α-(4-TOLYL)DOPAMINE, DERIVATIVES AND ANALOGUES; SYNTHESIS AND PHARMACOLOGICAL SCREENING*

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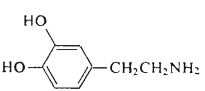
Received October 15th, 1982

The ketone *XIII*, obtained by Friedel–Crafts reaction of toluene with homoveratroyl chloride, was converted by the Leuckart reaction to the formamido derivative *IXb* which was used as the starting product for the synthesis of amines *IIIb*–*Vb*. Reduction of the ketone *XIII* gave the alcohol *XVI* which was treated with hydrogen chloride and afforded the chloro compound *XVII*. Its substitution reactions with 1-methylpiperazine, 1-(2-hydroxyethyl)piperazine and 1-phenylpiperazine resulted in the piperazines *VIb*–*VIIIb*. Acylations of the amine *IIIb* with acetic anhydride and homoveratroyl chloride gave the amides *Xb* and *XIb* which, together with the formamide *IXb*, were subjected to the Bischler–Napieralski reaction. 3,4-Dihydroisoquinolines *XXII*–*XXIV* were obtained and reduced to the 1,2,3,4-tetrahydroisoquinolines *XXVb*–*XXVIIb*. Treatment of *XXVIIb* with formaldehyde afforded the berbine derivative *XXVIII*. Demethylation of the amine *IIIb* with hydrobromic acid resulted in the title compound *IIIa*. Similar demethylations of the dimethoxyamines *IVb*–*VIIIb*, *XXVb* and *XXVIb* led to the dihydroxyamines *IVa*–*VIIIa*, *XXVa* and *XXVIa* which are dopamine derivatives. Reaction of *Va* with benzoyl chloride gave the dibenzoate *XXX*. The CNS activities of the compounds prepared are of a low degree. Several of them (*IIIa*–*VIa*, *IIIb*–*Vb*, *XXVb*) show in higher doses signs of central stimulant action but only for compound *IVa* an antireserpine effect was proven. The expected anticataleptic activity was found only in a low degree with compound *VIIIa*; on the contrary, compounds *IIIa* and *XXVa* are procataleptogenic. Some compounds (*IIIa*, *IXb*, *XXVIa*, *XXVIII*) potentiated thiopental. In single cases local anaesthetic, spasmolytic, hypotensive, hypertensive, hypoglycaemic, diuretic and antiarrhythmic effects were observed.

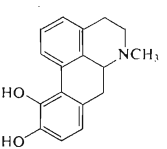
2-(3,4-Dihydroxyphenyl)ethylamine (dopamine, *I*) has a rich pharmacodynamic profile, especially in the central nervous and cardiovascular system. In the brain it is localized in the central dopamine neurons on several types of the dopamine receptors. A lowered dopamine level in some brain areas is evidently in close relation with Parkinson disease. On the other hand, compounds behaving at the receptor sites as dopamine antagonists (neuroleptics) are used as therapeutic agents in psychoses like schizophrenia; there evidently exists some direct relation (not yet completely understood) between the brain dopamine and the pathogenesis of schizophrenia. The orally or parenterally administered dopamine cannot function as a central

* Part CLXXXII in the series Neurotropic and Psychotropic Agents; Part CLXXXI: This Journal *48*, 1187 (1983).

neurotropic agent because it does not penetrate the blood-brain barrier; it is formed in the brain by decarboxylation of 3,4-dihydroxyphenylalanine which is an intermediate in the biotransformation of the amino acids (phenylalanine, tyrosine) to the physiologically important catecholamines. The mentioned defect of dopamine is evidently determined by the excessive hydrophilicity of its molecule. Apomorphine (*II*), which is the first known dopaminomimetic, *i.e.* an agonist for the central dopamine receptors, is a proof of the correctness of this assumption: its molecule is significantly more lipophilic due to the presence of further six aromatic and three aliphatic hydrocarbon members and apomorphine does penetrate the blocd-brain barrier. The design of new central neurotropic agents, starting from the dopamine structure, became in recent years an important area of medicinal chemistry and the development in this line was described in several review articles[1–6] and in one prognostic study[7]. The synthesis of new compounds of this type is being undertaken with the hope for finding new antiparkinsonic agents (dopamine agonists) or new antipsychotic neuroleptics (dopamine antagonists). The molecules of the substances synthesized, when compared with dopamine (*I*), show mostly a shifted balance between the hydrophilic and lipophilic fragments in the direction of increased lipophilicity.



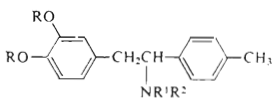
I



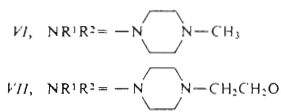
II

In the investigation presently described we attempted at preparing new dopaminergic substances derived from dopamine by the introduction of a hydrophobic aromatic residue to the dopamine α-carbon, *i.e.* the carbon atom carrying the amino group. The target compounds were thus in the first line the title compound *IIIa* and its N-methyl derivatives *IVa* and *Va*. The synthetic study started from the Friedel–Crafts reactions of homoveratroyl chloride[8] with benzene, toluene, anisole and thioanisole in the presence of aluminium chloride. In the first two cases the aromatic hydrocarbon was used at the same time as the reaction medium. While the reaction with benzene produced the ketone *XII* in a low yield and its isolation succeeded only after chromatography of the crude product, a similar reaction with toluene afforded smoothly the crystalline ketone *XIII* in a yield of 72% (its oxime was prepared for characterization). Reactions with anisole and thioanisole were carried out in dichloromethane and their course differed again greatly. While the reaction with anisole afforded the ketone *XIV* in high yield, a heterogeneous product was

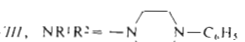
obtained from thioanisole, from which only by chromatography could the ketone *XV* be isolated in a very poor yield. The structure of the ketones *XII*–*XV* was confirmed by means of the ^{1}H NMR spectra. The easily accessible 2-(3,4-dimethoxyphenyl)--4'-methylacetophenone (*XIII*) was chosen as the starting compound for the prevailing part of the present study.



III, $R^1 = R^2 = H$
IV, $R^1 = H$, $R^2 = CH_3$
V, $R^1 = R^2 = CH_3$

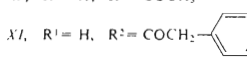


VIII, $NR^1R^2 =$



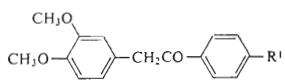
IX, $R^1 = H$, $R^2 = CHO$
X, $R^1 = H$, $R^2 = COCH_3$

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



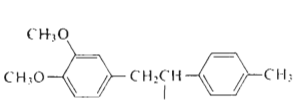
In Formulae *III*–*XI* and *XXV*–*XXVII*: *a*, R = H; *b*, R = CH_3

Heating the ketone *XIII* with formamide and formic acid to 170–180°C (Leuckar reaction[9]) afforded in a high yield the formamide derivative *IXb* which was heated with a concentrated potassium hydroxide solution in ethanol and gave 2-(3,4-dimethoxyphenyl)-1-(4-tolyl)ethylamine (*IIIb*). The methylamino derivative *IVb* was obtained by reduction of the formamide *IXb* with lithium aluminium hydride in ether and the dimethylamino compound *Vb* was prepared from the primary amine *IIIb* by the Eschweiler–Clarke procedure[10,11] by methylation with a boiling mixture of formic acid and aqueous formaldehyde. The oily bases *IIIb*–*Vb* were transformed to crystalline salts. Demethylations of compounds *IIIb*–*Vb* with boiling hydrobromic acid led to hydrobromides of the dopamine derivatives *IIIa*–*Va*. In the case of the title compound *IIIa* the crystalline base has likewise been prepared; its high melting point and IR spectrum indicate the character of an inner salt.

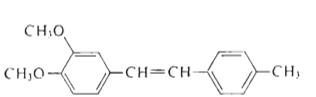


XII, $R^1 = H$
XIII, $R^1 = CH_3$
XIV, $R^1 = OCH_3$
XV, $R^1 = SCH_3$

Reduction of the ketone *XIII* with sodium borohydride in ethanol gave the secondary alcohol *XVI* which was converted by treatment with hydrogen chloride in benzene to the chloro derivative *XVII*. By substitution reactions of this compound with 1-methylpiperazine, 1-(2-hydroxyethyl)piperazine and 1-phenylpiperazine[12] in boiling chloroform the piperazine derivatives *VIb*–*VIIIb* were obtained in yields of 60 to 70%. Elimination proceeded concomitantly with the substitution reactions and its product was isolated in the case of preparation of the amine *VIb* and was identified as (*E*)-3,4-dimethoxy-4'-methylstilbene (*XVIII*). The dimethoxy compounds *VIb* to *VIIIb* were demethylated with boiling hydrobromic acid and the "catecholamines" *VIa*–*VIIIa* were isolated in the form of hydrobromides.



XVI, R^1 = OH
XVII, R^1 = Cl



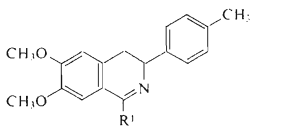
XVIII

The ketone *XIV* was also subjected to the Leuckart reaction[9] and the formamide derivative *XIX* obtained was hydrolyzed with potassium hydroxide to the primary amine *XX*. Its methylation by the Eschweiler–Clarke method[10,11] gave the dimethylamino derivative *XXI*. Attempts at demethylating the trimethoxy-amines *XX* and *XXI* with hydrobromic acid led to mixtures of partially demethylated products and were discontinued.

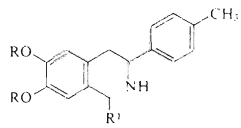
XIX, R^1 = H, R^2 = CHO
XX, R^1 = R^2 = H
XXI, R^1 = R^2 = CH_3

Acylations of the amine *IIIb* with acetic anhydride and homoveratroyl chloride[8] in pyridine, or its mixture with toluene, afforded the amides *Xb* and *XIb*. Together with the formamide derivative *IXb* these amides were cyclized using the Bischler–Napieralski reaction[13] by heating with phosphoryl chloride or its mixture with phosphorus pentoxide to the 3,4-dihydroisoquinoline derivatives *XXII*–*XXIV*; the products were prepared in the form of crystalline bases and were characterized by the ^{1}H NMR spectra. They were then reduced with sodium borohydride in ethanol either as the isolated intermediates or *in situ* to the 1,2,3,4-tetrahydroisoquinolines

XXVb–XXVIIb which were isolated as hydrochlorides. Compound *XXVb* was demethylated without difficulties with boiling hydrobromic acid and the hydrobromide of the dihydroxy base *XXVa* was obtained. With regard to the fact that attempts at demethylating compound *XXVIb* led to a partially demethylated product,



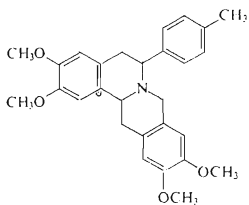
XXII, $R^1 = H$
XXIII, $R^1 = CH_3$
XXIV, $R^1 = CH_2$



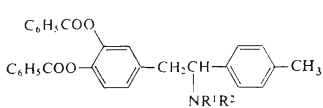
XXV, $R^1 = H$
XXVI, $R^1 = CH_3$
XXVII, $R^1 = CH_2$

compound *XXVIb* was demethylated by treatment with boron tribromide in chloroform at room temperature (method, *cf.*[14]); the reaction mixture was decomposed with ethanol and crystallization of the product from ethanol gave the hydrobromide of the dihydroxy base *XXVIa*.

Compound *XXVIIb* was subjected to the Pictet–Spengler reaction[8,15]: treatment with aqueous formaldehyde in methanol and heating the mixture with hydrochloric acid resulted in the hydrochloride of the berbine derivative *XXVIII*. The base has



XXVIII



XXIX, $R^1 = H$, $R^2 = COC_6H_5$
XXX, $R^1 = R^2 = CH_3$

also been prepared and its ^{1}H NMR spectrum confirmed the identity of the product.

Esterification of the hydroxyl groups of dopamine (*I*) leads to less hydrophilic compounds having the ability to penetrate the blood-brain barrier and having the central dopamine effects[16-19]. This approach was also used in our work. Treatment of compound *IIIa* with benzoyl chloride in pyridine or with benzoyl bromide in trifluoroacetic acid (method[11]) gave the N-benzoyl dibenzoate *XXIX*. Treatment of compound *Va* with benzoyl chloride in pyridine afforded the dibenzoate *XXX* which was isolated and tested as the hydrochloride.

Compounds *IIIab*–*VIIab*, *VIIIa*, *IXb*, *XIX*–*XXI*, *XXVab*, *XXVIab*, *XXVIIb*, *XXVIII* and *XXX* were pharmacologically tested in the form of salts described in the Experimental (with the exception of *IXb* and *XIX*) partly by methods of the general screening, partly by specific psychopharmacological methods oriented in some cases to the desired dopaminergic or potential antiparkinsonic effects (anticataleptic and antioxotremorine activity). In general, the pharmacological effects of the products are rather poor.

The values of acute toxicity in mice (LD_{50}) and the basic doses (D) (doses in mg/kg) used in the screening (intravenous administration) are given: *IIIa*, 75, 15; *IIIb*, 45, 9; *IVa*, 112, 20; *IVb*, 50, 10; *Va*, 20, 4; *Vb* 62, 12; *VIa*, 75, 15; *VIb* 50, 10; *VIIa* 100, 20; *VIIb*, 55, 11; *XX*, 45, 9; *XXI*, 60, 12; *XXVb*, 38, 7; *XXVIa*, 75, 15. Orally administered compounds: *IXb*, >2 500, 300; *XIX*, >2 500, 300; *XXVa*, >500; *XXVIb*, 1 000, 200; *XXVIIb*, >2 500, 300; *XXVIII*, >2 500, 300; *XXX*, >700.

Some of the compounds show a mild central stimulant activity in mice in doses above D (increase of the spontaneous motor activity): *IIIa*, *IIIb*, *IVa*, *IVb*, *Va*, *Vb*, *VIa*, *XX*, *XXVb*. Only compound *IVa* had antireserpine activity in the test of ptosis in mice: a dose of 60 mg/kg *i.v.* showed effect in 70% animals. Compound *VIa* had a mild hyperthermic effect in mice at the dose D. Only compound *VIIIa* in oral doses of 10–50 mg/kg showed a clear anticataleptic action in rats (towards perphenazine catalepsy); in an oral dose of 100 mg/kg it did not influence the oxotremorine tremor in mice. On the other hand, some of the compounds potentiated the cataleptic action of perphenazine (1·5 mg/kg *i.p.*) in rats: *IIIa*, a dose of 25 mg/kg *i.v.* increased the cataleptic effect by 50%; *XXVa*, an oral dose of 25 mg/kg showed a mild perphenazine potentiation; *XXX*, an oral dose of 50 mg/kg did not influence the perphenazine catalepsy. With some compounds, there were signs of central depression. The thiopental sleeping time in mice was prolonged to 200% of the control value by the following doses: *IIIa*, 25 mg/kg *i.p.*; *IXb*, 100–300 *p.o.*; *XIX*, 100–300 *p.o.*; *XXVIa*, 10–15 *i.v.*; *XXVIII*, 100–300 *p.o.* Compound *XXVIII* in oral doses of 10–100 mg/kg had hypothermic effect in rats (decrease of rectal temperature by 1°C). The discoordinating effect in the rotarod test in mice was brought about by compound *IVa* only in subtoxic doses (ED_{50} = 50 mg/kg *i.v.*); *VIIIa*, ED_{50} = = 100 mg/kg *p.o.* Compound *XXVIIb* had some anticonvulsant effect (towards pentetrazole) at the dose D.

Some of the compounds were shown to be effective in tests for peripheral neurotropic, neurovegetative, cardiovascular and other activities. Compounds *XXI* and *XXVb* had local anaesthetic effect at concentrations of 1% in the test of corneal anaesthesia in rabbits. In concentrations of 10 μg/ml compound *VIb* was spasmolytic towards barium chloride and compound *XXI* towards acetylcholine (reduced the contractions of the isolated rat duodenum, elicited by the mentioned spasmogens, by 50%). Compound *Vb* in a dose of 6 mg/kg *i.v.* brought about transient rises of blood pressure in normotensive rats; on the other hand 7·5 mg/kg *i.v.* of the administered compound *XXVIa* had hypotensive effect. Antiarrhythmic effect in rats towards aconitine was shown by three compounds (doses prolonging with statistical significance the latency of ventricular extrasystoles given): *IVa*, 15 *i.v.*; *VIIa*, 2·5 to 10 *i.v.*; *VIIb*, 5–10 *i.v.* Compound *VIIa* (20 mg/kg *i.p.*) was active also towards strophanthine arrhythmias. Compound *IIIb* prolonged the bleeding time in mice in the dose D. Influence on the heart inotropy and frequency on the isolated rabbit heart atrium (+ or − by 25%, concentrations in μg/ml given); negatively inotropic: *IVa* 25–50, *Va* 25–50, *VIb* 25, *XX* 25–50; negatively chronotropic: *Va* 25–50, *VIb* 25–50; positively chronotropic: *XX* 25–50. Diuretic effect in mice (doses in mg/kg increasing diuresis by 100%): *Vb*, 25–60 *p.o.*; *XXI*, 60 *p.o.* Compound *IXb* showed hypoglycaemic effect in rats (decrease of the blood sugar by 20%) at the dose D; on the other hand compounds *VIb* and *XX* had hyperglycemic effects.

The compounds prepared were also tested for antimicrobial activity *in vitro* (the microorganisms and the minimum inhibitory concentrations in μg/ml are given unless they exceed 100 μg/ml): *Streptococcus* β-*haemolyticus*, *IVa* 25, *XXVa* 100; *Streptococcus faecalis*, *IVa* 25, *Va* 100, *VIIa* 100, *XXVa* 100; *Staphylococcus pyogenes aureus*, *IVa* 25, *Va* 25, *VIIa* 100, *XXVIa* 50; *Pseudomonas aeruginosa*, *Va* 100, *VIIa* 100, *XXVIa* 50; *Escherichia coli*, *Va* 100; *Proteus vulgaris*, *Va* 100, *VIIa* 100, *XXVIa* 100; *Mycobacterium tuberculosis* H37Rv, *Va* 100, *VIIa* 100, *XXVIa* 100; *Saccharomyces pasterianus*, *Va* 100, *VIa* 100, *VIIa* 100, *VIIIa* 100, *XXVa* 100, *XXVb* 100, *XXVIa* 100, *XXVIb* 100, *XXVIIb* 100, *XXVIII* 100; *Trichophyton mentagrophytes*, *Va* 100, *VIa* 50, *VIIa* 100, *VIIIa* 50, *XXVa* 50, *XXVb* 100, *XXVIa* 100, *XXVIb* 100, *XXVIIb* 50, *XXVIII* 50, *XXX* 50; *Candida albicans*, *Va* 50, *VIa* 100, *VIIa* 100, *VIIIa* 100, *XXVa* 100, *XXVIIb* 100, *XXVIII* 100; *Aspergillus niger*, *Va* 100, *VIa* 100, *VIIa* 100, *VIIIa* 100, *XXVa* 100, *XXVb* 100, *XXVIb* 100, *XXVIIb* 100, *XXVIII* 100.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 70 Pa over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol) were registered with a Unicam SP 8000 spectrophotometer, IR spectra (mostly in KBr) with a Unicam SP 200G spectrophotometer and ^1H NMR spectra (in C^2HCl_3 unless stated otherwise) with a ZKR-60 (Zeiss, Jena) spectrometer. The homogeneity of the compounds was checked by thin-layer chromatography on alumina (Brockmann, act. II).

2-(3,4-Dimethoxyphenyl)acetophenone (*XII*)

A stirred suspension of 4·0 g $AlCl_3$ in 15 ml benzene was treated over 20 min with a solution of 4·5 g homoveratroyl chloride[8] in 10 ml benzene, added dropwise. The mixture was diluted

with 10 ml benzene, stirred for 3 h at room temperature, allowed to stand overnight and heated for 1 h to 75°C. After cooling the mixture was decomposed by addition of a solution of 2 ml hydrochloric acid in 40 ml water and extracted with chloroform. The organic layer was washed with water and 5% $NaHCO_3$, dried with $MgSO_4$ and evaporated. The inhomogeneous residue (4·3 g) was chromatographed on a column of 100 g neutral Al_2O_3 (activity II). Benzene eluted 0·6 g (11%) homogeneous product which crystallized from 90% ethanol m.p. 83—84°C. IR spectrum: 1 690 cm^{-1} (ArCOR). ^1H NMR spectrum: δ 7·90 (m, 2 H, 2 ArH adjacent to CO), 7·30 to 7·50 (m 3 H, remaining ArH of benzoyl), 6·30 (s, 3 H, remaining ArH), 4·15 (s, 2 H, $ArCH_2CO$), 3·75 (s, 6 H, 2 OCH_3). For $C_{16}H_{16}O_3$ (256·3) calculated: 74·98% C, 6·29% H; found: 75·08% C, 6·50% H.

2-(3,4-Dimethoxyphenyl)-4′-methylacetophenone (*XIII*)

A stirred suspension of 45 g $AlCl_3$ in 70 ml toluene was treated dropwise over 3 h at 15°C with a solution of 43 g homoveratroyl chloride[8] in 80 ml toluene, the mixture was stirred for 6·5 h at 15°C, allowed to stand overnight at room temperature and decomposed by pouring into a mixture of 500 ml 5M-HCl and 500 g ice. After stirring for 45 min the mixture was extracted with chloroform, the organic layer was washed with water, 5% NaOH and water, dried with $MgSO_4$ and evaporated; 38·7 g (72%), m.p. 98—102°C (softening from 94°C). Analytical sample, m.p. 104—105·5°C (methanol). UV spectrum: λ_{max} 252 nm (log ε 4·24), inflexes at 280 nm (3·80) and 232 nm (4·14). IR spectrum: 774, 804, 873 (2 adjacent and solitary Ar—H), 1 023, 1 233, 1 261 ($ArOCH_3$), 1 135, 1 163 (C—O of ketone), 1 453, 1 476, 1 515, 1 588, 1 604 (Ar), 1 681 cm^{-1} (ArCOR). ^1H NMR spectrum: δ 7·81 (d, J = 9·0 Hz, 2 H, 2 ArH adjacent to CO), 7·11 (d, J = = 9·0 Hz, 2 H, 2 ArH adjacent to methyl of tolyl), 6·66 (s 3 H, remaining ArH), 4·06 (s, 2 H, $ArCH_2CO$), 3·71 (s, 6 H, 2 OCH_3), 2·31 (s, 3 H, $ArCH_3$). For $C_{17}H_{18}O_3$ (270·3) calculated: 75·53% C, 6·71% H; found: 75·77% C, 7·06% H.

The oxime was prepared by refluxing a mixture of 2·7 g *XIII*, 1·2 g $NH_2OH.HCl$, 1·6 g $NaHCO_3$ and 100 ml ethanol for 6·5 h; 2·6 g (91%), m.p. 113—115·5°C (aqueous methanol). For $C_{17}H_{19}NO_3$ (285·3) calculated: 71·56% C, 6·71% H, 4·91% N; found: 71·25% C, 6·81% H, 4·94% N.

2-(3,4-Dimethoxyphenyl)-4′-methoxyacetophenone (*XIV*)

A mixture of 7·6 g anisole, 8 ml dichloromethane and 10·0 g $AlCl_3$ was stirred and treated dropwise over 45 min at 15—17°C with a solution of 10·7 g homoveratroyl chloride[8] in 8 ml dichloromethane. The stirring was continued for 5 h, the mixture was allowed to stand overnight at room temperature and decomposed by pouring into a mixture of 10 ml 5-MHCl and 50 g ice. It was extracted with chloroform and the extract was processed similarly like in the preceding case; 14·2 g (almost theoretical yield), m.p. 133—137°C (softening from 122°C). Analytical sample, m.p. 139—141°C (ethanol). UV spectrum: λ_{max} 276 nm (log ε 4·29), 239 nm (4·29). IR spectrum: 774, 799, 820, 834, 873 (2 adjacent and solitary Ar-H), 1 023, 1 215, 1 234, 1 263, 2 835 ($ArOCH_3$), 1 113, 1 134, 1 167, 1 180 (C—O of ketone), 1 460, 1 515, 1 596, 3 010 (Ar), 1 675 (ArCOR), 2 898, 2 940 cm^{-1} (C—H in CH_2 and CH_3). ^1H NMR spectrum: δ 7·90 (d, J = 9·0 Hz, 2 H, 2 ArH adjacent to CO), 6·80 (d, J = 9·0 Hz, 2 H, remaining 2 ArH of 4-methoxybenzoyl), 6·68 (s, 3 H, remaining ArH), 4·05 (s, 2 H, $ArCH_2CO$), 3·71 (s, 9 H, 3 $ArOCH_3$). For $C_{17}H_{18}O_4$ (286·3) calculated: 71·31% C, 6·33% H; found: 71·62% C, 6·40% H.

2-(3,4-Dimethoxyphenyl)-4'-methylthioacetophenone (*XV*)

The reaction of 6·2 g thioanisole, 10·7 g homoveratroyl chloride[8] and 8·0 g $AlCl_3$ in 40 ml dichloromethane was carried out similarly like in the preceding case. Evaporation of the chloroform extract gave 8·1 g inhomogeneous residue which was chromatographed on 200 g neutral Al_2O_3 (activity II). Benzene eluted only 0·6 g (4%) of the desired product, m.p. 121–123°C (methanol). UV spectrum: λ_{max} 228 nm (log ε 4·19), 317 nm (4·33). IR spectrum: 788, 812, 877 (2 adjacent and solitary Ar—H), 1 028, 1 220, 1 239, 1 269, 2 840 ($ArOCH_3$), 1 096, 1 139, 1 165 (C—O of ketone), 1 456, 1 473, 1 520, 1 558, 1 592 (Ar), 1 683 (ArCOR), 2 920, 2 945 cm^{-1} (C—H in CH_2 and CH_3). ^1H NMR spectrum: δ 7·85 (d, J = 9·0 Hz, 2 H, 2 ArH adjacent to CO), 7·15 (d, J = 9·0 Hz, 2 H, 2 ArH adjacent to SCH_3), 6·70 (s, 3 H, remaining ArH), 4·06 (s, 2 H, $ArCH_2CO$), 3·74 (s, 6 H, 2 OCH_3), 2·41 (s, 3 H, SCH_3). For $C_{17}H_{18}O_3S$ (302·4) calculated: 67·52% C, 6·00% H, 10·60% S; found: 67·43% C, 6·12% H, 10·46% S.

N-[2-(3,4-Dimethoxyphenyl)-1-(4-tolyl)ethyl]formamide (*IXb*)

A mixture of 27·0 g *XIII*, 68 g formamide and 14 g 98% formic acid was slowly heated until reaching the temperature of 170–180°C which was maintained for 12 h. After cooling the mixture was diluted with 300 ml water at 60°C, stirred for 1 h, cooled to 30°C and the solid product was filtered, washed with water and dried; 29·7 g (almost theoretical yield), m.p. 128–131°C. Analytical product, m.p. 134–135°C (aqueous methanol). IR spectrum: 815, 838, 874 (2 adjacent and solitary Ar—H), 1 023, 1 239, 1 266 ($ArOCH_3$), 1 462, 1 590 (Ar), 1 516, 1 566 (HCONH), 3 335 cm^{-1} (NH). ^1H NMR spectrum: δ 8·02 (s, 1 H, N-CHO), 6·40–7·20 (m, 7 H, ArH), 6·20 (m, 1 H, NH), (m, 1 H, Ar—CH—N), 3·71 and 3·61 (2 s, 3 + 3 H, 2 OCH_3), 2·95 (d, J = = 7·0 Hz, 2 H, $ArCH_2$), 2·25 (s, 3 H, $ArCH_3$). For $C_{18}H_{21}NO_3$ (299·4) calculated: 72·22% C, 7·07% H, 4·68% N; found: 72·19% C, 7·17% H, 4·64% N.

N-[1-(4-Methoxyphenyl)-2-(3,4-dimethoxyphenyl)ethyl]formamide (*XIX*)

A mixture of 13·7 g *XIV*, 33 g formamide and 6·8 g 98% formic acid was stirred and heated for 14 h to 170–180°C. Processing similar like in the preceding case gave 11·1 g (73%) crude product, m.p. 137–145°C. Analytical sample, m.p. 151–152°C (methanol). IR spectrum: 812, 826, 837, 880 (2 adjacent and solitary Ar—H), 1 033, 1 250, 1 273, 2 860 ($ArOCH_3$), 1 305, 1 523, 1 654 (CONH), 1 452, 1 595, 1 618, 3 020 (Ar), 2 940, 2 975 (C—H in CH_2 and CH_3), 3 355 cm^{-1} (NH). ^1H NMR spectrum: δ 7·99 (s 1 H, N—CHO), 6·15–7·20 (m, 8 H, ArH and NH), 5·11 (m, 1 H, Ar—CH—N), 3·74, 3·69 and 3·64 (3 s, 3 + 3 + 3 H, 3 OCH_3), 2·94 (d, J = = 7·0 Hz, 2 H, $ArCH_2$). For $C_{18}H_{21}NO_4$ (315·4) calculated: 68·55% C, 6·71% H, 4·44% N; found: 68·52% C, 6·77% H, 4·51% N.

2-(3,4-Dimethoxyphenyl)-1-(4-tolyl)ethylamine (*IIIb*)

A mixture of 29·9 g *IXb*, 35 ml ethanol and 31 g 85% KOH was stirred and refluxed for 3 h (bath temperature 120°C). It was then diluted with 160 ml water and the base was extracted with ether. The extract was dried with K_2CO_3 and evaporated; 25·2 g (93%) oil. This crude base *IIIb* was dissolved in 50 ml ethanol, the solution was treated with a slight excess of a solution of HCl in ether and with 100 ml ether. Standing and cooling led to crystallization of 24·0 g (78%) hydrochloride, m.p. 228–229·5°C (ethanol–ether). IR spectrum: 821, 899 (2 adjacent and solitary Ar—H), 1 033, 1 242, 1 272 ($ArOCH_3$), 1 118, 1 145, 1 163 (C—N of amine), 1 455, 1 470, 1 521, 1 593 (Ar), 2 615 cm^{-1} (NH_3^+). ^1H NMR spectrum ($C_5^2H_5N$): δ 9·75 (bs, 3 H, NH_3^+), 6·40–7·10 (m, 7 H, ArH), 4·90 (t, 1 H, Ar—CH—N), 3·54 and 3·45 (2 s, 3 + 3 H, 2 OCH_3), 2·00 (s, 3 H, $ArCH_2$). For $C_{17}H_{22}ClNO_2$ (307·8) calculated: 66·33% C, 7·20% H, 11·55% Cl, 4·55% N; found: 66·48% C, 7·20% H, 11·71% Cl, 4·38% N.

1-(4-Methoxyphenyl)-2-(3,4-dimethoxyphenyl)ethylamine (*XX*)

Similar hydrolysis of 16·5 g *XIX* with 18 g 85% KOH in 20 ml ethanol gave 15·0 g (100%) crude base *XX*, m.p. 68–72°C. Analytical sample, m.p. 75–75·5°C (cyclohexane–benzene). IR spectrum: 813, 830, 861 (2 adjacent and solitary Ar–H), 1 029, 1 240, 1 253, 1 264, 2 860 ($ArOCH_3$), 1 111, 1 142, 1 158, 1 176 (C–N of amine), 1 450, 1 475, 1 518, 1 593, 3 020 (Ar), 1 613, 3 272, 3 340 cm^{-1} (NH_2). ^1H NMR spectrum: δ 7·15 (d, J = 9·0 Hz, 2 H, 2,6-H_2 in methoxyphenyl), 6·75 (d, J = 9·0 Hz, 2 H, 3,5-H_2 in methoxyphenyl), 6·65 (s, 2 H, 5,6-H_2 in dimethoxyphenyl), 6·49 (s, 1 H, 2-H in dimethoxyphenyl), 4·00 (m, 1 H, Ar–CH–N), 3·77 and 3·72 (2 s, 3 + 6 H, 3 OCH_3), 2·75 (m, 2 H, $ArCH_2$), 1·46 (bs, disappears after ^2H_2O, 2 H, NH_2). For $C_{17}H_{21}NO_3$ (287·3) calculated: 71·05% C, 7·37% H, 4·87% N; found: 71·18% C, 7·27% H, 4·86% N.

Hydrochloride, m.p. 216–217° (ethanol–ether). For $C_{17}H_{22}ClNO_3$ (323·8) calculated: 63·05% C, 6·85% H, 10·95% Cl, 4·33% N; found: 63·25% C, 6·59% H, 11·00% Cl, 4·28% N.

N-Methyl-2-(3,4-dimethoxyphenyl)-1-(4-tolyl)ethylamine (*IVb*)

A mixture of 8·0 g *IXb*, 180 ml ether and 4·0 $LiAlH_4$ was stirred for 2 h at room temperature and refluxed for 2·5 h. After cooling it was decomposed by a careful addition of 4 ml water, 4 ml 20% NaOH and 10 ml water, the mixture was treated with 2 g K_2CO_3, stirred for 30 min and the solid was filtered off. The filtrate was evaporated *in vacuo* giving 5·6 g (77%) oily base. Neutralization with maleic acid in ethanol and treatment with ether precipitated the hydrogen maleate, m.p. 134–136°C (ethanol). For $C_{22}H_{27}NO_6$ (401·4) calculated: 65·82% C, 6·78% H, 3·49% N; found: 66·03% C, 6·75% H, 3·54% N.

Hydrochloride, m.p. 152–153°C (ethanol–ether). For $C_{18}H_{24}ClNO_2$ (321·8) calculated: 67·17% C, 7·52% H, 11·02% Cl, 4·35% N; found: 66·74% C, 7·78% H, 10·90% Cl, 4·18% N.

N,N-Dimethyl-2-(3,4-dimethoxyphenyl)-1-(4-tolyl)ethylamine (*Vb*)

A mixture of 6·2 g *IIIb*, 5·4 g 98% formic acid, 2·4 g 36% formaldehyde and 8 ml water was stirred and refluxed for 6 h. After cooling it was made alkaline with 30 ml 5M-NaOH and extracted with chloroform. The extract was washed with water, dried with K_2CO_3 and evaporated; 4·9 g (82%) oily base *Vb*. Neutralization with HCl in a mixture of ethanol and ether gave 4·9 g hydrochloride, m.p. 197–199°C with decomposition (ethanol–ether). For $C_{19}H_{26}ClNO_2$ (335·9) calculated 67·94% C, 7·80% H, 10·56% Cl, 4·17% N; found: 67·95% C, 7·64% H, 10·55% Cl, 4·12% N.

N,N-Dimethyl-1-(4-methoxyphenyl)-2-(3,4-dimethoxyphenyl)ethylamine (*XXI*)

A similar reaction of 15·0 g *XX*, 20 g 98% formic acid, 25·2 g 36% formaldehyde and 28 ml water gave 15·2 g (92%) crude oily base and 13·6 g (74%) hydrochloride, m.p. 237–237·5°C with decomposition (ethanol). For $C_{19}H_{26}ClNO_3$ (351·9) calculated: 64·85% C, 7·45% H, 10·08% Cl, 3·98% N; found: 65·24% C, 7·25% H, 10·01% Cl, 4·00% N.

2-(3,4-Dihydroxyphenyl)-1-(4-tolyl)ethylamine (*IIIa*)

A mixture of 10·7 g *IIIb*.HCl and 50 ml 46% hydrobromic acid was stirred and refluxed for 3 h. Standing overnight and cooling led to crystallization of 10·5 g (93%) *hydrobromide* of *IIIa*, m.p. 218–221°C (ethanol–ether). For $C_{15}H_{18}BrNO_2$ (324·2) calculated: 55·57% C, 5·59% H, 24·65% Br, 4·32% N; found: 55·52% C, 5·80% H, 24·47% Br, 4·33% N.

Treatment of the hydrobromide with NH_4OH released the base *IIIa* which was isolated by extraction with chloroform; m.p. 201·5—202° (ethanol–cyclohexane). IR spectrum: 797, 824, 867 (2 adjacent and solitary Ar—H), 1 048, 1 262 (ArOH), 1 120, 1138, 1 209 (C—N of amine), 1 444, 1 519, 1 591 (Ar), 1 612 (N—H), 2 490 (NH_3^+), 2 935 (CH_2), 3 285, 3 345 (NH_2), 3 450 cm^{-1} (OH). ^1H NMR spectrum ($C_5{}^2H_5N$): δ 6·50—7·40 (m, 7 H, ArH), 6·30 (bs, disappears after ^2H_2O, 4 H, NH_2 and 2 OH), 4·15 (t, 1 H, Ar—CH—N), 2·85 (d, 2 H, $ArCH_2$), 2·11 (s, 3 H, $ArCH_3$). For $C_{15}H_{17}NO_2$ (243·3) calculated: 74·05% C, 7·04% H, 5·76% N; found: 73·81% C, 7·06% H, 5·82% N.

Hydrogen maleate, m.p. 185—186·5°C (ethanol–ether). For $C_{19}H_{21}NO_6$ (359·4) calculated: 63·50% C, 5·89% H, 3·90% N; found: 63·88% C, 6·17% H, 3·98% N.

N-Methyl-2-(3,4-dihydroxyphenyl)-1-(4-tolyl)ethylamine (*IVa*)

IVb.HCl (9·0 g) was similarly demethylated by refluxing for 5·5 h with 40 ml 46% hydrobromic acid; 9·7 g (100%) hydrobromide hemihydrate, m.p. 98°C and after resolidification 124—128°C (95% ethanol). IR spectrum (Nujol): 830, 880 (2 adjacent and solitary Ar—H), 1120, 1 260 (ArOH), 1 535, 1 609 (Ar), 3 200 cm^{-1} (OH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 9·20 (bs, 2 H, NH_2^+), 8·78 (bs, 2 H, 2 OH), 7·40 and 7·16 (ABq, J = 9·0 Hz, 2 + 2 H, 4 ArH of tolyl), 6·56 (d, J = 9·0 Hz, 1 H, 6-H of dihydroxyphenyl), 6·50 (d, J = 2·0 Hz, 1 H, 2-H of dihydroxyphenyl), 6·30 (q, J = 9·0; 2·0 Hz, 1 H, 5-H of dihydroxyphenyl), 4·30 (m, 1 H, Ar—CH—N), *c.* 3·30 (m, 3 H, $ArCH_2$ and 0·5 H_2O), 2·33 and 2·25 (2 s, 3 + 3 H, NCH_3 and $ArCH_3$). For $C_{16}H_{20}BrNO_2 + 0·5\ H_2O$ (347·2) calculated: 55·34% C, 6·10% H, 23·01% Br, 4·03% N; found: 55·36% C, 6·30% H, 23·42% Br, 3·94% N.

N,N-Dimethyl-2-(3,4-dihydroxyphenyl)-1-(4-tolyl)ethylamine (*Va*)

Similar demethylation of 7·0 g *Vb*.HCl with 80 ml 46% hydrobromic acid (refluxing for 2 h) gave 6·7 g (71%) hydrobromide of *Va*, m.p. 246°C (ethanol–ether). IR spectrum: 819, 852, 872, 893 (2 adjacent and solitary Ar—H), 1 152, 1 206, 1 267 (ArOH), 1 458, 1 540, 1 619 (Ar), 2 640, 2 720 (NH^+), 2 920 (CH_2), 3 250 and 3 500 cm^{-1} (OH). ^1H NMR spectrum ($C_5{}^2H_5N$): δ 10·84 (s, 3 H, NH^+ and 2 OH), 7·75 and 7·02 (2 d, J = 9·0; 9·0 Hz, 2 + 2 H, 4 ArH of tolyl), 6·93 (bs, 3 H, 3 ArH of dihydroxyphenyl), 3·70—4·80 (m, 3 H, $ArCH_2CHAr$), 2·60 (s, 6 H, CH_3-NCH_3), 2·10 (s, 3 H, $ArCH_3$). For $C_{17}H_{22}BrNO_2$ (352·3) calculated: 57·96% C, 6·29% H, 22·69% Br, 3·98% N; found: 58·22% C, 5·88% H, 22·55% Br, 3·96% N.

2-(3,4-Dimethoxyphenyl)-1-(4-tolyl)ethanol (*XVI*)

A mixture of 5·4 g *XIII*, 85 ml ethanol and 3·8 $NaBH_4$ was stirred for 5 h at 50—60°C and ethanol was slowly distilled off. The residue was diluted with water and extracted with benzene. The extract was washed with 1M-HCl and water, dried with Na_2SO_4, evaporated and the residue was crystallized from 30 ml cyclohexane; 4·8 g (88%), m.p. 66—68°C. IR spectrum: 830, 860 (2 adjacent and solitary Ar—H), 1 150 (CHOH), 1 250, 1 270 ($ArOCH_3$), 1 530, 1 600 (Ar), 3 560 cm^{-1} (OH). For $C_{17}H_{20}O_3$ (272·3) calculated: 74·97% C, 7·40% H; found: 74·82% C, 7·70% H.

2-(3,4-Dimethoxyphenyl)-1-(4-tolyl)ethyl Chloride (*XVII*)

A solution of 25·8 g *XVI* in 525 ml benzene was treated with 26 g powdered $CaCl_2$ and the suspension was saturated for 4·5 h with gaseous HCl at 10—15°C. It was allowed to stand overnight at room temperature, filtered, the filtrate was evaporated under reduced pressure and the residue was crystallized from a mixture of 25 ml cyclohexane and 75 ml light petroleum; 24·7 g (90%),

m.p. 74—77°C (softening at 70°C). ^{1}H NMR spectrum: δ 7·23 and 7·07 (ABq, J = 9·0 Hz, 2 + 2 H, 4 ArH of tolyl), 6·68 (s, 2 H, 5,6-H_2 of dimethoxyphenyl), 6·48 (s, 1 H, 2-H of dimethoxyphenyl), 4·93 (t, J = 7·0 Hz, 1 H, Ar—CH—Cl), 3·76 and 3·68 (2 s, 3 + 3 H, 2 OCH_3), (3·23 d, J = 7·0 Hz, 2 H, $ArCH_2$), 2·28 (s, 3 H, $ArCH_3$). For $C_{17}H_{19}ClO_2$ (290·8) calculated: 70·22% C, 6·58% H, 12·20% Cl; found: 69·97% C, 6·53% H, 12·12% Cl.

1-[2-(3,4-Dimethoxyphenyl)-1-(4-tolyl)ethyl]-4-methylpiperazine (*VIb*)

A solution of 5·8 g *XVII* and 15·0 g 1-methylpiperazine in 15 ml chloroform was stirred and refluxed for 6 h, allowed to stand overnight at room temperature and evaporated under reduced pressure. The residue was diluted with 50 ml water and extracted with benzene. The extract was washed with water and shaken with 150 ml 1M-HCl. The benzene layer was washed with water, dried with $MgSO_4$ and evaporated to give 0·7 g (12%) (*E*)-3,4-dimethoxy-4′-methylstilbene (*XVIII*), m.p. 123—124°C (cyclohexane). UV spectrum: λ_{max} 230·5 nm (log ε 4·18), 237 nm (4·16), 300 nm (4·39), 321·5 nm (4·48), inflexes at 291 nm (4·34), 335 nm (4·33). IR spectrum (Nujol): 825, 857 (2 adjacent and solitary Ar—H), 971 (*trans*-CH=CH), 1 036, 1 255, 1 271 ($ArOCH_3$), 1 520, 1 585, 1 588 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 7·40 (d, J = 9·0 Hz, 2 H, 2,6-H_2 of 4-tolyl), 7·11 (d, J = 9·0 Hz, 2 H, 3,5-H_2 of 4-tolyl), 6·95 (s, 3 H, ArH of dimethoxyphenyl), 7·03 and 6·75 (ABq, J = 9·5 Hz, 1 + 1 H, CH=CH), 3·86 and 3·81 (2 s, 3 + 3 H, 2 OCH_3), 2·29 (s, 3 H, $ArCH_3$). For $C_{17}H_{18}O_2$ (254·3) calculated: 80·29% C, 7·13% H; found: 80·44% C, 7·50% H.

The acid aqueous layer was made alkaline with 50 ml 5M-NaOH and the base was extracted with benzene. The extract was dried with K_2CO_3 and evaporated under reduced pressure; 5·9 g (76%) oily *VIb*. Neutralization with HCl in a mixture of ethanol and ether gave 5·95 g dihydrochloride, m.p. 240—241·5°C (ethanol). For $C_{22}H_{32}Cl_2N_2O_2$ (427·4) calculated: 61·82% C, 7·55% H, 16·59% Cl, 6·55% N; found: 61·36% C, 7·91% H, 16·40% Cl, 6·41% N.

1-[2-(3,4-Dimethoxyphenyl)-1-(4-tolyl)ethyl]-4-(2-hydroxyethyl)piperazine (*VIIb*)

A similar reaction of 14·5 g *XVII* with 42 g 1-(2-hydroxyethyl)piperazine in 35 ml boiling chloroform gave 17·1 g (89%) base *VIIb*, m.p. 109·5—110·5°C (cyclohexane). IR spectrum (Nujol): 822, 880 (2 adjacent and solitary Ar—H), 1 035 (CH_2OH), 1 271 ($ArOCH_3$), 1 520, 1 590 (Ar), 3 315 cm^{-1} (OH). ^{1}H NMR spectrum: δ 7·40 (s, 4 H, ArH of tolyl), 6·61 (bs, 2 H, 5,6-H_2 of dimethoxyphenyl), 6·36 (bs, 1 H, 2-H of dimethoxyphenyl), 3·75 and 3·62 (2 s, 3 + 3 H, 2 OCH_3), 2·70—3·60 (m, 5 H, OCH_2 and $ArCH_2CHAr$), 2·76 (bs, disappears after ^2H_2O, 1 H, OH), 2·48 (bs, 10 H, 5 NCH_2), 2·25 (s, 3 H, $ArCH_3$). For $C_{23}H_{32}N_2O_3$ (384·5) calculated: 71·84% C, 8·39% H, 7·28% N; found: 71·44% C, 8·59% H, 7·22% N.

Dihydrochloride, m.p. 218—219°C (ethanol–ether). For $C_{23}H_{34}Cl_2N_2O_3$ (457·4) calculated: 60·39% C, 7·49% H, 15·50% Cl, 6·13% N; found: 60·65% C, 7·97% H, 15·24% Cl, 6·31% N.

1-[2-(3,4-Dimethoxyphenyl)-1-(4-tolyl)ethyl]-4-phenylpiperazine (*VIIIb*)

The reaction of 7·55 g *XVII* and 16·2 g 1-phenylpiperazine[12] in 8 ml chloroform was caried out by heating to 80°C for 6·5 h. Similar processing like in the preceding cases gave 13·9 g mixture of *VIIIb* and starting 1-phenylpiperazine which was separated by crystallization from ethanol (1-phenylpiperazine remained in solution); 6·7 g (63%) *VIIIb*, m.p. 116—117°C (ethanol). IR spectrum: 705, 810, 820, 880 (5 and 2 adjacent and solitary Ar—H), 1 040, 1 255 ($ArOCH_3$), 1 525, 1 610 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 7·05 (s, 4 H, ArH of tolyl), 6·40—7·50 (m, 8 H, remaining ArH), 3·73 and 3·60 (2 s, 3 + 3 H, 2 OCH_3), 3·00—3·50 (m, 7 H, $ArCH_2CHAr$

and $CH_2N^4CH_2$ of piperazine), 2·63 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·25 (s, 3 H, $ArCH_3$). For $C_{27}H_{32}N_2O_2$ (416·5) calculated: 77·85% C, 7·74% H, 6·73% N; found: 77·53% C, 7·92% H, 6·67% N.

Dihydrochloride, m.p. 207–211°C (ethanol–ether). For $C_{27}H_{34}Cl_2N_2O_2$ (489·5) calculated: 66·25% C, 7·00% H, 14·49% Cl, 5·72% N; found: 66·57% C, 7·34% H, 13·99% Cl, 5·98% N.

1-[2-(3,4-Dihydroxyphenyl)-1-(4-tolyl)ethyl]-4-methylpiperazine (*VIa*)

A mixture of 7·4 g *VIb*.2 HCl and 25 ml 46% hydrobromic acid was stirred for 4 h at 90°C and evaporated *in vacuo*. The residue was dissolved in 50 ml 98% ethanol and the solution was treated with ether; there crystallized 6·1 g (75%) *VIa* dihydrobromide monohydrate, m.p. 215·5°C (95% ethanol–ether). IR spectrum: 825, 880 (2 adjacent and solitary Ar–H), 1 125, 1 195, 1 290 (ArOH), 1 470, 1 525, 1 610 (Ar), 2 450, 2 530, 2 570, 2 640 (NH^+), 2 935 (CH_2), 3 285 cm^{-1} (OH). For $C_{20}H_{28}Br_2O_2 + H_2O$ (506·3) calculated: 47·45% C, 5·97% H, 31·57% Br, 5·53% N; found: 47·34% C, 5·87% H, 30·73% Br, 5·64% N.

1-[2-(3,4-Dihydroxyphenyl)-1-(4-tolyl)ethyl]-4-(2-hydroxyethyl)piperazine (*VIIa*)

A mixture of 7·4 g *VIIb* and 39 ml 46% hydrobromic acid was refluxed for 5 h, the solution was evaporated *in vacuo* and the residue crystallized from a mixture of ethanol and ether; 7·5 g (72%) *VIIa* dihydrobromide hemihydrate, m.p. 199–200 C. IR spectrum: 800, 818, 832, 872 (2 adjacen and solitary Ar–H), 1 055 (CH_2OH), 1 200, 1 295 (ArOH), 1 528, 1 610 (Ar), 2 470, 2 570, 2 655 (NH^+), 3 340 cm^{-1} (H_2O). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·50 and 7·20 (ABq, J = 9·0 Hz, 2 + 2 H, 4 ArH of tolyl), *c.* 6·50 (m, 3 H, remaining ArH), 4·85 (bs, 1 H, Ar–CH–N), 2·80–4·20 (m, 7 CH_2, 3 OH and 0·5 H_2O), 2·30 (s, 3 H, $ArCH_3$). For $C_{21}H_{30}Br_2N_2O_3 + 0·5\ H_2O$ (527·3) calculated: 47·83% C, 5·93% H, 30·31% Br, 5·31% N; found: 47·96% C, 5·94% H, 30·76% Br, 5·20% N.

1-[2-(3,4-Dihydroxyphenyl)-1-(4-tolyl)ethyl]-4-phenylpiperazine (*VIIIa*)

A mixture of 8·5 g *VIIIb*.2 HCl and 35 ml 46% hydrobromic acid was stirred for 4 h at 90°C, filtered with charcoal, diluted with ethanol and evaporated *in vacuo*. The residue was disolved in 50 ml ethanol and the solution was treated with 100 ml ether. The precipitated product was crystallized from a mixture of 96% ethanol and ether; 8·3 g (100%) *VIIIa* hydrobromide hemihydrate, m.p. 229–230·5°C. For $C_{25}H_{29}BrN_2O_2 + 0·5\ H_2O$ (478·4) calculated: 62·76% C, 6·32% H, 16·70% Br, 5·85% N; found: 62·67% C, 6·64% H, 16·46% Br, 5·67% N.

A sample of the salt was decomposed with NH_4OH and the base was isolated by extraction with chloroform; m.p. 115–116°C (ethanol). IR spectrum: 700, 770, 807, 818, 873 (5 and 2 adjacent and solitary Ar–H), 1 035, 1 161, 1 250, 1 270 (ArOH), 1 525, 1 607 (Ar), 2 845 (NH^+), 3 460 cm^{-1} (OH). For $C_{25}H_{28}N_2O_2$ (388·5) calculated: 77·29% C, 7·27% H, 7·21% N; found: 77·10% C, 7·47% H, 6·73% N.

N-[2-(3,4-Dimethoxyphenyl)-1-(4-tolyl)ethyl]acetamide (*Xb*)

A mixture of 15·4 g *IIIb*.HCl in 60 ml pyridine was stirred and treated dropwise over 1 h with 26 g acetic anhydride at 25–30°C. The solution was stirred for 3 h at room temperature and allowed to stand overnight. It was poured into 750 ml water and the precipitated product was filtered, washed with water and dried; 15·5 g (93%), m.p. 167·5–168·5°C (benzene). IR spectrum: 827, 892 (2 adjacent and solitary Ar–H), 1 040, 1 275 ($ArOCH_3$), 1 527, 1 540, 1 653 (CONH),

1 600 cm^{-1} (Ar). For $C_{19}H_{23}NO_3$ (313·4) calculated: 72·82% C, 7·39% H, 4·47% N; found 72·61% C, 7·80% H, 4·52% N.

N-[2-(3,4-Dimethoxyphenyl)-1-(4-tolyl)ethyl]-3,4-dimethoxyphenylacetamide (*XIb*)

A mixture of 6·2 g *IIIb*.HCl in 30 ml pyridine was treated with a solution of 5·8 g homoveratroyl chloride[8] in 10 ml toluene and the mixture was stirred for 7·5 h at 60—70°C. After cooling it was poured into 300 ml water, the precipitated crude product was filtered, washed with water, dried and crystallized from 100 ml toluene; 7·3 g (82%), m.p. 152—155°C and after resolidification at 163—164°C. IR spectrum: 825, 867 (2 adjacent and solitary Ar—H), 1 045, 1 245, 1 275 ($ArOCH_3$), 1 525, 1 650 (CONH), 3 340 cm^{-1} (NH). For $C_{27}H_{31}NO_5$ (449·5) calculated: 72·14% C, 6·95% H, 3·12% N; found: 71·91% C, 7·21% H, 2·74% N.

6,7-Dimethoxy-3-(4-tolyl)-3,4-dihydroisoquinoline (*XXII*)

A mixture of 2·99 g *IXb*, 15 ml toluene and 10 ml $POCl_3$ was stirred and refluxed for 4·5 h and poured under cooling into 150 ml 2M-HCl. The precipitated hydrochloride was filtered, washed with ethanol and ether, and dried; 2·1 g (66%), m.p. 187·5—188°C (ethanol–ether). For $C_{18}H_{20}ClNO_2$ (317·8) calculated: 68·02% C, 6·34% H, 11·16% Cl, 4·41% N; found: 68·02% C, 6·52% H, 11·16% Cl, 4·27% N.

The aqueous acid filtrate was made alkaline with 10% NaOH and extracted with chloroform. The extract gave by drying and evaporation 0·4 g base (raising the total yield to 80%), m.p. 92—94°C (cyclohexane and a small quantity of ethanol). ^{1}H NMR spectrum: δ 8·40 (d, J = = 2·0 Hz, 1 H, 1-H), 7·35 (d, J = 9·0 Hz, 2 H, 2,6-H_2 in tolyl), 7·13 (d, J = 9·0 Hz, 2 H, 3,5-H_2 in tolyl), 6·85 and 6·64 (2 s, 1 + 1 H, 5,8-H_2), 4·60 (m, 1 H, 3-H), 3·85 (s, 6 H, 2 OCH_3), 2·75 (m, 2 H, 4,4-H_2), 2·29 (s, 3 H, $ArCH_3$). For $C_{18}H_{19}NO_2$ (281·3) calculated: 76·84% C, 6·81% H, 4·98% N; found: 77·25% C, 6·97% H, 4·86% N.

6,7-Dimethoxy-1-methyl-3-(4-tolyl)-3,4-dihydroisoquinoline (*XXIII*)

A mixture of 3·1 g *Xb*, 15 ml toluene and 15 g $POCl_3$ was refluxed for 3·5 h, cooled and poured into 100 ml 1M-HCl under cooling. The separated aqueous layer was made alkaline at 10°C with 150 ml 5M-NaOH and the base was isolated by extraction with chloroform; 1·4 g (48%), m.p. 126·5—128°C (cyclohexane). ^{1}H NMR spectrum: δ 7·35 and 7·12 (ABq, J = 9·0 Hz, 2 + 2 H, 4 ArH of tolyl), 7·05 and 6·66 (2 s, 1 + 1 H, 5,8-H_2), 4·45 (t, J = 7·0 Hz, 1 H, 3-H), 3·85 (s, 6 H, 2 OCH_3), 2·75 (d, 2 H, 4,4-H_2), 2·40 (d, J = 2·0 Hz, 3 H, 1-CH_3), 2·26 (s, 3 H, $ArCH_3$). For $C_{19}H_{21}NO_2$ (295·4) calculated: 77·26% C, 7·17% H, 4·74% N; found: 77·43% C, 7·25% H, 4·62% N.

Hydrochloride monohydrate, m.p. 178—183°C (96% ethanol). For $C_{19}H_{22}ClNO_2 \cdot H_2O$ (349·8) calculated: 65·23% C, 6·91% H, 10·13% Cl, 4·00% N; found: 65·61% C, 6·68% H, 9·92% Cl, 3·94% N.

6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-3-(4-tolyl)-3,4-dihydroisoquinoline (*XXIV*)

A similar cyclization of 7·3 g *XIb* in 25 ml toluene with 15 ml $POCl_3$ gave only 1·3 g (19%) base, m.p. 97—100°C (cyclohexane–ethanol). IR spectrum: 820, 865 (2 adjacent and solitary Ar—H), 1 035, 1 275 ($ArOCH_3$), 1 522, 1 580, 1 611 (Ar), 1 665 cm^{-1} (C=N). ^{1}H NMR spectrum: δ 6·50—7·50 (m, 9 H, ArH), *c.* 4·55 (m, 1 H, 3-H), 3·50—4·20 (m, 14 H, 4 OCH_3 and $ArCH_2C$= =N), 2·50—3·00 (m, 2 H, 4,4-H_2), 2·30 (s, 3 H, $ArCH_3$). For $C_{27}H_{29}NO_4$ (431·5) calculated: 75·15% C, 6·77% H, 3·25% N; found: 75·02% C, 6·75% H, 3·13% N.

6,7-Dimethoxy-3-(4-tolyl)-1,2,3,4-tetrahydroisoquinoline (*XXVb*)

A solution of 14·6 g *XXII*.HCl in 300 ml ethanol was neutralized with 5M-NaOH (pH 6·5) and with stirring it was treated with 5·9 g $NaBH_4$ added in small portions over 1 h. The mixture was then refluxed for 6 h, after cooling decomposed with 200 ml water, treated with 50 ml 1M-NaOH and extracted with toluene. The extract was dried with K_2CO_3, evaporated under reduced pressure, the remaining oil was dissolved in 100 ml ethanol and the solution was treated with a slight excess of HCl in ether; 14·7 g (100%) *XXVb* hydrochloride, m.p. 255–257 °C (ethanol). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): δ 10·32 (bs, disappears after ^2H_2O, 2 H, NH_2^+), 7·62 (d, J = = 8·5 Hz, 2 H, 2,6-H_2 of tolyl), 7·26 (d, J = 8·5 Hz, 2 H, 3,5-H_2 of tolyl), 6·92 and 6·83 (2 s, 1 + 1 H, 5,6-H_2), 4·50 (m, 1 H, 3-H), 4·25 (bs, 2 H, 1,1-H_2), 3·71 (s, 6 H, 2 OCH_3), 3·00–3·50 (m, 2 H, 4,4-H_2), 2·31 (s, 3 H, $ArCH_3$). For $C_{18}H_{22}ClNO_2$ (319·8) calculated: 67·59% C, 6·94% H, 11·08% Cl, 4·38% N; found: 67·41% C, 7·04% H, 11·25% Cl, 4·29% N.

6,7-Dimethoxy-1-methyl-3-(4-tolyl)-1,2,3,4-tetrahydroisoquinoline (*XXVIb*)

A) A solution of 0·5 g *XXIII* in 15 ml ethanol was stirred and slowly treated with 0·2 g $NaBH_4$. The mixture was refluxed for 30 min, cooled, acidified with diluted hydrochloric acid and evaporated *in vacuo*. The residue was stirred with 20 ml 2·5M-NaOH and extracted with benzene. The extract was dried with K_2CO_3 and evaporated. The residue was dissolved in 5 ml ethanol and the solution was treated with a sligh texcess of HCl in ether; 0·5 g (88%) *XXVIb* hydrochloride, m.p. 245–246°C. Three crystallizations from ethanol gave 0·3 g product with a constant melting point of 252–253°C with decomposition which appears to be a homogeneous racemate. For $C_{19}H_{24}ClNO_2$ (333·9) calculated: 68·35% C, 7·25% H, 10·62% Cl, 4·19% N; found: 68·38% C, 7·46% H, 10·65% Cl, 4·04% N.

B) A mixture of 12·5 g *Xb*, 60 ml toluene, 40 ml $POCl_3$ and 4·0 P_2O_5 was stirred and refluxed for 4 h. It was then evaporated *in vacuo* and the evaporation was repeated after the addition of 100 ml benzene. The residue was dissolved in 200 ml ethanol, the solution was neutralized under cooling with 50 ml 2·5M-NaOH (pH 6·5) and slowly treated under stirring with 5·0 g $NaBH_4$, added over 30 min. The mixture was refluxed for 3 h, evaporated *in vacuo*, the residue was treated with 20 ml 5M-NaOH and extracted with benzene. The extract was shaken with 250 ml 1M-HCl and the precipitated hydrochloride was filtered; 8·0 g (60%), m.p. 250–258°C. Recrystallization from ethanol gave a product melting at 252–253°C with decomposition which was found identical with the product described under *A*.

6,7-Dimethoxy-1-(3,4-dimethoxybenzyl)-3-(4-tolyl)-1,2,3,4-tetrahydroisoquinoline (*XXVIIb*)

A mixture of 9·0 g *XIb*, 40 ml toluene, 30 ml $POCl_3$ and 3·0 g P_2O_5 was refluxed for 4 h and evaporated *in vacuo*. The residue was dissolved in 300 ml ethanol, the solution was neutralized with 35 ml 5M-NaOH and reduced similarly like in the preceding case under *B* with 3·0 g $NaBH_4$. Similar processing gave 6·1 g (65%) *XXVIIb* hydrochloride, m.p. 217–218·5°C with decomposition. Three crystallizations from 80% ethanol gave a product melting constantly at 220 to 221°C with decomposition. The product appears to be a homogeneous racemate. For $C_{27}H_{32}ClNO_4$ (470·0) calculated: 69·00% C, 6·86% H, 7·54% Cl, 2·98% N; found: 69·02% C, 6·69% H, 7·62% Cl, 2·85% N.

6,7-Dihydroxy-3-(4-tolyl)-1,2,3,4-tetrahydroisoquinoline (*XXVa*)

A mixture of 1·8 g *XXVb*.HCl and 20 ml 46% hydrobromic acid was stirred at 100°C for 6·5 h under reflux and cooled by standing overnight in a refrigerator. There crystallized 1·8 g (95%)

XXVa hydrobromide, m.p. 232—238°C. Analytical sample, m.p. 262—264°C (95% ethanol). IR spectrum: 820, 873, 900 (2 adjacent and solitary Ar—H), 1 035, 1 200, 1 250 (ArOH), 1 535, 1 575, 1 625 (Ar), 2 495, 2 620, 2 783 (NH_2^+), 3 105, 3 190 cm^{-1} (OH..N). For $C_{16}H_{18}BrNO_2$ (336·2) calculated: 57·15% C, 5·39% H, 23·77% Br, 4·16% N; found: 57·27% C, 5·78% H, 23·27% Br, 3·98% N.

6,7-Dihydroxy-1-methyl-3-(4-tolyl)-1,2,3,4-tetrahydroisoquinoline (*XXVIa*)

XXVIb.HCl (3·4 g) was decomposed with 20 ml 20% NH_4OH and the base was isolated by extraction with chloroform; 3·1 g oil. This base was dissolved in 30 ml chloroform and the stirred solution was treated under cooling to 0°C over 1 h with a solution of 10 g BBr_3 in 15 ml chloroform. It was then stirred for 6 h at room temperature, treated over 30 min with 30 ml ethanol and evaporated under reduced pressure. The residue was dissolved in 25 ml ethanol and crystallization was induced by addition of 25 ml ether; 2·1 g (78%) *XXVIa* hydrobromide, m.p. 254—257° with decomposition. The product appears homogeneous, theer crystallizations from ethanol led to a product melting constantly at 257—259°C with decomposition. IR spectrum (Nujol): 805, 826, 868, 871, 883 (2 adjacent and solitary Ar—H), 1 140, 1 286, 1 298 (ArOH), 1 520, 1 527, 1 581, 1 601, 1 627 (Ar), 2 505 (NH_2^+), 3 165, 3 255 (OH..N), 3 520 cm^{-1} (OH). For $C_{17}H_{20}$..$BrNO_2$ (350·3) calculated: 58·29% C, 5·76% H, 22·82% Br, 4·00% N; found: 58·10% C, 6·24% H, 22·82% Br, 3·90% N.

2,3,10,11-Tetramethoxy-6-(4-tolyl)berbine (*XXVIII*)

XXVIIb.HCl (4·7 g) was decomposed with 50 ml 20% NaOH and the base was isolated by extraction with chloroform; 4·5 g oil. It was dissolved in 25 ml methanol, treated with 5 ml 35% formaldehyde and the mixture was allowed to stand for 8 days at room temperature. It was then treated with 26 ml 5M-HCl and the solution was refluxed for 50 min. After standing for 14 days at room temperature the precipitated hydrochloride monohydrate was filtered; 4·0 g (83%), m.p. 170 to 174°C. Analytical sample (homogeneous), m.p. 176—177°C with decomposition (ethanol). For $C_{28}H_{32}ClNO_4 + H_2O$ (500·0) calculated: 67·25% C, 6·85% H, 7·09% Cl, 2·81% N; found: 67·08% C, 6·66% H, 7·13% Cl, 2·81% N.

A sample of the hydrochloride was decomposed with NH_4OH and the base was isolated by extraction with ether; m.p. 87—91°C (ether). ^1H NMR spectrum: δ 7·60 and 7·18 (ABq, $J = 8·5$ Hz, 2 + 2 H, 4 ArH of tolyl), 6·80, 6·88, 6·55 and 6·36 (4 s, 1 + 1 + 1 + 1 H, 1,4,9,12-H_4), 3·92, 3·85 and 3·75 (3 s, 3 + 6 + 3 H, 4 OCH_3), 2·50—3·90 (m, 8 H, 5,5,6,8,8,13,13,13a-H_8), 2·40 (s, 3 H, $ArCH_3$). For $C_{28}H_{31}NO_4$ (445·5) calculated: 75·48% C, 7·01% H, 3·14% N; found: 75·40% C, 7·43% H, 2·95% N.

N-[2-(3,4-Dibenzoyloxyphenyl)-1-(4-tolyl)ethyl]benzamide (*XXIX*)

A) A solution of 3·24 g *IIIa*.HBr in 30 ml pyridine was treated under stirring and cooling to 0—5°C over 30 min with a solution of 2·95 g benzoyl chloride in 3 ml chloroform. The stirring under cooling was continued for 30 min and the mixture was then stirred for 3·5 h at 15°C. After 48 h standing at room temperature the mixture was poured into a mixture of 40 ml hydrochloric acid and 40 g ice, neutralized with NH_4OH and extracted with chloroform. The extract was dried, evaporated *in vacuo* and the residue was crystallized from ethanol; 2·2 g (40%), m.p. 176—181°C. Analytical sample, m.p. 190·5—191·5°C (ethanol). UV spectrum: λ_{max} 227·5 nm ($\log \varepsilon$ 4·71). IR spectrum (Nujol): 704, 751, 821 (Ar—H), 1 260 (C—O of ester), 1 533, 1 632 (ArCONH), 1 580, 1 603, 3 005, 3 033 (Ar), 1 748 (ArCOOAr), 3 275 cm^{-1} (NH). ^1H NMR spectrum:

δ 8·05 (m, 4 H, 4 ArH adjacent to COO), 6·90–7·90 (m, 18 H, remaining ArH), 6·65 (bd, J = = 7·0 Hz, 1 H, CONH), 5·46 (m, 1 H, Ar–CH–N), 3·21 (d, J = 7·0 Hz, 2 H, $ArCH_2$), 2·25 (s, 3 H, $ArCH_3$). For $C_{36}H_{29}NO_5$ (555·6) calculated: 77·82% C, 5·26% H, 2·52% N; found: 78·14% C, 5·26% H, 2·47% N.

B) *IIIa*.HBr (2·43 g) was dissolved in trifluoroacetic acid (30 ml) at 70 °C and the stirred solution was treated dropwise with 4·2 g benzoyl bromide. The mixture was refluxed for 15 min and evaporated *in vacuo*. The residue was diluted with 20 ml 10% $NaHCO_3$ and the mixture was extracted with ether. The extract was dried with Na_2SO_4, evaporated and the inhomogeneous residue (1·7 g) was chromatographed on a colum of 50 g silica gel (Silpearl). Elution with benzene yielded 0·9 g (29%) homogeneous *XXIX*, m.p. 189–190 °C, identical with the product obtained under *A*.

N,N-Dimethyl-2-(3,4-dibenzoyloxyphenyl)-1-(4-tolyl)ethylamine (*XXX*)

A solution of 2·6 g *Va*.HBr in 26 ml pyridine was stirred and treated at 0–5 °C over 15 min with 4·0 g benzoyl chloride, added dropwise. The mixture was stirred for further 30 min with cooling and then for 6 h at room temperature. After standing overnight it was poured into a mixture of 30 ml hydrochloric acid and 30 g ice. The precipitated semisolid hydrochloride was isolated by a combination of filtration and decantation, it was decomposed with 10% $NaHCO_3$ and the base was extracted with benzene. The extract was dried and evaporated. The oily base was dissolved in 5 ml tert-butanol and the solution was neutralized with HCl in ether. There crystallized 3·6 g (100%) hydrochloride, m.p. 150–153 °C. Analytical sample, m.p. 156–158 °C (2-propanol–ether). UV spectrum: λ_{max} 228 nm (log ε 4·62), inflex at 265 nm (3·81). IR spectrum (Nujol): 706, 752, 821, 900 (5 and 2 adjacent and solitary Ar–H), 1 260 (C–O of ester), 1 510, 1 600 (Ar), 1 743 (ArCOOAr), 2 420 cm^{-1} (NH^+). For $C_{31}H_{30}ClNO_4$ (516·0) calculated: 72·15% C, 5·86% H, 6·87% Cl, 2·71% N; found: 72·10% C, 5·49% H, 6·81% Cl, 2·70% N.

The authors are indebted to Drs A. Šimek, J. Vintika and J. Turinová (Bacteriological department of this institute) for having supervised the microbiological in vitro *testing of the compounds, to Mrs M. Vlková for technical cooperation with the synthesis and to Mrs J. Komancová, Mrs V. Šmídová, Mr M. Čech, Dr Z. Volková, Mrs A. Slaviková and Mrs J. Kropáčová (Analytical department of this institute) for carrying out the analyses.*

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Translated by the author (M. P.).