POTENTIAL NOOTROPIC AGENTS: SYNTHESIS OF A SERIES OF (2-OXO-1-PYRROLIDINYL)ACETIC ACID PIPERAZIDES

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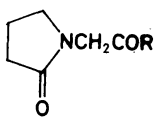
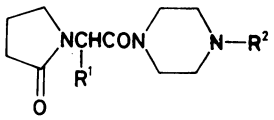
The title compounds *VI*—*XXIII* were prepared by heating ethyl (2-oxo-1-pyrrolidinyl)acetate (*II*) with a series of N-monosubstituted piperazines. The propionamides *XXVI* and *XXX* were obtained by reactions of the acid chlorides *IV* and *XXXIII* with 3-(1-piperazinyl)propionamide. Compounds *VI* (VÚFB-13 763) and *VIII* (VÚFB-14 745) proved more active than piracetam (*I*) by their antiamnesic effects in rats, by antagonizing the brain-damaging effects of cycloheximide in infantile rats, and by their potentiation of the effects of anticonvulsant agents.

(2-Oxo-1-pyrrolidinyl)acetamide (*I*) (piracetam, UCB 6215, Nootropil^{R}) (refs[1-6]) was characterized as a substance exerting a selective action on the cerebral cortex by activating, protecting and restoring the functions of nerve cells in distress. Its complex actions on the cortical cells include an increase of the energy reserve by stimulating the transformation of ADP into ATP, restoring to normal a decreased ATP level (e.g. after anoxia), and facilitating the physiological transfer of information between the two hemispheres via the corpus callosum. The result should be a favourable effect on patients with symptoms of psychoorganic senility such as failure of memory, reduced allertness, asthenia and psychomotor disorders. These properties were verified — at least partly — by clinical testing[7,8]. In this way, piracetam (*I*) represents the first member and prototype of a new subgroup of psychopharmaceutical agents which was called "nootropic agents" (refs[9-14]) differing from the other psychotropic agents by the lack of sedative or stimulating effects and by no influence on behaviour.



I, R = NH_2 *III*, R = OH
II, R = OC_2H_5 *IV*, R = Cl

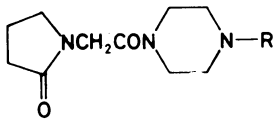
The necessity of using relatively high doses of piracetam (*I*) prompted a broad research oriented towards the series of piracetam analogues with the hope to find more active substances with a similar biological profile. Our research team, too, started rather early (cf. ref.[15]) pharmaco-chemical research in this line which was concentrated on piperazine analogues of *I*, i.e. piperazides of the acid *III*. The delay of publishing our results was caused by the very slow proceeding of pharmacological testing. Now, our publication cannot be postponed anymore because in the meantime some patents appeared[16-19] which deal with piperazides of the general formula *V*, where R^1 is H or a lower alkyl and R^2 is 4-methoxybenzyl, 4-hydroxybenzyl, allyl, cinnamyl, and 2-pyrimidinyl, which are claimed to have positive effects on supplying the brain with blood, on the "gasping reflex" in mice (acute brain ischemia induced by decapitation), in states of hypoxia and anoxia. The scope of these patents does not interfere with our own work.

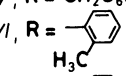
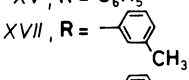
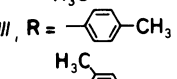
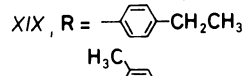
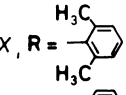
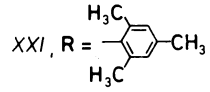
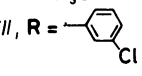
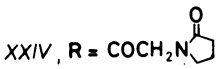


V

The main part of this communication deals with description of the synthesis of piperazides *VI*–*XXIII*. They were prepared by the general method consisting of reactions of the ethyl ester *II* (refs[2,20,21]) with a series of N-monosubstituted piperazines achieved by heating equimolecular mixtures of the components to 140–175°C for 5–14 h in the presence of catalytic amounts of sodium hydride or sodium methoxide. The following N-monosubstituted piperazines were used: 1-methylpiperazine, 1-(2-propyl)piperazine[22], 1-(2-methoxyethyl)piperazine[23], 1-(3-methoxypropyl)piperazine[23], 1-(2-ethoxyethyl)piperazine[23], 1-(2-methylthioethyl)piperazine[23], 1-(2-phenoxyethyl)piperazine[23], 1-(2-phenylthioethyl)piperazine[23], 1-benzylpiperazine[24], 1-phenylpiperazine[25], 1-(2-tolyl)piperazine[26], 1-(3-tolyl)piperazine[26], 1-(4-tolyl)piperazine[26], 1-(4-ethylphenyl)piperazine[27], 1-(2,6-dimethylphenyl)piperazine[28], 1-(2,4,6-trimethylphenyl)piperazine[29], 1-(3-chlorophenyl)piperazine[26], and 1-(ethoxycarbonyl)piperazine. The crude bases *VI*–*XXIII* were mostly chromatographed on aluminium oxide and the homogeneous bases obtained – oily or crystalline – were mostly characterized by spectra and transformed to crystalline salts (maleates or hydrochlorides). Compounds *VI*–*XXIII*, prepared by the general method, are assembled in Table I with the usual experimental data. The spectra of these compounds are assembled in Table II.

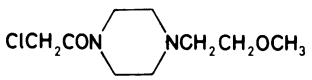
Compound *VIII* was also prepared by an alternative route which started by reaction of 1-(2-methoxyethyl)piperazine[23] with chloroacetyl chloride in chloroform at room temperature. The obtained *XXVII* was isolated as the crystalline hydro-



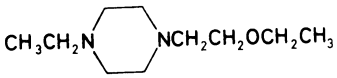
VI, R = CH_3
VII, R = $CH(CH_3)_2$
VIII, R = $CH_2CH_2OCH_3$
IX, R = $(CH_2)_3OCH_3$
X, R = $CH_2CH_2OCH_2CH_3$
XI, R = $CH_2CH_2SCH_3$
XII, R = $CH_2CH_2OC_6H_5$
XIII, R = $CH_2CH_2SC_6H_5$
XIV, R = $CH_2C_6H_5$
XV, R = C_6H_5
XVI, R = 
XVII, R = 
XVIII, R = 
XIX, R = 
XX, R = 
XXI, R = 
XXII, R = 
XXIII, R = $COOC_2H_5$
XXIV, R = 
XXV, R = H
XXVI, R = $CH_2CH_2CONH_2$

chloride (characterized by the mass and IR spectra). The oily base *XXVII* was released with aqueous ammonia and reacted with 2-pyrrolidone in the presence of sodium hydride in boiling benzene; the crude base *VIII* was transformed to the hydrogen maleate and purified in this form; the yield was 54%. In one batch of preparation of *X*, in which a slight excess (17%) of 1-(2-ethoxyethyl)piperazine[23] was used, an inhomogeneous base was obtained which gave an inhomogeneous maleate. Its crystallization separated the less soluble component derived from the base $C_{10}H_{22}N_2O$ (mass spectrum) to which the structure of *XXVIII* was assigned (analysis of the bis(hydrogen maleate) is in agreement). The mode of formation of this compound is unclear; it seems to be the product of a strange transfer of ethyl from the oxygen atom in *II* to the nitrogen atom of 1-(2-ethoxyethyl)piperazine. The reaction of *II* (ref.[20]) with piperazine (2 : 1) was carried out in order to prepare *XXIV* (it was mentioned in a patent[30] and reported to be useful in the treatment of cognitive disorders[31]). Under mild conditions (reaction in boiling toluene), the crystalline base *XXIV* was obtained in the yield of 37%. Processing of the mother liquor led to *XXV* which was isolated as hydrogen oxalate. Carrying out the reaction without solvent at 150–170°C led to 77% of *XXIV*. Reaction of (2-oxo-1-pyrrolidinyl)acetyl chloride (*IV*) (refs[32,33]) with 3-(1-piperazinyl)propionamide[34] in boiling chloroform in the presence of triethylamine gave 38% of crystalline *XXVI* (hemihydrate) which was characterized by spectra and transformed to the crystalline hydrogen maleate.

In connection with etiracetam (*XXIX*), another experimental nootropic agent[35,36],

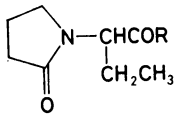


XXVII

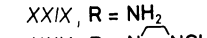


XXVIII

the piperazide *XXX* was synthesized. Reaction of 2-pyrrolidone, sodium hydride, and ethyl 2-bromobutyrate in boiling benzene gave *XXXI* (mentioned in refs[37–39]), which was hydrolyzed to *XXXII* with boiling ethanolic potassium hydroxide. The intermediates *XXXI* and *XXXII* were characterized by spectra. The acid *XXXII* was transformed by treatment with thionyl chloride in benzene to *XXXIII* which was processed in crude state by treatment with 3-(1-piperazinyl)propionamide[34] in boiling chloroform in the presence of triethylamine; the oily *XXX* was obtained which afforded the crystalline hydrogen maleate.



XXIX, R = NH_2

XXX, R = 

XXXI, R = OC_2H_5

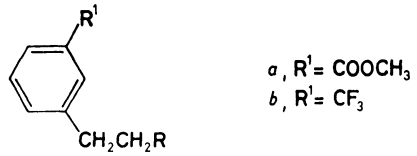
XXXII, R = OH

XXXIII, R = Cl

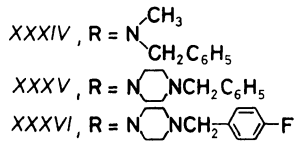
Another nootropic prototype is the compound *XXXIVa* (PRL-8-53), a spasmolytic papaverine-like agent with learning-facilitating properties[40,41]. It was reported to facilitate acquisition in rats and to improve retention in man[42,43]. In this communication, the synthesis of two piperazine analogues of *XXXIVa*, i.e. of compounds *XXXVa* and *XXXVIa*, is being reported. 2-(3-Trifluoromethylphenyl)ethyl chloride[44] was reacted by heating to 130–140°C with 1-benzylpiperazine[24] and 1-(4-fluorobenzyl)piperazine[45], respectively. Oily *XXXVb* and *XXXVIb* were obtained, purified by distillation and characterized by crystalline salts. The dihydrochlorides of *XXXVb* and *XXXVIb* were heated with sulfuric acid to 100°C and the resulting carboxylic acids were esterified "in situ" with methanol. The crude amino esters *XXXVa* and *XXXVIa* were transformed to crystalline hydrochlorides for pharmacological testing.

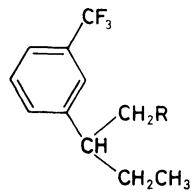
The last synthetic experiment described was discontinued in the stage of intermediate. The Grignard reagent, prepared from 1-bromo-3-(trifluoromethyl)benzene in tetrahydrofuran, was reacted with 1,2-epoxybutane. Distillation of the product gave 53% of a substance with the expected composition $C_{11}H_{13}F_3O$ (analysis) which was not homogeneous (^{1}H NMR spectrum), but evidently consisted mainly of *XXXVII*. Its reaction with thionyl chloride in boiling benzene in the presence of pyridine gave the inhomogeneous *XXXVIII* which was reacted in crude state with 1-benzylpiperazine[24] by heating to 150°C. The crude basic product was transformed

to the crystalline dihydrochloride and purified by its crystallization. The oily base, released with aqueous ammonia, was used for recording the ^{1}H NMR spectrum which corroborated its structure *XXXIX* and proved the homogeneity.



a, R^1 = $COOCH_3$
b, R^1 = CF_3





XXXVII, R = OH
XXXVIII, R = Cl
XXXIX, R = N(CH2C6H5)

Some of the compounds prepared were pharmacologically tested in the form of salts, described in the Experimental and in Table I. They were tested on the one hand in some specific tests in the nootropic line and using a general screening programme on the other. Acute toxicity in mice, LD_{50} in mg/kg. *VI*, 1 000 p.o. (507 i.v. in males, 405 i.v. in females); *VII*, >1 000 p.o. (177 i.v.); *VIII*, 625 i.v.; *X*, 600 i.v.; *XIII*, 100 i.v.; *XX*, 250 p.o.; *XXXVa*, 30 i.v.; *XXII*, after the oral dose of 250 mg/kg no lethality, 500 mg/kg was lethal for 80% of the animals.

In the test of passive avoidance in rats *VIII*, *XII*, *XIII*, and *XXIII* in single doses of 0·02 mg/kg s.c. or 0·1 mg/kg p.o. significantly prolonged the duration of the avoidance response which was interpreted as a positive influence on the retention. The compounds were further evaluated in the test of amnesia in rats induced by the halothan anaesthesia (the influence on the passive avoidance responses was evaluated); *VI* (cf. ref.[46]), *XIV*, and *XXXVI* in the s.c. doses of 100 mg/kg had significant antiamnesic effect, lower doses of 50 and 20 mg/kg s.c. had weaker but still significant effect (piracetam in the same doses was insignificantly effective); *IX*, the oral dose

of 0·1 mg/kg 30 min before the experiment was significantly active. A similar test in which amnesia was induced by the electroconvulsive shock (situation of passive avoidance): *VIII* in the oral dose of 0·1 mg/kg protected the animals from the amnesic action of the shock (the effect of piracetam in the same dose was insignificant). Effect against the brain damage by cycloheximide in infantile rats: *VIII* in daily doses of 1 mg/kg s.c. antagonized the cycloheximide effects (piracetam was practically without effect). The increased levels of dopamine and homovanillic acid in the rat brain striatum after cycloheximide were not influenced by *VIII* which, likewise, had no effect on the RNA and DNA content in cerebellum and in hippocampus. Influence on the duration of the gasping reflex in mice (acute ischemia induced by decapitation); oral doses of 100 mg/kg were administered 30 min before decapitation: *VII*, insignificant prolongation of the gasping reflex (to 105%); *XXII*, significant prolongation (to 127%). Potentiation of the anticonvulsant activity of valproate and diazepam in the test of electroshock in mice: *VI* in daily oral doses of 150 and 250 mg/kg significantly potentiated the effects of both anticonvulsant agents[47]. Influence on the blood pressure of anaesthetized normotensive rats: *X*, the dose of 110 mg/kg i.v. brought about sharp and brief drops of the blood pressure; *XXXVa*, the i.v. dose of 6 mg/kg brought about prolonged drops of the blood pressure and bradycardia. Antitussic activity in the test of citric acid aerosol in guinea-pigs: *X* in the oral dose of 300 mg/kg reduced the frequency of the cough attacks by 41%. In conclusion, compounds *VI* (VÚFB-13 763) and *VIII* VÚFB-14 745) proved more interesting than piracetam (*I*) by their antiamnestic effects in rats, by antagonizing the brain-dammaging effect of cycloheximide in infantile rats, and by their potentiation of the anticonvulsant effects of valproate and diazepam in mice.

EXPERIMENTAL

The melting points of analytical samples were determined in the Kofler block and they are not corrected; the samples were dried in vacuo of about 60 Pa at room temperature or at a suitably elevated temperature. UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded with the Unicam SP 8000 spectrophotometer; IR spectra (mosty in NUJOL, ν in cm^{-1}) with Unicam SP 200G or Perkin–Elmer 298 spectrophotometers; ^1H NMR spectra (in $CDCl_3$ unless stated otherwise, δ in ppm, J in Hz) on a CW-NMR spectrometer TESLA BS 487C (80 MHz) or partly on a FT-NMR spectrometer TESLA BS 567A (100 MHz), and the mass spectra (*m/z*, fragments and/or %) on MCH 1320 and Varian MAT 44S (GC-MS) spectrometers. The homogeneity of the substances and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). Preparative chromatographic separations were carried out on columns of neutral Al_2O_3 (activity II). The extracts were dried with $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure on a rotary evaporator.

1-(2-Methylthioethyl)-4-((2-oxo-1-pyrrolidinyl)acetyl)piperazine (*XI*) (General Method)

A stirred mixture of 5·9 g *II* (refs[2,20,21]), 5·3 g 1-(2-methylthioethyl)piperazine[23], and 0·1 g NaH was heated for 3 h to 100°C and for 5 h to 140°C. After cooling the inhomogeneous product was dissolved in benzene and the solution was chromatographed on 400 g Al_2O_3. Elution with

benzene afforded 5·8 g (64%) of the homogeneous oily *XI* which was used for recording the ^{1}H NMR spectrum. The neutralization with maleic acid in ethanol and addition of ether gave the hydrogen maleate, m.p. 138·5—140°C (2-propanol). The spectrum and analysis are included in Tables I and II.

1-(Chloroacetyl)-4-(2-methoxyethyl)piperazine (*XXVII*)

A stirred solution of 7·2 g 1-(2-methoxyethyl)piperazine[23] in 20 ml chloroform was treated over 1 h at 5—6°C with a solution of 6·9 g chloroacetyl chloride in 10 ml chloroform, added dropwise. The mixture was stirred for 2 h at room temperature, cooled to 2°C, the precipitated product was filtered, washed with ether, and recrystallized from a mixture of acetone and ethanol; 10·7 g (83%) of *XXVII* hydrochloride, m.p. 157—160°C. Mass spectrum: 220 (M^+, $C_9H_{17}ClN_2O_2$, 2), 175 ($C_7H_{12}ClN_2O$, 100), 146 (18), 120 (17), 99 (36), 70 (24), 56 (40), 42 (41). IR spectrum: 1 119 (R–O–R'); 1 664 (NCOR); 2 440, 2 520, 2 560 (NH^+). ^{1}H NMR spectrum (CD_3SOCD_3 at 80°C): 3·20—4·00 m, 12 H (5 × CH_2N and CH_2O); 3·28 s, 3 H (OCH_3); 4·40 s, 2 H ($ClCH_2$·.CO). For $C_9H_{18}Cl_2N_2O_2$ (257·2) calculated: 42·03% C, 7·05% H, 10·90% N; found: 41·93% C, 7·13% H, 10·93% N.

The oily base *XXVII* was released from the hydrochloride with 20% NH_4OH and isolated by extraction with benzene. Processing of the extract gave the base which was immediately used for the further step.

1-(2-Methoxyethyl)-4-((2-oxo-1-pyrrolidinyl)acetyl)piperazine (*VIII*)

A stirred solution of 2·8 g 2-pyrrolidone in 15 ml benzene was treated with 0·8 g 80% NaH (suspension in mineral oil) and the mixture was stirred for 2 h at 55°C. After cooling it was treated under stirring over 1 h with a solution of 6·2 g *XXVII* in 20 ml benzene, added dropwise. The mixture was refluxed for 4 h, after cooling the precipitated NaCl was filtered off, and the filtrate was evaporated in vacuo. The residue (7·4 g) was dissolved in 15 ml ethanol and the solution was neutralized with a solution of 3·1 g maleic acid in 6 ml ethanol. Addition of 30 ml ether and standing overnight led to crystallization of 5·8 g (54%) of *VIII* hydrogen maleate, m.p. 113 to 116°C. It was found identical (TLC and mixed melting point with the product, obtained by the general method (cf. in Table I).

1-(2-Ethoxyethyl)-4-ethylpiperazine (*XXVIII*)

A mixture of 5·15 g *II* (refs[2,20,21]), 5·55 g 1-(2-ethoxyethyl)piperazine[23], and 0·05 g NaH was stirred for 9 h at 145—155°C. After cooling the mixture was diluted with 70 ml chloroform, the solution was washed with water, and the basic product was extracted into 80 ml 3M-HCl. The aqueous layer was filtered at 60°C with active carbon, the filtrate was treated after cooling with NH_4OH and the bases were extracted with chloroform. Processing of the extract gave 4·3 g of inhomogeneous oil which was neutralized with 3·6 g maleic acid in 20 ml ethanol. Addition of ether led to crystallization of 5·3 g of inhomogeneous maleate melting at 140—163°C with decomposition. Crystallization of this product from 10 ml ethanol gave 1·7 g of a substance melting at 164—168·5°C. Further crystallization from ethanol gave the homogeneous produt melting at 174—175°C which was assigned to be *XXVIII* bis(hydrogen maleate). Mass spectrum: 186 (M^+, $C_{10}H_{22}N_2O$), 171, 140 ($C_8H_{16}N_2$), 127 ($C_7H_{15}N_2$). For $C_{18}H_{30}N_2O_9$ (418·4) calculated: 51·66% C, 7·23% H, 6·70% N; found: 51·59% C, 7·39% H, 6·56% N.

TABLE I
(2-Oxo-1-pyrrolidinyl)acetic acid piperazides

Compound Yield %	M.p., °C Solvent	Formula (M.w.)	Calculated/Found		
			% C	% H	% N
VI-HM[a]	138–142	$C_{15}H_{23}N_3O_6$	52·77	6·79	12·31
82	2-propanol–ether	(341·4)	52·53	6·88	12·19
VII-HM[a]	169·5–170	$C_{17}H_{27}N_3O_6$	55·27	7·37	11·37
66	2-propanol	(369·4)	55·01	7·67	11·24
VIII-HM[a]	113–116	$C_{17}H_{27}N_3O_7$	52·97	7·06	10·90
67	ethanol–ether	(385·4)	52·72	7·14	10·70
VIII-P[b]	172–175[c]	$C_{19}H_{26}N_6O_{10}$	45·78	5·26	16·86
	ethanol–ether	(498·5)	45·61	5·29	16·32
IX-HM[a]	116–119	$C_{18}H_{29}N_3O_7$	54·12	7·32	10·52
48	2-propanol–ether	(399·4)	54·29	7·54	10·33
X-HM[a]	146–147	$C_{18}H_{29}N_3O_7$	54·12	7·32	10·52
50	2-propanol	(399·4)	54·22	7·49	10·55
XI-HM[a]	138·5–140	$C_{17}H_{27}N_3O_6S$[d]	50·86	6·78	10·47
64[e]	2-propanol	(401·5)	50·89	6·86	10·47
XII-HM[a]	150–152	$C_{22}H_{29}N_3O_7$	59·05	6·53	9·39
67	ethanol	(447·5)	58·76	6·82	9·10
XIII	99–100	$C_{18}H_{25}N_3O_2S$[f]	62·22	7·25	12·09
75	cyclohexane–light petroleum	(347·5)	62·47	7·40	12·18
XIII-HM[a]	159–160	$C_{22}H_{29}N_3O_6S$[g]	57·00	6·31	9·07
	2-propanol	(463·5)	56·80	6·30	9·08
XIV-HCl	222–224	$C_{17}H_{24}ClN_3O_2$[h]	60·43	7·16	12·44
68	ethanol–ether	(337·3)	60·22	7·20	12·23
XV	153·5–154·5	$C_{16}H_{21}N_3O_2$	66·87	7·37	14·62
63	ethanol	(287·4)	67·02	7·47	14·40
XV-HCl	173–175	$C_{16}H_{22}ClN_3O_2$[i]	59·34	6·85	12·98
	ethanol	(323·8)	59·26	6·79	12·72
XVI-HCl	164–166	$C_{17}H_{24}ClN_3O_2$[j]	60·43	7·16	12·44
48	ethanol	(337·8)	60·69	7·39	12·22
XVII	105–107	$C_{17}H_{23}N_3O_2$	67·75	7·69	13·94
70	benzene–light petroleum	(301·4)	67·64	7·97	14·09
XVII-HCl	166–167	$C_{17}H_{24}ClN_3O_2$[k]	60·43	7·16	12·44
	ethanol–ether	(337·8)	60·50	7·26	12·47

TABLE I
(*Continued*)

Compound Yield %	M.p., °C Solvent	Formula (M.w.)	Calculated/Found		
			% C	% H	% N
XVIII 60	152—155 benzene–light petroleum	$C_{17}H_{23}N_3O_2$ (301·4)	67·75 68·05	7·69 7·88	13·94 13·87
XVIII-HCl[l]	162—164 ethanol–ether	$C_{17}H_{24}ClN_3O_2$[m] + 0·5 C_2H_6O (360·9)	59·91 59·65	7·54 7·46	11·64 11·97
XIX 50	108—109·5 benzene–cyclohexane	$C_{18}H_{25}N_3O_2$ (315·4)	68·54 68·25	7·90 8·24	13·32 13·54
XIX-HCl	171·5—172·5 2-propanol–ether	$C_{18}H_{26}ClN_3O_2$[n] (351·9)	61·44 61·52	7·45 7·64	11·94 11·91
XX 38	128—129 benzene–light petroleum	$C_{18}H_{25}N_3O_2$ (315·4)	68·54 68·53	7·99 8·19	13·32 13·53
XXI 45	151—152 cyclohexane–benzene	$C_{19}H_{27}N_3O_2$ (329·4)	69·27 68·99	8·26 8·35	12·76 12·80
XXII 30	114·5—115 benzene–light petroleum	$C_{16}H_{20}ClN_3O_2$[o] (321·8)	59·71 59·59	6·26 6·54	13·06 13·09
XXII-HCl	138—140 ethanol	$C_{16}H_{21}Cl_2N_3O_2$[p] (358·3)	53·64 53·72	5·91 6·15	11·73 11·74
XXIII 13	99·5—100·5 benzene–light petroleum	$C_{13}H_{21}N_3O_4$ (283·3)	55·11 55·11	7·47 7·69	14·83 14·94

[a] Hydrogen maleate; [b] picrate; [c] with decomposition; [d] calculated: 7·99% S, found: 8·01% S; [e] see Experimental; [f] calculated: 9·23% S, found: 9·50% S; [g] calculated: 6·92% S, found: 7·00% S; [h] calculated: 10·49% Cl, found: 10·74% Cl; [i] calculated: 10·95% Cl, found: 10·65% Cl; [j] calculated: 10·50% Cl, found: 10·25% Cl; [k] calculated: 10·50% Cl, found: 10·35% Cl; [l] 2 : 1 solvate with ethanol; [m] calculated: 9·83% Cl, found: 10·03% Cl; [n] calculated: 10·08% Cl, found: 10·10% Cl; [o] calculated: 11·02% Cl, found: 10·86% Cl; [p] calculated: 19·79% Cl, found: 19·50% Cl.

TABLE II

Spectra of (2-Oxo-1-pyrrolidinyl)acetic acid piperazides

Compound	Spectrum	Data
VI-HM[a]	MS	225 (M^+, $C_{11}H_{19}N_3O_2$)
	IR	1 660 (CON); 1 676 (CON of lactam); 2 420 (NH^+)
VII	IR[b]	1 635 (CON); 1 684 (CON of lactam); 2 760, 2 808 (N–CH_2, N–CH)
	^{1}H NMR	1·00 d, 6 H (2 × CH_3 of 2-propyl, J = 7·0); 2·00 m, 2 H (2 × H-4 of 2-pyrrolidone); 2·40 m, 6 H ($CH_2N^4CH_2$ of piperazine and CH_2CO of pyrrolidone); 2·70 m, 1 H (NCH); 3·40 m, 6 H $CH_2N^1CH_2$ of piperazine and CH_2N of pyrrolidone); 4·00 s, 2 H (NCH_2CO)
VIII	^{1}H NMR	2·12 m, 2 H (2 × H-4 of 2-pyrrolidone), 2·50 m, 8 H (3 × CH_2 around the N^1 of piperazine and CH_2CO of pyrrolidone); 3·48 s, 3 H (OCH_3); 3·52 m, 8 H ($CH_2N^4CH_2$ of piperazine, CH_2N of pyrrolidone and OCH_2); 4·12 s, 2 H (NCH_2CO)
VIII-HM[a]	MS	269 (M^+, $C_{13}H_{23}N_3O_3$, 0·1), 237, 224, 126, 99, 98 (100)
IX	^{1}H NMR	1·75 m, 2 H (CH_2 in position 2 of propane); 2·12 m, 2 H (2 × H-4 of 2-pyrrolidone); 2·40 bm, 8 H (3 × CH_2 around the piperazine N^1 and CH_2CO of pyrrolidone); 3·32 s, 3 H (OCH_3); 3·60 m, 8 H ($CH_2N^4CH_2$ of piperazine, OCH_2, and CH_2N of pyrrolidone); 4·10 s, 2 H (NCH_2CO)
X	^{1}H NMR	1·20 t, 3 H (CH_3); 2·10 m, 2 H (2 × H-4 of 2-pyrrolidone); 2·50 m, 8 H (3 × CH_2 around the piperazine N^1 and CH_2CO of pyrrolidone); 3·59 m, 10 H ($CH_2N^4CH_2$ of piperazine, CH_2N of pyrrolidone and CH_2OCH_2); 4·10 s, 2 H (NCH_2CO)
XI	^{1}H NMR	2·10 m, 2 H (2 × H-4 of 2-pyrrolidone); 2·12 s, 3 H (SCH_3); 2·40 m, 6 H ($CH_2N^1CH_2$ of piperazine and CH_2CO of pyrrolidone); 2·62 s, 4 H (SCH_2CH_2N); 3·50 m, 6 H ($CH_2N^4CH_2$ of piperazine and CH_2N of pyrrolidone); 4·08 s, 2 H (NCH_2CO)
XIII	IR	700, 740, 750 (5 adjacent Ar–H); 1 480, 1 580 (Ar); 1 645, 1 664 (CON); 1 689 (CON of lactam)
	^{1}H NMR	2·10 m, 2 H (2 × H-4 of 2-pyrrolidone); 2·40 m, 6 H ($CH_2N^4CH_2$ of piperazine and CH_2CO of pyrrolidone); 2·64 m, 2 H (CH_2N of thioethylamino); 3·00 m, 2 H (SCH_2); 3·50 m, 6 H ($CH_2N^1CH_2$ of piperazine and CH_2N of pyrrolidone); 4·05 s, 2 H (NCH_2CO); 7·00–7·40 m, 5 H (C_6H_5)

XIV-HCl	IR	710, 761 (5 adjacent Ar–H); 1 470 (Ar); 1 660 (CON); 1 692 (CON of lactam); 2 460, 2 530 (NH^+)
XV	IR	695, 760 (5 adjacent Ar–H); 1 505, 1 575, 1 600, 3 000, 3 020, 3 040, 3 080 (Ar); 1 648 (CON); 1 673 (CON of lactam); 2 825 (CH_2–N)
	^{1}H NMR	2·10 m, 2 H (2 × H-4 of 2-pyrrolidone); 2·41 m, 2 H (CH_2CO of pyrrolidone); 3·15 m, 4 H ($CH_2N^4CH_2$ of piperazine); 3·60 m, 6 H ($CH_2N^1CH_2$ of piperazine and CH_2N of pyrrolidone); 4·14 s, 2 H (NCH_2CO); 6·90 m, 2 H (H-2 and H-6 of phenyl); 7·25 m, 3 H (H-3, H-4, and H-5 of phenyl)
XVI-HCl	MS	301 (M^+, $C_{17}H_{23}N_3O_2$), 301 (2·4), 203 (2), 159 (8·8), 146 (100), 133 (20·8), 126 (11·2), 118 (26), 98 (18·4), 91 (9·6), 70 (10·8), 56 (18)
XVII	^{1}H NMR	2·10 m, 2 H (2 × H-4 of 2-pyrrolidone); 2·30 s, 3 H ($ArCH_3$); 2·45 m, 2 H (CH_2CO of pyrrolidone); 3·12 bm, 4 H ($CH_2N^4CH_2$ of piperazine); 3·60 bm, 6 H ($CH_2N^1CH_2$ of piperazine and CH_2N of pyrrolidone); 4·18 s, 2 H (NCH_2CO); 6·60–7·30 m, 4 H (ArH)
XVII-HCl	IR	694, 788, 803, 885 (3 adjacent and solitary Ar–H); 1 510, 1 590 (Ar); 1 665 (CON); 1 688 (CON of lactam); 2 260 (NH^+)
XVIII	IR	827 (2 adjacent Ar–H); 1 364 (Ar–N); 1 500, 1 519, 1 575, 1 615, 3 015, 3 055 (Ar); 1 700 (CON); 1 741 (CON of lactam); 2 800 (CH_2–N)
	^{1}H NMR	2·25 s, 3 H ($ArCH_3$); 1·90–2·60 m, 4 H (CH_2CH_2 in positions 3 and 4 of 2-pyrrolidone); 3·10 m, 4 H ($CH_2N^4CH_2$ of piperazine); 3·60 m, 6 H (CH_2N of pyrrolidone and $CH_2N^1CH_2$ of piperazine); 4·15 s, 2 H (NCH_2CO); 6·81 d, 2 H (H-2 and H-6 of 4-tolyl, $J = 8·5$); 7·10 d, 2 H (H-3 and H-5 of 4-tolyl, $J = 8·5$)
XIX	IR	830 (2 adjacent Ar–H), 1 492, 1 514, 1 547, 3 010, 3 040 (Ar); 1 642 (CON); 1 684 (CON of lactam); 2 790 (CH_2–N)
	^{1}H NMR	1·21 t, 3 H (CH_3, $J = 7·0$); 2·12 m, 2 H (2 × H-4 of 2-pyrrolidone); 2·40 bt, 2 H (CH_2CO of pyrrolidone); 2·60 q, 2 H ($ArCH_2$, $J = 7·0$); 3·18 bm, 4 H ($CH_2N^1CH_2$ of piperazine); 3·60 m, 6 H ($CH_2N^4CH_2$ of piperazine and CH_2N of pyrrolidone); 4·18 s, 2 H (NCH_2CO); 6·86 d, 2 H (H-2 and H-6 of ethylphenyl, $J = 8·5$); 7·12 d, 2 H (H-3 and H-5 of ethylphenyl, $J = 8·5$)
XX	IR	782 (3 adjacent Ar–H); 1 650 (CON); 1 675 (CON of lactam)
	^{1}H NMR	2·10 m, 2 H (2 × H-4 of 2-pyrrolidone); 2·30 s, 6 H (2 × $ArCH_3$); 2·40 m, 2 H (CH_2CO of pyrrolidone); 3·08 bm, 4 H ($CH_2N^1CH_2$ of piperazine); 3·60 m, 6 H ($CH_2N^4CH_2$ of piperazine and CH_2N of pyrrolidone); 4·15 s, 2 H (NCH_2CO); 6·95 s, 3 H (ArH)

TABLE II
(*Continued*)

Compound	Spectrum	Data
XXI	IR	877 (solitary Ar–H); 1 485 (Ar); 1 655 (CON); 1 684 (CON of lactam); 2 740 (CH_2–N)
	^{1}H NMR	2·11 m, 2 H (2 × H-4 of 2-pyrrolidone); 2·20 s, 3 H ($ArCH_3$ in position 4); 2·25 s, 6 H (remaining 2 × $ArCH_3$); 2·46 bt, 2 H (CH_2CO of pyrrolidone); 3·08 bm, 4 H ($CH_2N^1CH_2$ of piperazine); 3·60 m, 6 H ($CH_2N^4CH_2$ of piperazine and CH_2N of pyrrolidone); 4·18 s, 2 H (NCH_2CO); 6·82 s, 2 H (ArH)
XXII	IR	772, 838 (3 adjacent and solitary Ar–H); 1 485, 1 530, 1 560, 1 588 (Ar); 1 654 (CON); 1 696 (CON of lactam)
	^{1}H NMR	2·12 m, 2 H (2 × H-4 of 2-pyrrolidone); 2·40 bt, 2 H (CH_2CO of pyrrolidone); 3·20 nm, 4 H ($CH_2N^1CH_2$ of piperazine); 3·60 m, 6 H ($CH_2N^4CH_2$ of piperazine and CH_2N of pyrrolidone); 4·18 s, 2 H (NCH_2CO); 6·85 m, 4 H (ArH)
XXIII	IR	1 040, 1 072, 1 231, 1 256, 1 287, 1 702 (NCOOR); 1 470, 1 495 (Ar); 1 650 (CON); 1 692 (CON of lactam)
	^{1}H NMR	1·30 t, 3 H (CH_3, $J = 7·0$); 2·12 m, 2 H (2 × H-4 of 2-pyrrolidone); 2·45 bt, 2 H (CH_2CO of pyrrolidone); 3·52 bs, 10 H (4 × CH^2N of piperazine and CH_2N of pyrrolidone); 4·15 s, 2 H (NCH_2CO); 4·20, q 2 H (OCH_2, $J = 7·0$)

[a] Hydrogen maleate; [b] film.

1,4-Bis((2-oxo-1-pyrrolidinyl)acetyl)piperazine (*XXIV*)

A) A mixture of 6·85 g *II* (refs.[2,20,21]), 1·62 g piperazine, and 20 ml toluene was stirred and refluxed for 7 h. Toluene was distilled off (the temperature of the mixture rose for a short time to 140°C), the residue was cooled and diluted with 20 ml benzene. There crystallized 2·5 g (37%) of crude *XXIV* which was purified by recrystallization from a mixture of dimethylformamide and ethanol, m.p. 293—295°C with decomposition. Mass spectrum: 336 (M^+, $C_{16}H_{24}N_4O_4$). IR spectrum: 1 652 (CON of piperazide); 1 670 (CON of the lactam). For $C_{16}H_{24}N_4O_4$ (336·4) calculated: 57·13% C, 7·19% H, 16·66% N; found: 56·83% C, 7·53% H, 16·88% N.

Evaporation of the benzene mother liquor gave 4·4 g of oily residue which was neutralized with 1·6 g oxalic acid dihydrate in ethanol. There crystallized 2·0 g (35%) of 1-((2-oxo-1-pyrrolidinyl)-acetyl)piperazine (*XXV*) hydrogen oxalate, m.p. 194·5—195·5°C (ethanol–acetone). For $C_{12}H_{19}$·$.N_3O_6$ (301·3) calculated: 47·83% C, 6·36% H, 13·95% N; found: 47·54% C, 6·55% H, 13·82% N.

B) A stirred mixture of 1·62 g piperazine and 6·85 g *II* (ref.[20]) was heated for 10 h to 150 to 170°C (bath temperature). After cooling it was diluted with 20 ml benzene and 20 ml light petroleum. After standing overnight the crystalline *XXIV* was filtered, washed with a mixture of benzene, ethanol, and acetone, and dried in vacuo; 5·2 g (77%) of *XXIV*, m.p. 290—295°C, identical with the product obtained under *A*.

3-(4-((2-Oxo-1-pyrrolidinyl)acetyl)-1-piperazinyl)propionamide (*XXVI*)

A stirred solution of 5·5 g 3-(1-piperazinyl)propionamide[34] and 3·54 g triethylamine in 30 ml chloroform was treated at 40°C over 50 min with a solution of 5·7 g *IV* (refs[32,33]) in 15 ml chloroform and the mixture was refluxed for 1·5 h. After cooling the mixture was filtered, the filtrate was diluted with 50 ml chloroform and washed with a saturated solution of K_2CO_3. Processing of the chloroform solution gave 6·48 g of residue which was crystallized from a mixture of 2-propanol and light petroleum; 4·0 g (38%) of *XXVI* hemihydrate, m.p. 81—83°C. Mass spectrum: 282 (M^+, $C_{13}H_{22}N_4O_3$, 1·2), 165 (6·5), 238 (3), 224 (4), 211 (2·5), 197 (2), 140 (32), 127 (100), 115 (68), 98 (90), 79 (39), 65 (54), 42 (49). IR spectrum: 1 640 (CON); 1 648 (CON of the lactam); 1 670 ($CONH_2$); 2 680, 2 725 (CH_2–N); 3 190, 3 345, 3 475 (NH_2, H_2O). ^{1}H NMR spectrum (100 MHz): 2·00—2·80 m, 12 H (CH_2CH_2CO of pyrrolidone, $CH_2N^1CH_2$ of piperazine, and NCH_2CH_2CO); 3·52 bm, 6 H ($CH_2N^4CH_2$ of piperazine and CH_2N of pyrrolidone); 4·12 s, 2 H (NCH_2CO); 6·12 bs and 7·42 bs, 1 and 1 H ($CONH_2$). For $C_{13}H_{22}N_4O_3 + 0·5\ H_2O$ (291·4) calculated: 53·59% C, 7·95% H, 19·23% N; found: 53·29% C, 7·65% H, 19·14% N.

Hydrogen maleate, m.p. 147—148°C (2-propanol). For $C_{17}H_{26}N_4O_7$ (398·4) calculated: 51·25% C, 6·58% H, 14·06% N; found: 51·13% C, 6·61% H, 13·86% N.

Ethyl 2-(2-Oxo-1-pyrrolidinyl)butyrate (*XXXI*)

A stirred solution of 43·4 g 2-pyrrolidone in 200 ml benzene was treated over 1 h with 15·0 g 80% NaH (suspension in oil) and the mixture was stirred for 2·5 h at 55—65°C. It was then treated over 1 h at the same temperature with a mixture of 102 g ethyl 2-bromobutyrate and 60 ml benzene and it was refluxed for 5 h. After cooling the mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was distilled giving 83·7 g (84%) of *XXXI*, b.p. 100°C/47 Pa, n_D^{20} 1·4625. IR spectrum (film): 1 188, 1 284, 1 735 (RCOOR'); 1 685 (NCO). ^{1}H NMR spectrum (100 MHz): 0·91 t, 3 H (CH_3 of C-ethyl, J = 7·0); 1·26 t, 3 H (CH_3 of O-ethyl, J = 7·0); 1·60—2·20 m, 4 H (2 × H-4 of pyrrolidone and CH_2 of C-ethyl); 2·42 bt, 2 H (CH_2CO); 3·45 m, 2 H (CH_2N); 4·16 q, 2 H (OCH_2, J = 7·0); 4·70 dd, 1 H (NCHCO, J = 10·0; 5·0). For $C_{10}H_{17}NO_3$ (199·3) calculated: 60·27% C, 8·60% H, 7·03% N; found: 60·57% C, 8·75% H, 6·98% N.

2-(2-Oxo-1-pyrrolidinyl)butyric Acid (*XXXII*)

A mixture of 19·9 g *XXXI* and a solution of 6·5 g 85% KOH in 100 ml 96% ethanol was refluxed for 70 min. Ethanol was evaporated in vacuo, the residue was acidified with 20 ml 10M-HCl and the product was extracted with chloroform. Processing of the extract gave 15·6 g (91%) of *XXXII*, m.p. 156–157°C (chloroform–toluene). IR spectrum: 950, 1 200, 1 720, 2 460, 2 530, 2 570, 2 666 (COOH); 1 631 (NCO). ^{1}H NMR spectrum (100 MHz): 0·82 t, 3 H (CH_3, J = 7·0); 1·50–1·80 m, 2 H (CH_2 of ethyl); 2·00 m, 2 H (2 × H-4 of 2-pyrrolidone); 2·25 bt, 2 H (CH_2CO); 3·34 bm, 2 H (CH_2N); 4·40 dd, 1 H (NCHCO, J = 10·5; 5·0). For $C_8H_{13}NO_3$ (171·2) calculated: 56·13% C, 7·65% H, 8·18% N; found: 56·32% C, 7·62% H, 8·29% N.

3-(4-(2-(2-Oxo-1-pyrrolidinyl)butyryl)-1-piperazinyl)propionamide (*XXX*)

A suspension of 6·8 g *XXXII* in 30 ml benzene was treated with a solution of 5·2 g $SOCl_2$ in 20 ml benzene and the mixture was heated for 40 min to 50–65°C and refluxed for 5 min. The volatile components were evaporated completely in vacuo and the residue (7·6 g of crude *XXXIII*) was dissolved in 20 ml chloroform and the solution was added dropwise over 1 h at 40–42°C to a stirred solution of 6·28 g 3-(1-piperazinyl)propionamide[34] and 4·1 g triethylamine in 35 ml chloroform. The mixture was refluxed for 3 h. After standing overnight the precipitated solid was filtered off, the filtrate was filtered with active carbon ,the filtrate was washed with a solution of 20 g K_2CO_3 in 20 ml water, dried, and evaporated; 9·6 g of crude oily *XXX*. It was neutralized with 3·8 g maleic acid in 25 ml 2-propanol, the warm solution of the maleate was filtered with active carbon and the filtrate was allowed to crystallize. The crude maleate (8·74 g) was recrystallized from 80 ml ethanol giving 5·17 g (30% per the starting *XXXII*) of the pure *XXX* hydrogen maleate, m.p. 160–162·5°C (ethanol–ether). For $C_{19}H_{30}N_4O_7$ (426·5) calculated: 53·51% C, 7·09% H, 13·14% N; found: 53·14% C, 7·18% H, 13·03% N.

1-Benzyl-4-(2-(3-trifluoromethylphenyl)ethyl)piperazine (*XXXVb*)

A mixture of 30·5 g 2-(3-trifluoromethylphenyl)ethyl chloride[44] and 51·5 g 1-benzylpiperazine[24] was heated for 14 h to 130°C (bath temperature). After cooling th mixture was diluted with 100 ml ether and shaken with an excess of dilute hydrochloric acid. Evaporation of the organic layer recovered 5·5 g of the starting 2-(3-trifluoromethylphenyl)ethyl chloride. The aqueous layer was a suspension of the crude *XXXVb* dihydrochloride (could be isolated by filtration) in its acid solution. It was made alkaline with 20% NaOH and the base was isolated by extraction with ether. The extract was processed and the residue was distilled giving 33·5 g (80% per conversion) of *XXXVb*, b.p. 177–179°C/0·1 kPa. For characterization it was transformed to the bis(hydrogen maleate, m.p. 204·5–205·5°C (aqueous ethanol). For $C_{28}H_{31}F_3N_2O_8$ (580·6) calculated: 57·93% C, 5·38% H, 9·82% F, 4·83% N; found: 58·18% C, 5·13% H, 9·49% F, 4·73% N.

1-(4-Fluorobenzyl)-4-(2-(3-trifluoromethylphenyl)ethyl)piperazine (*XXXVIb*)

A mixture of 14·0 g 1-(4-fluorobenzyl)piperazine[45] and 15·0 g 2-(3-trifluoromethylphenyl)ethyl chloride[44] was heated for 7 h to 140°C and the mixture was processed similarly like in the preceding case. The starting chloride was partly recovered (5·6 g). The crude basic product was distilled giving 13·7 g (83% per conversion) of crude *XXXVIb*, b.p. about 175°C/0·13 kPa, which was transformed to the dihydrochloride, m.p. 274–278°C with decomposition (in a sealed capillary) (crystallized from ethanol–ether). For $C_{20}H_{24}Cl_2F_4N_2$ (439·3) calculated: 54·68% C, 5·51% H, 17·30% F, 6·38% H; found: 54·69% C, 5·61% H, 17·51% F, 6·46% N.

Methyl 3-(2-(4-Benzyl-1-piperazinyl)ethyl)benzoate (*XXXVa*)

A mixture of 34·4 g *XXXVb* dihydrochloride and 110 g H_2SO_4 was heated for 3 h to 100°C. After cooling the mixture was treated with 80 ml methanol and refluxed for 3 h. It was poured on ice, carefully made alkaline with 20% NaOH and at the end with Na_2CO_3, the product was extracted with ether. The extract was dried, filtered, and slightly acidified with HCl in ether; 27·6 g (83%) of *XXXVa* dihydrochloride, m.p. 229–233°C (methanol). For $C_{21}H_{28}Cl_2N_2O_2$ (411·4) calculated: 61·31% C, 6·86% H, 17·24% Cl, 6·81% N; found: 61·50% C, 6·82% H, 17·04% Cl, 7·00% N.

Methyl 3-(2-(4-(4-Fluorobenzyl)-1-piperazinyl)ethyl)benzoate (*XXXVIa*)

A mixture of 11·1 g *XXXVIb* dihydrochloride and 36 g H_2SO_4 was stirred and heated for 3 h to 100°C. After cooling, 27 ml methanol were added and the mixture was refluxed for 3 h. Similar processng like in the preceding case gave 9·2 g (85%) of *XXXVIa* dihydrochloride, m.p. 244 to 247°C with decomposition (methanol). UV spectrum: 263 (3·11), 270 (3·14), 275 (3·07), 282·5 (3·01). IR spectrum: 694, 752, 822, 830, 836, 861 (3 and 2 adjacent and solitary Ar–H); 1 235, 1 237, 1 243, 1 716 (ArCOOR); 1 520, 1 600, 1 609 (Ar); 2 300, 2 372 (NH^+). For $C_{21}H_{27}Cl_2 . FN_2O_2$ (429·4) calculated: 58·74% C, 6·34% H, 16·52% Cl, 4·43% F, 6·52% N; found: 58·52% C, 6·24% H, 16·66% Cl, 4·53% F, 6·57% N.

2-(3-Trifluoromethylphenyl)butanol (*XXXVII*)

Grignard reagent was prepared from 67·7 g 1-bromo-3-(trifluoromethyl)benzene and 7·8 g Mg in 150 ml tetrahydrofuran with the help of a grain of iodine. The solution of the reagent was refluxed for 1 h, cooled to 0°C, and treated under stirring with a solution of 43·3 g 1,2-epoxybutane in 100 ml benzene, added dropwise at 0–5°C. It was stirred for 1 h at the temperature indicated and was allowed to stand overnight at room temperature. It was refluxed for 1 h and after cooling poured into 200 ml ice-cold 10% H_2SO_4. The organic layer was separated, dried, and evaporated. The residue was distilled giving 35·3 g (53%) of the crude product boiling at 125–130°C/4 kPa. A sample for analysis was redistilled, b.p. 110°C/2 kPa. The product is contaminated by the position isomer (^{1}H NMR spectrum). For $C_{11}H_{13}F_3O$ (218·2) calculated: 60·54% C, 6·00% H, 26·12% F; found: 60·73% C, 6·06% H, 25·97% F.

1-Benzyl-4-(2-(3-trifluoromethylphenyl)butyl)piperazine (*XXXIX*)

A stirred solution of 35·2 g crude *XXXVII* and 16 g pyridine in 40 ml dichloromethane was treated at −5–0°C with 23·7 g $SOCl_2$, added dropwise. The mixture was allowed to stand for 48 h at room temperature, washed with water, dried ($CaCl_2$), and distilled; 19·8 g of inhomogeneous *XXXVIII*, b.p. 96–100°C/1·6 kPa. It was heated with 30 g 1-benzylpiperazine[24] to 150°C for 6 h. After cooling the mixture was diluted with 200 ml ether, the precipitated solid was filtered off and the filtrate was treated with HCl in ether. The precipitated mixture of hydrochlorides was filtered and fractionally crystallized from mixture of ethanol and ether. The homogeneous product obtained melted at 194–196°C (234–237°C in a sealed capillary) and was identified as *XXXIX* dihydrochloride. For $C_{22}H_{29}Cl_2F_3N_2$ (449·4) calculated: 58·80% C, 6·50% H, 15·78% Cl, 12·68% F, 6·23% N; found: 58·53% C, 6·52% H, 15·81% Cl, 12·45% F, 6·52% N.

Decomposition of a sample of this dihydrochloride with NH_4OH and extraction with dichloromethane gave the homogeneous oily *XXXIX* which was used for recording the ^{1}H NMR spec-

trum: 0·80 bt, 3 H (CH_3); 1·10 m, 2 H (CH_2 of ethyl); 1·80 m, 2 H (CH_2N^4); 2·50 s, 8 H (4 × CH_2N of piperazine); 3·30 dd, 1 H (ArCH); 3·42 s, 2 H ($ArCH_2N$); 7·21 s, 5 H (C_6H_5); 7·40 m, 4 H (remaining 4 ArH).

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