2-Aminoimidazo[1,5-*a*]pyridinium Salts: Some Further Oxidations

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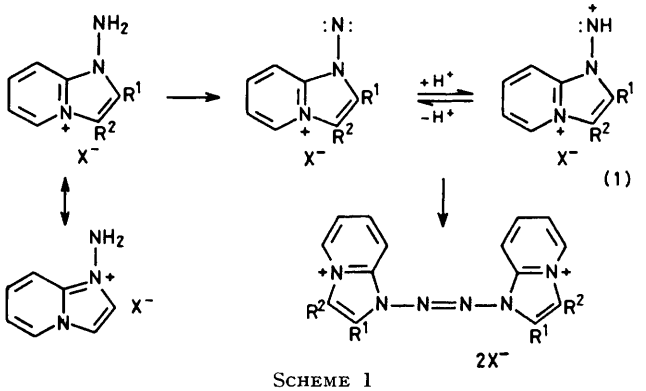
Oxidation of 1-substituted 2-aminoimidazo[1,5-*a*]pyridinium salts with an excess of concentrated nitric acid gave the corresponding 2-pyridylmethylenecarbamic acid hydro-salts. Oxidation of 3-substituted-2-aminoimidazo-[1,5-*a*]pyridinium bromide with nitric acid in acetic acid gave the corresponding 1-nitro-3-substituted imidazo-[1,5-*a*]-pyridines. The parent 2-aminoimidazo[1,5-*a*]pyridinium bromide yielded either type of product depending upon the reaction conditions.

Oxidation of 2-amino-1-phenylimidazo[1,5-*a*]pyridinium bromide with lead(IV) acetate in acetic acid solution gave 2-acetamido-3-oxo-1-phenyl-2,3-dihydroimidazo[1,5-*a*]pyridine.

We previously suggested [1] that tetrazene formation by the oxidation of quaternary *N*-amino-salts with aqueous bromine is only possible in those cases [2] in which delocalization of the positive charge onto a second heteroatom allows the formation of dicationic intermediates of the type (1) shown in Scheme 1.

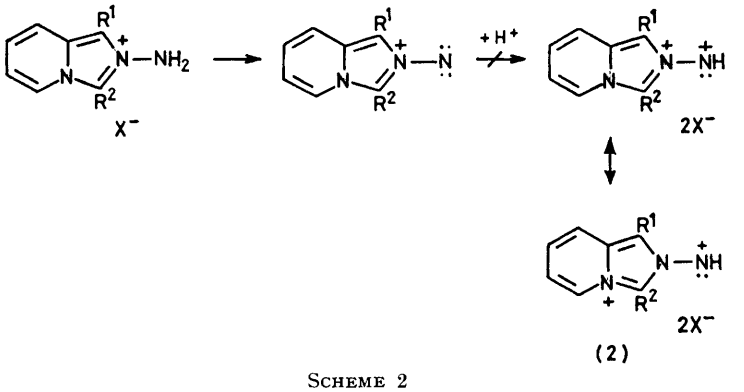


Scheme 1

Our failure [3] to obtain the corresponding tetrazenes by the oxidation of the title compounds with aqueous bromine may thus be explained by assuming that the cationic charge in 2-aminoimidazo[1,5-*a*]pyridinium salts is effectively localized on the 2-nitrogen atom thus preventing the formation of the corresponding aminonitrene conjugate acid as shown in Scheme 2. We thought to check the validity of this assumption by treating the title compounds with other oxidants and examining the products for evidence of the possible intermediacy of the aminonitrene conjugate acids (2).

Treatment of the *N*-aminoimidazopyridinium bromides or chlorides (3)—(5) with concentrated nitric acid followed by heating the resulting solution to 100 °C resulted, after a short induction period, in a vigorous reaction and the formation of the corresponding 2-pyridylmethylenecarbamic acids, isolated as their hydrohalide salts (11)—(13) respectively. The structure of these salts was deduced from their elemental analyses, their i.r. spectra which showed a strong band in the region of 1 830 cm^{-1} consistent with the stretching of a tight carbonyl group, and the decarboxylation and hydrolysis in the presence of base of (12) and (13) yielding the corresponding 2-acylpyridines (14) and (15) respectively.

Addition of nitric acid to suspensions of the *N*-aminoimidazopyridinium bromides (6) and (7) in acetic acid followed by heating of the resulting solutions to 100 °C again resulted in a vigorous reaction and on cooling the respective nitro-compounds (18) and (19) crystallized. Similar treatment of the unsubstituted *N*-aminoimidazopyridinium bromide (3) resulted in the formation of the brominated nitro-compound (20).

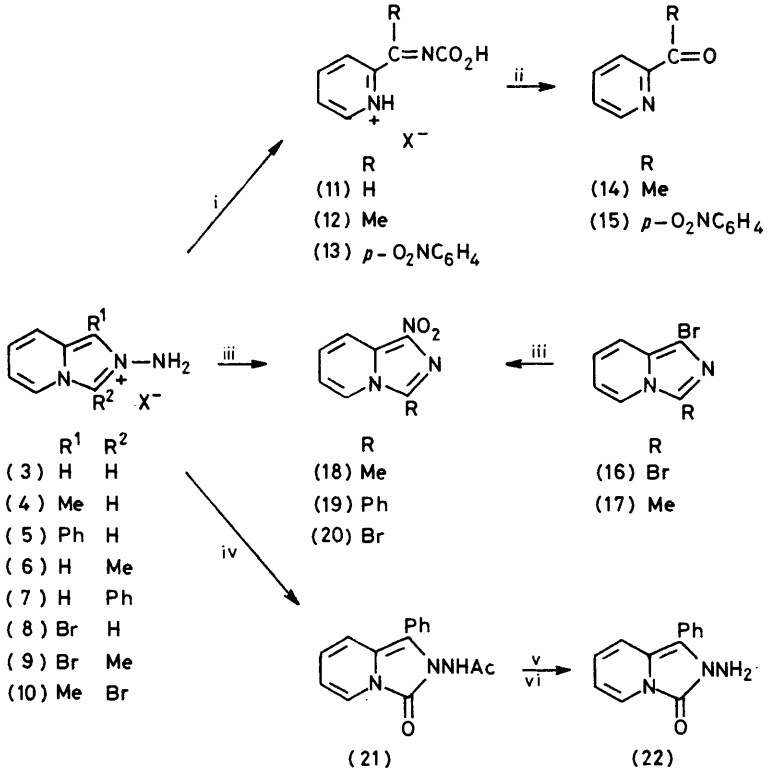


Scheme 2

The structures of the nitro-compounds (18)—(20) were deduced from their elemental analyses and their relative molecular masses determined mass spectrometrically. Further, the melting point and u.v.-spectrum of the 1-nitro-3-methylimidazo[1,5-*a*]pyridine (18) showed good agreement with the values previously reported.[4]

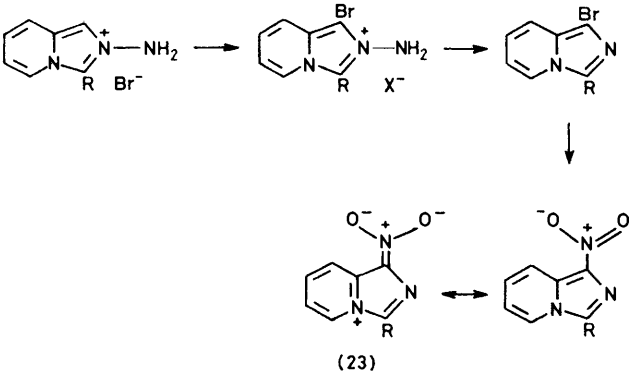
The nitro-compounds (18)—(20) are high melting solids, virtually insoluble in diethyl ether but which crystallize unchanged from concentrated hydrobromic acid. Their i.r. spectra show strong bands in the region of 1 350 and 1 250 cm^{-1} attributable to a nitro-group attached to a powerful electron donor. These facts together with the observation that the u.v. spectra of compounds (18)—(20) show a relatively intense band in the region of 400 nm, suggest that the compounds are more accurately represented by the structure (23).

Insight into the mechanism of formation of the nitro-compounds (18)—(20) came from the observation that oxidation of the methyl *N*-aminoimidazopyridinium bromide (6) with a solution of nitric acid in acetic acid containing an insufficiency of the former resulted in the isolation of the brominated *N*-aminoimidazopyridinium bromide (9). Further, it was found that acetic acid solutions of the bromoimidazopyridines (16) and (17) when treated with nitric acid soon deposited the corresponding nitro-compounds (20) and (18). Treatment of 3-methylimidazo[1,5-*a*]pyridinium toluene-*p*-sulphonate in acetic acid with concentrated nitric acid followed by heating to 100 °C was without effect in the absence of added bromide ions. It was concluded therefore that the reaction proceeded *via* bromination, by molecular bromine produced by the nitric acid oxidation of the bromide ion, followed by oxidative deamination of the five-membered ring and subsequent reaction of the resulting 1-bromoimidazopyridines with nitric acid as shown in Scheme 3. The formation of the brominated nitro-compound (20) from the unsubstituted *N*-aminoimidazopyridinium bromide (3) would similarly result from initial 1,3-dibromination followed by oxidative deamination and final replacement of the 1-bromine atom by a nitro-group.



Reagents: i, Conc. HNO_3; ii, Amberlite IRA 400(OH); iii HNO_3–AcOH; iv, $Pb(OAc)_4$–AcOH; v, aq. HBr; vi, aq. NaOH.

Oxidation of 2-amino-1-phenylimidazo[1,5-*a*]pyridi-



SCHEME 3

TABLE 1

2-Pyridylmethylenecarbamic acid hydrohalides

Reactants	Product	X	Yield (%)	M.p. (°C)	Crystallizing solvent	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
(3) [3] (0.9 g) + Conc. (70 w/w%) HNO_3 (2.25 cm³) [a]	(11) [b]	Br	39	191—192 [c]	MeOH	36.7	3.0	11.8	36.4	3.05	12.1
(4) [d] (0.2 g) + Conc. (70 w/w%) HNO_3 (0.5 cm³) [e]	(12) [f,g]	Br	72	175—185 [h]	MeOH–Et_2O	39.3	3.5	11.1	39.2	3.7	11.4
(4) [d] (1.0 g) + Conc. (70 w/w%) HNO_3 (5 cm³) in HOAc (10 cm³)	(12)	Cl	46	220—224 [j]	MeOH–Et_2O	47.7	4.3	13.9	47.9	4.5	14.0
(5) [3k] (1.5 g) + Conc. (70 w/w%) HNO_3 (7.5 cm³) in HOAc (15 cm³) [l]	(13) [m—o]	Br	47	178—184 [p]	MeOH–Et_2O	44.5	3.1	11.5	44.3	2.9	11.9
(5) [3q] (1.0 g) + Conc. (70 w/w%) HNO_3 (5 cm³) in HOAc (10 cm³) [r]	(13)	Cl	43	146	MeOH–Et_2O	50.9	3.4	13.3	50.75	3.3	13.7

[a] The solution of the bromide salt was set aside at room temperature for 2—3 min after which a vigorous reaction occurred. The solution was then cooled and treated with acetone (10 cm³) followed by an excess of diethyl ether. The precipitated gum was separated, washed with diethyl ether and dissolved in concentrated (48 w/w%) hydrobromic acid. Addition of ethanol (10 cm³) followed by diethyl ether precipitated the hydrobromide which was filtered off and recrystallized. Concentration of the mother liquors gave the hydrobromide of pyridine-2-carboxylic acid amide. [b] The i.r. spectrum (KBr disc) showed an intense ν(C=O) band at 1 825 cm^{-1}. [c] With decomposition. [d] The *toluene-p-sulphonate salt* was prepared in 98% yield from 1-methylimidazo[1,5-*a*]-pyridine using the procedure previously described [3] for the *N*-amination of the corresponding 3-methyl base. It was recrystallized from ethanol–diethyl ether and had m.p. 211 °C (Found: C, 56.4; H, 5.3; N, 13.1 $C_{15}H_{17}N_3SO_3$ requires C, 56.4; H, 5.4; N, 13.2%). The *bromide*, prepared by dissolving the toluene-*p*-sulphonate salt in concentrated (48 w/w%) hydrobromic acid followed by the addition of ethanol and diethyl ether, was recrystallized from ethanol–diethyl ether and had m.p. 252 °C (decomp.) (Found: C, 42.3; H, 4.4; N, 18.3. $C_8H_{10}BrN_3$ requires C, 42.1; H, 4.4; N, 18.4%). The *chloride* prepared similarly to the bromide but using concentrated hydrochloric acid was recrystallized from methanol-diethyl ether and had m.p. 226 °C (Found: C, 51.75; H, 5.7; N, 22.5. $C_8H_{10}ClN_3$ requires C, 52.3; H, 5.5; N, 22.9%). [e] The solution of the bromide salt was heated on a boiling water-bath. After a short induction period a vigorous reaction ensued after which the solution was cooled and treated with acetone (4 cm³) and diethyl ether (30 cm³). The precipitated gum was separated and treated with concentrated (48 w/w%) hydrobromic acid (1 cm³), ethanol (4 cm³), and diethyl ether (10 cm³). The solid which separated on cooling was filtered off and recrystallized. [f] A solution of the hydrobromide (0.22 g) in methanol (15 cm³) was passed through a column of Amberlite IRA 400 (OH). Evaporation of the eluate and treatment of the residue with concentrated (48 w/w%) hydrobromic acid (0.5 cm³), ethanol (3 cm³) followed by diethyl ether gave 2-acetylpyridine hydrobromide (0.7 g, 38%), the m.p. and i.r. spectrum of which were identical with those of an authentic sample. [g] The i.r. spectrum (KBr disc) showed an intense ν(C=O) band at 1 825 cm^{-1}. [h] Decomposition range after rapid heating to 160 °C. [i] The chloride salt was added to the mixed nitric and acetic acids at 100 °C. A vigorous reaction ensued after which the solution was cooled and treated with diethyl ether (65 cm³). The precipitated gum was dissolved in concentrated (36 w/w%) hydrochloric acid (5 cm³) and methanol (20 cm³). Diethyl ether was then added to the warmed solution to the point of incipient precipitation after which it was cooled and the solid which separated filtered off and recrystallized. [j] Decomposition range. [k] The bromide was prepared as previously described [3] but had m.p. 228 °C (lit.,[3] m.p. 217 °C) (Found: C, 53.3; H, 4.4; N, 14.4. Calc. for $C_{13}H_{12}BrN_3$: C, 53.8; H, 4.2; N, 14.5%). [l] The nitric acid was added to a solution of the bromide in acetic acid heated on a boiling water-bath. A vigorous reaction ensued after which the solution was cooled and treated with diethyl ether (200 cm³). The precipitated gum was treated with concentrated (48 w/w%) hydrobromic acid (4 cm³) and ethanol (20 cm³) followed by diethyl ether; the solid which separated was filtered off and recrystallized. [m] The i.r. spectrum (KBr disc) showed an intense ν(C=O) band at 1 830 cm^{-1}. [n] The hydrobromide (13) (0.2 g) in methanol (20 cm³) was passed through a column of Amberlite IRA 400 (OH) and the eluate evaporated. The residue (0.123 g, 95%) was recrystallized from aqueous methanol giving *p*-nitrobenzoylpyridine, m.p. 103 °C (lit.,[6] m.p. 105 °C) (Found: 62.9; H, 3.6; N, 12.2. Calc. for $C_{12}H_8N_2O_3$: C, 63.2; H, 3.5; N, 12.3%). The *hydrobromide* recrystallized from methanol–diethyl ether; the analytical sample was purified by sublimation at 140—150 °C/0.5 mmHg and had m.p. 192—195 °C (Found: C, 46.7; H, 3.2. $C_{12}H_8N_2O_3$, HBr requires C, 46.6; H, 2.9%). [o] Thermal decomposition of the hydrobromide at 140—150 °C and 0.5 mmHg gave *p*-nitrobenzoylpyridine hydrobromide identical with the sample described in *n*. [p] Decomposition range after a previous change in crystal form at 144 °C. [q] Prepared by dissolving the toluene-*p*-sulphonate salt [3] in concentrated (36 w/w%) hydrochloric acid and precipitating the chloride salt with ethanol–diethyl ether. Recrystallization from methanol–diethyl ether gave the *chloride* (5), m.p. 254 °C. (Found: C, 63.6; H, 5.0; N, 17.2. $C_{13}H_{12}ClN_3$ requires C, 63.6; H, 4.9; N, 17.1%). [r] The chloride was added to the mixture of nitric and acetic acids heated on a boiling water-bath. A vigorous reaction followed after which the reaction mixture was cooled and treated with diethyl ether (75 cm³). The gum which separated was treated with concentrated hydrochloric acid (5 cm³) and ethanol (20 cm³) followed by diethyl ether. The hydrochloride which separated was filtered off and recrystallized.

TABLE 2

1-Nitroimidazo[1,5-*a*] pyridines

Reactants	Product	Yield (%)	M.p. (°C)	Crystallizing solvent	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
(3) [3] (0.4 g) in HOAc (2 cm³) + Conc. (70 w/w%) HNO_3 (0.2 cm³) [a]	(20) [b,c]	49	230	HOAc	34.5	1.6	17.85	34.7	1.7	17.4
(16) [d] (0.1 g) in HOAc (2 cm³) + Conc. (70 w/w%) HNO_3 (2 drops ≃ 0.094 g) [e]	(20)	19	230	HOAc						
(6) [3] (0.2 g) in HOAc (2 cm³) + Conc. (70 w/w%) HNO_3 (0.1 cm³) [a,f]	(18) [g,h]	38	274	HOAc [i]	54.0	3.9	23.95	54.2	4.0	23.7
(17) [3] (0.05 g) in HOAc (1 cm³) + Conc. (70 w/w%) HNO_3 (1 drop ≃ 0.025 g) [e]	(18)	36	274	HOAc [i]						
(7) [3] (0.2 g) in HOAc (2 cm³) + Conc. (70 w/w%) HNO_3 (0.1 cm³) [j]	(19)	41	215	HOAc [k]	65.2	3.45	17.8	65.3	3.8	17.6

[a] The bromide was dissolved in the mixture of nitric and acetic acids and the solution heated in a boiling water-bath. A vigorous reaction occurred after about 1.5 min and the solution was then cooled in ice. The solid which crystallized was filtered off, washed with ethanol, and recrystallized. [b] The i.r. spectrum (KBr disc) showed intense bands at 1 240 and 1 350 cm^{-1}. [c] λ_{max}(MeOH) 234,

Footnotes to Table 2 (*Continued*)

275, and 390 (log ε 4.01, 3.57, and 4.15). [d] Prepared by treating imidazo[1,5-*a*]pyridine (0.3 g) with pyridine hydrobromide perbromide (0.8 g) in acetic acid (5 cm³) and stirring the solution for 2 min. Diethyl ether (50 cm³) was then added and the solution stirred and then set aside. After the solid had settled the diethyl ether was decanted and the residual solid shaken with water (50 cm³). The solid was then filtered off and recrystallized from aqueous methanol to give the dibrominated base (16) (0.18 g, 26%), m.p. 128 °C (decomp.) (lit.,[4] m.p. 124—126 °C) (Found: C, 30.4; H, 1.55; N, 9.6. Calc. for $C_7H_4Br_2N_2$: C, 30.5; H, 1.5; N, 10.15%). [e] The acetic acid solution of the base was treated with the nitric acid, stirred, and then set aside at room temperature for 0.5 h. It was then cooled and the product filtered off and recrystallized. [f] When the reaction was carried out using 0.4 g of the bromide but the same volumes of acetic and nitric acids the mixture became deep green on warming. The product which separated on cooling was filtered off and recrystallized from methanol to give the brominated *N*-amino-salt (9) (0.113 g, 21%), m.p. 223 °C (decomp.) (lit.,[3] m.p. 223 °C) (Found: C, 31.5; H, 3.0; N, 13.6. Calc. for $C_8H_9Br_2N_3$: C, 31.3; H, 3.0; N, 13.7%). [g] The i.r. spectrum (KBr disc) showed intense bands at 1 240 and 1 365 cm^{-1}. [h] λ_{max}(MeOH) 230sh, 260sh, and 399 (log ε 3.99, 3.5, and 4.13). [i] May also be purified by vacuum sublimation at 160 °C and 0.2 mmHg. [j] The bromide in acetic acid was heated on a boiling water-bath and then treated with the nitric acid. A vigorous reaction ensued after which the mixture was cooled. The solid which separated was filtered off, washed with ethanol, and recrystallized. [k] May also be purified by vacuum sublimation at 200 °C and 0.4 mmHg.

TABLE 3

Lead(IV) acetate oxidations

Reactants	Product	X	Yield (%)	M.p. (°C)	Crystallizing solvent	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
(3) [3] (0.428 g) in HOAc (100 cm³) + $Pb(OAc)_4$ (1.772 g) in HOAc (50 cm³) [a]	(8)	Br	8 [b]	207—208	MeOH–Et_2O	28.5	2.0	14.2	28.7	2.4	14.3
(4) [c] (0.456 g) in HOAc (100 cm³) + $Pb(OAc)_4$ (0.886 g) in HOAc (50 cm³) [d]	(10)	Br	46	>310 [e]	EtOH–H_2O	31.3	3.2	13.6	31.3	3.0	13.7
(5) [3] (0.58 g) in HOAc (80 cm³) + $Pb(OAc)_4$ (0.886 g) in HOAc (40 cm³) [f]	(21) [g]		37	84—86	H_2O	65.1	4.9	15.2	64.6	4.8	15.5 [h]

[a] The lead(IV) acetate solution was added in bulk to the solution of the bromide and the resulting mixture stirred overnight after which it was filtered and the filtrate saturated with H_2S. The precipitated lead sulphide was then filtered off and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in concentrated (48 w/w%) hydrobromic acid and the solution extracted with chloroform. Evaporation of the aqueous layer under reduced pressure gave the *bromide* (8) which was filtered off and recrystallized. [b] The reaction proved difficult to reproduce. [c] See Table 1 footnote *d*. [d] The bromide was dissolved in the acetic acid at 65—70 °C and the lead(IV) acetate solution was then added in bulk after which the reaction mixture was stirred overnight. It was then filtered and the filtrate saturated with H_2S; the precipitated lead sulphide was filtered off and the filtrate evaporated to dryness under reduced pressure. Treatment of the residue with concentrated (48 w/w%) hydrobromic acid (1 cm³), ethanol (9 cm³), followed by diethyl ether (10 cm³) gave the *bromide* (10) which was filtered off and recrystallized. [e] Slowly decomposed without melting below the temperature shown. [f] The lead(IV) acetate solution was added in bulk to the solution of the bromide and the reaction mixture stirred for 5 h. The reaction mixture was then evaporated to dryness under reduced pressure and re-evaporated several times with added volumes of water before being extracted successively with 30 cm³ and 20 cm³ volumes of boiling water. The yellow solid which separated from the cooled extracts was filtered off and recrystallized. [g] Compound (21) (0.43 g) was treated with concentrated (48 w/w%) hydrobromic acid and the mixture heated to boiling. The solution was then cooled, treated with ethanol, and evaporated to dryness under reduced pressure. The residue was dissolved in water and the solution made alkaline. The *N-amino-base* (22) which separated was filtered off and recrystallized from water (0.15 g, 43%), m.p. 186—188 °C (Found: C, 69.1; H, 4.7; N, 18.8. $C_{13}H_{11}N_3O$ requires C, 69.3; H, 4.9; N, 18.65%). The i.r. spectrum (KBr disc) of (22) showed ν(N–H) bands at 3 320 and 3 170 cm^{-1} and a ν(C=O) band at 1 700 cm^{-1}. [h] For the hemihydrate.

nium bromide (5) with lead(IV) acetate in acetic acid solution gave the acetylated hydrazide (21) hydrolysis of which yielded the corresponding *N*-amino-compound (22). The formation of (21) compares with the similar oxidation of 1-aminopyridinium bromide to 1-acetamido-2-oxo-1,2-dihydropyridine.[5] Similar oxidation of the unsubstituted *N*-amino-bromide (3) and the 1-methyl derivative (4) resulted only in the isolation of the corresponding brominated *N*-amino-salts (8) and (10) respectively.

We consider it unlikely that any of the above reactions proceeds *via* an aminonitrene conjugate acid of the type (2); this is consistent with the suggestion that the charge in 2-aminoimidazo[1,5-*a*]pyridinium salts is largely localized on the 2-nitrogen atom.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. U.v. and i.r. spectra were determined with Perkin-Elmer 137 and 377 spectrometers, respectively.

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