ^{1}H-nmr: 8.15(s,1H,H-4), 7.80(s,1H,H-11), 4.00(s,2H,SCH_2).

2-[5-Ethoxycarbonyl-1*H*-1-(2-pyridylmethyl)imidazol-2-ylthio]nicotinic Acid (VII)

An equimolecular mixture of 2-chloronicotinic acid chloride and IIIa in dry benzene was refluxed for 2h. The solid product which separated out was collected and treated with water to give the crude VII. Mp 211-212 °C from EtOH (yield 45%); ir: 1710 (cm^{-1}); ^{1}H-nmr: 7.92(s,1H,H-4 imidazole), 5.68(s,2H,NCH_2).

2-[5-Ethoxycarbonyl-1*H*-1-(2-pyridylmethyl)imidazol-2-ylthio]nicotinic Acid *tert*-Butylamide (VIII)

An equimolecular mixture of 2-chloronicotinic acid chloride and IIIa in dry benzene was refluxed for 2h. After cooling an excess of *tert*-butylamine was added to the reaction mixture. The solid product which separated out was collected, washed with water and then dried. Mp 110-111 °C from ligroine (bp 80-120 °C) (yield 40%); ir: 3260 (cm^{-1}), 1720 (cm^{-1}), 1660 (cm^{-1}); ^{1}H-nmr: 7.90(s,1H,H-4 imidazole), 5.70(s,2H,NCH_2), 1.39(s,9H,Me_3).

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* Author to whom correspondence should be addressed.

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7. Compounds IVb,d were not characterized because of their high hygroscopicity.

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