EXPERIMENTAL ANTIULCER AGENTS: N-SUBSTITUTED 2-(4-METHYL-1-PIPERAZINYL)ACETAMIDES AS PIRENZEPINE MODELS AND SOME RELATED COMPOUNDS

Hana HULINSKÁ[a], Zdeněk POLÍVKA[a], Jiří JÍLEK[a], Karel ŠINDELÁŘ[a], Jiří HOLUBEK[a], Emil SVÁTEK[a], Oluše MATOUŠOVÁ[a], Miloš BUDĚŠÍNSKÝ[b], Hana FRYCOVÁ[a] and Miroslav PROTIVA[a]

[a] *Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3 and*
[b] *Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6*

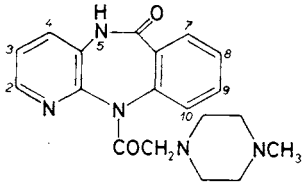
Received January 25th, 1988
Accepted February 15th, 1988

Reactions of N-cyclohexyl-2-chloroacetamide, N-phenyl-2-chloroacetamide, N-(4-dimethylaminophenyl)-2-chloroacetamide, N-(2-nitrophenyl)-N-phenyl-2-chloroacetamide, its 3-nitrophenyl and 4-nitrophenyl analogues, N-(2-benzylphenyl)-2-chloroacetamide, 5-(chloroacetyl)-dibenz[*b,f*]azepine, and its 10,11-dihydro derivative with piperazine, 1-methylpiperazine, 2-(1-piperazinyl)ethanol, and 3-(1-piperazinyl)propanol resulted in compounds *II*, *III*, *V*—*XV*, *XVIII*, *XXI*, and *XXIII*, simple analogues of the antiulcer agent pirenzepine (*I*). Contributions to the syntheses and characterization of mianserin (*XIX*), bisnor analogue of imipramine (*XXV*), and pirenzepine (*I*) are presented. Two 2-aryl-2-(2-pyridyl)thioacetamides *XXXVIII* and *XL* were synthesized via nitriles *XXXIX* and *XLI*. Compounds *XI* (VÚFB-17 104) and *XXI* (VÚFB-17 113) were found to be rather effective as anti-ulcer agents and anticholinergics.

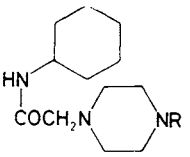
The attempts to develop new antiulcer and antisecretory drugs continue in several directions[1-5], one of them being the group of anticholinergic and antimuscarinic aminoacetamides with pirenzepine (*I*) (ref.[6]) as the leading representative. The fact that such simple pirenzepine models like hexaprazol (esaprazole) (*II*) (ref.[7]) exhibit also important antiulcer, antisecretory, and cytoprotective effects[8-13], led us to investigate further title compounds as experimental antiulcer drugs.

A sample of *II* was needed as the standard and was prepared by reaction of piperazine monohydrochloride with N-cyclohexyl-2-chloroacetamide[14] in water at 100°C (ref.[7]). The known base *II* was obtained in the yield of 82% transformed to new salts (dimethanesulfonate, dimaleate, and sesquimaleate). The methylpiperazine compound *III* was prepared by reaction of N-cyclohexyl-2-chloroacetamide[14] with an excess of 1-methylpiperazine at 130°C. It was obtained in the yield of 49% and was transformed to the dimaleate. A less soluble by-product was isolated and identified (analysis and spectra) as *IV*. The explanation of the formation of this compound

consists in the presence of a small amount of piperazine as impurity in the 1-methylpiperazine used (it was prepared by methylation of piperazine monohydrochloride with dimethyl sulfate[15]).

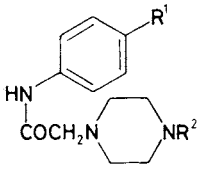


I



II, R = H
III, R = CH_3
IV, R = CH_2CONH—⬡

Out of the aromatic analogues of hexaprazol, the aniline derivative *V* was known[16]; it was prepared in a different connection as a potential analgesic. It was obtained by us by reaction of N-phenyl-2-chloroacetamide[17] with excessive 1-methylpiperazine at 50°C and transformed to the new dimaleate. Similar reactions with 2-(1-piperazinyl)ethanol and 3-(1-piperazinyl)propanol[18] afforded *VI* and *VII* which were characterized by spectra and transformed to dihydrochlorides. In the effort to introduce into the aniline fragment a slightly basic group and coming thus closer to the character of *I*, we started from N-(4-dimethylaminophenyl)-2-chloroacetamide[19] and prepared by similar transformations compounds *VIII*–*X*. The crystalline bases were characterized by spectra and were converted to dimaleates.

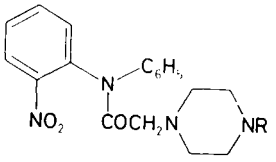


V, R^1 = H ; R^2 = CH_3
VI, R^1 = H ; R^2 = CH_2CH_2OH
VII, R^1 = H ; R^2 = $(CH_2)_3OH$

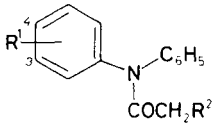
VIII, R^1 = $N(CH_3)_2$; R^2 = CH_3
IX, R^1 = $N(CH_3)_2$; R^2 = CH_2CH_2OH
X, R^1 = $N(CH_3)_2$; R^2 = $(CH_2)_3OH$

Based on the Erlenmeyer's concept of bioisosterism between pyridine and nitrobenzene[20,21], the formula of the open model of pirenzepine *XI*, containing the 2-nitroaniline residue instead of the 2-pyridineamine moiety, was designed. Its synthesis was carried out by reaction of the known N-(2-nitrophenyl)-N-phenyl-2-chloroacetamide[22] with 1-methylpiperazine at 50°C; the dimaleate was prepared

for pharmacological testing. Similar reactions with 2-(1-piperazinyl)ethanol and 3-(1-piperazinyl)propanol[18] gave oily bases *XII* and *XIII* which were characterized in the form of dimaleates. The released homogeneous base *XIIII* was used for recording the spectra; in the case of *XII*, the mass spectrum served as a proof of identity. For pharmacological comparison, the 3-nitrophenyl and 4-nitrophenyl analogues *XIV* and *XV* were also prepared. Reaction of 3-nitrodiphenylamine[23] with chloroacetyl chloride in dimethylacetamide at 70°C (method, ref.[24]) and reaction of 4-nitrodiphenylamine[25] with chloroacetyl chloride in boiling toluene afforded *XVI* and *XVII* which were reacted with excessive 1-methylpiperazine in boiling chloroform to give the oily bases *XIV* and *XV*. The products were purified in the form of dimaleates and their identity was confirmed by spectra (including mass spectra).



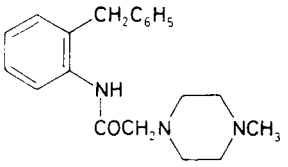
XI, R = CH_3
XII, R = CH_2CH_2OH
XIII, R = $(CH_2)_3OH$



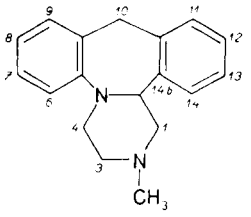
XIV, R^1 = 3-NO_2; R^2 = —N◯NCH$_3$ *XVI*, R^1 = 3-NO_2; R^2 = Cl
XV, R^1 = 4-NO_2; R^2 = —N◯NCH$_3$ *XVII*, R^1 = 4-NO_2; R^2 = Cl

A further member in our series of pirenzepine model compounds was *XVIII* which was obtained by reaction of the known N-(2-benzylphenyl)-2-chloroacetamide[26] with 1-methylpiperazine in chloroform and which was transformed for pharmacological testing to the dimaleate. The mentioned N-(2-benzylphenyl)-2-chloroacetamide is the intermediate of one synthesis[26,27] of the atypical antidepressant agent mianserin (*XIX*) (refs[28-31]) (for different syntheses, cf. refs[32,33]). In a different connection, we needed a sample of *XIX* as the standard, and we repeated therefore the mentioned synthesis[26]. In the last step, which consists in reduction of *XX*, we met with an unexpected phenomenon. In the first reduction experiment, lithiumaluminium hydride in a mixture of ether and tetrahydrofuran was used instead of the described[26] diborane (generated from sodium borohydride and boron trifluoride etherate in tetrahydrofuran and introduced into a suspension of *XX*). In the yield of 64% the practi-

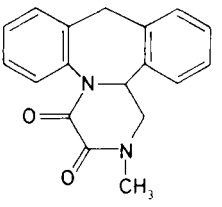
cally homogeneous (TLC) oily base *XIX* was obtained which afforded the hydrochloride melting at 281–284°C (with decomposition) which is in full agreement with the published value. In the second and third reduction experiment diborane was used (introduced into a suspension of *XX* in tetrahydrofuran, or used "in situ") which led to 87% of crystalline $C_{18}H_{20}N_2$ (analysis and mass spectrum) giving a seemingly homogeneous hydrochloride melting at 248–255°C. Because the literature – according to our knowledge – did not mention crystalline *XIX*, our product was subjected to full characterization. Its ^{1}H NMR spectrum (80 MHz) is practically identical with that published[34] for *XIX* (200 MHz). The mass spectra of the higher and lower melting hydrochlorides showed the same molecular ions and the same fragments (slight differences in the intensities of the peaks). Repeated recrystallization of our lower-melting hydrochloride led finally to the substance melting at 281–284°C. The question whether the lower-melting substance was a crystal modification or a relatively stable conformer, corresponding to the crystalline base, did not seem to be clearly answered. The molecule of *XIX* contains the chiral centre at C-14b. The resolution of racemic *XIX* and the characterization of the enantiomers were not described. On the other hand, the enantiomers are known and the stereoselectivity of pharmacological action was described[35]: the activity resides in the (*S*)(+)-enantiomer. An X-ray structure analysis of the hydrobromide of this enantiomer was also published[36,37]. Another X-ray analysis[38] relates to "mianserin $C_{18}H_{20}N_2$" and probably the racemic hydrochloride was the object of this study. Restricted inversion of the central, nonplanar, seven-membered ring leads sometimes (cf. ref.[39]) to very stable conformers. This possibility in the present case seems to be ruled out by the identity of the published ^{1}H NMR spectrum[34] and of the spectrum of our crystalline substance. The possibility of a fast equilibrium between two or more conformers is excluded by the absence of any temperature effect on the ^{1}H NMR spectrum[34]. We have thus to conclude that our crystalline substance $C_{18}H_{20}N_2$ is the base *XIX* and the lower-melting hydrochloride is an unstable crystal modification.



XVIII



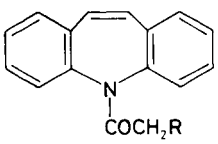
XIX



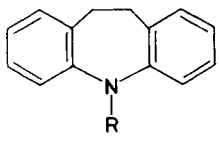
XX

Further to be prepared were the dideaza-deoxy analogues of pirenzepine (*I*) of formulae *XXI* and *XXIII*, i.e. derivatives of 5*H*-dibenz[*b*,*f*]azepine and its 10,11-

-dihydro derivative. The starting chloroacetamides *XXII* (ref.[40]) and *XXIV* (refs[40-42]) were known and reacted smoothly with excessive 1-methylpiperazine at 50–65°C giving in good yields the crystalline bases *XXI* and *XXIII* which were characterized by spectra and transformed to dihydrochlorides. After termination of our experiments, the preparation of *XXIII* has been reported quite recently[42]; the melting point reported is much lower than our value. In a different connection we needed 3-(10,11-dihydrodibenz[*b*,*f*]azepin-5-yl)propylamine (*XXV*) which is a metabolite of the well-known antidepressant agent imipramine (*XXVI*) (refs[43-46]). After unsuccessful attempts to prepare the nitrile *XXVII* by addition of 10,11-dihydrodibenz[*b*,*f*]azepine to acrylonitrile, *XXVII* was synthesized by the described[47] reaction sequence via *XXVIII* (ref.[48]) and reduced with aluminium hydride to give *XXV* (the published procedure consisted in reduction with sodium and ethanol). The identity of the product was confirmed by spectra; the hydrochloride melted by 7°C lower than reported[47].



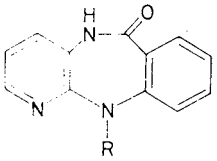
XXI, R = –N⟨⟩NCH$_3$
XXII, R = Cl



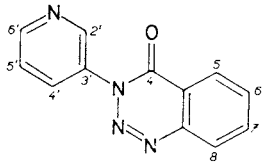
XXIII, R = COCH$_2$N⟨⟩NCH$_3$
XXIV, R = COCH$_2$Cl
XXV, R = (CH$_2$)$_3$NH$_2$
XXVI, R = (CH$_2$)$_3$N(CH$_2$)$_3$
XXVII, R = CH$_2$CH$_2$CN
XXVIII, R = CH$_2$CH$_2$Cl

Compound *I* (cf. refs[6,49]) was also needed as the standard for pharmacological comparison with the substances prepared and was also synthesized. The tricyclic key intermediate *XXIX* was obtained first by making use of the described procedure[50], which started from 2-chloro-3-aminopyridine and 2-nitrobenzoyl chloride, proceeded in two steps to N-(2-chloro-3-pyridyl)anthranilamide which was cyclized by heating to 205–210°C. The disadvantage of this method consists in the fact that a good yield of the final cyclization reaction was obtained only when working in very small batches (several grams); in batches over 10 g the yields are unsatisfactorily low. Formation of *XXIX* by heating methyl anthranilate with 3-aminopyridine in dimethyl sulfoxide in the presence of sodium amide[51] could not be confirmed. A mixture was obtained which was separated by chromatography on silica gel. The first to be eluted was a compound $C_{12}H_8N_4O$. The ^{1}H NMR spectrum (200 MHz) proved the presence of four hydrogen atoms of the 1,2-disubstituted benzene and four hydrogen atoms of the 3-substituted pyridine. The ^{13}C NMR spectrum shows signals of 11 aromatic carbon atoms (three of the type >C= and eight of the type

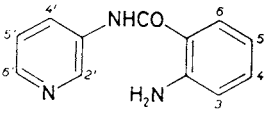
—CH=). The IR spectrum shows bands corresponding to 4 and 3 adjacent and to solitary Ar—H, further the amide band (1 683 cm^{-1}) and a band attributable to the —N=N— fragment (1 603 cm^{-1}). In the mass spectrum the base peak has m/z 196 corresponding to cleavage of N_2 from the intact molecule. All these facts are in agreement with formulating the product as 3-(3-pyridyl)-1,2,3-benzotriazin-4(3*H*)-one (*XXXI*). Because similar compounds are formed by treatment of N-substituted anthranilamides (e.g. anthranilic acid anilide) (refs[52–54]) with nitrous acid, the formation of *XXXI* in our reaction is rather obscure (it would request oxidation of the NH_2^- to NO_2^- by dimethyl sulfoxide). Anthranilic acid was eluted as the next component of the mixture and was followed by the main product which was identified as *XXXII* (cf. ref.[55]).



XXIX, R = H
XXX, R = $COCH_2Cl$



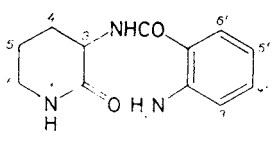
XXXI



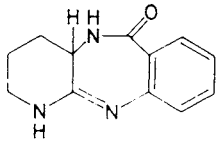
XXXII

In addition to some unsuccessful attempts[56] at preparing *XXIX* by a new way, Šunjić et al.[57,58] described a synthesis of *XXIX* from ornithine. Our experience with this synthesis differs partly from the published data and will, therefore, be mentioned. (*RS*)-3-Aminopiperidin-2-one[57,59] (prepared from (*RS*)-ornithine hydrochloride) was reacted with isatoic anhydride[60,61] in boiling acetonitrile which resulted in a compound $C_{12}H_{15}N_3O_2$ melting at 201–203°C. Because the literature[57,58] gave for the product of this reaction (*XXXIII*) the melting point of 169–170°C, our product was fully characterized by spectra which confirmed structure *XXXIII*. The only explanation of the difference in the melting points could be polymorphism (the literature product was crystallized from 2-propanol, our product from aqueous ethanol). An attempt to cyclize *XXXIII* by heating with phosphorus pentoxide to 220°C precisely according to Šunjić[57] was completely unsuccessful; no characterized product was obtained. For this reason, cyclization of *XXXIII* to *XXXIV* by heating with acetic acid was attempted. Reaction in boiling acetic acid afforded 28% compound $C_{12}H_{13}N_3O$ melting at 325–330°C with decomposition which was identified by spectra as the desired *XXXIV*; there is again an important difference in the melting point values: the literature[57] reported 293–295°C. For raising the yield, the cyclization with acetic acid was carried out in autoclave at 170°C. A completely different product, melting at 260–262°C was obtained; its elemental composition $C_{14}H_{15}N_3O_2$ (analysis and mass spectrum) showed that acetic acid parti-

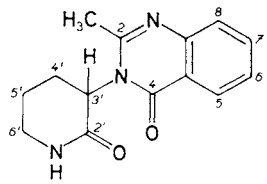
cipated in the reaction. Out of the three possible isomeric structures *XXXV* to *XXXVII*, the quinazolinone structure *XXXV* is preferred for the new product on the basis of the mass spectrum and of the following arguments: It is well known[62] that 2,3-disubstituted quinazolin-4(3*H*)-ones are easily formed by cyclization of 2-(acylamido)benzamides and N-acetylation of *XXXIII* has to be expected as proceeding under the rather hard conditions of our reaction. The ArCONH band in the IR spectrum of *XXXIV*, which appears at 1 642 cm^{-1}, and which should be very similar in *XXXVI* and *XXXVII*, appears with our product at 1 670 cm^{-1}. The ^1H (200 MHz) and ^{13}C NMR spectra prove the presence of 1,2-disubstituted benzene ring, NH, NCH_2, CH_3, and CH_2CH_2 fragments, as well as two amide carbonyls. The low-field position of the methyl signal at δ 2·69 is an argument against structures *XXXVI* and *XXXVII* (for comparison, this signal with N-acetylpiperidine is at δ 1·92). The unequivocal preference of structure *XXXV* resulted from the proof of the presence of the fragment CO—NH—CH_2 which was obtained by the decoupling experiment (irradiation of the NH proton signal brings about narrowing of the multiplet at δ 3·36 (H-6'eq) having evidently a geminal coupling with H-6'ax at δ 3·57). Heating of *XXXIII* with acetic acid in autoclave to 105°C gave a mixture containing 31% of *XXXIV* and 7% of *XXXV* which were separated on the basis of different solubility in dilute sodium hydroxide: *XXXIV* crystallized and *XXXV* was obtained from the mother liquor by extraction with chloroform. Compound *XXXIV* was finally dehydrogenated to *XXIX* by heating in pyridine in the presence of a 5% palladium-active carbon catalyst like described in ref.[57] The product was found identical with the product obtained by the first method mentioned[50].



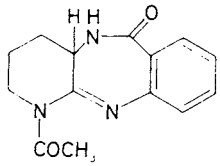
XXXIII



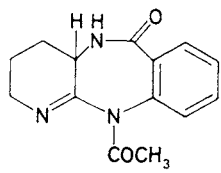
XXXIV



XXXV



XXXVI

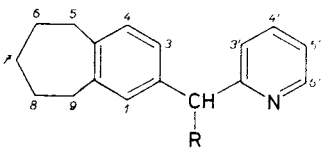


XXXVII

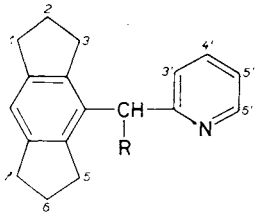
Treatment of *XXIX* with chloroacetyl chloride in boiling dioxane in the presence of triethylamine[63,64] afforded a mixture from which the pure *XXX* was obtained

by crystallization in relatively poor yields (about 50%). In larger batches, the yield was even lower (about 20%) and the main part of the mixture could be separated neither by chromatography nor by crystallization. For the final substitution reaction with excessive 1-methylpiperazine in boiling benzene[63,64], the crude *XXX* was used. The product was a mixture of two components which was separated by chromatography on silica gel. The first to be eluted was a nonidentified minor by-product which was followed by *I* as the main product (yield 87%). Crystalline *I* was transformed to the hydrochloride whose melting point was by 8°C lower than the value reported in literature[64]. The crystalline base (was not reported in the literature) was used for recording the spectra which confirmed structure *I*.

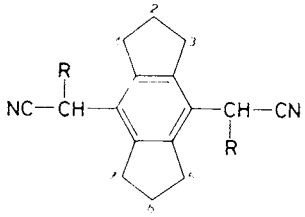
The last part of this communication is related to a different type of antiulcer and antisecretory agents which was started by the discovery of anti-gastrin potency of 2-phenyl-2-(2-pyridyl)thioacetamide (SC-15396), connected with its antisecretory and anti-ulcer activity[65,66]. Many similar thioacetamides proved interesting properties as nonanticholinergic antisecretory and anti-ulcer agents (cf. e.g. refs[67-69]) and are being investigated until recently[70]. The synthesis of two thioacetamides encompassing the 2-phenyl-2-(2-pyridyl)thioacetamide fragment in their molecules (*XXXVIII* and *XL*) is being described in this paper together with several nitriles which could be useful as intermediates in the same direction. Reaction of 2-(6,7,8,9-tetrahydro-5*H*-benzocycloheptene-2-yl)acetonitrile[71] with 2-bromopyridine in boiling toluene in the presence of sodium amide gave the nitrile *XLII* which was dis-



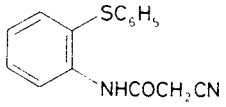
XXXVIII, R = $CSNH_2$
XXXIX, R = CN



XL, R = $CSNH_2$
XLI, R = CN



XLII, R = H
XLIII, R = 



XLIV

solved in a mixture of pyridine and triethylamine and the solution was saturated with hydrogen sulfide; thioamide *XXXVIII* was obtained and characterized. (*s*-Hydrindacen-4-yl)acetonitrile[72] was similarly transformed via *XLI* to *XL*. 4,8-Bis(chloromethyl)-*s*-hydrindacene[73] was treated with sodium cyanide in dimethyl sulfoxide to give the dinitrile *XLII* which reacted with 2-bromopyridine and sodium amide like in the preceding cases and afforded *XLIII*. This compound, in spite of the fact that its molecule contains two centres of chirality, seems to be homogeneous (TLC). In the last experiment, 2-(phenylthio)aniline (ref.[74], method[75]) was heated with ethyl cyanoacetate to 200–210°C and gave in good yield *XLIV*.

The piperazine derivatives prepared were tested pharmacologically as potential anti-ulcer agents and were compared with pirenzepine (*I*) as the standard. They were administered orally in the form of salts, described in the Experimental; the doses given were calculated per bases. The experimental data are assembled in Table I. The acute toxicities were determined with female mice and are expressed as the LD_{50} values. The testing of the anti-ulcer effect used the indomethacine-induced gastric lesions in rats (method[76]); medium inhibitory doses ED_{50} are given. The

TABLE I

Pharmacological properties of the N-substituted 2-(1-piperazinyl)acetamides (oral administration)

Compound	Acute toxicity LD_{50} (mg/kg)	Indomethacin inhibition ED_{50} (mg/kg)	Mydriatic effect % of positive 10 mg/kg	100 mg/kg	[^{3}H]QB inhibition IC_{50} nM
I	>2 500[a]	32·7	100	100	275·3
II	>1 000[a]	145	—[b]	40	36 783
III	>1 000[a]	132	—[b]	0	—[b]
V	1 457	<100	0	90	15 450
VI	>2 500[a]	>100	—[b]	—[b]	—[b]
VII	>2 500[a]	>100	—[b]	—[b]	—[b]
VIII	1 381	—[b]	—[b]	0	—[b]
IX	2 006	>100	—[b]	—[b]	—[b]
X	1 651	>100	—[b]	—[b]	—[b]
XI	788	66·1	90	100	1 461·5
XII	788	100	—[b]	—[b]	—[b]
XIII	2 000	c. 100	—[b]	—[b]	—[b]
XIV	1 538	c. 100	—[b]	—[b]	—[b]
XV	1 226	>100	—[b]	—[b]	—[b]
XVIII	476	<100	—[b]	—[b]	11 851
XXI	928	42·3	100	100	439·8
XXIII	703	58·9	0	100	745·6

[a] This dose did not cause lethality. [b] Not estimated.

anticholinergic activity, which is typical for pirenzepine (*I*), was assayed by two methods. In the first line it was the mouse mydriasis test[77]; the mydriatic effect was determined after the administration of oral doses of 10 and 100 mg/kg and it is expressed in per cent of the positively reacting animals. As the second criterion of the anticholinergic activity, the affinity of the compounds to muscarinic receptors in the rat brain was used. 0·5 nM [^{3}H]quinuclidinyl benzilate served as the ligand and the affinity of the compounds is expressed in medium inhibitory concentrations (IC_{50} in nM) which inhibit the binding of the ligand by 50% in comparison with the control. Hexaprazol (*II*) and its N-methyl derivative *III* showed some antiulcer activity but are almost devoid of the anticholinergic effects. The basic aniline derivative *V* appears similar. The nitrophenyl isoster of the open-ring analogue of pirenzepine (*XI*) (VÚFB-17104) is one of the most interesting substances with rather high anti-ulcer and anticholinergic activity. Out of the tricyclic analogues *XXI* and *XXIII*, the unsaturated *XXI* (VÚFB-17113) is more interesting, being almost equipotent with pirenzepine (*I*) in the lines of anti-ulcer and anticholinergic activities. With the two interesting substances (*XI* and *XXI*), the effect on gastric secretion with pyloric ligated rats[78] was evaluated. In both cases, the oral dose of 50 mg/kg did not inhibit the investigated parameters (gastric juice volume, free hydrochloric acid, and the total acidity); on the contrary, with *XXI* there was a clear indication of raising these parameters (*I* in the same dose had very high antisecretory effect). Compounds *II* and *III* were subjected to a general pharmacological screening; intravenous acute toxicities LD_{50} in mice and the screened doses i.v. were the following: *II*, 175, 35; *III*, 200, 40. Both compounds brought about brief and deep drops of blood pressure in normotensive rats and *II* showed some hypoglycaemic effects in rats (oral dose of 175 mg/kg cecreased the sugar level in 1 h by 12–27% and in 2 h by 24–36%).

The nitro compounds and some other members of the series showed antimicrobial activity in vitro (microorganisms and the minimum inhibitory concentrations in μg/ml given – unless they exceed 128 μg/ml): *Streptococcus β-haemolyticus*, *XI* 128, *XII* 128, *XIV* 128, *XV* 128, *XVIII* 128, *XXI* 64, *XXIII* 128; *Streptococcus faecalis*, *XI* 64, *XII* 128, *XIV* 128, *XV* 128, *XVIII* 64, *XXI* 64, *XXIII* 128; *Staphylococcus pyogenes aureus*, *XI* 128, *XII* 128, *XXI* 64; *Pseudomonas aeruginosa*, *XI* 128, *XII* 128, *XIV* 128, *XV* 128, *XVIII* 128, *XXI* 64, *XXIII* 128; *Escherichia coli*, *XI* 128, *XII* 128, *XIV* 128, *XV* 128, *XVIII* 128, *XXI* 64, *XXIII* 128; *Proteus vulgaris*, *XI* 128, *XII* 128, *XIV* 128, *XV* 128, *XVIII* 128, *XXI* 64, *XXIII* 128; *Trichophyton mentagrophytes*, *XII* 50, *XIV* 50, *XVIII* 50.

EXPERIMENTAL

The melting points of analytical samples were determined on the Kofler block and were not corrected. The samples were dried in vacuo of about 60 Pa at room temperature or at a suitably elevated temperature. The UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded on

a Unicam SP 8 000 spectrophotometer, the IR spectra (mostly in Nujol, ν in cm^{-1}) with a Perkin–Elmer 298 spectrophotometer, the NMR spectra (in C^2HCl_3 unless stated otherwise, δ, J in Hz) with a CW-NMR spectrometer Tesla BS 487 C (^1H at 80 MHz) or the FT-NMR spectrometer Varian XL-200 (^1H at 200 MHz; ^{13}C at 50·3 MHz), and the mass spectra (m/z, composition and/or %) with Varian MAT 311 and MCH 1 320 (unless stated otherwise) spectrometers. The homogeneity of the substances and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The extracts were processed by drying with $MgSO_4$ or K_2CO_3 and evaporation under reduced pressure on a rotating evaporator.

N-(3-Nitrophenyl)-N-phenyl-2-chloroacetamide (*XVI*)

A stirred solution of 20·0 g 3-nitrodiphenylamine[23] in 100 g N,N-dimethylacetamide was treated dropwise with 12·0 g chloroacetyl chloride and the mixture was stirred for 16 h at 70–80°C. After cooling the mixture was diluted with 400 ml chloroform, the solution was washed with dilute hydrochloric acid and water, dried, and evaporated in vacuo. The residue was crystallized from ethanol; 11·1 g (41%) of *XVI*, m.p. 96–98·5°C. UV spectrum: 239·4 (4·27). IR spectrum: 698, 737, 786, 899 (5 and 3 adjacent and solitary Ar-H); 1 350, 1 529 ($ArNO_2$); 1 493, 1 590, 3 005, 3 045, 3 085, 3 100 (Ar); 1 691 (CON<). ^1H NMR spectrum: 4·00 s, 2 H ($COCH_2Cl$); 7·00–7·70 m, 7 H (C_6H_5 and H-5,6 of nitrophenyl); 8·00 m, 2 H (H-2,4 of nitrophenyl). For $C_{14}H_{11}ClN_2O_3$ (290·7) calculated: 57·84% C, 3·81% H, 12·20% Cl, 9·64% N; found: 57·32% C, 3·81% H, 12·24% Cl, 9·61% N.

N-(4-Nitrophenyl)-N-phenyl-2-chloroacetamide (*XVII*)

A solution of 4·8 g 4-nitrodiphenylamine[25] in 100 ml toluene was treated with 6·5 g chloroacetyl chloride and refluxed for 20 h. Toluene was evaporated in vacuo, the residue was diluted with chloroform, the solution was washed with dilute NH_4OH and water, dried, and evaporated. The residue was crystallized from a mixture of chloroform, ether, and light petroleum; 5·2 g (80%) of *XVII*, m.p. 112–116·5°C. A sample for analysis (1·0 g) was chromatographed on 15 g silica gel; m.p. 113·5–116°C (benzene–ether). UV spectrum: 222 (4·10), 303 (4·00). IR spectrum: 754, 758, 781 (5 and 2 adjacent Ar-H); 1 346, 1 513 ($ArNO_2$); 1 487, 1 588, 1 593, 1 608, 3 000, 3 073, 3 100 (Ar); 1 690 (CON<). ^1H NMR spectrum: 4·00 s, 2 H ($COCH_2Cl$); c. 7·35 m, 7 H (C_6H_5 and C-2,6 of nitrophenyl); 8·15 d, 2 H (H-3, 5 of nitrophenyl, $J = 8·5$). For $C_{14}H_{21}Cl.N_2O_3$ (290·7) calculated: 57·84% C, 3·81% H, 12·20% Cl, 9·64% N; found: 57·64% C, 4·03% H, 12·26% Cl, 9·40% N.

N-Cyclohexyl-2-(1-piperazinyl)acetamide (*II*)

A solution of 35·6 g piperazine in 200 ml water was neutralized with 33·3 ml hydrochloric acid, the solution was treated with 35·1 g N-cyclohexyl-2-chloroacetamide[14], and the mixture was stirred for 2 h at 100°C like described in ref.[7] There were obtained 37·0 g (82%) of *II*, m.p. 108–111°C. Ref.[7], m.p. 111–112°C. Neutralization of the base (4·5 g) with methanesulfonic acid (2·0 g) gave 2·2 g dimethanesulfonate, m.p. 225–227°C (ethanol–ether). IR spectrum: 1 050, 1 160, 1 178, 1 204 (RSO_3^-); 1 558, 1 683 (RCONHR'); 2 555, 2 640, 2 745, 2 780 (NH^+ and NH_2^+); 3 288, 3 400 (NH). ^1H NMR spectrum (^2H_2O): 1·00–2·00 bm, 10 H (5 CH_2 of cyclohexyl); 2·80 s, 6 H (2 $CH_3SO_3^-$); 2·95 bt, 4 H ($CH_2N^1CH_2$ of piperazine); 3·34 s, 2 H (NCH_2CO); 3·38 bt, 4 H ($CH_2N^4CH_2$ of piperazine); 3·65 bm, 1 H (CH of cyclohexyl). For $C_{14}H_{31}N_3O_7S_2$ (417·6) calculated: 40·27% C, 7·48% H, 10·06% N, 15·36% S; found: 40·17% C, 7·57% H, 9·88% N, 15·43% S.

Dimaleate, m.p. 147–149°C (ethanol). For $C_{20}H_{31}N_3O_9$ (457·5) calculated: 52·51% C, 6·83% H, 9·19% N; found: 52·95% C, 7·05% H, 9·02% N.

Sesquimaleate, m.p. 140–143°C (ethanol–ether). For $C_{18}H_{29}N_3O_7$ (399·4) calculated: 54·12% C, 7·32% H, 10·52% N; found: 53·84% C, 7·56% H, 10·42% N.

N-Cyclohexyl-2-(4-methyl-1-piperazinyl)acetamide (*III*)

1-Methylpiperazine[15] (40·1 g, contaminated with piperazine) was treated under stirring with 17·6 g N-cyclohexyl-2-chloroacetamide[14] and the mixture was heated for 30 min to 130°C. It was allowed to stand overnight at room temperature, diluted with 200 ml water, and extracted with dichoromethane. From the organic layer the bases were extracted into 120 ml 2M-tartaric acid, the aqueous layer was made alkaline with 40% NaOH, and the bases were extracted with dichloromethane. Processing of the extract gave 21·9 g inhomogeneous product which was dissolved in 25 ml boiling benzene and after partial cooling, the solution was diluted with 40 ml hexane. After 3 days standing a small amount of solid precipitated. It was filtered, crystallized from benzene, and identified as 1,4-bis(cyclohexylaminocarbonylmethyl)piperazine (*IV*), m.p. 169–172°C. Mass spectrum: 364 (M^+, $C_{20}H_{36}N_4O_2$, 1), 347 ($C_{20}H_{35}N_4O$, 0·3), 238 ($C_{13}H_{24}N_3O$, 100), 224 ($C_{12}H_{22}N_3O$, 3), 208 ($C_{12}H_{20}N_2O$, 5), 196 ($C_{11}H_{20}N_2O$, 10), 111 ($C_6H_{11}N_2$, 32). IR spectrum: 1 526, 1 645 (RCONHR'); 2 763, 2 820 (N-CH_2); 3 305, 3 353 (NH). ^{1}H NMR spectrum: 0·90–2·00 m, 20 H (10 CH_2 of 2 cyclohexyls); 2·52 s, 8 H (4 CH_2N of piperazine); 2·95 s, 4 H (2 NCH_2CO); 3·70 bm, 2 H (2 CH of 2 cyclohexyls); 6·90 bd, 2 H (2 NH, J = 8·0). For $C_{20}H_{36}N_4O_2$ (364·5) calculated: 65·89% C, 9·96% H, 15·37% N; found: 66·39% C, 10·09% H, 15·46% N.

The mother liquor was evaporated and the residue was crystallized from a mixture of 5 ml benzene and 20 ml heptane; 11·7 g (49%) of *III*, m.p. 72–74°C (hexane). IR spectrum: 1 537, 1 650 (RCONHR'); 2 698, 2 722 (CH_3—N, CH_2—N); 3 305 (NH). ^{1}H NMR spectrum: 1·00 to 2·00 m, 10 H (5 CH_2 of cyclohexyl); 2·23 s, 3 H (NCH_3); 2·50 bm, 8 H (4 CH_2N of piperazine); 2·95 s, 2 H (NCH_2CO); 3·75 bm, 1 H (CH of cyclohexyl); 7·00 bd, 1 H (NH, J = 8·0). For $C_{13}H_{25}N_3O$ (239·4) calculated: 65·23% C, 10·53% H, 17·56% N; found: 65·23% C, 10·76% H, 17·34% N.

Dimaleate, m.p. 174–176°C (ethanol). For $C_{21}H_{33}N_3O_9$ (471·5) calculated: 53·50% C, 7·05% H, 8·91% N; found: 53·20% C, 7·22% H, 8·80% N.

N-Phenyl-2-(4-methyl-1-piperazinyl)acetamide (*V*)

A mixture of 37 g 1-methylpiperazine and 20·9 g N-phenyl-2-chloroacetamide[17] (spontaneous warming to 45–50°C) was stirred for 3·5 h without heating, distributed then between benzene and water, the benzene layer was washed with dilute NH_4OH and water, dried, and evaporated; 17·4 g (61%) of *V*, m.p. 100·5–102°C (benzene). Ref.[16], m.p. 100–102°C.

Dimaleate, m.p. 161–163·5°C (ethanol). For $C_{21}H_{27}N_3O_9$ (465·5) calculated: 54·19% C, 5·85% H, 9·03% N; found: 54·16% C, 5·80% H, 9·00% N.

N-Phenyl-2-(4-(2-hydroxyethyl)-1-piperazinyl)acetamide (*VI*)

A mixture of 45 g 2-(1-piperazinyl)ethanol and 15·0 g N-phenyl-2-chloroacetamide[17] was stirred for 4 h at 40°C, distributed between water and chloroform, and the organic layer was processed similarly (cf. *V*); 18·3 g (79%) of *VI*, m.p. 69–71°C (chloroform–ether). Recrystallization from a mixture of methanol and ether gave the 2 : 1 solvate with methanol, m.p. 69·5–71·5°C. IR spectrum: 693, 767 (C_6H_5); 1 010 (CH_2OH); 1 542, 1 655 (RCONHAr); 1 595, 3 030 (Ar);

3 115, 3 170, 3 360, 3 450 (NH and OH). ^{1}H NMR spectrum: c. 2·60 m, 11 H (5 CH_2N and OH); 3·15 s, 2 H ($COCH_2N$); 3·68 t, 2 H (CH_2O, J = 7·0); 7·00—7·70 m, 5 H (C_6H_5); 9·10 bs, 1 H (NH). For $C_{14}H_{21}N_3O_2$ + 0·5 CH_3OH (279·4) calculated: 62·34% C, 8·30% H, 15·04% N; found: 61·79% C, 8·21% H, 14·97% N.

Dihydrochloride, m.p. 182—186°C (aqueous ethanol). For $C_{14}H_{23}Cl_2N_3O_2$ (336·3) calculated: 50·01% C, 6·89% H, 21·09% Cl, 12·50% N; found: 50·10% C, 6·85% H, 20·70% Cl, 12·55% N.

N-Phenyl-2-(4-(3-hydroxypropyl)-1-piperazinyl)acetamide (*VII*)

A solution of 38 g 3-(1-piperazinyl)propanol[18] in 80 ml chloroform was treated with 15·0 g N-phenyl-2-chloroacetamide[17] and the mixture was stirred for 3 h at room temperature. It was then diluted with 200 ml chloroform, washed with dilute NH_4OH and water, dried, and evaporated. The residue was crystallized from a mixture of ethanol and ether; 20·4 g (83%) of *VII*, m.p. 79—80°C (methanol–ether). IR spectrum: 694, 765 (C_6H_5); 1 061 (CH_2OH); 1 544, 1 658 (RCONHAr); 1 490, 1 595, 3 030, 3 050 (Ar); 2 770, 2 810 (CH_2-N); 3 120, 3 175, 3 205 (NH and OH). ^{1}H NMR spectrum: 1·70 m, 2 H (O—C—CH_2—C—N); 2·60 bs and t, 10 H (5 CH_2N); 3·10 s, 2 H ($COCH_2N$); 3·75 t, 2 H (CH_2O, J = 7·0); 4·45 flat band, 1 H (OH); 6·90—7·60 m, 5 H (C_6H_5); 9·02 bs, 1 H (NH). For $C_{15}H_{23}N_3O_2$ (277·4) calculated: 64·96% C, 8·36% H, 15·15% N; found: 64·58% C, 8·37% H, 14·96% N.

Dihydrochloride, m.p. 184—187°C (aqueous ethanol–ether). For $C_{15}H_{25}Cl_2N_3O_2$ (350·3) calculated: 51·43% C, 7·19% H, 20·24% Cl, 12·00% N; found: 51·49% C, 7·13% H, 20·14% Cl, 12·28% N.

N-(4-Dimethylaminophenyl)-2-(4-methyl-1-piperazinyl)acetamide (*VIII*)

A mixture of 27 g 1-methylpiperazine and 10·0 g N-(4-dimethylaminophenyl)-2-chloroacetamide[19] was stirred for 4 h at 60°C, allowed to stand overnight at room temperature, dissolved in 100 ml chloroform, the solution was washed with dilute NH_4OH and water, dried, and evaporated; 8·6 g (66%) of *VIII*, m.p. 127—130°C (chloroform–ether). UV spectrum: 274·5 (4·25). IR spectrum: 819 (2 adjacent Ar-H); 1 573, 1 678 (RCONHAr); 1 619, 3 020 (Ar); 2 790 (N—CH_2); 3 265 (NH). ^{1}H NMR spectrum: 2·30 s, 3 H (piperazine N—CH_3); 2·60 m, 8 H (4 CH_2N of piperazine); 2·91 s, 6 H ($ArN(CH_3)_2$); 3·11, s, 2 H ($COCH_2N$); 6·70 d, 2 H (H-3,5 of aniline, J = 8·5); 7·40 d, 2 H (H-2, 6 of aniline, J = 8·5); 8·88 bs, 1 H (NH). For $C_{15}H_{24}N_4O$ (276·4) calculated: 65·18% C, 8·75% H, 20·27% N; found: 64·71% C, 8·98% H, 19·91% N.

Dimaleate hemihydrate, m.p. 161—164·5°C (ethanol–ether). For $C_{23}H_{32}N_4O_9$ + 0·5 H_2O (517·4) calculated: 53·38% C, 6·43% H, 10·83% N; found: 53·25% C, 6·56% H, 10·82% N.

N-(4-Dimethylaminophenyl)-2-(4-(2-hydroxyethyl)-1-piperazinyl)acetamide (*IX*)

A solution of 40 g 2-(1-piperazinyl)ethanol in 50 ml chloroform was treated with 10·0 g N-(4-dimethylaminophenyl)-2-chloroacetamide[19] and the mixture was refluxed for 3 h. After dilution with chloroform, the processing was similar (cf. *VIII*); 7·3 g (51%) of *IX*, m.p. 109—112°C (ethanol–ether). UV spectrum: 274 (4·26). IR spectrum: 814 (2 adjacent Ar-H); 1 018, 1 070 (CH_2OH); 1 595, 1 655 (RCONHAr); 1 617, 3 060 (Ar); 2·735 (CH_2—N); 3 175, 3 310 (NH, OH). ^{1}H NMR spectrum: 2·53 t, 2 H (NCH_2 in hydroxyethyl, J = 7·0); 2·60 s, 8 H (4 CH_2N of piperazine); 2·80 bs, 1 H (OH); 2·90 s, 6 H ($ArN(CH_3)_2$); 3·12 s, 2 H ($COCH_2N$); 3·65 t, 2 H (CH_2O, J = 7·0); 6·70 d, 2 H (H-3,5 of aniline, J = 8·5); 7·40 d, 2 H (H-2, 6 of aniline, J = 8·5), 8·85 bs, 1 H (NH). For $C_{16}H_{26}N_4O_2$ (306·4) calculated: 62·72% C, 8·55% H, 18·29% N; found: 62·75% C, 8·73% H, 17·99% N.

Dimaleate hemihydrate, m.p. 106–108·5°C (ethanol–ether). For $C_{24}H_{34}N_4O_{10} + 0{\cdot}5\ H_2O$ (547·6) calculated: 52·65% C, 6·44% H, 10·23% N; found: 52·84% C, 6·74% H, 9·91% N.

N-(4-Dimethylaminophenyl)-2-(4-(3-hydroxypropyl)-1-piperazinyl)acetamide (*X*)

A mixture of 30 g 3-(1-piperazinyl)propanol[18], 90 ml chloroform, and 12·4 g N-(4-dimethylaminophenyl)-2-chloroacetamide[19] was stirred and refluxed for 11 h. Similar processing (cf. *VIII*) yielded 14·0 g (75%) of *X*, m.p. 141·5–145°C (ethanol–ether). UV spectrum: 275 (4·20). IR spectrum: 815 (2 adjacent Ar-H); 1 070 (CH_2OH); 1 510, 1 574 (Ar); 1 570, 1 656 (RCONHAr); 2 760 (N—CH_2); 3 120, 3 300 (NH, OH). ^{1}H NMR spectrum: 1·72 m, 2 H (O—C—CH_2—C—N); 2·60 bs, 10 H (4 CH_2N of piperazine and NCH_2 in the propane chain); 2·88 s, 6 H ($ArN(CH_3)_2$); 3·08 s, 2 H ($COCH_2N$); 3·76 t, 2 H (CH_2O, J = 6·0); 4·62 bs, 1 H (OH); 6·69 d, 2 H (H-3, 5 of aniline, J = 9·0); 7·39 d, 2 H (H-2, 6 of aniline, J = 9·0); 8·81 bs, 1 H (NH). For $C_{17}H_{28}N_4O_2$ (320·4) calculated: 63·72% C, 8·81% H, 17·48% N; found: 63·30% C, 9·03% H, 17·28% N.

Dimaleate hemihydrate, m.p. 111–114·5°C (ethanol). For $C_{25}H_{36}N_4O_{10} + 0{\cdot}5\ H_2O$ (561·6) calculated: 53·47% C, 6·64% H, 9·98% N; found: 53·37% C, 6·56% H, 10·09% N.

N-(2-Nitrophenyl)-N-phenyl-2-(4-methyl-1-piperazinyl)acetamide (*XI*)

A mixture of 5·0 g 1-methylpiperazine and 4·7 g N-(2-nitrophenyl)-N-phenyl-2-chloroacetamide[22] was stirred and heated for 30 min to 50°C. After cooling the solidified mixture was dissolved in 100 ml chloroform and the solution was processed (cf. *VIII*); 4·7 g (82%) of *XI*, m.p. 139 to 142°C (ethanol–ether). UV spectrum: 233 (3·88), infl. 305 (3·18). IR spectrum: 700, 706, 755 (5 and 4 adjacent Ar-H); 1 350, 1 527 ($ArNO_2$); 1 480, 1 580, 1 590, 1 599, 3 005, 3 025, 3 040 (Ar); 1 679 ($RCONAr_2$); 2 780 (N—CH_2). ^{1}H NMR spectrum: 2·18 s, 3 H (NCH_3); 2·25 bs, 8 H (4 CH_2N of piperazine); 3·05 s, 2 H ($COCH_2N$); 7·00–7·60 m, 8 H (C_6H_5 and H-4, 5, 6 of 2-nitroaniline); 7·88 bm, 1 H (H-3 of 2-nitroaniline). For $C_{19}H_{22}N_4O_3$ (354·4) calculated: 64·39% C, 6·26% H, 15·81% N; found: 64·16% C, 6·45% H, 15·82% N.

Dimaleate hemihydrate, m.p. 184–187°C (ethanol). For $C_{27}H_{30}N_4O_{11} + 0{\cdot}5\ H_2O$ (595·6) calculated: 54·45% C, 5·25% H, 9·41% N; found: 54·49% C, 5·26% H, 9·45% N.

N-(2-Nitrophenyl)-N-phenyl-2-(4-(2-hydroxyethyl)-1-piperazinyl)acetamide (*XII*)

A mixture of 10·0 g 2-(1-piperazinyl)ethanol, 40 ml chloroform, and 4·6 g N-(2-nitrophenyl)-N--phenyl-2-chloroacetamide[22] was refluxed for 3 h and processed. There were obtained 10·0 g of crude oily *XII* which were dissolved in 25 ml ethanol and the solution was neutralized with a solution of 6·1 g maleic acid in 25 ml ethanol. Crystallization gave 8·3 g (84%) dimaleate which was identified as the hemihydrate, m.p. 164–167°C (ethanol). Mass spectrum (CI): 385 ($(M + 1)^+$); EI: 384 (M^+, $C_{20}H_{24}N_4O_4$, very weak), 366 ($C_{20}H_{22}N_4O_3$), 353 ($C_{19}H_{21}N_4O_3$), 210, 191, 167, 159, 143, 100, 98, 70, 54. For $C_{28}H_{32}N_4O_{12} + 0{\cdot}5\ H_2O$ (625·6) calculated: 53·76% C, 5·32% H, 8·96% N; found: 53·43% C, 5·30% H, 8·89% N.

N-(2-Nitrophenyl)-N-phenyl-2-(4-(3-hydroxypropyl)-1-piperazinyl)acetamide (*XIII*)

A mixture of 7·5 g 3-(1-piperazinyl)propanol[18] 20 ml chloroform and 4·6 g N-(2-nitrophenyl)--N-phenyl-2-chloroacetamide[22] was refluxed for 16 h and processed similarly like in the preceding cases; 6·0 g of crude oily *XIII*. It afforded 7·0 g (90%) of dimaleate m.p. 174–177°C (methanol–-ether) which proved to be the hemihydrate. For $C_{29}H_{34}N_4O_{12} + 0{\cdot}5\ H_2O$ (639·6) calculated: 54·46% C, 5·52% H 8·76% N; found: 54·29% C 5·59% H 8·68% N.

A sample of the dimaleate was decomposed with NH_4OH and the homogeneous oily base, isolated by extraction with ether was used for recording the spectra. UV spectrum: 234 (4·25), infl. 308 (3·17). IR spectrum: 1 070 (CH_2OH); 1 358, 1 530 ($ArNO_2$); 1 499, 1 591, 1 602, 2 995 (Ar), 1 680 ($RCONAr_2$); 3 280 (OH). ^{1}H NMR spectrum: 1·65 m, 2 H (O—C—CH_2—C—N); 2·45 s, 8 H (4 CH_2N of piperazine); 2·52 t, 2 H (NCH_2 in hydroxypropyl, J = 6·0); 3·05 s, 2 H ($COCH_2N$); 3·70 t, 2 H (CH_2O, J = 6·0); 4·20 bs, 1 H (OH); 7·00—7·60 m, 8 H (C_6H_5 and C-4, 5, 6 of 2-nitroaniline); 7·89 bm 1 H (H-3 of 2-nitroaniline).

N-(3-Nitrophenyl)-N-phenyl-2-(4-methyl-1-piperazinyl)acetamide (*XIV*)

Similar reaction of 10·0 g 1-methylpiperazine and 8·4 g *XVI* in 30 ml chloroform at 60°C (24 h) gave 10·0 g of crude oily *XIV* which was transformed to 7·75 g (46%) dimaleate, m.p. 175 to 178·5°C (ethanol). Mass spectrum: 354 (M^+, $C_{19}H_{22}N_4O_3$, 1·3) 337 (0·9), 311 (0·2), 298 (0·4), 297 (0·4), 284 (0·3), 255 (0·3), 241 (0·2), 227 (1·0), 214 (0·5), 180 (1·7), 167 (4·2), 141 (1·3), 113 (90), 98 (8), 70 (100), 42 (44). For $C_{27}H_{30}N_4O_{11}$ (586·6) calculated: 55·29% C, 5·16% H, 9·55% N; found: 55·70% C, 5·17% H, 9·58% N.

The homogeneous oily base, released from the pure dimaleate, was used for recording the spectra. UV spectrum: 238·9 (4·24). IR spectrum: 705, 738, 830, 855 (5 and 3 adjacent and solitary Ar-H); 1 345 1 527 ($ArNO_2$); 1 490, 1 590, 1 610, 3 030, 3 060, 3 080 (Ar); 1 675 ($RCONAr_2$); 2 690, 2 740, 2 790 (N—CH_2). ^{1}H NMR spectrum: 2·25 s, 3 H (NCH_3); 2·50 bs, 8 H (4 CH_2N of piperazine); 3·12 s, 2 H ($COCH_2N$); 7·20—7·80 m, 7 H (C_6H_5 and H-5, 6 of 3-nitroaniline); 8·03 m, 1 H (H-4 of 3-nitroaniline); 8·18 m, 1 H (H-2 of 3-nitroaniline).

N-(4-Nitrophenyl)-N-phenyl-2-(4-methyl-1-piperazinyl)acetamide (*XV*)

Similar reaction of 5·0 g 1-methylpiperazine and 4·3 g *XVII* in 20 ml chloroform (3 h at 55°C) gave 5·0 g of crude oily *XV* which was transformed to 8·2 g (95%) dimaleate m.p. 170—174°C (ethanol–ether). Mass spectrum: 354 (M^+, $C_{19}H_{22}N_4O_3$, 1·3). 311 (0·3), 298 (0·5), 297 (0·4), 284 (0·6), 255 (0·5), 241 (0·4), 227 (1·5), 214 (1·2), 180 (2·2), 167 (7), 141 (2), 113 (100), 98 (10·3), 70 (100), 42 (63). For $C_{27}H_{30}N_4O_{11}$ (586·6) calculated: 55·29% C, 5·16% H, 9·55% N; found: 54·67% C, 5·10% H, 9·35% N.

The homogeneous oily base, released from the pure dimaleate, was used for recording the spectra. UV spectrum: infl. 226 (4·04). 304 (3·90). IR spectrum: 700, 752, 831, 852 (5 and 2 adjacent Ar-H); 1 345 1 518 ($ArNO_2$); 1 492 1 590, 3 064 (Ar); 1 680 ($RCONAr_2$), 2 795 (N—CH_2). ^{1}H NMR spectrum: 2·20 s, 3 H (NCH_3); 2·50 bs, 8 H (4 CH_2N of piperazine); 3·10 s, 2 H ($COCH_2N$); 7·00—7·60 m, 7 H (C_6H_5 and H-2, 6 of 4-nitroaniline); 8·12 d, 2 H (H-3, 5 of 4-nitroaniline, J = 8·5).

N-(2-Benzylphenyl)-2-(4-methyl-1-piperazinyl)acetamide (*XVIII*)

A solution of 3·0 g N-(2-benzylphenyl)-2-chloroacetamide[26] in 20 ml chloroform was treated under stirring with 3·5 g 1-methylpiperazine and the mixture was stirred for 6 h at 45—50°C. After cooling it was diluted with 20 ml chloroform the solution was washed with water, dried, and evaporated. The residue was dissolved in ethanol and the solution was neutralized with 2·68 g maleic acid; 5·5 g (85%) bis(hydrogen maleate) of *XVIII*, m.p. 148—150·5°C (ethanol). For $C_{28}H_{33}N_3O_9$ (555·6) calculated: 60·53% C, 5·99% H, 7·56% N; found: 59·89% C, 5·92% H, 7·36% N.

The released base crystallized from a mixture of chloroform and ether m.p. 85·5—90°C. IR spectrum: 698, 727, 734, 759 (5 and 4 adjacent Ar-H); 1 520, 1 678 (RCONHAr): 1 584, 1 599,

3 015, 3 028, 3 060, 3 080 (Ar); 2 740, 2 800 (N—CH_2). ^{1}H NMR spectrum: 2·18 s, 3 H (NCH_3); 2·18 m, 4 H ($CH_2N^4CH_2$ of piperazine); 2·40 m 4 H ($CH_2N^1CH_2$ of piperazine); 3·00 s, 2 H ($COCH_2N$); 3·98 s, 2 H ($ArCH_2Ar$); 6·80—7·40 m and 8·10 m, 8 + 1 H (9 ArH); 9·00 bs, 1 H (NH). For $C_{20}H_{25}N_3O$ (323·4) calculated: 74·27% C, 7·79% H, 12·99% N; found: 74·41% C, 7·62% H, 12·88% N.

5-(2-(4-Methyl-1-piperazinyl)acetyl)-5*H*-dibenz[*bf*]azepine (*XXI*)

A mixture of 5·0 g *XXII* (ref.[40]) and 7·4 g 1-methylpiperazine was stirred for 6 h at 55°C and processed similarly like in the preceding cases; 4·9 g (79%) of *XXI*, m.p. 121—126·5°C. Analytical sample, m.p. 128·5—131°C (ethanol–ether). UV spectrum: 284·7 (4·07). IR spectrum: 735 780 (4 adjacent Ar-H); 800 810 820 (CH=CH); 1 485 1 596 3 018 3 048 (Ar); 1 683 ($RCONAr_2$); 2 690, 2 740, 2 795 (N—CH_2). ^{1}H NMR spectrum: 2·20 s, 3 H (NCH_3); 2·35 s, 8 H (4 CH_2N of piperazine); 2·75 d and 3·10 d 1 + 1 H ($COCH_2N$, J = 14·0); 6·90 s, 2 H (CH=CH); 7·30 bm, 8 H (8 ArH). For $C_{21}H_{23}N_3O$ (333·4) calculated: 75·65% C, 6·95% H, 12·60% N; found: 75·53% C, 6·89% H, 12·49% N.

Bis(*hydrogen maleate*) m.p. 107—110°C (ethanol–ether). For $C_{29}H_{31}N_3O_9$ (565·6) calculated: 61·59% C, 5·52% H, 7·43% N; found: 61·71% C, 5·60% H, 7·25% N.

Dihydrochloride, m.p. 203·5—207°C (aqueous ethanol–ether). For $C_{21}H_{25}Cl_2N_3O$ (406·4) calculated: 62·07% C, 6·20% H, 17·45% Cl, 10·34% N; found: 61·70% C, 6·21% H, 17·22% Cl, 10·49% N.

5-(2-(4-Methyl-1-piperazinyl)acetyl)-10,11-dihydro-5*H*-dibenz[*bf*]azepine (*XXIII*)

1-Methylpiperazine (14·5 g) and 10·0 g *XXIV* (refs[40–42]) were similarly reacted (8 h at 55—60°C) and the mixture was similarly processed; 11·5 g (94%) of *XXIII*, m.p. 96·5—98·5°C. Analytical sample, m.p. 114—116°C (ethanol). UV spectrum: 234 (3·95). IR spectrum: 750, 760, 775 (4 adjacent Ar-H); 1 485, 1 570, 1 580, 1 601, 3 030, 3 060 (Ar); 1 680 ($RCONAr_2$); 2 688, 2 735, 2 790 (N—CH_2). ^{1}H NMR spectrum: 2·20 s, 3 H (CH_3N); 2·40 bs, 8 H (4 CH_2N of piperazine); 2·50—3·70 m, 6 H ($COCH_2N$ and $ArCH_2CH_2Ar$); 7·00—7·50 bm, 8 H (8 ArH). For $C_{21}H_{25}N_3O$ (335·5) calculated: 75·19% C, 7·51% H, 12·53% N; found: 74·63% C, 7·58% H, 12·36% N. Ref.[42], m.p. 98—99°C (cyclohexane). Our higher melting sample, which was crystallized from ethanol, is probably a different crystal modification.

Dihydrochloride, m.p. 209—213°C (aqueous ethanol–ether). For $C_{21}H_{27}Cl_2N_3O$ (408·4) calculated: 61·77% C, 6·66% H, 17·36% Cl, 10·29% N; found: 61·77% C, 6·68% H, 17·36% Cl, 10·35% N.

2-Methyl-1,2,3,4,10,14b-hexahydrodibenzo[*c*,*f*]pyrazino[1,2-*a*]azepine (*XIX*)

A) A suspension of 1·5 g *XX* (ref.[26]) in 100 ml tetrahydrofuran was added dropwise over 20 min to a stirred solution of 2·0 g $LiAlH_4$ in 100 ml ether ar.d the mixture was refluxed for 1·5 h. After standing overnight it was decomposed under stirring by the successive slow addition of 2 ml water, 2 ml 15% NaOH and 6 ml water. The mixture was stirred for 20 min, the solid was filtered off, washed with tetrahydrofuran and ether, the filtrate was dried and evaporated. The inhomogeneous residue was chromatographed on a column of 20 g silica gel (Merck 40). Elution with chloroform removed first the less polar components and afforded then 0·8 g (64%) of homogeneous (TLC), oily *XIX*. It was transformed to the hydrochloride which melted in crude state at 272—283°C (decomposition), after two crystallizations from ethanol constantly at

281—284°C (decomposition). Mass spectrum: 264 (M^+, $C_{18}H_{20}N_2$, 37), 249 (6), 220 (19), 193 (100), 192 (41), 178 (36), 165 (45), 152 (8), 72 (39), 71 (44). Ref.[26], m.p. 282—284°C.

B) A precise repeating of the described reduction[26] of 6·5 g *XX* (ref.[26]) with B_2H_6, generated from 1·78 g $NaBH_4$ and 34 ml $BF_3.O(C_2H_5)_2$ in 25 ml tetrahydrofuran, which was introduced into the suspension of *XX* in tetrahydrofuran, gave the crude base which was dissolved in 25 ml ethanol and the solution was acidified with HCl in 30 ml ether; 6·5 g (96%) of crude hydrochloride were obtained. This was decomposed with NH_4OH, the base was isolated by extraction with chloroform, and purified by chromatography on 50 g silica gel. Elution with a mixture of chloroform, chloroform saturated with NH_3, and methanol gave 3·9 g crystalline base, m.p. 107 to 109°C. Recrystallization from a mixture of benzene and heptane and from heptane alone gave the constantly melting product. m.p. 111—113°C. Mass spectrum: 264 (M^+, $C_{18}H_{20}N_2$, 75), 249 (10), 220 (35), 193 (100), 179 (20), 165 (20), 71 (80), 43 (90). IR spectrum: 754 (4 adjacent Ar-H); 1 488, 1 579, 1 592, 3 012, 3 050 (Ar); 2 755, 2 790 (N—CH_3). ^{1}H NMR spectrum: 2·30 s, 3 H (NCH_3); 2·30 m, 2·90 m, and 3·20 m, 1 + 1 + 2 H (2 H-3 and 2 H-4); 2·45 m and 2·85 m, 1 + 1 H (2 H-1); 4·04 dd, 1 H (H-14b, J = 10·0; 2·5); 3·35 d and 4·78 d, 1 + 1 H (2 H-10, J = 13·0); 6·60—7·30 m, 8 H (8 ArH) (cf. ref.[34]). For $C_{18}H_{20}N_2$ (264·4) calculated: 81·78% C, 7·63% H, 10·59% N; found: 81·81% C, 7·74% H, 10·44% N.

The hydrochloride, prepared from the crystalline base, melted at 248—255°C and this melting point did not change in two consecutive crystallizations from ethanol. Mass spectrum: 264 (M^+, $C_{18}H_{20}N_2$, 45), 249 (7), 220 (24), 193 (100), 192 (25), 178 (22), 165 (23), 152 (4), 72 (64), 71 (55). For $C_{18}H_{21}ClN_2$ (300·8) calculated: 71·87% C, 7·04% H, 11·78% Cl, 9·31% N; found: 71·50% C, 7·19% H, 11·78% Cl, 9·28% N. Only repeated crystallization from ethanol led to the product melting at 278—283°C, evidently identical with the hydrochloride obtained under *A*) and identical with the product of ref.[26].

C) A suspension of 15·9 g *XX* (ref.[26]) in 200 ml tetrahydrofuran was treated with 16·5 g $NaBH_4$ and the stirred mixture was treated over 2 h at 25°C under nitrogen with 82·3 g $BF_3.O(C_2H_5)_2$, added dropwise under mild cooling. It was stirred for 15 min without heating and then refluxed for 2 h. After standing overnight, the mixture was decomposed by addition of 50 ml ethanol, acidified with 5% hydrochloric acid, made alkaline with 40% NaOH, diluted with 400 ml water, the solid was filtered off, and the filtrate was extracted with dichloromethane. Processing of the extract gave 14·1 g residue which was crystallized from a mixture of 20 ml benzene and 25 ml heptane. Crystallization and processing of the mother liquors gave 12·6 g (87%) of the base *XIX*, m.p. 111—113°C, identical with that obtained under *B*). The hydrochloride, prepared from this base, melted first unsharply at 262—282°C and only after repeated recrystallization from ethanol reached the literature[26] value of 281—283°C (cf. also under *A*) and *B*)).

3-(10,11-Dihydrodibenz[*b*,*f*]azepin-5-yl)propylamine (*XXV*)

A solution of 2·2 g $LiAlH_4$ in 50 ml ether was stirred and treated over 10 min with a solution of 6·2 g $AlCl_3$ in 50 ml ether, added dropwise. The stirred mixture was then treated over 20 min with a solution of 7·0 g *XXVII* (ref.[47]) in 50 ml tetrahydrofuran, the mixture was stirred for 30 min at room temperature, and refluxed for 3·5 h. After cooling it was decomposed by a slow addition of 10 ml water and 100 ml 3M-H_2SO_4. The precipitated sulfate of the product was filtered, decomposed with dilute NaOH, and the base was isolated by extraction with benzene; 5·5 g (77%) of oily *XXV*. Reaction with HCl in ether gave 6·2 g of hydrochloride, m.p. 268—269°C (ethanol–ether). Mass spectrum: 252 (M^+, $C_{17}H_{20}N_2$, 31·5); 235 (51·6), 220 (8·9), 208 (100), 193 (83), 180 (10·5), 165 (10·7), 152 (4·8), 130 (13·7), 91 (17), 77 (8·9). ^{1}H NMR spectrum ($C^2H_3.SOC^2H_3$): 1·80 bm, 2 H (N—C—CH_2—C—N); 2·80 bm, 2 H (1-CH_2N); 3·10 s, 4 H (ArCH_2.

·CH_2Ar); 3·80 bt, 2 H (3-CH_2N); 7·00–7·50 m, 8 H (8 ArH); 8·35 bs, 3 H (NH_3^+). For $C_{17}H_{21}$··ClN_2 (288·8) calculated: 70·70% C, 7·33% H, 12·28% Cl, 9·70% N; found: 70·29% C, 7·17% H, 12·16% Cl, 9·39% N. Ref.[47], m.p. 276°C.

A sample of the hydrochloride was decomposed with NH_4OH, the pure oily base *XXV* was isolated by extraction with ether, and used for recording the ^1H NMR spectrum: 1·00 bs, 2 H (NH_2); 1·68 m, 2 H (N—C—CH_2—C—N); 2·65 t, 2 H (1-CH_2N, J = 7·0); 3·10 s, 4 H ($ArCH_2$··CH_2Ar); 3·70 t, 2 H (3-CH_2N, J = 7·0); 7·00 m, 8 H (8 ArH).

N-(3-Pyridyl)-2-aminobenzamide (*XXXII*)

A solution of 15·1 g methyl anthranilate in 200 ml dimethyl sulfoxide was treated with 9·4 g 3-aminopyridine and to the stirred mixture 7·7 g 70% $NaNH_2$ were slowly added in small portions at room temperature (cf. ref.[51]). After heating the mixture to 40°C, the temperature rose spontaneously to 60°C indicating an exothermic reaction. When this was over, the mixture was heated for 3 h to 70°C. After cooling the mixture was diluted with water, neutralized with 3% hydrochloric acid (pH 7), and extracted with chloroform. Evaporation of the extract gave 15·8 g of a mixture consisting mainly of three components (TLC). It was chromatographed on 500 g silica gel. Elution with chloroform gave 1·1 g (5%) of the least polar component which was identified as 3-(3-pyridyl)-1,2,3-benzotriazin-4(3*H*)-one (*XXXI*), m.p. 135–136°C (hexane–benzene). Mass spectrum: 224 (M^+, $C_{12}H_8N_4O$, 17), 196 ($C_{12}H_8N_2O$, 100), 168 ($C_{11}H_8N_2$, 48), 140 ($C_{10}H_6N$), 108, 92 (36), 78 (63), 76 (38), 51 (55), 50 (57). UV spectrum: 295 (3·88), infl. 313 (3·85). IR spectrum: 685, 705, 754, 780, 860 (4 and 3 adjacent and solitary Ar-H); 1 580, 3 050, 3 070, 3 095 (Ar); 1 603 (N=N); 1 683 (ArCON). ^1H NMR spectrum (200 MHz): 7·53 ddd 1 H (H-5′, J(5′, 4′) = 8·2, J(5′, 6′) = 4·9, J(5′, 2′) = 0·8); 7·89 ddd, 1 H (H-7, J(7, 8) = 7·9, J(7, 6) = 7·2, J(7, 5) = 1·3); 8·03 ddd, 1 H (H-6, J(6, 5) = 8·0, J(6, 7) = 7·2, J(6, 8) = 1·5); 8·10 ddd, 1 H (H-4′, J(4′, 5′) = 8·2, J(4′, 2′) = 2·6, J(4′, 6′) = 1·5); 8·25 ddd, 1 H (H-5, J(5, 6) = 8·0, J(5, 7) = 1·3, J(5, 8) = 0·6); 8·46 ddd, 1 H (H-8, J(8, 7) = 7·9, J(8, 6) = 1·5, J(8, 5) = 0·6); 8·73 bddd, 1 H (H-6′, J(6′, 5′) = 4·9, J(6′, 4′) = 1·5, J(6′, 2′) < 1·0); 9·01 bd, 1 H (H-2′, J(2′, 4′) = 2·6, J(2′, 5′) = 0·8, J(2′, 6′) < 1·0). ^{13}C NMR spectrum (50·3 MHz): 120·13; 139·21 and 143·56 (3 arom. >C=); 123·57; 125·71; 128·79; 133·20; 133·30; 135·49; 146·46 and 149·41 (8 arom. —CH=); the carbonyl C-4 was not detected evidently because of its long relaxation time and the small quantity of the sample. For $C_{12}H_8N_4O$ (224·2) calculated: 64·29% C, 3·60% H, 24·99% N; found: 63·90% C, 3·58% H, 24·60% N.

Continued elution with chloroform containing 0·5% of methanol afforded 3·3 g substance melting at 146–147°C (ethanol) which was identified as anthranilic acid (comparison with an authetic sample by TLC).

Elution with chloroform containing 1·5% of methanol gave finally the main product (11·4 g, 54%), identified to be *XXXII*, m.p. 125–126°C (ethanol–benzene). UV spectrum: 255 (4·18), 339 (3·84). IR spectrum: 705, 740, 752, 803, 895 (4 and 3 adjacent and solitary Ar-H); 1 480, 1 570, 1 587, 3 030, 3 050 (Ar); 1 625 ($ArNH_2$); 1 645 (ArCONHAr); 3 175, 3 315, 3 440 (NH, NH_2). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): 6·50 m, 1 H (H-5); 6·88 dd, 1 H (H-3, J = 8·5; 1·5); 7·15 m, 1 H (H-4); 7·30 m, 1 H (H-5′); 7·55 dd, 1 H (H-4′, J = 8·0; 1·5); 8·11 m, 1 H (H-6); 8·25 dd, 1 H (H-6′, J = 5·0; 1·5); 8·89 bd, 1 H (H-2′, J = 2·5); 10·15 bs, 1 H (CONHAr). For $C_{12}H_{11}N_3O$ (213·2) calculated: 67·59% C, 5·20% H, 19·71% N; found: 67·85% C, 5·26% H, 19·57% N.

3-(2-Aminobenzamido)-2-piperidone (*XXXIII*)

A solution of 5·7 g 3-amino-2-piperidone[57,59] in 55 ml acetonitrile was heated to 60°C and treated under stirring over 10 min with 8·1 g of isatoic anhydride[60,61]. The stirred mixture was

refluxed for 3 h, cooled to 0°C, the crude *XXXIII* was filtered, and dried in vacuo; 10·5 g (90%), m.p. 193–198°C. Attempt to crystallize the product from 2-propanol (cf. refs[57,58]) was not successful and, therefore, it was recrystallized from aqueous ethanol, m.p. 201–203°C. Mass spectrum: 233 (M^+, $C_{12}H_{15}N_3O_2$), 120 (C_7H_9NO), 113 ($C_5H_9N_2O$), 92 (C_6H_6N). UV spectrum: 248 (3·92), 328 (3·59). IR spectrum: 755 (4 adjacent Ar-H); 1 500, 1 589, 3 060 (Ar); 1 535, 1 630 (ArCONHR); 1 610 ($ArNH_2$); 1 680 (CONH in the 6-membered ring); 3 190, 3 320, 3 440 (NH, NH_2). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): 1·80 bm, 4 H (2 H-4 and 2-H-5); 3·18 bt, 2 H (2 H-6); 4·35 bm, 1 H (H-3); 6·40 flat band, 2 H (NH_2); 6·52 m, 1 H (H-5′); 6·75 bd, 1 H (H-3′, J = 8·0); 7·20 m, 1 H (H-4′); 7·56 dd, 1 H (H-6′, J = 8·0; 2·0); 7·65 bs, 1 H (H-1); 8·35 bd, 1 H (remaining CONH, J = 8·0). For $C_{12}H_{15}N_3O_2$ (233·3) calculated: 61·79% C, 6·48% H, 18·01% N; found: 61·99% C, 6·45% H, 17·60% N. Ref.[57], m.p. 169–170°C.

1,2,3,4,5,6-Hexahydropyrido[2,3-*b*]-1,4-benzodiazepin-6-one (*XXXIV*)

A mixture of 4·66 g *XXXIII* and 15 ml acetic acid was refluxed for 11 h, after cooling diluted with 70 ml water, made alkaline with 20 ml 40% NaOH, and extracted with chloroform. The precipitated solid (1·7 g) was filtered and crystallized from dimethylformamide; 1·2 g (28%) of *XXXIV*, m.p. 325–330°C. Mass spectrum: 215 (M^+, $C_{12}H_{13}N_3O$), 186 ($C_{11}H_{10}N_2O$), 160 ($C_9H_8N_2O$), 145 (C_9H_7NO). UV spectrum: 272 (4·10), 311 (3·63). IR spectrum: 762, 770 (4 adjacent Ar-H); 1 480, 1 494, 1 598, 3 010 (Ar); 1 642 (ArCONH in a ring); 3 150, 3 250 (NH). For $C_{12}H_{13}N_3O$ (215·3) calculated: 66·96% C, 6·09% H, 19·52% N; found: 66·65% C, 6·01% H, 19·32% N. Ref.[57] (different synthesis), m.p. 293–295°C.

2-Methyl-3-(2-oxo-3-piperidinyl)quinazolin-4(3*H*)-one (*XXXV*)

A) A mixture of 13·2 g *XXXIII* and 40 ml acetic acid was heated for 3 h in an autoclave to 170°C. After cooling it was diluted with 20 ml acetic acid, evaporated in vacuo, the residue was diluted with 150 ml water, the solution was made alkaline with 40% NaOH, and extracted with chloroform. Processing of the extract gave 8·3 g residue which was crystallized from 125 ml ethanol; 6·3 g (43%) of *XXXV*, m.p. 261–263°C (aqueous ethanol). Mass spectrum: 257 (M^+, $C_{14}H_{15}N_3O_2$, 22), 200 (5), 187 (10), 160 (100), 143 (13), 117 (25), 76 (24). UV spectrum: 265 (3·92), 273 (3·87), 296 (3·44), 305 (3·52), 317 (3·41). IR spectrum: 775 (4 adjacent Ar-H); 1 490, 1 570, 3 070 (Ar); 1 599 (C=N—Ar); 1 670 (ArCON, RCONH); 3 195, 3 300 (NH). ^{1}H NMR spectrum (200 MHz, 1 : 1 C^2HCl_3 + $C^2H_3SOC^2H_3$): 1·82–2·33 m, 3 H (2 H-5′ and H-4′ eq); 2·46 m, 1 H (H-4′ax, J = 12·5; 12·5; 11·0; 4·0); 2·69 s, 3 H (CH_3); 3·36 dm, 1 H (H-6′ eq, J(6′, 6′) = 12·0); 3·57 dt, 1 H (H-6′ ax, J(6′, 6′) = 12·0, J(6′, 5′) = 11·0 and 4·0); 4·62 dd, 1 H (H-3′, J(3′, 4′) = 11·0; 7·0); 7·06 bs, 1 H (NH); 7·42 ddd, 1 H (H-7, J(7, 8) = 8·1, J(7, 6) = 7·0, J(7, 5) = 1·3); 7·60 ddd, 1 H (H-5, J(5, 6) = 8·1, J(5, 7) = 1·3, J(5, 8) = 0·5); 7·92 ddd, 1 H (H-6, J(6, 5) = 8·1, J(6, 7) = 7·0, J(6, 8) = 1·6); 8·15 ddd, 1 H (H-8, J(8, 7) = 8·1, J(8, 6) = = 1·6, J(8, 5) = 0·5). ^{13}C NMR spectrum (50·3 MHz, 1 : 1 C^2HCl_3 + $C^2H_3SOC^2H_3$): 22·12 (C-5′); 23·28 (CH_3); 25·47 (C-4′); 41·36 (C-6′); 56·88 (C-3′); 120·67; 146·86 and 154·30 (3 arom. >C=); 125·86 (2); 126·33 and 133·81 (4 arom. —CH=); 160·64 and 167·22 (2 C=O). For $C_{14}H_{15}N_3O_2$ (257·3) calculated: 65·35% C, 5·88% H, 16·33% N; found: 65·53% C, 5·92% H, 16·00% N.

B) A mixture of 9·33 g *XXXIII* and 40 ml acetic acid was heated for 15 h in an autoclave to 105°C. After cooling it was diluted with 20 ml acetic acid and evaporated in vacuo. The residue was dissolved in 60 ml water, the solution was made alkaline with 12 ml 40% NaOH, the precipitated solid was filtered, washed with water, dried in vacuo, and crystallized from a mixture of 165 ml dimethylformamide and 150 ml benzene; 2·7 g (31%) of *XXXIV*, m.p. 315–325°C.

The alkaline aqueous mother liquor was extracted with chloroform and the extract was processed to give 0·7 g (7%) of *XXXV*, m.p. 253–262°C (aqueous ethanol).

5,11-Dihydro-6*H*-pyrido[2,3-*b*]-1,4-benzodiazepin-6-one (*XXIX*)

A) N-(2-Chloro-3-pyridyl)anthranilamide[50] (6·1 g) was heated for 5 min in a bath of 210°C. The cyclization with formation of HCl took place at 205°C. After partial cooling the solid product was dissolved at 140°C in 30 ml dimethylformamide, the solution was filtered, and the filtrate was diluted with 100 ml boiling ethanol. Cooling overnight in the refrigerator gave 4·1 g (79%) of *XXIX*, m.p. 282–284°C. Crystallization from cyclohexanol gave the product melting at 286–289°C. Sublimation in vacuo (below 0·1 kPa) at 280–290°C gave the highly pure substance, m.p. 292–293°C. Ref.[50], m.p. 286–288°C. A similar cyclization of 23·6 g N-(2-chloro-3-pyridyl)-anthranilamide gave *XXIX* in the yield of only 30%.

B) A mixture of 2·2 g *XXXIV* and 60 ml pyridine was treated with 2·0 g 5% Pd catalyst on active carbon and the stirred mixture was refluxed for 17 h. After cooling the catalyst was filtered off, the filtrate was evaporated in vacuo, and the residue was crystallized from a mixture of 30 ml ethanol and 1 ml water; 1·2 g (57%) of *XXIX*, m.p. 285–288°C. Recrystallization from a 1 : 3 mixture of dimethylformamide and water gave the product melting at 286–288°C. In admixure with the product obtained under *A*) it melted without depression. Ref.[57], m.p. 283 to 285°C.

11-(Chloroacetyl)-5,11-dihydro-6*H*-pyrido[2,3-*b*]-1,4-benzodiazepin-6-one (*XXX*)

A) A suspension of 9·2 g *XXIX* in 170 ml dioxane was refluxed for 15 min to 25°C, treated with 7·0 g triethylamine, and then with stirring over 30 min with 7·4 g chloroacetyl chloride, added dropwise. The mixture was refluxed for 8 h, after cooling the precipitated triethylamine hydrochloride was filtered off, washed with dioxane, the filtrate was evaporated in vacuo, the residue was dissolved in 250 ml boiling acetonitrile, filtered with charcoal while hot through a 3 mm layer of silica gel. The filtrate was allowed to crystallize and the mother liquors were processed; 6·6 g (53%) of *XXX*, m.p. 212–219°C with decomposition. Refs[63,64] (similar procedure), m.p. 212 to 213°C with decomposition.

B) A stirred suspension of 47·7 g *XXIX* in 890 ml dioxane was simultaneously treated over 45 min with 36·3 g triethylamine and 38·3 g chloroacetyl chloride, added dropwise. The mixture was stirred and refluxed for 9·5 h. After standing overnight the precipitated solid was filtered off and the filtrate gave by evaporation in vacuo 49·6 g inhomogeneous product which was chromatographed on a column of 400 g neutral Al_2O_3 (activity II). Elution with chloroform gave first 3·9 g solid which did not melt until 280°C. The further fraction were 26·9 g (41%) crude product giving by crystallization from 500 ml acetonitrile 12·0 g (19%) substance melting at 221–228°C. Evaporation of the mother liquor gave 14·1 g of a similar substance. None of the fractions was homogeneous (it seems that chromatography and crystallization even worsen the quality of the substance). For further step the crude product was used.

11-((4-Methyl-1-piperazinyl)acetyl)-5,11-dihydro-6*H*-pyrido[2,3-*b*]-1,4-benzodiazepin-6-one (*I*)

A mixture of 6·6 g crude *XXX*, 13·8 g 1-methylpiperazine, and 135 ml benzene was refluxed under stirring for 18 h (cf. refs[63,64]). After standing for 7 days it was decomposed by addition of 150 ml water and the mixture was extracted with chloroform. Processing gave 8·3 g product shown by TLC to be a mixture of two compounds. It was chromatographed on a column of 150 g silica gel. Elution with a mixture of 95% chloroform and 5% chloroform saturated with NH_3 gave

1·0 g of the least polar substance melting at 193—195°C being according to the analysis, mass spectrum, and UV spectrum an isomer of *I* with a higher degree of conjugation; its identification was postponed because of difficulties with the interpretation of the NMR spectra.

Continued elution with a mixture of 85% chloroform, 10% chloroform saturated with NH_3, and 5% methanol afforded 7·0 g (87%) of crystalline base *I* (which we did not find in the literature), m.p. 224—226°C. Analytical sample, m.p. 226—230°C (ethanol–ether). Mass spectrum: 351 (M^+, $C_{19}H_{21}N_5O_2$, 2), 308 (2), 295 (3), 294 (3), 238 (0·5), 211 (12), 113 (100), 70 (73). UV spectrum: infl. 232 (4·15), 285 (3·89). IR spectrum: 690, 695, 709, 711, 750, 756, 780, 809, 835 (3 and 4 adjacent Ar-H); 1 488, 1 595, 3 035, 3 100 (Ar); 1 660 (ArCONHAr); 1 685(RCONAr$_2$); 2 765, 2 790 (N—CH_3, N—CH_2): 3 170 (NH). ^{1}H NMR spectrum: 2·12 s, 3 H (CH_3N); c. 2·40 bm, 8 m (4 CH_2N of piperazine); 3·18 d, 1 H and 3·60 bd, 1 H (NCOCH_2N, J = 14·0); 7·20—7·80 m, 5 H (H-3, 4, 8, 9, 10); 8·00 bd, 1 H (H-7); 8·30 dd, 1 H (H-2, J = 5·0; 1·5); 10·90 bs, 1 H (CONHAr). ^{13}C NMR spectrum (Jeol FX-60, 15·036 MHz): 45·7 (CH_3N); 52·8 (2) and 54·6 (2) (4 CH_2 of piperazine); 61·0 (remaining CH_2N); 124·0; 128·1; 128·7; 130·2; 131·1; 133·5; 144·8 (7 aromatic —CH=); 128·7; 130·9; 140·9; 147·2 (4 aromatic >C=); 168·5 and 169·7 (2 C=O of amides). For $C_{19}H_{21}N_5O_2$ (351·4) calculated: 64·94% C, 6·02% H, 19·93% N; found: 65·19% C, 6·25% H, 19·35% N.

Dihydrochloride, m.p. 248—251°C with decomposition (aqueous 2-propanol). Refs[63,64], m.p. 257—259°C with decomposition.

2-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)-2-(2-pyridyl)acetonitrile (*XXXIX*)

A solution of 18·5 g 2-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl)acetonitrile[71] in 70 ml toluene was treated with 16·0 g $NaNH_2$ and the mixture was stirred for 2 h. It was then treated over 2 h with 15·8 g 2-bromopyridine and the resulting mixture was refluxed under stirring for 4 h. After standing overnight it was decomposed under external cooling by slow addition of 100 ml water, the toluene layer was dried with K_2CO_3, filtered with active carbon, and evaporated under reduced pressure. The dark residue gave by distillation 11·8 g (45%) of *XXXIX*, b.p. 190—195°C/70 Pa, which crystallized from ethanol and melted at 111°C. IR spectrum: 768, 819, 880 (4 and 2 adjacent and solitary Ar-H); 1 500, 1 573, 1 590, 3 010, 3 070 (Ar); 2 250 (R—CN). ^{1}H NMR spectrum: c. 1·65 m, 6 H (2 H-6, 2 H-7, and 2 H-8); 2·75 m, 4 H (2 H-5 and 2 H-9); 5·22 s, 1 H (Ar_2CHCN); 7·00—7·80 m, 6 H (H-1, 3, 4, 3′, 4′, 5′); 8·60 m, 1 H (H-6′). For $C_{18}H_{18}N_2$ (262·4) calculated: 82·41% C, 6·91% H, 10·68% N; found: 81·96% C, 7·37% H, 10·48% N.

2-(*s*-Hydrindacen-4-yl)-2-(2-pyridyl)acetonitrile (*XLI*)

A mixture of 4·80 g (*s*-4-hydrindacen-4-yl)acetonitrile[72], 20 ml toluene, and 4·0 g $NaNH_2$ was stirred and treated with 4·74 g 2-bromopyridine which was followed after 20 min by an exothermic reaction. The mixture was allowed to stand overnight at room temperature, refluxed for 4 h, cooled, and distributed between water and benzene. The organic layer was dried, evaporated, and chromatographed on a column of 120 g neutral Al_2O_3 (activity II). Elution with benzene gave 4·6 g (69%) of almost homogeneous product which was crystallized from ethanol, m.p. 115—116°C. IR spectrum: 709, 761, 786, 881 (4 adjacent and solitary Ar-H); 1 577, 1 592, 3 045, 3 067 (Ar); 2 255 (R—CN). ^{1}H NMR spectrum: c. 2·00 m, 4 H (2 H-2 and 2 H-6); 2·40—3·30 m, 8 H (2 H-1, 2 H-3, 2 H-5, and 2 H-7); 5·49 s, 1 H (Ar_2CHCN); 7·00—7·30 m, 2 H (H-4′, 5′); 7·08 s, 1 H (H-8); 7·60 m, 1 H (H-3′); 8·59 q, 1 H (H-6′, J = 5·0). For $C_{19}H_{48}N_2$ (274·4) calculated: 83·18% C, 6·61% H, 10·21% N; found: 83·12% C, 6·75% H; 10·28% N.

s-Hydrindacene-4,8-bis(acetonitrile) (*XLII*)

A mixture of 60 ml dimethyl sulfoxide and 12·0 g NaCN was heated to 90°C and treated under stirring over 10 min with 25·5 g 4,8-bis(chloromethyl)-*s*-hydrindacene[73]. The exothermic reaction increased the temperature of the mixture to 150°C. After it was over, the mixture was heated for 20 min to 130—140°C. After cooling the mixture was diluted with 700 ml water and the product was filtered after 2 h standing; 22·4 g (95%), m.p. 218—223°C. Analytical sample, m.p. 217 to 220°C (xylene or acetic acid). IR spectrum: 2 258 (R—CN). ^{1}H NMR spectrum: 2·18 m, 4 H (2 H-2 and 2 H-6); 2·82 t, 8 H (2 H-1, 2 H-3, 2 H-5, and 2 H-7); 3·55 s, 4 H (2 $ArCH_2CN$). For $C_{16}H_{16}N_2$ (236·3) calculated: 81·32% C, 6·83% H, 11·85% N; found: 81·56% C, 6·79% H 11·70% N.

s-Hydrindacene-4,8-bis(2-(2-pyridyl)acetonitrile) (*XLIII*)

A mixture of 11·8 g *XLII*, 100 ml xylene, and 10·0 g $NaNH_2$ was treated with 19·0 g 2-bromopyridine and was refluxed under stirring for 25 h. After cooling the mixture was diluted with 50 ml benzene and decomposed with 100 ml water. The dark solid was filtered off, the filtrate was separated, the organic layer was evaporated, and the glassy residue (12·4 g) was chromatographed on a column of 300 g neutral Al_2O_3 (activity II). Benzene eluted 3·80 g of the starting *XLII* and a mixture of benzene and 3% ethanol eluted then 0·95 g (7% per conversion) of crystalline *XLIII*, m.p. 283—297°C (benzene–ethanol). Mass spectrum (MS 902): 390 (M^+, $C_{26}H_{22}N_4$, 22), 313 (10), 274 (22), 273 (100), 246 (16), 196 (27), 176 (27), 175 (24). IR spectrum (KBr): 769 (4 adjacent Ar-H of pyridine); 1 572, 1 590, 3 000, 3 055 (Ar); 2 240 (RCN). For $C_{26}H_{22}N_4$ (390·5) calculated: 79·97% C, 5·68% H, 14·35% N; found: 79·51% C, 5·82% H, 14·33% N.

2-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-2-yl)-2-(2-pyridyl)thioacetamide (*XXXVIII*)

A solution of 3·20 g *XXXIX* in 3·5 ml pyridine and 2 ml triethylamine was saturated for 30 h with H_2S, the solvents were evaporated in vacuo and the glassy residue (4·05 g) was chromatographed on a column of 120 g neutral Al_2O_3 (activity II). Elution with benzene recovered 1·0 g of the starting *XXXIX* and elution with benzene containing 3% of ethanol afforded 2·40 g (97% per conversion) of *XXXVIII*, m.p. 112—114°C (ethanol). IR spectrum: 739, 829, 900 (4 and 2 adjacent and solitary Ar-H); 1 474, 1 500, 1 578, 1 596 (Ar); 1 490 ($CSNH_2$); 1 640, 3 220 (NH_2). ^{1}H NMR spectrum: c. 1·60 m, 6 H (2 H-6, 2 H-7, and 2 H-8); 2·68 bm, 4 H (2 H-5 and 2 H-9); 5·55 s, 1 H (Ar_2CHCS); 6·90—7·40 m, 5 H (H-1, 3, 4 and H-3′,5′); 7·61 q, 1 H (H-4′, J = 7·0; 2·0); 8·54 q, 1 H (H-6′, J = 5·0; 1·0); 8·25 bs, 1 H and 10·02 bs, 1 H ($CSNH_2$). For $C_{18}H_{20}N_2S$ (296·4) calculated: 72·93% C, 6·80% H, 9·45% N, 10·81% S; found: 73·12% C, 6·69% H, 9·47% N, 10·67% S.

2-(*s*-Hydrindacen-4-yl)-2-(2-pyridyl)thioacetamide (*XL*)

A mixture of 2·50 g *XLI*, 3·5 ml pyridine and 2·0 ml triethylamine was saturated for 40 h with H_2S, then diluted with 20 ml benzene, and evaporated in vacuo. The residue crystallized during an attempt to dissolve it in 15 ml boiling benzene; 2·0 g (71%) orange *XL*, m.p. 175—179°C (benzene). IR spectrum: 761 (4 adjacent Ar-H of pyridine); 880 (solitary Ar-H); 1 529, 1 597 (Ar); 1 638, 3 152, 3 285, 3 395, 3 435 (NH_2). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): 1·85 m, 4 H (2 H-2 and 2 H-6); c. 2·65 m, 8 H (2 H-1, 2 H-3, 2 H-5, and 2 H-7); 5·60 s, 1 H (Ar_2CHCS); 6·92 s, 1 H (H-8); 7·22 m, 2 H (H-3′, 5′); 7·70 t, 1 H (H-4′, J = 8·0); 8·48 q, 1 H (H-6′, J = 5·0); 9·20 bs, 1 H and 9·75 bs, 1 H ($CSNH_2$). For $C_{19}H_{20}N_2S$ (308·5) calculated: 73·99% C, 6·54% H, 9·08% N, 10·39% S; found: 74·19% C, 6·68% H, 8·93% N, 10·27% S.

N-(2-(Phenylthio)phenyl)cyanoacetamide (*XLIV*)

A mixture of 13·8 g 2-(phenylthio)aniline[74,75] and 31·0 g ethyl cyanoacetate was heated for 15 h in a bath of 200—210°C. After standing overnight the crystalline melt was dissolved in 25 ml benzene and treatment with 25 ml light petroleum induced crystallization; 13·3 g (72%) of *XLIV*, m.p. 109—109·5°C (benzene–light petroleum). IR spectrum: 695, 744, 765, 771 (5 and 4 adjacent Ar-H); 1 517, 1 530, 3 055 (Ar); 1 580, 1 704 (ArNHCOR); 2 263 (R-CN); 3 280 (NH). ^{1}H NMR spectrum: 3·30 s, 2 H ($COCH_2CN$); 6·90—7·60 m, 8 H (C_6H_5 and H-3, 4, 5 of thioaniline); 8·21 bd, 1 H (H-6 of thioaniline); 8·70 bs, 1 H (ArNHCO). For $C_{15}H_{12}N_2OS$ (268·3) calculated: 67·14% C, 4·51% H, 10·44% N, 11·95% S; found: 67·19% C, 4·61% H, 10·79% N, 11·83% S.

*The authors wish to thank their colleagues at the Research Institute for Pharmacy and Biochemistry for their contributions to the present study: Drs M. Ryska, I. Koruna, and J. Schlanger (mass spectra); Dr B. Schneider, Mrs A. Hrádková, and Mrs Z. Janová (*UV *and* IR *spectra); Mrs I. Lichá, Mr J. Pomykáček, and Mr Z. Šedivý (participation in the synthetic part); Mrs J. Komancová and Mrs V. Šmídová (elemental analyses); Dr V. Holá (microbiological screening); Dr M. Valchář, Dr S. Wildt, Mrs S. Schubertová, Mrs Z. Paduanová (pharmacology and biochemical pharmacology). Our thanks are due to Dr J. Urban (Institute of Physical Chemistry of the Czechoslovak Academy of Sciences, Prague (*^{13}C NMR *spectrum of* I*).*

REFERENCES

1. Bristol J. A., Long J. F.: Annu. Rep. Med. Chem. *16*, 83 (1981).
2. Bristol J. A., Kaminski J. J.: Annu. Rep. Med. Chem. *17*, 89 (1982).
3. Bays D. E., Stables R.: Annu. Rep. Med. Chem. *18*, 89 (1983); *19*, 81 (1984).
4. Garay G. L., Muchowski J. M.: Annu. Rep. Med. Chem. *20*, 93 (1985).
5. Gladziwa U.: Dtsch. Apoth. Ztg. *126*, 1817 (1986).
6. Kitagawa H., Kurahashi K., Fuhiwara M., Kohei H.: Arneim.-Forsch. *28*, 2122 (1978).
7. Corvi-Mora C. (Camillo Corvi, S.p.A.): Ger. Offen. 2,702,536 (Ital Appl. 23. 01. 1976); Belg. 850,628; U.S. 4,278,796; Chem. Abstr. *87*, 152273 (1977).
8. Scuri R., Mondani G., Fantini P. L., Dalla Valle V., Valsecchi B.: Boll. Chim. Farm. *123*, 425 (1984).
9. Ventura P., Schiavi M., Risoli G.: Farmaco, Ed. Prat. *39*, 190 (1984).
10. Coruzzi G., Adami M., Signorini G., Bertaccini G.: Farmaco, Ed. Prat. *40*, 313 (1985).
11. Coruzzi G., Adami M., Bertaccini G.: Farmaco, Ed. Prat. *40*, 324 (1985).
12. Angelis L. de: Drugs Future *11*, 263 (1986).
13. Ardizzone S., Sangaletti O., Ghirardosi C., Bianchi Porro G.: J. Int. Med. Res. *14*, 321 (1986).
14. Speziale A. J., Hamm P. C.: J. Am. Chem. Soc. *78*, 2556 (1956).
15. Boggiano B. G., Jackman G. B., Petrow V., Stephenson O. (British Drug Houses, Ltd.): Brit. 840,358 (1960); Chem. Abstr. *55*, 588 (1961).
15. Okada J., Shimabayashi M.: Yakugaku Zasshi *98*, 1619 (1978).
17. Meyer P. J.: Ber. Dtsch. Chem. Ges. *8*, 1152 (1875).
18. Zawisza T., Machoń Z., Kuczynski L.: Acta Pol. Pharm. *22*, 477 (1965).
19. Rupe H., Všetečka J.: Justus Liebgs Ann. Chem. *301*, 75 (1898).
20. Erlenmeyer H., Jung J. P., Sorkin E.: Helv. Chim. Acta *29*, 1960 (1946).
21. Erlenmeyer H., Aeberli M., Sorkin E.: Helv. Chim. Acta *30*, 2066 (1947).
22. Schulenberg J. W., Archer S.: J. Org. Chem. *30*, 1279 (1965).
23. Moore G. G. I., Harrington J. K. (Riker Laboratories, Inc.): U.S. 3,755, 605 (Appl. 13. 04. 70); Chem. Abstr. *79*, 115308 (1973).

24. Weisz I., Ötvös L.: Arch. Pharm. *318*, 766 (1985).
25. Goodyear Tire & Rubber Co.: Brit. 834,510 (1960); Chem. Abstr. *55*, 2567 (1961).
26. Van der Burg W. J., Bonta I. L., Delobelle J., Ramon C., Vargaftig B.: J. Med. Chem. *13*, 35 (1970).
27. Van der Burg W. J., Delobelle J. (N. V. Organon): Neth. Appl. 66 3,256 (Appl. 12. 03. 66); Ger. Offen. 1,695,556; U.S. 3,534,041; Chem. Abstr. *70*, 47499 (1969).
28. Anonym: Med. Actual. (Drugs Today) *12*, 31 (1976).
29. Brogden R. N., Heel R. C., Speight T. M., Avery G. S.: Drugs *16*, 273 (1978).
30. Van Riezen H., Pinder R. M., Nickolson V. J., Hobbelen P., Zayed I., Van Der Veen F.: Pharmacol. Biochem. Prop. Drug Subst. *3*, 56 (1981); Chem. Abstr. *98*, 172307 (1983).
31. Pinder R. M.: Drugs Future *10*, 841 (1985).
32. Olivie J. (AKZO N. V.): Neth. Appl. 74 01,807 (Appl. 09. 02. 74); Ger. Offen. 2,505 239; Chem. Abstr. *83*, 193392 (1975); *84*, 121903 (1976).
33. Van der Burg W. J. (AKZO N. V.): Eur. Pat. Appl. 9,284; Neth. Appl. 78 09,726 (Appl. 26. 09. 78); Chem. Abstr. *93*, 186409 (1980).
34. Funke C. W.: Rec. Trav. Chim. Pays-Bas *101*, 437 (1982).
35. Schoemaker H., Berendsen H. H. G., Stevens H. J. T., Nickolson V. J.: Psychopharmacology *74*, 137 (1981).
36. Van Rij C., Feil D.: Tetrahedron *29*, 1891 (1973).
37. Van Wendel de Joode M. D., Zeelen F. J.: Rec. Trav. Chim. Pays-Bas *101*, 81 (1982).
38. Van Meerssche M., Declercq J. P.: Bull. Soc. Chim. Belg. *92*, 307 (1983).
39. Ebnöther A., Jucker E., Stoll A.: Helv. Chim. Acta *48*, 1237 (1965).
40. Arya V. P., Grewal R. S., Kaul C. L., David J., Shenoy S. J., Honkan V.: Indian J. Chem., B *15*, 148 (1977).
41. Häfliger F., Schindler W. (J. R. Geigy A.-G.): U.S. 2,666,051 (1954); Chem. Abstr. *49*, 9041 (1955).
42. Eberlein W. G., Trummlitz G., Engel W. W., Schmidt G., Pelzer H., Mayer N.: J. Med. Chem. *30*, 1378 (1987).
43. Bickel M. H. in the book: *Psychotherapeutic Drugs* (E. Usdin and I. S. Forrest, Eds), Pt. II, p. 1131. M. Dekker, New York 1977.
44. Herrmann B. in the book: *Tofranil* (imipramine) (J. Angst and W. Theobald, Eds), p. 94. Stämpfli, Bern 1970.
45. Pfeifer S.: *Biotransformation von Arzneimitteln.* Vol. 2, p. 177, VEB Verlag Volk und Gesundheit, Berlin 1977.
46. Pfeifer S., Borchert H.-H.: *Biotransformation von Arzneimitteln.* Vol. 5, p. 268. VEB Verlag Volk und Gesundheit, Berlin 1983.
47. J. R. Geigy A.-G.: Brit. 907,785 (Swiss Appl. 04. 03. 60); Chem. Abstr. *58*, 5646 (1963).
48. Cusic J. W. (G. D. Searle & Co.): U.S. 3,123,610 (Appl. 14. 12. 59); Chem. Abstr. *60*, 15847 (1964).
49. Eberlein W., Schmidt G., Reuter A., Kutter E.: Arzneim.-Forsch. *27*, 356 (1977).
50. Schmidt G. (Dr. Karl Thomae G.m.b.H.): Ger. 1,179,943 (Appl. 08. 11. 62); Chem. Abstr. *62*, 1677 (1965).
51. Diethelm E. (Grissman Chemicals Limited): Brit. 1,176,867 (Appl. 09. 07. 79); Eur. Pat. Appl. 22,174; Chem. Abstr. *95*, 43185 (1981).
52. Finger H.: J. Prakt. Chem. [2] *37*, 431 (1888).
53. Mehner H.: J. Prakt. Chem. [2] *63*, 241 (1901).
54. Meyer H.: Justus Liebigs Ann. Chem. *351*, 267 (1907).
55. Bernath G., Gera L., Goudos G., Ecsery Z., Hermann M., Szentivanyi M., Janvari L. (Chinoin): Australian 507,798 (Hung. Appl. 03. 10. 75); Chem. Abstr. *94*, 175144 (1981).

56. Oklobdžija M., Comisso G., Decorte E., Kovač T., Angeli C., Moimas F., Zanon P., Zonno F., Toso R., Šunjić V.: J. Heterocycl. Chem. *20*, 1335 (1983).
57. Oklobdžija M., Comisso G., Decorte E., Fahdiga T., Gratton G., Moimas F., Toso R., Šunjić V.: J. Heterocycl. Chem. *20*, 1329 (1983).
58. Šunjić V., Toso R. (CRC Compagnia di Ricerca Chimica S.p.A.): Ger. Offen. 3,211,973 (Ital. Appl. 24. 04. 81); Chem. Abstr. *98*, 89402 (1983).
59. Bladé-Font A.: Tetrahedron Lett. *21*, 2443 (1980).
60. Bredt J., Hof H.: Ber. Dtsch. Chem. Ges. *33*, 21 (1900).
61. Wagner E. C., Fegley M. F.: *Org. Synth., Coll. Vol. 3*, 488 (1964).
62. Armarego W. L. F: *The Chemistry of Heterocyclic Compounds.* Vol. 24. *Fused Pyrimidines* (D. J. Brown, Ed.), Pt. I, p. 74. Wiley-Interscience, New York 1967.
63. Dr. Karl Thomae GmbH: Fr. 1,505,795 (Ger. Appl. 17. 12. 65); Chem. Abstr. *70*, 4154 (1969).
64. Schmidt G., Engelhorn R., Leitold M. (Dr. Karl Thomae, GmbH): Ger. 1,175,183 (Appl. 20·08. 68); S. African 69 05,933; Chem. Abstr. *73*, 77292 (1970).
65. Cook D. L., Bianchi R. G.: Life Sci. *6*, 1381 (1967).
66. Lee Y.-H., Phillips E., Sause H. W.: Arch. Int. Pharmacodyn. Ther. *195*, 402 (1972).
67. Beattie D. E., Crossley R., Curran A. C. W., Dixon G. T., Hill D. G., Lawrence A. E., Shepherd R. G.: J. Med. Chem. *20*, 714 (1977).
68. Yamada T., Nobuhara Y., Shimamurá H., Yoshihara K., Yamaguchi A., Ohki M.: Chem. Pharm. Bull. *29*, 3433 (1981).
69. Yamada T., Nobuhara Y., Yamaguchi A., Ohki M.: J. Med. Chem. *25*, 975 (1982).
70. Aloup J.-C., Bouchaudon J., Farge D., James C., Deregnaucourt J., Hardy-Houis M.: J. Med. Chem. *30*, 24 (1987).
71. Aspinall G. O., Baker W.: J. Chem. Soc. *1950*, 743.
72. Vejdělek Z. J., Bartošová M., Ryska M., Protiva M.: Collect. Czech. Chem. Commun. *43*, 1732 (1978).
73. Vejdělek Z. J., Holubek J., Bartošová M., Protiva M.: Collect. Czech. Chem. Commun. *42*, 3094 (1977).
74. Foster D. G., Reid E. E.: J. Am. Chem. Soc. *46*, 1936 (1924).
75. Suter C. M.: J. Am. Chem. Soc. *51*, 2581 (1929).
76. Okabe S., Takeuchi K., Urushidani T., Takagi K.: Am. J. Dig. Dis. *22*, 677 (1977); Chem. Abstr. *90*, 66781 (1979).
77. Pulewka P.: Arch. Exp. Pathol. Pharmakol. *168*, 307 (1932); Chem. Abstr. *27*, 777 (1933).
78. Shay H., Komarov S. A., Fels S. S., Meranze D., Gruenstein M., Siplet H.: Gastroenterology *5*, 43 (1945).

Translated by the author (M.P.).