SYNTHESIS AND MASS SPECTRAL STUDIES OF *N*-ARYLPHTHALIMIDES

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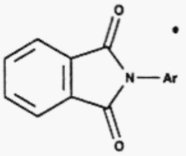
Abstract

Seven phthalimides 1 - 7 have been prepared by heating phthalic anhydride with appropriate arylamines. The structures of these compounds were verified by their ^{1}H-NMR spectra. Their electron-impact fragmentation patterns have been investigated. Compounds 4 - 6 are new.

Introduction

N-Arylphthalimides are gaining importance. For example, *N*-phenylphthalimide and its derivatives have been found to reduce serum cholesterol and triglyceride levels in mice at 20mg/kg/day, ip(1). Among ten phthalimides examined(1), *ortho*-(*N*-phthalimido)acetophenone was most effective and caused the lowering of 57% serum cholesterol after 16 days and most serum triglyceride by 44% after 14 days. Two arylphthalimides, i.e. 4-amino-*N*-(2,6-dimethylphenyl) phthalimide (ADD213063) and *N*-(3-amino-2-methylphenyl) phthalimide (ADD219048) have been tested for anticonvulsant activity and found to be potent anti-Maximal Electroshock Seizure pattern (MES) agents after oral dosing in rats, showing a broad window between anti-convulsant and toxic effects. In fact, they are about four-fold more potent than phenytoin(2). A series of fifteen more *N*-phenylphthalimides, including twelve 4-amino-*N*-phenylphthalimides and three *N*-(3-amino-2-methylphenyl)phthalimides have been investigated by Bailleux et al.(3) and showed promising anticonvulsant activity(4). Besides the above-mentioned biological activities, *N*-phenylphthalimide has been used as a corrosion inhibitor for the dissolution of Fe and C-steel in 0.1M oxalic acid(5).

The importance of *N*-arylphthalimides led us to synthesize the following seven compounds 1 - 7 (Fig. 1) with a view to studying the fragmentation mode of these substances by mass spectrometry and also to test them for biological activity. This paper describes the synthesis and fragmentation pattern of compounds 1 - 7.



1) 4-BrPh
2) 4-NO$_2$Ph
3) 4-MeSPh
4) 4-MeS(O)Ph
5) 2-Me-4-CO$_2$Me-Ph
6) 4-CONH$_2$Ph
7) 5-NO$_2$-2-pyridinyl

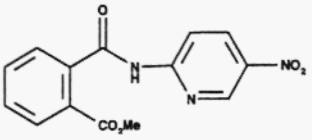
Figure 1

RESULTS AND DISCUSSION

Synthesis

The syntheses of *N*-arylphthalimides 1 - 7 were carried out by heating an appropriate arylamine with phthalic anhydride. Three methods were used. *A*: Heating an equimolar quantity of an arylamine and phthalic anhydride in an appropriate solvent, *B*: heating the mixture of the above-mentioned reagents without a solvent and *C*: heating an intimate mixture of the two without a solvent in a domestic microwave oven. However, only compound 7 could be synthesized in this manner. The structures of the phthalimides were verified by spectroscopic means.

Compound 7 showed an interesting behavior. After its preparation, this phthalimide could be crystallized from ethyl acetate and melted at 224-225°C. The structure of this product tallied with 7. However, prolonged boiling of 7 in methanol transformed this compound to **8**. This ester formation is undoubtedly due to the attack of methanol at the carbonyl carbon of the phthalimide. It is obvious that the electron withdrawing power of the nitrogen atom of the 2-pyridyl function in conjuction with the nitro group at position-5 facilitates this kind of phthalimide methanolysis with the formation of ester **8**.



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Mass Spectra

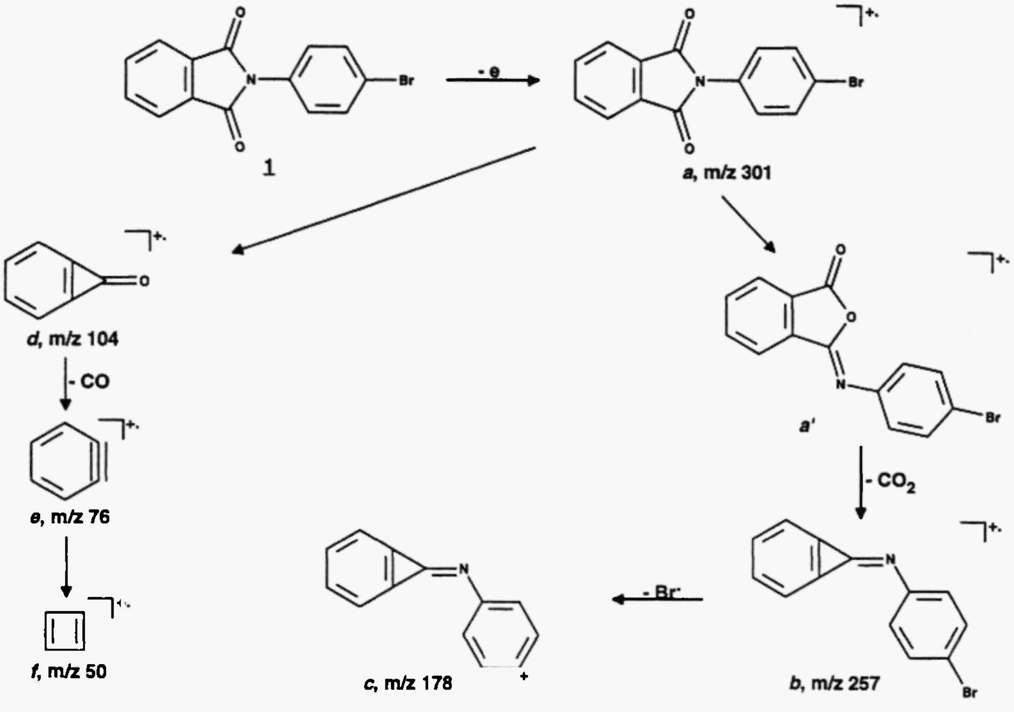
The electron-impact fragmentation pattern of *N*-phenylphthalimide was initially studied by Cotter and Dine-Hart(6,7), Bentley and Johnstone(8), and El-Garby et al.(9). In 1991 an analysis of *N*-phenyl-, *N*-methylphenyl-, and *N*-(dimethylphenyl)phthalimides was carried out by Cermak et al.(10). To our knowledge, compounds 1 - 7 have not been examined by mass spectrometry. The following describes the results obtained by electron ionization of these compounds.

Compound 1 produced the molecular ion *a* at 301 as the base peak. In fact, the other phthalimides also showed strong molecular ion peaks, and in most cases this ion was the base peak. The species *a* loses a neutral fragment of mass 44 to give a fragment at m/z 257. The formation of an ion at m/z 257 is explained by isomerization of N-*p*-bromophenylphthalimide to N-*p*-bromophenyl*iso*phthalimide followed by the loss of CO_2. This kind of isomerization followed by the loss of CO_2 has been established(11) for *N*-methylphthalimide. Later on Cermak et al.(10) did extensive work to prove that imide and *iso*imide isomers cannot be distinguished by mass spectrometry. Thus, it is clear that this isomerization occured in 1 also and then carbon dioxide was lost to provide *b*. This phenomenon was common to all phthalimides which we studied. In the case of 1, fragment *b* ejects a bromine atom to provide ion *c* at m/z 178. Ion *a* of compound 1 also loses *p*-bromophenyl*iso*cyanate to give species *d* at m/z 104 which in turn eliminates CO to furnish fragment *e*. The relative intensities of important ions are given in Table 1.

Table 1 Approximate relative abundance (% base peak) of important ions in the 70 eV mass spectra of *N*-arylphthalimides, 1 - 7.

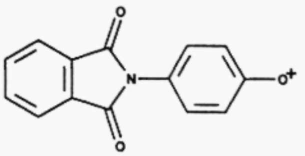
Ion type	1	2	3	4	5	6	7
M + 2	303(100)	270(3)	271(6)	287(1)	297(2)	268(2)	271(1)
M + 1	302(17)	269(20)	270(16)	266(2)	296(20)	267(12)	270(8)
M	301(98)	268(100)	269(100)	285(8)	295(100)	266(65)	269(40)
M - 15	-	-	254(47)	270(100)	280(4)	-	-
M - 16	-	-	-	269(9)	-	250(100)	-
M - 18	-	-	-	-	277(16)	-	-
M - 28	-	-	-	-	-	-	241(100)
M - 15 - 16	-	-	-	254(6)	264(56)	-	-
M - 46	-	-	-	-	-	-	223(8)
M - 18 - 31	-	-	-	-	246(55)	222(23)	-
M - 59	-	-	-	-	236(23)	-	-
M - 31 - 44	-	-	-	-	220(18)	-	-
b	257(35)	224(13)	225(4)	-	251(10)	-	225(2)
c	178(29)	178(14)	-	-	-	-	-
d	104(40)	104(29)	104(11)	104(11)	104(30)	104(16)	104(82)
e	76(68)	76(37)	76(30)	76(27)	76(50)	76(26)	76(81)
f	50(22)	50(12)	50(12)	50(11)	50(18)	50(9)	50(31)
g	-	238(31)	-	238(8)	-	238(1)	-
h	-	222(18)	-	-	-	194(3)	-
i	-	194(5)	-	194(<1)	-	-	-
j	-	-	210(4)	-	-	-	-
k	-	-	-	-	251(10)	-	-
l	-	-	-	-	220(18)	-	-
n	-	-	-	-	-	248(3)	-
r	-	-	-	-	-	-	196(14)
s	130(4)	130(10)	130(11)	130(11)	130(5)	130(3)	130(11)

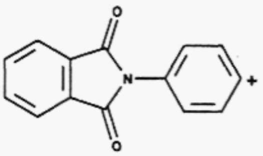
M = Molecular ion (M+')

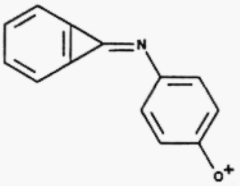


Scheme 1

Compound **2** first showed the usual loss of NO (M-30) and NO_2 (M-46) from the molecular ion giving *g* at m/z 238 and *h* at m/z 222 respectively. This kind of fragmentation is common for nitroaryl compounds(12).


g, m/z 238


h, m/z 222

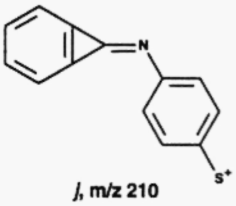

i, m/z 194

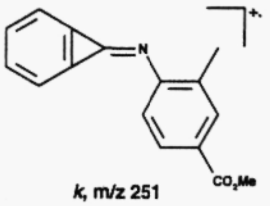
The successive losses of NO(M-30) and CO_2(M-30-44) from the molecular ion gives a fragment *i* at m/z 194(5%). Besides this, compound 2 showed usual ejections from M^+ and other fragments to provide ions *c*(m/z 178), *d*(m/z 104) and *e*(m/z 76) *etc.* as shown analogously for compound 1 in Scheme 1.

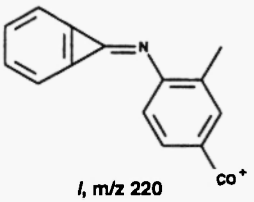
Electron-impact on 3 resulted first in the loss of $CH_3^{\cdot}$ giving a peak at m/z 254. Although ejection of CO_2 from the molecular ion occurred in this case too, the relative intensity of this peak was low (ca. 4%). Successive ejection of CH_3 and CO_2 took place from the molecular ion to yield a species at m/z 210 in low abundance (ca. 4%). This corresponds to species *j* in analogy to *i*.

Compound **4** provided M^+ in much lower abundance (8%). However, M^+-CH_3 at m/z 270 is the base peak. Also M^+-16 was observed at 269. It is interesting to note that M^+-44 was not observed in this case. Loss of $CH_3^{\cdot}$ and $O^{\cdot}$ occurred to yield an ion at 254 in relatively low abundance. One more point needs to be mentioned. The sulfoxide ion rearranges to methylthioxy compound which then loses $CH_3S^{\cdot}$ to afford an ion at 238. Its' ion structure is presumed to be *g*.

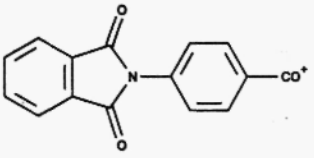
Compound **5** showed M^{+}-15, M^{+}-18, M^{+}-31, M^{+}-49 and M^{+}-59 *etc.* due to presence of the ester function. In this case the molecular ion at 295 was the base peak. Both this ion as well as the fragment at m/z 264 suffered loss of CO_2 to provide species *k* (cf. *b*) and *l* (cf. *i*, *j*) at m/z 251 and m/z 220 respectively. Once again the usual peaks at 104, 76 and 50, corresponding to *d*, *e* and *f* were observed.

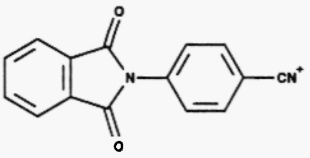

j, m/z 210

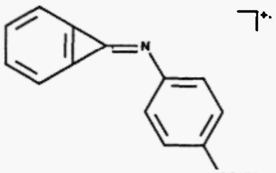

k, m/z 251


l, m/z 220

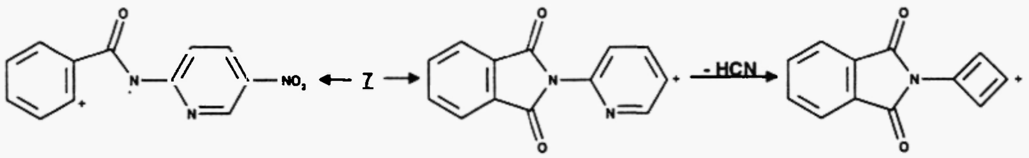
Compound **6** loses mainly NH_2 radical on one hand and a small percentage of water molecule on the other hand from the molecular ion to afford fragments *m* at m/z 250 (base peak) and *n* at m/z 248 (2%) respectively. There is another interesting species *o* (cf. *b*) at m/z 222 originating from the molecular ion. Loss of either CO_2 or $CONH_2$ could yield this ion. However the ejection of the former from M^{+} is most likely.


m, m/z 250


n, m/z 248


o, m/z 222

Phthalimide **7** behaved somewhat differently. Here the molecular ion ejects two species: *firstly* CO instead of CO_2 and *secondly* NO_2 to provide fragments *p* at m/z 241 and *q* at m/z 223 respectively. Another fragment *r* at m/z 196 was observed. It has presumably come from ion *q* by the ejection of HCN.

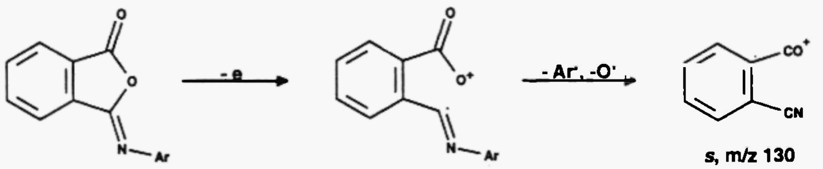


p, m/z 241

q, m/z 223

r, m/z 196

An interesting ion is obtained in all cases at m/z 130. It is due to *s* and may arise from *iso*phthalimide(13).



s, m/z 130

The charge ionisation mass spectra of compounds 1 - 7 were also investigated. Not surprisingly few fragmentation patterns were seen. In fact, the only observable fragments were for compounds 3(m/z 254(15): M^{+}-Me$^{\cdot}$), 4(m/z 270(75): M^{+}-Me$^{\cdot}$), 5(m/z 264(20): M^{+}-MeO$^{\cdot}$), 6(m/z 250(24): M^{+}-NH$_2^{\cdot}$) and 7(m/z 241(22): M^{+}-CO$^{\cdot}$). All these peaks were either the base peak (for 4, 6 and 7) or second strongest peak (for 3 and 5) in the EI mass spectra of these compounds.

Experimental

Melting points were obtained with a Digital Melting Point Apparatus, series IA-9100, Eletctrothermal Engineering Ltd., England, and are uncorrected. A Sanyo microwave oven (2450MHz and 1350watts) was employed for the synthesis of compound 7. N.m.r. spectra were recorded with a Bruker or Varian instrument. Electron ionization mass spectra were done on a VG TS 250 instrument. A direct inlet system was employed to vaporize the samples followed by electron-impact at 70eV. CI mass spectra were recorded on a Finnigan TSQ 70 instrument. IR spectra were run on a Perkin-Elmer Model 1720-FTIR spectrometer. Thin layer chromatography (tic) was done on plates coated with silica gel g (Merck) having fluorescent indicator (F_{254}) and the spots were detected by uv light.

Three methods (*A*,*B* and *C*) were used to prepare *N*-arylphthalimides, 1 - 7.

Procedure A:

An equimolar mixture of an appropriate amine and phthalic anhydride was refluxed in toluene or nitrobenzene for an extended period of time. After cooling, toluene was evaporated and the product crystallized from the solvent indicated. For reactions in nitrobenzene, the cooled reaction mixture was treated with hexane and the resulting precipitate was purified by crystallization from an appropriate solvent.

Procedure B:

Equimolar quantities of an amine and phthalic anhydride were heated neat at 200-210°C for an extended period of time. The products were purified by recrystallization

Procedure C:

An intimate mixture of an appropriate amine and phthalic anhydride was heated in a domestic microwave oven for 30-45 min. at its highest potency. The resultant crude product was cooled and then crystallized from an appropriate solvent.

N-4-Bromophenylphthalimide 1:

Using procedure *A* for three days in toluene and recrystallization from toluene gave the product 1 in 85% yield, mp 204-205°C, (lit.(14,15): 203-204°C (from EtOH)). The same result was obtained when an intimate mixture of the two (procedure *B*) was heated at 200° in a test tube. The product sublimes and could be purified this way.

N-4-Nitrophenylphthalimide 2:

Procedure *A* was employed for 45 min. Recrystallization from EtOH gave 2 as needles, 74%, mp 267-269°C, (lit.(16): 262-265°C (from AcOH)).

N-4-Methylthiophenylphthalimide 3:

An equimolar mixture of phthalic anhydride and *p*-methylthioaniline was heated at 212°C for 25min according to procedure *B*. Cooling, crystallization and recrystallization from MeOH gave product 3, 82%, mp 202-204°C, (lit.(17): 202-203°).

N-(4-Methylthiooxidophenyl)phthalimide 4:

Compound 3 (100 mg, 0.37mmol) was dissolved in CH_2Cl_2 and to this solution were added glacial AcOH (2 drops) and H_2O_2 (42mg, 0.37mmol, 0.0126ml of a 30% aqoues solution). The solution was stirred at room temperature for 48h. Evaporation of the solvent left a residue which showed three spots on tlc ($CHCl_3$:EtOAc; 1:1) with R_f values of 0.77, 0.57 and 0.26 respectively. The fastest running spot was due to the unreacted starting material, the second one (a trace) was due to the sulfone and the third one was due to compound 4. Chromatography over silica gel using $CHCl_3$ as solvent eluted the starting compound. Further elution with 5% EtOAc in $CHCl_3$ provided 80mg (75%) of the desired product 4. Crystallization from EtOAc provided fine, white needles, 54mg (51%), mp 251-252°C. ^{1}H NMR(360MHz, d^6-DMSO): δ = 7.97(2H, m), 7.92(2H, m), 7.85(2H, d, J = 9Hz), 7.68(2H, d, J = 9Hz), 2.81(3H, s); IR (KBr) ν_{max} = 1746,1707, 1595, 1499, 1388, 822, 717 cm^{-1}; Anal: calcd for $C_{15}H_{11}NO_3S$: C, 63.14%; H, 3.89%; N, 4.91%, found: C, 63.31%; H, 4.05%; N, 5.18%.

N-(4-Carboxymethyl-2-methylphenyl)phthalimide 5:

4-Amino-3-methylbenzoic acid (250mg, 1.65mmol) and phthalic anhydride (245mg, 1.65mmol) were refluxed in nitrobenzene (2ml) for 45 min. according to procedure *A*. Work-up provided 420mg (90%) of hexagonal crystals, mp 262-263°C. Recrystallization from a large excess of ethanol improved the mp to 263-264°C. This product is *N*-(4-carboxy-2-methylphenyl)phthalimide. The identity of this product was confirmed by transforming it to its methyl ester 5 as follows: To the above acid (360mg, 1.28mmol) was added Et_2O followed by a solution of diazomethane in Et_2O at room temperature. Recrystallization from EtOAc gave fine needles, (380mg, 100%), mp 196-198°C. ^{1}H NMR(360MHz, d^6-DMSO): δ = 7.97 (3H, m), 7.92(3H, m), 7.53(1H, d, J = 8Hz), 3.88(3H, s), 2.21(3H, s); IR (KBr) ν_{max} = 1780, 1719, 1695, 1605, 1499, 881, 722 cm^{-1}; Anal: calcd for $C_{17}H_{13}NO_4$: C, 69.15%; H, 4.44%; N, 4.74%; found: C, 68.96%; H, 4.46%; N, 4.97%.

N-(4-Carboxamidophenyl)phthalimide 6:

Following method *A* phthalic anhydride (540mg, 3.64mmol) and 4-aminobenzamide (500mg, 3.67mmol) in nitrobenzene (3ml) were heated at reflux temperature for 20 min and then cooled to room temperature. By the addition of *n*-hexane a solid was precipitated which was filtered and washed thoroughly with *n*-hexane to remove nitrobenzene. Crystallization and recrystallization of the product from methanol gave 6, (490mg, 74%), mp 277-278°C. The compound showed one spot by tlc when EtOAc was used as solvent. ^{1}H NMR(360MHz, d^6-DMSO): δ = 8.03(1H, s), 7.98(4H, m), 7.91(2H, m), 7.53(2H, d, J = 8Hz), 7.45(1H, s); IR (KBr) ν_{max} = 3463, 3177, 1746, 1724, 1710, 1695, 1652, 1616, 1577, 1516, 885, 850, 766, 710 cm^{-1}; Anal: calcd for $C_{15}H_{10}N_2O_3$: C, 67.67%; H, 3.79%; N, 10.52%; found: C, 67.37%; H, 3.93%; N, 10.54%.

N-(5-Nitro-2-pyridinyl)phthalimide 7:

An intimate equimolar mixture of phthalic anhydride and 2-amino-5-nitropyridine was heated in a microwave oven without solvent for 45 min at the maximum potency. Crystallization and recrystallization of the product from EtOAc provided pure crystals (58%), mp 220-221°C, (lit.(18): 238-238.5°C (from EtOAc)). The product was pure by tlc (solvent 15% EtOAc in $CHCl_3$). ^{1}H NMR(400MHz, $CDCl_3$): δ = 9.51(1H, d, J = 2.6Hz), 8.69(1H, dd, J = 8.5, 2.6Hz), 8.03(2H, dd, J = 5.6, 2.8Hz), 7.90(2H, dd, J = 5.6, 2.8Hz), 7.76(1H, d, J = 8.5Hz); Anal: calcd for $C_{13}H_7N_3O_4$: C, 58.00%; H, 2.62%; N, 15.61%; found: C, 57.95%; H, 2.73%; N, 15.60%.

Methyl *N*-(5-nitro-2-pyridinyl)phthalamic acid 8:

Phthalimide 7 was boiled in MeOH. Cooling gave crystals, (82%), mp 157-158°C. The R_f value of this product was 0.38 whereas the R_f of compound 7 was 0.5 in the solvent system described above. The product is sparingly soluble in cold MeOH, but can be dissolved in a large quantity of boiling methanol. ^{1}H NMR($CDCl_3$, 300MHz): δ = 9.79(1H, br s), 8.58 (1H, dd, J = 9.0, 0.9 Hz), 8.51(1H, dd, J = 9.0, 2.4Hz), 8.43(1H, dd, J = 2.4, 0.9 Hz), 7.99(1H, m), 7.59(3H, m); IR (KBr) ν_{max} = 3310, 3070, 1711, 1682, 1607, 1584, 1574, 1545, 1510, 1351, 1286, 767, 702 cm^{-1}; Anal: calcd for $C_{14}H_{11}N_3O_5$: C, 55.82%; H, 3.68%; N, 13.94%; found: C, 55.69%; H, 3.51%; N, 13.93%.

Acknowledgments

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