Synthesis of Benzazole N-Mannich bases and 4-[N-(Morpholino/piperidino) phenylimino]-2-indolinones as Potential Anthelmintic Agents+

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Summary:A series of 3[4-(N-morpholino/piperidino)phenylaminomethyl]-benzazoles (IV,VII) and 4-[N-(morpholino/piperidino)phenylimino]-2- indolinones (VI) has been synthesised and screened for their anthelmintic activity against H.nana and N.brasiliensis.

Introduction

Benzazoles are biologically versatile compounds[1]. Benzoxazoles[2], benzothiazoles[3-4] benzimidazoles[5-6],and homomorpholine [7] derivatives have been found to be potential anthelmintics against different types of helminths. Isatin derivatives have also been associated with anthelmintic[8],antibacterial [9] and herbicidal[10] properties.

In view of these observations the syntheses of the title compounds have been undertaken.

In the present communication the synthesis of 4-(N-morpholino/piperidino)-aniline, a novel aromatic amine incorporating basic morpholino/piperidino residue and its applications in the Mannich reaction using a variety of proton donors are reported.

Benzazoles and phthalimides were prepared by the published procedures[11-14].p-Chloronitrobenzene was condensed with morpholine/piperidine to yield I, which on reduction gave 4-(N-morpholino/piperidino)aniline(II)[15-17].

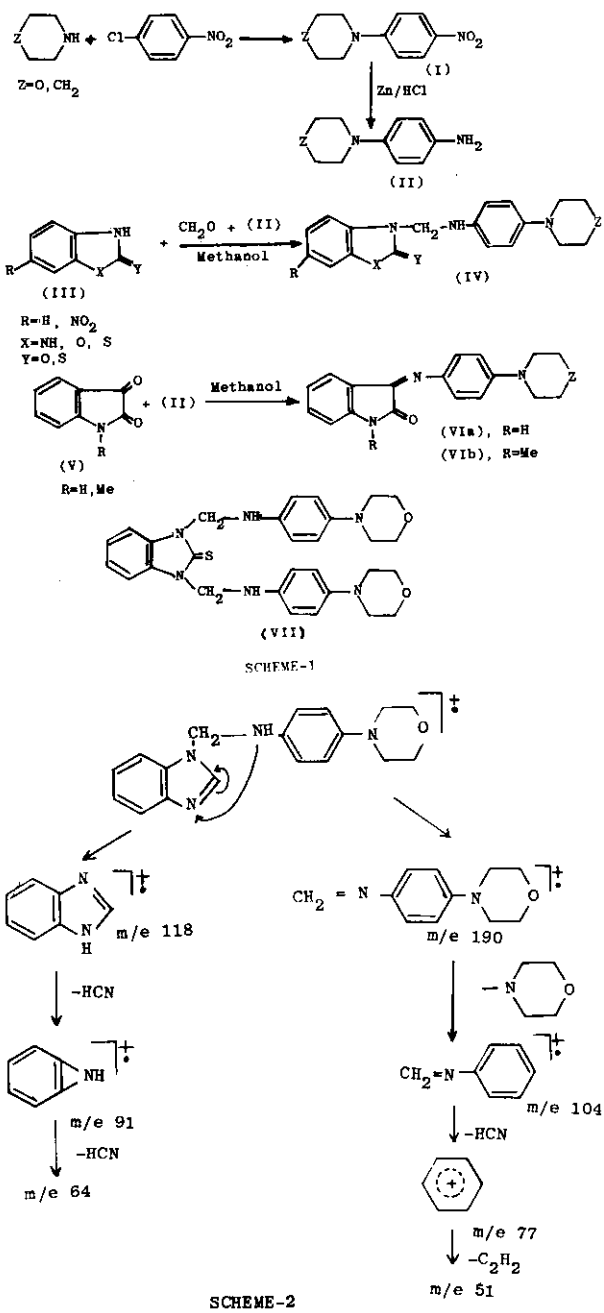
Mannich reaction of 4-(N-morpholino/piperidino)aniline with benzazoles in equimolar quantities gave IV. Treatment of isatin with dimethyl sulphate in ethanolic potassium hydroxide gave N-methylisatin. Isatin and N-methylisatin were condensed with 4-(N-morpholino/piperidino)aniline in equimolar quantities to give VI. The structures of the products prepared were checked by t.l.c.,m.p., m.m.p., sepctral data and satisfactory elemental analysis.

The PMR spectrum of compound 1 (Table 1)shows characteristic absorption peaks at δ 2.86 [$N(CH_2)_2$],3.66 $O(CH_2)_2$, 5.20(N-CH_2-N), 5.86(-NH) and 6.6 - 7.4(Ar-H). The mass spectrum of compound 9(Table 1) is in conformity with the assigned structure. The molecular ion undergoes McLafferty rearrangement leading to fragements at m/e 190 & 118 as a major pathway. Further break up of the fragment at m/e 190 leads to ions at m/e 104, 77 & 51. Likewise fragments at m/e 91 and 64 emerge from the peak at m/e 118(Scheme 2).

Anthelmintic Activity

All the compounds described in the table 1 & 2 were screened for their anthelmintic activity against H.nana and

+Part XL of the series Potential Biologically Active Agents.



SCHEME-2

N.brasiliensis in the dose of 250 mg/kg. None of them was found to be active against the helminth.

Experimental

The melting points were taken in open capillaries and are uncorrected, I.R. were taken in KBr, on a Perkin-Elmer 137 spectrometer. NMR was taken in $CDCl_3$ on a Varian EM-360 at 60 MHz machine. Mass spectrum was taken at 70 eV.

N-(4-Nitrophenyl)-morpholine/piperidine(I).

A mixture of 15.7 g.(0.1 mole) p-Chloronitrobenzene and 0.1 mole of morpholine/piperidine was refluxed for 4-5 h. on a water bath. The reaction mixture was allowed to cool to room temperature. A solid mass separated which was recrystallised from methanol, yield 80% m.p.N-(4-nitrophenyl)-morpholine 149° (Lit.15 m.p.150-151°).N-(4-nitrophenyl) piperidine 103-104° (Lit[15] m.p. 104-105).

4-(N-Morpholino/piperidino)-aniline (II)

N-(4-Nitro phenyl)morpholine/piperidine(0.01 mole) was dissolved in 30 ml of 20% HCl. It was treated with zinc dust with gentle warming until the contents were colourless. The zinc dust was filtered off and filterate was made strongly basic with 50% NaOH to give crude II. It was recrystallised from chloroform. Yield 65%, m.p. 4-(N-morpholino)-aniline 129-130° (Lit. 16 m.p. 129.5-130.5°) 4-(N-piperidino)-aniline 22° (Lit.17 m.p. 22°)

3-[4-(N-morpholino/piperidino)phenylaminomethyl]benzazoles(IV)

Benzazole(0.01 mole) was dissolved in 10 ml of boiling methanol. Formalin(1 ml) and II (0.01 mole) were added to it with good stirring. The contents were further stirred for 10 min. and left overnight at room temperature. The product thus obtained was filtered and recrystallised from methanol (Table 1).

Table - 1

Benzazole N-Mannich Bases (IV)

Compd. No.	Benzazolyl Moiety	Z	M.P. °C	Yield %	Mol. formula		Analysis % Calcd.	Found
1.	Benzoxazolin-2-onyl	O	165-67	54	$C_{18}H_{19}N_3O_3$	C H	66.46 5.84	66.10 5.75
2.	Benzoxazolin-2-thionyl	O	169-70	60	$C_{18}H_{19}N_3O_2S$	C H N	63.34 5.57 12.31	63.5 5.22 12.71
3.	Benzoxazolin-2-onyl	CH_2	159	55	$C_{19}H_{21}N_3O_2$	C H N	70.50 6.50 13.00	70.0 6.60 13.10
4.	Benzoxazolin-2-thionyl	CH_2	170-71	55	$C_{19}H_{21}N_3OS$	C H	67.25 6.19	67.1 6.4
5.	Benzimidazolyl	CH_2	177-78	60	$C_{19}H_{22}N_4\frac{1}{2}H_2O$	C H	72.38 7.30	72.50 6.81
6.	5-Nitrobenzoxazolin-2-onyl	CH_2	159-60	65	$C_{19}H_{20}N_4O_4H_2O$	C H	59.06 5.69	59.3 5.21
7.	Phthalimidyl	CH_2	137-38	58	$C_{20}H_{21}N_3O_2\frac{1}{2}H_2O$	N	12.20	11.79
8.	5-Nitrobenzoxazolin-2-onyl	0	170-d	60	$C_{18}H_{18}N_4O_5$	C H	58.3 4.8	57.80 4.70
9.	Benzimidazolyl	O	163-64	55	$C_{18}H_{20}N_4O$	C H	70.12 6.49	69.62 6.64
10.	4-Nitrophthalimidyl	O	176-77	60	$C_{19}H_{18}N_4O_5$	C H	59.68 4.71	59.40 4.70
11.	4-Nitrophthalimidyl	CH_2	198-99	60	$C_{20}H_{20}N_4O_4\cdot\frac{1}{2}H_2O$	C H	61.69 5.39	61.20 5.15
12.	Benzothiazolin-2-thionyl	O	156-58	55	$C_{18}H_{19}N_3O\ S_2$	C H	60.5 5.32	60.90 5.60
13.	Benzothiazolin-2-thionyl	CH_2	130-32	60	$C_{19}H_{21}N_3S_2$	C H	64.22 5.91	64.30 6.10

Table 2. 4-[N-(Morpholino/Piperidino)phenylimino]-2-Indolinones(VI)

Compd. No.	R	X	M.P.°C	Yield"	Mol.formula		Analysis% Calcd.	Found
14	H	O	263-64	60	$C_{18}H_{17}N_3O_2$	C H	70.35 5.53	70.05 5.29
15	H	CH_2	239-40	60	$C_{19}H_{19}N_3O$	C H	74.75 6.22	74.80 5.90
16	CH_3	O	244-45	58	$C_{19}H_{19}N_3O_2$	C H	71.02 5.91	70.58 6.01
17	CH_3	CH_2	145-46	55	$C_{20}H_{21}N_3O.\frac{1}{2}H_2O$	C H	73.17 6.70	73.00 6.43

4-[N-(morpholino/piperidino)phenylimino]-2-indolinones(VIa)

Isatin(0.01 mole) and II (0.01 mole) were dissolved in 10 ml of ethanol. 2-3 drops of glacial acetic acid were added to it. The contents were refluxed on a water bath for 5 h. The crude product obtained on cooling was recrystallised from methanol(Table 2).

1-Methyl-4-[N-(morpholino/piperidino)-phenylimino]-2-indolinones(VIb)

These were obtained by using N-methylisatin in place of isatin(Table 2).

1,3-Bis[4-(-N-Morpholino)phenylaminomethyl]benzimidazolin-2-thione(VII)

Benzimidazolin-2-thioness(1.5 g., 0.01 mole) was suspended in 15 ml of warm ethanol. 4-(N-morpholino) aniline (3.56 g., 0.02 mole) and formalin (2 ml) were added to it with stirring. The reaction mixture was heated on a water bath for 10 min. and then it was allowed to remain at room temp. overnight . The product thus deposited was collected and recrystallised from methanol m.p. 185°, yield 58%.

Anal: Calcd. for $C_{29}H_{34}N_6O_2S$,C, 65.66,H,6.41%;Found, C, 65.60,H,6.26%

I.R.(cm^{-1}):3400 (NH) 2830(CH_2), 1520 (aryl)1120(C-O-C)

NMR (δ):2.91[$-N(CH_2)_2$], 3.65[O $(CH_2)_2$],4.56(N-CH_2-N),5.85 (-NH-), 6.30 - 7.20 (ArH)

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