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COVALENT ADDUCTS FROM 1,3-DISUBSTITUTED PYRIDINIUM SALTS AND PIPERIDINE

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Abstract—Covalent adducts **3a–f** have been isolated from the reaction between piperidine and pyridinium salts **1a–f**. **3a–f** are stable both in the solid state and in apolar solvents, whereas their fast dissociation back to piperidine and pyridinium ions occurs in aqueous solution. The latter, in the alkaline environment produced by the amine, yields the correspondent pseudobases, which are key intermediates of the subsequent reactions. For instance, the pseudobases from **1a,b** can undergo either a ring-opening reaction or a redox process with the corresponding pyridinium cations.

We have previously reported[1] that the reaction of the 3-cyano-1-methylpyridinium iodide (**1a**) with aqueous solutions of aliphatic amines can follow two competing pathways, namely a heterocyclic ring opening and a redox process. The former yields imino derivatives of type **9** or aldehydes of type **11**, the latter gives the dihydropyridines **4a–6a** and pyridones **7a** and **8a**, in equimolar amounts. While both reaction pathways require the initial addition of the nucleophile (i.e. the amine or the hydroxide ion) to the heterocyclic cation, in the systems so far studied[1] no direct evidence on the formation of the amination adducts or pseudobases could be obtained.

It should be noted that only a few cases, where amination adducts have been isolated or detected, are reported in the literature. For instance, Zoltewicz *et al.*[2] have found that 1,3-disubstituted pyridinium ions undergo reversible covalent amination in liquid ammonia, the addition site depending on the nature of the substituent at the C atom. It has been also reported the isolation of 1-benzyl-3-carbamoyl-6-diethylamino-1,6-dihydropyridine[3] from **1f** and diethylamine, and of 1-methyl-3-nitro-4-piperidino-1,4-dihydropyridine[4] from 1-methyl-3-nitropyridinium iodide and piperidine.

As to the pseudobases, only in a few cases has their isolation has been accomplished,[5] despite their generally postulated occurrence in the alkaline solutions of pyridinium salts, in equilibrium with the correspondent quaternary hydroxides.

In the present paper we report the results obtained from the study of the reaction between piperidine and pyridinium salts substituted at position 3 with electron-withdrawing groups. Addition of piperidine to an aqueous solution of **1a** under suitable conditions, causes the immediate formation of a precipitate, identified as 3-cyano-1-methyl-6-piperidino-1,6-dihydropyridine (**3a**) on the basis of the data reported in Tables 1 and 2. **3a** can be also obtained in good yields from the reaction between **1a** and neat piperidine. Analogous adducts have been obtained from the salts **1b–f** on reaction with piperidine. The structure of the adducts **3b–f** has been assigned on the ground of the data shown in Tables 1 and 2.

While **3a–f** are stable in the solid state under vacuum,

Table 1. ^{1}H NMR data for adducts 3

Compd (solv)	H-2	H-4	H-5	H-6	Other protons
3a (CCl_4)	6.99, d $J_{2,4}$=1.5	6.15, dd $J_{4,5}$=10.5	5.05, dd $J_{5,6}$=4.5	4.80, d	3.08 (s, 3, N-CH_3). Piperidine H: 2.7–2.3 (bs, 4), and 1.7–1.3 (bs, 6).
3b ($CDCl_3$)	7.05, d $J_{2,4}$ = 1.5	6.16, dd $J_{4,5}$ = 10.5	5.02, dd $J_{5,6}$ = 4.5	4.75, d	7.4–7.1 (group of signals, 5, aromatic H), 4.66 (d, 1, benzylic H, J = 15), 4.25 (d, 1, benzylic H, J = 15). Piperidine H: 2.7–2.3 (bs, 4), and 1.8–1.2 (bs, 6).
3c (CCl_4)	7.30, d $J_{2,4}$=1.5	6.71, dd $J_{4,5}$=10.5	4.99, dd $J_{5,6}$=4.5	4.76, d	3.13 (s, 3, N-CH_3), 2.00 (s, 3, $COCH_3$). Piperidine H: 2.6–2.3 (bs, 4) and 1.7–1.2 (bs, 6).
3d (CCl_4)	7.48, d $J_{2,4}$=1.5	6.74, dd $J_{4,5}$=10.5	4.99, dd $J_{5,6}$=4.5	4.66, d	7.3–7.1 (group of signals, 5, aromatic H), 4.77 (d, 1, benzylic H, J=15), 4.27 (d, 1, benzylic H, J=15), 2.00 (s, 3, $COCH_3$). Piperidine H: 2.6–2.3 (bs, 4), and 1.7–1.3 (bs, 6).
3e (CD_3NO_2)	7.11, d $J_{2,4}$=1.5	6.10, dd $J_{4,5}$=7.5	4.77, dd $J_{5,6}$=4.5	4.23, d	3.07 (s, 3, N-CH_3). Piperidine H: 2.9–2.6 (bs, 4), and 1.8–1.2 (bs, 6). Amide protons undergo deuterium exchange.
3f (CD_3NO_2)	7.21, d $J_{2,4}$=1.5	6.16, dd $J_{4,5}$=9.0	4.82, dd $J_{5,6}$=4.5	4.17, d	7.6–7.3 (group of signals, 5, aromatic H), 4.47 (s, 2, benzylic H). Piperidine H: 2.9–2.6 (bs, 4), and 1.7–1.3 (bs, 6). Amide protons undergo deuterium exchange.

Table 2. Melting points and spectroscopic properties of adducts 3

Compd.	Proced.	Yield %	m.p. °C	IR, $\bar{\nu}$ cm^{-1}	UV max, nm	*m/e*
3a	a or b	80	88–90°	2190,1650 1585	330(CCl_4) 245, 317(EtOH)	203
3b	a	85	†	2190, 1640 1575	335(CCl_4) 245, 318(EtOH)	279
3c	a	70	89–91°	1650, 1610 1580	340(CCl_4) 275, 325(EtOH)	220
3d	a	80	99–101°	1645, 1610 1575	340(CCl_4) 275, 330(EtOH)	296
3e	a	70	118–20°	3280, 3120 1685, 1650 1580	330(CCl_4) 270, 323(EtOH)	221
3f	c	80	113–15° (dec.)	3400, 3200 1700, 1655 1600, 1555	330(CCl_4) 273, 330(EtOH)	‡

†Viscous, not crystallizable oil, containing minor amounts of the isomeric addition products at positions 2 and 4.

‡The *m/e* value could not be measured, since the product is thermally unstable.

their stability in solution depends on the nature of both the substituent group at C-3, and the solvent. In general, they are stable in apolar solvents such as CCl_4, while in a protic solvent such as 95° EtOH, only **3a–d** are stable. Fast decomposition of all adducts occurs in water. For instance, the UV spectrum of a freshly prepared aqueous solution of **3a** displays only the typical absorption maximum of the pyridinium cation at *ca* 270 nm, while on standing other absorptions appear in the 330–400 nm region. A similar behaviour is displayed by the other adducts.

In order to study the nature of the chemical changes, **3a** has been dissolved in water and the solution extracted with CH_2Cl_2. From the organic phase have been isolated the dihydropyridines **4a–6a**, the pyridones **7a,8a**, the iminoaldehyde **9a**, the pyridinaldehyde **10a**, and the pentadienenitrile **11**, whereas **12a** has been recovered from the aqueous solution.

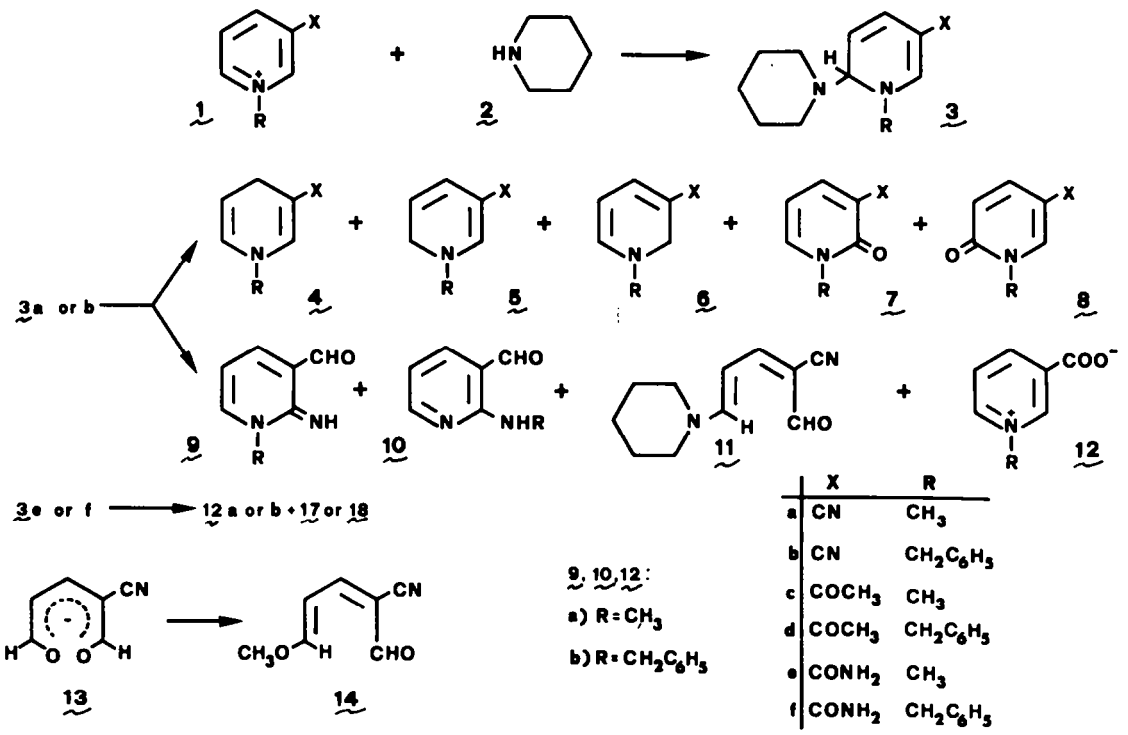
Because of its insolubility in water, **3b** has been dissolved in a H_2O–EtOH 1:1 mixture. After removal of the ethanol, the compounds **4b–10b** and **11** have been extracted with CH_2Cl_2 from the aqueous solution. By evaporation of the latter, a residue is obtained that yields 2-formyl-5-methoxy-2,4-pentadienenitrile (**14**) on SiO_2 column chromatography (MeOH–AcOEt 1:1 as eluent).

Compound **3d**, also insoluble in water, has been dissolved in to a H_2O–EtOH 1:1 mixture, and the solution evaporated to give one product, **15**, identical in every respect to the compound obtained by Anderson *et al.*[6] from **1d** and NaOH, to which these Authors have assigned the 2,2'-oxybis(3-acetyl-1-benzyl-1,2-dihydropyridine) structure. Likewise, evaporation of an aqueous solution of **3c** yields a product **16**, whose UV spectrum is quite similar to that of **15**. **16** can be obtained as well from the reaction of **1c** with NaOH, and, as reported[6] for **15**, could not be crystallized, or otherwise futher purified, owing to its lack of stability, especially in solution. In particular, no meaningful ^{1}H NMR spectrum on the sample could be recorded. While formation conditions and similar properties suggest that **16** could represent the N-Me analogue of **15**, the available data are nevertheless too meagre to support any conclusion on its structure.

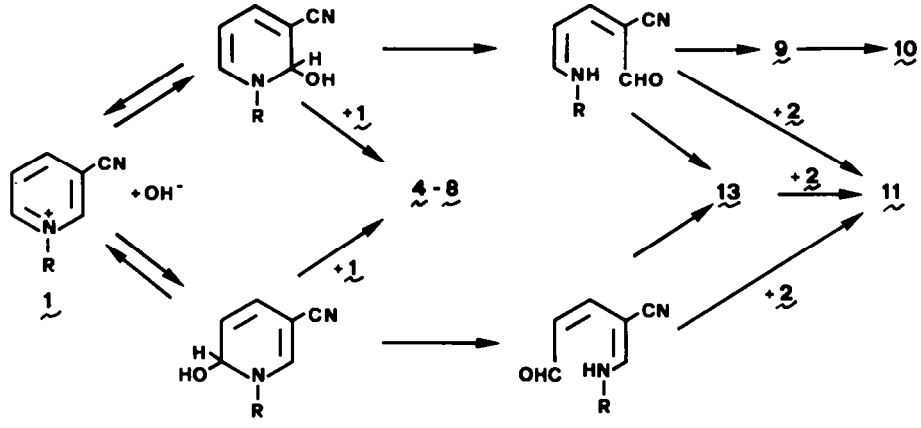
Finally, aqueous solutions of **3e** and **3f** have been extracted with CH_2Cl_2 to yield minor amounts of the compounds **17** and **18**, respectively, while the betaines **12a** and **12b** have been recovered from the aqueous solutions. **18** is identical in any respect to the product obtained by Dittmer *et al.*[7] from **1f** and NaOH, to which these authors have assigned the 4,4'-oxybis(1-benzyl-3-carbamoyl-1,4-dihydropyridine) structure. The UV spectrum of **17**, that can be obtained as well from the treatment of **1e** with NaOH, is quite similar to that of **18**. As reported[7] for **18**, **17** could not be crystallized or otherwise further purified owing to its lack of stability, especially in solution. In particular, no meaningful ^{1}H NMR spectra on the sample could be recorded. While formation conditions and similar properties suggest that **17** may represent the N-Me analogue of **18**, the available data fail to support any firm conclusion concerning its structure.

The reported results clearly suggest that adducts **3** are invariably incapable of surviving in aqueous or hydroalcoholic solutions, owing to their immediate dissociation back into pyridinium cations and piperidine, and that the subsequent reactions must be regarded as typical of these pyridinium cations in the alkaline environment produced by the piperidine. Thus the products from the solutions of the adducts **3a,b** are throughly correspondent to those obtained from the two competing reaction channels that, as mentioned above, occur when 3-cyanopyridinium salts are treated with aqueous amine solutions. The formation of dihydropyridines and pyridones has been easily traced to a redox process involving the pyridinium cation and the pseudobases, while no univocal pathway could be postulated concerning the ring-opening reaction.[1] In fact, the results could be interpreted assuming initial formation of either pseudobases or of amination adducts as well. From the recognized lack of stability of the adducts **3** in aqueous solution, it is now suggested that the pseudobases are key intermediates in the ring-opening process as well. Formation of the products **4–11**, **13** can be therefore illustrated as in Scheme 2.

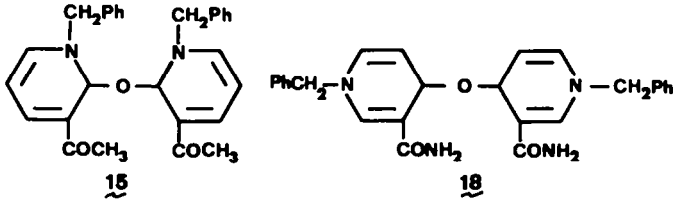
It can be further noted that when the reaction of the salt **1a** with piperidine occurs under conditions where precipitation of the adduct **3a** is prevented, the reactivity pattern of the same adduct in water is duplicated, except for the fact that in the aqueous solution, after extraction with organic solvent, the nicotinamide salt **1e** replaces the betaine **12a**. As previously mentioned, products such as **12b** or **1f**, arising from the saponification of the cyano group of the cation **1b**, are not obtained from the hydro-



Scheme 1.



Scheme 2.



Scheme 3.

alcoholic solution of **3b**. In fact, by working up this solution, after isolation of the products **4b–10b** and **11**, **14** has been obtained, which clearly represents an artefact formed on the SiO_2 column during elution with the MeOH–AcOEt mixture. Formation of **14** can be plausibly traced to the reaction between methanol and the ring-opened enolate **13**.[8]

It is evident that all products from the hydroalcoholic solution of **3b** arise from the correspondent pseudobases, via either a redox process, or a ring-opening reaction. This finding can be rationalized taking into account the fact that the position of the equilibrium between the pseudobases and the quaternary hydroxides depends on the polarity of the solvent. In fact, covalent adduct from heteroaromatic cations are stabilized by moderately polar solvents.[6,9] This would explain the shift of the equilibrium between the quaternary hydroxides and the pseudobases in favour of the latter in hydroalcoholic medium. According to this view, when **3a** is dissolved into a strongly polar medium, e.g. water, the betaine **12a** is formed in good yield, while in a solvent of lower polarity, e.g. the H_2O-EtOH 1:1 mixture, the enolether **14** replaces the betaine **12a**.

As to the **3d** and **3f** adducts, the pseudobases arising from these products exhibit a particular reactivity pattern, since only the ethers **15** and **18** are formed. It should be noted that the nicotinamide cation undergoes predominantly hydrolysis of the carbamoyl group, showing that this ion is scarcely prone to the ring addition of the hydroxide ion.

EXPERIMENTAL

The m.ps were taken on a Tottoli apparatus, and are uncorrected. The UV spectra were recorded on a Perkin–Elmer 402 spectrophotometer and the IR spectra, as Nujol mulls or liquid films, on a Perkin–Elmer 177 grating spectrophotometer. The ^1H NMR spectra were recorded on a Varian EM-390 spectrometer, the chemical shifts are reported as δ units from TMS as internal standard, and the coupling constants (J) in Hertz. The *m/e* values were measured with a Hewlett–Packard 5890A low resolution mass spectrometer. Column chromatography was carried out on Merck silica gel 70–230 mesh. Pyridinium salts **1a–f** were obtained from the correspondent substituted pyridines and methyl iodide or benzyl chloride, according to standard procedures. All known compounds were identified by comparison with authentic samples. All new compounds gave elemental analyses (C, H, N) within ±0.3% of the theoretical values.

Synthesis of compounds **3**

(a) The pyridinium salt (0.015 mol) was added to neat piperidine (30 ml), and the mixture stirred 2 hr at room temp. The solid was filtered off, and the filtrate diluted with light petroleum ether. The ppt formed was collected by suction, washed with light petroleum ether, and dried under vacuum over P_2O_5.

(b) Piperidine (0.03 mol) was added to a soln of pyridinium salt (0.01 mol) in H_2O (35 ml). The ppt was collected by suction, dried under vacuum over P_2O_5, and crystallized from light petroleum ether.

(c) The pyridinium salt (0.014 mol) was added to a soln of piperidine (60 ml) in anhydrous benzene (60 ml). The mixture was stirred 2 hr at room temp., the solid filtered off, and the filtrate diluted with light petroleum ether. The ppt formed was collected by suction, washed with light petroleum ether, and dried under vacuum over P_2O_5.

Reactivity of adducts **3**

Compound **3a** *in* H_2O. A suspension of **3a** (1.5 g) in H_2O (50 ml) was stirred at room temp to complete dissolution, and then extracted with CH_2Cl_2. The aqueous layer was evaporated under vacuum to give a residue (0.68 g), which was further purified by crystallization from 2-propanol, and identified as **12a**, by comparison with an authentic sample prepared from nicotinic acid, via quaternization with MeI and dehydrohalogenation with triethylamine in benzene. The CH_2Cl_2 soln was dried (Na_2SO_4), and evaporated under vacuum to give a residue (0.70 g) and resolved by column chromatography (SiO_2, 140 g). By using a mixture CH_2Cl_2–AcOEt 9:1, the following fractions were eluted in the order: (i) a mixture of **4a–6a** (0.04 g); (ii) **10a** (0.04 g); (iii) a mixture of **7a** and **8a** (0.05 g). Compound **11** (0.26 g) was eluted with a mixture CH_2Cl_2–AcOEt 1:1. Finally, **9a** (0.14 g) was eluted with a mixture H_2O–AcOH 1:1, and recovered from the acidic soln by careful alkalinization with Na_2CO_3, followed by several extractions with CH_2Cl_2.

Compound **11**. M.p. 156–57° (2-propanol); mol wt: Calc 190.24. Found 190 (from mass spectrum); UV max (EtOH) 257, 386 nm; IR $\bar{\nu}$ 2200, 1610, 1565, 1555, 1540 cm^{-1}; NMR ($CDCl_3$) δ 9.23 (s, 1, CHO), 7.60 (d, 1, H-5, $J_{5,4}$=13.5), 7.33 (d, 1, H-3, $J_{3,4}$=12), 5.80 (dd, 1, H-4), 3.70–3.30 (bs, 4, CH_2–N–CH_2), and 1.90–1.50 ppm [bs, 6, $-(CH_2)_3-$].

Compound **3a** *in* H_2O–EtOH. A soln of **3a** (1.5 g) in H_2O–EtOH (25 + 25 ml) was stirred 2 hr at room temp, EtOH evaporated under vacuum, and the aqueous phase extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4) and evaporated under vacuum. Column chromatography (SiO_2, 150 g) of the residue (0.75 g), using the above eluents, gave: (i) a mixture of **4a–6a** (0.03 g); (ii) **10a** (0.03 g); (iii) a mixture of **7a** and **8a** (0.04 g); (iv) **11** (0.15 g); (v) **9a** (0.14 g). The aqueous layer was evaporated under vacuum, and the residue (0.60 g) chromatographed on SiO_2 column (120 g, MeOH–AcOEt 1:1 as eluent) to give **14** (0.30 g), UV max (EtOH) 265, 358 nm; IR $\bar{\nu}$ 2210, 1650, 1600 cm^{-1}; NMR (DMSO-d_6) δ 9.10 (d, 1, H-5, $J_{5,4}$=9), 8.82 (s, 1, CHO), 7.42 (d, 1, H-3, $J_{3,4}$=13.5), 5.52 (dd, 1, H-4), and 3.52 (s, 3, CH_3). The mass spectrum and m.p. could not be determined, since **14** is thermally unsatable.

Compound **3b** *in* H_2O–EtOH. A soln of **3b** (1.6 g) in H_2O–EtOH (25 + 25 ml) was stirred 2 hr at room temp, EtOH evaporated under the vacuum, and the aqueous phase extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), and evaporated under vacuum. Column chromatography (SiO_2, 200 G) of the residue (1.0 g), using the above eluents, gave: (i) a mixture of **4b–6b** (0.03 g); (ii) **10b** (0.05 g); (iii) a mixture of **7b** and **8b** (0.04 g); (iv) (0.13 g); (v) **9b** (0.65 g). The aqueous layer was evaporated under evaporated under vacuum, and the residue (0.15 g) chromatographed on SiO_2 and (30 g, MeOH–AcOEt 1:1 as eluent) to give **14** (0.10 g).

Compound **3d** *in* H_2O–EtOH. A soln of **3d** (0.25 g) in H_2O–EtOH (15+15 ml) was stirred 2 hr at room temp, the solvent evaporated under vacuum, and the residue dried over P_2O_5 (0.17 g). The solid **15** was identical to the product obtained from the reaction of **1d** with NaOH, carried out in the described conditions.[6]

Compound **3c** *in* H_2O. A suspension of **3c** (1.5 g) in H_2O (50 ml) was stirred at room temp to complete dissolution, the solvent evaporated under vacuum, and the residue dried over P_2O_5 (0.96 g). The solid **16**, UV max (EtOH) 275,330 nm, was identical to the product we have obtained from the reaction of **1c** with NaOH, carried out in the conditions described for the reaction of **1d** with NaOH.[6]

Compound **3f** *in* H_2O. A suspension of **3f** (0.85 g) in H_2O (40 ml) was stirred at room temp to complete dissolution, and then extracted with CH_2Cl_2. The aqueous layer was evaporated under vacuum to give a residue (0.48 g), further purified by crystallization from 2-propanol, and identified as **12b**. The CH_2Cl_2 soln was dried (Na_2SO_4), and evaporated under vacuum to give a residue **18** (0.12 g) identical to the product isolated from the reaction of **1f** with NaOH, carried out in the described conditions.[7]

Compound **3e** *in* H_2O. A suspension of **3e** (0.20 g) in H_2O (10 ml) was stirred at room temp to complete dissolution, and then extracted with CH_2Cl_2. The aqueous phase was evaporated under vacuum to give a residue (0.11 g), further purified by crystallization from 2-propanol, and identified as **12a**. The CH_2Cl_2 soln was dried (Na_2SO_4), and evaporated under vacuum to give a residue **17** (0.01 g), UV max (EtOH) 270, 360 nm, identical to the product we have obtained from the reaction of **1e**

with NaOH, carried out in the same conditions described for the reaction of **1f** with NaOH.[7]

Reaction of **1a** *with piperidine.* Piperidine (1.7 g, 0.02 mol) was added to a soln of **1a** (2.46 g, 0.01 mol) in H_2O (500 ml), the mixture stirred 2 hr at room temp, and extracted CH_2Cl_2. The aqueous phase was evaporated under vacuum to give a residue (2.1 g) identified as the salt **1e**. The CH_2Cl_2 soln was dried (Na_2SO_4) and evaporated under vacuum to give a residue (0.3 g), resolved by column chromatography (SiO_2, 60 g) in the following fractions: (i) a mixture of **4a–6a** (0.03 g); (ii) in a mixture of **7a** and **8a** (0.04 g); (iii) **11** (0.18 g); (iv) **9a** (0.02 g).

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