NAPHTHYLPIPERAZINES AND TETRALYLPIPERAZINES: SYNTHESIS AND PHARMACOLOGICAL PROPERTIES*

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Heating of 1- and 2-naphthylamine hydrochlorides and of 5- and 6-tetralylamine hydrochlorides with diethanolamine hydrochloride produced naphthylpiperazines *Ia* and *IIa* and tetralylpiperazines *IIIa* and *IVa*. These secondary amines were treated with ethyl chloroformate or with acetic anhydride and then reduced; or underwent an addition of methyl acrylate or acrylonitrile and then were reduced; or finally underwent alkylation by 4-methoxyphenacyl bromide and 4-chloro-*p*-fluorobutyrophenone to the corresponding N-alkyl derivatives which were evaluated pharmacologically. 1-(6-Tetralyl)-4-methylpiperazine (*IVd*) displayed a marked antireserpine effect in the test of eyelid ptosis in mice, 4-[3-(4-fluorobenzoyl)propyl]-1-(6-tetralyl)piperazine (*IVk*) was active neuroleptically.

1-Arylpiperazine derivatives have been often reported as neurotropic and cardiovascular agents; for the case that the aryl substituent is phenyl or a substituted phenyl, several examples of this type were reported recently[1]. The aryl in these compounds can also be bicyclic or tricyclic and can contain heteroatoms; thus, *e.g.*, 1-(2-pyridyl)piperazine derivative "azaperone" is a sedative used in veterinary practice[2], the 1-(2-pyrimidyl)piperazine derivative "piribedil" has the properties of a peripheral vasodilatant and a potential antiparkinsonic[3], 1-(2-quinolyl)piperazine is the "quipazine"[4] with serotoninergic and antitremorine activity, the 1-(2-purinyl)-piperazines are central depressants[5], 1-(thieno [2,3-d] pyrimidine-4-yl)piperazines show antihistamine activity[6], 1-(5-methyl-5*H*-pyrimido [3,4-*b*]-1,4-benzoxazin-3-yl)-4-methylpiperazine is the antidepressant agent "azaphene"[7]; on the other hand, 1-(2- and 3-phenothiazinyl)piperazines displayed no interesting pharmacodynamic activity[8]. Little attention has been devoted to the naphthylpiperazines; patents[9,10] report a central depressant activity for 1-(1-aryl-2-propyl)-4-(naphthyl)-piperazines and a sedative, myorelaxant and analgesic activity for 1-(dihydronaphthyl)piperazines. The present communication contributes to the present knowledge of the pharmacodynamics of naphthylpiperazines and tetralylpiperazines.

Prelog and Blažek[11] described the preparation of 1-(1-naphthyl)piperazine (*Ia*) and 1-(2-naphthyl)piperazine (*IIa*) by reactions of naphthylamines with bis(2-bromo-

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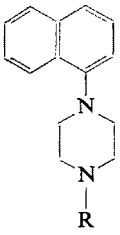
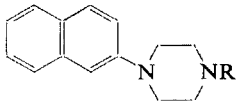
ethyl)amine hydrobromide; Cerkovnikov and Štern[12] studied some aspects of their pharmacology. The same compounds *Ia*, *IIa* were prepared here by the method of Pollard and coworkers[13,14], *i.e.* by heating the hydrochlorides of 1-naphthylamine and 2-naphthylamine with diethanolamine hydrochloride to 220–230°C (method A). When using 5-tetralylamine[15,16] and 6-tetralylamine[17] as starting compounds, 1-(5-tetralyl)piperazine (*IIIa*) and 1-(6-tetralyl)piperazine (*IVa*) were prepared in a similar way (see ref.[9]).



I



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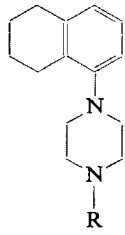
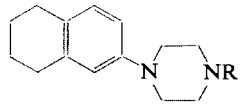


III



IV

a, R = H
b, R = $COOC_2H_5$
c, R = $COCH_3$
d, R = CH_3

e, R = CH_2CH_3
f, R = $CH_2CH_2COOCH_3$
g, R = CH_2CH_2CN
h, R = $CH_2CH_2CH_2OH$

i, R = $CH_2CH_2CH_2NH_2$
j, R = 4-$CH_2COC_6H_4OCH_3$
k, R = 4-$(CH_2)_3COC_6H_4F$

Reaction of amines *Ia*, *IIa* and *IVa* with ethyl chloroformate in benzene (method B) led to the carbamates *Ib*, *IIa* and *IVb*; reaction of *Ia* with acetic anhydride in toluene resulted in amide *Ic*. All the four products were reduced with lithium aluminium hydride in ether (method C), this giving rise to the N-methyl derivatives *Id*, *IId*, and *IVd*, and the N-ethyl derivative *Ie*. Addition of *Ia* to methyl acrylate led to the ester *If*; similarly, addition of *IIa* to acrylonitrile led to nitrile *IIg*. Ester *If* was reduced with lithium aluminium hydride to aminoalcohol *Ih*; nitrile *IIg* was similarly reduced to amine *IIi*. Compounds *IIa* and *IVa* were alkylated either with 4-methoxyphenacyl bromide[18] or with 4-chloro-*p*-fluorobutyrophenone[19] in dimethylformamide in the presence of potassium carbonate (method D), giving rise to *IIj*, *IIk*, *IVj* and *IVk*. All the bases prepared were characterized and pharmacologically tested in the form of crystalline maleates (prepared by neutralization with maleic acid in ethanol; see Table I).

Most of the piperazine derivatives were pharmacologically evaluated by methods of general screening, some compounds underwent psychopharmacological screening (under cooperation of Dr J. Metyšová and Dr J. Metyš) and all the compounds were tested for antimicrobial activity in vitro at the bacteriological department of this institute (Drs J. Turinová and A. Čapek). The results of the biological tests are shown in Table II reporting the method of application, an orientation value of acute toxicity for mice and the dose at which the compound was applied in a series of basic tests *in vivo*.

TABLE I

Naphthylpiperazines and Tetralylpiperazines

Compound[a]	Method (yield, %)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found		
				% C	% H	% N
Ia	*A* (30)	144—147/1[b]	$C_{14}H_{16}N_2$ (212·3)	79·20 79·47	7·60 7·62	13·20 12·66
Ia-M	—	164—167 (ethanol)	$C_{18}H_{20}N_2O_4$ (328·4)	65·84 66·05	6·14 6·27	8·53 8·68
Ib	*B*[c] (98)	200—204/17	$C_{17}H_{20}N_2O_2$ (284·4)	71·80 71·60	7·09 7·13	9·85 9·74
Ic	[c]	111—113 (cyclohexane)	$C_{16}H_{18}N_2O$ (254·3)	75·76 75·86	7·13 7·39	11·02 11·09
Id	*C*[c] (98)	54—55 (hexane)	$C_{15}H_{18}N_2$ (226·3)	79·60 79·87	8·02 8·20	12·38 12·45
Id-M	—	122—124 (ethanol–ether)	$C_{19}H_{22}N_2O_4$ (432·4)	66·65 66·67	6·48 6·52	8·18 8·16
Ie	*C* (93)	79—81[d] (cyclohexane)	$C_{16}H_{20}N_2$ (240·3)	79·95 80·28	8·39 8·58	11·66 11·64
Ie-M	—	105—107 (ethanol–ether)	$C_{20}H_{24}N_2O_4$ (356·4)	67·39 67·08	6·79 6·89	7·86 7·80
If	[c]	65—66 (hexane)	$C_{18}H_{22}N_2O_2$ (298·4)	72·45 72·34	7·43 7·50	9·39 9·46
If-M	—	135—136 (methanol)	$C_{22}H_{26}N_2O_6$ (414·5)	63·75 63·79	6·32 6·40	6·76 6·95
Ih	[c]	194—195 (ethanol)	$C_{17}H_{22}N_2O$ (270·4)	75·51 75·25	8·20 8·26	10·36 10·38
IIa	*A* (42)	130—135/0·4[e]	—	—	—	—
IIa-M	—	161—163 (methanol)	$C_{18}H_{20}N_2O_4$ (328·4)	65·84 66·05	6·14 6·25	8·53 8·56
IIb	*B* (87)	172—174/0·5	$C_{17}H_{20}N_2O_2$ (284·4)	71·80 72·07	7·09 7·17	9·85 9·75
IId	*C* (95)	92—94[f] (ethanol)	$C_{15}H_{18}N_2$ (226·3)	79·60 79·43	8·02 8·17	12·38 12·35
IId-M	—	176—178 (ethanol)	$C_{19}H_{22}N_2O_4$ (342·4)	66·65 66·64	6·48 6·55	8·18 8·22
IIg	[c]	83—85 (ethanol)	$C_{17}H_{19}N_3$ (265·3)	76·94 76·96	7·22 7·46	15·84 16·26
IIg-M	—	129—130 (ethanol)	$C_{21}H_{23}N_3O_4$ (381·4)	66·13 66·38	6·08 6·16	11·02 11·07

TABLE I
(*Continued*)

Compound[a]	Method (yield, %)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found		
				% C	% H	% N
IIi-2M	[c]	173—175 (aqueous ethanol)	$C_{25}H_{31}N_3O_8$ (501·5)	59·87 59·70	6·23 6·23	8·38 8·24
IIj	*D*[c] (32)	152—156 (benzene)	$C_{23}H_{24}N_2O_2$ (360·4)	76·64 76·71	6·71 6·70	7·77 7·82
IIj-M	—	178—181 (aqueous ethanol)	$C_{27}H_{28}N_2O_6$ (476·4)	68·05 68·00	5·92 5·91	5·88 5·92
IIk	*D* (27)	135—138[g] (ethanol)	$C_{24}H_{25}FN_2O$ (376·5)	76·56 76·53	6·69 6·65	—
IIk-M	—	168—170 (ethanol)	$C_{28}H_{29}FN_2O_5$ (492·5)	68·28 67·88	5·93 5·97	3·86[h] 3·63
IIIa	*A*[c] (41)	176—180/16	$C_{14}H_{20}N_2$ (216·3)	77·73 77·84	9·32 9·45	12·95 12·56
IIIa-M	—	168—171 (ethanol)	$C_{18}H_{24}N_2O_4$ (332·4)	65·04 65·49	7·28 7·48	8·43 8·50
IVa	*A* (55)	155/0·5[i]	$C_{14}H_{20}N_2$ (216·3)	77·72 77·80	9·32 9·57	12·95 13·18
IVa-M	—	150—152 (ethanol)	$C_{18}H_{24}N_2O_4$ (332·4)	65·04 64·92	7·27 7·11	8·43 8·32
IVb	*B* (87)	172—174/0·6	$C_{17}H_{24}N_2O_2$ (288·4)	70·80 70·77	8·39 8·43	9·72 9·69
IVd-M	*C* (95)	175—176 (ethanol)	$C_{19}H_{26}N_2O_4$ (346·4)	65·87 65·80	7·57 7·58	8·09 7·77
IVj	*D* (23)	140—144[j] (benzene–ethanol)	$C_{23}H_{28}N_2O_2$ (364·5)	75·79 76·03	7·74 7·74	7·69 7·67
IVj-M	—	165—169 (ethanol)	$C_{27}H_{32}N_2O_6$ (480·6)	67·47 67·48	6·71 6·71	5·83 5·74
IVk	*D* (25)	116—118[k] (benzene)	$C_{24}H_{29}FN_2O$ (380·5)	75·76 75·86	7·68 7·59	4·99[h] 4·72
IVk-M	—	157—159 (ethanol)	$C_{28}H_{33}FN_2O_5$ (496·6)	67·72 68·10	6·70 6·69	3·83[h] 4·29

[a] M maleate, 2M dimaleate. [b] Ref.[11] describes the preparation of the compound in a different way and characterizes the product as a crystalline monohydrochloride and monohydrobromide. [c] See Experimental. [d] NMR spectrum: δ 7·00—8·50 (m, 7 H, aromatic protons of naphthyl), 2·60—3·30 (m, 8 H, 4 NCH_2 of piperazine), 2·51 (q, 2 H, CH_2 of ethyl), 1·12 (t, 3 H, CH_3). [e] Ref.[11] described the preparation of the compound by a different procedure and reports a m.p. for the base of 78°C. [f] NMR spectrum: δ 7·05—7·90 (m, 7 H, aromatic protons of naphthyl),

With regard to central neurotropic activity, Table II indicates that naphthylpiperazines and tetralylpiperazines where the N^4-substituent is represented by a hydrogen or a methyl group (*Ia–IVa, Id, IId, IVd*) act at high doses as stimulants, at lower doses hyperthermically, and possess some antireserpine and anorectic activity. Ataxia in mice is brought about only at subtoxic doses when they slightly potentiate thiopental sleep; they are inactive as cataleptics. They thus display in part the pharmacological spectrum of central stimulants and antidepressants. The most interesting in this group is 4-methyl-1-(6-tetralyl)piperazine (*IVd*) which, in the ptosis test, showed antireserpine activity of a degree similar to that of the practically used antidepressants "imipramine"[20] and "prothiadene"[21]. With increasing the N^4-substituent, the central activity reverts gradually from stimulation to depression as may be observed already in the ethyl derivative *Ie*. It is most expressed in the fluorobutyrophenone derivatives *IIk* and *IVk* where, of course, the specific role of the fluorobutyrophenone fragment is apparent[22]. The most interesting compound of all is 1-[3-(4-fluorobenzoyl)propyl]-4-(6-tetralyl)piperazine (*IVk*) which displays the whole pharmacodynamic spectrum of a typical neuroleptic with central depressant, hypothermic, antiamphetamine and cataleptic activities. In a number of compounds, some structurally little specific effects were observed, such as locally anaesthetic, antiarrhythmic, slight and brief hypotensive, spasmolytic of papaverine type, *etc.* Practically all the compounds are without interest as antimicrobial agents.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* at about 0·5 Torr over P_2O_5 at a suitable temperature (at most 100°C). The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, IR spectra (in Nujol) in a Unicam SP 200G spectrophotometer and the NMR spectra ($CDCl_3$) in a ZKR 60 (Zeiss, Jena) spectrometer. The homogeneity of the compounds was tested by thin-layer chromatography on alumina. The analyses of all the compounds prepared are shown in Table I.

3·24 (m, 4 H, $CH_2N(Ar)CH_2$), 2·60 (m, 4 H, remaining NCH_2 of piperazine), 2·32 (s, 3 H, NCH_3). [g] UV spectrum: λ_{max} 244·5 nm (log ε 4·76), 270 nm (3·98); IR spectrum: 742, 810, 828, 830, 870 (4 and 2 adjacent Ar—H), 1005 (C—F), 1200 (ArCO), 1510, 1598 (Ar), 1680 (Ar—CO), 2780 cm^{-1} (N—CH_2). [h] Content of fluorine. [i] NMR spectrum: δ 7·02 (d, J = 9·0 Hz, 1 H, 8-H of tetraline), 6·74 (q, J = 9·0; 2·5 Hz, 1 H, 7-H of tetraline), 6·65 (bs, 1 H, 5-H of tetraline), 3·01 (s, 8 H, 4 NCH_2 of piperazine), 2·68 (m, 4 H, CH_2—Ar—CH_2), 1·74 (m, 4 H, 2,2,3,3-H_4 of tetraline), 1·65 (disappears after D_2O, 1 H, NH); patent[9] reports a b.p. of 140°C/0·15 Torr without describing the method of preparation. [j] UV spectrum: λ_{max} 272 nm (log ε 4·29); IR spectrum: 838, 878 (2 adjacent and solitary Ar—H), 1238 (C—O), 1265 (Ar—O—CH_3), 1510, 1575, 1600, 1615 (Ar), 1690 (Ar—CO), 2780 cm^{-1} (N—CH_2). [k] UV spectrum: λ_{max} 246·5 nm (log ε 4·34); IR spectrum: 840, 870 (2 adjacent and solitary Ar—H), 1010 (Ar—F), 1240 (C—O), 1598 (Ar), 1682 (Ar—CO), 2785 (N—CH_2), 3075 cm^{-1} (Ar).

TABLE II

Pharmacological Properties of Naphthylpiperazine and Tetralylpiperazine Maleates

Compound (application)[a]	LD_{50}[b] (D)	Observed effects
Ia (*p.o.*)	100 (20)	At doses above D signs of central excitation; slightly potentiates thiopental sleep in mice; mydriatic effect on mice; increases the blood glucose level in rats; prolongs the survival of an asphyctic mouse myocard; see ref.[12].
Id (*i.v.*)	22·5	The compound causes discoordination in the rotating-rod test in mice only at subtoxic doses; 10 mg/kg causes ataxia in only two mice out of ten; an *i.p.* dose of 10 ml/kg is inactive cataleptically in a test on rats.
Ie (*i.v.*)	42 (8)	At doses above D signs of central depression in mice; at dose D prolongs thiopental sleep in mice; at D/2 causes in normotensive rats a slight and brief drop of blood pressure, while after D a deep drop of blood pressure is observed; antiarrhythmic effect in mice toward chloroform arrhythmia; increases the level of blood glucose in rats; in the *in vitro* test on isolated rat duodenum it has spasmolytic effect toward acetylcholine spasms of an intensity similar to that of adiphenine; negatively inotropic and negatively chronotropic effect on isolated rabbit atrium
If (*i.v.*)	65	It has an incoordinating effect in the rotating-rod test in mice only at subtoxic doses; dose of 30 mg/kg causes ataxia in 3 mice out of ten; an *i.p.* dose of 10 mg/kg is ineffective cataleptically in the test on rats.
IIa (*i.v.*)	75 (15)	At doses above D signs of central excitation; at dose D it increases slightly the body temperature of rats; at D/2 it causes a slight and brief drop of blood pressure in normotensive rats, dose D brings about a deep brief drop; a negatively inotropic effect on isolated rabbit atrium; a sign of antireserpine and anorectic effect on mice; a slight locally anaesthetic effect in tests of infiltration anaesthesia in guinea pigs and corneal anaesthesia in rabbits (weaker than procaine or cocaine); spasmolytic effect of papaverine type and intensity toward barium chloride spasms of isolated rat duodenum; at 50 μg/kg inhibits growth of *Mycobacterium tuberculosis* H37Rv *in vitro*.
IId (*i.v.*)	54	The compound has a discoordinating effect in the rotating-rod test in mice only at high doses; 30 mg/kg brings about ataxia in 4 mice out of ten; *i.p.* dose of 10 mg/kg is in effective cataleptically in the test on rats.
IIg (*i.v.*)	275 (55)	At doses above D a pronounced central depression in mice; at dose D it decreases slightly the body temperature of rats, causes a brief drop of blood pressure in normotensive rats, it increases the blood sugar level in rats and has a slight mydriatic effect in mice

TABLE II
(*Continued*)

Compound (application)[a]	LD_{50}[b] (D)	Observed effects
IIi (*i.v.*)	110 (20)	At D/2 a brief, at D a protracted drop of blood pressure in rats; antiarrhythmic effect in mice against chloroform arrhythmias.
IIj (*p.o.*)	>2 500 (300)	At dose D an antiarrhythmic effect against chloroform arrhythmias in mice.
IIk (*p.o.*)	>500	Causes ataxia in the rotating-rod test in mice, $ED_{50} = 43$ mg/kg; at dose 50 mg/kg causes catalepsy in 10% of rats.
IIIa (*i.v.*)	30 (6)	At doses above D signs of central excitation in mice, at D it slightly inhibits motility in known surroundings; slightly prolongs thiopental sleep in mice; a spasmolytic effect against barium chloride contractions in isolated rat duodenum stronger than with papaverine; a slight locally anaesthetic effect in the infiltration test and in corneal anaesthesia; a sign of mydriatic effect in mice; a brief vasodilatory effect displayed by increased skin temperature in guinea-pig earlobe; negatively inotropic effect on isolated rabbit atrium; sign of antiarrhythmic effect against chloroform arrhythmias in mice; at 50 μg/ml inhibits growth of *Mycobacterium tuberculosis* H37Rv *in vitro*.
IVa (*i.v.*)	80 (15)	At doses above D brings about central excitation in mice; at D increases body temperature in rats; at 20 mg/kg *i.p.* it has a significant antireserpine effect in the test of eyelid ptosis in mice (c. 50% effect of prothiadene); at D it decreases the blood sugar level in rats, shows signs of antiinflammatory effect in the test of kaolin arthritis in rats and has a slight negatively inotropic effect on isolated rabbit atrium.
IVd (*i.v.*)	100 (20)	At doses above D signs of central excitation in mice; at D a pronounced increase of body temperature of rats; slight potentiation of thiopental sleep in mice; at D/2, *i.p.*, a significant antireserpine effect in the test of eyelid ptosis in mice, comparable with that of imipramine and prothiadene; at D/2 a pronounced brief, at D a protracted drop of blood pressure in rats; an antiarrhythmic effect toward chloroform arrhythmias in mice; blood sugar level first increased, then decreased.
IVj (*p.o.*)	<2 000	In the rotating-rod test it causes ataxia at 500 mg/kg in only 30% mice; at 50 mg/kg does not inhibit locomotor activity in mice; does not affect apomorphine chewing or agitation in rats; in general, it has a weaker central activity than mesylphenacyrazine[1].

TABLE II
(Continued)

Compound (application)[a]	LD_{50}[b] (D)	Observed effects
IVk (*p.o.*)	2 000 (300)	Brings about central depression in mice; in the rotating-rod test causes ataxia in mice with ED_{50} = 15 mg/kg; decreases body temperature in rats; even at D/2 prolongs thiopental sleep in mice; has an antiamphetamine effect in mice and a cataleptic effect on rats; even at 50 mg/kg significantly antagonizes pentetrazol spasms in mice; increases blood sugar level in rats; a sign of antiarrhythmic effect against chloroform arrhythmias in mice.

[a] *p.o. per os*, *i.v.* intravenously, *i.p.* intraperitoneally. [b] LD_{50} acute toxicity in mice expressed by the mean lethal dose in mg/kg; D dose in mg/kg at which the compound was applied *in vivo*.

1-(5-Tetralyl)piperazine (*IIIa*) (Method *A*)

A mixture of 14·7 g 5-tetralylamine[15,16] (b.p. 150°C/18 Torr) and 15·8 g diethanolamine was slowly combined at 100°C with 40 ml water, 40 ml concentrated hydrochloric acid and 40 ml ethanol. Ethanol was then evaporated at normal pressure; this was followed by evaporation of water and the residue was heated for 8 h to 220–230°C. After cooling, 80 ml water and an excess of 50% NaOH was added. The product was extracted with benzene, the extract was dried and evaporated and the residue distilled; 8·9 g (41%) base, b.p. 176–180°C/16 Torr. NMR spectrum: δ 6·50–7·25 (m, 3 H, aromatic protons), 2·30–3·50 (m, 12 H, CH_2—Ar—CH_2 and 4 NCH_2 of piperazine), 1·50–2·80 (m, 5 H, isolated CH_2CH_2 of tetraline and NH).

1-(Ethoxycarbonyl)-4-(1-naphthyl)piperazine (*Ib*) (Method *B*)

Ethyl chloroformate (13 g) was added to a solution of 21·2 g *Ia* in 100 ml benzene and the mixture was refluxed for 2·5 h. After cooling, it was diluted with 100 ml benzene, decomposed with 300 ml 15% solution of Na_2CO_3, shaken and the benzene layer was separated. After washing with water it was dried with Na_2SO_4 and the benzene was evaporated. The remaining oil (27·9 g, 98%) was processed further without purification. Sample for analysis was distilled, b.p. 200 to 204°C/17 Torr.

1-Acetyl-4-(1-naphthyl)piperazine (*Ic*)

Acetic anhydride (30 ml) was added to a solution of 17·0 g *Ia* in 80 ml toluene and the mixture was refluxed for 2 h. The volatile fractions were distilled at reduced pressure, the residue was dissolved in 150 ml benzene and the solution was extracted with dilute hydrochloric acid. The aqueous solution of the hydrochloride was separated, made alkaline with NH_4OH and extracted with benzene. Evaporation of the extract produced an oil which crystallized on mixing with a small amount of ether; 15·3 g (75%), m.p. 108–111°C. The pure product melts at 111–113°C

(cyclohexane). NMR spectrum: δ 6·90—8·40 (m, 7 H, protons of naphthyl), 3·75 [m, 4 H, $CH_2N(CO—)CH_2$], 3·04 (t, 4 H, remaining 2 NCH_2 of piperazine), 2·15 (s, 3 H, CH_3).

1-Methyl-4-(1-naphthyl)piperazine (*Id*) (Method *C*)

A solution of 27·9 g *Ib* in 30 ml tetrahydrofuran and 200 ml ether was added dropwise to a solution of 11·2 g $LiAlH_4$ in 100 ml ether. The mixture was refluxed under stirring for 4 h and, after cooling, decomposed with 12 ml water, 12 ml 15% NaOH and 33 ml water. The precipitate formed was filtered. Evaporation of the extract yielded a crude oily product (21·7 g, 98%). It distils without decomposition at 180—182°C/14 Torr and the distillate crystallizes on cooling; m.p. 54—55°C (hexane).

1-(2-Methoxycarbonylethyl)-4-(1-naphthyl)piperazine (*If*)

A solution of 14·6 g *Ia* in 100 ml tertiary butyl alcohol was treated with 2·7 ml of 40% solution of trimethylbenzylammonium hydroxide in methanol and 17·7 g methyl acrylate, the mixture was heated under stirring for 4 h to 50—60°C and the volatile fractions were evaporated at reduced pressure. The residue was dissolved in benzene, the solution was washed several times with water and evaporated. The crude base obtained (17·9 g, 87%) crystallized from hexane, m.p. 65—66°C. IR spectrum: 782 and 804 (1-naphthyl Ar—H), 1139 (COOR), 1573, 1590 (Ar), 1723 (ester CO), 2815 cm^{-1} (NCH_2). NMR spectrum: δ 7·00—8·50 (m, 7 H, protons of naphthyl), 3·70 (s, 3 H, $COOCH_3$), 3·14 (t, $J = 6·0$ Hz, 4 H, $CH_2N(Ar)CH_2$), c. 3·70 (m, 8 H, remaining 4 CH_2). Neutralization with maleic acid in ethanol produces the maleate.

1-(2-Cyanoethyl)-4-(2-naphthyl)piperazine (*IIg*)

A 40% methanolic solution of trimethylbenzylammonium hydroxide (2 ml) and 8·0 g acrylonitrile were added to a solution of 10·6 g *IIa* in 130 ml tertiary butyl alcohol. The mixture was heated under stirring for 5 h to 55—65°C, the tertiary butyl alcohol was evaporated at that temperature at a reduced pressure and the residue crystallized after dissolving in ethanol; 8·7 g (66%) base, melting at 74—82°C; after another recrystallization from ethanol, m.p. 83—85°C.

1-(3-Hydroxypropyl)-4-(1-naphthyl)piperazine (*Ih*)

A solution of 2·6 g *If* in 50 ml ether was added dropwise under stirring to a solution of 1·0 g $LiAlH_4$ in 30 ml ether. The mixture was refluxed for 4 h, decomposed after cooling with 1 ml water, 1 ml 15% NaOH and 3 ml water. The precipitate was filtered, washed with ether, boiled with 100 ml benzene, filtered and the benzene filtrate was combined with the original ether solution. Evaporation yielded 1·1 g (48%) crude base which crystallized from ethanol; m.p. 194 to 195°C. IR spectrum: 774, 783 (1-naphthyl Ar—H), 1063 (CH_2OH), 1505, 1578, 1595 (Ar), 2818 (NCH_2), 3165 cm^{-1} (OH).

1-(3-Aminopropyl)-4-(2-naphthyl)piperazine (*IIi*)

A solution of 23·7 g *IIg* in 400 ml ether and 50 ml tetrahydrofuran was added dropwise under stirring to 10·2 g $LiAlH_4$ in 100 ml ether. The mixture was refluxed for 6 h, cooled, decomposed with 10 ml water, 10 ml 15% NaOH and 30 ml water, stirred for 30 min, left to stand for 1 h of room temperature, filtered, the precipitate was boiled with 250 ml ethyl acetate and filtered. Evaporation of both filtrates yielded 19·6 g (82%) crude base.

1-(4-Methoxyphenacyl)-4-(2-naphthyl)piperazine (*IIj*) (Method *D*)

A mixture of 8·5 g *IIa*, 6·1 g K_2CO_3, 50 ml dimethylformamide and 10·8 g 4-methoxyphenacyl bromide[18] was heated under stirring for 2 h at 70°C. Then it was cooled, the precipitate was filtered and separated between water and chloroform. The dimethylformamide filtrate was partly evaporated *in vacuo*, the residue was decomposed with water and extracted with chloroform. The combined chloroform extracts were washed with water, dried and evaporated. The crude base obtained crystallizes from benzene and melts at 152—156°C (4·60 g, 32%). UV spectrum: λ_{max} 247·5 nm (log ε 4·64), 280 nm (4·42), 335·5 nm (3·39). IR spectrum: 748, 805, 838, 870 (4 and 2 adjacent and solitary Ar—H), 1220 (Ar—O—CH_3), 1550, 1600, 1630 (Ar), 1688 cm^{-1} (Ar—CO). NMR spectrum: δ 8·04 (d, J = 9·0 Hz, 2 H, aromatic protons in the vicinity of the keto group), 7·00—7·85 (m, 7 H, aromatic protons of naphthyl), 6·90 (d, J = 9·0 Hz, 2 H, aromatic protons in the vicinity of methoxyl), 3·78 (s, 5 H, OCH_3 and NCH_2CO), 3·34 (t, 4 H, CH_2N.(Ar)CH_2), 3·74 (t, 4 H, remaining NCH_2 of piperazine).

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