SYNTHESIS OF PIPERIDINE DERIVATIVES AS POTENTIAL ANALGETIC AGENTS

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Reaction of N-(1-(2-phenylethyl)-4-piperidinyl)propionanilide (*I*) with phosphorus pentasulfide gave the thioamide *VI*. Acylation of N-(1-(2-phenylethyl)-4-piperidinyl)aniline with 2-(methoxy)-acetic and 2-(methylthio)acetic anhydrides afforded the amides *II* and *III*. Treatment of 4-anilino--1-benzylpiperidine-4-methanol with thionyl chloride gave the spirocyclic sulfurous acid ester amide *XIV*. Reduction of the hydrochloride of ethyl 3-(1-ethoxycarbonyl-4-phenylimino-3--piperidinyl)propionate (*XXII*) with sodium cyanoborohydride gave the perhydro-1,6-naphthyridine derivative *XIX*, a model compound in the synthesis of the cyclic analogue of fentanyl (*I*). Ethyl 4-anilino-1-(2-phenylethyl)-1,2,3,6-tetrahydropyridine-3-carboxylate (*XXIX*) hydrochloride, obtained by reaction of ethyl 4-oxo-1-(2-phenylethyl)piperidine-3-carboxylate hydrochloride with aniline, was reduced with lithium aluminium hydride to 4-anilino-1-(2-phenylethyl)piperidine-3-methanol (*XXXI*). 1-Methyl- and 1-benzyl-4-piperidone were reacted with 4-cyclopropylphenylmagnesium bromide and the tertiary alcohols *XXXVII* and *XXXVIII* obtained were acylated with propionyl chloride to give the esters *XXXIX* and *XL*. The piperidine derivatives *XLI*, *XLVI* and *XLVIII* were prepared as potential neurotropic agents. Alkylation of 8-hydroxy--6,11-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (*XLIX*) with 2-(2-chloroethyl)--1,3-dioxane and -1,3-dioxolane resulted in the 6,7-benzomorphan derivatives *L* and *LI*. Out of the compounds prepared, only the closest fentanyl analogues *II*, *III*, and *VI* showed very strong analgetic activity.

The piperidine moiety forms an important part of the morphine molecule and the fact, that many simple piperidine derivatives (e.g. pethidine, ethyl 1-methyl-4-phenylpiperidine-4-carboxylate) exert a more or less important morphine-like narcotic--analgetic properties, stimulated an extensive research in the field of piperidine derivatives as potential analgetics[1-3]. Since the discovery of the extremely active N-(1-(2-phenylethyl)-4-piperidinyl)propionanilide (*I*, refs[4-8]), called "fentanyl" (Fentanyl[R]), which is about 300 times more potent than morphine, its molecule became a prototype for designing structures of further potential analgetic agents. Many papers[9-21] deal with the synthesis and testing of fentanyl analogues but most of the molecular manipulations resulted in decrease or loss of activity. Only the introduc-

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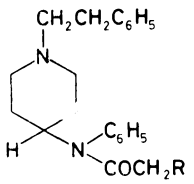
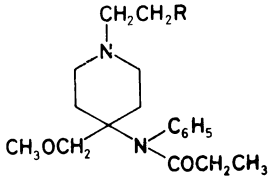
tion of the methyl group to position 3 of piperidine[22] and substitution in position 4 by methoxycarbonyl or methoxymethyl[23] led to further increase of the activity. The last mentioned modifications together with a change of piperidine N-substituent resulted in further two highly potent narcotic analgetics with a rapid onset and shorther duration of action which also found practical use: "sufentanil" (*IV*, Sufenta[R], refs[23–26]) and "alfentanil" (*V*, Rapifen[R], refs[27–31]). Structure–activity relationships in the fentanyl series were discussed in ref.[32] taking into account the conformation analysis and molecular graphics.

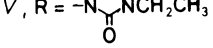


I, R = CH_3
II, R = OCH_3
III, R = SCH_3

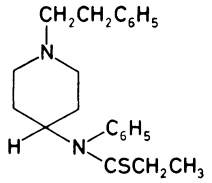


IV, R =

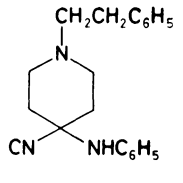
V, R =



The present paper in its first part is also devoted to manipulations with the structure of fentanyl (*I*) and in general to some synthetic experiments in the related field. We started with the carba-oxa-thia isosterism in the fentanyl series. The first compound to be prepared was the thioamide *VI* related to fentanyl (*I*) which was obtained from *I* (refs[4,5]) by treatment with phosphorus pentasulfide in boiling pyridine. The crystalline base (IR spectrum) afforded a crystalline hydrogen maleate. The further two analogues had the acyl group prolonged by one atom, cf. *II* and *III*. They were prepared by acylation of N-(1-(2-phenylethyl)-4-piperidinyl)aniline[33,34] with anhydrides of 2-(methoxy)acetic[35] and 2-(methylthio)acetic acid[36] in boiling benzene. The crystalline bases *II* and *III* (characterized by IR and ^{1}H NMR spectra) were transformed to crystalline hydrogen maleates. The maleate of *III* was found to be a 2 : 1 solvate with toluene (it was crystallized from ethanol which was denaturated with 2% of toluene; compare with ref.[37]). An attempt to acylate the amino nitrile *VII* (ref.[23]) with propionyl chloride in pyridine led only to the hydrochloride of the starting *VII*.

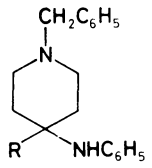


VI

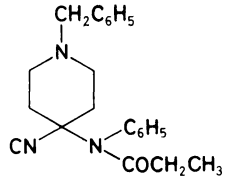


VII

A similar attempt to acylate the amino nitrile *VIII* (ref.[38]) with propionyl chloride in pyridine gave similarly only the hydrochloride of *VIII*. On the other hand, the acylation with boiling propionic anhydride afforded the amide *XIII* which was transformed to the crystalline hydrogen oxalate (its mass and IR spectra were recorded). The hydration of the nitrile *VIII* to the amide *IX* was carried out by heating with 90% sulfuric acid[38]. The hydrolysis of *VIII* with potassium hydroxide in boiling ethanol did not proceed at all and the similar reaction in ethane-1,2-diol at 200°C proceeded very slowly (the yield of *X* after 16 h of heating was only 11%). On the other hand, the hydrolysis of the amide *IX* with potassium hydroxide in ethane-1,2-diol at 200–215°C proceeded smoothly and yielded almost 90% of the amino acid *X* which was characterized by the IR spectrum. Reduction of this acid with sodium dihydridobis(2-methoxyethoxo)aluminate[39] in benzene gave the alcohol *XI* (was prepared by reduction of the ethyl ester of *X* by the same reducing agent[23]) which was transformed to crystalline salts (dihydrochloride, dihydrobromide).



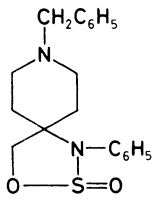
VIII, R = CN
IX, R = $CONH_2$
X, R = COOH
XI, R = CH_2OH
XII, R = CH_2Cl



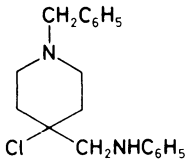
XIII

In an attempt at preparing *XII*, the alcohol *XI* was subjected to treatment with thionyl chloride in benzene and in the presence of pyridine at room temperature. The primary product was treated with a solution of sodium hydroxide and then isolated by extraction with benzene. Processing of the extract gave 53% of a homogeneous crystalline compound $C_{19}H_{22}N_2O_2S$ (mass spectrum and analysis) which gave a crystalline hydrogen maleate. The ^1H NMR spectrum showed the presence of 10 aromatic protons (belonging evidently to the benzyl and aniline phenyls), the benzyl CH_2 group, 4 piperidine CH_2 groups, and in addition a further CH_2 with differentiated signals of the two protons (δ 4·55 d and 4·78 d), ascribed to the fragment C—CH_2—O in a ring. The band at 1 170 cm^{-1} in the IR spectrum is ascribed to the presence of an S=O group. On the basis of theses fact the product is formulated as the spirocyclic compound *XIV*. It is easily hydrolyzed with water at 70°C and under formation of sulfur dioxide, the starting alcohol *XI* is recovered which is considered a further proof of correctness of formula *XIV*. A reaction of *XI* with

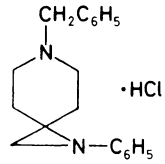
an excess of thionyl chloride in boiling chloroform led to a solution which was decomposed with water and made alkaline with sodium hydroxide. Processing of the chloroform solution and chromatography of the crude product on aluminium oxide gave a homogeneous oily base which afforded a crystalline oxalate and a crystalline maleate. The analyses of both of these salts corresponded to the composition $C_{19}H_{23}$. .ClN_2 for the base, i.e. composition of the wanted *XII*. The ^{1}H NMR spectrum of the released base, however, denied the presence of the fragment CH_2Cl and instead of that the presence of the fragment $CH_2NHC_6H_5$ was suggested. The mass spectrum of the maleate of this compound showed in addition to a negligible peak corresponding to the molecular ion of m/z 314 (i.e. $C_{19}H_{23}ClN_2$) a very important peak of the ion $C_{19}H_{22}N_2$, i.e. of a product of dehydrochlorination. All these facts led to the formulation of the isomeric chloro compound as *XV*. This compound could be formed from the presumably unstable *XII* via the spiro-aziridinium salt *XVI*. Compound *XV* with the character of a tertiary alkyl chloride could easily eliminate hydrogen chloride and form *XVII* which appeared in the mass spectrum.



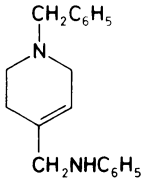
XIV



XV



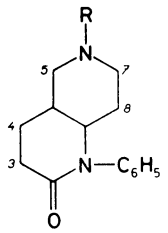
XVI



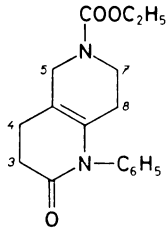
XVII

From the stereochemical point of view there is a big difference between the rigid molecule of morphine and the flexible molecule of fentanyl (*I*). This fact induced some authors to design and prepare several types of conformationally restrained cyclic analogues of *I* (refs[12,20,21]) which, however, were inactive. We had also a program in this line, the objective of which was the perhydro-1,6-naphthyridine derivative *XVIII*. The work was started but discontinued in the stage of model compounds *XIX* and *XX* because in the meantime the synthesis of *XVIII* was published[40]. Our approach was different from that used in ref.[40] and was connected with some other

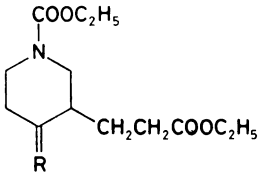
synthetic experiments and, therefore, is being reported here. We started from 1--(ethoxycarbonyl)-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine[41] which was added to ethyl acrylate and the enamine was cleaved by hydrolysis with dilute hydrochloric acid to give *XXI*. Its heating with aniline in boiling toluene under continual removal of water, formed by the reaction, resulted in *XXII*. It was attempted to reduce the double bond in *XXII* with sodium borohydride with the hope that cyclization directly to *XIX* could take place. Processing of the mixture led to a crystalline product $C_{17}H_{20}N_2O_3$ (mass spectrum and analysis) which was identified as *XX*. The heating during the processing forced probably the cyclization which proceeded under shifting of the double bond to the neighbouring position. The structure *XX* was unequivocally supported by the ^{1}H NMR spectrum. The Schiff base *XXII* was further reduced in the form of the iminium salt (cf. refs[42,43]) with sodium cyanoborohydride in a mixture of tetrahydrofuran and methanol. In this case, the double bond was really removed and the cyclization proceeded under mild conditions giving the lactam--carbamate *XIX*. It is a constantly melting solid $C_{17}H_{22}N_2O_3$ (mass spectrum and analysis) whose structure was corroborated by spectra (IR and ^{1}H NMR). The configuration on carbons 4a and 8a remained unsolved. In this stage the work was interrupted.



XVIII, R = $CH_2CH_2C_6H_5$
XIX, R = $COOC_2H_5$



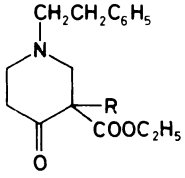
XX



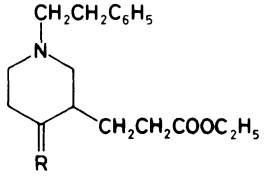
XXI, R = O
XXII, R = NC_6H_5

Some synthetic experiments preceded the approach to *XVIII* just described. The keto ester *XXIII* was synthesized according to refs[44,45] and its addition to acrylo-

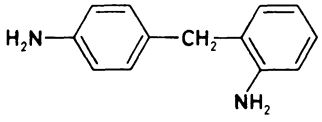
nitrile gave *XXIV* which was characterized as the crystalline hydrogen oxalate. The acid cleavage of *XXIV* (boiling dilute hydrochloric acid) and the following esterification of the crude product with ethanol and hydrogen chloride gave directly the crystalline hydrochloride of *XXV*. The released oily base was used for recording the ^{1}H NMR spectrum which confirmed the structure *XXV*. In the effort to prepare the Schiff base *XXVI*, the hydrochloride of *XXV* was reacted with aniline in boiling toluene under continual removal of the water formed. On standing the reaction mixture deposited a crystalline product which was identified as 2-phenylethylamine hydrochloride, obtained in the yield of 69%. Its melting point (221–226°C) was a little higher than the literature[46] value (217°C) and, therefore, an authentic sample was prepared from commercial 2-phenylethylamine. Its melting point was 220 to 221·5°C and in mixture with our product it melted without depression. From the mother liquors the basic fraction was isolated and chromatographed on aluminium oxide. From the eluate the volatile components (aniline) were removed by distillation and the residue was a crystalline minor product $C_{13}H_{14}N_2$ (mass spectrum and analysis) appearing to be a diaminodiphenylmethane which is in agreement with the IR and ^{1}H NMR spectra. Out of the isomeric diaminodiphenylmethanes known, the melting point of our product (82·5–84°C) is close to the values given for 2,4'--diaminodiphenylmethane (88–89°C, ref.[47]), 3,4'-diaminodiphenylmethane (89 to 90°C, ref.[48]), and 4,4'-diaminodiphenylmethane (85°C, ref.[49]). The 4,4'-diamino isomer is excluded by the ^{1}H NMR spectrum and the 2,4'-diamino compound is preferred by the IR spectrum: in this way, formula *XXVIII* is ascribed to this minor by-product. Its appearing here is very strange and especially the source of the central diphenylmethane carbon is completely obscure.



XXIII, R = H
XXIV, R = CH_2CH_2CN

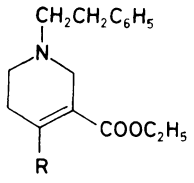


XXV, R = O
XXVI, R = NC_6H_5
XXVII, R = $C(OC_2H_5)_2$

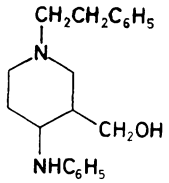


XXVIII

Similar processing of *XXIV* like in the preparation of *XXV* with the difference that the primary product was refluxed only with ethanol (without hydrogen chloride) gave a mixture from which the basic product was isolated and chromatographed on aluminium oxide. The homogeneous oily product was transformed to the crystalline hydrogen oxalate which was identified as the salt of the diethyl ketal *XXVII*. In addition to the analysis, the identity of this product was supported only by the IR spectrum of the released base (absence of the ketone band at 1 715 cm^{-1}). The hydrochloride of *XXIII* (refs[44,45]) reacted smoothly with aniline in ethanol at room temperature and afforded in a high yield the hydrochloride $C_{22}H_{27}ClN_2O_2$, identified by the ^1H NMR spectrum of the released base as the enamino ester *XXIX* which was considered to be a potentially useful synthon. In fact, the results of the attempts to use it in the line of our program, were very poor. The attempts to reduce the double bond in *XXIX*.HCl with sodium borohydride in methanol or ethanol, or by catalytic hydrogenation on Adams' catalyst in ethanol did not lead to identified products. The reduction with zinc in boiling acetic acid proceeded as a hydrogenolysis: aniline was cleaved, the double bond remained, and the product, isolated as crystalline hydrochloride, was identified by the ^1H NMR spectrum of the released base as *XXX*. Only reduction of *XXIX* with lithium aluminium hydride in ether led to saturation of the double bond, of course together with reduction of ethoxycarbonyl to hydroxymethyl and the amino alcohol *XXXI* was obtained and isolated first in the form of the crystalline oxalate. Reduction of *XXIX* with sodium dihydridobis(2-methoxyethoxo)aluminate[39] in benzene gave the same result. The base *XXXI*, which was released from the oxalate, crystallized, which indicated homogeneity. Its ^1H NMR spectrum, however, is not well resolved making the conclusion about homogeneity doubtful (mixture of diastereoisomers is more likely). An attempt to acylate *XXIX* with propionyl chloride in chloroform led only to *XXIII* hydrochloride.



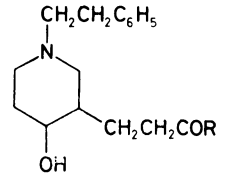
XXIX, R = NHC_6H_5
XXX, R = H



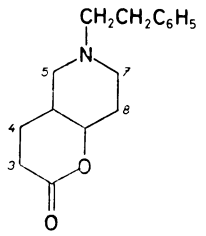
XXXI

Acid cleavage of *XXIV* (boiling dilute hydrochloric acid) followed by reduction with sodium borohydride and final esterification with ethanol gave the hydrochloride of the hydroxy ester *XXXII* (IR and ^1H NMR spectra of the salt were recorded). A similar sequence of reactions without the final esterification (only acidification) led to a crystalline base $C_{16}H_{21}NO_2$ (analysis) which corresponds to

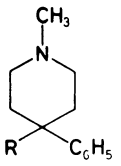
the lactone *XXIV* (IR and ^{1}H NMR spectra are in agreement). Attempts to transform *XXXIV* to *XVIII* by heating with aniline to 180–230°C were not successful (no identified products). A reaction of *XXXII*.HCl with thionyl chloride in chloroform gave a product corresponding to *XXXIV* hydrochloride. Heating of *XXXII* with aniline to 120°C gave the anilide *XXXIII*. Attempts to convert *XXXIII* to *XVIII* by treatment with thionylchloride or with methanesulfonylchloride in pyridine and then by cyclization of the supposed intermediates with sodium hydride in toluene did not lead to the goal.



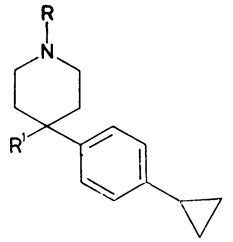
XXXII, R = OC_2H_5
XXXIII, R = NHC_6H_5



XXXIV



XXXV, R = $COOC_2H_5$
XXXVI, R = $OCOC_2H_5$

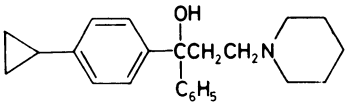


XXXVII, R = CH_3 ; R^1 = OH
XXXVIII, R = $CH_2C_6H_5$; R^1 = OH
XXXIX, R = CH_3 ; R^1 = $OCOC_2H_5$
XL, R = $CH_2C_6H_5$; R^1 = $OCOC_2H_5$

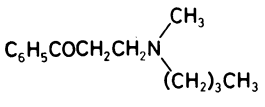
After many years we come back to the series of pethidine analogues (cf. ref.[50]). It is known that pethidine (*XXXV*) was the first member of the simple morphine-like analgetics of the piperidine series[51]. Its "reversed ester" analogue *XXXVI* was found to be even more active as an analgetic[52]. We are now describing the synthesis of two new "reversed esters" of this type whose molecules encompass the 4-cyclopropylphenyl residue. 1-Bromo-4-cyclopropylbenzene[53] was transformed to the Grignard reagent in ether[54] and this was reacted with 1-methyl-4-piperidone and 1-benzyl-4-piperidone. The crystalline tertiary alcohols *XXXVII* and *XXXVIII* were obtained in moderate yields, were characterized by IR and ^{1}H NMR spectra and

transformed to crystalline hydrogen maleates. The bases were acylated with propionyl chloride in ether or pyridine and gave either directly or via the oily base the crystalline hdrochlorides of the esters *XXXIX* and *XL* in high yields.

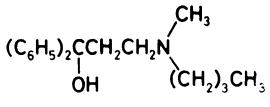
3-Amino-1,1-diarylpropanols are intermediates of the synthesis of the corresponding 3,3-diarylpropylamines having analgetic and antispasmodic activity[55]. In this context, the reaction of 4-cyclopropylphenylmagnesium bromide[54] with 1-phenyl-3-(1-piperidinyl)propan-1-one[56,57] was carried out. The amino alcohol *XLI* was obtained in a high yield and was directly transformed to the crystalline hydrochloride. The expected dehydration was not observed. The Mannich reaction[57] of acetophenone with N-butylmethylamine hydrochloride and paraformaldehyde in boiling ethanol gave directly the crystalline hydrochloride of the amino ketone *XLII*. The released base was reacted with phenylmagnesium bromide in ether and gave the amino alcohol *XLIII* which distilled in vacuo without decomposition and then crystallized. Reaction of 2-(N-butylmethylamino)ethanol[58] with methyl iodide in acetone gave the quaternary salt *XLIV*, a choline iodide analogue. Reaction of 2-adamantanone with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran gave the crystalline alcohol *XLV* affording a crystalline hydrochloride. Attempt to dehydrate *XLV* with boiling dilute sulfuric acid was unsuccessful (the complete dehydration did not take place).



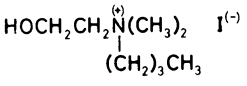
XLI



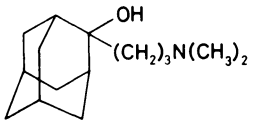
XLII



XLIII



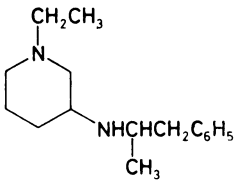
XLIV



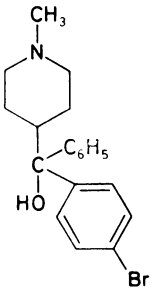
XLV

Another type of piperidine derivative prepared was the amphetaminoid *XLVI* which was obtained by reductive alkylation of 3-amino-1-ethylpiperidine[59] with phenylacetone and sodium borohydride in aqueous methanol. The oily base was distilled and the ^{1}H NMR spectrum did not clarify the question of homogeneity (probably a mixture of both racemates). It afforded a crystalline hydrogen maleate. Some 4-(benzhydrylidene)piperidines were described in patents[60,61] as antihistaminics. A longer time ago a member of this series had been prepared by our team. Reaction of 4-bromobenzophenone[62] with 1-methyl-4-piperidylmagnesium chloride[63]

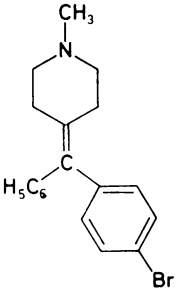
in tetrahydrofuran afforded the amino alcohol *XLVII* which was transformed to the stable crystalline hydrochloride (no dehydration). The dehydration of *XLVII* did not proceed by refluxing with 1·5M-H_2SO_4. Finally it was carried out by a boiling mixture of acetic and hydrochloric acid; the oily base *XLVIII* was transformed to the crystalline hydrochloride.



XLVI



XLVII

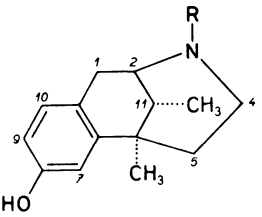


XLVIII

The last part of this paper deals with the preparation of two 6,7-benzomorphan derivatives. 6,7-Benzomorphan, i.e. 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine, is also a part of the morphine molecule, and some of its derivatives, especially N-substituted 8-hydroxy-6,11-dimethyl derivatives[64], exhibit strong morphine-like analgetic activity. Various N-substituents were used in this connection and we remembered our good experience with 2-(1,3-dioxan-2-yl) ethyl and 2-(1,3-dioxolan--2-yl)ethyl in the same role in a different sries of psychotropic agents[65]. The starting compound *XLIX* was obtained by the synthesis of Kametani et al.[66]. It was alkylated with 2-(2-chloroethyl)-1,3-dioxane[67] and 2-(2-chloroethyl)-1,3-dioxolane[67] in boiling dimethylformamide in the presence of sodium hydrogen carbonate. The products *L* and *LI* were obtained in reasonable yields as crystalline bases which were fully characterized by spectra and transformed to crystalline hydrogen maleates. After the termination of this part of our work, *LI* was mentioned in a paper[68] (similar method of preparation and only the melting point of the fumarate was reported).

Only a part of the compounds prepared was pharmacologically tested (i) in some specific tests, e.g. for analgetic, antihistamine, and CNS effects, and (ii) in a general screening program. The compounds were tested in the form of salts, described in the Experimental (the doses given were calculated per base). Unless otherwise stated, they were administered intravenously. Acute toxicity in mice, LD_{50} in mg/kg: *II*, 38 (toxic symptoms: dyspnea, loss of the righting reflex, transient convulsive symptoms, Straub phenomenon); *III*, 12·2 (toxic symptoms similar as with *II*); *VI*, 20 (toxic symptoms similar like with the preceding compounds); *XXIX*, 2 500 orally (toxic symptoms: reduced activity and reactivity, ataxia, tremor, miosis, and ptosis);

XXXVII, 87·5 (sedation); *XXXVIII*, 36; *XXXIX*, 45 (sedation); *XL*, 30; *XLI*, 17·5; *XLVI*, 40 (transient excitation after high doses); *XLVIII*, 48·5; *L*, 37·3; *LI*, 35. Doses used in the screening, D in mg/kg: *XXIX*, 300 orally; *XXXVII*, 16; *XXXVIII*, 7; *XXXIX*, 9; *XL*, 6; *XLI*, 3; *XLVI*, 8.



XLIX, R = H

L, R = CH_2CH_2–(1,3-dioxolan-2-yl)

LI, R = CH_2CH_2–(1,3-dioxolan-2-yl)

Analgetic effect in the peritoneal test in mice (inhibition of the writhing syndrome): *II*, 0·1 mg/kg subcutaneously was active in 90% of the animals (fentanyl at 0·01 mg/kg active in 80%); *III*, 0·01 and 0·1 mg/kg s.c. was active in more than 50% of animals, 0·2 mg/kg s.c. gave full protection; *VI*, full activity at 0·1 mg/kg s.c.; *XIII*, active at 100 mg/kg orally. Analgetic activity in the Haffner's test in mice (pethidine as a standard, ED = 2·5 mg/kg i.v.): *II*, inactive in the s.c. dose of 1 mg/kg (for fentanyl D_{50} = 0·06 mg/kg s.c.); *III*, D_{50} 0·3–0·6 mg/kg s.c.; *VI*, D_{50} 0·18 mg/kg s.c. (33% of the activity of fentanyl); *XXIX*, *XXXVII–XXXIX*, inactive at doses D; *XL*, ED about 15 mg/kg (50% of the LD_{50}); *L*, D_{50} 57·8 mg/kg s.c. (for morphine less than 2 mg/kg s.c.); *LI*, D_{50} 8·3 mg/kg s.c. Analgetic activity in the mouse hot plate method: *L*, the dose of 50 mg/kg s.c. had only insignificant effect; *LI*, ED_{50} 29·9 mg/kg s.c.

CNS effects in the sense of central depression: *XXXVII* inhibited the locomotor activity and decreased the body temperature of mice at the dose D; *XXXIX*, similar effects like with *XXXVII*; *XLI*, hypothermic effect in mice at the dose D; *XLVIII*, at 10 mg/kg mild prolongation of the thiopental sleeping-time in mice; in the rotarod test in mice, ataxia at ED_{50} 19·6 mg/kg; *L*, at 8 mg/kg mild prolongation of the thiopental sleeping-time in mice, ataxia in mice only in subtoxic doses; *LI*, at 7 mg/kg mild prolongation of the thiopental sleeping-time in mice, ataxia only in subtoxic doses, no significant inhibition of locomotor activity of mice.

Spasmolytic activity on the isolated rat duodenum: (i) against acetylcholine contractions: *XXXVIII*, effect in a concentration of 1 mg/l; *XLI*, similar effect like with *XXXVIII*; (ii) against barium chloride contractions, active concentrations given: *XXXVIII*, 1–10 mg/l; *XL*, 10 mg/l; *XLI*, 1–10 mg/l, in the dose of 10 mg/kg s.c.

no protective effect towards oxotremorine in mice and no antagonization of the arecoline tremor in mice, no inhibition of the ulcerogenic effect of reserpine in rats. Local anaesthetic effect: *XL*, a 0·5% concentration brought about a complete anaesthesia in 50% of guinea-pigs in the experiment (infiltration anaesthesia, for procaine as a standard, EC = 1%). Corneal anaesthesia: *XL*, a 0·5% concentration brought about in 50% of rabbits a complete anaesthesia of the eye cornea (for trimecaine as a standard, EC = 1%); *XLI*, EC = 0·5%. Antiarrhythmic effect: *XXXVIII*, a dose of 5–7 mg/kg prolonged significantly the latency of ventricular extrasystoles in rats induced by aconitine (for quinidine as a standard, ED = = 5–10 mg/kg i.v.); *XLVI*, ED = 2·5–5·0 mg/kg. Hypotensive effects: *XXXVIII* and *XXXIX* in doses D brought about prolonged drops of the blood pressure in anaesthetized normotensive rats. Diuretic effect, oral doses which significantly increased diuresis in mice: *XXXVII*, 50–80 mg/kg; *XXXVIII*, 35 mg/kg.

Antihistamine effects: *XLVIII* showed in the in vivo tests a mild antihistamine effect; in the i.p. dose of 5 mg/kg it protected 40% of guinea-pigs in the aerosol test from the histamine bronchospasm; in the same dose, administered s.c., it protected 20% of guinea-pigs in the test of detoxication of histamine. In the i.p. dose of 5 mg/kg it had a significant antireserotonin effect in the test of rat paw oedema.

In conclusion: Only compounds which are most closely related to fentanyl (*I*), i.e. *II* (VÚFB-13758), *III* (VÚFB-13 759), and *VI* (VÚFB-13757) showed strong analgetic activity, the thioamide *VI* being the most active. Out of the 6,7-benzomorphan derivatives, *LI* (VÚFB-10 584) is rather active, having 25% of the morphine activity in the Haffner's test.

EXPERIMENTAL

The melting points were determined in the Kofler block and are not corrected; the samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at a suitably elevated temperature. The UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded with a Unicam SP 700 spectrophotometer, IR spectra (mostly in NUJOL, ν in cm^{-1}) with a Unicam SP 200G spectrophotometer, ^1H NMR spectra (in $CDCl_3$ unless otherwise stated, δ in ppm, J in Hz) with a CW-NMR spectrometer TESLA BS 487C (80 MHz), and the mass spectra (m/z, %) with MS 902 (AEI) spectrometer. The homogeneity of the products and compostion of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). The extracts were dried with $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure on a rotary evaporator. Column chromatography was mostly carried out on neutral Al_2O_3 (activity II).

N-(1-(2-Phenylethyl)-4-piperidinyl)thiopropionanilide (*VI*)

A mixture of 5·4 g *I* (refs[4,5]), 4·0 g P_4S_{10}, and 20 ml pyridine (ontaining 0·7% H_2O) was stirred and refluxed for 2 h. After cooling the mixture was diluted with 200 ml water, it was made alkaline with 10% NaOH, and extracted with a mixture of benzene and chloroform (1 : 1). The extract was washed with water and processed; 5·60 g of a glassy residue which crystallized from acetone and gave 2·0 g (35%) of *VI*, m.p. 126°C. IR spectrum (KBr): 700, 722, 756(5adjacent

Ar–H); 1 423 (N—C=S); 1 497, 1 600, 3 010, 3 048 (Ar); 2 745, 2 790 (CH_2–N). For $C_{22}H_{28}N_2S$ (352·5) calculated: 74·95% C, 8·00% H, 7·95% N, 9·09% S; found: 75·11% C, 8·03% H, 7·95% N; 9·29% S.

Hydrogen maleate, m.p. 148—149°C (ethanol). For $C_{26}H_{32}N_2O_4S$ (468·6) calculated: 66·64% C, 6·88% H, 5·98% N, 6·84% S; found: 66·94% C, 6·95% H, 5·92% N, 6·64% S.

N-(1-(2-Phenylethyl)-4-piperidinyl)-2-(methoxy)acetanilide (*II*)

A mixture of 4·0 g N-(1-(2-phenylethyl)-4-piperidinyl)aniline[33,34], 6·0 g 2-(methoxy)acetic anhydride[35], and 50 ml benzene was refluxed for 6 h, benzene was evaporated and the residue was dissolved in 80 ml chloroform. The solution was shaken for 30 min with 80 ml dilute NH_4OH (1 : 1), dried, and evaporated. The remaining oil (5·5 g) crystallized from 11 ml acetone giving 3·85 g (77%) of *II*, m.p. 96—97°C (acetone). IR spectrum: 702, 709, 752 (5 adjacent Ar–H); 1 132 (ROR'); 1 499, 1 598, 3 020, 3 050 (Ar); 1 679 (RCON). ^{1}H NMR spectrum: 1·30—3·20 m, 12 H ($ArCH_2CH_2N$ and 4 × CH_2 of piperidine); 3·48 s, 3 H (OCH_3); 3·68 s, 2 H ($COCH_2O$); 4·75 m, 1 H (H-4 of piperidine); 7·00—7·60 m, 10 H (2 × C_6H_5). For $C_{22}H_{28}N_2O_2$ (352·5) calculated: 74·97% C, 8·01% H, 7·95% N; found: 75·01% C, 7·84% H, 7·79% N.

Hydrogen maleate, m.p. 141—142°C (ethanol). For $C_{26}H_{32}N_2O_6$ (468·6) calculated: 66·65% C, 6·88% H, 5·98% N; found: 67·14% C, 6·80% H, 6·12% N.

N-(1-(2-Phenylethyl)-4-piperidinyl)-2-(methylthio)acetanilide (*III*)

Similar reaction of 3·50 g N-(1-(2-phenylethyl)-4-piperidinyl)aniline[33,34] with 6·0 g 2-(methylthio)acetic anhydride[36] in 50 ml boiling benzene gave 4·9 g of oily product which crystallized on standing. Recrystallization from 8 ml acetone gave 3·20 g (70%) of *III*, m.p. 85—86°C. IR spectrum: 704, 740 (5 adjacent Ar–H); 1 500, 1 600, 3 015, 3 043, 3 058 (Ar); 1 652 (RCON). ^{1}H NMR spectrum: 1·20—3·10 m, 12 H ($ArCH_2CH_2N$ and 4 × CH_2 of piperidine); 2·16 s, 3 H (SCH_3); 2·90 s, 2 H ($COCH_2S$); 4·65 m, 1 H (H-4 of piperidine); 7·00—7·50 m, 10 H (2 × C_6H_5). For $C_{22}H_{28}N_2OS$ (368·5) calculated: 71·70% C, 7·66% H, 7·60% N, 8·70% S; found: 71·54% C, 7·53% H, 7·65% N, 8·48% S.

Hydrogen maleate, 2 : 1 solvate with toluene, m.p. 175°C (ethanol denaturated with toluene). For $C_{26}H_{32}N_2O_5S + 0{\cdot}5\ C_7H_8$ (530·7) calculated: 66·77% C, 6·84% H, 5·28% N, 6·04% S; found: 66·98% C, 6·93% H, 5·40% N, 5·96% S.

4-Anilino-1-(2-phenylethyl)piperidine-4-carbonitrile (*VII*)

A) Reaction of 22·5 g 1-(2-phenylethyl)-4-piperidone[45,69,70], 10·3 g aniline, and 8·15 g 97% KCN in 80 ml acetic acid and 25 ml water was carried out according to ref.[23] and gave 15·0 g (44%) of *VII*, m.p. 117—119°C (di(2-propyl)ether). Ref.[23] reported the yield of 29·5% and the m.p. 121°C.

Hydrochloride, m.p. 175—176°C with decomposition (aqueous ethanol). For $C_{20}H_{24}ClN_3$ (341·9) calculated: 70·26% C, 7·08% H, 10·37% Cl, 12·29% N; found: 69·96% C, 7·31% H, 10·35% Cl, 12·25% N.

B) A stirred solution of 2·0 g *VII* in 13 ml pyridine (containing 0·2% of water) was treated with 0·67 g propionyl chloride, added dropwise. The mixture was allowed to stand for 24 h at room temperature and the crystalline solid was filtered; 1·95 g of *VII*.HCl, m.p. 172—173°C.

Crystallization from aqueous ethanol gave the pure compound melting at 173–175°C (without depression in mixture with the authetic hydrochloride, prepared according to *A*)).

4-Anilino-1-benzylpiperidine-4-carbonitrile (*VIII*)

A) Reaction of 117 g 1-benzyl-4-piperidone, 57·4 g aniline, and 45·5 g KCN in 420 ml acetic acid and 150 ml water was carried out according to ref.[38] and gave 112 g (62%) of *VIII*, m.p. 143–145°C (di(2-propyl) ether-benzene). Ref.[38], m.p. 143·5–147°C.

Hydrochloride, m.p. 186–188°C (aqueous ethanol). For $C_{19}H_{22}ClN_3$ (327·9) calculated: 69·60% C, 6·71% H, 10·81% Cl, 12·82% N; found: 69·38% C, 6·88% H, 11·05% Cl, 12·95% N.

B) A stirred solution of 2·0 g *VIII* in 15 ml pyridine was treated dropwise with 0·70 g propionyl chloride and after standing overnight at room temperature, the precipitated solid was filtered, washed with pyridine and dried in vacuo; 1·90 g of *VIII*.HCl, m.p. 186–188°C with decomposition (aqueous ethanol). The identity was established by the mixed melting point with the authetic compound, prepared under *A*).

1-Benzyl-4-(propionanilido)piperidine-4-carbonitrile (*XIII*)

A solution of 5·0 g *VIII* in 30 ml propionic anhydride was stirred and heated for 6 h to 180°C under reflux. It was poured on 200 g ice, made alkaline with NH_4OH and extracted with benzene. Processing gave 6·0 g of a dark oil (crude *XIII*), which was transformed to the hydrogen oxalate, m.p. 205–207°C with decomposition (ethanol). Mass spectrum: 347·1998 (M^+, $C_{22}H_{25}N_3O$, 10), 290 (5), 199 (15), 172 (10), 150 (75), 107 (100), 91 (100). IR spectrum: 716, 760 (5 adjacent Ar–H); 1 497, 1 600 (Ar); 1 663 (RCON); 1 722 (COOH of oxalic acid); 2 248 (R–CN); 2 560 (NH^+). For $C_{24}H_{27}N_3O_5$ (437·5) calculated: 65·89% C, 6·22% H, 9·60% N; found: 65·65% C, 6·11% H, 9·55% N.

4-Anilino-1-benzylpiperidine-4-carboxamide (*IX*)

Heating of 75 g *VIII* with 500 ml 90% H_2SO_4 to 70°C according to ref.[38] gave 60 g (75%) of *IX*, m.p. 190–191°C. Ref.[38], m.p. 187–188°C.

4-Anilino-1-benzylpiperidine-4-carboxylic Acid (*X*)

A) A stirred mixture of 25 g *IX*, 16 g KOH and 85 ml ethane-1,2-diol was heated for 15 h to 210°C (bath temperature) under reflux. It was diluted with 500 ml water, filtered, the filtrate was acidified with 16 ml acetic acid, the separated semi-solid material was quickly filtered off and the filtrate was allowed to crystallize overnight. It was filtered, washed with water and ethanol, dried, and crystallized from dimethyl sulfoxide; 19·5 g (79%), m.p. 230–231°C. IR spectrum: 704, 750 (5 adjacent Ar–H); 1 384, 1 609 (COO^-); 1 502, 1 540, 3 055, 3 122 (Ar); 2 100 (NH^+); 3 328 (NH). For $C_{19}H_{22}N_2O_2$ (310·4) calculated: 73·52% C, 7·15% H, 9·02% N; found: 73·53% C, 7·26% H, 9·08% N. Ref.[23], m.p. 263 and 268°C (obtained by hydrolysis of the ethyl ester or by catalytic hydrogenolysis of the benzyl ester).

4-Anilino-1-benzylpiperidine-4-methanol (*XI*)

A stirred suspension of 19·5 g *X* in 200 ml benzene was treated over 1·5 h with 75 ml 50% $NaAlH_2(OCH_2CH_2OCH_3)_2$ in benzene and after 2 h of stirring the mixture was heated for a short time to the boiling point of benzene. After standing overnight it was decomposed under stirring by a slow addition of 170 ml 10% NaOH. It was stirred for 45 min, the benzene layer

was separated, washed with 10% NaOH and water, dried, and evaporated. The oily residue (17·5 g) slowly crystallized from 40 ml ether; 10·0 g (54%), m.p. 71–74°C. Ref.[23], m.p. 73·9°C (obtained by reduction of the ethyl ester).

Dihydrochloride, m.p. 223–226°C (aqueous ethanol). For $C_{19}H_{26}Cl_2N_2O$ (369·4) calculated: 61·78% C, 7·10% H, 19·20% Cl, 7·59% N; found: 61·49% C, 7·21% H, 18·90% Cl, 7·62% N.

Dihydrobromide, m.p. 256–259°C (water). For $C_{19}H_{26}Br_2N_2O$ (458·3) calculated: 49·80% C, 5·72% H, 34·88% Br, 6·11% N; found: 50·09% C, 5·81% H, 34·64% Br, 5·98% N.

1′-Benzyl-3-phenylspiro[4,5-dihydro-3*H*-1,2,3-oxathiazol-4,4′-piperidine] (*XIV*)

A stirred solution of 5·0 g *XI* and 2·0 g pyridine in 30 ml benzene was treated with 2·5 g $SOCl_2$. The mixture was stirred for 4 h at room temperature, decomposed by slow addition of 30 ml water, made alkaline with 10% NaOH, and after addition of 30 ml benzene shaken for 2 h. The benzene layer was separated, dried, and evaporated. The oily residue (5·6 g) slowly crystallized and the product was recrystallized from 20 ml acetone; 3·10 g (53%) of *XIV*, m.p. 140 to 142°C (ethanol). Mass spectrum: 342·1429 (M^+, $C_{19}H_{22}N_2O_2S$, 10), 263 (17), 250 (20), 186 (43), 172 (7), 160 (13), 146 (70), 91 (100), 77 (16). UV spectrum: 238 (3·44). IR spectrum (KBr): 703, 759 (5 adjacent Ar–H); 1 170 (S=O); 1 490, 1 592, 3 000, 3 030, 3 045, 3 080 (Ar); 2 770 (CH_2–N). ^{1}H NMR spectrum: 1·50–2·20 m, 6 H (H-2ax, 2 × H-3, 2 × H-5, and H-6ax of piperidine); 2·85 m, 2 H (H-2eq and H-6eq of piperidine); 3·40 s, 2 H ($ArCH_2N$); 4·55 d and 4·78 d (ABq), 1 and 1 H (C–CH_2–O, J = 8·0); 7·00–7·50 m, 10 H (2 × C_6H_5). For $C_{19}H_{22}N_2O_2S$ (342·5) calculated: 66·64% C, 6·47% H, 8·18% N, 9·36% S; found: 66·35% C, 6·59% H, 8·16% N, 9·09% S.

Hydrogen maleate, m.p. 128–129°C (acetone). For $C_{23}H_{26}N_2O_6S$ (458·5) calculated: 60·25% C, 5·72% H, 6·11% N, 6·99% S; found: 60·27% C, 5·55% H, 6·01% N, 6·94% S.

4-(Anilinomethyl)-1-benzyl-4-chloropiperidine (*XV*)

A solution of 14·0 g *XI* in 120 ml chloroform was treated with 22·5 g $SOCl_2$ and the mixture was refluxed for 2 h. After cooling it was decomposed by slow addition of 100 ml water (external cooling) and was made alkaline with 35 ml 10% NaOH. After shaking the chloroform layer was separated, dried, and evaporated. The oily residue (13·5 g) was chromatographed on 300 g Al_2O_3. The least polar fraction, eluted with benzene, was considered to be the main product and was transformed to salts.

Oxalate, m.p. 126–127°C with decomposition (ethanol). For $C_{21}H_{25}ClN_2O_4$ (404·9) calculated: 62·29% C, 6·22% H, 8·76% Cl, 6·92% N; found: 62·13% C, 6·38% H, 8·53% Cl, 6·64% N. The released base (dilute NH_4OH and extraction with dichloromethane) was used for recording the ^{1}H NMR spectrum: 1·70–2·80 m, 8 H (4 × CH_2 of piperidine); 3·31 d (after D_2O s), 2 H (CH_2NAr); 3·48 s, 2 H ($ArCH_2N$); 4·00 bt (disappears after D_2O), 1 H (NH); 6·50–7·10 m, 5 H (ArH of aniline); 7·23 s, 5 H (ArH of benzyl).

Maleate, m.p. 138–140°C (acetone). Mass spectrum: 314 (M^+, $C_{19}H_{23}ClN_2$, low intensity), 278 ($C_{19}H_{22}N_2$, 100). For $C_{23}H_{27}ClN_2O_4$ (430·9) calculated: 64·10% C, 6·32% H, 8·23% Cl, 6·50% N; found: 64·40% C, 6·52% H, 7·82% Cl, 6·30% N.

Ethyl 3-(1-Ethoxycarbonyl-4-oxo-3-piperidinyl)propionate (*XXI*)

A mixture of 8·15 g 1-ethoxycarbonyl-4-(1-pyrrolidinyl)-1,2,3,6-tetrahydropyridine[41], 36·4 g ethyl acrylate, and 100 ml dioxane was refluxed for 4 h and after standing overnight, the volatile

components were evaporated in vacuo. The residue was treated with 60 ml water and 40 ml hydrochloric acid, the mixture was refluxed for 10 min and after cooling extracted with benzene. The extract was processed and the residue was distilled; 63 g (66%) of *XXI*, b.p. 170–200°C/0·2–0·3 kPa. For analysis a sample was redistilled, b.p. 170°C/0·2 kPa. ^{1}H NMR spectrum: 1·24 t and 1·29 t, 3 and 3 H (2 × CH_3); 1·50–4·20 m, 11 H (3 × CH_2 and CH of piperidine and CH_2CH_2 of the propionate chain); 4·11 q and 4·20 q, 2 and 2 H (2 × OCH_2). For $C_{13}H_{21}$·.NO_5 (271·3) calculated: 57·55% C, 7·80% H, 5·16% N; found: 57·58% C, 7·67% H, 5·26% N.

Ethyl 3-(1-Ethoxycarbonyl-4-(phenylimino)-3-piperidinyl)propionate (*XXII*)

A mixture of 23·2 g *XXI*, 9·6 g aniline and 75 ml toluene was slowly distilled through a short column and the distillate (azeotropic mixture of toluene with water) was continually substituted by fresh toluene. The solvent was then evaporaed under reduced pressure and the residue was distilled in vacuo; 16·3 g (55%) of *XXII*, b.p. 200–210°C/0·13 kPa. For analysis a sample was redistilled, b.p. 210°C/0·13 kPa. UV spectrum: 225 (3·99), infl. 239 (3·94), infl. 280 (3·50). IR spectrum (film): 700, 765 (5 adjacent Ar–H); 1 240 (COOR); 1 606 (Ar); 1 705 (NCOOR); 1 732 (RCOOR'). For $C_{19}H_{26}N_2O_4$ (346·4) calculated:65·87% C, 7·57% H, 8·09% N; found: 65·90% C, 7·36% H, 8·23% N.

6-(Ethoxycarbonyl)-1-phenyl-3,4,5,6,7,8-hexahydro-1,6-naphthyridin-2(1*H*)-one (*XX*)

A solution of 3·0 g *XXII* in 10 ml dioxane was treated with 0·3 g $NaBH_4$ and the solution was allowed to stand overnight at room temperature. The solvent was evaporated and the residue was distributed between water and benzene. The benzene layer was washed with dilute hydrochloric acid and water, dried, and evaporated in vacuo. The residue was crystallized from 2·8 ml di(2-propyl) ether; 0·7 g (27%) of *XX*, m.p. 88–90·5°C. Analytical sample, m.p. 91–93°C (di(2-propyl)ether). Mass spectrum: 300 (M^+, $C_{17}H_{20}N_2O_3$), 271 ($C_{15}H_{15}N_2O_3$), 77. IR spectrum: 700, 760 (5 adjacent Ar–H); 1 149, 1 215, 1 244 (COOR); 1 493, 1 600, 3 010, 3 030, 3 045, 3 052 (Ar); 1 682 (CON of lactone); 1 700 (NCOOR). ^{1}H NMR spectrum: 1·31 t, 3 H (CH_3, J = 7·0); 1·85 bm, 2 H (2 × H-8); 2·35 bt and 2·75 bt, 2 and 2 H (2 × H-3 and 2 × H-4); 3·52 t, 2 H (2 × H-7, J = 5·0); 4·02 bs, 2 H (2 × H-5); 4·21 q, 2 H (OCH_2, J = 7·0); 7·00 to 7·60 m, 5 H (C_6H_5). For $C_{17}H_{20}N_2O_3$ (300·4) calculated: 67·98% C, 6·71% H, 9·33% N; found: 67·77% C, 6·82% H, 9·33% N.

6-(Ethoxycarbonyl)-1-phenylperhydro-1,6-naphthyridin-2-one (*XIX*)

A solution of 10·4 g *XXII* in 50 ml tetrahydrofuran was saturated with HCl until a clearly acid reaction. This stirred solution was treated with a solution of 1·3 g $NaBH_3CN$ in 37 ml methanol, added in parts. The mixture was stirred for 3·5 h at room temperature, treated with further 0·7 g $NaBH_3CN$ and stirred for further 3 h.

The precipitated solid was filtered off and the filtrate was evaporated in vacuo. The residue was distributed between 5% $NaHCO_3$ and benzene, the benzene layer was dried and evaporated. The residue (8·7 g) was chromatographed on 260 g Al_2O_3. The benzene eluates were discarded and chloroform eluted 2·0 g (22%) of almost homogeneous *XIX* which crystallized from a mixture of benzene and light petroleum, m.p. 126–128°C. Mass spectrum: 302 (M^+, $C_{17}H_{22}N_2O_3$, 100), 200. IR spectrum: 707, 757, 776 (5 adjacent Ar–H); 1 236, 1 350, 1 377 (COOR); 1 497, 1 596, 3 020 (Ar); 1 642 (CON of lactam); 1 698 (NCOOR). ^{1}H NMR spectrum: 1·21 t, 3 H (CH_3, J = 7·0); 1·20–2·80 m, 10 H (5 × CH_2 in positions 3, 4, 5, 7, 8 of perhydronaphthyridine); 3·40 m and 4·20 m, 1 and 1 H (H-4a and H-8a); 4·08 q, 2 H (OCH_2, J = 7·0); 6·90–7·50 m, 5 H

(C_6H_5). For $C_{17}H_{22}N_2O_3$ (302·4) calculated: 67·52% C, 7·34% H, 9·27% N; found: 67·39% C, 7·50% H, 8·97% N.

3-(3-Ethoxycarbonyl-4-oxo-1-(2-phenylethyl)-3-piperidinyl)propionitrile (*XXIV*)

A solution of 19·7 g *XXIII* (the base was released from the hydrochloride[44,45]) and 3·8 g acrylonitrile in 20 ml dioxane was treated under stirring with a solution of 0·9 g KOH in 0·9 ml water and the mixture was allowed to stand overnight at room temperature. Then it was distributed, between benzene and water. The benzene layer was dried and evaporated leaving 20·2 g (86%) of oily *XXIV*. It was transformed to the hydrogen oxalate, m.p. 121·5–122·5°C (ethanol–ether). For $C_{21}H_{26}N_2O_7$ (418·4) calculated: 60·27% C, 6·26% H, 6·70% N; found: 60·43% C, 6·15% H, 6·92% N.

Ethyl 3-(4-Oxo-1-(2-phenylethyl)-3-piperidinyl)propionate (*XXV*)

Hydrogen oxalate of *XXIV* (29 g) was treated with NH_4OH and the base was isolated by extraction with benzene (22·6 g). This base was refluxed for 5 h with 55 ml hydrochloric acid and 30 ml water. The mixture was evaporated in vacuo and the residue was refluxed with 200 ml ethanol for 4 h. The precipitated solid was filtered off and the filtrate was evaporated in vacuo. The esterification was concluded by refluxing with further 100 ml ethanol and 2 ml ether saturated with HCl. After standing overnight it was filtered again and the filtrate was evaporated leaving 23 g of crude oily *XXV*.HCl which slowly crystallized; 11·5 g (49%) of *XXV*.HCl, m.p. 131–134°C (ethanol–ether). For $C_{18}H_{26}ClNO_3$ (339·9) calculated: 63·61% C, 7·71% H, 10·43% Cl, 4·12% N; found: 63·28% C, 7·98% H, 10·73% Cl, 3·87% N.

The released base was used for recording the ^{1}H NMR spectrum: 1·20 t, 3 H (CH_3, J = 7·0); 1·80–3·20 m, 15 H (2 × CH_2 of phenethyl, 3 × CH_2 and CH of piperidine, and 2 × CH_2 of propionyl); 4·05 q, 2 H (OCH_2, J = 7·0); 7·15 s, 5 H (C_6H_5).

Reaction of *XXV*.HCl with aniline

A mixture of 3·4 g *XXV*.HCl, 5·6 g aniline and 20 ml toluene was slowly distilled for 4 h and the distillate was continually substituted by fresh toluene. After standing overnight the separated crystalline product (1·1 g, 69%) which was identified as 2-phenylethylamine hydrochloride, m.p. 221–226°C (ethanol). For $C_8H_{12}ClN$ (157·7) calculated: 60·95% C, 7·68% H, 22·49% Cl, 8·89% N; found: 61·23% C, 7·81% H, 22·80% Cl, 9·03% N. A sample of this compound was prepared from commercial 2-phenylethylamine and melted at 222–224°C. The mixed melting point of both samples was without depression. Ref.[46], m.p. 217°C.

The toluene mother liquor was washed with dilute hydrochloric acid, the aqueous acid solution was made alkaline with 5M-NaOH and the bases were extracted with benzene. Processing of the extract gave 4·4 g of a residue which was dissolved in benzene and the solutino was chromatographed on 140 g Al_2O_3. The benzene eluate (1·9 g) was heated in vacuo for removing aniline. The residue (0·4 g) crystallized from a mixture of benzene and light petroleum, m.p. 82·5–84°C, and was assigned to be 2,4′-diaminodiphenylmethane (*XXVIII*). Mass spectrum: 198 (M^+, $C_{13}H_{14}N_2$, 18), 180 (3), 107 (9), 106 (100), 104 (5), 93 (22), 79 (10), 78 (6), 77 (25). UV spectrum: 242·5 (4·30), 287 (3·67). IR spectrum: 695, 1 619 ($ArNH_2$); 756, 822 (4 and 2 adjacent Ar–H); 1 490, 1 500, 1 596, 3 010 (Ar); 3 285, 3 320, 3 360 (NH_2). ^{1}H NMR spectrum: 3·82 s (disappears after D_2O), 2 and 2 H (2 × $ArNH_2$); 4·12 s, 2 H ($ArCH_2Ar$); 6·40–7·30 m, 8 H (ArH). For $C_{13}H_{14}N_2$ (198·3) calculated: 78·75% C, 7·12% H, 14·13% N; found: 79·16% C, 7·35% H, 14·02% N. Ref.[47], m.p. 88–89°C.

Ethyl 3-(4,4-Diethoxy-1-(2-phenylethyl)-3-piperdinyl)-propionate (*XXVII*)

A mixture of 5·4 g *XXIV* (the base was released from the hydrochloride), 7 ml water, and 13 ml hydrochloric acid was refluxed for 5 h. After standing for 48 h the volatile components were evaporated in vacuo, the residue was dissolved in 50 ml ethanol and the solution was refluxed for 2 h. The solution was filtered, the filtrate was evaporated in vacuo and the residue was dissolved in chloroform. The solution was washed with 3% NaOH and water, dried, and evaporated. The oily residue (3·8 g) was dissolved in benzene and the solution was filtered through a column of 75 g Al_2O_3. The filtrate was evaporated giving 2·3 g (46%) of almost homogeneous oily *XXVII* which was transformed to the hydrogen oxalate, m.p. 141–146°C (ethanol). For $C_{24}H_{37}NO_8$ (467·6) calculated: 61·65% C, 7·98% H, 3·00% N; found: 61·77% C, 8·01% H, 3·11% N.

The oily base, released from a sample of the oxalate, was used for recording the IR spectrum (CS_2): 704, 753 (5 adjacent Ar–H) 1 063, 1 099, 1 130, 1 167 (RCOOR', ROR'); 1 739 (RCOOR').

Ethyl 4-Anilino-1-(2-phenylethyl)-1,2,3,6-tetrahydropyridine-3-carboxylate (*XXIX*)

Hydrochloride of *XXIII* (refs[44,45]) was dissolved in 20 ml warm ethanol, the solution was treated with 4·2 g aniline and the mixture was allowed to stand for 2 h at room temperature. After standing overnight the crystalline product was filtered, washed with 10 ml ethanol and 10 ml ether, and dried in vacuo; 10·1 g of *XXIX*.HCl, m.p. 180–181·5°C (ethanol). UV spectrum: 304 (4·30). IR spectrum: 710, 760, 785 (5 adjacent Ar–H); 1 242, 1 260 (RCOOR'); 1 502, 1 598, 3 033 (Ar); 1 620 (C=C); 1 661 (C=C—COOR in hydrogen bond with N); 2 360, 2 460, 2 505 (NH^+); 3 190, 3 245, 3 310 (NH). For $C_{22}H_{27}ClN_2O_2$ (386·9) calculated: 68·29% C, 7·04% H, 9·16% Cl, 7·24% N; found: 67·99% C, 7·35% H, 8·90% Cl, 7·23% N.

The released base was used for recording the ^1H NMR spectrum: 1·29 t, 3 H (CH_3, J = 7·0); 2·52 s, 4 H ($ArCH_2CH_2N$); 2·50–3·00 m, 4 H (2 × CH_2 in positions 2 and 3 of tetrahydropyridine); 3·32 s, 2 H (NCH_2C=C); 4·19 q, 2 H (OCH_2, J = 7·0); 6·80–7·50 m, 10 H (2 × C_6H_5); 10·60 bs, 1 H (NH).

Ethyl 1-(2-Phenylethyl)-1,2,3,6-tetrahydropyridine-3-carboxylate (*XXX*)

A stirred solution of 2·0 g *XXIX*.HCl in 20 ml acetic acid was treated with 4·0 g Zn and the mixture was refluxed for 30 min. It was filtered, the filtrate was evaporated in vacuo and the residue was distributed between dilute NH_4OH and benzene. Processing of the benzene solution gave 1·4 g of oil which was chromatographed on 50 g Al_2O_3. The benzene eluates of the more polar components gave 0·2 g of homogeneous oily *XXX* which afforded the hydrochloride melting at 148–151°C (ethanol–ether). For $C_{16}H_{22}ClNO_2$ (295·8) calculated: 64·96% C, 7·50% H, 11·99% Cl, 4·74% N; found: 64·79% C, 7·67% H, 12·16% Cl, 4·72% N.

A sample of the released oily base was used for recording the ^1H NMR spectrum: 1·21 t, 3 H (CH_3); 2·10–3·30 m, 10 H ($ArCH_2CH_2N$ and $CH_2CH_2NCH_2$ of tetrahydropyridine); 4·12 q, 2 H (OCH_2, J = 7·0); 6·95 m, 1 H (C=CH); 7·15 s, 5 H (C_6H_5).

4-Anilino-1-(2-phenylethyl)piperidine-3-methanol (*XXXI*)

A) A Solution of 3·4 g *XXIX* (released from 3·9 g of hydrochloride) in 10 ml ether was added to a stirred solution of 1·2 g $LiAlH_4$ in 60 ml ether, the mixture was stirred for 4·5 h at room temperature and allowed to stand overnight. Under stirring it was decomposed by slow addition of 1 ml water, 1·5 ml 20% NaOH and 3·6 ml water. After 30 min standing the solid was filtered off, the filtrate was dried and evaporated. The residue (2·9 g of oil) was chromatographed on

150 g Al_2O_3. The benzene eluates contained mixtures of the less polar components. Chloroform eluted 1·8 g (62%) of almost homogeneous *XXXI* which was transformed to the oxalate, m.p. 174·5—177°C (ethanol–ether). IR spectrum: 712, 760 (5 adjacent Ar–H); 1 200, 1 724 (COOH); 1 605 (COO^-); 2 625, 2 720 (NH^+ and O–H···N); 3 405 (NH). For $C_{22}H_{28}N_2O_5$ (400·5) calculated: 65·98% C, 7·05% H, 7·00% N; found: 65·86% C, 7·12% H, 7·04% N.

The base was released by treatment of the oxalate with NH_4OH and was isolated by extraction with ether. After its evaporation, it crystallized; m.p. 83—87°C (cyclohexane). ^{1}H NMR spectrum: unresolved m (all the CH_2 and CH groups); 6·40—7·40 m, 10 H (2 × C_6H_5). For $C_{20}H_{26}N_2O$ (310·4) calculated: 77·38% C, 8·44% H, 9·03% N; found: 77·40% C, 8·70% H, 8·79% N.

B) A solution of 3·5 g *XXIX* in 20 ml benzene was stirred and treated with 14 ml 64% $NaAlH_2(OCH_2CH_2OCH_3)_2$ in benzene and the mixture was refluxed for 2 h. After cooling the mixture was decomposed under stirring by slow addition of a solution of 3·0 g NaOH in 30 ml water. The benzene layer was dried and evaporated leaving 3·0 g of an inhomogeneous residue. Reaction with 1·2 g oxalic acid dihydrate in 5 ml ethanol gave only 0·3 g of the oxalate melting at 173 to 176°C, which is identical with the product obtained under *A*).

Ethyl 4-Oxo-1-(2-phenylethyl)piperidine-3-carboxylate (*XXIII*)

A) Compound *XXIII* was prepared in several batches by cyclization of N,N-bis(2-ethoxycarbonylethyl)-2-phenylethylamine[70] with sodium ethoxide (from NaH and ethanol) in toluene according to refs[44,45]. The crude base was transofrmed to the hydrochloride which was obtained in yields of 40—58% and melted at temperatures between 147 and 158°C. Refs[44,45], m.p. 165—167°C.

B) A solution of 1·1 g *XXIX* (the base released from the hydrochloride) in 5 ml chloroform was treated with 0·35 g propionyl chloride and the mixture was allowed to stand overnight at room temperature. After dilution with ether the precipitated solid was filtered, crystallized from a mixture of ethanol and ether, and dried in vacuo (0·2 g, m.p. 149—155°C). It was evidently *XXIII*.HCl whose IR spectrum indicated complete enolization: 708, 760 (5 adjacent Ar–H); 1 104, 1 226, 1 253, 1 310 (RCOOR'); 1 637, 1 667 (HO—C=C—COOR); 2 400, 2 460, 2 515 (NH^+ and O–H···O=C). For $C_{16}H_{22}ClNO_3$ (311·8) calculated: 61·63% C, 7·11% H, 11·38% Cl, 4·49% N; found: 61·60% C, 6·81% H, 11·07% Cl, 4·68% N. The discrepancies with the melting point of this hydrochloride are mentioned already under *A*).

Ethyl 3-(4-Hydroxy-1-(2-phenylethyl)-3-piperidinyl)propionate (*XXXII*)

A mixture of 15·9 g *XXIV*, 40 ml hydrochloric acid and 10 ml water was refluxed for 10 h. The solution was filtered with active carbon and evaporated in vacuo. The residue was dissolved in 30 ml water, the solution was made alkaline with 20% NaOH, and filtered again with active carbon. The filtrate was treated with 2·0 g $NaBH_4$, added in portions. The mixture was heated for 2 h to 100°C (water bath) and allowed to stand for 48 h at room temperature. It was acidified with hydrochloric acid and evaporated in vacuo. The residue was refluxed for 20 min with 80 ml ethanol, the solid was filtered off, and the filtrate was evaporated in vacuo. The crystalline residue (17 g) was recrystallized from 40 ml boiling ethanol; 8·0 g (48%) of *XXXII*.HCl, m.p. 162—164°C (ethanol). IR spectrum: 695, 727, 759, 773 (5 adjacent Ar–H); 1 070 (CHOH in the ring); 1 181, 1 730 (RCOOR'); 1 502, 1 587, 1 607, 3 040, 3 080, 3 100 (Ar); 2 595, 2 645, 2 695 (NH^+); 3 350 (OH). ^{1}H NMR spectrum (CD_3SOCD_3): 1·14 t, 3 H (CH_3); 1·50—3·70 m, 16 H (2 × CH_2 and 2 × CH of piperidine, $ArCH_2CH_2N$, and CH_2CH_2CO); 4·00 q, 2 H (OCH_2); 5·16 bs, 1 H

(OH); 7·20 s, 5 H (C_6H_5); 11·20 bs, 1 H (NH^+). For $C_{18}H_{28}ClNO_3$ (341·9) calculated: 63·23% C, 8·25% H, 10·37% Cl, 4·10% N; found: 63·07% C, 8·32% H, 10·38% Cl, 4·18% N.

6-(2-Phenylethyl)-3,4,4a,5,6,7,8,8a-octahydro-2*H*-pyrano[3,2-*c*]pyridin-2-one (*XXXIV*)

A) A solution of 6·4 g *XXIV* (released from the oxalate) in 12 ml hydrochloric acid and 6 ml water was refluxed for 6 h. The mixture was evaporated in vacuo and the residue was dissolved in a boiling mixture of 25 ml ethanol and 4 ml water. The solution was made slightly alkaline with 8 ml 20% NaOH and treated with 0·8 g $NaBH_4$, added in portions. The mixture was refluxed for 1 h, acidified with 5 ml hydrochloric acid, and evaporated in vacuo. The residue (10·2 g) was dissolved in 25 ml ethanol, the undissolved salts were filtered off, and the filtrate was evaporated again. The glassy residue was distributed between 25 ml chloroform and a solution of 1·6 g $NaHCO_3$ in 50 ml water. Evaporation of the chloroform layer gave 4·2 g (83%) of crude *XXXIV* which was chromatographed on 200 g silica gel. Benzene eluted the less polar contaminants. One of the chloroform eluates (0·6 g) ws the homogeneous *XXXIV*, m.p. 96–99°C (cyclohexane). IR spectrum (KBr): 704, 751 (5 adjacent Ar–H); 1 042, 1 222 (RCOOR'); 1 735 (δ-lactone). ^1H NMR spectrum: 1·30–3·10 m, 15 H ($ArCH_2CH_2N$, 5 × CH_2 and CH in positions 3, 4, 4a, 5, 7, 8); 3·80 m, 1 H (H-8a); 7·13 s, 5 H (C_6H_5). For $C_{16}H_{21}NO_2$ (259·3) calculated: 74·10% C, 8·16% H, 5·40% N; found: 74·07% C, 8·07% H, 5·19% N.

B) A stirred suspension of 3·4 g *XXXII*.HCl in 20 ml chloroform was treated over 5 min with a solution of 1·4 g $SOCl_2$ in 2 ml chloroform and the mixture was refluxed for 45 min. After cooling the crystallized product was filtered and washed with ether; 2·7 g (91%) of a substance appearing to be *XXXIV*.HCl, m.p. 236–240°C ethanol. IR spectrum (KBr): 706, 754, (5 adjacent Ar–H); 1 071, 1 109, 1 212, 1 260 (COO of lactone); 1 502, 1 608, 3 033, 3 065 (Ar); 1 757 (COO of lactone); 2 480, 2 535, 2 620, 2 680 (NH^+). For $C_{16}H_{22}ClNO_2$ (295·8) calculated: 64·96% C, 7·50% H, 11·99% Cl, 4·74% N; found: 65·00% C, 7·75% H, 11·99% Cl, 4·77% N.

N-Phenyl-3-(4-hydroxy-1-(2-phenylethyl)-3-piperidinyl)propionamide (*XXXIII*)

A mixture of *XXXII* (released from 3·4 g hydrochloride), 2·1 g aniline, and a small piece of Na was heated for 5 h to 120°C. After partial cooling the mixture was dissolved in 10 ml boiling benzene and the solution was allowed to crystallize; 1·9 g (54%) of *XXXIII*, m.p. 158–159°C (acetone). IR spectrum: 697, 719, 751, 781 (5 adjacent Ar–H); 1 057, 1 193, 1 247, 1 315, 1 331 (CHOH); 1 495, 1 605, 3 028, 3 060, 3 082 (Ar); 1 550, 1 691 (RCONHR'); 3 200, 3 261, 3 300 (NH). ^1H NMR spectrum (CD_3SOCD_3): 1·20–3·00 m, 16 H (3 × CH_2 and 2 × CH of piperidine, $ArCH_2CH_2N$, and CH_2CH_2CO); 4·60 d, 1 H (OH); 7·15 s, 5 H (C_6H_5 of phenethyl); 6·90–7·40 m, 3 H (H-3, H-4, and H-5 of aniline); 7·60 q, 2 H (H-2 and H-6 of aniline); 9·85 s, 1 H (CONH). For $C_{22}H_{28}N_2O_2$ (352·5) calculated: 74·96% C, 8·01% H, 7·95% N; found: 74·95% C, 8·31% H, 7·92% N.

4-(4-Cyclopropylphenyl)-1-methylpiperidine-1-ol (*XXXVII*)

The Grignard reagent was prepared by reaction of 19·7 g 1-bromo-4-cyclopropylbenzene[53] with 2·6 g Mg in 50 ml ether with the help of small amounts of iodine and 1,2-dibromoethane[54] and under stirring it was treated over 2·5 h with a solution of 10·6 g 1-methyl-4-piperidone in 15 ml ether, added dropwise. The mixture was refluxed for 2 h, at 5–10°C it was decomposed by slow addition of 120 ml 10% NH_4Cl, and after addition of 50 ml ether it was stirred for 30 min. The organic layer was separated, the aqueous one was extracted with ether and the combined organic layers wre processed. The residue distilled in vacuo without decomposition and the main

fraction (b.p. 208—210°C/1·6 kPa) crystallized; 6·4 g (29%), m.p. 121—122°C (cyclohexane). IR spectrum (KBr): 820 (2 adjacent Ar–H); 1 042, 1 099, 1 154, 1 275 (C–OH); 1 562, 1 630 (Ar); 2 690, 2 740 (CH_2–N); 3 180 (OH). ^{1}H NMR spectrum: 0·50—1·10 m, 4 H (2 × CH_2 of cyclopropyl); 1·70 m, 4 H (2 × H-3 and 2 × H-5 of piperidine); 1·85 m, 1 H (CH of cyclopropyl); 2·20 s, 3 H (NCH_3); 2·52 m, 4 H (2 × H-2 and 2 × H-6 of piperidine); 2·38 s (disappears after D_2O), 1 H (OH); 6·95 d and 7·32 d (ABq), 2 and 2 H (4 × ArH). For $C_{15}H_{21}NO$ (231·3) calculated: 77·87% C, 9·15% H, 6·06% N; found: 77·87% C, 9·46% H, 6·05% N.

Hydrogen maleate, m.p. 144°C (2-propanol–ether). For $C_{19}H_{25}NO_5$ (347·4) calculated: 65·69% C, 7·25% H, 4·03% N; found: 65·66% C, 7·46% H, 4·02% N.

1-Benzyl-4-(4-cyclopropylphenyl)piperidine-4-ol (*XXXVIII*)

The Grignard reagent [54] from 39·5 g 1-bromo-4-cyclopropylbenzene[53] and 5·15 g Mg in 100 ml ether was treated under stirring over 2 h with a solution of 30·3 g 1-benzyl-4-piperidone in 50 ml ether and the mixture was refluxed for 2 h. Similar processing like in the preceding case gave the crude solid product (47·7 g) which was crystallized from 75 ml cyclohexane giving 19·5 g (40%) of *XXXVIII*, m.p. 91—93°C (cyclohexane). IR spectrum (KBr): 703, 745, 807, 829 (5 and 2 adjacent Ar–H); 1 048, 1 138 (C–OH); 1 500, 1 570, 1 620 (Ar); 2 720, 2 800 (CH_2–N); 3 250 (OH). ^{1}H NMR spectrum: 0·50—1·10 m, 4 H (2 × CH_2 of cyclopropyl); 1·64 bs (disappears after D_2O), 1 H (OH); 1·50—2·80 m, 9 H (4 × CH_2 of piperidine and CH of cyclopropyl); 3·46 s, 2 H ($ArCH_2N$); 7·21 s, 5 H (C_6H_5); 6·95 d and 7·30 d (ABq), 2 and 2 H (4 × ArH, J = 9·0). For $C_{21}H_{25}NO$ (307·4) calculated: 82·04% C, 8·20% H, 4·56% N; found: 82·18% C, 8·32% H, 4·53% N.

Hydrogen maleate, m.p. 155—158°C (2-propanol). For $C_{25}H_{29}NO_5$ (423·5) calculated: 70·90% C, 6·90% H, 3·31% N; found: 71·23% C, 7·17% H, 3·15% N.

4-(4-Cyclopropylphenyl)-1-methyl-4-piperidinyl Propionate (*XXXIX*)

A stirred solution of 4·6 g *XXXVII* in 100 ml ether was treated over 40 min with a solutio of 2·02 g propionyl chloride in 25 ml ether and the mixture was stirred for further 1 h at 30—33°C. After standing overnight the separated *XXXIX*.HCl (6·1 g, 94%) was filtered and recrystallized from a mixture of 2-propanol and ether, m.p. 155—158°C (ethanol–ether). For $C_{18}H_{26}ClNO_2$ (323·9) calculated: 66·85% C, 8·09% H, 10·95% Cl, 4·33% N; found: 66·49% C, 8·37% H, 11·04% Cl, 4·39% N.

1-Benzyl-4-(4-cyclopropylphenyl)-4-piperidinyl Propionate (*XL*)

A solution of 4·5 g *XXXVIII* in 15 ml pyridine was stirred and treated at 18—22°C over 20 min with a solution of 2·5 g propionyl chloride in 10 ml ether. The mixture was stirred for 45 min at room temperature, diluted with water and extracted with benzene. Processing of the extract gave 5·2 g of oily base *XL* which was dissolved in 15 ml ethanol and the solution was treated with HCl in ether; 3·5 g (62%) of *XL*.HCl, m.p. 186—187°C (ethanol–ether). IR spectrum (KBr): 711, 758, 824 (5 and 2 adjacent Ar–H); 1 188, 1 755 (RCOOR'); 2 565 (NH^+). For $C_{24}H_{30}ClNO_2$ (400·0) calculated: 72·07% C, 7·56% H, 8·87% Cl, 3·50% N; found: 72·23% C, 7·67% H, 9·13% Cl, 3·72% N.

1-(4-Cyclopropylphenyl)-1-phenyl-3-(1-piperidinyl)propanol (*XLI*)

The Grignard reagent[54] from 21·8 g 1-bromo-4-cyclopropylbenzene[53] and 2·9 g Mg in 60 ml ether was stirred and treated over 1·5 h with a solution of 11·0 g 1-phenyl-3-(1-piperidinyl)-

propan-1-one (released from the hydrochloride[56,57]) in 60 ml ether and the mixture was refluxed for 4 h. After standing overnight at room temperature it was decomposed at 20°C under stirring with 250 ml 10% NH_4Cl and extracted with ether. The extract was shaken with 100 ml 1M-HCl and the precipitated *XLI*.HCl (12·7 g, 68%) was filtered and crystallized from a mixture of ethanol and ether, m.p. 225—227°C. IR spectrum (KBr): 708, 738, 771, 830 (5 and 2 adjacent Ar–H); 1 080, 1 202 (C–OH); 1 500, 1 510 (Ar); 2 675 (NH^+); 3 260 (OH). For $C_{23}H_{30}ClNO$ (371·9) calculated: 74·27% C, 8·13% H, 9·53% Cl, 3·77% N; found: 73·98% C, 8·23% H, 9·64% Cl, 3·72% N.

3-(N-Butylmethylamino)-1-phenylpropan-1-one (*XLII*)

A mixture of 11·9 g N-butylmethylamine, 4·5 g paraformaldehyde, 12·0 g acetophenone, 30 ml ethanol, and 0·25 ml hydrochloric acid was refluxed for 1 h and after the addition of further 3·0 g paraformaldehyde the refluxing was continued for further 2 h. After cooling the mixture was dissolved in a warm mixture of 20 ml ethanol and 30 ml acetone and addition of 40 ml ether led to crystallization of 16·5 g (65%) of *XLII*. HCl, m.p. 140—142°C (acetone–ether). For $C_{14}H_{22}$·.ClNO (255·8) calculated: 65·74% C, 8·67% H, 13·86% Cl, 5·47% N; found: 65·88% C, 8·77% H, 13·96% Cl, 5·67% N.

3-(N-Butylmethylamino)-1,1-diphenylpropanol (*XLIII*)

The Grignard reagent was prepared from 13·8 g bromobenzene and 2·14 g Mg in 50 ml ether and was treated under external cooling with ice-cold water and under stirring with a solution of 14·6 g *XLII* (released from the hydrochloride) in 20 ml ether, added dropwise over 30 min. The mixture was refluxed for 3 h, after cooling decomposed with 200 ml 10% NH_4Cl, and extracted with ether. The extract was processed and the residue was distilled; 5·2 g (26%) of *XLIII*, b.p. 166—172°C/70 Pa, m.p. 91—93°C (methanol). For $C_{20}H_{27}NO$ (297·4) calculated: 80·76% C, 9·15% H, 4·71% N; found: 80·80% C, 9·22% H, 4·46% N.

N-Butyl-N-(2-hydroxyethyl)dimethylammonium Iodide (*XLIV*)

A solution of 0·5 g 2-(N-butylmethylamino)ethanol[58] in 5 ml acetone was treated with 2·5 g methyl iodide and the mixture was allowed to stand for 24 h at room temperature. The crystalline product was filtered and recrystallized from acetone; 0·70 g (69%), m.p. 120—121°C. For $C_8H_{20}INO$ (273·2) calculated: 35·17% C, 7·38% H, 46·47% I, 5·12% N; found: 35·42% C, 7·64% H, 46·24% I, 4·85% N.

2-(3-Dimethylaminopropyl)adamantane-2-ol (*XLV*)

Grignard reagent[81] was prepared from 2·4 g 3-dimethylaminopropyl chloride and 0·5 g Mg in 20 ml tetrahydrofuran and under stirring it was treated over 10 min with a solution of 1·5 g 2-adamantanone in 10 ml tetrahydrofuran. After standing overnight at room temperature the mixture was decomposed with 10 ml 20% NH_4Cl and extracted with benzene. The extract was washed with water and processed giving 2·3 g (97%) of *XLV*, m.p. 71—73°C (light petroleum). IR spectrum (KBr): 1 042, 1 107, 1 209 (C–OH); 2 796, 2 830 (CH_3–N); 3 190, 3 300 (OH). ^1H NMR spectrum: 2·10 s, 6 H ($N(CH_3)_2$); 5·45 bs, 1 H (OH); the CH_2 and CH groups in an unresolved multiplet. For $C_{15}H_{27}NO$ (237·4) calculated: 75·89% C, 11·47% H, 5·90% N; found: 76·14% C, 11·54% H, 6·05% N.

Hydrochloride, m.p. 223°C (ethanol–ether) with decomposition. IR spectrum: 1 108, 1 135,

1 150, 1 162 (C–OH); 2 695, 2 720 (NH^+); 3 360, 3 435, 3 500 (OH). For $C_{15}H_{28}ClNO$ (273·8) calculated: 65·79% C, 10·30% H, 12·95% Cl, 5·12% N; found: 65·52% C, 10·23% N, 12·71% Cl, 5·30% N.

1-Ethyl-3-(1-phenyl-2-propylamino)piperidine (*XLVI*)

A solution of 8·2 g phenylacetone and 7·8 g 3-amino-1-ethylpiperidine[59] in a mixture of 100 ml methanol and 7 ml water was stirred for 7 h at 50°C. After cooling to 20°C it was treated under stirring with 3·1 g $NaBH_4$, added in small portions over 15 min. The mixture was stirred for 1 h at room temperature and refluxed for 1 h. After cooling the mixture was slightly acidified with acetic acid, methanol was evaporated, the residue was diluted with water, made alkaline with 10% NaOH, and the product was extracted with benzene. Processing of the extract and distillation of the residue gave 7·3 g (49%) of *XLVI*, b.p. 95–97°C/90 Pa. ^{1}H NMR spectrum: 1·02 t, 3 H (CH_3 of ethyl, J = 8·0); 1·05 d, 3 H (CH_3 of 2-propyl, J = 7·0); 1·30–2·00 m, 5 H (CH and 2 × CH_2 in positions 3, 4, 5 of piperidine); 2·50 bs, 1 H (NH); 2·40 q, 2 H (NCH_2 of N-ethyl, J = 8·0); 2·50–3·30 m, 7 H ($ArCH_2CHN$ and CH_2NCH_2 of piperidine); 7·35 s, 5 H (C_6H_5). For $C_{16}H_{26}N_2$ (246·4) calculated: 77·99% C, 10·64% H, 11·37% N; found: 77·72% C, 10·45% H, 11·46% N.

Hydrogen maleate, m.p. 131–133°C (ethanol–ether). For $C_{20}H_{30}N_2O_4$ (362·5) calculated: 66·27% C, 8·34% H, 7·73% N; found: 66·47% C, 8·64% H, 7·93% N.

1-(4-Bromophenyl)-1-(1-methyl-4-piperidinyl)-1-phenylmethanol (*XLVII*)

Grignard reagent[63] was prepared from 27·5 g 4-chloro-1-methylpiperidine[63] and 5·0 g Mg in 150 ml tetrahydrofuran. It was treated under stirring with a solution of 53·6 g 4-bromobenzophenone[62] in 170 ml tetrahydrofuran and the mixture was refluxed for 4 h. After standing overnight it was decomposed with 550 ml 10% NH_4Cl and extracted with benzene. Processing of the extract gave 41·5 g (45%) of crystalline *XLVII*, m.p. 149·5–150°C (benzene–light petroleum). For $C_{19}H_{22}BrNO$ (360·3) calculated: 63·34% C, 6·15% H, 22·18% Br, 3·89% N; found: 63·70% C, 6·44% H, 22·19% Br, 3·98% N.

Hydrochloride, m.p. 292–294·5°C (ethanol–ether). For $C_{19}H_{23}BrClNO$ (396·8) calculated: 57·51% C, 5·84% H, 8·94% Cl, 3·53% N; found: 57·58% C, 5·92% H, 8·82% Cl, 3·72% N.

4-(4-Bromobenzhydrylidene)-1-methylpiperidine (*XLVIII*)

A mixture of 6·0 g *XLVII*, 100 ml acetic acid and 40 ml hydrochloric acid was refluxed for 1 h. The volatile components were evaporated in vacuo, the residue was diluted with water, made alkaline with 20% NaOH, and extracted with benzene. Processing of the extract and neutralization of the residue in ethanol with HCl in ether gave 3·1 g (50%) of *XLVIII*.HCl, m.p. 262–265°C (ethanol–ether). For $C_{19}H_{21}BrClN$ (378·7) calculated: 60·25% C, 5·59% H, 9·36% Cl, 3·70% N; found: 60·55% C, 5·80% H, 9·28% Cl, 3·82% N.

3-(2-(1,3-Dioxan-2-yl)ethyl)-8-hydroxy-6,11-dimethyl-
-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (*L*)

A mixture of 2·17 g *XLIX* (ref.[66]), 30 ml dimethylformamide, 1·5 g $NaHCO_3$, and 1·5 g 2-(2-chloroethyl)-1,3-dioxane[67] was stirred and refluxed for 7 h. After cooling the solid was filtered off, the filtrate was evaporated in vacuo, the residue was dissolved in 70 ml benzene, the solution was washed with water, dried, and evaporated. The residue crystallized on trituration with ether;

2·60 g (79%) of *L*, m.p. 183—186°C (90% ethanol). IR spectrum: 802, 863 (2 adjacent and solitary Ar–H); 1 143, 1 267 (ArOH); 1 494, 1 577, 1 610 (Ar); 3 050 (OH). ^{1}H NMR spectrum (CD_3.$SOCD_3$): 0·72 d, 3 H (11-CH_3, J = 6·5); 1·23 s, 3 H (6-CH_3); 1·30—2·80 m, 14 H (NCH_2CH_2 of ethylamino, 2 × H-1, H-2, 2 × H-4, 2 × H-5, H-11, and CH_2 in position 5 of 1,3-dioxane); 3·50—4·10 m, 4 H (2 × CH_2O); 4·52 t, 1 H (H-2 of 1,3-dioxanyl, J = 5·5); 6·51 q, 1 H (H-9, J = 9·0; 2·0); 6·60 d, 1 H (H-7, J = 2·0); 6·87 d, 1 H (H-10, J = 9·0); 9·00 bs, 1 H (OH). For $C_{20}H_{29}NO_3$ (331·4) calculated: 72·47% C, 8·82% H, 4·23% N; found: 72·26% C, 9·12% H, 4·03% N.

Hydrogen maleate, m.p. 157—159°C (ethanol). For $C_{24}H_{33}NO_7$ (447·5) calculated: 64·41% C, 7·43% H, 3·13% N; found: 64·17% C, 7·50% H, 3·08% N.

3-(2-(1,3-Dioxolan-2-yl)ethyl)-8-hydroxy-6,11-dimethyl-
-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (*LI*)

A similar reaction of 1·0 g *XLIX* (ref.[66]), 0·90 g 2-(2-chloroethyl)-1,3-dioxolane[67] and 0·75 g $NaHCO_3$ in 13 ml dimethylformamide and similar processing gave 0·73 g (50%) of *LI*, m.p. 183—185°C (95% ethanol). IR spectrum (KBr): 810, 875 (2 adjacent and solitary Ar–H); 1 045, 1 245 (R–O–C–O–R); 1 150 (ArOH); 1 500, 1 585, 1 625 (Ar); 2 582, 2 675, 2 790 (NH^+); 3 440 (OH). ^{1}H NMR spectrum (CD_3SOCD_3): 0·73 d, 3 H (11-CH_3, J = 6·5); 1·25 s, 3 H (6-CH_3); 1·50—3·00 m, 12 H (NCH_2CH_2 of ethylamino, 2 × H-1, H-2, 2 × H-4, 2 × H-5, and H-11); 3·78 m, 4 H (OCH_2CH_2O); 4·80 t, 1 H (H-2 of 1,3-dioxolane, J = 5·0); 6·42 q, 1 H (H-9, J = 8·0; 2·0); 6·55 d, 1 H (H-7); 6·85 d, 1 H (H-10, J = 8·0); 9·01 bs (disappears after D_2O), 1 H (OH). For $C_{19}H_{27}NO_3$ (317·4) calculated: 71·89% C, 8·57% H, 4·41% N; found: 71·60% C, 8·49% H, 4·22% N.

Hydrogen maleate, m.p. 186—188°C (ethanol). For $C_{23}H_{31}NO_7$ (433·5) calculated: 63·72% C, 7·21% H, 3·23% N; found: 64·05% C, 7·28% H, 3·50% N.

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REFERENCES

1. Beckett A. H., Casy A. F.: Prog. Med. Chem. *4*, 171 (1965).
2. Hardy R. A. Jr., Howell M. G. in: *Medicinal Chemistry* (G. de Stevens, Ed.), Vol. 5 p. 179. Academic Press, New York 1965.
3. Johnson M. R., Milne G. M. in: *Burger's Medicinal Chemistry*, 4th ed. (M. E. Wolff, Ed.), Pt. III, p. 699. Wiley, New York 1981.
4. Janssen P. A. J., Gardocki J. (N. V. Research Laboratorium, Dr C. Janssen): U.S. 3,141,823; Chem. Abstr. *61*, 10689 (1964).
5. Janssen P. A. J. (N. V. Research Laboratorium Dr C. Janssen): U.S. 3,164,600; Fr. 2,430 M; Chem. Abstr. *62*, 14634 (1965).
6. Gardocki J. K., Yelnosky J., Kuehn W. F., Hunster H.: Toxicol. Appl. Pharmacol. *6*, 48 (1964).
7. Hess R., Herz A., Friedel K.: J. Pharmacol. Exp. Ther. *179*, 474 (1971).

8. Cass J., Frederik W. S.: Curr. Ther. Res. *3*, 97 (1961).
9. Janssen P. A. J., Van der Eycken C. A. M. in: *Drugs Affecting the Central Nervous System* (A. Burger, Ed.), Vol. 2, p. 25. Dekker, New York 1968.
10. Riley T. N., Hale D. B., Wilson M. C.: J. Pharm. Sci. *62*, 983 (1973).
11. Klein W., Back W., Mutschler E.: Arch. Pharm. *308*, 910 (1975).
12. Berger J. G., Davidson F., Langford G. E.: J. Med. Chem. *20*, 600 (1977).
13. Grossmann S., Moser U., Mutschler E.: Arch. Pharm. *311*, 1010 (1978).
14. Burkatsmaier K., Mutschler E.: Arch. Pharm. *311*, 843 (1978).
15. Lobbezoo M. W., Soudijn W., Wijngaarden I.v.: Eur. J. Med. Chem. *15*, 357 (1980).
16. Finney Z. G., Riley T. N.: J. Med. Chem. *23*, 895 (1980).
17. Lobbezoo M. W., Soudijn W., van Wijngaarden I.: J. Med. Chem. *24*, 777 (1981).
18. Casy A. F., Ogungbamila F. O.: J. Pharm. Pharmacol. *34*, 210 (1982).
19. Essawi M. Y. H., Portoghese P. S.: J. Med. Chem. *26*, 348 (1983).
20. Fifer E. K., Davis W. M., Borne R. F.: Eur. J. Med. Chem. *19*, 519 (1984).
21. Klein C. L., Stevens E. D., Fifer E. K., Borne R. F.: J. Pharm. Sci. *74*, 1147 (1985).
22. Van Bever W. F. M., Niemegeers C. J. E., Janssen P. A. J.: J. Med. Chem. *17*, 1047 (1974).
23. Van Daele P. G. H., De Bruyn M. F. L., Boey J. M., Sanczuk S., Agten J. T. M., Janssen P. A. J.: Arzneim.-Forsch. *26*, 1521 (1976).
24. Van Bever W. F. M., Niemegeers C. J. E., Schellekens K. H. L., Janssen P. A. J.: Arzneim.-Forsch. *26*, 1548 (1976).
25. Niemegeers C. J. E., Schellekens K. H. L., Van Bever W. F. M., Janssen P. A. J.: Arzneim.-Forsch. *26*, 1551 (1976).
26. Arrigoni-Martelli E.: Drugs Future *2*, 334 (1977); *3*, 410 (1978); *8*, 472 (1983); *9*, 386 (1984).
27. Janssens F. (Janssen Pharm. N. W.): Belg. 866,710; Ger. Offen. 2, 819,873; Fr. 2,389,622; Neth. Appl. 78 4,844; Chem. Abstr. *90*, 87468 (1979).
28. Janssens F.: *7th Int. Symp. Med. Chem., Torremolinos, Sept. 1980*; Abstr. P68.
29. Niemegeers C. J. E., Janssen P. A. J.: Drug Dev. Res. *1*, 83 (1981).
30. Hopkins S. J.: Drugs Future *6*, 335 (1981); *7*, 418 (1982); *8*, 539 (1983); *9*, 460 (1984).
31. Owen R. T.: Med. Actual. (Drugs Today) *20*, 7 (1984).
32. Tollenaere J. P., Moereels H., Van Loon M. in: *Progress in Drug Research* (E. Jucker, Ed.), Vol. 30, p.91. Birkhäuser, Basel 1986.
33. Casy A. F., Hassan M. M. A., Simmonds A. B., Staniforth D.: J. Pharm. Pharmacol. *21*, 434 (1969).
34. Benke B., Jager S., Szporny L., Palos E., Lenkefi Z., Visky G. (Gedeon Richter): Hung. 157,325; Chem. Abstr. *73*, 25305 (1970).
35. Malm C. J., Fordyce C. R. (Eastman Kodak Co.): U.S. 2,017,182; Chem. Zentralbl. *1936*, I, 880.
36. Mooradian A., Cavallito C. J., Bergman A. J., Lawson E. J., Suter C. M.: J. Am. Chem. Soc. *71*, 3372 (1949).
37. Šindelář K., Kopicová Z., Metyšová J., Protiva M.: Collect. Czech. Chem. Commun. *40*, 3530 (1975).
38. N. V. Research Laboratorium Dr C. Janssen: Belg. 633,914; Chem. Abstr. *60*, 15880 (1964).
39. Štrouf O., Čásenský B., Kubánek V.: *Sodium Dihydridobis(2-methoxyethoxo)aluminate (SMAD), A Versatile Organometallic Hydride*, p. 124. Academia, Prague 1985.
40. Borne R. F., Fifer E. K., Waters I. W.: J. Med. Chem. *27*, 1271 (1984).
41. Schenker E. (Sandoz Ltd.): Ger. Offen. 2,221,808; Chem. Abstr. *78*, 43502 (1973).
42. Borch R. F., Bernstein M. D., Durs H. D.: J. Am. Chem. Soc. *93*, 2897 (1971).
43. Fieser M., Fieser L. F.: *Reagents for Organic Synthesis*, Vol. 4, p. 450. Wiley, New York 1974.

44. Thayer J. R., McElvain S. M.: J. Am. Chem. Soc. *49*, 2862 (1927).
45. Bolyard N. W., McElvain S. M.: J. Am. Chem. Soc. *51*, 922 (1929).
46. Schiff H.: Ber. Dtsch. Chem. Ges. *12*, 294 (1879).
47. Zincke T., Prenntzell W.: Ber. Dtsch. Chem. Ges. *38*, 4116 (1905).
48. Gattermann L., Ruedt H.: Ber. Dtsch. Chem. Ges. *27*, 2293 (1894).
49. Doer W. H.: Ber. Dtsch. Chem. Ges. *5*, 795 (1872).
50. Protiva M., Jílek J. O., Pomykáček J., Jirkovský I., Vejdělek Z. J.: Collect. Czech. Chem. Commun. *28*, 2627 (1963).
51. Eisleb O.: Ber. Dtsch. Chem. Ges. *74*, 1433 (1941).
52. Jensen K. A., Lindquist F., Rekling E., Wolfbrandt C. G.: Dans. Tids. Farm. *17*, 173 (1943); Chem. Abstr. *39*, 2506 (1945).
53. Levina P. J., Gembickji P. A., Treshova E. G.: Zh. Obshch. Khim. *33*, 371 (1963).
54. Valenta V., Metyšová J., Šedivý Z., Protiva M.: Collect. Czech. Chem. Commun. *38*, 783 (1974).
55. Janssen P. A. J.: *Synthetic Analgetics*, Pt. I., p. 110. Pergamon Press, Oxford 1960.
56. Mannich C., Lammering D.: Ber. Dtsch. Chem. Ges. *55*, 3510 (1922).
57. Blicke F. F.: Org. React. *1*, 303 (1942).
58. Wright J. B., Lincoln E. H., Heinzelmann R. V., Hunter J. H.: J. Am. Chem. Soc. *72*, 3536 (1950).
59. Tchelitcheff S. (Société des Usines Chimiques Rhone-Poulenc): Ger. 812,911; Chem. Abstr. *52*, 1279 (1958).
60. Carr A. A., Kinsolving C. R. (Richardson-Merrell Inc.): U.S. 3,878,217; Ger. Offen. 2,303,306; Chem. Abstr. *79*, 105083 (1973).
61. Carr A. A., Kinsolving C. R. (Richardson-Merrell Inc.): Ger. Offen. 2,506,770; Belg. 826,012; Chem. Abstr. *84*, 59210 (1976).
62. Novák L., Protiva M.: Collect. Czech. Chem. Commun. *24*, 3966 (1959).
63. Adlerová E., Seidlová V., Protiva M.: Cesk. Farm. *12*, 122 (1963).
64. Eddy N. B., May E. L. in: *Synthetic Analgesics*, Pt. IIB, p. 113. Pergamon Press, Oxford 1966.
65. Jílek J. O., Metyšová J., Protiva M.: Collect. Czech. Chem. Commun. *39*, 3153 (1974).
66. Kametani T., Kisagawa K., Hiiragi M., Hayasaka T., Wagatsuna N., Wakisaka K.: J. Heterocycl. Chem. *6*, 43 (1969).
67. Ratouis R., Boissier J. R.: Bull. Soc. Chim. Fr. *1966*, 2963.
68. Bellora E., Cereda E., Ezhaya A., Marazzi-Uberti E., Pala G., Donetti A.: Farmaco, Ed. Sci. *35*, 490 (1980).
69. Elpern B., Wetterau W., Carabateas P., Grumbach L.: J. Am. Chem. Soc. *80*, 4916 (1958).
70. Beckett A. H., Casy A. F., Kirk G.: J. Med. Pharm. Chem. *1*, 37 (1959).
71. Protiva M., Rajšner M., Adlerová E., Seidlová V., Vejdělek Z. J.: Collect. Czech. Chem. Commun. *29*, 2161 (1964).

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