POTENTIAL ANTITUSSIVES: SYNTHESIS AND PHARMACOLOGY OF A SERIES OF 1-[2-AMINO-2-(4-FLOROPHENYL)ETHYL]-4-(2-BENZOYLPROPYL)PIPERAZINES*

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Compound *V*, obtained by a reaction of 2-chloro-4'-fluoroacetophenone with 1-(ethoxycarbonyl)-piperazine, was reduced with sodium borohydride to the amino alcohol *VIf*. The hydrochloride of *VIf* was treated with thionyl chloride to give the hydrochloride of 1-[2-chloro-2-(4-fluorophenyl)ethyl]-4-(ethoxycarbonyl)piperazine (*VIg*). The crude *VIg* was subjected to substitution reactions with diethylamine, pyrrolidine, piperidine, morpholine and 1-methylpiperazine in benzene at 60°C. The obtained aminocarbamates *VIa*–*VIe* were hydrolyzed with concentrated ethanolic potassium hydroxide and gave the amines *VIIa*–*VIIe*. Mannich reactions of the hydrochlorides of these compounds with paraformaldehyde and propiophenone (and 4-hydroxypropiophenone, respectively) resulted in the title compounds *IIIa*–*IIIe*, *IVa,b* and *IVd,e*. Only substances *IIIa* and *IIId* were found to have an antitussic activity in rats and guinea-pigs comparable to that of eprazinone (*I*). In higher doses they brought about central depression, ataxia and ptosis in mice and some of them adrenolytic and hypotensive effects in rats.

In connection with our studies of the neurotropic piperazine derivatives we were attracted by the structure of compound *I* which is known under the generic name eprazinone (ref.[1]). It was characterized[2] as an antitussive agent with a central mechanism of action which has further some analgesic, antihistamine, antispasmodic and central depressant activity. An electroencephallographic investigation[3] confirmed the character of the central neurotropic effects. The fate of the substance in the animal organism was described in two pharmacokinetic[4,5] and three metabolic studies[6–8]. A feasible synthetic method was described in patents[9,10] and the substance found practical use (Eftapan^R, Mucitux^R) as an antitussive and bronchosecretolytic drug[8,11]. In an attempt at finding new substances of similar activity we modified the structure of eprazinone (*I*) by substitution of the ethoxy group in position 2 of phenethyl by a tertiary amino group, further by substitution with fluorine in the *para*-position of the phenethyl group, and finally by substitution with the hydroxy group in the *para*-position of the propiophenone moiety. In this way we designed the structures of the title compounds *IIIa*–*IIIe* and *IVa*–*IVe*.

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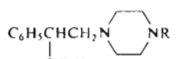
For comparison we prepared a sample of eprazinone (*I*) using the described procedure[9,10]. In the final stage of the synthesis, 2-ethoxy-2-phenylethyl bromide[12,13] was subjected to a substitution reaction with piperazine in boiling ethanol and in a yield of 45% the oily 1-(2-ethoxy-2-phenylethyl)piperazine (*II*) (ref.[9,10]) was obtained which appeared almost homogeneous (gas chromatography) and which was characterized as a crystalline dipicrate. The Mannich reaction of the dihydrochloride of *II* with paraformaldehyde and propiophenone in boiling ethanol in the presence of a small quantity of hydrochloric acid (*cf*[9,10]) afforded in a yield of 50% a dihydrochloride which was crystallized from aqueous methanol and identified as a hemihydrate. From this substance, which is apparently a mixture of two racemates, the oily base was released, This base was neutralized with hydrogen chloride in ether and crystallization from aqueous ethanol led to an unsolvated dihydrochloride. The melting point values of both of our dihydrochlorides are substantially higher than the value reported in the literature[9,10]. The mentioned patents[9,10] did not solve the problem of stereoisomerism of compound *I* and the question of the homogeneity of the commercial product *I* remains unanswered..

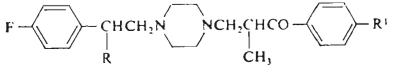


I, R = $CH_2CHCOC_6H_5$ (with CH_3 on the CH)

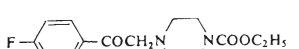
II, R = H

The synthesis of substances *III* and *IV* started from the known 2-chloro-4'-fluoroacetophenone[14–16] which was transformed by a substitution reaction with an excess of 1-(ethoxycarbonyl)piperazine in chloroform to 1-(ethoxycarbonyl)-4-(4-fluorol phenacyl)piperazine (*V*). Reduction with sodium borohydride in aqueous ethanos gave the alcohol *VIf*, a sample of which was hydrolyzed with potassium hydroxide to the amino aclohol *VIIf*. Structures of compounds *V*, *VIf* and *VIIf* were corroborated by spectra. A suspension of the hydrochloride of compound *VIf* in benzene was treated with thionyl chloride at 50°C and gave the hydrochloride of the chloro derivative *VIg*. A decomposition of this substance with aqueous ammonia in the cold and extraction with ether gave the oily base *VIg* which was used in crude state for the substitution reactions with diethylamine, pyrrolidine, piperidine, morpholine and 1-methylpiperazine. The reactions were carried out by using an excess of the amines in benzene at 60°C (method *A*); oily bases *VIa*–*VIe* were obtained which were characterized in the form of salts. The carbamates *VIa*–*VIe* were hydrolyzed with concentrated solution of potassium hydroxide in ethanol (method *B*) to the monosubstituted piperazines *VIIa*–*VIIe*. The final step was the Mannich reaction

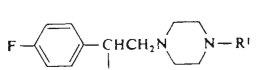
in which the ethanolic solutions of the hydrochlorides of compounds *VIIa – VIIe* were refluxed with paraformaldehyde and propiophenone (method *C*); there resulted the title compounds *IIIa – IIIe*. In cases of the piperazines *VIIab* and *VIIde*, 4-hydroxypropiophenone was also used as the ketone component in the Mannich reaction which led to products *IVa,b* and *IVd,e*. The obtained bases were altogether oily which indicates their inhomogeneity with regard to the fact that their molecules contain two centres of chirality and the reactions result thus in mixtures of two racemates. In some cases (modification C-1) crystalline hydrochlorides were direcly obtained and purified by crystallization until the constant melting points were attained. In other cases the resulting hydrochlorides did not crystallize, it was necessary to release the bases and convert them to the better crystallizing maleates (modificationC-2). Somewhat atypical was the case of compound *IIIa*, the base of which had to be purified by chromatography and gave only then a crystalline oxalate. The bases, which were released from the salts, were characterized by spectra. The salts, which were mostly solvated with water, behaved indeed as chemical individuals but the question of their homogeneity must be considered open; the separation to both possible racemates did succeed in no case. Compounds prepared by methods *A – C* (*III*, *IV*, *VI*, *VII*) are assembled in Table I with the usual experimental data and the Experimental contains only the descriptions of examples of these preparations.



III, R^1 = H
IV, R^1 = OH



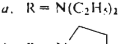
V

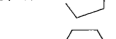


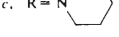
VI, R^1 = $COOC_2H_5$
VII, R^1 = H

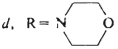
In formulae *III*, *IV*, *VI*, *VII*:

a, R = $N(C_2H_5)_2$

b, R = 

c, R = 

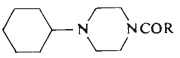
d, R = 

e, R = 

f, R = OH
g, R = Cl

In a different connection we attempted at preparing 1-cyclohexyl-4-(ethoxycarbonyl)piperazine (*VIII*) by a reaction of ethyl bis(2-chloroethyl)carbamate[17] with cyclohexylamine in boiling 1-butanol in the presence of sodium iodide and potas-

sium carbonate. The conditions used were evidently too severe which led to a mixture from which in addition to the desired compound *VIII* N,N'-dicyclohexylurea[18] and a further substituted urea *IX* were isolated. The formation of both of these products has to be explained by aminolysis of the primary product *VIII* in the first line in the ester fragment of the carbamate residue and then even in the amide fragment.



VIII, R = OC_2H_5

IX, R = NH

The compounds *IIIa–IIIe*, *IVa,b*, *IVd,e* and *IX* were pharmacologically evaluated in the form of salts, described in the Experimental and in the Table I, by methods of the general pharmacological screening (Dr M. Bartošová, affiliated unit of this institute at Pardubice–Rosice). Eprazinone dihydrochloride (*I*·2 HCl), which was used as a standard, showed on oral administration an acute toxicity in mice expressed by the dose LD_{50} = 450 mg/kg. Subtoxic doses brought about inhibition of activity and reactivity, ataxia, convulsions and mydriasis. The antitussive activity was determined in rats and guinea-pigs on oral administration with eliciting the cough with an aerosol of citric acid solution. Codeine phosphate and „l-propoxyphene napsylate" were tested for comparison. In rats the mean antitussive effective dose ED_{50} was 122·5 mg/kg (for codeine phosphate 11 mg/kg and for „l-propoxyphene napsylate" 310 mg/kg). In guinea-pigs the mean effective antitussive dose of eprazinone was 72 mg/kg (for codeine phosphate 16 mg/kg and for „l-propoxyphene napsylate" *c.* 75 mg/kg).

For the new compounds there are given in the first line the way of administration in the screening, the approximative value of LD_{50} in mice and finally the dose D, in which the compound was administered in most of the tests: *IIIa*, *p.o.*, 1 500, 300; *IIIb*, *i.v.*, 50, 10; *IIIc*, *i.v.*, 62·5, 12; *IIId*, *i.v.*, 62·5, 12; *p.o.*, 500, 100; *IIIe*, *i.v.*, 75, 15; *IVa*, *p.o.*, 1 500, 300; *IVb*, *i.v.* 75, 15; *IVd*, *i.v.* 125, 25; *IVe*, *p.o.*, 2 000, 300; *IX*, *i.v.*, 30, 6. With all of these compounds, doses higher than D bring about after a transient phase of mild excitation a central depression, characterized by a decrease of motoric activity, ataxia and in some cases by ptosis. These symptoms were followed by tremor, convulsions and the Straub phenomenon.

Results of evaluation of the antitussive activity (oral administration): *IIIa*, ED_{50} = = 100 mg/kg (rat); *IIIb*, a dose of 50 mg/kg reduced the frequency of the fits of cough by 21 % (rat); *IIIc*, a dose of 60 mg/kg (rat) was ineffective; *IIId*, a dose of 100 mg/kg decreased the frequency of the fits in the rat by 41%, and in the guinea-pig by 63%

TABLE I

Piperazine derivatives of the series *VI*, *VII*, *III* and *IV* and their salts

Compound	Method (yield, %)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
				% C	% H	% F	% N
VIa-2 M[a]	*A* (85)	84—85 (ethanol–ether)	$C_{27}H_{38}FN_3O_{10}$ (583·6)	55·56 55·28	6·56 6·76	3·26 3·12	7·20 7·42
VIb-2 M[a]	*A* (95)	127—128 (ethanol–ether)	$C_{27}H_{36}FN_3O_{10}$ (581·6)	55·76 56·43	6·24 6·24	3·27 3·27	7·22 7·19
VIc-2 M[a]	*A* (87)	145—146 (ethanol–ether)	$C_{28}H_{38}FN_3O_{10}$ (565·6)	56·46 56·20	6·43 6·17	3·19 3·24	7·06 6·71
VId-2 M[a,b]	*A*[c] (93)	114—116 (ethanol–ether)	$C_{27}H_{36}FN_3O_{11}$ + 0·5 H_2O (606·6)	53·46 53·43	6·15 6·38	3·13 2·85	6·93 6·68
VIe-3 HCl[d]	*A* (89)	177—178 (aqueous ethanol-ether)	$C_{20}H_{34}Cl_3FN_4O_2$[e] + H_2O (505·9)	47·49 47·36	7·17 6·49	3·75 3·46	11·07 10·69
VIIa	*B*[c] (100)	158°C/0·13 kPa[f]	$C_{10}H_{26}FN_3$ (279·4)	68·78 68·42	9·38 9·28	6·80 6·66	15·04 14·58
VIIa-3 M[g]		156—157 (ethanol)	$C_{28}H_{38}FN_3O_{12}$ (627·6)	53·58 53·10	6·10 5·93	3·03 3·23	6·70 6·35
VIIa-2 M[a]	—	153—154 (ethanol–ether)	$C_{24}H_{34}FN_3O_8$ (511·5)	56·35 56·56	6·70 6·64	— —	8·22 8·22
VIIb-2 M[a]	*B* (100)	152—153 (ethanol–ether)	$C_{24}H_{32}FN_3O_8$ (509·5)	56·57 56·77	6·33 6·30	3·73 3·49	8·25 8·11
VIIc-3 HCl[b]	*B* (97)	174—175 (ethanol)	$C_{17}H_{29}Cl_3FN_3$[h] + 0·5 H_2O (409·8)	49·82 49·56	7·36 6·99	4·63 4·82	10·25 10·14
VIIc-3 M[g]	—	165—166 (ethanol)	$C_{29}H_{38}FN_3O_{12}$ (639·6)	54·45 54·14	5·99 6·00	3·00 3·39	6·54 5·92
VIId-2 M[a]	*B* (88)	155—156 (ethanol–ether)	$C_{24}H_{32}FN_3O_9$ (525·5)	54·85 54·70	6·14 6·32	3·62 3·45	7·99 7·88
VIIe-3 M[g]	*B* (83)	132—133 (ethanol)	$C_{29}H_{39}FN_4O_{12}$ (654·6)	53·20 52·83	6·00 5·96	2·90 2·63	8·56 8·52
IIIa-3 OX[b,i]	*C*[c] (43)	108—110 (ethanol–ether)	$C_{32}H_{42}FN_3O_{13}$ + 0·5 H_2O (704·7)	54·54 54·28	6·15 6·15	2·70 2·53	5·96 5·76
IIIb-3 HCl[d]	C—1[c] (97)	175—176 (ethanol–ether)	$C_{26}H_{37}Cl_3FN_3O$[j] + H_2O (551·0)	56·67 56·73	7·13 6·95	3·44 3·74	7·64 8·20

TABLE I
(*Continued*)

Compound	Method (yield %)	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
				% C	% H	% F	% N
IIIc-2 M[a,d]	*C*—2[c] (81)	146—147 (ethanol–ether)	$C_{35}H_{44}FN_3O_9$ + H_2O (687·7)	61·11 60·89	6·74 6·53	2·76 2·48	6·12 6·28
IIId-2 M[a]	*C*—2 (68)	156—157[k] (aqueous ethanol)	$C_{34}H_{42}FN_3O_{10}$ (671·7)	60·79 60·54	6·30 6·17	2·83 2·59	6·26 6·17
IIIe-3 M[b,g]	*C*—2 (62)	154—155[l] (aqueous ethanol)	$C_{39}H_{49}FN_4O_{13}$ + 0·5 H_2O (809·8)	57·84 57·74	6·22 6·08	2·35 2·21	6·94 7·22
IVa-3 OX[i]	*C*—2 (75)	174—176[m] (ethanol–ether)	$C_{32}H_{42}FN_3O_{14}$ (711·7)	54·00 53·64	5·96 6·30	2·67 2·68	5·90 6·01
IVb-3 HCl[d]	*C*—1 (80)	173—174[n] (ethanol–ether)	$C_{26}H_{37}Cl_3FN_3O_2$[o] + H_2O (567·0)	55·07 55·32	6·92 6·66	3·35 3·48	7·41 7·51
IVd-2 M[a,d]	*C*—2 (85)	105—107[p] (aqueous ethanol–ether)	$C_{34}H_{42}FN_3O_{11}$ + H_2O (705·7)	57·86 57·45	6·28 6·30	2·69 2·63	5·97 5·64
IVe-3 M[d,g]	*C*—2 (84)	122—124[q] (aqueous ethanol–ether)	$C_{39}H_{49}FN_4O_{14}$ + H_2O (834·8)	56·11 56·11	6·15 6·02	2·28 2·17	6·74 7·25

[a] Dimaleate. [b] Hemihydrate. [c] See Experimental. [d] Monohydrate. [e] Calculated: 21·02% Cl; found: 20·99% Cl. [f] Boiling point. [g] Trimaletate. [h] Calculated: 25·95% Cl; found: 25·07% Cl. [i] Trioxalate. [j] Calculated: 19·30% Cl; found: 19·78% Cl. [k] The base released from the salt was used for recording the ^{1}H NMR spectrum: δ 7·90 (m, 2 H, 2,6-H_2 of benzoyl), 7·40 (m, 3 H, 3,4,5-H_3 of benzoyl), 6·80—7·30 (m, 4 H, ArH of 4-fluorophenyl), 2·00—3·80 (m, 22 H, 8 CH_2N, 2 CH_2O and 2 CH), 1·15 (d, 3 H, CH_3). [l] The oily base was released from the salt. IR spectrum: 709, 839 (5 and 2 adjacent Ar—H), 1 505, 1 510, 1 600, 3 022 (Ar), 1 680 (ArCO), 2 775 cm^{-1} (N—CH_3, N—CH_2). ^{1}H NMR spectrum: δ 7·94 (m, 2 H, 2,6-H_2 of benzoyl), 6·80—7·55 (m, 7 H, remaining ArH), 3·50 (m, 2 H, Ar—CH—N and CHCO), 2·20 (s, 3 H, N—CH_3), 1·16 (d, 3 H, C—CH_3). — [m] The oily base was released from the salt. UV spectrum: λ_{max} 275 nm (log ε 4·07). IR spectrum (film): 844 (2 adjacent Ar—H), 1 160, 1 220, 3 240 (ArOH), 1 503, 1 510, 1 580, 1 600 (Ar), 1 665 cm^{-1} (ArCO...HOAr). ^{1}H NMR spectrum: δ 7·80 (d, J = 8·5 Hz, 2 H, 2,6-H_2 of benzoyl), 6·50—7·30 (m, 4 H, ArH of 4-fluorophenyl), 6·65 (d, J = 8·5 Hz, 2 H, 3,5-H_2 of benzoyl), 6·10 (bs, 1 H, OH), 2·00—4·00 (m, 18 H, 8 CH_2N and 2 CH), 1·00 (m, 9 H, 3 CH_3). [n] The oily base was released from the salt. UV spectrum: λ_{max} 276 nm (log ε 4·12). IR spectrum ($CHCl_3$): 840 (2 adjacent Ar—H), 1 169, 1 240, 1 290 (ArCH), 1 510, 1 583, 1 602 (Ar), 1 668 (ArCO), infl. 2 500 (NH^+), infl. 3 150 cm^{-1} (OH...C=C). ^{1}H NMR spectrum: δ 7·98 (bs, 1 H OH), 7·68 (d, J = 8·5 Hz, 2 H, 2,6-H_2 of benzoyl), 6·70—7·20 (m, 4 H, ArH of 4-fluorophenyl), 6·55 (d, J = 8·5 Hz, 2 H, 3,5-H_2 of benzoyl), 3·20—3·70 (m, 2 H, Ar—CH—N and CHCO),

(in comparison with the control groups); *IIIe*, a dose of 75 mg/kg (rat) was without effect; *IVa*, a dose of 300 mg/kg inhibited the cough in guinea-pigs by 42%; *IVb*, a dose of 75 mg/kg had only a weak effect in rats; *IVd*, a dose of 125 mg/kg was ineffective in rats; *IVe*, in the test on guinea-pigs a dose of 300 mg/kg inhibited the cough by 86%, a dose of 100 mg/kg only by 22%. In general, the compounds have antitussive activity which, however, only with compounds *IIIa* and *IIId* equals by the intensity the activity of eprazinone (*I*).

Other pharmacological effects: *IIIb*, adrenolytic effect in rats in a dose of 1 mg/kg *i.v.*; *IIIc*, brief and deep drops of blood pressure in normotensive rats after the dose D; *IIIe*, a mild drop of blood pressure in normotensive rats in 24 h after the oral administration of a dose of 75 mg/kg; *IVa*, mydriasis in mice after doses higher than D; *IVb*, a brief and deep drop of blood pressure in rats after the dose D.

In the tests of antimicrobial activity *in vitro* (Dr J. Turinová, bacteriological department of this institute) some compounds showed inhibitory effects towards *Trichophyton mentagrophytes* (minimum inhibitory concentrations in μg/ml): *I* 25, *IIIa* 12·5, *IIIb* 25, *IIId* 25, *IIIe* 25, *IVa* 50, *IVb* 50, *IVe* 50, *IX* 50. Compound *IIIb* showed an effect in a concentration of 100 μg/ml towards *Streptococcus* β-*haemolyticus*, and compounds *IIIe* and *IVb* in concentrations of 100 μg/ml towards *Mycobacterium tuberculosis* H37Rr. All compounds were ineffective until the concentration of 100 μg/ml towards *Streptococcus faecalis*, *Staphylococcus pyogenes aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus vulgaris*, *Saccharomyces pasterianus*, *Candida albicans* and *Aspergillus niger*.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol) were recorded with a Univam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, ^{1}H NMR spectra (in C^2HCl_3) and the ^{19}F NMR spectra (in $CHCl_3$, $\delta_{CFCl_3} = 0$) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectrum was recorded with the MCH-1320 spectrometer. The homo-

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2·00–3·00 (m, 16 H, 8 CH_2N), 1·60 (bm, 4 H, 3,4-CH_2CH_2 of pyrrolidine), 1·10 (d, J = 7·0 Hz, 3 H, CH_3). ^{19}F NMR spectrum: δ −116·85 (m). [o] Calculated: 18·76% Cl; found: 19·18% Cl. [p] The oily base was released from the salt. UV spectrum: λ_{max} 277 nm (lcg ε 4·10). IR spectrum: 842 (2 adjacent Ar—H), 1 235 (ArOH), 1 503, 1 510, 1 580, 1 600, 3 000, 3 033, 3 058 (Ar), 1 665 (ArCO...HOAr), infl. 2 500 (NH^+), infl. 3 240 cm^{-1} (ArOH). ^{1}H NMR spectrum: δ 7·78 (d, = 8·5 Hz, 2 H, 2,6-H_2 of benzoyl), 6·70–7·10 (m, 4 H, ArH of 4-fluorophenyl), 6·54 (d, J = 8·5 Hz, 2 H, 3,5-H_2 of benzoyl), 3·50 (bm, 6 H, CH_2OCH_2 and 2 CH), 2·00–3·20 (m, 16 H, 8CH_2N), 1·08 (d, J = 7·0 Hz, 3 H, CH_3). ^{19}F NMR spectrum: δ −116·05 (m). [q] The oily base was released from the salt. IR spectrum: 840 (2 adjacent Ar—H), 1 165, 1 222, 1 290, infl. 3 240 (ArOH), 1 503, 1 510, 1 580, 1 600, 3 000, 3 035, 3 060 (Ar), 1 666 (ArCO), 2 540, 2 665, 2 780 cm^{-1} (NH^+). ^{1}H NMR spectrum: δ 7·75 (d, J = 8·5 Hz, 2 H, 2,6-H_2 of benzoyl), 7·00, (m, 4 H, ArH of 4-fluorophenyl), 6·61 (d, J = 8·5 Hz, 2 H, 3,5-H_2 of benzoyl), 2·00–4·00 (m, 22 H, 10 CH_2N and 2 CH), 2·20 (s, 3 H, NCH_3), 1·13 (d, J = 7·0 Hz, 3 H, C—CH_3).

geneity of the compounds and composition of the mixtures were checked by thin-layer chromatography on silica gel.

1-(2-Ethoxy-2-phenylethyl)piperazine (*II*)

A mixture of 68·6 g 2-ethoxy-2-phenylethyl bromide[12,13], 65 g anhydrous piperazine and 180 ml ethanol was stirred and refluxed for 8 h. Processing (ref.[9,10]) gave 31·9 g (45%) crude product which was distilled; 29·9 g (43%), b.p. 164–172°C/2·4 kPa, n_D^{24} 1·525. Gas chromatography indicated the purity of 99·5%. Lit.[9,10], b.p. 174°C/1·9 kPa, n_D^{20} 1·526.

Dipicrate, m.p. 234·5–236·5°C with decomposition (aqueous acetone). For $C_{26}H_{28}N_8O_{15}$ (692·6) calculated: 45·09% C, 4·08% H, 16·18% N; found: 45·15% C, 4·06% H, 16·52% N.

1-(2-Ethoxy-2-phenylethyl)-4-(2-benzoylpropyl)piperazine (*I*)

The salt *II*.2 HCl (7·3 g, a hygroscopic solid melting at 113–117°C which was obtained by neutralization of *II* with HCl in ethanol–ether), 4·0 g propiophenone, 0·95 g paraformaldehyde and 0·05 ml hydrochloric acid was stirred and refluxed for 5 h (ref.[9,10]). Processing gave 6·3 g (58%) crude dihydrochloride melting at 180–205°C with decomposition. Crystallization from aqueous methanol afforded the dihydrochloride hemihydrate, m.p. 171–203°C with decomposition. For $C_{24}H_{34}Cl_2N_2O_2 + 0{\cdot}5\ H_2O$ (462·5) calculated: 62·33% C, 7·63% H, 15·33% Cl, 6·06% N; found: 62·04% C, 7·51% H, 15·52% Cl, 5·84% N.

The salt was decomposed with 10% NaOH and the base was isolated by extraction with ether; oil. ^{1}H NMR spectrum: δ 7·98 (m, 2 H, 2,6-H_2 of benzoyl), 7·50 (m, 3 H, 3,4,5-H_3 of benzoyl), 7·22 (s, 5 H, C_6H_5 of phenethyl), 4·42 (dd, 1 H, Ar—CH—O), 3·70 (m, 1 H, CHCO), 3·30 (q, J = 7·0 Hz, 2 H, OCH_2), 2·20–3·00 (m, 4 H, 2 CH_2N outside of piperazine), 2·48 (s, 8 H, 4 CH_2N of piperazine), 1·21 (d, J = 7·0 Hz, CH_3 in 2-benzoylpropyl), 1·15 (t, J = 7·0 Hz, 3 H, CH_3 in ethoxyl).

Neutralization of this base with HCl in a mixture of ethanol and ether and crystallization from aqueous ethanol gave a sharply melting unsolvated dihydrochloride, m.p. 203–206°C with decomposition. For $C_{24}H_{34}Cl_2N_2O_2$ (453·4) calculated: 63·57% C, 7·56% H, 15·64% Cl, 6·18% N; found: 63·54% C, 7·79% H, 15·48% Cl, 6·20% N. Lit.[9,10], m.p. 160°C. The papers[4–8] give the melting point of 201°C without describing the procedure of preparation of the compound used.

1-Ethoxycarbonyl-4-(4-fluorophenacyl)piperazine (*V*)

A solution of 32 g 1-ethoxycarbonylpiperazine in 50 ml chloroform was treated with a solution of 17·3 g 2-chloro-4′-fluoroacetophenone[14–16] in 70 ml chloroform, the mixture was stirred for 1·5 h at room temperature and refluxed for 1 h. Chloroform was evaporated under reduced pressure, the residue was treated with 50 ml dilute NH_4OH and extracted with benzene. The extract was washed with water and the base was transferred into the aqueous layer by shaking with a mixture of 20 ml hydrochloric acid and 180 ml water. The aqueous solution was made alkaline with NH_4OH, the base was extracted with benzene, the extract was dried with Na_2SO_4 and evaporated; 27·5 g (93%) crude base which slowly crystallized by standing; b.p. 200°C/0·4 kPa, m.p. 49–50°C (benzene–cyclohexane). UV spectrum: λ_{max} 244 nm (log ε 3·92). IR spectrum (film): 770, 840 (2 adjacent Ar—H), 1 130, 1240, 1 290, 1 695 (NCOOR, ArCOR), 3 053 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 8·03 (dd, J_{H-H} = 8·5 Hz; J_{H-F} = 5·0 Hz, 2 H, 2,6-H_2 of benzoyl), 7·12 (t, $J_{H-H} = J_{H-F}$ = 8·5 Hz, 2 H, 3,5-H_2 of benzoyl), 4·14 (q, J = 7·0 Hz, 2 H, $COOCH_2$), 3·89 (s, 2 H, $COCH_2N$), 3·53 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·53 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 1·22 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{15}H_{19}FN_2O_3$ (294·3) calculated: 61·21% C, 6·51% H, 6·45% F, 9·52% N; found: 61·14% C, 6·44% H, 6·20% F, 9·50% N.

2-(4-Ethoxycarbonylpiperazino)-1-(4-fluorophenyl)ethanol (*VIf*)

A stirred solution of 29·4 g *V* in 150 ml ethanol was treated dropwise at 30–40°C with a solution of 4·0 g $NaBH_4$ in 21 ml water containing 1 drop 20% NaOH. The mixture was stirred for 1 h without heating and then for 1 h at 50°C. After cooling ethanol was evaporated under reduced pressure, the residue was diluted with 50 ml water and extracted with chloroform. The extract was washed with water, dried with Na_2SO_2 and evaporated; 27·3 g (92%) crude product which crystallized on standing, m.p. 56–58°C (cyclohexane). IR spectrum (KBr): 770, 840 (2 adjacent Ar—H), 1 085 (CHOH), 1 140, 1 225, 1 695 (NCOOR), 1 490, 1 515, 1 610 (Ar), 3 240 cm^{-1} (OH). ^1H NMR spectrum: δ 7·30 (dd, $J_{H-H} = 8·5$ Hz; $J_{H-F} = 5·0$ Hz, 2 H, 2,6-H_2 of benzoyl) 7·00 (t, $J_{H-H} = J_{H-F} = 8·5$ Hz, 2 H, 3,5-H_2 of benzoyl), 4·70 (bt, 1 H, Ar—CH—O), 4·12 (q, $J = 7·0$ Hz, 2 H, OCH_2), 3·71 (bs, 1 H, OH), 3·50 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·20 to 2·80 (m, 6 H, remaining 3 CH_2N), 1·22 (t, $J = 7·0$ Hz, 3 H, CH_3). ^{19}F NMR spectrum: δ −115·8 (m). For $C_{15}H_{21}FN_2O_3$ (296·4) calculated: 60·80% C, 7·14% H, 6·41% F, 9·45% N; found: 60·71 C, 7·01% H, 5·93% F, 9·60% N.

Hydrochloride, m.p. 177–178°C (ethanol–ether). For $C_{15}H_{22}ClFN_2O_3$ (332·8) calculated: 54·13% C, 6·67% H, 10·65% Cl, 5·71% F, 8·42% N; found: 53·82% C, 6·78% H, 10·40% Cl, 5·85% F, 8·16% N.

Hydrogen oxalate, m.p. 179–180°C (ethanol–ether). For $C_{17}H_{23}FN_2O_7$ (386·4) calculated: 52·84% C, 6·00% H, 4·92% F, 7·25% N; found: 52·97% C, 6·06% H, 4·93% F, 7·09% N.

1-(4-Fluorophenyl)-2-piperazinoethanol (*VIIf*)

A solution of 11·0 g *VIf* in 12 ml ethanol was treated with 10·0 g KOH and the mixture was stirred and refluxed for 3 h (bath temperature of 130–140°C). After cooling the mixture was diluted with 20 ml water and the product was extracted with a mixture of benzene and ether. The extract was dried with Na_2SO_4 and evaporated; 8·3 g (95%) oily product which crystallized from a mixture of benzene and hexane, m.p. 94–95°C. IR spectrum: 830 (2 adjacent Ar—H), 1 129 (CHOH), 1 220 (Ar—F), 1 503, 1 510, 1 600 (Ar), 3 050 (OH), 3 265 cm^{-1} (NH). ^1H NMR spectrum: δ 7·30 (dd, $J_{H-H} = 9·0$ Hz; $J_{H-F} = 6·5$ Hz, 2 H, 2,6-H_2 of phenyl), 6·95 (t, $J_{H-H} = J_{H-F} = 9·0$ Hz, 2 H, 3,5-H_2 of phenyl), 4·65 (dd, 1 H, Ar—CH—O), 2·00–3·00 (m, 12 H, 5 NCH_2, NH and OH). For $C_{12}H_{17}FN_2O$ (224·3) calculated: 64·27% C, 7·64% H, 8·47% F, 12·49% N; found: 64·49% C, 7·80% H, 8·01% F, 12·19% N.

Bis(hydrogen maleate) hemihydrate, m.p. 144–145°C (aqueous ethanol). For $C_{20}H_{25}FN_2O_9 + \frac{1}{2} H_2O$ (465·4) calculated: 51·61% C, 5·63% H, 4·08% F, 6·02% N; found: 51·96% C, 5·87% H, 3·71% F, 6·12% N.

1-[2-Chloro-2-(4-fluorophenyl)ethyl]-4-ethoxycarbonylpiperazine (*VIg*)

A suspension of 27·7 g *VIf*.HCl in 65 ml benzene was stirred and treated dropwise at 50°C over 20 min with 8·0 ml $SOCl_2$. The solution obtained was stirred for further 2 h at room temperature and evaporated *in vacuo*. After the addition of 50 ml benzene, the evaporation was repeated. The residue was mixed with 50 ml 1 : 1 mixture of benzene and ether and the crude crystalline hydrochloride of *VIg* was filtered, washed with ether and dried; 28·3 g (97%), m.p. 168–170°C. Analytical sample, m.p. 176–177°C (ethanol–ether). For $C_{15}H_{21}Cl_2FN_2O_2$ (351·3) calculated: 51·28% C, 6·03% H, 20·19% Cl, 5·41% F, 7·98% N; found: 51·10% C, 6·08% H, 20·30% Cl, 5·70% F, 7·82% N.

A suspension of the crude hydrochloride (28·3 g) in 150 ml ice-cold water was treated with 15 ml NH_4OH and the base was extracted with benzene. The extract was dried with Na_2SO_4, filtered with charcoal and evaporated *in vacuo* at 40—45°C. The obtained oily base *VIg* (25·3 g, 100%) was directly used in reactions with amines.

1-Ethoxycarbonyl-4-[2-(4-fluorophenyl)-2-morpholinoethyl]piperazine (*VId*) (Method A)

A mixture of 20 g crude *VIg*, 50 ml benzene and 11 g morpholine was stirred and heated for 4 h to 60°C. After standing overnight the mixture was diluted with 100 ml ether and the precipitated morpholinium chloride (6·8 g, 87%) was filtered off. The filtrate was shaken with a solution of 25 ml hydrochloric acid in 175 ml water, the separated aqueous layer was made alkaline with 30 ml NH_4OH and the base was extracted with a 1 : 2 mixture of ether and benzene. The extract was dried with Na_2SO_4 and evaporated *in vacuo*; 21·4 g (93%) crude oily *VId*.

Bis(hydrogen maleate)hemihydrate, m.p. 114—116°C (ethanol–ether). Mass spectrum, *m/z*: 320 ($M-C_2H_5O$), 194 ($C_{11}H_{13}FNO$), 171 ($C_8H_{15}N_2O_2$). The spectrum did not show the molecular ion but the fragmentation confirms the structure. The analysis is given in Table I.

1-[2-Diethylamino-2-(4-fluorophenyl)ethyl]piperazine (*VIIa*) (Method B)

A mixture of 21·5 g *VIa*, 22 ml ethanol and 20 g KOH was stirred and refluxed for 3 h (bath temperature 140—150°C). After cooling the mixture was diluted with 25 ml water and the base extracted with a mixture of benzene and ether. Drying (Na_2SO_4) and evaporation of the extract gave 17·1 g (100%) crude base. A sample was distilled; b.p. 158°C/0·13 kPa. ^{19}F NMR spectrum: δ −117·32 (m). Neutralization with 3 mol maleic acid in ethanol–ether gave the tris(hydrogen malcate), m.p. 156—157°C (ethanol). Evaporation of the mother liquor and crystallization of the residue from ethanol–ether gave the dimaleate, m.p. 153—154°C. Analytical data are included in Table I.

1-(2-Benzoylpropyl)-4-[2-diethylamino-2-(4-fluorophenyl)ethyl]piperazine (*IIIa*) (Method C)

A mixture of 10·7 g *VIIa*, 3 HCl (obtained from the crude *VIIa* by neutralization with an excess of HCl in ethanol–ether, hygroscopic solid), 4·50 g propiophenone, 1·7 g paraformaldehyde, 25 ml ethanol and 0·1 ml hydrochloric acid was stirred and refluxed for 4 h. After cooling the precipitated hydrochloride of the product was filtered, washed with ether, suspended in water and treated with NH_4OH. The released base was isolated by extraction with benzene; 9·5 g inhomogeneous oil. It was chromatographed on a column of 160 g neutral Al_2O_3 (activity II). Elution with benzene gave in the first fractions (600 ml) 5·0 g (43%) homogeneous oily base which was dissolved in ether and the solution was neutralized with a solution of oxalic acid dihydrate in ethanol giving the tris(hydrogen oxalate) hemihydrate, m.p. 108—110°C (ethanol–ether). For analysis, *cf.* Table I.

1-(2-Benzoylpropyl)-4-[2-(4-fluorophenyl)-2-pyrrolidinoethyl]piperazine (*IIIb*) (Method C-1)

A mixture of 10·8 g *VIIb*.3 HCl (obtained by treatment of the crude *VIIb* with an excess of HCl in ethanol and evaporation of the solution in vacuo, crystalline solid), 5·0 g propiophenone, 1·7 g paraformaldehyde, 22 ml ethanol and 2 drops hydrochloric acid was stirred and refluxed for 4 h. After cooling the solution was diluted with 80 ml ether and the precipitated trihydrochloride of the product was filtered after several hours of standing; 14·5 g (97%), m.p. 173—175°C. The analytical sample which was obtained by crystallization from a mixture of aqueous ethanol

and ether appears to be the monohydrate, m.p. 175–176°C. For the analysis, *cf.* Table I. A sample of the salt was treated with NH_4OH and the base was isolated by extraction with ether and used for recording the spectra. UV spectrum: λ_{max} 241 nm (log ε 4·12). IR spectrum (film): 706, 836 (5 and 2 adjacent Ar—H), 1 502, 1 510, 1 601, 3 008, 3 030, 3 035, 3 060 (Ar), 1 680 (ArCO), inflexes at 2 680 and 2 720 cm^{-1} (N—CH_2). ^1H NMR spectrum: δ 7·80 (m, 2 H, 2,6-H_2 of benzoyl), 7·35 (m, 3 H, 3,4,5-H_3 of benzoyl), 6·70–7·20 (m, 4 H, ArH of 4-fluorophenyl), 3·50 (q, J = 7·0 Hz, 1 H, CHCO), 3·15 (m, 1 H, Ar—CH—N), 2·00–3·20 (m, 16 H, 8 CH_2N), 1·60 (bm, 4 H, 3,4-CH_2CH_2 of pyrrolidine), 1·10 (d, J = 7·0 Hz, 3 H, CH_3). ^{19}F NMR spectrum: δ −116·85 (m).

1-(2-Benzoylpropyl)-4-[2-(4-fluorophenyl)-2-piperidinoethyl]piperazine (*IIIc*) (Method C-2)

A mixture of *VIIc*.3 HCl, 3·22 g propiophenone, 1·2 g paraformaldehyde, 18 ml ethanol and 1 drop hydrochloric acid was stirred and refluxed for 4 h. After standing overnight the solution was evaporated under reduced pressure, the remaining oily hydrochloride was dissolved in 20 ml water, the solution was washed with ether, treated with NH_4OH and the base *IIIc* was isolated by extraction with ether; 7·1 g (81%) oil. It was dissolved in 100 ml ether and the solution was neutralized with a solution of 3·8 g maleic acid in 8 ml ethanol; 10·2 g dimaleate monohydrate, m.p. 146 to 147°C (ethanol–ether). For the analysis, *cf.* Table I. A sample of this salt was decomposed with NH_4OH, the base was isolated by extraction with ether and used for recording the spectra. UV spectrum: λ_{max} 241 nm (log ε 4·09). IR spectrum (film): 709, 840 (5 and 2 adjacent Ar—H), 1 510, 1 603, 3 008, 3 035, 3 060 (Ar), 1 682 (ArCO), 2 680, 2 718 cm^{-1} (N—CH_2). ^1H NMR spectrum: δ 7·85 (m, 2 H, 2,6-H_2 of benzoyl), 7·35 (m, 3 H, 3,4,5-H_3 of benzoyl), 6·70–7·20 (m, 4 H, of 4-fluorophenyl), 3·50 (m, 2 H, Ar—CH—N and CHCO), 2·00–3·00 (m, 16 H, 8 CH_2N), 1·40 (bm, 6 H, 3,4,5-$CH_2CH_2CH_2$ of piperidine), 1·10 (d, J = 7·0 Hz, 3 H, CH_3). ^{19}F NMR spectrum: δ −117·04 (m).

1-Cyclohexyl-4-ethoxycarbonylpiperazine (*VIII*)

A mixture of 157 g ethyl bis(2-chloroethyl)carbamate[17], 89 g cyclohexylamine, 400 ml 1-butanol and 4·0 g NaI was stirred and refluxed for 8 h and then for further 24 h with successive addition of 124 g K_2CO_3. After cooling the inorganic salts were filtered off and washed with benzene and the filtrate was evaporated under reduced pressure. The residue (216 g mixture of crystals and oil) was stirred with 700 ml benzene and the crystals were filtered off. The filtrate was extracted with a solution of 80 ml hydrochloric acid in 220 ml water, the acid aqueous layer was made alkaline with 20% NaOH and the bases (90 g) were isolated by extraction with a mixture of benzene and ether. Distillation of the extract gave 35·2 g (20%) crude *VIII*, b.p. 150–160°C/ /0·5 kPa. The analytical sample was obtained by chromatography of this fraction (17 g) on a column of 550 g neutral Al_2O_3 (activity II) (elution with benzene) and by redistillation of the homogeneous eluate, b.p. 130°C/0·13 kPa. For $C_{13}H_{24}N_2O_2$ (240·3) calculated: 64·99% C, 10·06% H, 11·65% N; found: 65·36% C, 10·32% H, 11·73% N.

The benzene-insoluble solid was stirred with 400 ml water and 10 ml hydrochloric acid. A small part remained undissolved, was filtered off, and crystallized from ethanol; 7·4 g (5%) N,N'-dicyclohexylurea, m.p. 234–235°C. IR spectrum: 1 539, 1 578, 1 629 (NHCONH), 3 300 cm^{-1} (NH). Lit.[18], m.p. 229–230°C.

The aqueous layer was made alkaline with 20% NaOH and the released base was extracted with a mixture of benzene and ether. Processing of the extract gave 28·7 g (14%) 1-cyclohexyl--4-(cyclohexylaminocarbonyl)urea (*IX*) which distilled at 200–202°C/0·4 kPa, and the distillate crystallized from cyclohexane, m.p. 89–90°C. IR spectrum: 1 503, 1 675 (NCONH), 3 260 cm^{-1}

(NH). ^{1}H NMR spectrum: δ 3·70 (bm, 1 H, CON—CH), 2·65—3·50 (m, 8 H, 4 CH_2N of piperazine), 2·45 (bm, 1 H, N—CH), 0·90—2·00 (m, 20 H, 10 CH_2 of cyclohexyls). For $C_{17}H_{31}N_3O$ (293·4) calculated: 69·58% C, 10·65% H, 14·32% N; found: 69·00% C, 10·83% H, 14·17% N.

Hydrochloride, m.p. 216°C (ethanol). For $C_{17}H_{32}ClN_3O$ (329·9) calculated: 61·88% C, 9·78% H, 10·75% Cl, 12·74% N; found: 61·58% C, 9·92% H, 11·08% Cl, 12·81% N.

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