

# Synthesis of N-[3-(4-Aryl-1-piperaziny)propyl]-4,4-bis(4-methoxyphenyl)piperidine-2,6-diones/Tetrahydrophthalimides/Camphorimides as Sedatives

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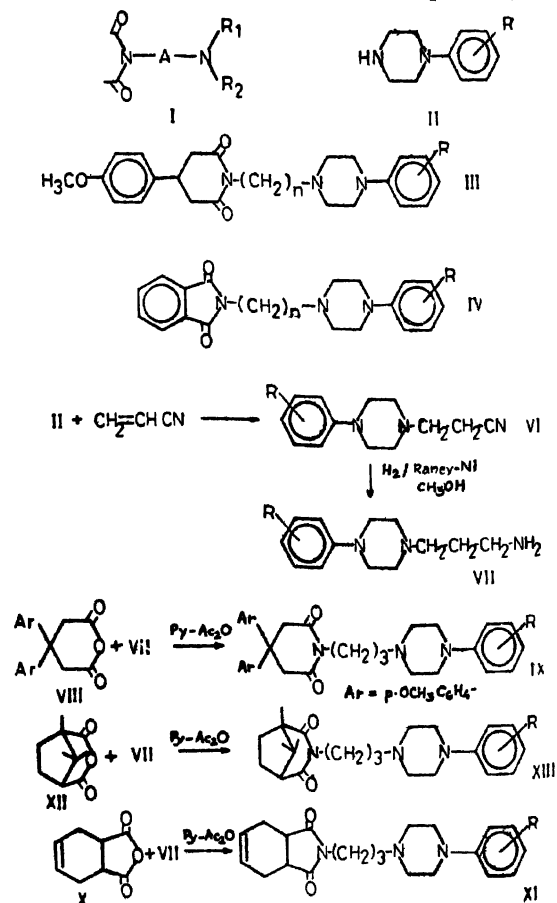
N-[3-(4-Aryl-1-piperaziny)propyl]-4,4-bis(4-methoxyphenyl)piperidine-2,6-diones (IX), camphorimides (XIII) and tetrahydrophthalimides (XI) were prepared by condensing 3-(4-aryl-1-piperaziny)propylamine with 3,3-bis(4-methoxyphenyl)pentanedioic acid anhydride, camphoric acid anhydride and tetrahydrophthalic acid anhydride, respectively. IX were found to be inactive but XIII and XI exhibited significant sedative effect on mice.

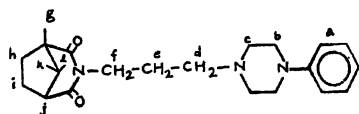
N-( $\omega$ -Aminoalkyl)imides (I) is a potent pharmacophore and the compounds incorporating it show CNS depressant activity<sup>1-4</sup>. Wide variations can be achieved in the activity of imides by introducing variety of substituents on the imide skeleton.

The work on I had been undertaken in our laboratory and Samant has prepared a number of 1-[ $\omega$ -(4-aryl-1-piperaziny)alkyl]-4-(methoxyphenyl)piperidine-2,6-diones (III)<sup>5,6</sup> and the corresponding phthalimides (IV)<sup>7</sup>. It was also shown that a propylene chain between the piperazine N and the imide N was a desirable feature and the corresponding compounds showed maximum activity. This work prompted us to synthesize 1-[3-(4-aryl-1-piperaziny)propyl]-4,4-bis(4-methoxyphenyl)piperidine-2,6-diones (IX) and N-[3-(4-aryl-1-piperaziny)propyl]tetrahydrophthalimides (XI). IX had an additional 4-methoxyphenyl ring on the 4-carbon atom making the carbon atom quaternary which would have a marked effect on the CNS depressant activity. In XI, loss of aromaticity and destruction of planarity of the imide part were thought to have a significant effect on the CNS action of the title compounds as compared to IV. It was also observed that hypnotic action of a drug largely depends on its physical characteristics, such as lipid solubility<sup>8</sup>. Terpenic moieties are endowed with hydrophobicity (lipophilicity). It was thought interesting to introduce a terpenic moiety at the imide part of I. N-Substituted camphorimides have been reported to be CNS depressant<sup>9-11</sup>. Hence, synthesis of N-[3-(4-aryl-1-piperaziny)propyl] camphorimides (XIII) was also attempted.

1-Arylpiperazines (II) were heated with acrylonitrile (V) to obtain 4-aryl-1-(2-cyanoethyl)piperazines (VI) which were subsequently reduced by catalytic hydrogenation to 1-(3-aminopropyl)-4-arylpiperazines (VII). VII were refluxed in dry pyridine

with 3,3-bis(4-methoxyphenyl)pentanedioic acid anhydride (VIII), camphoric acid anhydride (XII) and tetrahydrophthalic acid anhydride (X) to obtain the desired products IX, XIII and XI, respectively.





### Experimental

Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were run on a Beckmann Acculab-10 spectrophotometer and the values are in  $\text{cm}^{-1}$  (wave numbers). PMR spectra were recorded on a Varian-60 instrument at 60 MHz frequency and the chemical shift values are in  $\delta$  units (ppm) with TMS as internal reference. 1-Arylpiperazines (II) were prepared by condensing diethanolamine with anilines according to the reported method<sup>12,13</sup>. Synthesis of VIII has already been reported by us<sup>14</sup>.

1-(2-Cyanoethyl)-4-phenylpiperazines (VI) : 1-Arylpiperazine (0.01 mole) and acrylonitrile (0.8 g ; 0.015 mole) were heated on a water bath for 1 hr. The resultant crystalline mass was washed with water and the product crystallised from alcohol or distilled under reduced pressure.

1-(3-Aminopropyl)-4-arylpiperazines (VII) : VI (5 g) was dissolved in methanol (100 ml) and the solution was saturated with ammonia gas. Raney-nickel (W-6) (1 g) was added to the solution and the compound reduced on a Parr hydrogenator at 50 psi. The reduction required 6-8 hr at room temp. After removing the catalyst the solution was concentrated and the product purified by vacuum distillation.

1-[3-(4-Aryl-1-piperazinyl)propyl]-4,4-bis(4-methoxyphenyl)-piperidine-2,6-diones (IX) : VII (0.01 mole) and VIII (0.01 mole) were refluxed in 50 ml

TABLE I—ANALYTICAL AND PHARMACOLOGICAL DATA OF IX, XI AND XIII

No.	R	Molecular formula	m.p. °C	Yield %	*Analysis% ; Found/(Calcd.)		%Decrease in spontaneous motor activity**	LD <sub>50</sub> (mg/kg)
					N	Cl		
IXa	H	C <sub>22</sub> H <sub>27</sub> N <sub>3</sub> O <sub>4</sub> .2HCl	195-96	64	6.99 (7.00)	11.79 (11.81)	15.6	—
IXb	2-CH <sub>3</sub>	C <sub>23</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub> .2HCl	199-200	60	6.80 (6.84)	11.50 (11.54)	21.2	—
IXc	3-CH <sub>3</sub>	C <sub>23</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub> .2HCl	177-78	59	6.79 (6.84)	11.49 (11.54)	14.1	—
IXd	4-CH <sub>3</sub>	C <sub>23</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub> .2HCl	202-03	59	6.78 (6.84)	11.51 (11.54)	9.1	—
IXe	2-Cl	C <sub>22</sub> H <sub>26</sub> ClN <sub>3</sub> O <sub>4</sub> .2HCl	205-06	66	6.59 (6.62)	16.73 (16.75)	32.1	—
IXf	3-Cl	C <sub>22</sub> H <sub>26</sub> ClN <sub>3</sub> O <sub>4</sub> .2HCl	223-24	69	6.60 (6.62)	16.70 (16.75)	16.9	—
IXg	4-Cl	C <sub>22</sub> H <sub>26</sub> ClN <sub>3</sub> O <sub>4</sub> .2HCl	196-97	70	6.58 (6.62)	16.73 (16.75)	13.1	—
XIa	H	C <sub>21</sub> H <sub>27</sub> N <sub>3</sub> O <sub>4</sub> .2HCl	264-65	61	9.80 (9.86)	16.70 (16.63)	65.0	—
XIb	2-CH <sub>3</sub>	C <sub>22</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub> .2HCl	190-92	52	9.48 (9.54)	16.19 (16.10)	81.8	170
XIc	3-CH <sub>3</sub>	C <sub>22</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub> .2HCl	234-35	58	9.49 (9.54)	16.16 (16.10)	65.4	—
XId	4-CH <sub>3</sub>	C <sub>22</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub> .2HCl	214-15	55	9.52 (9.54)	16.14 (16.10)	51.0	225
XIe	2-Cl	C <sub>21</sub> H <sub>25</sub> ClN <sub>3</sub> O <sub>4</sub> .2HCl	207-08	48	9.16 (9.12)	23.00 (23.08)	100.0	160
XIf	3-Cl	C <sub>21</sub> H <sub>25</sub> ClN <sub>3</sub> O <sub>4</sub> .2HCl	217-18	49	9.08 (9.12)	23.16 (23.08)	73.2	—
XIg	4-Cl	C <sub>21</sub> H <sub>25</sub> ClN <sub>3</sub> O <sub>4</sub> .2HCl	200-01	52	9.14 (9.12)	23.12 (23.08)	68.2	—
XIIIa	H	C <sub>22</sub> H <sub>27</sub> N <sub>3</sub> O <sub>4</sub> .2HCl	243-45	59	9.18 (9.21)	15.50 (15.54)	40.2	—
XIIIb	2-CH <sub>3</sub>	C <sub>23</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub> .2HCl	213-14	52	8.91 (8.97)	15.19 (15.14)	62.8	375
XIIIc	3-CH <sub>3</sub>	C <sub>23</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub> .2HCl	220-21	54	8.92 (8.97)	15.10 (15.14)	42.1	—
XIIId	4-CH <sub>3</sub>	C <sub>23</sub> H <sub>29</sub> N <sub>3</sub> O <sub>4</sub> .2HCl	240-41	49	8.94 (8.97)	15.09 (15.14)	55.3	220
XIIIe	2-Cl	C <sub>22</sub> H <sub>25</sub> ClN <sub>3</sub> O <sub>4</sub> .2HCl	205-06	47	8.51 (8.56)	21.74 (21.67)	64.4	280
XIIIf	3-Cl	C <sub>22</sub> H <sub>25</sub> ClN <sub>3</sub> O <sub>4</sub> .2HCl	224-26	57	8.50 (8.56)	21.71 (21.67)	50.9	850
XIIIg	4-Cl	C <sub>22</sub> H <sub>25</sub> ClN <sub>3</sub> O <sub>4</sub> .2HCl	231-32	54	8.54 (8.56)	21.69 (21.67)	40.6	—

\* C and H analyses were found to be satisfactory.

\*\* IX were administered at a dose of 200 mg/kg (i.p.) and XI and XIII at 50 mg/kg (i.p.).

dry pyridine for 12 hr. Acetic anhydride (10 ml) was added and the solution refluxed further for 6 hr to complete the cyclization. The solution was concentrated in vacuum. The residue was stirred in alcohol and the solution was saturated with HCl gas. The precipitated product was filtered and crystallized from ethanol (Table I). IR (KBr) of IXe: 1730 and 1677 (CO-N-CO), 1250 (Ar-OCH<sub>3</sub>). PMR (CDCl<sub>3</sub>) of IXg: 1.65 (2H, m, >N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-N<), 2.28 (2H, t, -CH<sub>2</sub>-CH<sub>2</sub>-N<), 2.6 [4H, t, -CH<sub>2</sub>-N(CH<sub>2</sub>-)<sub>2</sub>], 3.2 [4H, t, ArN(CH<sub>2</sub>-)<sub>2</sub>], 3.4 [4H, s, Ar<sub>2</sub>C(CH<sub>2</sub>-)<sub>2</sub>], 3.8 [8H, m, Ar-OCH<sub>3</sub> and (CO)<sub>2</sub>N-CH<sub>2</sub>-] and 6.83-7.25 (12H, m, ArH).

*N*-[3-(4-Aryl-1-piperazinyl)propyl]tetrahydrophthalimides (XI): XI were prepared from VII (0.01 mole) and tetrahydrophthalic anhydride (X) (0.01 mole)<sup>16</sup>. The reaction mixture required chilling to obtain the product. The product was crystallised from ethanol. IR (KBr) of XIa: 1700 and 1780 (CO-N-CO). PMR (CDCl<sub>3</sub>) of XIa: 2.05-2.48 [6H, m, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-, -CH<sub>2</sub>-N(CH<sub>2</sub>-)<sub>2</sub>], 2.5-2.68 [2H, t, -CH<sub>2</sub>-N(CH<sub>2</sub>-)<sub>2</sub>], 2.89-3.35 [4H, m, Ar-N(CH<sub>2</sub>-)<sub>2</sub>], 3.38-3.89 [8H, m, (CO)<sub>2</sub>N-CH<sub>2</sub>-, -CH<sub>2</sub>-CH-CO-], 6.03 (2H, m, CH=) and 7.05-7.6 (4H, m, ArH).

*N*-[3-(4-Aryl-1-piperazinyl)propyl]camphorimides (XIII): XIII were prepared from VII (0.01 mole) and camphoric acid anhydride<sup>16</sup> (0.01 mole). The compounds were crystallised from ethanol. IR (KBr) of XIIIa: 1740 and 1690 (CO-N-CO). PMR (CDCl<sub>3</sub>) of XIIIa: 1.0 (6H, s, H<sub>k</sub>, H<sub>g</sub>), 1.22 (3H, s, H<sub>l</sub>), 1.85-2.4 (6H, m, H<sub>b</sub>, H<sub>i</sub>, H<sub>e</sub>), 2.8 (1H, m, H<sub>j</sub>), 3.1-3.3 (4H, m, H<sub>o</sub>), 3.5-4.0 (8H, m, H<sub>t</sub>, H<sub>d</sub>, H<sub>b</sub>), 7.3-7.7 (4H, m, ArH).

#### Pharmacology:

Gross behavioural observations and the acute toxicity studies were carried out on albino mice of Haffkin strain. Effect of the compounds on the spontaneous motor activity of the mice was studied using actophotometer. The compounds were injected in CMC suspension in distilled water and injected intraperitoneally to the mice. Compound

IX showed LD<sub>50</sub> > 900 mg/kg, but at the dose level of 200 mg/kg they did not show any observable CNS depressant activity. XI and XIII showed significant depressant activity. At a dose of 50 mg/kg, all the compounds showed significant CNS depression. Parallel observations were made in both the series. In general, *o*-substitution was found to be favourable; in addition, *o*-chloro substitution was desirable for the maximum activity. The tetrahydrophthalimides (XI) were found to be more active than the corresponding camphorimides (XIII). XIe was the most active compound and it produced 35% decrease in the spontaneous motor activity at a dose of 25 mg/kg and the effect lasted for 5 hr.

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