Use of NMR and Mass Spectrometry in Establishing the Structures of Ring Opening products of 3- Methyl- 4,1- Benzoxazepine-2,5- Dione in Acid and Basic Media.

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Summary: 3-Methyl-4,1-benzoxazepine-2,5-dione (I) when stirred for 5 hours in methanolic solution with a few drops of 10 % NaOH below 60°C gave solid crystalline product (m.p. 100-102°C, 51% yield). ^{1}H NMR and MS analysis confirmed structure (II) which suggest the cleavage of C-O bond, but when (I) was treated with a few drops of 10% HCl under similar temperature yielded compound (III) as a liquid which gave evidence for C-N bond cleavage giving no traces of the former product (II).

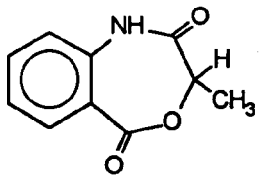
Introduction

Benzoxazepine diones are synthetic heterocyclic compounds, which show diverse biological activities, e. g; diuretic, CNS depressant, muscle relaxant, hypnotic, sedative and tranquilizing activities [1-5]. They are also reported as anesthetic, psychotropic and analgesic agents [6-8]. Antibacterial [9] and antitumour [10] activities are also reported.

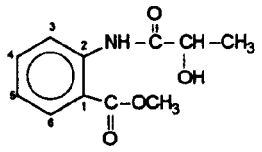
Inspite of the fact that these compounds show important medicinal properties, the reports of study of their chemical properties are scanty. The only one report is that the ring contraction products obtained after treatment of 4,1- benzoxazepine- 2,5- dione with hydrazine or hydroxylamine lead to the important heterocyclic moiety found in quinazolinone alkaloids [12]. The present study discusses the formation of ring opening products of 3- Methyl-4,1- benzoxazepine- 2,5- dione in acidic and alkaline media. ^{1}H NMR, GCMS and accurate mass measurement of the molecular ion have identified two new products.

Results and Discussion

The compound (1) when stirred in a solution of methanol in the presence of 0.16 ml of 10% aqueous NaOH, a crystalline solid (II) was obtained, 51% yield, which gave an elemental analysis corresponding to $C_{11}H_{13}NO_4$ and a molecular ion at m/z 223.0840. In the infrared spectrum it showed an absorption band at 3316 cm^{-1} which may be assigned to O-H str. vib. and a band at 3214 cm^{-1} which may correspond to N-H str. vib. Besides, there was a band due to lactone carbonyl at 1713 and a band due to lactam carbonyl at 1668 cm^{-1}. The proton NMR gave a doublet at δ 1.45 with a coupling constant of 7Hz which may be due to CH_3-CH-O methyl and a quartet at δ 4.3 assigned to the methine proton next to the above methyl group as the J value was the same. A singlet for OCH_3 at δ 3.9. A singlet at δ 5.2 integrating to one proton may be attributed to OH. The four aromatic protons resonated at δ at 7.1-8.8 with the splitting pattern and J values corresponding to o-disubstituted aromatic ring type (similar to 1). The NH-C=O resonated at δ 11.8 as a singlet (see data in experimental procedures).



3-Methyl-4,1-benzoxazepine-2,5-(1H,3H)dione (1)



Methyl 2-[N-hydroxy-1-oxopropyl)amino]benzenecarboxlate (II)

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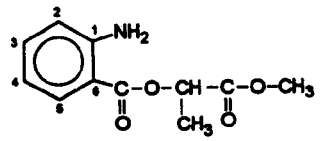


(1-Carbmethoxyethyl)2-aminobenzenecarboxylate (III)

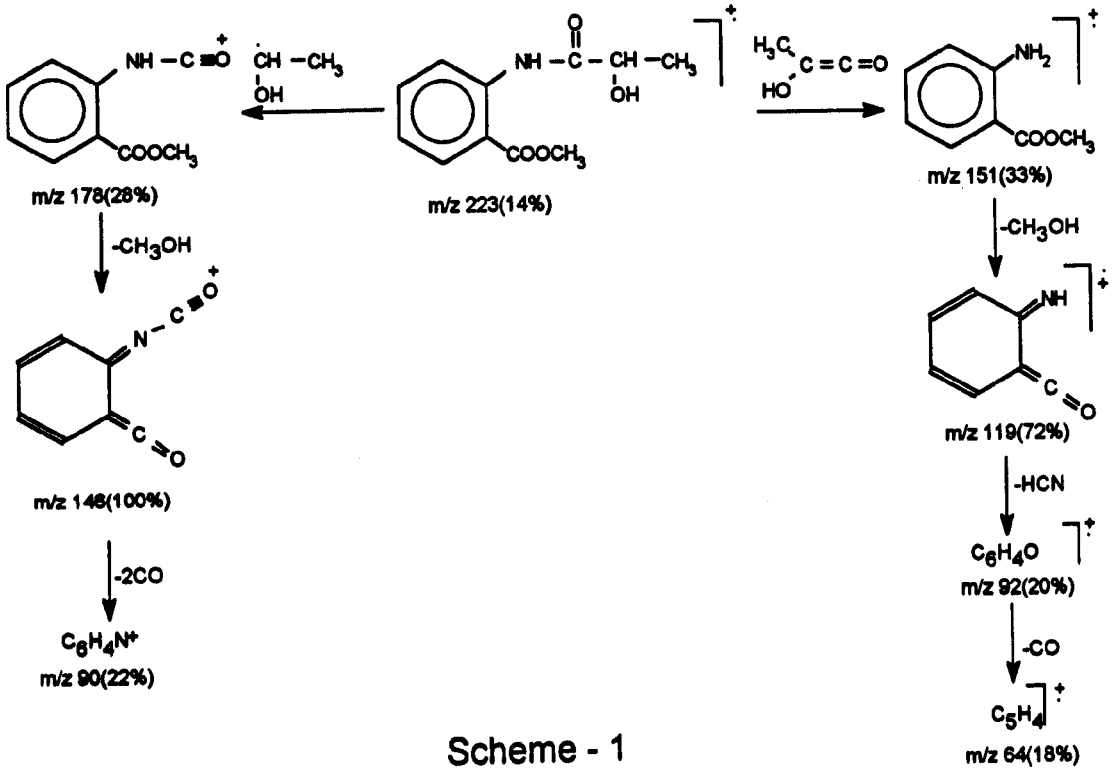
The ^{13}C spectrum DEPT gave a signal at δ 21 for methyl group at 53 for O-CH_3 and at 69 for O-CH. THE aromatic carbons resonated at δ114, 121, 123, 135, 132, 141 which have been assigned to respective carbons according to calculations based on modified Karplus equation and lactone and lactam C=O are at 175 and 168 respectively. The fragmentation further confirmed structure II as indicated in Scheme-1.

When compound 1 was hydrolyzed in methanol solution with a few drops of 10% hydrochloric acid, the usual work up yielded an oily liquid (II) in about 45% yield which showed a proton NMR different from (III). The CH_3-CH resonated as a doublet at δ 3.7 as a singlet. The aromatic resonated in the range of 6.4-7.8 again showing the ortho disubstitution of benzene ring. NH_2 protons resonated as singlet at δ 6.4. The ^{13}C DEPT spectrum gave methyl signal at δ 16 O-CH_3 at δ 51, the CH carbon at δ 68. The aromatic carbons resonated at δ 109, 115, 116, 131, 134, 152, 167 and 171, which also showed a slight change in the chemical shift values. The mass fragmentation pattern also confirmed the structure III (Scheme 2).

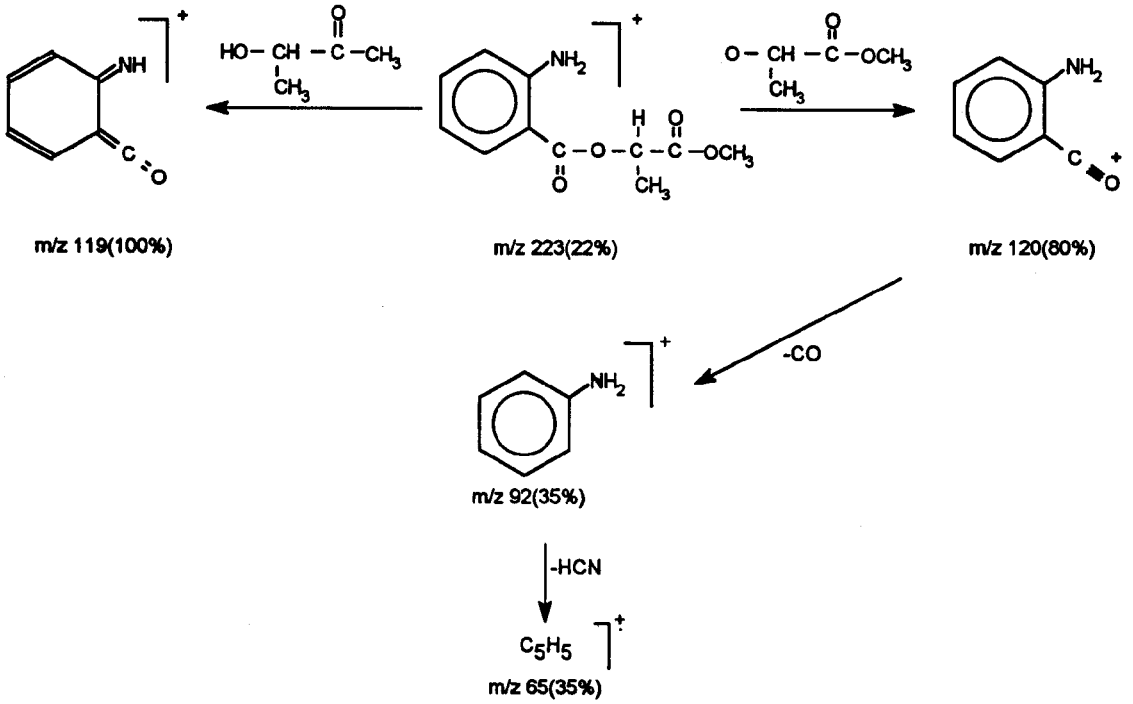
Experimental

All the solvents were purified and dried by standard methods [11]. The melting points were recorded on MEL-Temp. MP-D apparatus, the IR spectra on Hitachi Infrared spectrophotometer Model 270, the NMR spectra on Bruker Sohoohar 001 in δ ppm with TMS as standard, and the mass spectra on MOT 1125 elemental analysis was done on Clarlo Elba Mod 1106.. Rf values were calculated using silica gel (60 HF_{254}).

Preparation of 3-Methyl-4,1-benzoxazepine-2,5-(1H,3H) dione (1) was carried out according to Wenner's method [12].



Scheme - 1



Scheme - 2

Preparation of Methyl 2-[N- (2-hydroxy-1-oxopropyl) amino] benzenecarboxylate (11)

A solution of (1) 0.5g (5.2mmol) and 0.16 ml of 10% NaOH in methanol (12.5ml) was stirred below 60°C for five hours. Excess methanol was removed under reduced pressure. The crude product was recrystalized from acetone n-hexane. Chromatography with acetone: pet. ether (2:3) gave Rf value 0.50, yield after recrystalization 51.42%, m.p. 100-102°C. ν_{max} (KBr): 3316(OH), 3214(NH), 1713(C=O ester), 1668(C=O amide), 1299, 1272 and 1224(C-O-C) cm^{-1}. λ_{max} ($CHCl_3$): 254.6, 312.0 nm. **Anal. Calc.** for $C_{11}H_{13}NO_4$: C 59.19, H 5.83, N 6.28. Found: C 58.58, H 5.84, N 6.18. **H^1NMR** (300 MHz, acetone-d_6): δ: 1.45 (d, 3H, J=6.9Hz), 4.3(q, 1H, J=6.9Hz), 3.9 (s, 3H,), 5.2 (s, 1H,), 11.8(s, 1H,), 8.03 (dd, 1H, J=7.95, 1.5-1.8Hz), 7.58 (td, 1H, J=7.8, 1.35Hz), 7.15 (td, 1H, J=7.8, 1.2Hz), 8.82 (dd 1H, J=8.55, 1.2Hz). **^{13}CNMR** δ (100 MHz acetone-d_6): δ 21.23($\underline{C}H_3$-CH), 52.59($\underline{C}H_3$-O), 69.53($\underline{C}H$-CH_3), 168.39(Ar$\underline{C}$O), 174.85 (ArNH$\underline{C}$), 114.1 (C-1), 140.8 (C-2), 120.73 (C-3), 123.26 (C-4), 131.69 (C-5), 134.96 (C-6). **m/z** (%) 223($M^{+\bullet}$,14): 191(3), 178(28), 151(33), 146(100), 119(72).

Preparation of (1-Carbmethoxyethyl) 2-aminobenzenecarboxylate (III).

A solution of (1) (1.56mmol) and 0.08 ml of 10% HCl in methanol (3.75ml) was stirred with heating below 60°C. After six hours heating, excess methanol was removed under reduced pressure. The residue was oil. TLC showed two spots, which were separated on preparative thick layer chromatography. The lower spot had a Rf value of 0.42, which matched with the starting material. The Rf value of upper spot was 0.56 in acetone: pet. ether (2:3), yield 45% after recrystallization. **^{1}HNMR** (300 MHz acetone-d_6): δ: 1.57(d, 3H, J=4.84), 3.7248(s, 3H,), 5.234(q, 1H, J=1.02), 6.4068(s, 2H,), 6.568(t, 1H,), 6.806(dd, 1H, J=0.69, 4.41, 7.23), 7.2776(t, 1H, J=1.47-1.53), 7.846(d, 1H, J=1.65, 8.1), 6.4(s, 2H, NH_2), **^{13}CNMR** (MHz acetone-d_6) δ: 16.27($\underline{C}H_3$-CH), 51.38(OCH_3), 68.21($\underline{C}H$-CH_3), 108.74(C-2), 114.97(C-6), 116.42(C-4), 130.85(C-5), 134.20(C-3), 151.72(C-1), 166.91(Ph$\underline{C}$OO), 170.97(CH$\underline{C}$OOCH_3). **m/z** (%) 223($M^{+\bullet}$, 22), 192(2.0), 137(3.0), 120(79), 119(100), 92(47), 65(48).

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