Electron Impact Ionization Mass Spectra of 3-Substituted-2-hydroxy-4(3H)-quinazolinones

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3-Amino-2-hydroxy-4(3H)-quinazolinone (**3**) was prepared via condensation of **1** with hydrazine hydrate. Treatment of **3** with appropriate acid in $POCl_3$, ethyl chloroacetate and activated olefinic compounds in DMF yielded the corresponding 3-(substituted)amino-2-hydroxy-4(3H)-quinazolinones **4**, **5** and **6**. The electron impact ionization mass spectra of compounds **3** and **4** show a weak molecular ion peak and a base peak of *m/z* 146 resulting from a cleavage fragmentation. The compounds **5** and **6** give a characteristic fragmentation pattern with a very stable fragment of benzopyrazolone (*m/z* 132).

Key Words : Mass spectroscopy, 3-Substituted-2-hydroxy-quinazolinones

Introduction

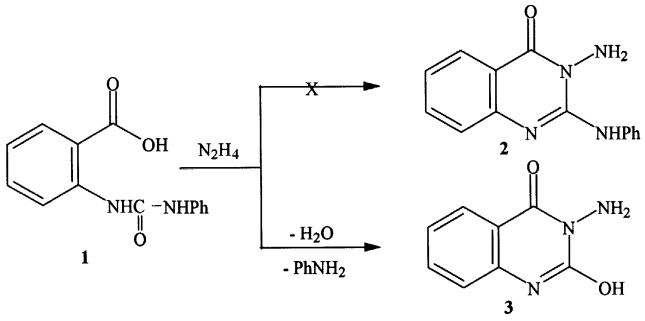
In the course of recent investigations[1-8] involving anthranilic acid and phenyl isocyanate, it was found that 2-(3-phenylureido)-benzoic acid (**1**) is converted into 3-amino-2-hydroxy-4(3H)-quinazolinone (**3**) by the action of hydrazine hydrate under fussion. The fact that only limited information is available on the mass spectra of 3-amino-2-hydroxy-4(3H)-quinazolinone (**3**), along with the preparation of a novel 3-substituted-2-hydroxy-4(3H)-quinazolinone, has prompted us to report their synthesis and study their electron impact (EI) mass spectral fragmentation.

Results and Discussion

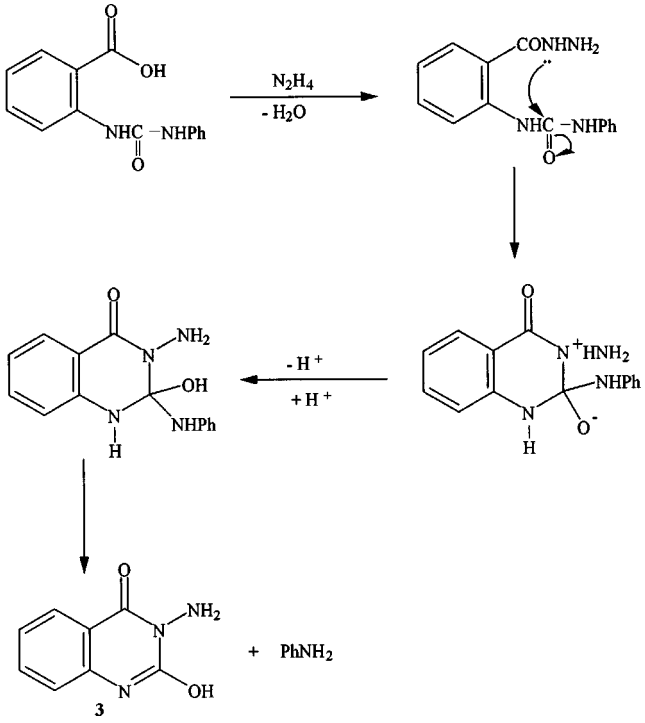
Chemistry. Hydrazinolysis of 2-(3-phenylureido)benzoic acid (**1**) with hydrazine hydrate by fusion at 150 °C, gave the corresponding 3-amino-2-hydroxy-4(3H)-quinazolinone (**3**), which does not give the expected structure **2** (Scheme 1). Compound **3** may be formed by the nucleophilic attack at carbonyl groups in compound **1** with ring cyclization via the removal of water and aniline as shown in Scheme 2.

The 3-(alkylcarbonyl)amino-2-hydroxy-4(3H)-quinazolinones (**4a-c**) were synthesized by a acylation or benzoylation of the 3-amino-2-hydroxy-4(3H)-quinazolinone (**3**) with appropriate acid (such as acetic acid, chloroacetic acid, and benzoic acid) in phosphours oxychloride.

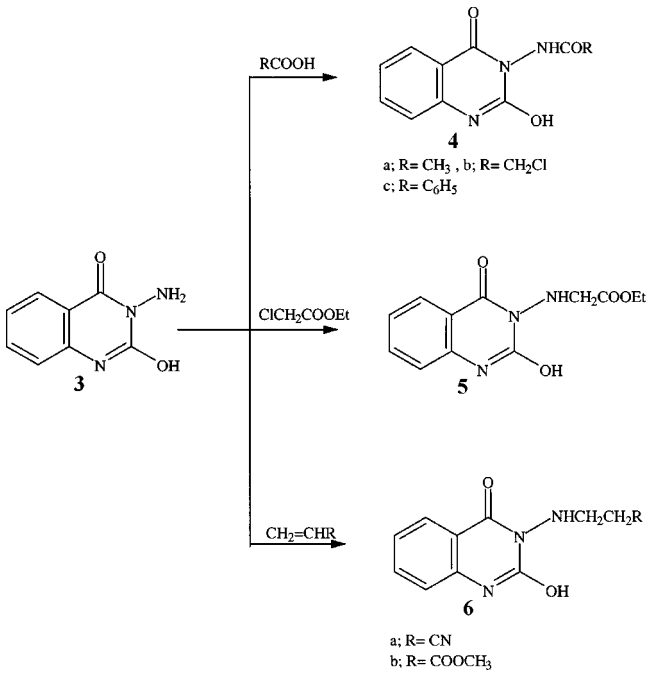
Alkylation of compound **3** with ethyl chloroacetate in dimethyl formamide under reflux formed the ethyl 2-hydroxy-4(3H)-oxo-quinazoline-3-ylaminoacetic ester (**5**, Scheme 3). The reaction of 3-amino-2-hydroxy-4(3H)-quinazolinone (**3**) with activated olefinic compound (such as acrylonitrile and methyl acrylate) in dimethyl formamide resulted in the formation of 3-(cyanoethyl)amino-2-hydroxy-4(3H)-quinazolinone (**6a**) and ethyl 2-hydroxy-4(3H)-oxo-quinazolin-3-yl-3-aminopropionic ester (**6b**, Scheme 2), respectively.



Scheme 1



Scheme 2



Scheme 3

Mass spectroscopy. Tables 1 and 2 list the *m/z* (relative abundance, %) values of the principal fragments of the studied compounds, while Figures 1, 2 and 3 illustrate, as examples, the mass spectra of **3**, **4c** and **6a**, respectively.

Compounds 3 and 4a-c. The mass spectra (Table 1) of compounds **3** and **4a-c** show relatively small molecular ions and peaks typical of a cleavage and rearrangement process type fragmentation. The main fragmentation pathway of compound **3** was summarized in Scheme 4. The detection of both complementary fragments of the cleavage and rearrangement processes is attributed to their comparable ionization potentials. From the study of the mass spectra of compound **3** (Figure 1), it was found that the molecular ion had fragmented to the *m/z* 146. The ion of *m/z* 146 was broken to give the *m/z* 119 by losing HCN. This fragmentation led to ion of *m/z* 92 and ion of *m/z* 64, respectively. However, pathway A in Table 1 is the predominant one, since the *m/z* 146 which arises from the ion of *m/z* 177, is the base peak of the spectrum for all these compounds **3** and **4a**, **b**.

The molecular ion of compound **4c** fragmented further and involved two pathways as illustrated in Scheme **5**. The molecular ion of *m/z* 281 fragment *via* the pathway A to give the *m/z* 176 by losing benzoyl radical group. The *m/z* 176 fragmented to give the ion of *m/z* 146 by losing hydrogen cyanide molecule to give the ion of *m/z* 119.

Accordingly, the same molecular ion of *m/z* 281 fragmented *via* the pathway B by a cleavage of 3-amino-2-hydroxyquinazolinone radical, has relatively low abundance (Figure 2) to give the ion of *m/z* 105 which lost CO to give the ion of *m/z* 77 (phenyl radical).

Compounds 5 and 6a, b. The mass spectra of compounds **5** and **6a**, **b** show relatively small molecular ions and peaks typical of a cleavage and rearrangement processes type fragmentation. From the study of the mass spectra of

Table 1. EI Mass spectra (70 eV) of compound **3** and **4** m/z (relative intensity, %)

Compound	M^+	Pathway A		Pathway B		Other Ions
		M-	m/z	M-	m/z	
3	$[C_8H_7N_3O_2]^{\cdot+}$ 177 (50.21)	O = NH	$[C_8H_6N_2O]^{\cdot+}$ 146 (100)	–	–	147 (9.50), 120 (3.06), 118 (3.08), 105 (1.47), 104 (3.10), 93 (3.17), 90 (20.75), 77 (5.30), 76 (6.37), 74 (6.15), 70 (2.72), 65 (10.80), 64 (20.44), 63 (21.04), 62 (7.53), 53 (3.50), 52 (10.03)
		HCN	$[C_7H_5NO]^{\cdot+}$ 119 (11.02)			
		HCN	$[C_6H_4O]^{\cdot+}$ 92 (27.01)			
4a	$[C_{10}H_9N_3O_3]^{\cdot+}$ 219 (2.30)	CH_2=C=O	$[C_8H_7N_3O_2]^{\cdot+}$ 177 (84.10)	–	–	178 (6.80), 147 (80.60), 120 (1.50), 118 (1.60), 93 (1.00), 92 (14.30), 91 (3.10), 90 (11.20), 77 (1.80), 76 (2.7), 75 (1.00), 65 (4.71), 64 (9.30), 63 (7.6), 62 (1.91), 52 (3.10), 51 (2.32), 50 (4.70)
		O=NH	$[C_8H_6N_2O]^{\cdot+}$ 146 (100)			
		HCN	$[C_7H_5NO]^{\cdot+}$ 119 (7.20)			
4b	$[C_{10}H_8ClN_3O_3]^{\cdot+}$ 253 (2.30)	Cl CH=C=O	$[C_8H_7N_3O_2]^{\cdot+}$ 177 (79.30)	–	–	178 (8.10), 148 (2.80), 147 (9.91), 120 (1.50), 118 (1.80), 104 (1.20), 102 (1.44), 93 (1.20), 92 (16.00), 91 (4.3), 90 (12.00), 77 (5.20), 76 (3.20), 75 (1.20), 74 (1.30), 65 (6.50), 64 (11.20), 63 (8.82), 53 (1.00), 52 (3.60), 51 (5.00), 50 (5.00)
		O=NH	$[C_8H_6N_2O]^{\cdot+}$ 146 (100)			
		HCN	$[C_7H_5NO]^{\cdot+}$ 119 (8.30)			
4c	$[C_{15}H_{11}N_3O_3]^{\cdot+}$ 281 (4.30)	Ph-CO	$[C_8H_6N_3O_2]^{\cdot+}$ 176 (3.25)	$C_8H_6N_3O_2$	[Ph-CO]$^{\cdot+}$ 105 (100)	147 (1.30), 106 (7.78), 91 (3.55), 90 (5.27), 78 (4.84), 75 (3.44), 74 (3.05), 65 (5.12), 64 (8.07), 63 (9.10), 62 (2.01), 53 (1.32), 52 (5.12), 51 (27.00)
		NO	$[C_8H_6N_2O]^{\cdot+}$ 146 (8.50)	CO	$[C_6H_5]^{\cdot+}$ 77 (61.23)	
		HCN	$[C_7H_5NO]^{\cdot+}$ 119 (12.35)			

Table 2. EI Mass spectra (70 eV) of compounds **5** and **6** m/z (relative intensity, %)

Compound	M^+	Pathway A		Pathway B		Other Ions
		M-	m/z	M-	m/z	
5	$[C_{12}H_{13}N_3O_4]^{\cdot+}$ 263 (18.30)	CH_3 CH_2O	[RNH $CH_2CO]^{\cdot+}$ 218 (2.60)	CH_2 COOEt	$[C_8H_6N_3O_2]^{\cdot+}$ 176 (3.50)	217 (7.30), 192 (1.2), 191 (2.20), 184 (2.40), 175 (2.60), 133 (11.00), 118 (2.21), 105 (7.40), 103 (2.00), 92 (1.10), 90 (3.40), 77 (30.30), 78 (3.70), 64 (1.80), 63 (2.41), 51 (13.30), 50 (5.50)
		CO	$[RNH\ CH_2]^{\cdot+}$ 190 (17.50)	NO	$[C_8H_6N_2O]^{\cdot+}$ 146 (3.60)	
		CH_2=NH, CHO	$[C_7H_4N_2O]^{\cdot+}$ 132 (100)	HCN	$[C_7H_4NO]^{\cdot+}$ 119 (1.8)	
		N_2	$[C_7H_4O]^{\cdot+}$ 104 (5.40)			
		CO	$[C_6H_4]^{\cdot+}$ 76 (5.70)			
6a	$[C_{11}H_{10}N_4O_2]^{\cdot+}$ 230 (16.00)	CH_2-CN	[R-NH $CH_2]^{\cdot+}$ 190 (19.21)	CH_2=CHCN	$[C_8H_7N_3O_2]^{\cdot+}$ 177 (3.84)	178 (1.20), 147 (2.53), 133 (9.10), 130 (3.08), 120 (9.10), 130 (3.08), 120 (1.55), 117 (7.55), 116 (3.18), 105 (11.93), 92 (8.72), 91 (10.20), 90 (35.08), 77 (65.42), 75 (16.71), 65 (10.20), 64 (24.70), 63 (27.50), 62 (11.36), 58 (30.13), 54 (25.51), 53 (10.34), 52 (33.40), 51 (40.30)
		CH_2=NH, CHO	$[C_7H_4N_2O]^{\cdot+}$ 132 (100)	HN=O	$[C_8H_6N_2O]^{\cdot+}$ 146 (25.85)	
		N_2	$[C_7H_4O]^{\cdot+}$ 104(10.55)	HCN	$[C_7H_5NO]^{\cdot+}$ 119 (3.06)	
		CO	$[C_6\ H_4]^{\cdot+}$ 76 (24.72)	–	–	
6b	$[C_{12}H_{13}N_3O_4]^{\cdot+}$ 263 (24.05)	CH_3O	[RNHCH$_2$-CH$_2$CO]$^{\cdot+}$ 232 (5.78)	CH_2CHCOO Me	$[C_8H_7M_3O_2]^{\cdot+}$ 177 (4.83)	23.1 (8.30), 192 (5.35), 178 (2.21), 147 (3.05), 133 (10.05), 130 (4.02), 120 (1.62), 117 (11.25), 116 (6.21), 105 (16.13), 62 (14.23), 91 (15.37), 90 (43.12), 77 (62.71), 75 (16.20), 65 (13.20), 64 (27.21), 63 (32.01), 62 (13.26)
		CH_2=C=O	$[RNHCH_2]^{\cdot+}$ 190 (23.50)	HN=O	$[C_8H_6N_2O]^{\cdot+}$ 146 (21.38)	
		CH_2=NH, CHO	$[C_7H_4N_2O]^{\cdot+}$ 132 (100)	HCN	$[C_7H_5NO]^{\cdot+}$ 119 (7.31)	
		N_2	$[C_7H_4O]^{\cdot+}$ 104 (9.35)	–	–	

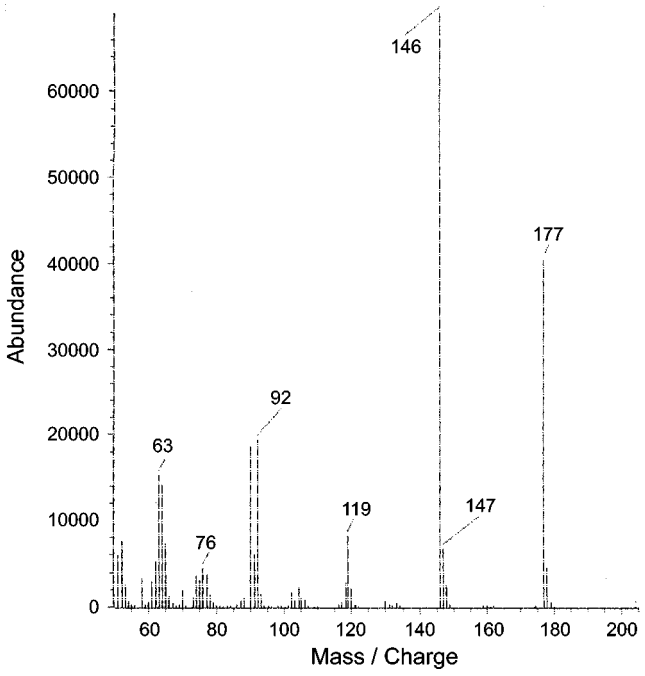


Figure 1. 70 eV mass spectrum of **3**.

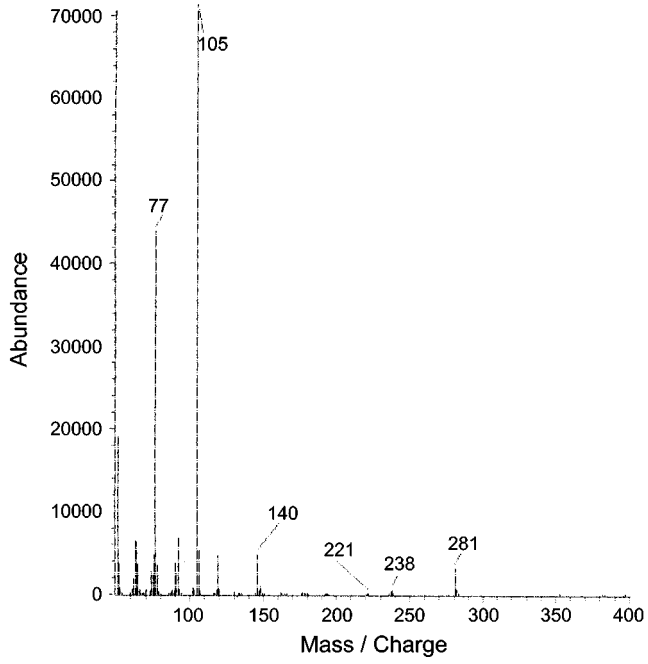


Figure 2. 70 eV mass spectrum of **4c**.

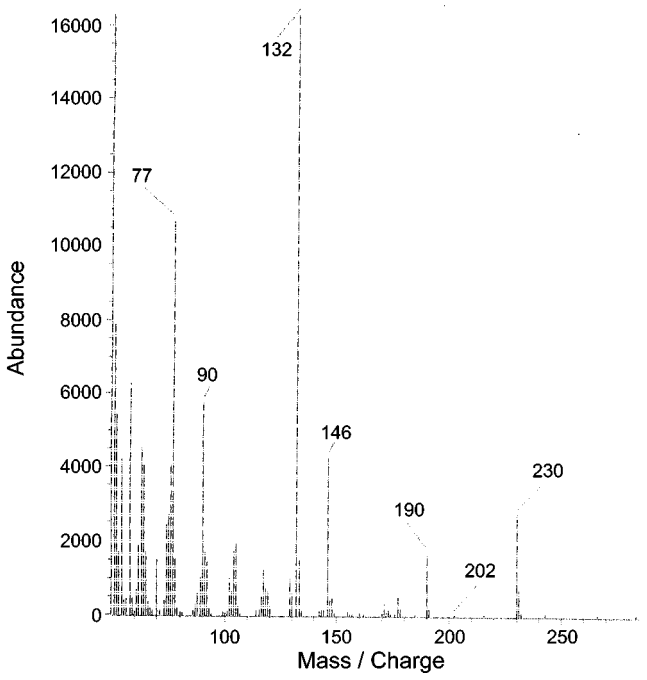


Figure 3. 70 eV mass spectrum of **6a**.

compounds **5** and **6a**, **b**, it was found that the molecular ion for all these compounds fragmented further and involved two various pathways as illustrated by Scheme 6 as representative examples.

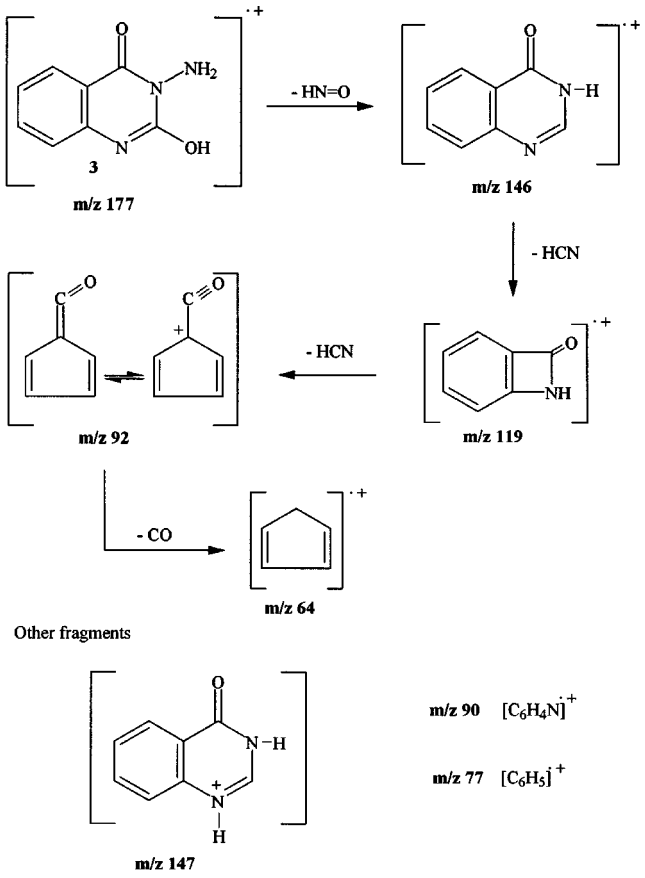
The main fragmentation pathways of compounds **5**, and **6a**, **b** are summarized in Table 2. However, the molecular ion of *m/z* 230 fragmented via the pathway A to gave the ion of *m/z* 190, which fragmented further to give the stable ion of *m/z* 132 by losing CH_2 = NH and fromyl radical group.

Subsequently, the molecular ion of *m/z* 230 was broken *via* pathway B in the same fragmentation processes which was observed for compounds **3**, and **4a**, **c** (Pathway A).

Experimental Section

Melting points were determined on a Boetium Hostage apparatus and uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR 1725 spectrometer. The ^{1}H-NMR spectra were recorded on a General Electric QE 300, and chemical shifts were given with respect to TMS. Mass spectra were recorded on a VG Autspec CEI FAB$^+$ and a Hewlett Packard Ms-Engine thermospray and ionization by electron impact at 70 eV. The accelerating voltage was 6 kV, the temperature of the ion source was ~200 °C and the emission current was ~100 mA. Microanalyses were conducted using an elemental analyzer 116.

3-Amino-2-hydroxy-4 (3H)-quinazolinone (3). A mixture of **1** (0.01 mol) and hydrazine hydrate (0.03 mol) was fused on a hot plate for 10-15 min. the reaction mixture was added to boiling methanol (50 mL) and heated under reflux for 2 h, then cooled. The solid formed was filtered off, washed with methanol, dried and purified by recrystallization with dimethyl formamide to give **3** as colourless crystals, yield



Scheme 4. Main fragmentation pathway of compound **3**.

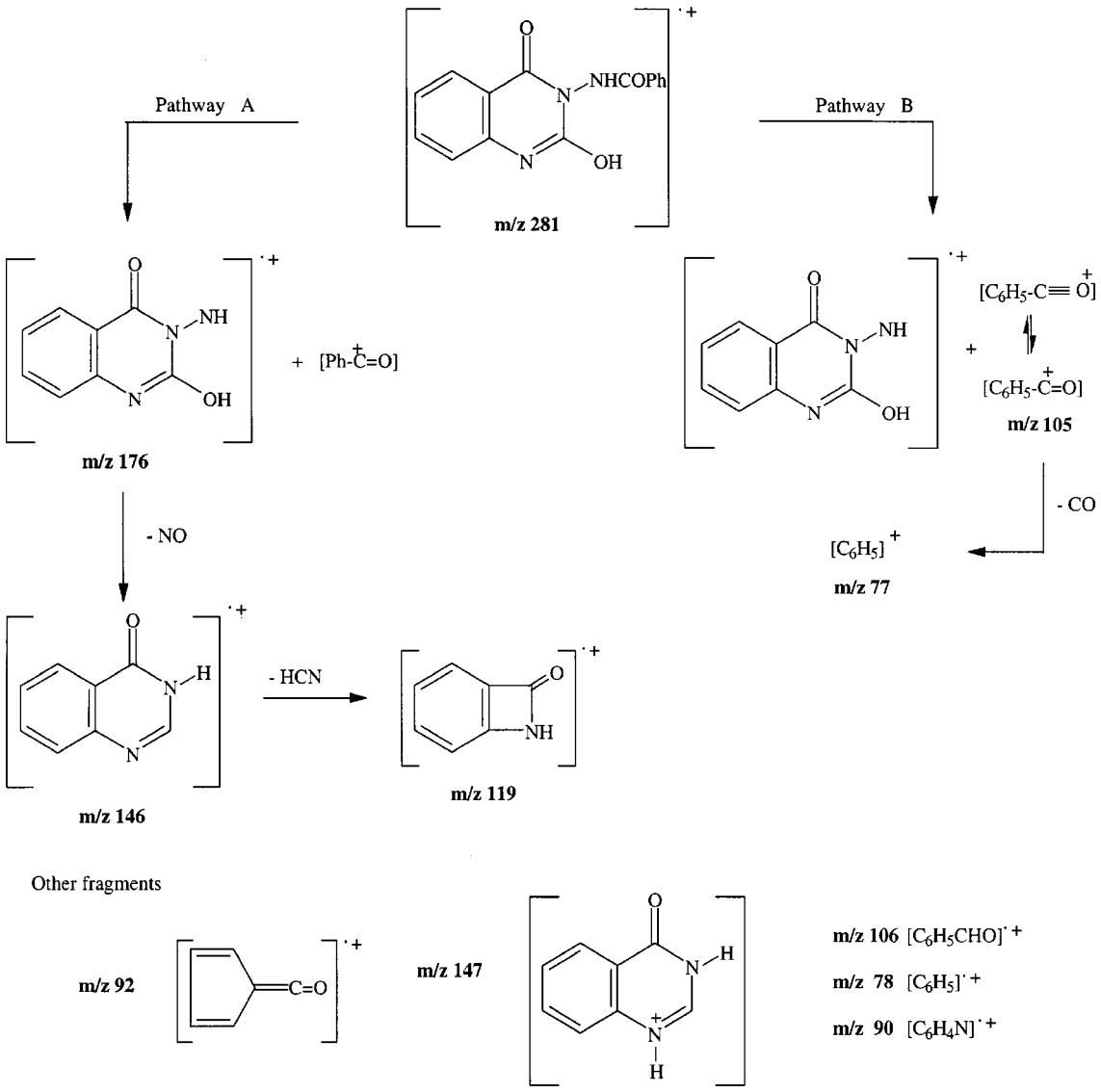
73%, mp 275°, IR (KBr) 3320, 3215 (NH_2), 3390-2850 (br. OH), 1689 (CO), 1625 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 5.48 (s, 2H, NH_2), 7.22-7.95 (m, 4H, ArH) ppm; Found: C, 54.03; H, 3.62; N, 23.57. $C_8H_7N_3O_2$ requires: C, 54.24; H, 3.95; N, 23.73.

3-(Alkylcarbonyl)amino-2-hydroxy-4(3H)-quinazolinones (4a-c). A mixture of **3** (0.01 mol) and appropriate acids such as acetic acid, chloroacetic acid, and benzoic acid (0.01 mol) in phosphours oxychloride (30 mL) was heated on a water bath under reflux for 30 min, then cooled and poured onto ice-water. The resulting product was filtered, washed with water, dried and purified by recrystallization with ethanol to give **4**.

3-(Acetyl)amino-2-hydroxy-4(3H)-quinzaolinone (4a): yield 63%, mp 220°, IR (KBr) 3225 (NH), 3389-2850 (br. OH) 1695-1686 (C=O), 1623 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.01 (s, 3H, CH_3), 7.21-7.96 (m, 4H, ArH), 10.49 (s, 1H, NH) ppm; Found: C, 54.54; H, 4.02; N, 19.06. $C_{10}H_9N_3O_3$ requires: C, 54.79; H, 4.11; N, 19.18.

3-(Chloroacetyl)amino-2-hydroxy-4 (3H)-quinazolinone (4b): yield 64%, mp 205°, IR(KBr) 3229 (NH), 3396-2851 (br. OH), 1699-1682 (C=O), 1625 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 5.03 (s, 2H, CH_2), 7.21-7.95 (m, 4H, ArH), 10.50 (s, 1H, NH) ppm; Found: C, 47.11; H, 3.01; N, 16.32, Cl, 13.68. $C_{10}H_8ClN_3O_3$ requires: C, 47.34; H, 3.16; N, 16.57; Cl, 14.00.

3-(Benzoyl)amino-2-hydroxy-4(3H)-quinazolinone (4c):



Scheme 5. Main fragmentation pathway of compound **4c**.

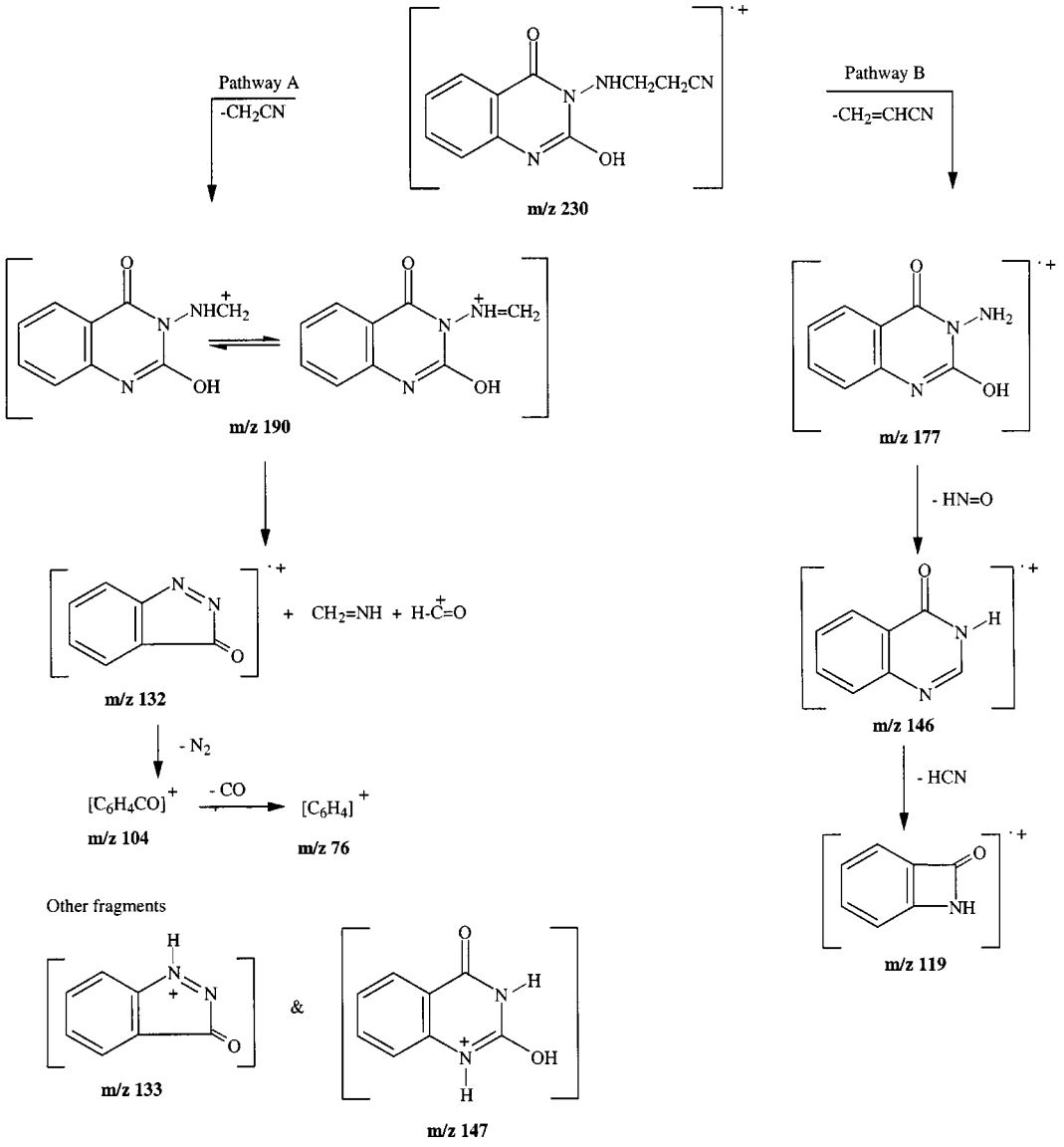
yield 67%, mp 227°, IR (KBr) 3215 (NH), 3345-2821 (br. OH), 1695-1681 (C=O), 1624 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 7.21-8.01 (m, 9H, ArH), 10.61 (s, 1H, NH) ppm; Found: C, 63.89; H, 3.66; N, 14.59. $C_{15}H_{11}N_3O_3$ requires: C, 64.06; H, 3.91; N, 14.95.

3-(Alkyl)amino-2-hydroxy-4(3H)-quinazolinones 5 and 6. A mixture of **3** (0.01 mol) and a reagent such as ethyl chloroacetate, acrylonitrile and methyl acrylate (0.01 mol) in dimethyl formamide (30 mL) was heated under relux for 4h, then cooled and poured into water, the deposited solid was filtered off, washed with water, dried and purified by recrystallization with ethanol to give **5** an **6**, respectively.

Ethyl 2-hydroxy-4(3H)-quinazolin-3-ylminoacetic ester (5), yield 67%, mp 135°; IR (KBr) 3225 (NH), 3396-2852 (br. OH), 1765 (C=O of ester), 1686 (CO), 1622 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.30 (t, J = 9.04 Hz, 3H, CH_3), 3.52 (s, 2H, CH_2), 4.35 (q, J = 6.23 Hz, 2H, OCH_2), 5.81 (s, 1H, $NHCH_2$), 7.21-7.96 (m, 4H, ArH) ppm; Found: C, 54.52, H, 4.69; N, 15.59. $C_{12}H_{13}N_3O_4$ requires: C, 54.75, H, 4.94; N, 15.97.

3-(Cyanoethyl)amino-2-hydroxy-4(3H)-quinazolinone (6a): yield 67%, mp 185°, IR (KBr) 3225 (NH), 3389-2851 (br, OH), 2225 (C=N), 1689 (CO), 1626 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.93-2.97 (t, J = 9.04 Hz, 2H, $NHCH_2$), 4.43-4.47 (t, J = 9.12 H_2, 2H, CH_2CN), 5.61 (s, 1H, NH), 7.21-7.96 (m, 4H, ArH) ppm; Found: C, 57.02; H, 4.12; N, 24.10. $C_{11}H_{10}N_4O_2$ requires: C, 57.39; H, 4.35; N, 24.35.

Methyl 2-hydroxy-4 (3H)-oxo-quinazolin-3-ylamino-propionic ester (6b): yield 65%, mp 145°, IR (KBr) 3229 (NH), 3396-2851 (br. OH), 1766 (CO of ester), 1687 (CO), 1624 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.53-2.56 (t, J = 9.04 Hz, 2H, $COCH_2$), 2.92-2.97 (t, J = 9.12 Hz, 2H, $NHCH_2$), 3.93 (s, 3H, OCH_3), 5.62 (s, 1H, NH), 7.22-7.96 (m, 4H, ArH) ppm; Found: C, 54.51; H, 4.73; N, 15.72. $C_{12}H_{13}N_3O_4$ requires: C, 54.75; H, 4.94, N, 15.97.



Scheme 6. Main fragmentation pathway of compound **6a**, as a representative example for compounds **5**, and **6a**, **b**.

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