IMIDAZOLECARBOXYLIC ACIDS AND THEIR DERIVATIVES. SYNTHESIS OF 10*H*-IMIDAZO[1,5-a]PYRIDO[1,2-d]PYRAZIN-10-ONE, A NOVEL RING SYSTEM

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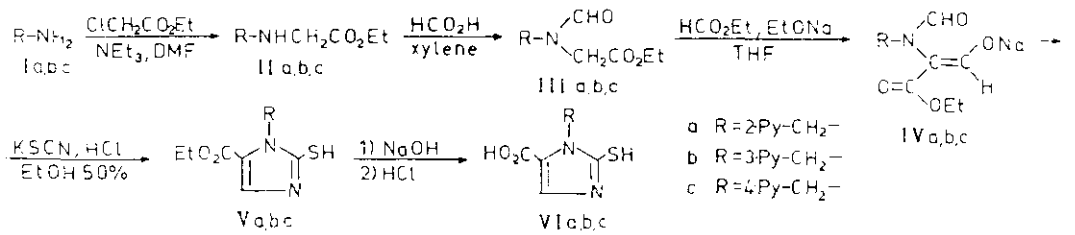
Abstract- Some derivatives of 10*H*-imidazo[1,5-a]pyrido[1,2-d]pyrazin-10-one (XV), a novel ring system, were prepared starting from 2-mercapto-1-(2-pyridylmethyl)-1*H*-imidazole-5-carboxylic acid (VIa)[1] and acetic or propionic anhydride. Analogously the synthesis of the unsubstituted ring was achieved starting from 1-(2-pyridylmethyl)-1*H*-imidazole-5-carboxylic acid (XIV).

In our previous papers[2-4] we described some 1-arylalkyl- and 1-(2-thienylmethyl)-1*H*-imidazole derivatives having antimicrobial activity. It was reported[5] that antimicotic activity of 1-arylalkyl-1*H*-imidazoles must be related to the electron-withdrawing effect of the substituent. We therefore decided to prepare a series of imidazole derivatives having isomeric pyridylmethyl groups at the 1-position. The synthesis was accomplished following the synthetic method previously reported[2,3] and summarized in Scheme 1.

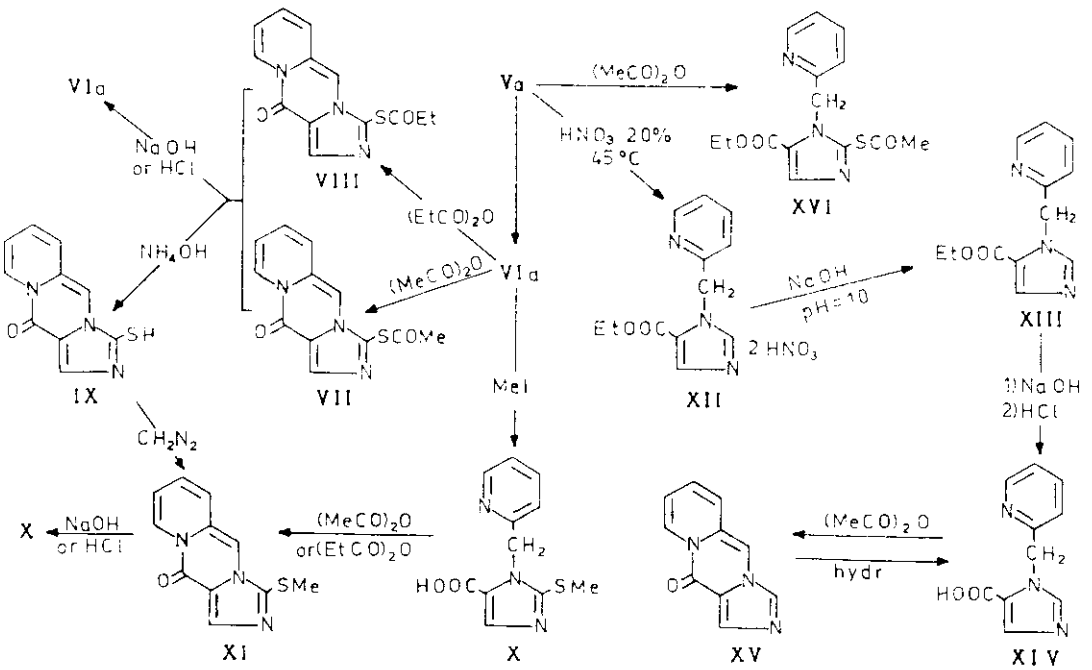
Scheme 1



Since attempts to prepare 2-mercapto-1-(pyridylmethyl)-1*H*-imidazole-5-carbohydroxamic acids starting from esters Va-c and hydroxylamine failed, we attempted their synthesis starting from the corresponding acid chlorides. To avoid the intermolecular reaction between the chlorocarbonyl group and the mercapto one, we decided to acetylate the mercapto group. During this acetylation we dis-

covered a very interesting behaviour of VIa. In fact on brief heating with an excess of acetic anhydride, besides the S-acetylation, VIa underwent a ring-closure reaction to give 2-acetylthio-10*H*-imidazo[1,5-a]pyrido[1,2-d]pyrazin-10-one (VII) in almost quantitative yields (Scheme 2).

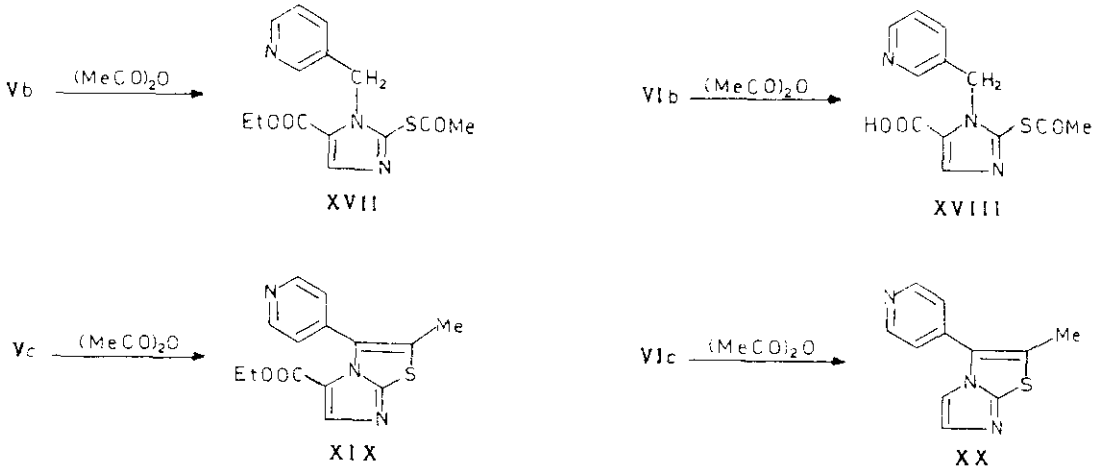
Scheme 2



The structure of VII was assigned on the basis of its spectroscopical and chemical behaviour. The ir spectrum shows two peaks at 1740 and 1690 cm^{-1} attributable to the thiolester carbonyl group and to the amide carbonyl group respectively. Useful indications were obtained by comparing the ^{1}H-nmr spectrum of VII with that of VIa: the singlet at δ 5.57 due to the exocyclic methylene group disappears and a singlet at δ 7.50 due to the H-4 of the cyclic compound appears. In addition it must be noted that the H-6 of the pyridine ring of VIa gives a multiplet at δ 8.50-8.42 whereas the corresponding H-8 of the cyclic compound gives a multiplet at δ 7.92-7.80. This fact agrees with the loss of aromaticity of the pyridine ring. In the ^{1}H-nmr spectrum of VII the singlets due to the methyl of the acetylthio group and to the H-11 are revealed at δ 2.98 and δ 8.19 respectively. In the mass spectrum of VII are detectable the ions $[M]^+$ m/z 259, $[M-CO-COCH_3]^+$ m/z 188 and the ion $[C_4H_4]^+$ m/z 52 which agrees with a dienic structure of the pyridine ring. As expected treatment of VIa with propionic anhydride or propionyl chloride in the presence of triethylamine afforded 2-propionylthio-10*H*-imidazo[1,5-a]pyrido[1,2-d]pyrazin-10-one (VIII). Further evidence for the assigned structure was provided by reactivity of VIa and its related compounds Va, X and XIV: on treatment of the ester Va with acetic anhydride, only S-acetylation occurred whereas on treatment of

2-methylthio-1-(2-pyridylmethyl)-1*H*-imidazole-5-carboxylic acid (X) and 1-(2-pyridylmethyl)-1*H*-imidazole-5-carboxylic acid (XIV) with acetic, propionic or succinic anhydride, 2-methylthio-10*H*-imidazo[1,5-a]pyrido[1,2-d]pyrazin-10-one (XI) and 10*H*-imidazo[1,5-a]pyrido[1,2-d]pyrazin-10-one (XV) were respectively obtained. Hydrolysis with aqueous sodium hydroxide or dilute hydrochloric acid converted the cyclic compounds VII, XI and XV into the corresponding starting acids VIa, X, and XIV. *Compound* VIII behaves as VII. 2-Mercapto-10*H*-imidazo[1,5-a]pyrido[1,2-d]pyrazin-10-one (IX) was obtained by treating VII or VIII with 30% aqueous ammonia. Methylation of IX with diazomethane gave a product which was identical to XI. The reactivity of VIa must be related to the presence of a 2-pycolyl group linked at the 1-position of the imidazole ring. In fact apart from the activation of the methylene group, the position of the pyridine nitrogen atom allows the ring-closure reaction. As expected on treatment of 1-(3-pyridylmethyl)-1*H*-imidazole derivatives Vb and VIb with acetic anhydride no ring-closure reaction took place and only S-acetyl derivatives XVII and XVIII were obtained. On treatment of 1-(4-pyridylmethyl)-1*H*-imidazole derivatives Vc and VIc with acetic anhydride a different ring-closure reaction occurred, involving the *activated methylene group only*: Vc afforded ethyl 2-methyl-3-(4-pyridyl)imidazo[2,1-b]thiazole-5-carboxylate (XIX) whereas VIc along with the ring-closure reaction underwent decarboxylation, giving 2-methyl-3-(4-pyridyl)imidazo[2,1-b]thiazole (XX) (Scheme 3).

Scheme 3



It must be noted that recently the chemistry of imidazo[2,1-b]thiazole derivatives has been extensively explored because of the variety of biological activities[6]. All the compounds described in this paper, except the starting amines Ia-c and compound IIa[7], were hitherto unknown.

EXPERIMENTAL

Melting points are uncorrected. Unless otherwise stated, the ir spectra (cm^{-1}) were recorded for potassium bromide discs with a Perkin-Elmer 283 spectrophotometer and the ^1H-nmr spectra (ppm δ

from TMS) with a Perkin-Elmer R 32 instrument. The mass spectra were recorded with a Kratos MS 80 intrument. All compounds gave correct microanalyses.

N-Substituted Ethyl Aminoacetates (IIa-c)

General procedure— The calculated amount of $ClCH_2COOEt$ was added during 2 h to a well-stirred solution of I and NEt_3 in DMF maintaining the temperature at 40-50 °C. The reaction mixture was then cooled and filtered. Fractional distillation *in vacuo* of the filtrate gave II. IIa, bp 138 °C/0.4 mm Hg[7] (yield 69%); ir(film): 3340,1740. IIb, bp 130 °C/0.2 mm Hg (yield 60%); ir(film): 3315,1740. IIc, bp 127 °C/0.4 mm Hg (yield 20%); ir(film): 3340,1740.

N-Substituted Ethyl *N*-Formylaminoacetates (IIIa-c)

General procedure— A mixture of II and HCOOH (molar *ratio* 1:2.5) in xylene was refluxed for 3 h in a Dean-Stark apparatus. Removal of the solvent left a residue which was distilled under reduced pressure to give III. IIIa, bp 149 °C/0.05 mm Hg (yield 84%); ir(film): 1750,1680. IIIb, bp 188 °C/0.5 mm Hg (yield 85%); ir(film): 1740,1670. IIIc, bp 80 °C/0.1 mm Hg (yield 87%); ir(film): 1750,1680.

1-Substituted Ethyl 2-Mercaptoimidazole-5-carboxylates (Va-c)

General procedure— A mixture of III and HCOOEt was slowly added to a saturated solution of EtONa in dry THF (molar *ratio* III:HCOOEt:EtONa = 1:3:1.1) and the resulting mixture was stirred for 48 h at room temperature. Enolate IV was collected by filtration[8]. A solution of IV and KNCS (molar *ratio* 1:1.5) in 50% aq. EtOH was treated with dil. HCl until the pH was 1 then heated at 50-60 °C for 5 h. The reaction mixture was cooled, treated with dil. NaOH until the pH was 5 and evaporated to dryness *in vacuo*. The residue was washed with H_2O and collected by filtration. Va, mp 237 °C from EtOH/H_2O (2:1)(yield 36% based on IIIa); ir: 2540,1720; ^{1}H-nmr(DMSO-d_6): 12.98(br s,1H,SH), 7.86(s,1H,H-4 of imidazole),5.70(s,2H,NCH_2). Vb, mp 200-201 °C from MeOH (yield 27% based on IIIb); ir: 2530,1715; ^{1}H-nmr(DMSO-d_6): 13.09(br s,1H,SH),7.90(s,1H,H-4 of imidazole),5.58(s,2H,NCH_2). Vc, mp 200-202 °C from EtOH (yield 25% based on IIIc); ir: 2540,1725; ^{1}H-nmr(DMSO-d_6): 13.10(br s, 1H, SH),7.92(s,1H,H-4 of imidazole),5.60(s,2H,NCH_2).

1-Substituted 2-Mercaptoimidazole-5-carboxylic Acids (VIa-c)

General procedure— A solution of VI (20 mmoles) in 40 ml of 2*N* NaOH was refluxed for 2 h then cooled and acidified with dil. HCl until the pH was 4. Removal of the solvent left crude VI which was washed with H_2O and collected by filtration. VIa, mp 227-228 °C (dec.) from EtOH/H_2O (1:1) (yield 71%); ir: 2570,1700; ^{1}H-nmr(DMSO-d_6/$CDCl_3$). 12.90(br s,1H,SH),7.78(s,1H,H-4 of imidazole), 5.57(s,2H,CH_2). VIb, mp 225 °C (dec.) from EtOH/H_2O (1:1) (yield 74%); ir: 2560,1650; ^{1}H-nmr (DMSO-d_6): 12.94(br s,1H,SH),7.80(s,1H,H-4 of imidazole),5.63(s,2H,CH_2). VIc, mp 210-211 °C (dec.) from EtOH/H_2O (1:1) (yield 76%); ir: 2570,1640; ^{1}H-nmr(DMSO-d_6): 13.00(br s,1H,SH),7.85(s,1H,H-4

of imidazole), 5.65(s,2H,CH_2).

2-Acetylthio-10*H*-imidazo[1,5-a]pyrido[1,2-d]pyrazin-10-one (VII)

A mixture of VIa and an excess of Ac_2O was refluxed for 10 min. After cooling crude VII was collected by filtration. Red needles, mp 197-198 °C from DMF (yield 85%); ir: 1735,1690; ^{1}H-nmr (DMSO-d_6/$CDCl_3$): 8.19(s,1H,H-11),7.50(s,1H,H-4),2.98(s,3H,$SCOCH_3$); ms(30 eV): m/z 259 $[M]^+$,m/z 188 $[M-(CO+COCH_3)]^+$, m/z 156 $[M-(CO+SCOCH_3)]^+$,m/z 52 $[C_4H_4]^+$.

2-Propionylthio-10*H*-imidazo[1,5-a]pyrido[1,2-d]pyrazin-10-one (VIII)

It was prepared as described above for VII employing $(EtCO)_2O$. Mp 199-200 °C from DMF (yield 80%); ir: 1730,1690.

2-Mercapto-10*H*-imidazo[1,5-a]pyrido[1,2-d]pyrazin-10-one (IX)

Compound VII (or VIII) was briefly heated with 30% aq. NH_3. The reaction mixture was cooled and acidified with dil. HCl until the pH was 5. Compound IX which separated out was collected by filtration. Mp 255-256 °C from EtOH (yield 80%); ir: 2580,1690; ^{1}H-nmr(DMSO-d_6): 13.60(br s,1H,SH), 8.12(s,1H,H-11),7.52(s,1H,H-4).

2-Methylthio-1-(2-pyridylmethyl)-1*H*-imidazole-5-carboxylic Acid (X)

A mixture of VIa, MeI and KOH (molar ratio 1:1:2) in MeOH was allowed to react at room temperature for 24 h. Removal of the solvent left a residue which was dissolved in H_2O. On acidification of this solution X separated out. Mp 206-208 °C from EtOH (yield 80%); ir: 1700; ^{1}H-nmr(DMSO-d_6): 7.78(s,1H,H-4 of imidazole),5.63(s,2H,CH_2),2.57(s,3H,CH_3).

2-Methylthio-10*H*-imidazo[1,5-a]pyrido[1,2-d]pyrazin-10-one (XI)

A mixture of X and an excess of Ac_2O was refluxed for 10 min. After cooling XI separated out. Mp 128-129 °C from toluene (yield 95%); ir: 1680; ^{1}H-nmr(DMSO-d_6): 8.10(s,1H,H-11),7.68(s,1H,H-4),2.63 (s,3H,CH_3); ms(30 eV): m/z 231 $[M]^+$,m/z 216 $[M-CH_3]^+$, m/z 188 $[M-(CH_3+CO)]^+$,m/z 52 $[C_4H_4]^+$. The same compound was also prepared by treating an ethereal suspension of IX with CH_2N_2.

Ethyl 1-(2-Pyridylmethyl)-1*H*-imidazole-5-carboxylate Dinitrate Salt (XII)

Compound Va (2 g, 7.6 mmoles) was added in small portions to a solution of 50 mg of $NaNO_2$ in 11 ml of 20% HNO_3 maintaining the temperature at 45 °C. Compound XII separated out by treating the cooled reaction mixture with $NaNO_3$. Mp 175 °C (dec.) (1.7 g, 63%).

Ethyl 1-(2-Pyridylmethyl)-1*H*-imidazole-5-carboxylate (XIII)

It separated out by treating an aqueous solution of XII with dil. NaOH until the *p*H was 10. Mp 70 -71 °C from EtOH/H_2O (1:1) (Yield 95%).

1-(2-Pyridylmethyl)-1*H*-imidazole-5-carboxylic Acid (XIV)

A suspension of XIII (20 mmoles) in 40 ml of 2*N* NaOH was refluxed for 2 h. Compound XIV separated out on acidification of the cooled reaction mixture. Mp 219-220 °C from H_2O (yield 76%); ir: 1690; ^{1}H-nmr(DMSO-d_6): 8.18(s,1H,H-2 of imidazole),7.72(s,1H,H-4 of imidazole),5.78(s,2H,CH_2).

10*H*-Imidazo[1,5-a]pyrido[1,2-d]pyrazin-10-one (XV)

A mixture of XIV and an excess of Ac_2O was heated at 50 °C for 2 h. On cooling XV separated out. Mp 180-181 °C from EtOH (yield 85%); ir 1675; ^{1}H-nmr(DMSO-d_6): 8.53(s,1H,H-2),8.07(s,1H,H-11), 7.85(s,1H,H-4).

Ethyl 2-Acetylthio-1-(2-pyridylmethyl)-1*H*-imidazole-5-carboxylate (XVI)

A mixture of VIa and an excess of Ac_2O was refluxed for 7 h. Removal of the solvent left an oily residue which on treatment with *n*-hexane gave XVI. Mp 85-86 °C from *n*-hexane (yield 95%); ir: 1750, 1715; ^{1}H-nmr(DMSO-d_6): 8.17(s,1H,H-4 of imidazole),2.95(s,3H,CH_3).

Ethyl 2-Acetylthio-1-(3-pyridylmethyl)-1*H*-imidazole-5-carboxylate (XVII)

It was obtained as described for XVI employing Vb as the starting material. Mp 80-81 °C from *n*-hexane (yield 90%); ir: 1730; ^{1}H-nmr(DMSO-d_6): 8.18(s,1H,H-4 of imidazole),5.80(s,2H,NCH_2),2.97 (s,3H,$SCOCH_3$).

2-Acetylthio-1-(3-pyridylmethyl)-1*H*-imidazole-5-carboxylic Acid (XVIII)

A mixture of VIb and an excess of Ac_2O was refluxed for 4 h. On cooling XVIII separated out. Mp 210-211 °C from DMF (yield 80%); ir: 1725; ^{1}H-nmr(DMSO-d_6): 8.10(s,1H,H-4 of imidazole),5.82(s,2H, NCH_2),2.92(s,3H,$SCOCH_3$).

Ethyl 2-Methyl-3-(4-pyridyl)imidazo[2,1-b]thiazole-5-carboxylate (XIX)

A mixture of Vc and an excess of Ac_2O was refluxed for 4 h. Removal of the solvent left a residue which on recrystallization from ligroine gave XIX. Mp 134-135 °C (yield 54%); ir: 1715; ^{1}H-nmr ($CDCl_3$): 7.74(s,1H,H-6),2.46(s,3H,CH_3); ms(30 eV): m/z 287 $[M]^+$, m/z 242 $[M-EtO]^+$, m/z 214 $[M-CO_2Et]^+$, m/z 117 $[Py-C{=}C-CH_3]^+$, m/z 58 $[SCN]^+$.

2-Methyl-3-(4-pyridylmethyl)imidazo[2,1-b]thiazole (XX)

A mixture of VIc and an excess of Ac_2O was refluxed for 4 h. Removal of the solvent left an oil

which on treatment with Et_2O followed by filtration gave XX; mp 57-58 °C from *n*-hexane (yield 73%); ir: 1740; ^{1}H-nmr($CDCl_3$): 2.25(s,3H,CH_3); ms (30 eV): m/z 215 $[M]^+$, m/z 117 $[Py\text{-}C\text{=}C\text{-}CH_3]^+$, m/z 90 $[Py\text{-}C]^+$, m/z 58 $[SCN]^+$.

REFERENCES AND NOTES

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1. Although the compounds Va-c, VIa-c, X, XII, XIII, XIV, XVI, XVII and XVIII should be named, by IUPAC rules, as pyridine derivatives, they are reported as substituted imidazoles since our interest is focused on the synthesis of this heterocyclic system.

2. E.Belgodere, R.Bossio, V.Parrini, and R.Pepino, *Arzneim.-Forsch.*, 1980, 30(II), 1051.

3. E.Belgodere, R.Bossio, S.Chimichi, S.Marcaccini, and R.Pepino, *Heterocycles*, 1983, 20, 2019.

4. E.Belgodere, R.Bossio, R.Cencioni, S.Marcaccini, and R.Pepino, *Heterocycles*, 1984, 22, 807.

5. H.Tolkmith, J.N.Seiber, P.B.Budde, and D.R.Mussel, *Science*, 1957, 158, 1462.

6. *See for example:* T.Muro, T.Nakao, K.Ogawa, Y.Maruyama, and K.Anami, *Yakugaku Zasshi*, 1977, 97(8), 835; J.Symoens,"Pharmacological and Biochemical Properties of Drug Substances", vol.2, M.E.Goldberg, Ed., Washington, 1979, pp. 407-464; J.A.Lewis, C.H.Wu, J.H.Levine, and H.Berg, *Neuroscience*, 1980, 5(6), 967; A.Andreani, D.Bonazzi, and M.Rambaldi, *Farmaco Ed.Sci.*, 1980, 35(II), 896; L.J.Powers, S.W.Fogt, Z.S.Ariyan, D.J.Rippin, R.D.Heilman, and R.J.Mattews, *J. Med.Chem.*, 1981, 24, 614; H.Schneiden, *Int.J.Immunopharmacol.*, 1981, 3, 139; J.Papanicolaou, R.J.Summers, F.J.E.Vaida, and W.J.Louis, *Brain Res.*, 1982, 241(2), 393; G.D.Gupta, K.K.Jain, R.P.Gupta, and H.K.Pujari, *Indian J.Chem.,Sect.B*, 1983, 22B(3), 268; K.Kubo, Y.Isomura, S.Sakamoto, and H.Homma, *Eur.Pat.Appl.*, 1982, EP 59,090;*Chem.Abstr.*, 1983, 98, 53905d; B.J.Banks and A.B.Penrose, *Eur.Pat.Appl.*, 1983, EP 80,359;*Chem.Abstr.*, 1983, 99, 158424v; R.A.B.Webster and R.J.Dorgan, *Eur.Pat.Appl.*, 1983, EP 76,622;*Chem.Abstr.*,1983, 99, 212522r.

7. K.Winterfeld and G.Gierenz, *Ber.*, 1959, 92, 240.

8. The analytical and spectral data for compounds IVa-c could not be determined because of their high hygroscopicity.

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