NEUROTROPIC AND PSYCHOTROPIC AGENTS. LXVII.*

1-[4,4-BIS(4-FLUOROPHENYL)BUTYL]-4-HYDROXY-4-(3-TRIFLUOROMETHYL-4-CHLOROPHENYL)PIPERIDINE AND RELATED COMPOUNDS: NEW SYNTHETIC APPROACHES

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New syntheses of the title compound, the neuroleptic "penfluridol" (*I*) are described. Their final stages consist (*I*) in the reaction of 1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidone (*II*) with 3-trifluoromethyl-4-chlorophenylmagnesium bromide and (*2*) in the reduction of 1-[4,4-bis(4-fluorophenyl)butyryl]-4-(3-trifluoromethyl-4-chlorophenyl)-4-piperidinol (*XL*) with lithium aluminium hydride. Several variants of the synthesis are described together with several model experiments and synthetic attempts.

During pharmacochemical studies of neuroleptics of the 10-piperazinodibenzo-[*b*,*f*]thiepin series we encountered indications of a protracted effect after oral application. For an objective test of this phenomenon we needed a reference compound, the most suitable in this connection appearing to be 1-[4,4-bis-(4-fluorophenyl)butyl]-4-(3-trifluoromethyl-4-chlorophenyl)-4-piperidinol (*I*), known under the code number R 16·341 or under the generic name "penfluridol"[1,2]. The first report on the chemistry and on the protracted effect of penfluridol upon oral administration was published by Janssen[3]. A pharmacological study[4] showed the substance to be a typical neuroleptic, the antiapomorphine effect of which for dogs after a single oral dose persisting for a whole week. The protracted effect was then borne out even in clinical studies, both during maintenance therapy of schizophrenic patients[5] and during the acute phase of schizophrenic psychosis[6].

The preparation of *I* has been reported in the literature[7] by a condensation of 4,4-bis(4-fluorophenyl)butyl chloride (*VI*) with 4-(3-trifluoromethyl-4-chlorophenyl)-4-piperidinol[8] (*XI*). The chloride *VI* was obtained from 4,4'-difluorobenzophenone[9] through a reaction with cyclopropylmagnesium bromide, a subsequent reaction of the formed di(4-fluorophenyl)cyclopropylmethanol with thionyl chloride and

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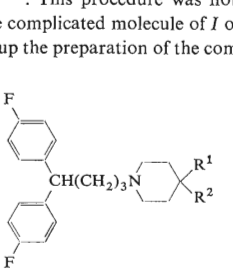
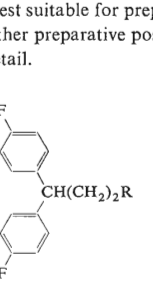
a catalytic hydrogenation of the 1,1-bis(4-fluorophenyl)-4-chlorobutene obtained[10-12]. This procedure was not considered here best suitable for preparation. Since the complicated molecule of *I* offers a number of other preparative possibilities we took up the preparation of the compound in greater detail.



I, $R^1 = OH$, $R^2 = 3,4\text{-}C_6H_3(CF_3)Cl$
II, $R^1R^2 = =O$
III, $R^1R^2 =$ 
IV, $R^1 = OH$, $R^2 = 3\text{-}C_6H_4CF_3$
V, $R^1 = R^2 = H$

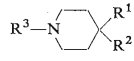


VI, CH_2Cl
VII, $R = CH_2I$
VIII, $R = COOH$
IX, $R = COCl$
X, $R = CONH_2$

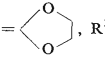
The first approach tested was through the reaction of ketone *II* with 3-trifluoromethyl-4-chlorophenylmagnesium bromide. The ketone *II* was prepared in two ways. In the first one 4,4'-difluorobenzophenone[9] reacted with 3-(4,4-ethylenedioxypiperidino)propylmagnesium chloride[13] to yield the tertiary alcohol *XIV* which was converted in a low yield to ketone *II*, using reduction with hydroiodic and hypophosphorous acid. The second way proceeded via the ketal *III* which was obtained in a moderate yield by a catalytic hydrogenation of the hydrochloride of the tertiary alcohol *XIV* on palladium in acetic acid in the presence of perchloric acid. Acid hydrolysis of the ketal *III* provides a fine yield of the oily ketone *II* which was characterized in the form of a crystalline hydrochloride containing one molecule of water by analysis. The IR spectrum of the hydrochloride displays a very weak absorption of the keto group (at 1733 cm^{-1}); on the other hand, it shows a heavy band at 3320 cm^{-1} (OH). In the form of hydrochloride the ketone *II* thus appears to exist probably as the corresponding 4,4-dihydroxypiperidine. As will be shown below, the base behaves as normal ketone.

The ketal *III* was obtained from 1-methyl-4-piperidone and 1-benzyl-4-piperidone. 1-Methyl-4-piperidone was converted to ethyleneketal *XVI* which was demethylated by a reaction with ethyl chloroformate and converted to carbamate *XVIII*. A by-product then obtained was the hydrochloride of the starting base *XVI*. Alkaline hydrolysis of the carbamate *XVIII* represents a new and powerful procedure for the ethyleneketal *XII* which has been hitherto accessible only through ketalization of the un-

stable 4-piperidone[13]. Similarly, 1-benzyl-4-piperidone was converted to ethyleneketal *XXII* which is debenzylated by the action of ethyl chloroformate in boiling benzene and produces a high yield of the carbamate *XVIII*. Ketal *XXII* can also be debenzylated by pressure hydrogenation on palladium directly to the base *XII* but our experience with this reaction was not good.



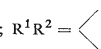
XI; $R^1 = OH$, $R^2 = 3,4\text{-}C_6H_3(CF_3)Cl$, $R^3 = H$

XII; $R^1R^2 =$  , $R^3 = H$,

XIII; $R^1 = OH$, $R^2 = 3\text{-}C_6H_4CF_3$, $R^3 = H$

XVI; $R^1R^2 =$  , $R^3 = CH_3$

XVII; $R^1 = OH$, $R^2 = 3,4\text{-}C_6H_3(CF_3)Cl$, $R^3 = CH_3$

XVIII; $R^1R^2 =$  , $R^3 = COOC_2H_5$

XIX; $R^1R^2 = =O$, $R^3 = COOC_2H_5$

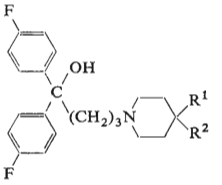
XX; $R^1 = OH$, $R^2 = 3,4\text{-}C_6H_3(CF_3)Cl$, $R^3 = COOC_2H_5$

XXI; $R^1 = OH$, $R^2 = 3\text{-}C_6H_4CF_3$, $R^3 = COOC_2H_5$

XXII, $R^1R^2 =$  , $R^3 = CH_2C_6H_5$

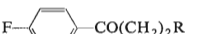
To obtain a suitable arylaliphatic component for condensation with ketal *XII* we attempted to find new ways of preparing the chloride *VI*, proceeding from the known 4-chloro-*p*-fluorobutyrophenone[14] (*XXIII*). This compound was first subjected to a reaction with a Grignard reagent prepared from 4-fluorobromobenzene[15,16]. We obtained thus an oily product in which apparently the expected tertiary alcohol *XXVIII* predominates but it could not be isolated in a pure state. Reaction of this crude product with a boiling mixture of hydroiodic acid and acetic acid in the presence of red phosphorus produced a product which could be redistilled in only a small amount and even under these conditions the distillation was accompanied by a partial decomposition, giving rise to iodine vapour. The distillate contained a high amount of iodine and its NMR spectrum is compatible with its formulation as the iodide *VII*. The reduction of the tertiary alcohol was thus accompanied by a replacement of the halogen at the chain terminus. Neither this iodide is a pure compound but it could be employed even in a crude state since in the reaction with ethyleneketal *XII* it yields satisfactorily compound *III*. The by-product occurring here was ketone *XXIV* which indicates that one of the contaminations of the crude iodide *VII* is the starting ketone *XXIII* or rather its iodinated analogue. The preparation of the iodide *VII* has not yet been described in the literature but its formula appears in the scheme of synthesis of the ^{14}C-labelled neuroleptic "fluspirilene"[17]. As a possible contaminant of the tertiary alcohol *XXVIII* one must consider 4-(4-fluorophenyl)-*p*-fluorobutyrophenone (*XXV*) which could be formed by a con-

densation reaction of 4-fluorophenylmagnesium bromide with the relatively reactive chlorine atom in ketone *XXIII*. The formation of *XXV* as a by-product was noted during the Friedel–Crafts reaction of fluorobenzene with 4-chlorobutyryl chloride[18]. We carried out this reaction under conditions when the formation of *XXV* was clearly preferred and the compound was characterized by its spectra. It could not be demonstrated that *XXV* is formed during the reaction of ketone *XXIII* with 4-fluorophenylmagnesium bromide. Condensation of this type does take place, however, since the most polar fraction isolated from the crude alcohol *XXVIII* was a small amount of liquid which was identified analytically and spectrally as 1,4-bis(4-fluorophenyl)butanol (*XXIX*). The Grignard reagent apparently also partly reduces the keto group whereupon the above condensation plays its role. During distillation of crude alcohol *XXVIII* a dehydration apparently takes place, the main product having been analyzed as 1,1-bis(4-fluorophenyl)-4-chlorobutene (*XXXI*) prepared already before in a different way[10]. Reduction of the ketone *XXIII* with sodium borohydride yielded 1-(4-fluorophenyl)-4-chlorobutanol (*XXX*), but this could not be converted to chloride *VI* by a reaction with fluorobenzene in sulfuric acid, non-homogeneous oily products resulting from the reaction. Likewise, attempts at dehydration of alcohol *XXX* did not yield a definable product.

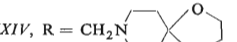


XIV, $R^1R^2 =$

XV, $R^1 = R^2 = H$



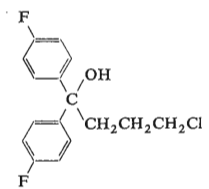
XXIII, R = CH_2Cl

XXIV, R = 

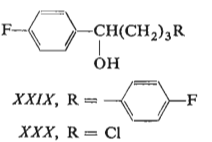
XXV, R = 4-$CH_2C_6H_4F$

XXVI, R = COOH

XXVII, R = $COOC_2H_5$



XXVIII

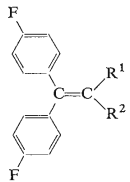


XXIX, R =

XXX, R = Cl

Reaction of ketone *II* with 3-trifluoromethyl-4-chlorophenylmagnesium bromide in tetrahydrofuran yielded an adequate amount of base *I*. Preparation of the starting 2-chloro-5-bromobenzotrifluoride (*XXXV*) has been described so far[19] only through a bromination of 2-chlorobenzotrifluoride[20] in the presence of chlorine and antimony pentachloride. It was observed that the bromination can be conducted with a fine yield under catalysis with iron. Compound *I* was further prepared by condensation of crude iodide *VII* with 4-(3-trifluoromethyl-4-chlorophenyl)-4-piperidinol (*XI*). In comparison with literature reports[8], preparation of *XI* from 1-methyl-4-piperidone or from 1-benzyl-4-piperidone, proceeding *via* the carbamates[21] *XIX* and *XX* has been pronouncedly modified.

In another possible synthesis of *I* we intended to employ as the last step the saturation of the double bond in the olefinic precursor *XXXVI*. The hydroxyketal *XIV* was dehydrated by the action of anhydrous hydrogen chloride in chloroform to the olefinic ketal *XXXVII* where the dioxolane residue was retained. The application of this compound as an intermediate was not necessary since exposure to boiling aqueous hydrochloric acid dehydrates the hydroxyketal *XIV* and simultaneously cleaves the dioxolane ring directly, giving rise to the unsaturated ketone *XXXVIII*.

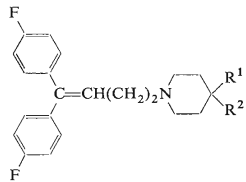


XXXI, $R^1 = H$, $R^2 = CH_2CH_2Cl$

XXXII, $R^1 = COOC_2H_5$, $R^2 = CH_2COOH$

XXXIII, $R^1 = COOH$, $R^2 = CH_2COOH$

XXXIV, $R^1 = H$, $R^2 = CH_2COOH$



XXXVI, $R^1 = OH$, $R^2 = 3,4\text{-}C_6H_3(CF_3)Cl$

XXXVII, $R^1R^2 =$ 

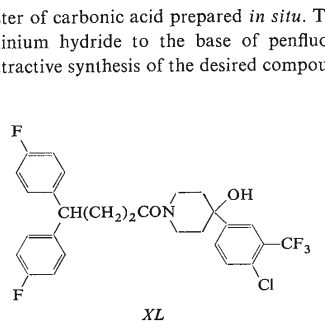
XXXVIII, $R^1R^2 = =O$

XXXIX, $R^1 = R^2 = H$

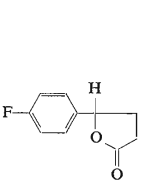
This ketone reacts with 3-trifluoromethyl-4-chlorophenylmagnesium bromide in tetrahydrofuran, giving rise to a nonhomogeneous product, from which the unsaturated base *XXXVI* was isolated in a fine yield by chromatography. When it was hydrogenated on a palladium catalyst under normal conditions the consumption of hydrogen did not stop after absorption of 2 H but continued smoothly to an absorption of 4 H. A chlorine-free base was then isolated from the reaction mixture which was identified as a product of hydrogenolysis *IV*. It is not clear whether the hydrogenation of the double bond precedes hydrogenolysis or whether the two reactions proceed in parallel. However, it may be assumed that conditions could be found when the

double bond is selectively saturated. In connection with compound[7] *IV* we took up the preparation of piperidine *XIII*, the synthesis of which has been described[22,23] only through a hydrogenolysis of the corresponding N-benzyl derivative. In the present work we applied the reaction of 1-ethoxycarbonyl-4-piperidone (*XIX*) with a Grignard reagent prepared from 3-bromobenzotrifluoride[24] to obtain the hydroxycarbamate[25] *XXI* which was hydrolyzed by a highly concentrated potassium hydroxide to the desired compound *XIII*.

In the last variant of the synthesis of *I* we used a procedure where the immediate precursor of *I* was the amide *XL*. For its preparation we needed 4,4-bis(4-fluorophenyl)butyric acid (*VIII*) described without characterization as a metabolite of the neuroleptics "fluspirilene"[17] and "pimozide"[26]. Two synthetic procedures for the preparation of the acid *VIII* were developed. In the first of these we proceeded from the application of Stobbe's reaction (for methods see[27,28]) to 4,4'-difluorobenzophenone[9] and, using diethyl succinate, we obtained a roughly 50% yield of the ester acid *XXXII*. Alkaline hydrolysis gave rise to the diacid *XXXIII* which was heated with a mixture of hydrobromic and acetic acids to decarboxylate it to 4,4'-bis(4-fluorophenyl)-3-butenic acid (*XXXIV*). The same compound is obtained directly from the ester acid *XXXII* by heating it with a mixture of hydrobromic and acetic acids. Hydrogenation of this acid on Adams catalyst under normal conditions led to the oily acid *VIII* which was characterized by conversion to the chloride *IX* and further to the crystalline amide *X*. In another, more suitable, synthesis of the acid *VIII* the starting compound was 3-(4-fluorobenzoyl)propionic acid[29–31] (*XXVI*), giving smoothly the ethyl ester *XXVII*. Reduction of the acid *XXVI* with sodium borohydride in ethanol and distillation of the acidic product formed resulted in a high yield of the oily 4-(4-fluorophenyl)butyrolactone (*XLI*). Its reaction with excess fluorobenzene and aluminium chloride at reduced temperature led to a 90% yield of acid *VIII*. Its conversion to amide *XL* in a reaction with piperidine *XI* was carried out either *via* the crude chloride *IX* or *via* the anhydride with the monoethyl ester of carbonic acid prepared *in situ*. The amide *XL* was reduced with lithium aluminium hydride to the base of penfluoridol (*I*) whereby the preparatively most attractive synthesis of the desired compound was terminated.



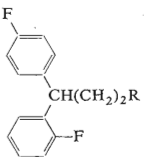
XL



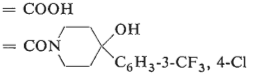
XLI

When carrying out the reaction of lactone *XLI* with fluorobenzene and aluminium chloride in larger batches when coarser granulation of aluminium chloride was employed, the exothermic character of the reaction caused the temperature to rise spontaneously above 30°C. In these batches the acid did not crystallize from benzene, yielding either a noncrystalline amide or a crystalline amide melting 20°C lower than amide *XL* obtained from crystalline acid *VIII*. This amide yielded a poorly crystallizing base after hydride reduction, the base being convertible to a hydrochloride, corresponding by its composition to the hydrochloride of *I* but melting some 20°C higher than the hydrochloride prepared previously. The IR and NMR spectra of the noncrystalline acid *VIII* showed significant differences in comparison with the spectra of products obtained by reduction of acid *XXXIV* or on small batches from lactone *XLI* which apparently have the structure of the *p,p'*-isomer *VIII*. This authentic acid displays a single sharp peak at 837 cm^{-1} in the region of deformation vibrations. On the other hand, the spectrum of the noncrystalline acid shows three pronounced absorption bands at 692 and 792 cm^{-1}, characteristic for the *m*-substitution, and further at 758 cm^{-1}, characteristic for the *o*-substitution. A similar difference in the behaviour of the two compounds under comparison is observed in the region of valence vibrations. In accord with the *p*-substitution, the standard shows two pronounced peaks at 1 510 and 1 605 cm^{-1} while the noncrystalline compound possesses besides the two peaks three further bands at 1 490, 1 590 and 1 615 cm^{-1}. Even if it cannot be decided in the given case whether this reflects *o*- or *m*-substitution it is beyond doubt that the analyzed sample contains besides the *p*-isomer *VIII* also the *o*-isomer *XLII* and probably also the corresponding *m*-isomer. This finding is borne out also by the behaviour of these compounds in the region of deformation bands at 1 800 – 2 000 cm^{-1}. The pure *p*-isomer *VIII* contains in this region a single sharp peak at 1 890 cm^{-1} (another charateristic peak at 1 700 cm^{-1} is covered by the carbonyl band); on the other hand, the noncrystalline acid shows a clear further peak at 1 915 cm^{-1}. The results of the IR spectra were fully borne out by NMR spectra. The spectrum of the standard displays in agreement with structure *VIII* a triplet at 6·89 p.p.m. ($J = 10$ Hz), corresponding to 4 protons in an *o*-position with respect to the fluorine atoms and a twin doublet at 7·14 p.p.m. ($J = 9{\cdot}0; 5{\cdot}0$ Hz), corresponding to the remaining 4 hydrogens in *m*-position toward fluorine. The methine hydrogen (in the α-position of diphenylmethane) is represented in this case by an indistinguishable multiplet at 3·84 p.p.m. On the other hand, the noncrystalline acid shows an indistinguishable multiplet in the region of about 7 p.p.m. with an indication of a triplet at 6·89 p.p.m. and, besides the multiplet at 3·83. p.p.m., another one at 4·18 p.p.m., the sum of the integrated areas of the two multiplets corresponding to 1 proton. We are thus apparently dealing here again with a mixture of the *p*-isomer *VIII* with the *o*-isomer *XLII* or with the corresponding *m*-isomer, It cannot be excluded that the peaks of the two multiplets represent components of a doublet ($J = c.$ 20 Hz) which would support the presence of the *o*-isomer *XLII* (due to interaction of the methine proton with a fluorine atom). This view was supported by the IR spectra of the corresponding crystalline amide and further of the crystalline hydrochloride of the final base as recorded with substances highly purified by crystallization. Thus the spectrum of the amide shows a heavy band at 760 cm^{-1} which is accounted for by a strong representation of the *o*-isomer *XLIII*. The spectrum of the hydrochloride of the final base shows a very intense band at 754 cm^{-1} which indicates that we are dealing here with a practically pure *o*-isomer *XLIV*. It follows from these results that the orientation of the Friedel–Crafts alkylation of fluorobenzene with lactone *XLI* is markedly dependent on the reaction conditions. This agrees with the previously described results obtained with alkylation of chlorobenzene with cyclohexanol[32,33]. In greater batches of *I*, obtained by reduction of amide *XL*, thin-layer chromatography revealed the presence of a small amount of a more polar contaminant. This compound could be separated by chromatography on a column of alumina and was identified as 1-methyl-4-(3-trifluoromethyl-4-chlorophenyl)-4-piperidinol (*XVII*). Its presence can be

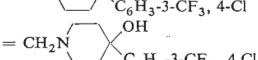
accounted for by assuming that the employed amide *XL* contained a small amount of the starting carbamate *XX* which was reduced to the N-methyl analogue.



XLII, R = COOH

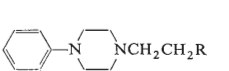


XLIII, R = C_6H_3-3-CF_3, 4-Cl



XLIV, R = C_6H_3-3-CF_3, 4 Cl

In connection with a the model experiment, reaction of 4,4′-difluorobenzophenone[9] with a Grignard reagent prepared from 3-piperidinopropyl chloride[34] produced the tertiary alcohol *XV* which was dehydrated by heating with dilute sulfuric acid to the unsaturated amine *XXXIX* and reduced with hydroiodic acid to the saturated amine *V*. The same product was prepared by a reaction of the crude iodide *VII* with piperidine. Another model experiment was unsuccessful: reaction of the known 1-(2-tolyl)--4-(3-hydroxypropyl)piperazine[35] with thionyl chloridē resulted in chloride *XLV* which was converted to the Grignard reagent and this was employed in the attempt at a reaction with 4,4′-difluorobenzophenone[9]. The only product isolated was identified as 1-(2-tolyl)-4-(n-propyl)piperazine (*XLVI*) which indicates that the Grignard reagent did not react much with the ketone and the conventional treatment by hydrolysis yielded the above product.



XLV, R = CH_2Cl
XLVI, R = CH_3

The hydrochlorides of *V*, *XIII*, *XIV* and *XV* and further the hydrogen maleate of the base *XXXIX* were subjected to a pharmacological screening at the affiliated unit of this Institute at Rosice n/L. For every substance, the review contains the mode of administration, its mean lethal dose LD_{50} in mg/kg for white mice and the dose D in mg/kg at which it was applied in most of the *in vivo* tests.

Compound *V* (*i.v.*, 30, 6) at high doses (>D) brings about in mice a short-term excitation followed by depression. It has a slight anticonvulsant effect toward pente-

trazol in mice. At a concentration of 1 μg/ml it reduces by 50% contractions of isolated rat duodenum, caused by acetylcholine or barium chloride. At a concentration of 0·5 – 1·0% it has a locally anaesthetic effect on rabbit cornea. Compound *XIII* (*i.v.*, 62·5, 12) at high doses also has a short-lived excitatory effect. There are indications of analgetic, anti-inflammatory, antiarrhythmic and diuretic effects. Compound *XIV* (*p.o.*, 500, 100) at high doses in mice inhibits the CNS, at a dose of 50 – 100 mg/kg it brings about a significant drop of body temperature (rectal) in rats, at a dose of 10 to 50 mg/kg it protracts thiopental sleep in mice to the two-fold of the control and at a dose of 25 mg/kg it protects 50% mice from lethal effects of amphetamine; it has thus an overall character of a central depressant. At a dose of 10 – 25 mg/kg it increases diuresis in mice by 100% of the control; this result has not been confirmed in rats. Compound *XV* (*i.v.*, 50 – 62·5, 10) shows also indications of a central depressant activity even if weaker than the preceding compound. In contrast it is a relatively stronger spasmolytic toward isolated rat duodenum, using acetylcholine contractions, at a concentration of 0·1 – 1·0 μg/ml, and toward barium chloride contractions, at a concentration of 1 – 10 μg/ml. Similarly to the previous compound it increases diuresis of mice by 100% at a dose of 10 – 25 mg/kg *p.o.* In rats the diuretic and natriuretic effect is marked at a dose of 20 mg/kg *p.o.* and that only under conditions of slight hydration. Compound *XXXIX* (*i.v.*, 40, 8) shows similarly to the two preceding ones a slight centrally depressant activity (it potentiates thiopental and antagonizes amphetamine), a locally anaesthetic activity toward rabbit cornea, spasmolytic activity in isolated intestine and a negatively inotropic effect in isolated rabbit auricles.

Penfluridol hydrochloride (*I*) showed a marked antibacterial activity *in vitro* (microorganism and the minimum inhibitory concentration in μg/ml are shown): *Streptococcus* β-*haemolyticus* 1·57, *Staphylococcus pyogenes aureus* 1·57 (similarly in the penicillin-resistant strain), *Mycobacterium tuberculosis* H37Rv 0·79.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried at room temperature at 0.5 Torr over P_2O_5. The UV spectra were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in KBr unless stated otherwise) in an Infrascan (Hilger and Watts) spectrophotometer and the NMR spectra (in $CDCl_3$ unless stated otherwise) in a ZKR-60 (Zeiss Jena) spectrometer.

8-[4,4-Bis(4-fluorophenyl)-4-hydroxybutyl]-1,4-dioxa-8-azaspiro[4,5]decane (*XIV*)

Reaction of 3·5 g Mg with 30·8 g 3-(4,4-ethylenedioxypiperidino)propyl chloride[13] in 60 ml tetrahydrofuran gave rise to a solution of a Grignard reagent (to trigger the reaction, 0·8 ml 1,2-dibromoethane was used and the mixture was refluxed for 2 h). Over a period of 10 min, a solution of 25·5 g 4,4'-difluorobenzophenone[9] (m.p. 107 – 109°C) in 40 ml tetrahydrofuran was added dropwise and the mixture was refluxed for 2·5 h. After cooling, it was decomposed with 250 ml 20% solution NH_4Cl, filtered, the filtrate was extracted with ether, the extract dried with K_2CO_3 and evaporated. The residue was dissolved in 50 ml ethanol and the hydrochloride was

precipitated with an ether solution of HCl: 41·6 g (81%), m.p. 212—213°C (ethanol–ether). IR spectrum (Nujol): 820, 830 and 840 (2 vicinal aromatic C—H), 1090 (Ar—F), 1160 (R_3C—OH), 1218 (C—O—C in a ring), 1504 and 1600 (Ar), 2440 and 2500 (NH^+), 3265 and 3320 cm^{-1} (OH). NMR spectrum (CD_3SOCD_3): δ 11·00 (bs, 1 H, disappears on deuteration, HCl), 6·80—7·60 (m, 8 H, aromatic protons), 5·80 (s, 1 H, disappears on deuteration, OH), 3·84 (s, 4 H, OCH_2CH_2O), 1·40—3·60 (indistinguishable multiplet, other CH_2 groups). For $C_{23}.H_{28}ClF_2NO_3$ (439·9) calculated: 62·79% C, 6·42% H, 8·06% Cl; found: 62·57% C, 6·40% H, 8·28% Cl.

8-Methyl-1,4-dioxa-8-azaspiro[4,5]decane (*XVI*)

A mixture of 1-methyl-4-piperidone hydrochloride (from 113·2 g aminoketone), 150 ml anhydrous ethylene glycol, 600 ml benzene and 5 g 4-toluenesulfonic acid was distilled for 24 h. After cooling, the clear benzene solution was decanted from the precipitated crystals, these were decomposed with an aqueous solution of K_2CO_3 and the product was isolated by extraction with chloroform: 136·4 g (87%) base boiling at 90°C/15 Torr. Hydrochloride, m.p. 252—254°C (ethanol). For $C_8H_{16}ClNO_2$ (193·7) calculated: 49·61% C, 8·33% H, 18·31% Cl, 7·23% N; found: 49·82% C, 8·52% H, 18·25% Cl, 7·06% N.

8-Benzyl-1,4-dioxa-8-azaspiro[4,5]decane (*XXII*)

A mixture of 31·0 g hydrochloride of 1-benzyl-4-piperidone[36,37] (m.p. 158—162°C under decomposition), 11·3 g ethylene glycol and 250 ml benzene was refluxed for 8 h and benzene was then distilled off and replaced with anhydrous benzene until the distillate appeared turbid. Benzene was then evaporated and the remaining hydrochloride of the product was mixed with some acetone and filtered; 33·0 g (89%), m.p. 249—252°C (decomposition). Using ethanol, a different crystalline modification is obtained, melting at 232°C (decomposition). For $C_{14}H_{20}ClNO_2$ (269·8) calculated: 62·33% C, 7·47% H, 13·14% Cl, 5·19% N; found: 62·03% C, 7·60% H, 13·14% Cl, 5·01% N. Decomposition of the hydrochloride with excess 5M-NaOH and extraction with ether yielded a base, boiling at 130°C/0·7 Torr, 122°C/0·4 Torr. The NMR spectrum: δ 7·30 (s, 5 H, C_6H_5), 4·86 (s, 4 H, OCH_2CH_2O), 3·46 (s, 2 H, Ar—CH_2—N), 2·50 (t, J = 6·0 Hz, 4 H, CH_2—N—CH_2 in a ring), 1·70 (t, J = 6·0 Hz, 4 H, CH_2—C—CH_2 in a ring). For $C_{14}H_{19}NO_2$ (233·3) calculated: 72·07% C, 8·21% H, 6·00% N; found: 72·18% C, 8·28% H, 5·79% N.

8-Ethoxycarbonyl-1,4-dioxa-8-azaspiro[4,5]decane (*XVIII*)

A. Ethyl chloroformate (180 ml) was added dropwise over an hour to a boiling mixture of 135·1 g base *XVI* and 800 ml benzene. The mixture was refluxed for 4 h and cooled. Filtration removed the crystals of hydrochloride of the starting compound *XVI* (16·4 g, m.p. 252—254°C). The filtrate was washed with 2M-HCl, then with a solution of $NaHCO_3$ and water and was distilled after drying; 156·8 g (85%), b.p. 101—105°C/0·8 Torr. For $C_{10}H_{17}NO_4$ (215·2) calculated: 55·80% C, 7·96% H, 6·51% N; found: 54·74% C, 7·96% H, 6·08% N.

B. Base *XXII* (35·5 g) was processed analogously using a reaction of 36·5 g ethyl chloroformate in 150 ml boiling benzene, A total of 28·2 g (86%) neutral product boiling at 98—102°C/0·5 Torr was obtained, the product being identical with that prepared under *A*.

1,4-Dioxa-8-azaspiro[4,5]decane (*XII*)

A. A mixture of 15·3 g carbamate *XVIII*, 20 g solid KOH and 25 ml ethanol was refluxed for 4 h in a bath at 120—130°C. It was then diluted with 40 ml water and the product was extracted with benzene. Drying of the extract and distillation yielded 9·2 g (90%) base, boiling at 86—89°C / 9 Torr. For a product prepared differently, the literature[13] reports a b.p. of 108—110°C/26 Torr. The base absorbs atmospheric CO_2 and hence cannot be analyzed satisfactorily. For characterization, *hydrogen maleate* was prepared, m.p. 147·5—148°C (ethanol–ether). For $C_{11}H_{17}NO_6$ (259·3) calculated: 50·96% C, 6·61% H, 5·40% N; found: 51·36% C, 6·91% H, 5·52% N.

B. Palladium catalyst (10%, 50 g) on charcoal was added to a solution of 70·5 g base *XXII* in 400 ml ethanol and the mixture was hydrogenated in an autoclave at an initial pressure of hydrogen of 100 atm and at 100°C. After 4 h the hydrogenation was interrupted, the mixture was filtered and the filtrate distilled. A total of 14·5 g (32%) base *XII* was obtained: b.p. 90°C/8 Torr; the remainder yielded 35·5 g of the starting base *XXII*, b.p. 126—130°C/0·7 Torr.

4,4-Bis(4-fluorophenyl)butyl Iodide (*VII*)

Reaction of 8·8 g 4-fluorobromobenzene[15,16] (b.p. 53—55°C/12 Torr) with 1·35 g Mg in 40 ml ether yielded a Grignard reagent. A solution of 10·0 g 4-chloro-*p*-fluorobutyrophenone[14] (*XXIII*, b.p. 137—139°C/6 Torr) in 15 ml ether was added dropwise to a boiling solution of the Grignard reagent and the mixture was refluxed for 45 min. After standing overnight, 100 ml of a 15% solution of NH_4Cl was added dropwise and the mixture was extracted with ether. The extract was dried with $MgSO_4$ and evaporated. A total of 13·35 g (90%) crude alcohol *XXVIII* was obtained which, on chromatography on a thin layer of alumina displays two more polar contaminants but still appears to be sufficiently suitable for further processing. One of the contaminants was isolated from a different batch of crude alcohol *XXVIII* (12·8 g) by chromatography on a column of 250 g alumina (activity II). It was eluted with benzene with 2% ethanol and redistilled without signs of decomposition, b.p. 139—140°C/0·2 Torr. We are dealing here with 1,4-*bis*(4-*fluorophenyl*)*butanol* (XXIX). UV spectrum (ethanol): λ_{max} 227 nm (log ε 4·06), 251 nm (4·16). IR spectrum ($CHCl_3$): 813 and 833 (2 vicinal aromatic C—H), 1010 and 1095 (CHOH), 1548, 1565, 1593 and 1606 (Ar), 3610 cm^{-1} (OH). NMR spectrum: δ 6·75—7·40 (m, 8 H, aromatic protons), 6·06 (t, J = 7·5 Hz, 1 H, CH—O), 3·67 (t, J = 6·5 Hz, 2 H, Ar—CH_2), 2·84 (q, 2 H, middle CH_2 group), 1·70 (s, 1 H, disappears on deuteration, OH). For $C_{16}H_{16}F_2O$ (262·3) calculated: 73·26% C, 6·15% H; found: 73·53% C, 5·50% H.

Another batch of the crude alcohol *XXVIII* (27·3 g) was distilled *in vacuo*. A partial decomposition took place and redistillation yielded 10·8 g liquid, b.p. 119—120°C/0·1 Torr, which is considered to be 1,1-*bis*(4-*fluorophenyl*)-4-*chlorobutene* (XXXI). Ref.[10] gives a b.p. of 165—167°C / 6 Torr. For $C_{16}H_{13}ClF_2$ (278·7) calculated: 68·95% C, 4·70% H; found: 69·44% C, 4·72% H.

A mixture of 13·35 g crude alcohol *XXVIII*, 15 ml acetic acid, 15 ml 57% hydroiodic acid and 2 g red phosphorus was refluxed under stirring for 6 h. It was diluted while hot with 50 ml water and filtered. The solid was washed with benzene and ether and the filtrate was extracted with ether. The extract was washed with 1·5M-HCl, then with 5% NaOH, 5% $Na_2S_2O_3$ and with water, dried with Na_2SO_4 and evaporated. The residue (16·2 g, 97%) is the crude iodide *VII*, utilizable in further work. The sample was redistilled under partial decomposition; b.p. 160 to 162°C/3·6 Torr. NMR spectrum: δ 6·80—7·40 (m, 8 H, aromatic protons), 3·89 (t, J = 7·0 Hz, 1 H, Ar_2CH), 3·15 (t, J = 6·0 Hz, 2 H, CH_2I), c. 1·90 (m, 4 H, C—CH_2CH_2—C). The elementary composition of the compound is only approximative. For $C_{16}H_{15}F_2I$ (372·2) calculated: 51·63% C, 4·06% H, 34·10% I; found: 53·66% C, 4·14% H, 30·68% I.

8-[4,4-Bis(4-fluorophenyl)butyl]-1,4-dioxa-8-azaspiro[4,5]decane (*III*)

A. Perchloric acid (0·5 ml) was added to a solution of 3·0 g hydrochloride of base *XIV* in 40 ml acetic acid and the mixture was hydrogenated on a catalyst prepared from 200 mg $PdCl_2$ and 1 g charcoal at room temperature and normal pressure until the theoretical consumption of hydrogen has been reached. It was then filtered, the filtrate was evaporated at reduced pressure and the residue was separated between chloroform and 10% NaOH. Evaporation of the chloroform extract yielded a crude base (2·8 g) which was chromatographed on a column of 120 g alumina (activity II). Elution with a mixture of chloroform and benzene yielded 0·54 g base which was converted in the usual way to *hydrogen maleate*, m.p. 131–133°C (acetone–ether). For $C_{27}H_{31}F_2NO_6$ (503·6) calculated: 64·40% C, 6·21% H; found: 63·89% C, 5·79% H.

B. A mixture of 16·2 g crude iodide *VII*, 6·5 g base *XII*, 10 g anhydrous K_2CO_3 and 50 ml diethyl ketone was refluxed under stirring for 3 h (120°C bath). After standing overnight, the inorganic salts were filtered, the filtrate evaporated under reduced pressure to dryness, the residue diluted with water and extracted with benzene. The extract was shaken with excess 10% HCl, the benzene layer was separated, the two lower layers were made alkaline with 15% NaOH and the released base was extracted with benzene. After drying with $MgSO_4$, the extract was evaporated and the residue chromatographed on a column of 440 g alumina (activity II). Elution with a mixture of benzene and chloroform (3 : 1) yielded 11·3 g base *III* which crystallizes from a mixture of cyclohexane and light petroleum and melts at 94–95°C. NMR spectrum: ϑ 6·80–7·50 (m, 8 H, aromatic protons), 3·94 (s, 4 H, OCH_2CH_2O), 3·88 (t, $J = 7{\cdot}0$ Hz, 1 H, Ar_2CH), 2·42 (t, $J = 6{\cdot}0$ Hz, 4 H, CH_2NCH_2 in the ring), 1·70 (t, $J = 6{\cdot}0$ Hz, 4 H, CH_2—C—CH_2 in the ring), 1·30–2·40 (m, 6 H, 3 CH_2 in the chain). For $C_{23}H_{27}F_2NO_2$ (387·5) calculated: 71·29% C, 7·02% H; found: 71·53% C, 6·86% H. *Hydrogen maleate*, m.p. 132–133·5°C (acetone–ether), is identical with the product obtained under *A*. For $C_{27}H_{31}F_2NO_6$ (503·6) calculated: 64·40% C, 6·21% H, found: 64·22% C, 5·77% H.

Continuation of the chromatography and elution with a mixture of chloroform and ethanol yielded 2·22 g 8-[3-(4-*fluorobenzoyl*)*propyl*]-1,4-*dioxa*-8-*azaspiro*[4,5]*decane* (XXIV) characterized as hydrogen maleate, m.p. 156–158°C (acetone–ether). For $C_{21}H_{26}FNO_7$ (423·4) calculated: 59·57% C, 6·19% H; found: 59·90% C, 6·31% H. For spectral characterization a base (oil) was liberated from the hydrogen maleate. IR spectrum: 841 (2 vicinal aromatic C—H), 1 510, 1 604 (Ar), 1 687 cm^{-1} (Ar—CO). NMR spectrum: ϑ 8·02 (m, 2 H, aromatic protons in the vicinity of the keto group), 7·10 (m, 2 H, aromatic protons in the vicinity of fluorine), 3·85 (s, 4 H, OCH_2·CH_2O), 2·93 (t, $J = 7{\cdot}0$ Hz, 2 H, $COCH_2$), 2·49 (t, $J = 6{\cdot}0$ Hz, 4 H, CH_2NCH_2 in the ring), 2·39 (t, $J = 6{\cdot}0$ Hz, 2 H, CH_2N in the chain), 1·95 (m, 2 H, CH_2 in the middle of the chain), 1·64 (t, $J = 7{\cdot}0$ Hz, 4 H, CH_2—C—CH_2 in the ring).

1-[4,4-Bis(4-fluorophenyl)butyl]-4-piperidone (*II*)

A. A solution of 11·0 g hydrochloride of *XIV* in 25 ml acetic acid was added to a mixture of 30 ml 56% hydroiodic acid and 6·0 g $NaH_2PO_2.H_2O$ at 80°C. The mixture was refluxed for 4 h (120°C bath). After cooling, it was made alkaline with 40% NaOH and the product was extracted with chloroform. Treatment of the extract yielded only 1·6 g oily base which was dissolved in ethanol and, after treatment with an ether solution of HCl, yielded a *hydrochloride*, m.p. 94–96°C (acetone–ether). According to analysis and spectra, the salt contains chemically bound water and it is thus apparently, a 4,4-dihydroxypiperidine derivative. IR spectrum: 825, 845 (2 vicinal aromatic C—H), 1 227 (Ar—F), 1 510, 1 607 (Ar), 2 590, 2 740 (NH^+), 3 330 cm^{-1} (OH). For $C_{21}H_{26}ClF_2NO_2$ (397·9) calculated: 63·39% C, 6·59% H, 8·91% Cl, 3·52% N; found: 63·24% C, 6·91% H, 8·90% Cl, 3·53% N.

B. A mixture of 11·3 g base *III*, 150 ml water and 10 ml concentrated hydrochloric acid was refluxed for 7·5 h and, after cooling, it was made alkaline with a solution of Na_2CO_3 and extracted with benzene. Drying and evaporation of the extract yielded the crude base (10·0 g) which was converted like under *A.* to the *hydrochloride*, m.p. 97—100°C (acetone–ether) which was identical with the product under *A.*

4-(4-Fluorophenyl)-*p*-fluorobutyrophenone (*XXV*)

Aluminium chloride (6·2 g) was added over a period of 30 min under stirring to a 50°C mixture of 150 ml fluorobenzene and 28·2 g 4-chlorobutyryl chloride[38] (b.p. 81°C/20 Torr). The mixture was stirred for 2 h at 60°C and poured on to 1 kg ice and 200 ml concentrated hydrochloric acid. The product was extracted with benzene, the extract was washed with a dilute solution of NaOH, dried with Na_2SO_4 and distilled; 39·2 g (75%), b.p. 132—134°C/0·14 Torr, m.p. 71—73°C (hexane). Ref.[18] gives a b.p. of 157—158°C/1 Torr and m.p. of 45°C. UV spectrum (ethanol): λ_{max} 246 nm (log ε 4·18), 273 nm (3·35). IR spectrum ($CHCl_3$): 835 (2 vicinal aromatic C—H), 1243 (C—F), 1510, 1597 (Ar), 1678 cm^{-1} (Ar—CO). NMR spectrum: ϑ 8·10 (m, 2 H, aromatic protons in *o*-position to CO), 6·90—7·50 (m, 6 H, other aromatic protons), 2·98 (t, J = = 7·0 Hz, 2 H, $COCH_2$), 2·76 (t, J = 8·0 Hz, 2 H, $ArCH_2$), 2·12 (m, 2 H, middle CH_2 in the chain). For $C_{16}H_{14}F_2O$ (260·3) calculated: 73·83% C, 5·42% H; found: 74·14% C, 5·23% H.

1-(4-Fluorophenyl)-4-chlorobutanol (*XXX*)

To a solution of 5·0 g 4-chloro-*p*-fluorobutyrophenone[14] (*XXIII*) in 50 ml ethanol, 0·3 g $NaBH_4$ was added in parts under stirring and the mixture was left for 1 h at room temperature. After evaporation of the ethanol, water was added and the product was extracted with ether: 4·0 g, b.p. 117°C/0·3 Torr. IR spectrum (film): 652 (C—Cl), 840 (2 vicinal aromatic C—H), 1070 (CHOH), 1100 and 1226 (C—F), 1510 and 1605 (Ar), 3400 cm^{-1} (OH). NMR spectrum: ϑ 6·80—7·50 (m, 4 H, aromatic protons), 4·64 (t, 1 H, Ar—CH—O), 3·50 (m, 2 H, CH_2Cl), 2·09 (s, 1 H, OH), 1·80 (m, 4 H, CH_2CH_2 in the chain). For $C_{10}H_{12}ClFO$ (202·7) calculated: 59·26% C, 5·97% H, 17·50% Cl; found: 59·15% C, 6·07% H, 17·33% Cl.

2-Chloro-5-bromobenzotrifluoride (*XXXV*)

A mixture of 250 g 2-chlorobenzotrifluoride[20] (b.p. 150—152°C) and 5 g powder iron was heated to 70 °C and combined with about 1/5 of the total of 116·5 ml bromine. After 30 min, HBr began to develop and the remaining bromine was added dropwise under stirring over a period of 3 h. The mixture was stirred and heated for 5 h to 80—95°C. After standing overnight, it was poured into 500 ml 5% solution of $Na_2S_2O_5$ and the product was extracted with chloroform. The extract was washed with water, dried, filtered with charcoal and distilled; 288 g (80%), b.p. 193—195°C. Ref.[19] gives for a product obtained by bromination of 2-chlorobenzotrifluoride in the presence of chlorine and antimony pentachloride, a b.p. of 197—198°C/740 Torr. For $C_7H_3BrClF_3$ (259·5) calculated: 32·40% C, 1·16% H, 13·67% Cl; found: 32·47% C, 1·12% H, 13·20% Cl.

1-Ethoxycarbonyl-4-piperidone (*XIX*)

A. 1-Methyl-4-piperidone (100 g) was added dropwise and under stirring to a boiling solution of 130 g ethyl chloroformate in 350 ml benzene. The mixture was refluxed for 5 h, cooled, washed with 3M-HCl, with 5% $NaHCO_3$ and water, dried with K_2CO_3 and distilled; 82·1 g (54%), b.p. 95—98°C/1 Torr. IR spectrum (film): 1695 and 1710 cm^{-1} (CO and NCOOR). For C_8H_{13}· $.NO_3$ (171·2) calculated: 56·12% C, 7·65% H, 8·18% N; found: 56·19% C, 7·68% H, 7·63% N.

B. In analogy to *A*, 189 g 1-benzyl-4-piperidone was processed with 135 g ethyl chloroformate in 400 ml benzene. A total of 114 g (67%) product boiling at 135°C/12 Torr was obtained and was found to be identical with the product prepared under *A*. Ref.[21] describes debenzylation of 1-benzyl-4-piperidone with ethyl chloroformate under different conditions. The product is reported to boil at 93—94°C/1 Torr.

1-Ethoxycarbonyl-4-(3-trifluoromethyl-4-chlorophenyl)-4-piperidinol (*XX*)

Reaction of 14·5 g Mg and 156 g 2-chloro-5-bromobenzotrifluoride (*XXXV*) in 800 ml ether gave rise to a solution of Grignard's reagent (the reaction was initiated with grains of iodine and with ethylene dibromide). A solution of 68 g carbamate *XIX* in 200 ml ether was then added dropwise over a period of 20 min at room temperature and the mixture was stirred for 1 h. This was followed by an addition of 500 ml 20% NH_4Cl, the ether layer was dried with K_2CO_3, filtered with charcoal and evaporated. The residue was triturated with 100 ml ether and the crystalline product was filtered; 76·8 g (72%), m.p. 123—125°C (aqueous ethanol). Patent[8] gives for the product of this reaction in tetrahydrofuran a m.p. of 114—116°C. IR spectrum: 852 (2 vicinal aromatic C—H), 882 (isolated aromatic C—H), 1040 (C—OH), 1143 and 1320 (CF_3), 1672 (NCOOR), 3390 cm^{-1} (OH). NMR spectrum: δ 7·55—8·10 (m, 3 H, aromatic protons), 4·15 (q, $J = 7{\cdot}0$ Hz, 2 H, CH_2OCO), 3·00—4·20 (m, 4 H, CH_2NCH_2), 2·90 (s, disappears on deuteration, 1 H, OH), 1·65—2·20 (m, 4 H, CH_2—C—CH_2 in the ring), 1·25 (t, $J = 7{\cdot}0$ Hz, 3 H, C—CH_3). For $C_{15}H_{17}ClF_3NO_3$ (351·8) calculated: 51·22% C, 4·87% H, 10·08% Cl, 3·98% N; found: 51·30% C, 5·04% H, 10·24% Cl, 4·14% N.

4-(3-Trifluoromethyl-4-chlorophenyl)-4-piperidinol (*XI*)

A mixture of 200 g carbamate *XX*, 165 g KOH and 235 ml ethanol was refluxed for 2 h under stirring (a 120°C bath). After cooling it was diluted with 1 500 ml water and extracted with chloroform. The extract was dried, filtered with charcoal and evaporated. A total of 153 g (96%) residue was obtained; this was recrystallized from a mixture of 500 ml benzene and 250 ml light petroleum: 142 g (89%), m.p. 139—142°C. Patent[8] reports for the product of hydrolysis of carbamate *XX* a m.p. of 134—135·5°C. IR spectrum: 815 (2 vicinal aromatic C—H), 893 (isolated aromatic C—H), 1140, 1155 (R_3C—OH and CF_3), 1185, 1320 (CF_3), 3120 and 3320 (NH), 3420 cm^{-1} (OH). For $C_{12}H_{13}ClF_3NO$ (279·7) calculated: 51·53% C, 4·68% H, 12·69% Cl, 5·01% N; found: 51·89% C, 4·84% H, 12·77% Cl, 5·16% N.

8-[4,4-Bis(4-fluorophenyl)-3-butene-1-yl]-1,4-dioxa-8-azaspiro-[4,5]decane (*XXXVII*)

Anhydrous powdery $CaCl_2$ (0·9 g) was added to a solution of 2·0 g hydrochloride of base *XIV* in 50 ml chloroform and the mixture was saturated for 15 min with anhydrous HCl. After 2 h of stirring at room temperature it was left overnight, filtered and the filtrate was evaporated. The residue crystallized after mixing with a small amount of ether: 1·85 g, m.p. 176—179°C (acetone–ether). According to analysis we are dealing here with a hydrochloride-hemihydrate. UV spectrum (methanol): λ_{max} 228 nm ($\log \varepsilon$ 4·10), 251 nm (4·15). IR spectrum (Nujol): 840 (2 vicinal aromatic C—H), 1160 and 1220 (C—O—C in a ring), 1502, 1510, 1600 (Ar), 1645 (CH=C), 2400 and 2580 (NH^+), 3170 cm^{-1} (H_2O). For $C_{23}H_{27}ClF_2NO_{2,5}$ (430·9) calculated: 64·10% C, 6·32% H, 8·23% Cl, 3·25% N; found: 64·45% C, 6·44% H, 8·34% Cl, 3·28% N. The base (oil) was liberated from the hydrochloride in the usual way and the NMR spectrum was recorded: δ 6·80—7·50 (m, 8 H, aromatic protons), 6·00 (t, $J = 6{\cdot}0$ Hz, 1 H, C=CH), 3·90 (s, 4 H, OCH_2CH_2O), 2·70 [m, 8 H, $CH_2CH_2N(CH_2—)_2$], 1·87 (t, $J = 6{\cdot}0$ Hz, 4 H, CH_2—C—CH_2 in the ring).

1-[4,4-Bis(4-fluorophenyl)-3-buten-1-yl]-4-piperidone (*XXXVIII*)

A mixture of 4·75 g hydrochloride of base *XIV*, 100 ml water and 5 ml concentrated hydrochloric acid was refluxed for 6 h. After cooling, it was made alkaline with a 20% solution of NaOH and extracted with chloroform. By processing the extract, a total of 3·9 g oil was obtained and it was chromatographed on a column of 200 g alumina (activity II). Chloroform was used to elute 3·15 g base which yielded in the usual way 3·69 g hydrogen maleate, m.p. 129—131°C (acetone–ether). NMR spectrum: δ 6·80—7·40 (m, 8 H, aromatic protons), 6·23 (s, CH=CH of maleic acid), 6·00 (t, $J = 8{\cdot}0$ Hz, 1 H, C=CH), 3·00—3·70 [m, 6 H, $N(CH_2—)_3$], 2·40—2·90 (m, 6 H, remaining CH_2 groups). For $C_{25}H_{25}F_2NO_5$ (457·5) calculated: 65·63% C, 5·51% H; found: 65·80% C, 5·53% H.

Base *XXXVIII* yields also a hydrochloride, according to analysis a monohydrate (*cf.* the analogous hydrochloride of amino ketone *II*), m.p. 92—95°C (acetone–ether). For $C_{21}H_{24}ClF_2NO_2$ (395·9) calculated: 63·71% C, 6·11% H, 3·54% N; found: 63·11% C, 6·32% H, 3·79% N.

1-[4,4-Bis(4-fluorophenyl)-3-butene-1-yl]-4-(3-trifluoromethyl-4-chlorophenyl)-4-piperidinol (*XXXVI*)

Reaction of 3·9 g 2-chloro-5-bromobenzotrifluoride (*XXXV*) with 0·36 g Mg in 15 ml tetrahydrofuran led to a Grignard reagent which was combined with a solution of 2·46 g base *XXXVIII* in 10 ml tetrahydrofuran. The mixture was refluxed for 6 h, cooled, diluted with ether and decomposed with a 20% solution of NH_4Cl. The organic phase was separated, dried with K_2CO_3 and evaporated. A total of 4·8 g oil was obtained which was chromatographed on a column of 250 g alumina (activity II). Elution with benzene removed the least polar contaminants. A mixture of benzene and chloroform was applied to elute 0·43 g base *XXXVIII*. On continuation of the chromatography, the same mixture eluted 2·5 g base *XXXVI* which was treated with HCl and ether to yield a *hydrochloride* melting at 175—176·5°C (acetone–ether). IR spectrum: 842 (2 vicinal aromatic C—H), 1133 (C—OH), 1186 and 1326 (CF_3), 1124 (Ar—F), 1476, 1513, 1607 (Ar), 2548 (NH^+), 3280 cm^{-1} (OH). NMR spectrum: δ 11·50 (bs, 1 H, NH^+), 6·80—8·10 (m, 11 H, aromatic protons), 6·04 (*t*, $J = 7{\cdot}0$ Hz, 1 H, C=CH), 5·05 (bs, 1 H, OH), 1·80—3·50 (m, remaining CH_2 groups). For $C_{28}H_{26}Cl_2F_5NO$ (558·4) calculated: 60·22% C, 4·70% H, 12·70% Cl, 2·51% N; found: 60·27% C, 4·93% H, 12·90% Cl, 2·64% N.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-(3-trifluoromethylphenyl)-4-piperidinol (*IV*)

A solution of 0·61 g hydrochloride of base *XXXVI* in 20 ml ethanol was hydrogenated using 1·0 g 20% Pd catalyst on charcoal, until spontaneous cessation of consumption (practically the theoretical amount for 4 H). The mixture was filtered, the filtrate evaporated, the residue was dissolved in acetone and a small fraction of the insoluble substance was removed by filtration. The filtrate was evaporated again, the base was released with a solution of sodium carbonate and extracted with a mixture of ether and benzene. The extract was dried with $MgSO_4$ and evaporated. The oily residue was treated with HCl in ether to yield 0·51 g *hydrochloride*, m.p. 92—94°C (acetone–ether). According to analysis we are dealing here with a monohydrate. For $C_{28}H_{31}ClF_5NO_2$ (544·0) calculated: 61·82% C, 5·74% H, 6·52% Cl, 2·58% N; found: 62·26% C, 5·81% H, 6·89% Cl, 2·67% N. Decomposition of the hydrochloride with a solution of sodium carbonate liberated the base which was isolated by extraction with benzene; m.p. 108—110°C (cyclohexane). IR spectrum: 819 (3 vicinal aromatic C—H), 840 (2 vicinal aromatic C—H), 898 (isolated aromatic C—H), 1122 (C—OH), 1169 and 1330 (CF_3), 1230 (Ar—F), 1510 and 1608 (Ar), 3230 and 3400 cm^{-1} (OH). NMR spectrum: δ 6·80—8·00 (m, 12 H, aromatic protons), 3·88 (t, $J = 7{\cdot}0$ Hz, 1 H, Ar_2CH), 1·95 (s, 1 H, disappears on deuteration, OH), 1·20—2·80 (m, 14 H, CH_2 groups).

For $C_{28}H_{28}F_5NO$ (489·5) calculated: 68·70% C, 5·77% H, 2·86% N; found: 68·44% C, 6·01% H, 2·81% N. In the patents[7] a m.p. of 108°C has been reported for a substance prepared by a different procedure.

1-Ethoxycarbonyl-4-(3-trifluoromethylphenyl)-4-piperidinol (*XXI*)

Reaction of 1·2 g Mg with 12·8 g 3-bromobenzotrifluoride[24] (b.p. 152—155°C) in 40 ml ether yielded a Grignard reagent which was processed by a reaction with a solution of 7·0 g carbamate *XIX* in 40 ml ether (similarly to the preparation of *XX*). A total of 12·6 g (79%) crude product was obtained which crystallized from ethanol and had then a m.p. of 151—153°C. IR spectrum: 812 (3 vicinal aromatic C—H), 915 (isolated aromatic C—H), 1103 (C—OH), 1170 and 1335 (CF_3), 1492 (Ar), 1670 (NCOOR), 3385 cm^{-1} (OH). NMR spectrum: δ 7·50—8·00 (m, 4 H, aromatic protons), 4·12 (q, J = 7·0 Hz, 2 H, CH_2OCO), 3·30 and 4·10 (2 m, 4 H, CH_2NCH_2), 2·80 (s, disappears on deuteration, 1 H, OH), 1·50—2·30 (m, 4 H, CH_2—C—CH_2 in the ring), 1·25 (t, J = 7·0 Hz, 3 H, C—CH_3). For $C_{15}H_{18}F_3NO_3$ (317·3) calculated: 56·78% C, 5·72% H; found: 56·63% C, 5·56% H.

4-(3-Trifluoromethylphenyl)-4-piperidinol (*XIII*)

Carbamate *XXI* (6·50 g) was hydrolyzed with the aid of 3·5 g KOH in 6 ml ethanol similarly as when preparing *XI*. A total of 3·42 g was obtained which crystallized from a mixture of benzene and light petroleum, m.p. 96—97°C. IR spectrum (Nujol): 794 and 805 (3 vicinal aromatic C—H), 880 (isolated aromatic C—H), 1030 (C—OH), 1120, 1165, 1340 (CF_3), 1570, 1598 (Ar), 3160 cm^{-1} (OH, NH). For $C_{12}H_{14}F_3NO$ (245·2) calculated: 58·77% C, 5·76% H; found: 59·09% C, 5·62% H. *Hydrochloride*, m.p. 176—177°C (ethanol–ether). For $C_{12}H_{15}$·ClF_3NO (281·7) calculated: 51·16% C, 5·37% H, 12·59% Cl; found: 51·04% C, 5·03% H, 12·81% Cl. Patents[22,23] give for the hydrochloride of base *XIII* obtained by hydrogenolysis of the benzyl derivative a m.p. of 168·5—169·5°C (ref.[22]) and 170—172°C (ref.[23]).

4,4-Bis(4-fluorophenyl)-3-ethoxycarbonyl-3-butenic Acid (*XXXII*)

A mixture of 26·1 g diethyl succinate and 10·9 g 4,4′-difluorobenzophenone[9] was combined under stirring with 2·4 g NaH and then with 8 drops of ethanol. After a vigorous reaction the mixture was diluted with 25 ml ether and stirred for 6 h at room temperature. After diluting with further 50 ml ether a mixture of 50 ml acetic acid and 50 ml water was added dropwise. From the ether layer the product was extracted with 300 ml 5% solution of $NaHCO_3$, from the alkaline solution it was liberated with dilute hydrochloric acid and extracted with ether. On drying and evaporating the extract a residue was obtained which was recrystallized from a mixture of benzene and light petroleum: 8·1 g (47%), m.p. 116—117°C. UV spectrum (methanol): λ_{max} 225 nm (log ε 4·16), 268 nm (4·00). IR spectrum (Nujol): 848 (2 vicinal aromatic C—H), 940 (COOH), 1100 (Ar—F), 1225 and 1327 (C—O), 1508, 1605 (Ar), 1696 (COOH), 1715 (COOR), 3000 cm^{-1} (COOH). NMR spectrum: δ 11·30 (bs, disappears on deuteration, 1 H, COOH), 6·90—7·40 (m, 8 H, aromatic protons), 4·00 (q, J = 8·0 Hz, 2 H, $COOCH_2$—), 3·50 (s, 2 H, CH_2COO), 0·92 (t, J 8·0 Hz, 3 H, C—CH_3). For $C_{19}H_{16}F_2O_4$ (346·3) calculated: 65·89% C, 4·66% H; found: 65·86% C, 4·43% H.

2-[Bis(4-fluorophenyl)methylene]butanedioic Acid (*XXXIII*)

A mixture of 31·7 g acid *XXXII* in 115 ml ethanol and 15·6 g KOH in 115 ml water was refluxed for 1 h. After evaporation of ethanol the residue was diluted with water, the solution was filtered

with charcoal and the filtrate made acid with hydrochloric acid. Filtration and drying yielded 22·1 g (76%) product which was recrystallized from a mixture of benzene and methanol: m.p. 178—180°C (under decomposition). UV spectrum (methanol): λ_{max} 223 nm (log ε 4·17), 276 nm (4·0). IR spectrum: 843 (2 vicinal aromatic C—H), 927 (COOH), 1160 (Ar-F), 1227 (C—O), 1508, 1605 (Ar), 1680 (C=C—COOH), 1710 (CH_2COOH), 2560, 2700 and 3020 cm^{-1} (COOH). NMR spectrum: (CD_3SOCD_3): δ 12·50 (bs, 2 H, 2 COOH), 7·00—7·50 (m, 8 H, aromatic protons), 3·21 (s, 2 H, CH_2). For $C_{17}H_{12}F_2O_4$ (318·3) calculated: 64·15% C, 3·80% H; found: 64·05% C, 3·92% H.

4,4-Bis(4-fluorophenyl)-3-butenic Acid (*XXXIV*)

A. A mixture of 8·0 g ester-acid *XXXII*, 72 ml 48% hydrobromic acid, 110 ml acetic acid and 40 ml water was refluxed for 5 h (bath temperature of 150—160°C), evaporated at reduced pressure, the residue diluted with water and extracted with ether. From the ether solution the product was extracted with 300 ml 5% solution of K_2CO_3, the alkaline solution was filtered with charcoal and made acid with hydrochloric acid. The separated oil was extracted with ether; the residue weighed 5·1 g. After dissolving in benzene with an addition of light petroleum the acid *XXXIV* was obtained in an amount of 2·1 g (33%), m.p. 105—106°C (cyclohexane). UV spectrum (ethanol): λ_{max} 228 nm (log ε 4·42), 251 nm (4·75), 281 nm (4·15). IR spectrum ($CHCl_3$): 845 (2 vicinal aromatic C—H), 940, 1238 (COOH), 1510, 1598 (Ar), 1705 cm^{-1} (COOH). NMR spectrum: δ 11·20 (bs, disappears on deuteration, 1 H, COOH), 6·80—7·50 (m, 8 H, aromatic protons), 6·20 (t, J = 8·0 Hz, 1 H, C=CH), 3·18 (d, J = 8·0 Hz, 2 H, CH_2COO). For $C_{16}H_{12}F_2O_2$ (274·3) calculated: 70·06% C, 4·41% H; found: 69·82% C, 4·45% H.

B. A mixture of 18·4 g diacid *XXXIII*, 185 ml 48% hydrobromic acid, 270 ml acetic acid and 100 ml water was refluxed for 5 h and processed as under *A*. The acid was obtained in a 5·3 g (34%) yield, m.p. 105—106°C (cyclohexane) and is identical with the product prepared under *A*.

Ethyl 3-(4-fluorobenzoyl)propionate (*XXVII*)

During crystallization of crude 3-(4-fluorobenzoyl)propionic acid[30] (*XXVI*) (it was not completely freed of hydrogen chloride by washing) from ethanol ethyl ester was formed: m.p. 46—49°C (benzene–light petroleum). IR spectrum: 840 (2 vicinal aromatic C—H), 1230 (COOR), 1480, 1520 and 1595 (Ar), 1680 (ArCO), 1720 cm^{-1} (COOR). NMR spectrum: δ 7·95 (dd, J = 9·0; 5·0 Hz, 2 H, aromatic protons in *o*-position with respect to the keto group), 7·04 (t, J = 9·0 Hz, 2 H, aromatic protons in *o*-positions to fluorine), 4·10 (q, J = 7·0 Hz, 2 H, $COOCH_2$), 3·22 (t, J = 6·0 Hz, 2 H, $COCH_2$), 2·69 (t, J = 6·0 Hz, 2 H, CH_2COO), 1·22 (t, J = 7·0 Hz, 3 H, C—CH_3). For $C_{12}H_{13}FO_3$ (224·2) calculated: 64·27% C, 5·84% H; found: 64·56% C, 5·96% H.

4-(4-Fluorophenyl)butyrolactone (*XLI*)

A solution of 4·0 g $NaBH_4$ in 80 ml ethanol was added dropwise under stirring to a solution of 10·0 g 3-(4-fluorobenzoyl)propionic acid[29-31] (*XXVI*, m.p. 104—106°C) in 60 ml ethanol. The mixture was stirred for 4 h and, after standing overnight, it was decomposed with dilute hydrochloric acid. The ethanol was evaporated, the residue dissolved in chloroform, the solution dried with Na_2SO_4 and distilled under reduced pressure: 8·1 g (88%), b.p. 108°C/0·05 Torr. In larger batches the yields were as high as 94% and the product was practically homogeneous in gas chromatography. IR spectrum ($CHCl_3$): 838 (2 vicinal aromatic C—H), 1140, 1158 and 1175 (C—O), 1513 and 1605 (Ar), 1770 cm^{-1} (CO in a five-membered lactone ring). NMR spectrum: δ 6·90—7·50 (m, 4 H, aromatic protons), 5·45 (m, 1 H, ArCH), 1·70—3·70 (m, 4 H, CH_2CH_2). For $C_{10}H_9FO_2$ (180·2) calculated: 66·66% C, 5·03% H; found: 66·95% C, 4·70% H.

4,4-Bis(4-fluorophenyl)butyric Acid (*VIII*)

A. A solution of 6·9 g acid *XXXIV* in 20 ml ethanol was hydrogenated on Adams'catalyst (from 0·2 g PtO_2) at room temperature and under normal pressure. After about 1 h (theoretical uptake of hydrogen) hydrogenation was stopped, the mixture was filtered and the filtrate evaporated. A total of 6·9 g oily acid *VIII* was obtained. A mixture of 2·1 g acid and 2 ml $SOCl_2$ was refluxed for 2 h on a boiling-water bath, diluted with benzene and the volatile fractions were evaporated at reduced pressure. The residue (2·2 g) is the oily chloride *IX*, which does not crystallize and cannot be purified by distillation. A solution of 2·2 g chloride *IX* in 10 ml acetone was added dropwise under stirring to 50 ml concentrated aqueous ammonia. The precipitated product was filtered, dissolved in chloroform, the solution was washed with 10% KOH, dried with K_2CO_3 and evaporated. A total of 1·9 g (92%) 4,4-bis(4-fluorophenyl)butyramide (*X*) was obtained, m.p. 90–93°C (benzene–cyclohexane). IR spectrum ($CHCl_3$): 837 (2 vicinal aromatic C—H), 1515, 1603 (Ar), 1685 ($CONH_2$), 3410 and 3530 cm^{-1} (NH_2). NMR spectrum: δ 6·80–7·50 (m, 8 H, aromatic protons), 6·10 and 5·52 (2 bs, 2 H, $CONH_2$), 3·90 (t, $J = 6·5$ Hz, 1 H, Ar_2CH), 2·15 (m, 4 H, CH_2CH_2). For $C_{16}H_{15}F_2NO$ (275·3) calculated: 69·80% C, 5·49% H; found: 69·76% C, 5·36% H.

B. A solution of 7·0 g lactone *XLI* in 35 ml fluorobenzene was combined with small parts of 6·2 g ground $AlCl_3$ under stirring over a period of 15 min. The mixture was stirred for 2 h at room temperature, left to stand overnight, diluted with chloroform and decomposed with 70 ml ice-cold diluted (1 : 2) hydrochloric acid. The organic phase was separated, washed with water, dried with Na_2SO_4 and the volatile fractions were evaporated at reduced pressure. An oily acid was obtained in a 99% yield (10·6 g) and was distilled: b.p. 167°C/0·05 Torr, during redistillation 184°C/1 Torr. IR spectrum (in a 5% solution in chloroform in a 0·1 mm NaCl cuvette or in a 10% solution in chloroform in a 1·0 mm NaCl cuvette): 837 (2 vicinal aromatic C—H), 1510 and 1605 (Ar), 1890 cm^{-1}. NMR spectrum: δ 10·85 (bs, disappears on deuteration, 1 H, COOH), 7·14 (dd, $J = 9·0$; 5·0 Hz, 4 H, aromatic protons in *m*-positions toward fluorine), 6·89 (t, $J = 10$ Hz, 4 H, aromatic protons in *o*-positions toward fluorine), 3·84 (m, 1 H, Ar_2CH), 2·30 (m, 4 H, CH_2CH_2). For $C_{16}H_{14}F_2O_2$ (276·3) calculated: 69·56% C, 5·11% H; found: 69·45% C, 5·27% H. The acid *VIII* crystallized from a mixture of benzene and light petroleum and melts at 65–67°C. The crystalline product does not yield useful analytical values (found: 70·44% C, 5·36% H).

1-[4,4-Bis(4-fluorophenyl)butyryl]-4-(3-trifluoromethyl-4-chlorophenyl)-4-piperidinol (*XL*)

A. A solution of 1·0 g crude chloride *IX* in 2 ml benzene was added to a solution of 0·65 g base *XI* in 2 ml pyridine and the mixture was left for 2 h at room temperature. After dilution with benzene it was washed with water, further with 5% hydrochloric acid, 5% NaOH and again with water, dried with K_2CO_3 and benzene was evaporated. The residue (0·85 g) was chromatographed on a column of 25 g alumina (activity II). After separation of the less polar fractions by elution with benzene the desired product was eluted with chloroform (0·4 g). It crystallizes from benzene and melts at 141–143°C. IR spectrum: 827 (2 vicinal aromatic C—H), 914 (isolated aromatic C—H), 1135 and 1150 (C—OH), 1177 and 1322 (CF_3), 1222 (Ar—F), 1509 (Ar), 1625 cm^{-1} ($CONR_2$). NMR spectrum: δ 6·90–8·10 (m, 11 H, aromatic protons), 2·89 (s, disappears on deuteration, 1 H, OH), 1·80 (m, 4 H, CH_2—C—CH_2 in the ring), 2·20–4·50 (indistinguishable m, 9 H, remaining CH_2 and CH). For $C_{28}H_{25}ClF_5NO_2$ (537·9) calculated: 62·51% C, 4·68% H, 6·59% Cl, 2·60% N; found: 62·76% C, 4·71% H, 6·66% Cl, 2·54% N.

B. A solution of 7·5 g acid *VIII* and 2·74 g triethylamine in 30 ml chloroform was cooled with ice and water and 2·9 g ethyl chloroformate was added dropwise under stirring. The mix-

ture was stirred under cooling for 45 min and then a solution of 7·6 g base *XI* in 25 ml chloroform was added to it dropwise. The mixture was stirred for 1·5 g at room temperature, washed with water, 10% NaOH, 5% hydrochloric acid and water, dried with K_2CO_3 and evaporated. The residue (13·7 g, 94%) is a chromatographically uniform product which crystallizes from a mixture of benzene and light petroleum and melts at 139—142°C. It is identical with the product obtained under *A*.

Using procedure *B*, the acid, which contained not only the *p,p'*-isomer *VIII* but also the isomeric *p,o'*-acid (*XLII*), yielded the oily amide which crystallized after prolonged standing from a benzene–light petroleum solution. After repeated crystallization from benzene its m.p. settled at 116 to 118°C. Although it follows from the NMR spectrum that we are dealing here with a mixture, the strong band in the IR spectrum at 760 cm^{-1} (4 vicinal aromatic C—H) shows that the major component is 1-[4-(4-*fluorophenyl*)-4-(2-*fluorophenyl*)*butyryl*]-4-(3-*trifluoromethyl*-4-*chlorophenyl*)-4-*piperidinol* (XLIII). For $C_{28}H_{25}ClF_5NO_2$ (537·9) calculated: 62·51% C, 4·68% H, 6·59% Cl, 2·60% N; found: 62·65% C, 4·70% H, 6·73% Cl, 2·62% N.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-(3-trifluoromethyl-4-chlorophenyl)-4-piperidinol (*I*)

A. Reaction of 10·4 g 2-chloro-5-bromobenzotrifluoride (*XXXV*) with 0·98 g Mg in 30 ml tetrahydrofuran led to a solution of a Grignard reagent to which a solution of 9·2 g ketone *II* in 25 ml tetrahydrofuran was added. The mixture was refluxed for 5 h, a greater part of tetrahydrofuran was evaporated, 50 ml toluene was added and the mixture was refluxed for 13 h. After cooling, it was decomposed with a solution of NH_4Cl, diluted with benzene, the organic layer was washed with water, dried with K_2CO_3 and evaporated. A total of 15 g oil was obtained and chromatographed on a column of 550 g alumina (activity II). After separating the less polar contaminants the base was eluted with chloroform, m.p. 67—70°C (light petroleum). IR spectrum ($CHCl_3$): 833 (2 vicinal aromatic C—H), 900 (isolated aromatic C—H), 1 140 (C—OH), 1 508, 1 572, 1 600 (Ar), 2 770 and 2 810 (NCH_2), 3 590 cm^{-1} (OH). NMR spectrum: ϑ 6·80—8·00 (m, 11 H, aromatic protons), 3·88 (t, $J = 8·0$ Hz, 1 H, Ar_2CH), 1·40—2·80 (m, 14 H, all CH_2 groups), 1·92 (s, disappears on deuteration, OH). For $C_{28}H_{27}ClF_5NO$ (524·0) calculated: 64·18% C, 5·19% H, 6·77% Cl, 2·67% N; found: 64·50% C, 5·41% H, 6·98% Cl, 2·66% N.

A *hydrochloride* was obtained from the ether solution of the base with an ether solution of HCl, m.p. 166—168°C (acetone–ether). For $C_{28}H_{28}Cl_2F_5NO$ (560·5) calculated: 60·01% C, 5·04% H, 12·65% Cl, 2·50% N; found: 59·97% C, 5·18% H, 12·69% Cl, 2·53% N. Patents[7] give a m.p. of 166°C for the hydrochloride.

B. A mixture of 6·0 g base *XI*, 11·6 g crude iodide *VII*, 7·2 g K_2CO_3 and 40 ml dimethylformamide was refluxed for 1·5 h under stirring in a 120—140°C bath. After cooling, the mixture was dissolved with water and extracted with benzene. The extract was shaken with dilute hydrochloric acid. The benzene phase was removed and the two lower phases were made alkaline with 5M-NaOH. The base was extracted with benzene, the extract was dried and evaporated. The residue (13·1 g) was chromatographed on a column of 440 g alumina (activity II). Chloroform was used to elute 6·5 g base *I* which crystallizes from cyclohexane in the form of a solvate containing 0·5 molecule of cyclohexane; m.p. 82—84°C. For $C_{31}H_{33}ClF_5NO$ (566·0) calculated: 65·77% C, 5·88% H, 2·47% N; found: 66·04% C, 6·26% H, 2·44% N. The presence of cyclohexane was demonstrated also by the NMR spectrum. The hydrochloride prepared from this base melts at 166—168°C (acetone–ether) and is identical with the product obtained under *A*.

C. Amide *XI* (5·0 g) was added in parts to 0·44 g $LiAlH_4$ in 70 ml ether and the mixture was refluxed for 4 h. After cooling, it was decomposed by adding 0·4 ml water, 0·5 ml 20% solution of NaOH and 1·3 ml water, the mixture was filtered and the solid was washed with ether.

The filtrate was dried with K_2CO_3 and evaporated. The residue (4·6 g, 90%) represents the almost pure *I* which crystallizes from cyclohexane in the form of the reported solvate melting at 82—84°C. *Hydrochloride* m.p. 167—168·5°C (ethanol–ether). For $C_{28}H_{28}Cl_2F_5NO$ (560·5) calculated: 60·01% C, 5·04% H, 12·65% Cl, 2·50% N; found: 59·80% C, 5·20% H, 12·63% Cl, 2·63% N.

When preparing a greater batch of *I* according to C, both the base and the hydrochloride were shown by chromatography on a thin layer of alumina to contain a more polar contaminant which could not be removed by crystallization of either the base or the hydrochloride. Therefore, chromatography on a column of alumina (activity II) was carried out. Benzene eluted only the pure base *I*. Chloroform eluted the remaining bases which were rechromatographed by the same procedure. Finally, some 2% (per weight of starting base) of a compound melting at 140—142°C (benzene–light petroleum) were eluted and identified as 1-*methyl*-4-(3-*trifluoromethyl*-4-*chlorophenyl*)-4-*piperidinol* (XVII). For $C_{13}H_{15}ClF_3NO$ (293·7) calculated: 53·16% C, 5·15% H, 12·07% Cl, 4·77% N, 19·41% F; found: 53·37% C, 5·20% H, 11·98% Cl, 4·70% N, 19·14% F.

1-[4-(4-Fluorophenyl)-4-(2-fluorophenyl)butyl]-4-(3-trifluoromethyl-4-chlorophenyl)-4-piperidinol (*XLIV*)

A mixture of amides *XL* and *XLIII* (10·0 g) was reduced with $LiAlH_4$ in ether similarly to the procedure under C above. A total of 5·0 g mixture of bases melting at 60—90°C was obtained. The mixture was converted to the *hydrochloride* which was repeatedly crystallized from a mixture of ethanol and ether and led to a product melting at 192—194°C, the melting point being unchanged on further crystallization. The IR spectrum corresponds to isomer *XLIV*: intense band at 754 (4 vicinal aromatic C—H), 836 (2 vicinal aromatic C—H), 866 (isolated aromatic C—H), 1135 (C—OH), 1187, 1316 (Ar—CF_3), 1585, 1606 (Ar), 2555 (NH^+), 2935 and 3270 cm^{-1} (OH). For $C_{28}H_{28}Cl_2F_5NO$ (560·5) calculated: 60·01% C, 5·04% H, 12·65% Cl, 16·95% F, 2·50% N; found: 60·36% C, 4·98% H, 12·90% Cl, 17·21% F, 2·70% N.

1,1-Bis(4-fluorophenyl)-4-piperidinobutanol (*XV*)

Reaction of 25·1 g 3-piperidinopropyl chloride[34] (b.p. 78°C/7 Torr) with 4·0 g Mg in 50 ml tetrahydrofuran (iodine and ethylene bromide were used to trigger the reaction) led to a solution of Grignard's reagent. After cooling to room temperature, a solution of 17·2 g 4,4'-difluorobenzophenone[9] in 50 ml tetrahydrofuran was added dropwise over a period of 30 min and the mixture was refluxed for 2 h. After cooling, a solution of 20 g NH_4Cl in 115 ml water was slowly added and, after thorough mixing, it was extracted with benzene. The extract was dried with Na_2SO_4 and evaporated. The residue was mixed with light petroleum and the base was filtered; 21·3 g (80%), m.p. 81·5—82·5°C (light petroleum). IR spectrum (Nujol): 840 (2 vicinal aromatic C—H), 1080 (Ar—F), 1150 (C—OH), 1220 (C—O—C), 1500, 1595 (Ar), 3040 cm^{-1} (OH). NMR spectrum: δ 9·15 (bs, disappears on deuteration, 1 H, OH), 6·70—7·60 (m, 8 H, aromatic protons), 2·25 (m, 8 H, CH_2—C—O and $N(CH_2—)_3$), 1·48 (m, 8 H, remaining CH_2 groups). For $C_{21}H_{25}F_2NO$ (345·4) calculated: 73·02% C, 7·29% H; found: 73·45% C, 7·29% H.

Hydrochloride, m.p. 198°C (ethanol–ether). For $C_{21}H_{26}ClF_2NO$ (381·9) calculated: 66·03% C, 6·86% H, 9·28% Cl; found: 65·89% C, 6·57% H, 9·20% Cl.

1,1-Bis(4-fluorophenyl)-4-piperidinobutene (*XXXIX*)

A mixture of 3·0 g base *XV* and 50 ml 35% sulfuric acid was refluxed for 6 h. After cooling, it was diluted with water, made alkaline with 2·5M-NaOH and the base was isolated by extraction with benzene. After evaporation, the residue was converted by neutralization with maleic acid in etha-

nol and an addition of ether to *hydrogen maleate*; 3·3 g (86%), m.p. 163·5—164·5°C (ethanol–ether). For $C_{25}H_{27}F_2NO_4$ (443·5) calculated: 67·71% C, 6·14% H; found: 67·89% C, 6·08% H.

1,1-Bis(4-fluorophenyl)-4-piperidinobutane (*V*)

A. A mixture of 3·45 g base *XV*, 12·5 ml acetic acid, 12·5 ml 56% hydroiodic acid and 1·5 g red phosphorus was refluxed for 6 h. It was filtered while hot and the filtrate crystallized to 2·6 g *hydroiodide*, m.p. 185—186°C (ethanol–ether). NMR spectrum: δ 9·70 (bs, 1 H, NH^+), 6·70 to 7·60 (m, 8 H, aromatic protons), 3·98 (t, 1 H, Ar_2CH), 3·40 (t, 2 H, CH_2N in the chain), c. 3·00 (m, 4 H, CH_2NCH_2 in the ring), c. 2·00 (m, 10 H, remaining CH_2 groups). For $C_{21}H_{26}F_2IN$ (457·3) calculated: 55·14% C, 5·73% H, 27·75% I; found: 55·40% C, 5·72% H, 28·00% I.

Decomposition of the hydroiodide with 5M-NaOH yielded the base which was isolated by extraction with benzene. Then it was converted in the usual way to the hydrochloride, m.p. 168 to 170°C (ethanol–ether). For $C_{21}H_{26}ClF_2N$ (365·9) calculated: 68·93% C, 7·16% H, 9·69% Cl, 3·83% N; found: 68·95% C, 7·28% H, 9·68% Cl, 3·75% N.

B. A mixture of 15·3 g crude iodide *VII* and 10·0 g piperidine was refluxed under stirring for 4 h in a 120°C bath. After cooling, it was diluted with 100 ml water and extracted with benzene. From the benzene layer the basic fraction was extracted with dilute hydrochloric acid whence the base was liberated by treatment with concentrated aqueous ammonia. Extraction with ether yielded 10·5 g oil which was chromatographed on a column of 250 g alumina (activity II). Benzene eluted 8·0 g of a base which was treated with 57% hydroiodic acid in ethanol and converted to the *hydroiodide*, m.p. 185—187°C (ethanol). For $C_{21}H_{26}F_2IN$ (457·3) calculated: 55·14% C, 5·73% H, 27·75% I; found: 54·85% C, 5·57% H, 27·93% I. The compound is identical with the hydroiodide prepared under *A*.

1-(3-Chloropropyl)-4-(2-tolyl)piperazine (*XLV*)

A solution of 14 g $SOCl_2$ in 20 ml benzene was added dropwise under cooling to a solution of 23·1 g 1-(3-hydroxypropyl)-4-(2-tolyl)piperazine[35] (m.p. 97—100°C) in 75 ml benzene. The mixture was stirred for 30 min at room temperature and refluxed for 4 h. After cooling, the precipitated *dihydrochloride* was filtered and washed with ether; 26·0 g (90%), m.p. 217—218°C under decomposition (ethanol–ether). For $C_{14}H_{23}Cl_3N_2$ (325·7) calculated: 51·62% C, 7·13% H, 8·60% N; found: 51·60% C, 7·15% H, 8·13% N. Decomposition of the hydrochloride with 5M-NaOH and extraction with ether led to a base boiling at 140°C/0·9 Torr. Ref.[39] shows for a base prepared from 1-(2-tolyl)piperazine and 1-bromo-3-chloropropane a b.p. 143—151°C/1·2 Torr

1-(n-Propyl)-4-(2-tolyl)piperazine (*XLVI*)

Reaction of 10·3 g chloride *XLV* with 1·1 g Mg in 30 ml tetrahydrofuran led to a Grignard reagent to which a solution of 6·0 g 4,4'-difluorobenzophenone[9] in 25 ml tetrahydrofuran was added dropwise. The mixture was refluxed for 5 h, cooled, and a solution of 17·5 g NH_4Cl in 100 ml water was added and the mixture was extracted with benzene. The basic fraction (5·8 g) was isolated in the usual way and, on treatment with maleic acid in ethanol and an addition of ether it yielded as the single product the *maleate* of base *XLVI*, m.p. 165—169°C (ethanol–ether). For $C_{18}H_{26}N_2O_4$ (334·4) calculated: 64·65% C, 7·84% H, 8·38% N; found: 64·95% C, 8·06% H, 7·97% N.

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Note added in proof:

During the printing of this paper a patent application[40] appeared describing the synthesis of *I via* the amide *XL*, giving, however, less experimental data than the present paper.