1-[3-(4-FLUOROBENZOYL)PROPYL]-4-ACYLPIPERAZINES AND SOME RELATED COMPOUNDS*

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Whereas the hydrolysis of carbamate *VI* with ethanolic potassium hydroxide proceeds under simultaneous replacement of the fluorine atom with an ethoxy group (giving rise to *XXI*), acid hydrolysis yields 1-[3-(4-fluorobenzoyl)propyl]piperazine (*V*) which was converted to its acyl derivatives *VII*—*XX*. Amides *XXIII*—*XXVI* were prepared from 4-fluorobenzoyl chloride and a mixed anhydride of 3-(4-fluorobenzoyl)propionic acid with the monoethyl ester of carbonic acid. The compounds display a central depressant activity only at high doses; no cataleptic activity was found.

A typical group of neuroleptics and of compounds with central depressant activity are the base-substituted butyrophenones, in particular *p*-fluorobutyrophenones[1]. A particularly potent type is represented by piperidine derivatives *I*, of which "haloperidol" (*I*, R^1 = OH, R^2 = = 4-C_6H_4Cl) is being applied in the therapy of psychic disorders, especially of the schizophrenic type[1]. In a series of similar piperazine derivatives, highest activity being reported for N-arylpiperazines[2] where the basic character of the piperazine $N_{(4)}$ atom is greatly reduced and a situation resembling that with piperidines *I* is obtained. Of these arylpiperazines, "butropipazon" (*II*) and "fluanison"[1] (*III*) are known as medicinal preparations. Recently, a psychotropic and a central depressant activity has been reported for piperazines with other N^4-substituents, in particular aralkyls[3-5], 2-hydroxyethyl[6], alkenyls and alkinyls[7].

It is the objective of the present communication to establish the effect of acyl as N^4-substituent in piperazine derivatives of the above general formula on the character of psychotropic activity. The acyl group reduces the basicity of $N_{(4)}$ even more than aryl does, whereby compounds might be obtained that would resemble derivatives *I* more than arylpiperazines of the type *II*. Several $N_{(4)}$-aroyl derivatives are known from the literature, such as the benzoyl derivative *IV* which is reported to possess a central depressant and a hypnotic activity[8].

The starting compound was 1-[3-(4-fluorobenzoyl)propyl]-4-(ethoxycarbonyl) piperazine[9] (*VI*) which was obtained by reaction of 4-chloro-p-fluorobutyrophenone[10] with 1-(ethoxycarbonyl)piperazine[11]. The product is obtained in the same yield if the reaction is done in ethoxycarbonylpiperazine as medium at 120°C or if equi-

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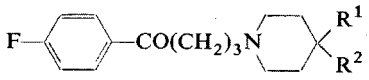
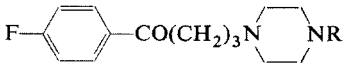


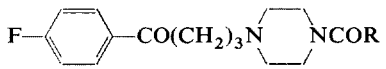
I

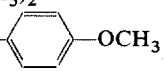
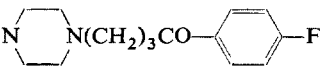


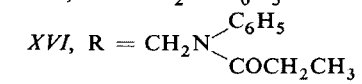
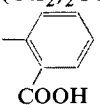
II, R = C_6H_5
III, R = 2-$C_6H_4OCH_3$
IV, R = COC_6H_5
V, R = H

valent amounts of the two components are combined in boiling toluene in the presence of triethylamine. An attempt at hydrolysis of carbamate *VI* with potassium hydroxide in ethanol (ref.[12]) was not successful since, at the same time, the fluorine atom, being activated by the carbonyl group in the *p*-position was replaced with an ethoxy group. The result was a secondary amine *XXI*, the structure of which was supported by analysis and by NMR spectrum of its hydrochloride and the N-benzoyl derivative *XXII*. Hydrolysis of carbamate *VI* to the secondary amine *V* was done by boiling with hydrobromic acid in acetic acid. Compound *V* was established[8] as the product of reaction of 4-chloro-*p*-fluorobutyrophenone with piperazine. It is also reported together with the acetyl derivative *VII* among the metabolites of the sedative preparation "azaperone" (2-pyridyl analogue of *II*) (ref.[13]).

The acetyl derivative *VII* was obtained on a preparative scale through the reaction of amine *V* with acetic anhydride in pyridine. A homologous propionyl derivative *VIII* was obtained by reaction of amine *V* with propionyl chloride in pyridine. In analogy (method *A*), amides *IX* and *X* were prepared, using capryloyl chloride[14] or phenylacetyl chloride[15]. In the preparation of diphenylacetyl derivative *XI*, the reaction of amine *V* with diphenylacetyl chloride[16] in ethanol was found useful. Similarly (method *B*), amide *XII* was prepared by using 4-methoxy phenoxyacetyl chloride[17]. For the preparation of the chloroacetyl derivative *XIII*, the reaction of amine *V* with an equivalent of chloroacetyl chloride in the presence of sodium carbonate in aqueous ethanol was used. When using excess amine *V*, a double substitution in the molecule of chloroacetyl chloride took place and a mixture was formed from which compound *XIV* was isolated on the basis of its low solubility. Its mass spectrum was used for identification. Heating of the chloroacetyl derivative *XIII* with aniline yielded the anilinoacetyl derivative *XV* which was acylated with propionyl chloride to convert it to the diamide *XVI*. Heating of amine *V* with succinic anhydride in ethanol gave rise to amino acid *XVII*. In analogy (method *C*), phthalic anhydride was used to obtain acid *XVIII*. Reaction of amine *V* with potassium cyanate in aqueous acetic acid resulted in substituted urea *XIX*. Homologous



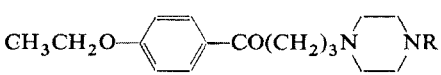
VI, R = OCH_2CH_3
VII, R = CH_3
VIII, R = CH_2CH_3
IX, R = $(CH_2)_6CH_3$
X, R = $CH_2C_6H_5$
XI, R = $CH(C_6H_5)_2$
XII, R = 
XIII, R = CH_2Cl
XIV, R = 

XV, R = $CH_2NHC_6H_5$
XVI, R = 
XVII, R = $(CH_2)_2COOH$
XVIII, R = 
XIX, R = NH_2
XX, R = $N(CH_3)_2$

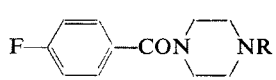
compound *XX* was obtained in a reaction of amine *V* with dimethylcarbamoyl chloride, using method *A* or *B*.

In connection with these preparations, further four amides were synthesized, with 4-fluorobenzoyl group in their molecules. Reaction of 4-fluorobenzoyl chloride[18,19] with 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine in aqueous ethanol (method *D*) yielded amides *XXIII* and *XXIV*. 3-(4-Fluorobenzoyl)propionic acid[20] reacted with ethyl chloroformate and triethylamine in chloroform, giving rise to a mixed anhydride with carbonic monoethyl ester which reacted "*in situ*" with 2-phenylethylamine or homoveratrylamine (method *E*), giving rise to amides *XXV* and *XXVI*, respectively. All the compounds prepared are shown in Table I. The experimental section includes only examples of preparations by general methods and further syntheses carried out by other methods.

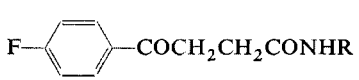
All the compounds prepared were subjected to an orientative biological testing; compounds *VI*–*XII*, *XIX*, *XX*, *XXIII* and *XXIV* were tested in the form of hydro-



XXI, R = H
XXII, R = COC_6H_5



XXIII, R = CH_3
XXIV, R = CH_2CH_2OH



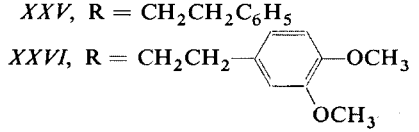
XXV, R = $CH_2CH_2C_6H_5$
XXVI, R = 

TABLE I

1-[3-(4-Fluorobenzoyl)propyl]piperazines and Other Related Compounds

Compound	Method (%yield)	M.p., °C (solvent) or b.p., °C/Torr	Formula (m.w.)	Calculated/Found			
				% C	% H	% F	% Cl
IV	*A*	123—125[a] (benzene–light petroleum)	$C_{21}H_{23}FN_2O_2$ (354·4)	71·16 71·25	6·54 6·53	5·36 5·19	— —
V. H_2O	*a*	69—71 (ether)	$C_{14}H_{21}FN_2O_2$ (268·3)	62·66 62·85	7·89 7·95	7·08 6·68	— —
V. 2 HBr	—	209—211 (95% ethanol)	$C_{14}H_{21}Br_2FN_2O$ (412·2)	40·79 40·83	5·14 5·13	4·61 4·13	38·78[b] 38·88
V-M[c]	—	196 (ethanol)	$C_{18}H_{23}FN_2O_5$ (366·4)	59·00 58·97	6·33 6·39	5·19 5·10	— —
VI	*a*	195/0·1	$C_{17}H_{23}FN_2O_3$ (322·4)	63·33 63·62	7·19 7·28	5·89 6·09	— —
VI. HCl	—	195—197 (ethanol–ether)	$C_{17}H_{24}ClFN_2O_3$ (358·8)	56·90 56·72	6·74 6·62	5·29 5·43	9·88 9·81
VII	[a]	89—91 (benzene–light petroleum)	$C_{16}H_{21}FN_2O_2$ (292·4)	65·73 65·51	7·24 6·86	6·50 6·39	— —
VII. HCl	—	183—185 (ethanol–ether)	$C_{16}H_{22}ClFN_2O_2$ (328·8)	58·44 58·51	6·74 6·50	5·78 5·99	10·79 10·97
VIII	*A* (94)	65—67 (cyclohexane)	$C_{17}H_{23}FN_2O_2$ (306·4)	66·64 66·92	7·57 7·44	6·20 5·99	— —
VIII. HCl-A[d]	—	196—198 (ethanol)	$C_{17}H_{24}ClFN_2O_2$ (342·8)	59·55 59·08	7·06 6·83	5·54 5·20	— —
VIII. HCl-B[d]	—	211—212 (ethanol)	$C_{17}H_{24}ClFN_2O_2$ (342·8)	59·55 58·95	7·06 7·06	5·54 5·24	— —
IX	*A* (92)	67—68 (cyclohexane)	$C_{22}H_{33}FN_2O_2$ (376·5)	70·18 70·69	8·83 8·68	5·05 4·78	— —
IX. HCl	—	207—209 (ethanol)	$C_{22}H_{34}ClFN_2O_2$ (413·0)	63·98 63·99	8·30 8·24	4·60 4·55	8·59 8·63
X	*A*[a]	89—91 (benzene–light petroleum)	$C_{22}H_{25}FN_2O_2$ (368·4)	71·71 72·47	6·84 6·77	5·16 4·88	— —
X. HCl	—	209—211 (90% ethanol)	$C_{22}H_{26}ClFN_2O_2$ (404·9)	65·26 65·18	6·47 6·45	4·69 4·39	8·76 9·03

TABLE I
(*Continued*)

Compound	Method (% yield)	M.p., °C (solvent) or b.p., °C/Torr	Formula (m.w.)	Calculated/Found			
				% C	% H	% F	% Cl
XI	*B*[a]	68—69 (benzene–light petroleum)	$C_{28}H_{29}FN_2O_2$ (444·5)	75·65 75·92	6·58 6·54		— —
XI . HCl	—	206—208 (ethanol)	$C_{28}H_{30}ClFN_2O_2$ (481·0)	69·91 70·11	6·29 6·15	3·95 3·82	7·37 7·33
XII . HCl	*B* (85)	164—166 (ethanol)	$C_{23}H_{28}ClFN_2O_4$ (450·9)	61·26 61·02	6·26 6·32	4·21 4·23	7·86 8·02
XIII . HCl	[a]	190—192 (ethanol)	$C_{16}H_{21}Cl_2FN_2O_2$ (363·3)	52·90 53·15	5·83 6·09	5·23 5·00	— —
XIV . 3 HCl[e]	[a]	260—262 (90% ethanol)	$C_{30}H_{43}Cl_3F_2N_4O_4$ (668·0)	53·93 54·18	6·49 6·44	5·69 5·76	15·92 15·63
XV	[a]	114—116 (ethanol)	$C_{22}H_{26}FN_3O_2$ (383·5)	69·91 69·92	6·83 6·82	4·95 4·97	— —
XVI . HCl[e]	[a]	187—189 (ethanol)	$C_{25}H_{33}ClFN_3O_4$ (494·0)	60·78 60·62	6·73 6·55	8·50[f] 8·39	7·18 7·54
XVII	*C*[a]	112—116 (ethanol)	$C_{18}H_{23}FN_2O_4$ (350·4)	61·70 62·30	6·62 6·82	5·42 5·05	— —
XVIII[g]	*C* (87)	183—185[h] (60% ethanol)	$C_{22}H_{27}FN_2O_6$ (434·5)	60·82 61·47	6·26 6·03	4·37 4·02	— —
XIX	[a]	150—152 (ethanol)	$C_{15}H_{20}FN_3O_2$ (293·3)	61·42 61·55	6·87 6·94	6·48 6·44	— —
XIX . HCl	—	209—210 (95% ethanol)	$C_{15}H_{21}ClFN_3O_2$ (329·8)	54·62 54·62	6·42 6·24	5·76 5·65	10·75 10·56
XX	*B* (54)	68—70 (cyclohexane)	$C_{17}H_{24}FN_3O_2$ (321·4)	63·53 63·98	7·53 7·44	5·91 5·68	— —
XX . HCl		200—202 (ethanol–ether)	$C_{17}H_{25}ClFN_3O_2$ (357·9)	57·05 56·91	7·04 7·05	5·31 5·42	9·91 10·15
XXI-2 HM[i]	[a]	154—155 (90% ethanol)	$C_{24}H_{32}N_2O_{10}$ (508·5)	56·68 55·88	6·34 6·52	5·51[f] 5·40	— —
XXII	*A*[a]	97—99 (benzene–light petroleum)	$C_{23}H_{28}N_2O_3$ (380·5)	72·60 72·66	7·42 7·57	7·36[f] 7·38	—
XXII . HCl		252—254 (90% ethanol)	$C_{23}H_{29}ClN_2O_3$ (416·9)	66·25 66·15	7·01 7·22	6·72[f] 7·28	8·50 8·51

TABLE I
(*Continued*)

Compound	Method (%yield)	M.p., °C (solvent) or b.p., °C/Torr	Formula (m.w.)	Calculated/Found % C	% H	% F	% Cl
XXIII. HCl	*D*[a]	261—264 (ethanol)	$C_{12}H_{16}ClFN_2O$ (258·7)	55·70 56·12	6·23 6·13	7·34 7·60	13·71 13·48
XXIV. HCl	*D* (71)	205—207 (ethanol)	$C_{13}H_{18}ClFN_2O_2$ (288·8)	54·07 54·22	6·28 6·33	6·58 6·61	12·28 12·48
XXV	*E*[a]	106—108 (ethanol)	$C_{18}H_{18}FNO_2$ (299·3)	72·22 72·24	6·06 5·96	6·35 5·93	— —
XXVI	*E* (85)	128—129 (ethanol)	$C_{20}H_{22}FNO_4$ (359·4)	66·83 66·91	6·17 6·19	— —	— —

[a] See Experimental. [b] Content of Br. [c] Maleate. [d] Crystal modifications. [e] Monohydrate. [f] Content of N. [g] Dihydrate. [h] UV spectrum: λ_{max} 238 nm (log ε 4·19); IR spectrum: 730, 750, 778, 848 (4 and 2 adjacent Ar—H), 990 (C—F), 1232 (CO), 1504 (Ar), 1595 (ArCON), 1655 (ArCO), 1672 (ArCOOH), 3260, 3520 cm^{-1} (H_2O); NMR spectrum (CD_3SOCD_3): δ 7·95 (m, 3 H, aromatic protons 2,6-H_2 in fluorobenzoyl and 3'-H in carboxybenzoyl), 7·05—7·60 (m, 5 H, remaining aromatic protons), 3·50 (m, 2 H, $COCH_2$), 2·95 (m, 4 H, $CH_2N^4CH_2$), 2·50 (m, 6 H, 3 N^1CH_2), 1·85 (m, 2 H, middle CH_2 of trimethylene). [i] Di(hydrogen maleate).

chlorides. The tests were focussed on the expected central activity – hence the incoordinating effect on mice (rotating-rod test) and cataleptic effect on rats. The compounds were further studied by the methods of general pharmacological screening. All of them were run through an antimicrobial screening *in vitro* at the bacteriological department of this institute (Dr J. Turinová, Dr A. Čapek). Finally, some of them were screened for anthelminthic activity at the Research Institute for Biofactors and Veterinary Drugs at Pohoří-Chotouň (Dr B. Ševčík, Dr J. Daněk). The compounds prepared show only a slight central depressant activity which is apparent only in high doses. In the rotating-rod test, the highest activity was found with the urea derivatives *XIX* and *XX* which almost equal the standard of "haloperidol" (*I*, $R^1 = OH$, $R^2 = 4\text{-}C_6H_4Cl$)[1]. With most of the compounds the depressant action is displayed by a slight hypothermic effect on rats and a slight to pronounced potentiation of thiopental narcosis in mice. In a single case (*XX*) an antiamphetamine effect was observed. In no case was it possible to determine the mean effective dose (ED_{50}) in the catalepsy test. The compounds were either inactive or showed only traces of activity (on using very high doses less than 50% animals

TABLE II

Results of Orientative Biological Tests of Compounds (mg/kg)

Compound	Method of application[a]	Acute[b] toxicity LD_{50}	Basal dose[c] D	Rotating rod[d] ED_{50}	Catalepsy[d] ED_{50}	Other effects
VI. HCl	*p.o.*	195	—	54	>50[e]	—
VI. HCl	*i.v.*	88	—	—	—	—
VII. HCl	*p.o.*	—	—	50	[f]	[g]
VIII. HCl	*i.v.*	44	8	[h]	—	[i]
IX. HCl	*i.v.*	50	10	[h]	[j]	[k]
X. HCl	*p.o.*	—	—	>50[l]	>50[e,g]	—
XI. HCl	*p.o.*	—	50	[j]	[gj]	—
XII. HCl	*p.o.*	—	—	>50[m]	—	—
XVII	*p.o.*	>2 500	300	[j]	—	—
XVIII	*p.o.*	>2 500	300	[j]	—	[n]
XIX. HCl	*p.o.*	—	50	16·5	[g,j]	—
XX. HCl	*p.o.*	—	50	<50[o]	—	—
XX. HCl	*i.v.*	87·5	17	[p]	[j]	[q]
XXIII. HCl	*p.o.*	1 500	300	[j]	[j]	[r]
XXIV. HCl	*i.v.*	400	80	[j]	[j]	[s]
XXV	*p.o.*	>2 500	300	[j]	—	[t]
XXVI	*p.o.*	>2 500	300	[j]	—	—
Haloperidol[1]	*p.o.*	—	—	20[u]	0·7	—

[a] *p.o.* per os, *i.v.* intravenously, *i.p.* intraperitoneally, [b] Acute toxicity was determined in mice. [c] Basal dose D in mg/kg as used in *in vivo* tests. [d] For the method of the rotating-rod test and the catalepsy test see also ref.[21]. [e] The dose shown brings about catalepsy in 20% animals. [f] At a dose of 50 mg/kg it is cataleptically ineffective. [g] On *i.p.* administration of 10 mg/kg it is cataleptically ineffective. [h] At dose D it has a brief incoordinating effect. [i] At dose D there are symptoms of central depression in mice, a slight hypothermic effect on rats and a slight potentiation of thio pental sleep in mice; dose D/2 brings about a brief, dose D a protracted drop of blood pressure in rats with normal blood pressure; it has an adrenolytic effect on rats; it prolongs bleeding in mice. [j] Ineffective. [k] Symptoms of central depression in mice only in doses greater than D; slightly protracts thiopental sleep in mice; has an anticonvulsant effect toward pentetrazol in mice; after a dose D/2 a pronounced and brief decrease of blood pressure in rats; 0·5% and 1% solution has a pronounced locally anaesthetic effect on rabbit cornea; a spasmolytic effect on isolated rat duodenum toward acetylcholine and barium chloride approximately like papaverine; a negatively inotropic and chronotropic effect on isolated rabbit atrium; prolongs bleeding in mice; inhibits growth of *Mycobacterium tuberculosis* H37Rv *in vitro* at a concentration of 15 μg/ml. [l] A dose of 50 mg/kg brings about incoordination in two mice out of ten. [m] A dose of 50 mg/kg

reached the cataleptic state). On the contrary, "haloperidol" used as standard is highly effective in this test and thus differs strikingly from the compounds prepared here. Other biological effects may be seen in Table II.

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 phosphorus pentoxide at a suitable temperature (below 100°C). The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in Nujol unless stated otherwise) in a Unicam SP 200G spectrophotometer or in an Infrascan (Hilger and Watts), the NMR spectra (in $CDCl_3$ unless stated otherwise) in a ZKR 60 (Zeiss, Jena) spectrometer. The homogeneity of the compounds was tested by thin-layer chromatography on alumina or silica gel.

1-[3-(4-Fluorobenzoyl)propyl]-4-(ethoxycarbonyl)piperazine (*VI*)

A. A mixture of 15·0 g 4-chloro-*p*-fluorobutyrophenone[10] and 29·5 g 1-(ethoxycarbonyl)piperazine[11] was heated for 5 h to 120°C. After cooling, it was diluted with water and the product was isolated by extraction with chloroform. The extract was washed with water, dried with K_2CO_3, filtered with charcoal and distilled: 11·5 g (48%), b.p. 195°C/0·1 Torr. NMR spectrum: δ 8·05 (m, 2 H, aromatic 2,6-H_2), 7·15 (m, 2 H, aromatic 3,5-H_2), 7·10 (q, $J = 8{\cdot}0$ Hz, 2 H, $NCOOCH_2$), 3·40 (t, $J = 6{\cdot}0$ Hz, 4 H, $CH_2N^4CH_2$), 2·96 (t, $J = 7{\cdot}0$ Hz, 2 H, CH_2N in a chain), 2·45 (t, $J = 6{\cdot}0$ Hz, 4 H, $CH_2N^1CH_2$ in a ring), c. 2·40 (2 H, $COCH_2$), 1·97 (m, 2 H, middle CH_2 of a trimethylene residue), 1·22 (t, $J = 8{\cdot}0$ Hz, 3 H, CH_3).

Hydrochloride, m.p. 195—197°C (ethanol–ether). Analyses of the base and of the hydrochloride are shown in Table I. Ref.[9] reports a m.p. of 190°C for the hydrochloride of a product prepared in a basically similar method.

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brings about incoordination in 1—4 mice out of ten. [n] At a dose of 200 mg/kg *p.o.* has an anthelminthic effect (54%) toward the tapeworm *Hymenolepis nana* var. *fraterna* in an *in vivo* test in mice. [o] The dose shown brings about incoordination in 6—9 mice out of ten. [p] Even at a dose of D/2 shows a pronounced and protracted incoordinating effect. [q] At dose D in mice it shows a pronounced central depression 1 h after application; has a hypothermic effect on rats and even at dose D/2 clearly potentiates thiopental narcosis; decreases amphetamine toxicity in mice; has an analgesic effect in Haffner's test in mice; dose D/2 brings about a brief, dose D a protracted drop of blood pressure in rats; has an adrenolytic effect on rats and a protracted peripheral vasodilatory effect on guinea-pigs; a positively inotropic effect on the isolated rabbit atrium; prolongs bleeding in mice without affecting blood coagulation. [r] Signs of central depression in mice at doses greater than D; slight potentiation of thiopental sleep in mice; at dose D an analgesic effect in Haffner's test in mice such as is not apparent at dose D/2; sign of antihistamine effect in the histamine detoxication test in guinea-pigs. [s] At dose D/2 a pronounced brief, at dose D a protracted drop of blood pressure in rats; prolongs bleeding in mice without affecting blood coagulation; at a dose of 200 mg/kg *p.o.* has a slight anthelminthic effect (44%) toward the tapeworm *Hymenolepis nana* var. *fraterna* in an in *vivo* test in mice and further toward the roundworm *Nippostrongylus brasiliensis* in an *in vivo* test on rats (14%; "pyrantel" at a dose of 25 mg/kg *p.o.* has a 100% effect). [t] Signs of central depression in mice at doses greater than D; slightly potentiates thiopental sleep in mice. [u] The dose shown brings about incoordination in 2—7 mice out of ten.

B. A mixture of 120 g 4-chloro-*p*-fluorobutyrophenone[10], 105 g 1-(ethoxycarbonyl)piperazine[11], 360 ml toluene and 61 g triethylamine was refluxed under stirring for 8 h. After cooling, the bases were extracted with a mixture of 120 ml hydrochloric acid and 400 ml water, the acid aqueous solution was filtered with charcoal, made alkaline with a solution of NaOH and the base was isolated by extraction with benzene; 104 g (55%), b.p. 177°C/0·05 Torr.

1-[3-(4-Ethoxybenzoyl)propyl]piperazine (*XXI*)

A mixture of 4·7 g *VI*, 5 g KOH and 7 ml ethanol was refluxed under stirring for 3 h in a 120°C bath. After dilution with water, it was extracted with benzene and the extract was processed to obtain 2·9 g (72%) crude oily base. Neutralization with maleic acid in ethanol yielded di(hydrogenmaleate), m.p. 154—155°C (aqueous ethanol). NMR spectrum (CD_3SOCD_3): δ 9·70 (bs, 5 H, NH^+, NH_2^+ and 2 COOH), 7·98 (d, J = 9·0 Hz, 2 H, aromatic 2,6-H_2), 7·02 (d, J = 9·0 Hz, 2 H, aromatic 3,5-H_2), 6·14 (s, 4 H, 2 CH=CH of maleic acid), 4·10 (q, J = 8·0 Hz, 2 H, OCH_2), 2·60—3·40 (m, 12 H, $COCH_2$ and 5 NCH_2), 1·90 (m, 2 H, middle CH_2 of trimethylene), 1·34 (t, J = 8·0 Hz, 3 H, CH_3 of ethyl). Analysis of the maleate is shown in Table I.

The N^4*-benzoyl derivative* XXII was prepared by benzoylation of base *XXI* with benzoyl chloride in pyridine (method *A*); 1·5 g *XXI* yielded 1·6 g (73%) of base *XXII*, m.p. 97—99°C (benzene–light petroleum). UV spectrum: λ_{max} 272 nm (log ε 4·26). IR spectrum (KBr): 704, 720, 750, 789, 819 and 839 (5 and 2 adjacent Ar—H), 1260 (Ar—O—R), 1510, 1595 (Ar), 1637 (NCOAr), 1670 (ArCO), 2779 and 2820 cm^{-1} (N—CH_2). NMR spectrum: δ 8·00 (d, J = 9·0 Hz, 2 H, aromatic 2,6-H_2 in ethoxybenzoyl), 7·44 (5 H, C_6H_5), 6·95 (d, J = 9·0 Hz, 2 H, aromatic 3,5-H_2 of ethoxybenzoyl), 4·10 (q, J = 8·0 Hz, 2 H, OCH_2), 3·55 (m, 4 H, $CH_2N^4CH_2$), 2·96 (t, J = 8·0 Hz, 2 H, CH_2N in a chain), c. 2·45 (m, 6 H, $COCH_2$ and $CH_2N^1CH_2$), 2·00 (m, 2 H, middle CH_2 of trimethylene), 1·42 (t, J = 8·0 Hz, 3 H, CH_3 of ethyl).

Hydrochloride, m.p. 252—254°C (aqueous ethanol). Analyses of the base and the hydrochloride are shown in Table I.

1-[3-(4-Fluorobenzoyl)propyl]piperazine (*V*)

A mixture of 125 g *VI*, 400 ml acetic acid and 230 ml 48% hydrobromic acid was refluxed for 7 h, evaporated at reduced pressure and the residue recrystallized from 500 ml 95% ethanol; 142 g (89%), m.p. 209—211°C (plates). The compound is a dihydrobromide which liberates the base on action of a solution of NaOH. The base was isolated by extraction with ether; m.p. 69—71°C (ether). According to analysis it is a monohydrate. NMR spectrum δ 8·05 (m, 2 H, aromatic 2,6-H_2), 7·10 (m, 2 H, aromatic 3,5-H_2), 2·95 (t, 2 H, $COCH_2$), 2·76 (m, 4 H, $CH_2N^4CH_2$), 2·35 (m, 9 H, CH_2N in the chain, $CH_2N^1CH_2$, H_2O and NH), 1·95 (m, 2 H, middle CH_2 of trimethylene).

Maleate, m.p. 196°C under decomposition (ethanol). Ref.[8] reports the preparation of *V* by another method and characterizes only a hydrochloride.

The N^4*-benzoyl derivative* IV was prepared from *V* through the action of benzoyl chloride in pyridine (method *A*), m.p. 123—125°C (benzene–light petroleum). UV spectrum: λ_{max} 240 nm (log ε 4·19), 323 nm (2·91). IR spectrum: 712, 734, 836 (5 and 2 adjacent Ar—H), 1000 (C—F), 150,0, 1595 (Ar), 1620 (NCOAr), 1685 (Ar—CO), 2780 cm^{-1} (NCH_2). NMR spectrum: δ 8·05 (m 2 H, aromatic 2,6-H_2 of fluorobenzoyl), 7·42 (s, 5 H, C_6H_5), 7·15 (m, 2 H, aromatic 3,5-H_2 of fluorobenzoyl), 3·55 (m, 4 H, $CH_2N^4CH_2$), 2·96 (t, J = 7·0 Hz, 2 H, $COCH_2$), c. 2·42 (m, 6 H,

3 N^1CH_2), 1·98 (m, 2 H, middle CH_2 of trimethylene). Patent[8] describes only the hydrochloride. Table I includes the analyses of base *V*, its dihydrobromide, maleate and benzoyl derivative *IV*.

1-[3-(4-Fluorobenzoyl)propyl]-4-acetylpiperazine (*VII*)

Acetic anhydride (4 ml) was added dropwise under cooling and stirring to a mixture of 8·2 g dihydrobromide of *V* and 25 ml pyridine. The mixture was left for 1 h at room temperature, diluted with 200 ml water and the product was isolated by extraction with benzene. Processing of the extract yielded 5·4 g (93%) product which crystallized, m.p. 89—91°C (benzene–light petroleum). UV spectrum: λ_{max} 242 nm (log ε 4·09). IR spectrum: 830 (2 adjacent Ar—H), 992 (C—F), 1 500, 1 590 (Ar), 1 640 ($NCOCH_3$), 1 684 cm^{-1} (Ar—CO). NMR spectrum: δ 8·05 (m, 2 H, aromatic 2,6-H_2), 7·15 (m, 2 H, aromatic 3,5-H_2), 3·42 (m, 4 H, $CH_2N^4CH_2$), 2·96 (t, J = 7·0 Hz, 2 H, $COCH_2$), c. 2·40 (m, 6 H, 3 N^1CH_2), 2·02 (s, 3 H, $COCH_3$), 1·97 (m, 2 H, middle CH_2 of trimethylene).

Hydrochloride, m.p. 183—185°C (ethanol–ether). The analyses of the base and of the hydrochloride are in Table I. Ref.[13] reports this compound without characterizing it.

1-[3-(4-Fluorobenzoyl)propyl]-4-(phenylacetyl)piperazine (*X*) (Method *A*)

Phenylacetyl chloride[15] (1·7 g) was added to a cold mixture of 4·1 g dihydrobromide of *V* in 15 ml pyridine. The mixture was left to stand overnight at room temperature, diluted with 100 ml water and the product was isolated by extraction with benzene. Treatment of the extract yielded 3·0 g (81%) product: m.p. 89—91°C (benzene–light petroleum). UV spectrum: λ_{max} 241·5 nm (log ε 4·07). IR spectrum: 700, 732, 820, 835 (5 and 2 adjacent Ar—H), 1 000 (C—F), 1 235 (CO), 1 505, 1 600 (Ar), 1 620 (NCOR), 1 680 (ArCO), 2 720 cm^{-1} (NCH_2). NMR spectrum: δ 8·05 (m, 2 H, aromatic 2,6-H_2 of fluorobenzoyl), 7·30 (s, 5 H, C_6H_5), 7·15 (m, 2 H, aromatic 3,5-H_2 of fluorobenzoyl), 3·70 (s, 2 H, $ArCH_2$), 3·45 (m, 4 H, $CH_2N^4CH_2$), 2·95 (t, J = 7·0 Hz, 2 H, $ArCOCH_2$), c. 2·31 (m, 6 H, 3 N^1CH_2), 1·84 (m, 2 H, middle CH_2 of trimethylene).

Hydrochloride, m.p. 209—211°C (aqueous ethanol). Compound *X* was also prepared by method *B* in a yield of 78%. Analyses of the base and of the hydrochloride are shown in Table I. Analogously method *A* was applied to the preparation of amides *VIII* and *IX* (Table I).

1-[3-(4-Fluorobenzoyl)propyl]-4-(diphenylacetyl)piperazine (*XI*) (Method *B*)

Diphenylacetyl chloride[16] (5·1 g) was added in small parts under stirring to a solution of 5·0 g base *V* in 15 ml ethanol, the mixture was briefly boiled and, after partial cooling, combined with 17 ml ether. Standing led to the crystallization of 8·7 g (97%) hydrochloride, m.p. 206 to 208°C (ethanol). The base was liberated from a sample of this salt by treatment with NaOH and isolated by extraction with benzene; m.p. 68—69°C (benzene–light petroleum). UV spectrum: λ_{max} 260 nm (log ε 4·60), 315 nm (3·99). IR spectrum (KBr): 700, 747, 840 (5 and 2 adjacent Ar—H), 1 000 (Ar—F), 1 235 (CO), 1 504, 1 595 (Ar), 1 640 (NCOR), 1 685 (Ar—CO), 2 780 cm^{-1} (N—CH_2). NMR spectrum: δ 8·00 (m, 2 H, aromatic 2,6-H_2 of fluorobenzoyl), 7·25 (s, 10 H, 2 C_6H_5), 7·10 (m, 2 H, aromatic 3,5-H_2 of fluorobenzoyl), 5·14 (s, 1 H, Ar_2CHCO), 3·15—3·70 (m, 4 H, $CH_2N^4CH_2$), 2·90 (t, 2 H, $COCH_2$), 2·00—2·50 (m, 6 H, 3 N^1CH_2), 1·90 (m, 2 H, middle CH_2 of trimethylene). Analyses of the base and of the hydrochloride are shown in Table I. Analogously, amide *XII* and substituted urea *XX* were prepared (the last-named also by the method *A* in a 92% yield).

1-[3-(4-Fluorobenzoyl)propyl]-4-(chloroacetyl)piperazine (*XIII*)

Chloroacetyl chloride (4·8 g) and a solution of 2·0 g Na_2CO_3 in 8 ml water were added simultaneously dropwise under external cooling and stirring to a solution of 10·0 g base *V* in 40 ml ethanol. The mixture was stirred for 10 min at room temperature, evaporated at reduced pressure and the residue (after adding Na_2CO_3 to a clearly alkaline reaction) was separated between water and benzene. Treatment of the benzene layer yielded 10·5 g (86%) crude product which was dissolved in 40 ml ethanol and, by adding an ether solution of hydrogen chloride, was converted to a hydrochloride, m.p. 190—192°C under decomposition (ethanol). The analysis appears in Table I.

4,4'-Bis[3-(4-fluorobenzoyl)propyl]piperazinoacetopiperazide (*XIV*)

A solution of 25 g base *V* in 100 ml ethanol was processed similarly to the preceding case by treatment with 10·8 g chloroacetyl chloride and a solution of 4·5 g Na_2CO_3 in 20 ml water. A total of 25 g nonhomogeneous hydrochloride was obtained, a greated part of which (17·6 g) did not dissolve during an attempt to recrystallize it from 500 ml ethanol. Recrystallization of a sample from 90% ethanol yielded the pure compound; m.p. 260—262°C (decomp.). According to analysis and spectra it is a monohydrate of the trihydrochloride of *XIV*. IR spectrum (KBr): 837, 868 (2 adjacent Ar—H), 1232 (CO), 1508, 1598 (Ar), 1668 (NCOR), 1686 (ArCO), 2430, 2530 (NH^+), 3430 cm^{-1} (H_2O). The mass spectrum displays a molecular ion at *m/e* 540·2914 ± ± 0·0015, corresponding to the composition of base *XIV* $C_{30}H_{38}F_2N_4O_3$ (theoretically 540·2912) principal fragments at *m/e* 403 and 263 being formed by splitting off C_8H_6FO and $C_{15}H_{20}FN_2O$. The analysis of the compound is shown in Table I.

1-[3-(4-Fluorobenzoyl)propyl]-4-(anilinoacetyl)piperazine (*XV*)

A mixture of 6·0 g hydrochloride of *XIII* and 8 ml aniline was heated for 2 h to 100°C. After partial cooling, the solidified mixture was combined with 100 ml benzene, the solid (9·4 g) was filtered, washed with benzene, suspended in water and decomposed with NH_4OH. The base was isolated by extraction with chloroform. Treatment of the extract yielded only 3·0 g (47%) base, melting at 114—116°C (ethanol). The analysis is shown in Table I.

1-[3-(4-Fluorobenzoyl)propyl]-4-(N-phenylpropionamidoacetyl)piperazine (*XVI*)

A solution of 0·5 g propionyl chloride in 4 ml benzene was added dropwise to a solution of 2·0 g *XV* in 20 ml benzene and the mixture was briefly boiled. Cooling led to 2·3 g (89%) crude hydrochloride of the product which was rectystallized from ethanol, m.p. 187—189°C. According to analysis it is a monohydrate. IR spectrum (KBr): 703, 775, 817, 830 (5 and 2 adjacent Ar—H), 1500, 1600 (Ar), 1660 (NCOR), 1688 (ArCO), 2430, 2580 (NH^+), 3410, 3525 cm^{-1} (H_2O). The analysis is shown in Table I.

1-[3-(4-Fluorobenzoyl)propyl]-4-(3-carboxypropionyl)piperazine (*XVII*) (Method *C*)

Succinic anhydride (2·44 g) was added to a solution of 6·1 g base *V* in 20 ml ethanol and the mixture was briefly boiled until dissolution. After standing overnight, ether was added to turbidity whereupon the product crystallized on standing; 5·8 g (73%), m.p. 112—116°C (ethanol). UV spectrum: λ_{max} 244·5 nm (log ε 4·06). IR spectrum: 840 (2 adjacent Ar—H), 1000 (Ar—F), 1235 (CO), 1510, 1600 (Ar), 1634 (NCOR), 1653 (ArCO···H), 1685 cm^{-1} (COOH). NMR spectrum: δ 10·04 (bs, 1 H, COOH), 8·00 (m, 2 H, aromatic 2,6-H_2 of fluorobenzoyl), 7·10 (m, 2 H, aromatic

3,5-H_2 of fluorobenzoyl), 3·55 (m, 4 H, $CH_2N^4CH_2$), 2·99 (t, 2 H, $ArCOCH_2$), c. 2·55 (m, 10 H, 3 N^1CH_2, $COCH_2CH_2COO$), 2·00 (m, 2 H, middle CH_2 of trimethylene). The analysis is in Table I. Acid *XVIII* was prepared similarly.

1-[3-(4-Fluorobenzoyl)propyl]-4-(aminocarbonyl)piperazine (*XIX*)

KOCN (4·3 g) was added by parts under stirring to a solution of 6·0 g base *V* in 50 ml 90% acetic acid. The mixture was left to stand for 1 h at room temperature, heated for 2 h to 60°C and left to stand overnight at room temperature. After evaporation at reduced pressure, the residue was dissolved in water, the solution made alkaline with NaOH and the liberated base was crystallized and filtered: 5·5 g (84%), m.p. 150–152°C (ethanol.) NMR spectrum: δ 8·05 (m, 2 H, aromatic 2,6-H_2), 7·15 (m, 2 H, aromatic 3,5-H_2), 4·95 (bs, 2 H, $CONH_2$), 3·31 (t, 4 H, $CH_2N^4CH_2$), 2·97 (t, 2 H, $COCH_2$), 2·40 (t, 6 H, 3 N^1CH_2), 1·98 (m, 2 H, middle CH_2 of trimethylene).

Hydrochloride, m.p. 209–210°C under decomposition (95% ethanol). Analysis of the base and the hydrochloride is shown in Table I.

1-(4-Fluorobenzoyl)-4-methylpiperazine (*XXIII*) (Method *D*)

4-Fluorobenzoyl chloride (b.p. 72°C/10 Torr)[19] (3·2 g) was added dropwise under stirring to a solution of 4·0 g 1-methylpiperazine in a mixture of 13 ml ethanol and 5 ml water. The mixture was stirred for 1 h at room temperature, evaporated at reduced pressure, the residue was dissolved in water and, after treatment with a solution of NaOH, the base was isolated by extraction with chloroform. Processing of the extract yielded 4·1 g (91%) oily base which was converted (ethanol, ether solution of HCl) to the hydrochloride, m.p. 261–264°C (ethanol). The analysis is shown in Table I. The piperazide *XXIV* was prepared in a similar way.

N-(2-Phenylethyl)-3-(4-fluorobenzoyl)propionamide (*XXV*) (Method *E*)

Triethylamine (5·1 g) was added to a solution of 9·8 g 3-(4-fluorobenzoyl)propionic acid[20] in 35 ml chloroform; this was followed by a dropwise addition under stirring and external cooling of 4·8 ml ethyl chloroformate over a period of 30 min. The mixture was stirred for 1·5 h at room temperature, cooled and then 6·1 g 2-phenylethylamine was added dropwise. After stirring for 1 h at room temperature 100 ml water was added and the whole was extracted with chloroform. The extract was washed with 5% solution of NaOH, water and diluted hydrochloric acid, dried with $MgSO_4$ and evaporated. The residue crystallized: 11·1 g (74%), m.p. 106–108°C (ethanol). UV spectrum: λ_{max} 244·5 nm (log ε 4·09). IR spectrum: 700, 752, 836 (5 and 2 adjacent Ar—H), 990 (Ar—F), 1 235 (CO), 1 549 (CONH), 1 594 (Ar), 1 640 (CONH), 1 686 (Ar—CO), 3 315 cm^{-1} (NH). NMR spectrum: δ 7·95 (m, 2 H, aromatic 2,6-H_2), 7·17 (s, 5 H, C_6H_5), 7·05 (m, 2 H, aromatic 3,5-H_2 of fluorobenzoyl), 5·95 (m, 1 H, CONH), 3·00–3·65 (m, 4 H, $COCH_2CH_2CO$), 2·30–2·90 (m, 4 H, $ArCH_2CH_2N$). The analysis is shown in Table I. Amide *XXVI* was prepared in a similar way.

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