Ring-cyclized Products from the Delepine Reaction

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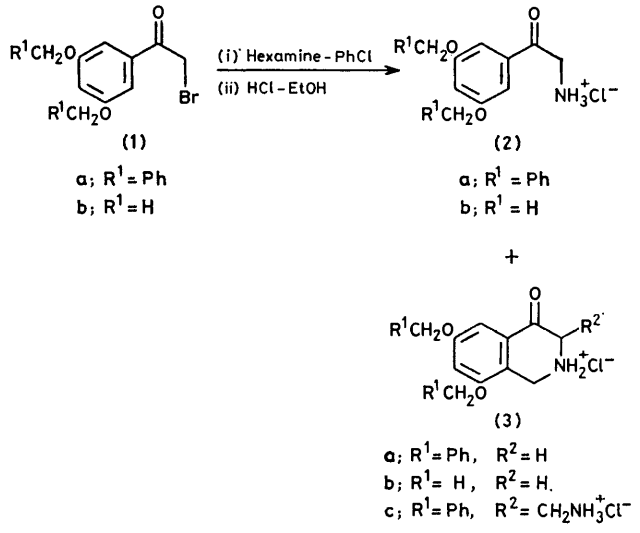
Reaction of 2-bromo-3',5'-bisbenzyloxyacetophenone (1a) with hexamine (hexamethylenetetramine) in chlorobenzene gave an insoluble hexaminium salt which on hydrolysis with hydrochloric acid in ethanol afforded a mixture of 3',5'-bisbenzyloxyphenacylammonium chloride (2a) and 6,8-bisbenzyloxy-4-oxo-1,2,3,4-tetrahydroisoquinolinium chloride (3a). When ethanol-free chloroform was used as solvent for the reaction no insoluble hexaminium salt was formed and acid hydrolysis of the product gave 3-ammoniomethyl-6,8-bisbenzyloxy-4-oxo-1,2,3,4-tetrahydroisoquinolinium dichloride (3c).

As part of our studies towards the synthesis of 4-hydroxytetrahydroisoquinoline derivatives[1] with potential biological activity we have prepared various ring-substituted phenacylammonium chlorides from phenacyl bromides using the Delepine reaction.[2] Reactions of phenacyl bromides with hexamine (hexamethylenetetramine) in chloroform usually give insoluble hexaminium salts that can thus be separated from any unchanged acetophenone or hexamine, which remain in solution. When the hexaminium salts are hydrolysed with hydrochloric acid the phenacylammonium chlorides



SCHEME 1

are obtained in good yield. However when 2-bromo-3',5'-bisbenzyloxyacetophenone (1a) reacted with hexamine in chloroform only a trace amount of hexamine salt was precipitated. Evaporation gave a material which was hydrolysed by acid to give a mixture of products. We report here the reaction of 2-bromo-3',5'-bisbenzyloxyacetophenone with hexamine in various solvents and the separation and identification of the materials formed by acid hydrolysis of the products from the Delepine reaction.

Delepine Reactions.—In an attempt to prepare 3',5'-bisbenzyloxyphenacylammonium chloride (2a), the phenacyl bromide (1a) was treated with hexamine in chloroform. Although only a trace of precipitate was formed, a study of the reaction in an n.m.r. tube using deuteriochloroform as solvent revealed that a reaction had occurred. On addition of hexamine to the phenacyl bromide the signal at δ 4.3 (CH_2Br) moved to 5.45 and that for the benzylic protons moved upfield by *ca.* 1 p.p.m. The peak at δ 4.7 (hexamine protons) disappeared and new peaks appeared at δ 5.9 and 4.5. Reaction was complete after 15 h at room temperature. Evaporation followed by addition of diethyl ether gave a cream powder showing a ketonic absorbance in its i.r. spectrum. This material was not purified due to its thermal instability.

Hydrolysis of the crude material with 2N-hydrogen chloride–ethanol gave a 50% yield of precipitated salts, but the mass spectrum showed *m/e* 359 and 371 indicating the presence of material with higher molecular weight than the required phenacylammonium chloride (2a). The ethanolic solution contained the phenacylammonium chloride (2a), which was contaminated by traces of material with higher molecular weight. When the total hydrolysate was acetylated, t.l.c. revealed a complex mixture. Three of these products were separated and shown to be the acetamides (4), (5), and (6). Impurities, present in the material that was hydrolysed, were responsible for at least some of the other products detected.

These impurities were successfully eliminated when chlorobenzene was used as solvent for the reaction between the phenacyl bromide (1a) and hexamine, as in this case the insoluble hexaminium salt was hydrolysed with 2N-hydrogen chloride–ethanol to give a precipitate of 3',5'-bisbenzyloxyphenacylammonium chloride (2a) and 6,8-bisbenzyloxy-4-oxo-1,2,3,4-tetrahydroisoquinolinium chloride (3a) (Scheme 1). The structures of these compounds were assigned on the basis of the spectral properties of their acetylated derivatives (4) and (5), respectively.

The relative proportion of each of the amine hydrochlorides in the mixture was ascertained, after acetylation of the salts obtained from hydrolysis, by comparing the areas of the Me peaks in the ^1H n.m.r. spectrum of the crude acetates. The mixture was found to consist of the two acetamides (4) and (5) in the approximate ratio 2 : 3. This ratio did not alter significantly when the concentration of hydrogen chloride in ethanol, used for the hydrolysis of the hexaminium salt, was varied between 0.1 and 5N.

The dilution of the hexaminium salt also appeared to

have no influence on the ratio of the two salts. The ammonium chloride (2a) was more soluble in ethanol and when larger volumes of solvent were used smaller yields of precipitated salts were obtained. These contained a larger proportion of the tetrahydroisoquinolinium salt (3a), which could be obtained pure in 50% yield after recrystallization from ethanol. The more soluble ammonium chloride (2a) was obtained free from the isoquinolinium salt with difficulty in 10% yield after several recrystallizations from ethanol–ether.

The ratio of the ammonium chloride (2a) to cyclized product (3a) was maximized at *ca.* 3 : 1 when the hydrolysis of the hexaminium salt was performed in aqueous acid. Under these conditions all the salts were precipitated and pure (2a) was obtained in *ca.* 50% yield after several recrystallizations.

Attempts to increase the proportion of ring cyclized product by addition of formaldehyde or hexamine to the hexaminium salt as it was hydrolysed were unsuccessful. Addition of formaldehyde to the ammonium chloride (2a) in ethanol–hydrogen chloride also did not cause ring closure indicating that this product is not an intermediate in the formation of the cyclized product. A reported attempt to effect ring closure of 3′,4′-dimethoxyphenylacylamine with aqueous formaldehyde was also unsuccessful, although the reaction with the corresponding phenylethanolamine did proceed.[3] The cyclization reported here may occur readily because the deactivating effect of the carbonyl group is surmounted by the activating effect of the two appropriately placed benzyloxy ether groups on the intermediate immonium salt ($ArCOCH_2\overset{+}{N}H{=}CH_2$) formed during the hydrolysis of the hexaminium salt.

Two appropriately placed methoxy-groups can also activate the ring for cyclization, and we have obtained 6,8-dimethoxy-4-oxo-1,2,3,4-tetrahydroisoquinolinium chloride (3b) as expected, along with 3,5-dimethoxyphenacylammonium chloride (2b), in a ratio of *ca.* 2 : 1, respectively, from hydrolysis of the hexaminium salt obtained from 2-bromo-3′,5′-dimethoxyacetophenone (1b).

Assignment of Structures.—The structure of the uncyclized acetamide (4) was readily assigned on the basis of its i.r. and ^{1}H n.m.r. spectra. This compound suffered extensive fragmentation in the electron impact (e.i.) mass spectrum (run at 70 eV) but the chemical ionization (c.i.) mass spectrum, using ammonia as the reagent gas, was more informative, exhibiting the pseudo-molecular ion ($M + 1$) at *m/e* 390 and an addition product ion ($M + 18$) at *m/e* 407. These two ions accounted for most of the ion current above *m/e* 60.

The structure of (4) was confirmed by analysis of its natural abundance ^{13}C-n.m.r. spectrum obtained in deuteriochloroform solution. The assignment of the chemical shifts of each of the carbon atoms was made by comparison with the spectrum of the phenacyl bromide (1a). The signals for the ring carbons C-2 and C-6 were distinguished from that for carbon C-4 after consideration of the integrated spectrum.

The structure of the cyclized acetamide (5) was assigned in a similar way. Its i.r. spectrum revealed an amide carbonyl band at 1 650 cm^{-1} and the lack of an NH stretching band, as expected for a tertiary amide. The presence of two one-proton doublets at δ 6.90 and 7.30 (J 2.5 Hz) in the aromatic region of the ^{1}H n.m.r. confirmed that cyclization on to the aromatic ring had occurred. Examination of the e.i. mass spectrum of this compound revealed the molecular ion at M^+ 401, and its c.i. spectrum, using ammonia as the reagent gas, revealed the pseudo-molecular ion ($M + 1$) at *m/e* 402 as well as an addition ion ($M + 18$) at *m/e* 419.

The structure (5) was confirmed by analysis of the ^{13}C n.m.r. spectrum. The assignment of resonances (Figure 1) was based on a comparison with those for α-tetralone,[4] the amide (4), and *N*-acetylpiperidine, and utilised data collected under conditions of noise decoupling, off-resonance single frequency decoupling, and extended

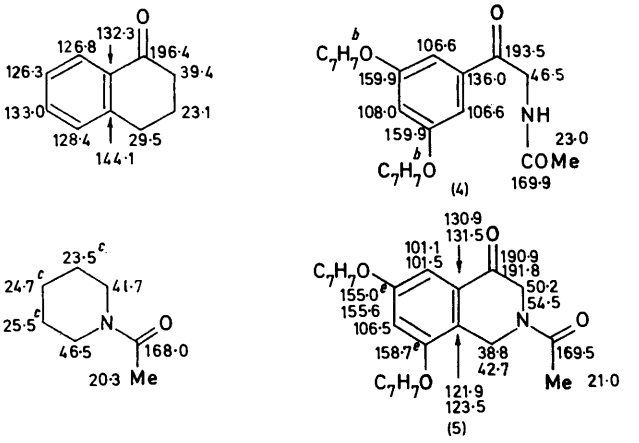


FIGURE 1

[a] δ Values in p.p.m. downfield from TMS: δ (TMS) = δ $CDCl_3$) − 76.9 p.p.m. [b] The benzyloxy δ (CH_2) = 70.3 p.p.m. δ (*i*) = 136.0 p.p.m., δ (*o*) = 128.4 p.p.m., δ (*m*) = 127.2 p.p.m., δ (*p*) = 128.0 p.p.m. [c–e] Values bearing the same superscript may be interchanged.

pulse interval. As expected, a 1 : 1 duplicity of carbon shifts was observed for most nuclei in or near the heterocyclic ring of (5), due to isomerization about the amide bond.[5] The methines C-5 and C-7 were distinguished through off-resonance decoupling at δ 6 resulting in less residual coupling being associated with the proton at higher field (H-7, δ 6.9). The methylenes C-1 and C-3 gave double resonance with Δδ *ca.* 4 p.p.m., the mean downfield shift associated with nitrogen insertion (*cf.* α-tetralone) being diminished at C-1 due to the presence of the substituent at C-8. The off-resonance decoupling experiment allowed the distinction between H-1 and H-3 since the carbon absorbing at lower field (C-3) showed the larger residual coupling and is therefore attached to the protons at higher field (δ 4.4).

Delepine Reactions in Acid Solution.—Some of the unidentified materials from the mixture of products formed from the reaction of the phenacyl bromide (1a) with hexamine in chloroform may have resulted from

reaction with decomposition products of hexamine caused by traces of hydrogen chloride in the solvent. An attempt was made to increase the proportion of these materials so that they might be separated and identified. Hence, the reaction was performed in dry redistilled chloroform which, without ethanol as stabilizer, was acidic. Under these conditions there was again only a trace of precipitate and so the solvent was evaporated to obtain an orange solid which showed $\nu_{max.}$ 1 695 cm^{-1}. This material, however, was not identical with the product obtained from the reaction in chlorobenzene as it was soluble in chlorobenzene.

Although the resolution of the n.m.r. spectrum of the orange solid was poor, it did indicate the absence of any signals due to the CH_2–Br protons of the bromide or to free hexamine.

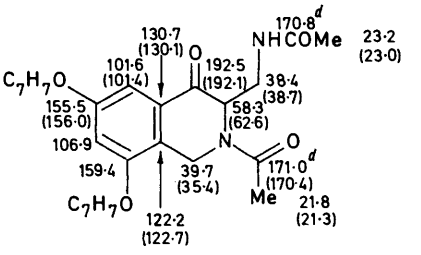
When the solid residue was hydrolysed with 2N-hydrogen chloride–ethanol in the usual way, a diamine was obtained which was shown to be 3-ammoniomethyl-6,8-dibenzyloxy-4-oxo-1,2,3,4-tetrahydroisoquinolinium dichloride (3c) on the basis of the spectral properties of the diacetylated derivative (6).

The diacetamide (6) was homogeneous on t.l.c. and elemental analysis showed a molecular formula of $C_{28}H_{28}N_2O_5$. Its i.r. spectrum showed two amide carbonyl bands at 1 630 and 1 670 cm^{-1} which were confirmed in the ^1H n.m.r. spectrum by the appearance of two methyl singlets at δ 1.94 and 2.15. The presence of two *meta*-coupled doublets at δ 6.83 and 7.20 (J 2.5 Hz) in the spectrum revealed that cyclization on to the aromatic ring had taken place.

When (6) was examined by e.i. mass spectrometry, it showed no molecular ion at the expected value (*m/e* 472); however, ions at *m/e* 413 and 400 were observable. Metastable defocusing experiments revealed that the ion at *m/e* 400 was derived from a species with molecular weight 472, but there were no precursor ions for the species at *m/e* 413. It appears that (6) readily undergoes thermal elimination of acetamide to give the species with molecular weight 413.[6]

Thermal elimination of acetamide was confirmed in the c.i. mass spectrum (using ammonia) by the appearance of additional ions for the species with molecular weight 413 (giving ions at *m/e* 414 and 431) and acetamide (giving ions at *m/e* 60 and 77). Under these milder ionizing conditions the pseudo-molecular ion was observed (*m/e* 473) and the presence of a weak metastable peak confirmed its fragmentation to the ion at *m/e* 414.

The ^{13}C n.m.r. spectrum of the bis-amide (6) was consistent with the attachment of the side-chain to C-3 in the amide (5) and the existence of two stereoisomers in unequal proportion [$Z:E$ *ca.* 2.7 : 1 based on the integrals of protonated carbon atoms close to the amide site (Figure 2)]. The carbon shift for C-3 at 58.3 (62.6) p.p.m. showed the downfield shift (8 p.p.m.) associated with the attachment of the side-chain. The shift for C-1 at 39.7 (35.4) p.p.m. showed the same shift difference (4.3 p.p.m.) between the stereoisomers and an upfield shift of 3 p.p.m. [*cf.* (6)] attributable to the removal of a partial β-hydrogen [7] interaction between H-1 and H-3. The side-chain methylene group showed little variation at 38.4 (38.7) p.p.m. as did the resonance attributable to the amide carbonyl and methyl groups.



(6)

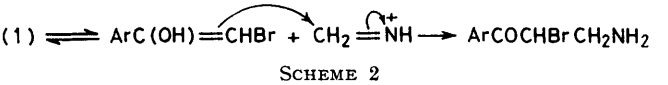
FIGURE 2

[a] See Figure 1 for *d*.

In ethanol-free chloroform there was evidently sufficient hydrogen chloride to liberate formaldehyde and ammonia or similar electrophilic species, which reacted with the active methylene group in a Mannich-type condensation to give the side-chain methylamine. Similar conditions have been reported to effect the aminomethylation of aromatic compounds including *m*-xylene.[8]

Due to its thermal instability we did not elucidate the precise chemical constitution of the product obtained from the reaction of the phenacyl bromide (1a) with hexamine under these acidic conditions. It is probable that the methylamine side-chain has been introduced by this stage as the product was soluble in chlorobenzene, different to the hexaminium salt.

We suggest that the introduction of the methylamine substituent is favoured by both acidic and anhydrous conditions, possibly with occurrence of the reaction sequence shown in Scheme 2. When the authentic



SCHEME 2

hexaminium salt was hydrolysed in ethanolic hydrogen chloride containing hexamine the usual amine salts (2a) and (3a) were obtained with only a trace of the diamine (3c) being detected. Treatment of the hexaminium salt in ethanol with hydrogen chloride gas under anhydrous conditions gave a complicated mixture of products containing material of high molecular weight. The mass spectrum of the crude product showed a predominant peak at *m/e* 371 which was indicative of the presence of (3c), but no attempt was made to separate the constituents of the orange mixture.

EXPERIMENTAL

Melting points were determined on a Gallenkamp Melting Point apparatus. I.r. spectra were recorded on a Perkin-Elmer 197 spectrophotometer, ^1H n.m.r. spectra on a Varian A60D spectrometer (Me_4Si as internal standard), and ^{13}C n.m.r. spectra on a Bruker WP60 instrument with deuterium

lock and using deuteriochloroform as solvent, pulse angle of 40° and pulse interval of 1.1 s (4 K real data points, *ca.* 1 Hz/data point). Electron impact mass spectra were obtained with an A.E.I. MS12 spectrometer and chemical ionization mass spectra with an A.E.I. MS902 instrument using ammonia as reagent gas. Microanalyses were performed by the Australian Microanalytical Service, Melbourne. Light petroleum refers to the fraction of b.p. 40—60 °C.

Reaction of the Phenacyl Bromide (1a) *with Hexamine.*—(a) *In chlorobenzene.* The preparation of 3,5-dibenzyloxyphenacylhexaminium bromide and its hydrolysis with EtOH–HCl has been described previously.[1] The insoluble material was filtered off to yield 6,8-*bisbenzyloxy*-4-*oxo*-1,2,3,4-*tetrahydroisoquinolinium chloride* (3a) as fine needles, m.p. 215—218 °C (decomp.) (from EtOH). Acetylation of the chloride (3a) (1.9 g, 5 mmol) gave an oil (1.8 g) which crystallized from chloroform–light petroleum to give N-(6,8-*bisbenzyloxy*-4-*oxo*-1,2,3,4-*tetrahydroisoquinolin*-2-*yl*)*acetamide* (5) as needles (1.3 g, 65%), m.p. 133—134 °C (part decomp.) (Found: C, 74.8; H, 5.9; N, 3.3. $C_{25}H_{23}NO_4$ requires C, 74.8; H, 5.8; N, 3.5%).

Evaporation of the mother liquor from the hydrolysis gave a powder from which 3′,5′-bisbenzyloxyphenacylammonium chloride (2a) containing a trace of its hydrobromide salt was obtained as needles, m.p. 152—154 °C (after several recrystallizations from EtOH–Et_2O).

Acetylation of the chloride (2a) (820 mg) gave N-(3′,5′-*bisbenzyloxyphenacyl*)*acetamide* (4) as colourless needles (360 mg, 43%), m.p. 104—106° (from chloroform–light petroleum). The crystals occluded chloroform, which was removed with difficulty at 60 °C *in vacuo* (Found: C, 74.4; H, 6.4; N, 3.6. $C_{24}H_{23}NO_4$ requires C, 74.0; H, 6.0; N, 3.6%).

(b) *In dry chloroform.** (i) 3-*Ammoniomethyl*-6,8-*bisbenzyloxy*-4-*oxo*-1,2,3,4-*tetrahydroisoquinolinium dichloride* (3c). A solution of the bromide (1a) (12.3 g, 60 mmol) in dry chloroform (50 ml) was added to a solution of finely powdered hexamine (4.2 g, 60 mmol) in dry chloroform (50 ml) and the solution was stirred overnight. Evaporation gave an orange solid ($\nu_{max.}$ 1 690 cm^{-1}), m.p. 75—85 °C, which was left for 3 days in EtOH–conc. HCl (150 ml; 4 : 1 v/v). The solid obtained by filtration was washed thoroughly with cold water, ethanol, and ether, and then dried over phosphorus pentaoxide under reduced pressure overnight to give a light brown powder (8.8 g, 64%) which decomposed at *ca.* 170—219 °C. Attempts to recrystallize this material resulted in decomposition, and it was therefore used without further purification, $\nu_{max.}$ 1 700 cm^{-1}, *m/e* 388 (M^+, 0%), 371 (8), 280 (1), 181 (3), and 91 (100).†

(ii) N-[(2-*Acetyl*-6,8-*bisbenzyloxy*-4-*oxo*-1,2,3,4-*tetrahydroisoquinolin*-3-*yl*)*methyl*]*acetamide* (6). The chloride (3c) (3.9 g, 9 mmol) was treated with acetic anhydride in the usual way to give an oil (2.7 g) which crystallized from methanol to give the diacetamide (6) (2.0 g, 46%) as rosettes, m.p. 178—180 °C (slight decomp.) (Found: C, 71.3; H, 6.0; N, 6.1. $C_{28}H_{28}N_2O_5$ requires C, 71.2; H, 6.0; N, 5.9%), $\nu_{max.}$ 3 240 (NH), 1 690 (ketone), and 1 670 and 1 630 cm^{-1} (amide), δ($CDCl_3$) 1.94 and 2.15 (each s, 3 H, $NRCOCH_3$), 3.2—4.3 (m, 2 H, side-chain CH_2NR_2), 4.72 and 4.87 (each s, 2 H, $PhCH_2NR_2$), 5.07 (s, 4 H, 2 × $PhCH_2OR$), 5.5 (m, 1 H, 3-H), 6.83 (d, *J* 2.5 Hz, 7-H), 7.20 (d, *J* 2.5 Hz, 2- and 5-H), 7.47 (s, 10 H, Ph), *m/e* (electron impact) 472 (M^+, 0%), 413 (10), 400 (15), 371 (12), 358 (7), 280 (12), 91 (100), and 59 (18), *m/e* (chemical ionization) 490 (3), 473 (8), 431 (52), 414 (99), 77 (100), and 60 (44).

(c) *In chloroform.* A solution of the bromide (1a) (2.0 g, 5 mmol) in chloroform (5 ml) was added to finely powdered hexamine (700 mg, 5 mmol) in chloroform (10 ml). The mixture was stirred overnight and then the solvent was removed and the residue was treated with ether. Filtration gave a cream solid (2.0 g) which was hydrolysed in ethanol–conc. HCl (40 ml; 4 : 1 v/v) at room temperature for 3 days to give an off-white powder (680 mg) consisting of (2a), (3a), and (3c), *m/e* 371 (1%), 359 (5), 358 (4), 347 (<1), 268 (33), 91 (100), 330 (2), and 317 (<1). Evaporation of the mother liquor gave a solid which was washed with H_2O and then dried under reduced pressure to give an off-white solid (336 mg) consisting of (2a) and (3a), *m/e* 359 (<1%), 347 (2), 332 (3), 317 (5), 268 (3), and 91 (100).

(d) *In acidified chloroform.* An intimate mixture of the bromide (1a) (1.0 g) and hexamine (350 g) was added to chloroform (10 ml) to which a few drops of Et_2O–HCl had been added. The mixture was stirred overnight, the solvent removed, and the residue treated with ethanol–conc. HCl (28 ml; 2.5 : 1 v/v) for 3 days. Work-up as previously gave (3c) as a light brown solid (820 mg, 72%), *m/e* 371 (10%), 280 (2), 181 (4), and 91 (100).

Decomposition of the Hexaminium Salt.—(a) *Using aqueous hydrochloric acid.* 3′,5′-Bisbenzyloxyhexaminium bromide (500 mg) was treated with 2N-hydrochloric acid (10 ml) for 5 days at room temperature. The mixture was then filtered and dried under reduced pressure to give an off-white powder (365 mg). Acetylation gave the acetamides (4) and (5) in the ratio 3 : 1 (n.m.r.). Hydrolysis of the hexaminium salt using aqueous HBr followed by purification as above gave the hydrobromide salt (49%).

(b) *In anhydrous conditions.* HCl gas was bubbled into a suspension of 3′,5′-bisbenzyloxyphenacylhexaminium bromide (1.0 g) in anhydrous ethanol (20 ml) until all the solid had dissolved. After 3 days at room temperature no precipitate had formed, and so the solvent was evaporated off and the residue washed with cold water and dried under reduced pressure to give an orange powder (600 mg). Mass spectral analysis revealed ions indicative of (3c) and of materials of higher molecular weight. There were also ions indicative of (3a) at *m/e* 359 but none indicative of (2a) at *m/e* 347 or 317.

(c) *With excess of hexamine.* A finely powdered mixture of 3′,5′-bisbenzyloxyphenacylhexaminium bromide (550 mg) and hexamine (140 mg) was treated with ethanol–conc. HCl (5 ml; 4 : 1 v/v). After 3 days the solvent was evaporated off and the residue was acetylated to yield crude acetamides (330 mg). T.l.c. (EtOAc) revealed the presence of acetamides (4) and (5) with a trace of (6). The ratio (4) : (5) was estimated to be 1 : 1 (n.m.r.).

6,8-*Dimethoxy*-4-*oxo*-1,2,3,4-*tetrahydroisoquinolinium Chloride* (3b).—3′,5′-Dimethoxyphenacylhexaminium bromide (prepared from the phenacyl bromide and hexylamine 4.0 g, 10 mmol) was treated with ethanol–conc. HCl (100 ml; 4 : 1 v/v) at room temperature for 3 days. Usual work-up afforded the chloride as tiny needles (1.0 g, 41%), m.p. 232—235 °C (decomp.) (from ethanol), *m/e* 207 (M^+, 63), 206 (45), 178 (69), and 150 (89).

The hydrobromide salt had m.p. 222—223 °C (decomp.)

* Dry ethanol-free chloroform was prepared by storage over $CaCl_2$ for 1 week followed by distillation.

† β-Aminoketones lose the amine when heated (F. F. Blicke, *Org. Reactions*, 1942, **1**, 303).

(Found: C, 46.0; H, 5.0; N, 5.0; Br, 27.5. $C_{11}H_{15}BrNO_3$ requires C, 45.9; H, 4.9; N, 4.9; Br, 27.7%).

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