# Fragmentation of Enamides Derived from 6,7-Dimethoxy-4-methyl-2*H*-1,3-benzothiazin and 3,4-Dihydro-6,7-dimethoxy-1-methylisoquinoline

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The electron impact mass spectra of several enamides have been examined. The enamides were prepared by reaction of aroyl halides with 6,7-dimethoxy-4-methyl-1,3-benzothiazin, and with 3,4-dihydro-6,7-dimethoxy-1methylisoquinoline. The fragmentation pathways that have been proposed are supported by ion composition determinations and by mass-analysed ion kinetic energy spectrometry experiments carried out on the molecular ions and major fragment ions. The spectra are characterized by a loss of carbon monoxide from the molecular ion of each compound, a process which is accompanied by migration of the aryl group.

## INTRODUCTION

3,4-dihydro-1-methyl-Enamides derived from isoquinolines and 3,4-dihydro- $\beta$ -carbolines have been used extensively in the synthesis of alkaloids and related heterocyclic systems.<sup>1,2</sup> We have applied this approach to the synthesis of sulfur analogues of the alkaloids using benzothiazines as starting materials.<sup>3,4</sup> The utility of the enamides in synthesis rests upon their ability to undergo cyclization photochemically, and in some cases thermally, as illustrated in Scheme 1. The ratio of the products A: B, is a function of the reaction conditions.<sup>1,2</sup> In the course of our research we prepared several enamides of the type shown in Scheme 1 and reported their electron impact (EI) mass spectra.<sup>3,4</sup> However, we made no attempt to interpret the spectra and as far as we are aware a detailed examination of the spectra of this class of compounds has never been undertaken. We report here on the mass spectra of enamides derived from 3,4-dihydro-6,7-dimethoxy-1methylisoquinoline (1) and aroylhalides, compounds 3 and 4, and enamides derived from 6,7-dimethoxy-4methyl-2H-1,3-benzothiazine (2) and aroyl halides, compounds 5, 6 and 7. The compounds were prepared by standard procedures and were characterized by spectroscopic methods.

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We were led to undertake a detailed examination of the spectra of compounds 3–7 because of the facile loss of CO. The loss of CO implies that aryl group migration must occur and it was of interest to find out whether the aryl group migrated to carbon or nitrogen.



Scheme 1

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Figure 1. El mass spectra at 70 eV of (a) compound 3 and (b) compound 4.

Examination of the literature of related systems was not helpful. Simple amides<sup>5,6</sup> do not lose CO from the molecular ion. The cyclic enamides,  $\alpha$ - and  $\gamma$ -pyridone,<sup>7</sup> and the fused  $\alpha$ -pyridones,<sup>8</sup> 2(1H)-quinolinone and 1(2H)-isoquinolinone, all exhibit ions in their spectra corresponding to loss of CO from their molecular ions. In the last compound, however, the intensity of the (M - CO) peak is relatively weak, ~8%. However, compounds in which the 1(2H)-isoquinolinone system or its naphthyridine analogue are incorporated into more complex ring systems show no tendency to lose CO in their EI spectra. For example oxyberberine (8), and the related compounds 9,10 10,11 and 11,3 and analogues of these, do not show significant peaks for the loss of CO from their molecular ions in their EI spectra. Similarly, 13,13a-dihydro analogues of 99 and 104 show no tendency to lose CO from the molecular ion in their EI spectra.

# **RESULTS AND DISCUSSION**

The spectra of enamides 3 and 4 are shown in Fig. 1. The most intense fragment ions in the high-mass region of each of the spectra correspond in composition to the loss of  $H [m/z \ 308 \ (309)]$ , CO  $[m/z \ 281 \ (282)]$ , HCO  $[m/z \ 280 \ (281)]$ , CO + CH<sub>3</sub>  $[m/z \ 266 \ (267)]$  and CO + OCH<sub>3</sub>  $[m/z \ 250 \ (251)]$  from the molecular ion in 3 and 4, respectively. Values for 4 are in parentheses. In the low-mass region aroyl ions  $[m/z \ 105 \ (106)]$  and aryl ions  $[m/z \ 77 \ (78)]$  are present. In the intermediate mass region only ions of low intensity are observed.

The molecular ion and each of the major fragment ions in the high-mass region were examined by massanalysed ion kinetic energy scans (MIKES).<sup>12</sup> The results for 3 are summarized in Scheme 2; those from 4 are similar and will not be discussed.

Examination of Scheme 2 reveals that m/z 280, the most intense ion in the spectrum, is derived from M<sup>++</sup> by two routes, namely (M – H – CO) and (M – CO – H) and that m/z 266 and 250 are derived from m/z 281 through loss of CH<sub>3</sub> and OCH<sub>3</sub>, respectively. The formation of the last two ions may involve hydrogen rearrangement. The MIKES spectra do not reveal the origin of the ions at m/z 105 and 77. They are





Figure 2. El mass spectra at 13 eV of (a) compound 3 and (b) compound 5.



Scheme 3



Figure 3. El mass spectra at 70 eV of (a) compound 5, (b) compound 6 and (c) compound 7.

considered to be derived from  $M^{+}$  by scission of the amide linkage affording the aroyl cation which then loses CO to yield the aryl cation. The absence of m/z105 in the MIKES of m/z 309 may be a consequence of the fact that the molecular ions that are transmitted from the source lack sufficient internal energy for this process to occur. In support of this contention we have found that m/z 105 and 77 are virtually absent in EI spectra recorded below 14 eV although the ions in the high-mass region are still present in the low-voltage spectrum. The spectrum of 3, recorded at 13 eV, is shown in Fig. 2(a).

Collisional activation experiments, however, indicated the presence of ions at m/z 105 and m/z 77 in the MIKES experiment for 3, and at m/z 106 and m/z 78 for 4 when the molecular ion was examined. These ions were barely perceptible at ion energies of 7 keV but appeared well above background noise when the experiments were run at ion energies of 8 keV with the main beam transmission set at 50%. A MIKES experiment on m/z 105 indicated that it also served as a source of m/z 77.

A mechanism to account for the formation of the major ions of 3, which in some ways is akin to the photochemical process of Scheme 1, is outlined in Scheme 3. The proposed mechanism is consistent with the observation that m/z 280 is formed by two routes and that the aryl group must migrate coincident with the loss of CO. In one pathway it is proposed that the aryl group of the molecular ion a migrates to nitrogen affording ion b which cyclizes to c and loses a hydrogen atom giving the resonance-stabilized species d. In a second pathway, more analogous to the photochemical cyclization, it is proposed that the molecular ion cyclizes to e which may then lose CO yielding c, followed by hydrogen elimination. Alternatively, ion e may lose H forming f, followed by loss of CO. In both cases ion d is the stable moiety ultimately obtained.

The spectra of the sulfur compounds, 5, 6 and 7, are shown in Fig. 3. The compositions of all major ions in the three compounds were established by accurate mass measurement and MIKES experiments were carried out in order to ascertain the sequence of fragmentation. Since all three compounds had similar behaviour only one compound, 5, will be treated in detail in the subsequent discussion.

In the high-mass region of the spectra of the sulfur compounds the  $[M - CO]^{+}$  ion is more intense than the  $[M - CHO]^{+}$  ion but otherwise the spectra resemble those of 3 and 4. In the low-mass region the aroyl and aryl ions are present as before. The intermediate mass region, however, has a number of ions of medium intensity which were absent or much less intense in the spectra of 3 and 4. These ions are  $[M - C_7H_5O]^+$  (m/z 222),  $[M - C_8H_7O]^+$  (m/z 208),  $[M - C_8H_7NO]^{+}$ : (m/z 194), and  $[M - C_9H_{10}NO]^+$  (m/z 179).

MIKES experiments were carried out on all three compounds and the results for 5 are illustrated in Scheme 4. The fragmentation pathway outlined in



Scheme 3 (X = S) will accommodate many of the ions found in the high-mass region of the sulfur compounds. For example, loss of H and CO, in either order, from the molecular ion may be used to explain the formation of m/z 298. Examination of m/z 299 by MIKES reveals

that it loses  $CH_3$  and  $OCH_3$ , just as the corresponding ion of 3 does, affording the ions at m/z 284 and 268, respectively.

The MIKES experiments show that the ion at m/z 222 is formed from M<sup>++</sup> by ejection of C<sub>6</sub>H<sub>5</sub>CO. However, the MIKES spectrum of the molecular ion does not have a peak corresponding to the formation of C<sub>6</sub>H<sub>5</sub>CO. The same explanation as that given for the formation of the aroyl ion in 3 and 4 must also apply here, namely, that the molecular ions transmitted from the source lack sufficient internal energy to generate the aroyl cation. Just as in the case of 3 it has been found that m/z 105 is virtually absent in the spectrum of 5, recorded below 14 eV. See Fig. 2(b) for the low-voltage spectrum of 5. After collisional activation, ions were observed at m/z 105 and m/z 77 in 5, and at m/z 106 and m/z 78 in 6 and 7, just as in the case of 3 and 4.

The MIKES data of Scheme 4 reveal that m/z 299 is a source of ions at m/z 208 and 194, and that m/z 299 fragments to m/z 222 by loss of phenyl. The ion at m/z 194 is also formed from m/z 222 through loss of CH<sub>2</sub>N, and m/z 194 serves as the source of m/z 179.

A proposal for the formation of the ions at m/z 222, 208, 194 and 179 is outlined in Scheme 5. The molecular ion a (X = S) loses CO with migration of the phenyl group to nitrogen affording ion b (m/z 299) which, by loss of phenyl, affords g (m/z 222). The latter is also formed direct from M<sup>++</sup> through loss of the aroyl group. Ion g loses CH<sub>2</sub>N to give h (m/z 194) which is also formed from b by loss of C<sub>7</sub>H<sub>7</sub>N. The ion at m/z 179 is formed from h by loss of CH<sub>3</sub>.

The process leading to m/z 208 from M<sup>++</sup> is more complex. The ion at m/z 299 which affords m/z 208 may have a structure different from that which afforded h at m/z 194. This second ion of m/z 299 may form from M<sup>++</sup> by migration of phenyl to carbon at the same time that CO is ejected. We propose that the second ion of m/z 299 may be formulated as j and that it may arise from e (Scheme 3) by loss of CO accompanied by H rearrangement. In this case a bond to nitrogen is not formed when CO is ejected. The expulsion of  $C_7H_7$ from j would yield m/z 208 which may be formulated as



k or l. It is also possible that a single ion of appropriate structure or two rapidly equilibrating structures could lead to the observed result.

A re-examination of the spectrum of 3, revealed the presence of ions of low intensity at m/z 204  $[C_{12}H_{14}NO_2]^+$ , and m/z 190  $[C_{11}H_{12}NO_2]^+$  corresponding in composition, respectively, to g and k where  $X = CH_2$  (Scheme 5). In the spectra of 3 and 4 the ion at m/z 188, which is more intense than m/z 190, differs in composition from m/z 190 by two hydrogen atoms and may have an isoquinolinium structure. We were unable to identify an ion corresponding to h. The presence and intensity of ions g, h and k(l) in 5, 6 and 7 may be attributed to the presence of the sulfur atom and its involvement in charge and radical stabilization.

This work has discussed the mass spectra of aroyl enamides derived from 1 and 2. The spectra are characterized by a facile loss of CO from the molecular ion. Evidence has been presented that aryl group migration to nitrogen and carbon accompanies the loss of CO. Further investigations on these systems with labelled compounds will be undertaken.

## EXPERIMENTAL

Proton NMR spectra were recorded at room temperature on a Varian EM 390 at 90 MHz or a Bruker AM 500 instrument at 500 MHz, and <sup>13</sup>C NMR spectra were recorded-on a Bruker AM 500, (at 125.8 MHz), using tetramethylsilane (TMS) as internal standard. Chemical shifts, quoted as  $\delta$  values, were measured in relation to TMS. The symbols, s (singlet), d (doublet), t (triplet), m (multiplet), and br (broadened) are used in reporting spectra. The EI mass spectra and mass-analysed ion kinetic energy scans (MIKES)<sup>12</sup> were recorded on a VG ZAB-E double-focusing mass spectrometer using a probe inlet system. Typical experimental conditions were: source temperature, 200°C; electron energy, 70 eV unless otherwise stated; resolution, 1000 for low resolution and MIKES, and 5000 for elemental composition determination. Infrared spectra were run on a Perkin-Elmer 283 spectrometer.

The following compounds were prepared by standard procedures and gave satisfactory physical data: 6,7-dimethoxy-4-methyl-2H-1,3-benzothiazine (1),<sup>13,14</sup> 3,4-dihydro-5,6-dimethoxy-1-methylisoquinoline (2),<sup>15</sup> 6,7-dimethoxy-4-methylidene-3-nicotinoyl-2H-1,3-benzothiazine (6),<sup>3</sup> and 3-benzoyl-6,7-dimethoxy-4-methylidene-2H-1,3-benzothiazine (5).<sup>4</sup>

#### 2-Benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1methylideneisoquinoline (compound 3)

To a solution of 6,7-dimethoxy-3,4-dihydro-1-methylisoquinoline (1.025 g, 5 mmol) and triethylamine (1.01 g, 10 mmol) in anhydrous benzene (50 cm<sup>3</sup>) was added dropwise a solution of benzoyl chloride (0.703 g, 5 mmol) in benzene (15 cm<sup>3</sup>). The reaction mixture was kept at room temperature and stirred during the addition. The mixture was then heated at reflux for 2 h, cooled, and extracted with water (3  $\times$  50 cm<sup>3</sup>). The organic layer was dried over sodium sulfate (anhydrous) and evaporated under reduced pressure. The residual oil was triturated with ether (5 cm<sup>3</sup>) affording yellow crystals (1.31 g, 88% yield, mp 105-107°C) which were washed with ether. Recrystallization from benzenehexane (1:1) afforded a sample of 3 with mp 107–109°C) lit. mp<sup>16</sup> 125–126°C, lit. mp<sup>17</sup> 121–124°C. This substance must be dimorphic; the solution spectra recorded by us agree well with literature values.<sup>16,17</sup> IR  $(v_{max}, cm^{-1}, nujol)$ , 1652, 1630, 1610, 1580, 1513; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  2.95 (2H, t, C(4) hydrogens), 3.86, 3.88 (6H, s's, 2 × OCH<sub>3</sub>), 4.08 (2H, t, C(3) hydrogens), 4.40, 5.24, (2H, s's, methylidene hydrogens), 6.63, 6.96 (2H, s's, C(5) hydrogen and C(8) hydrogen), 7.24-7.41 (5H, m, aromatic hydrogens of benzoyl group); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>):  $\delta$  29.1  $(C(4)), 42.7 (C(3)), 55.9, 56.0 (2 \times 0 CH_3), 105.2 (=CH_2),$ 106.7, 111.3, 128.1 (corresponds to two C atoms), 127.9 (corresponds to two C atoms), 129.8 (aromatic CH), 123.4, 127.5, 136.2 142.6, 147.9, 149. 9 (aromatic and olefinic quaternary), 169.8 (C=O).

Anal. (hrms). Calculated for  $C_{19}H_{19}NO_3$ : 309.1365. Found: 309.1368.

From the mother liquors from which 3 was isolated, a second compound (0.13 g, 9% yield) separated which was recrystallized from hexane-dichloromethane (1:1) affording crystals that melted at 142–144°C. IR( $v_{max}$ , cm<sup>-1</sup>, nujol), 3340, 1680, 1630, 1600, 1560, 1545, 1515; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  2.59 (3H, s, (CH<sub>3</sub>CO)), 3.07 (2H, t, CH<sub>2</sub>Ar), 3.72 (2H, m, CH<sub>2</sub>-N), 3.87, 3.90 (6H, 2s,  $2 \times OCH_3$ ), 6.77 and 7.13 (2H, 2 s's, C(5) hydrogen and C(8) hydrogen), 7.34–7.75 (6H, m, aromatic hydrogens of benzoyl group and NH); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>):  $\delta$  29.4 (CH<sub>3</sub>CO), 32.1 (ArCH<sub>2</sub>), 42.4 (CH<sub>2</sub>N), 55.9, 56.2 (2 × OMe), 112.7, 114.1, 126.9, 152.1 (aromatic quaternary), 167.4 (amide CO), 201.6 (ketone CO).

Anal. (hrms). Calculated for  $C_{19}H_{21}NO_4$ : 327.1447. Found: 327.1459.

From its composition and spectroscopic properties this compound was identified as 2-(*N*-benzoyl- $\beta$ -aminoethyl)-4,5-dimethoxyacetophenone. The melting point agrees with the literature value.<sup>18</sup> Compounds of this type are often observed as by-products in preparation of the enamides.

#### 2-Isonicotinoyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1methylideneisoquinoline (compound 4)

A mixture of isonicotinic acid (615 mg, 5 mmol) and thionyl chloride (4 cm<sup>3</sup>) was heated at reflux for 3 h under an argon atmosphere. The mixture was taken to dryness and the last traces of thionyl chloride were removed by co-distillation with benzene (20 cm<sup>3</sup>), a process that was twice repeated. The residue was dissolved in benzene (50 cm<sup>3</sup>) and treated with a solution of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (1.025 g, 5 mmol) and triethylamine (1.01 g, 10 mmol) in benzene (15 cm<sup>3</sup>). The mixture was heated at reflux for 2 h, cooled to room temperature, and extracted with distilled water (3 × 50 cm<sup>3</sup>). The organic layer was dried over sodium sulfate (anhydrous), filtered, and evapo-

rated to yield an oily residue. Treatment of the residue with benzene  $(3 \text{ cm}^3)$  followed by ether  $(5 \text{ cm}^3)$  yielded a white powder (1.224 g, 79% yield). The solid was crystallized from ethyl acetate affording crystals of 4 melting at 135°C (d). IR ( $\nu_{max}$ , cm<sup>-1</sup>, nujol), 1640, 1603, 1590, 1545, 1509; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  2.96 (2H, m, C(4) hydrogens), 3.86 and 3.88 ( $2 \times OMe$ ), 4.08 (2H, m, C(3) hydrogens), 4.38 and 5.24 (1H each, s's, methylidene hydrogens), 6.63 and 6.93 (1H each, s's, C(5) hydrogen and C(8) hydrogen), 7.26 (2H, m,  $J \approx 4.6$  Hz, pyridine hydrogens  $\beta$ - to nitrogen), 8.57 (2H, d,  $J \approx 4.6$ Hz, pyridine hydrogens  $\alpha$ - to nitrogen); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>):  $\delta$  29.0 (C(4)), 42.5 (C(3)), 55.9 and 56.0 ( $2 \times OMe$ ), 106.1 (methylidene), 106.6, 111.3, 122.0, 149.8 (four signals representing six carbon atoms, aromatic CH), 122.9, 127.3, 142.0, 143.9, 148.1, 150.2 (aromatic and olefinic quaternary), 167.2 (CO).

Anal. (hrms). Calculated for  $C_{18}H_{18}N_2O_3$ : 310.1317. Found: 310.1314.

#### 3-Isonicotonyl-6,7-dimethoxy-4-methylidene-2*H*-1,3-benzothiazine (compound 7)

The title compound was prepared by the procedure described previously<sup>3</sup> for its isomer 6 from 6,7-

dimethoxy-4-methyl-2H-1,3-benzothiazine (0.557 g, 2.5 mmol) and isonicotinic acid. Compound 7 (0.735 g, 90% yield) so obtained was recrystallized from ethanol, mp 185–186°C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 3.88, 3.90 (6H, 2 s's, 2 × OMe), 4.54, 5.38 (2H, 2 s's, methylidene hydrogens), 5.17 (2H, s, C(2) hydrogens), 6.67, and 7.00 (2H, 2 s's, C(5) hydrogen and C(8) hydrogen), 7.28 (2H, d,  $J \approx 5.8$  Hz, pyridine hydrogens  $\beta$ - to nitrogen), 8.61 (2H, d,  $J \approx 5.8$  Hz, pyridine hydrogens  $\alpha$ - to nitrogen); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>):  $\delta$  40.3 (C(2)), 56.3, 56.4  $(2 \times OMe)$ , 108.9 (C=CH<sub>2</sub>), 108.5, 110.5, 122.2, (corresponding to two carbon atoms), 149.4 (corresponding to two carbon atoms) (aromatic CH), 119.4, 124.6, 141.0, 144.2, 147.9, 150.8 (aromatic and olefinic quaternary), 166.7 (CO).

Anal. (hrms). Calculated for  $C_{17}H_{16}N_2O_3S$ : 328.0882. Found: 328.0875.

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