SYNTHESIS OF 3-(2-ALKOXYPHENOXY)-2-METHYL (OR PHENYL)PROPYLAMINES AS POTENTIAL ANTIDEPRESSANTS*

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Reactions of potassium salts of 2-methoxy-, 2-ethoxy- and 2-benzyloxyphenol with 2-methyl-3-dimethylaminopropyl chloride and 3-dimethylamino-2-phenylpropyl chloride in boiling 2-butanone in the presence of potassium iodide gave the title compounds *IV*—*VI* which were partially demethylated by treatment with ethyl chloroformate in boiling benzene and by the following alkaline hydrolysis of the crude intermediates. In series *a* (3-aryloxy-2-methylpropylamines) the demethylation proceeded normally under the formation of the methylamino compounds *VIIa*—*IXa*; in series *b* (3-aryloxy-2-phenylpropylamines), however, the treatment with ethyl chloroformate effected a double cleavage resulting, after the alkaline hydrolysis, in N-methyl-2-phenylallylamine (*XIII*). The pharmacological testing did not confirm the expected thymoleptic effects of the compounds (*IVa*, *VIIa*); on the other hand, the benzyl ethers *IXa* and especially *VIb* exhibited strong antiarrhythmic activity.

The antidepressant activity was discovered in the series of amines with tricyclic skeletons and the tricyclic antidepressants have been for a long time the only type of agents used in the treatment of depressive states[1]. Their rather important cardiotoxicity led to the search after new types of compounds suitable to a similar therapeutic use. It has been established that the antidepressant activity shows a relatively low degree of structural specificity and potential antidepressants were described among the tetracyclic and bicyclic compounds and finally even among amines with isolated rings in the molecules ("monocyclic antidepressants") (ref.[2]). Viloxazine (*I*) was one of the first substances of this type which was discovered during investigations of new β-adrenergic blocking agents[3]; on the basis of a strong antireserpine and rather high central depressant activity it was recognized as a potential antidepressant and has found a wide use[4-6]. Structural analogues of viloxazine are the experimental antidepressant agents femoxetine (*II*) (ref.[7,8]) and paroxetine (*III*) (ref.[9-11]) acting as selective inhibitors of the neuronal uptake of 5-hydroxytryptamine. Molecules of all the three compounds (*I*—*III*) show the common 3-aryloxypropylamine fragment with the branched chain on the middle carbon atom of the propane residue;

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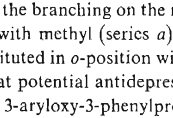
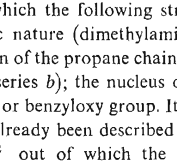
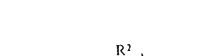
the amino group forms a part of a saturated heterocycle (morpholine, piperidine). In the present communication, the synthesis of several analogous 3-aryloxypropylamines *IV–IX* is being described, for which the following structural features are typical: the amino group is of aliphatic nature (dimethylamino or methylamino group), the branching on the middle carbon of the propane chain is effected by substitution with methyl (series *a*) or phenyl (series *b*); the nucleus of the aryloxy group is substituted in *o*-position with an alkoxy or benzyloxy group. It is necessary to mention that potential antidepressants have already been described in the series of analogous 3-aryloxy-3-phenylpropylamines[12] out of which the experimental agents nisoxetine (*X*) (ref.[13]) and fluoxetine (*XI*) (ref.[14]) were found most interesting.



I



II, R = H, $R^1 = CH_3$, R^2 = 4-OCH_3
III, R = F, R^1 = H, R^2 = 3,4-OCH_2O

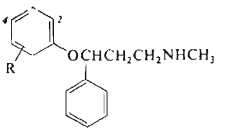


IV, $R^1 = R^2 = CH_3$
V, $R^1 = CH_3$, $R^2 = C_2H_5$
VI, $R^1 = CH_3$, $R^2 = CH_2C_6H_5$
VII, R^1 = H, $R^2 = CH_3$
VIII, R^1 = H, $R^2 = C_2H_5$
IX, R^1 = H, $R^2 = CH_2C_6H_5$

In formulae *IV–IX*: *a* R = CH_3, *b* R = C_6H_5.

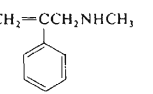
Our synthesis in series *a* started from 2-methyl-3-dimethylaminopropanol[15], the hydrochloride of which was transformed by treatment with thionyl chloride in benzene to the hydrochloride of 2-methyl-3-dimethylaminopropyl chloride[16]. The preparation of this intermediate in the synthesis of a number of psychotropic agents was described only by reaction of 1-bromo-3-chloro-2-methylpropane with dimethylamine[17,18]. In series *b*, ethyl 3-dimethylamino-2-phenylpropionate[19] was the starting product, which was reduced with lithium aluminium hydride to 3-dimethylamino-2-phenylpropanol (the literature[20] described a different method of reduction). The transformation to 3-dimethylamino-2-phenylpropyl chloride was carried out again by reaction with thionyl chloride[20].

Reactions of 2-methyl-3-dimethylaminopropyl chloride and 3-dimethylamino--2-phenylpropyl chloride with potassium salts of guaiacol, 2-ethoxyphenol[21] and 2-benzyloxyphenol[22] in boiling 2-butanone in the presence of potassium iodide (method *A*) resulted in compounds *IVa*, *Vab* and *VIab*. In syntheses of compounds *Vb* and *VIb*, considerable amounts of lower boiling fractions were isolated in addition to the desired products. In the first case, the by-product was characterized. It afforded a crystalline and homogeneous hydrochloride. The mass spectrum estimated the composition of the base to be $C_{13}H_{19}NO_2$; this is in agreement with the analysis of the hydrochloride. The ^{1}H-NMR spectrum excluded the possibility that we are dealing here with ethyl 3-dimethylamino-2-phenylpropionate (melting point of the hydrochloride does not agree with the literature[19] value) which was used in the synthesis as an intermediate and corresponds to the mentioned elemental composition. The ^{1}H-NMR spectrum indicated that the structure of 3-dimethylamino-2-phenylpropyl acetate (*XII*) should be assigned to this product. The compound could be formed by a reactioh of 3-dimethylamino-2-phenylpropyl chloride with potassium acetate, the only source of which could be the oxidation of the used 2-butanone *via* diacetyl. It is not clear why this reaction took place only in cases of the 2-phenylpropylamine derivatives.



X, R = 2-OCH_3
XI, R = 4-CF_3

XII



XIII

In the group of tricyclic antidepressant agents, methylamino derivatives are very often more active than the corresponding dimethylamino compounds (ref.[1]). For this reason, the synthesis of methylamino compounds was also included in this work. In series *a*, a procedure analogous like in the tricyclic amine series[23–25] was used to this end (method *B*): In the first step the treatment of the dimethylamino compounds *IVa*–*VIa* with ethyl chloroformate in boiling benzene effected demethylations, the products of which were chloromethane and the corresponding carbamates

which in the second step were hydrolyzed in crude state with a very concentrated boiling solution of potassium hydroxide in ethanol resulting in the desired methylamino compounds *VIIa–IXa*. The application of this procedure to dimethylamino compounds of the series *b*, *i.e.* to compounds *Vb* and *VIb*, did not lead to the desired result. In the case of compound *Vb*, the products obtained were identified as 2-ethoxyphenol and N-methyl-2-phenylallylamine (*XIII*) (*cf.*[20]). The treatment with ethyl chloroformate effected thus not only cleavage of the C—N bond but also of the C—O bond and the primary products evidently were ethyl N-(3-chloro-2-phenylpropyl)-N-methylcarbamate and ethyl 2-ethoxyphenyl carbonate. The alkaline hydrolysis of the former was accompanied by hydrogen chloride elimination and led to the amine *XIII*; the mixed carbonate was hydrolyzed to 2-ethoxyphenol. In the case of compound *VIb*, an analogous procedure led to a mixture of bases which afforded a hydrochloride with a constant melting point. The released base was characterized by means of the ^{1}H-NMR spectrum as a mixture of compounds *IXb* and *XIII* in a ratio of 1 : 1; the mentioned hydrochloride is thus considered to be a molecular complex of hydrochlorides of the compounds *IXb* and *XIII*. The mass spectrum proved only the component with the lower molecular weight, *i.e.* $C_{10}H_{13}N$ (*m/e* 147), whereas the component with the greater molecule (*IXb*) is unstable under the conditions used (probably eliminates 2-benzyloxyphenol and gives a further quantity of *XIII*). Compounds prepared by methods *A* and *B* are assembled in Table I.

Hydrogen maleates of compounds *IVa* (VÚFB-12.415) and *VIIa* (VÚFB-13.704) were pharmacologically tested in comparison with viloxazine (*I*) (ref.[3–5]) with regard to the expected antidepressant activity; the doses (mg/kg) given were calculated for the bases. Methods described in an earlier communication[26] were used for the testing. Acute toxicity in mice (*i.v.*), LD_{50}: *I*, 55·5; *IVa*, 30·2; *VIIa*, 24·5. Rotarod test in mice (*i.v.*), ED_{50}: *I*, 30·2; *IVa*, >10 (ataxia in 40% animals), *VIIa*, inactive at 15 mg/kg. Effect on the thiopental sleeping time in mice (compounds were given *i.v.* in a dose corresponding to 10% of the intravenous LD_{50}, the time between the loss and return of righting reflex was taken as a criterion of the narcotic effect; for control animals, administered only with 40 mg/kg thiopental *i.v.*, the duration of the narcotic effect was taken equal 1): *I*, 1·9; *IVa*, 1·7; *VIIa*, 4·8. In the test of antagonization of reserpine-induced hypothermia in mice, only *I* exhibited at a dose of 4 mg/kg *i.p.* a statistically significant effect; *IVa* and *VIIa* were inactive. In the test of reserpine-induced ptosis in mice, the compounds were administered *i.p.* in a relatively high dose of 40 mg/kg and the antireserpine effect of all three compounds was statistically significant. While for *I* it could be considered specific, *IVa* and *VIIa* elicited in the mentioned dose convulsions which interfered nonspecifically with the reserpine ptosis. In the test of antagonism of the ulcerogenic effect in rats the compounds were inactive in a dose of 50 mg/kg *s.c.* In conclusion, compounds *IVa* and *VIIa* did not show the spectrum of effects typical for potential antidepressants.

The other compounds were tested by a series of methods (especially for the incoordinating, hypotensive, α- and β-adrenolytic, antiarrhythmic and antireserpine effects) within a general screening programme (*i.v.* administration). Numbers of the compounds, type of salt used, code numbers, LD_{50} values in mg/kg and the doses D (mg/kg) used in the screening are given: *Va*, hydrogen maleate, VÚFB-13.700, 25, 5; *VIa*, hydrogen maleate, VÚFB-13.701, 17·5, 3; *VIIIa*, hydrogen maleate, VÚFB-13.705, 30, 6; *IXa*, hydrogen maleate, VÚFB-13.706, 25, 5; *Vb*, hydrochloride, VÚFB-13.702, 12·5; 3; *VIb*, hydrogen maleate, VÚFB-13.703, 20, 4. In the doses indicated, compounds *Va*, *VIa* and *VIIIa* are devoid of any of the mentioned effects. In doses higher than D, compounds *Va* and *VIIIa* increase the activity and reactivity of mice and are thus slightly excitant. The same effect is shown by the compound *Vb* which raised the blood pressure of normotensive rats in doses of 0·5 – 1·0 mg/kg *i.v.* Compound *IXa* in higher doses than D is also excitant, brings about ataxia in the rotarod test in mice (ED_{50} = 2·5 – 5·0 mg/kg *i.v.*), decreases the blood pressure of normotensive rats (ED = 1·0 – 2·5 mg/kg *i.v.*) by 20% for at least 10 min and has antiarrhythmic effect (ED = 2·5 – 5·0 mg/kg *i.v.*, dose prolonging with statistical significance the latency of ventricular extrasystoles in rats elicited with aconitine; for quinidine as a standard, ED = 5 – 10 mg/kg *i.v.*). Compound *VIb* is also hypotensive (ED = 2 mg/kg *i.v.*) and has a strong antiarrhythmic effect (ED = = 0·5 – 1·0 mg/kg).

The compounds were also tested for antimicrobial activity *in vitro* (Dr L. Langšádl and Dr J. Turinová, bacteriological department of this institute). The microorganisms, numbers of compounds and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, *Va* 50, *VIa* 25, *Vb* 50, *VIb* 25; *Mycobacterium tuberculosis* H37Rv, *IVa* 100, *VIa* 25, *IXa* 50, *VIb* 25; *Trichophyton mentagrophytes*, *VIIIa* 50, *Vb* 50.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried at about 60 Pa over P_2O_5 at room temperature or at 77°C. IR spectra were registered mostly with a Unicam SP 200G spectrophotometer in Nujol, ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra were recorded with MS 902 (AEI) and Varian MAT-311 spectrometers. The homogeneity of the compounds was checked by thin-layer chromatography on silica gel (Silufol).

3-Dimethylamino-2-phenylpropanol

A solution of 75·7 g ethyl 3-dimethylamino-2-phenylpropionate[19] (b.p. 135—140°C/1·87 kPa) in 200 ml ether was dropped over 4 h into a stirred suspension of 8·2 g $LiAlH_4$ in 150 ml ether and the mixture was refluxed for 2 h. After cooling it was decomposed with a solution of 12 g NaOH in 33 ml water added dropwise, the mixture was stirred for 30 min, the solid filtered off and washed with ether. The filtrate was dried with K_2CO_3 and distilled; 50·1 g (82%) crude product, b.p. 136—146°C/1·6 kPa. The literature[20] reported for the pure alcohol, obtained by reduction of the ester by the Bouveault–Blanc method, the b.p. of 148°C/2·4 kPa.

TABLE I

3-(2-Alkoxyphenoxy)-2-methyl(phenyl)propylamines *IV*—*IX*

Compound	Method (% yield)	B.p., °C/Pa or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found		
				% C	% H	% N
IVa	*A* (77)	95—97/40[a]	$C_{13}H_{21}NO_2$ (223·3)	69·92 69·64	9·48 9·25	6·27 6·31
IVa-HM[b]		121—122 (ethanol–ether)	$C_{17}H_{25}NO_6$ (339·4)	60·16 59·96	7·42 7·36	4·13 4·40
Va	*A*[c] (81)	111—113/60	$C_{14}H_{23}NO_2$ (237·3)	70·85 71·18	9·77 9·72	5·90 5·95
Va-HM[b]		83—84 (ethanol–ether)	$C_{18}H_{27}NO_6$ (353·4)	61·17 61·08	7·70 7·70	3·96 4·08
Vb	*A*[c] (46)	148/93	$C_{19}H_{25}NO_2$ (299·4)	76·22 76·56	8·42 8·49	4·68 4·66
Vb-HCl		157—159 (acetone)	$C_{19}H_{26}ClNO_2$ (335·9)	67·94 67·80	7·80 7·78	4·17[d] 4·25
VIa	*A* (84)	163—166/173	$C_{19}H_{25}NO_2$ (299·4)	76·22 76·78	8·42 8·32	4·68 4·69
VIa-HM[b]		95—97 (ethanol–ether)	$C_{23}H_{29}NO_6$ (415·5)	66·49 66·86	7·04 7·20	3·37 3·49
VIb	*A* (47)	197—200/93[e]	$C_{24}H_{27}NO_2$ (361·5)	79·74 79·74	7·53 7·73	3·88 3·71
VIb-HM[b]		64—68 (ethanol–ether)	$C_{28}H_{31}NO_6$ (477·6)	70·42 70·89	6·54 6·74	2·93 2·89
VIIa	*B*[c] (82)	102/93	$C_{12}H_{19}NO_2$ (209·3)	68·87 68·86	9·15 8·95	6·69 6·76
VIIa-HM[b]		84—86 (ethanol–ether)	$C_{16}H_{23}NO_6$ (325·4)	59·06 58·94	7·13 7·22	4·31 4·21
VIIIa	*B* (70)	103/80	$C_{13}H_{21}NO_2$ (233·3)	69·92 68·77	9·48 9·60	6·27 6·11
VIIIa-HM[b]		90—92 (ethanol–ether)	$C_{17}H_{25}NO_6$ (339·4)	60·16 60·43	7·42 7·67	4·13 4·34
IXa	*B* (47)	153—156/67[f]	$C_{18}H_{23}NO_2$ (285·4)	75·76 75·77	8·12 8·34	4·91 5·06
IXa-HM[b]		75—77 (ethanol–ether)	$C_{22}H_{27}NO_6$ (401·5)	65·82 65·81	6·78 7·05	3·49 3·59
IXa-HCl		87—90[g] (acetone–ether)	$C_{18}H_{24}ClNO_2$ (321·9)	67·17 67·63	7·52 7·51	4·35[h] 4·42

2-Methyl-3-dimethylaminopropyl Chloride

A stirred solution of 47·3 g 2-methyl-3-dimethylaminopropanol[15] (b.p. 47—48°C/1·33 kPa, n_D^{20} 1·4310) in 200 ml benzene was saturated with anhydrous HCl and then treated dropwise with 72 g $SOCl_2$. The mixture was refluxed for 3 h and the precipitated hydrochloride was filtered with suction after cooling; 66·4 g (96%), m.p. (160)—172°C (*cf.*[16]). Decomposition with 50% NaOH released the base which was extracted with ether, the extract dried with K_2CO_3 and evaporated. The remaining base was used for further work without purification.

3-Dimethylamino-2-phenylpropyl Chloride

A stirred solution of 50·2 g 3-dimethylamino-2-phenylpropanol in 250 ml benzene was saturated with hydrogen chloride and treated dropwise with 50 g $SOCl_2$. The mixture was refluxed for 2·5 h, allowed to stand overnight at room temperature, the precipitated hydrochloride filtered, washed with light petroleum and dried *in vacuo*; 56·4 g (86%), m.p. 179—181°C (ref.[20], m.p. 174°C). The base was released with 50% NaOH, isolated by extraction with ether and used in the crude state.

N,N-Dimethyl-3-(2-ethoxyphenoxy)-2-methylpropylamine (*Va*)
(Method *A*)

A mixture of 9·5 g potassium 2-ethoxyphenoxide (prepared by neutralization of 2-ethoxyphenol[21], b.p. 116°C/4·8 kPa, with KOH in ethanol and evaporation of the solution), 7·5 g crude 2-methyl-3-dimethylaminopropyl chloride, 80 ml 2-butanone and 2·0 g KI was stirred and refluxed for 16 h. The cooled mixture was filtered, the filtrate evaporated under reduced pressure, the residue diluted with 5% NaOH and extracted with benzene. The extract was dried with K_2CO_3 and distilled; 10·4 g (81%), b.p. 111—113°C/60 Pa. ^{1}H-NMR spectrum: δ 7·85 (s, 4 H, Ar—H), 4·05 (q, J = 7·0 Hz, 2 H, OCH_2 in ethoxyl), 4·00 (m, 2 H, OCH_2 in the propylamine residue), 2·00—2·50 (m, 3 H, $CHCH_2N$ in the propylamine residue), 2·18 (s, 6 H, CH_3NCH_3), 1·41 (t, J = 7·0 Hz, 3 H, CH_3 in ethoxyl), 1·09 (d, J = 6·0 Hz, 3 H, CH_3 in position 2 of the propylamine residue). Neutralization of the base (3·0 g) with maleic acid (1·5 g) in ethanol and addition of ether gave 4·2 g hydrogen maleate, m.p. 83—84°C (ethanol–ether). Analyses in Table I.

N,N-Dimethyl-3-(2-ethoxyphenoxy)-2-phenylpropylamine (*Vb*)

A solution of 7·0 g 2-ethoxyphenol[21] and 3·4 g KOH in ethanol was evaporated *in vacuo* to give the potassium salt. 2-Butanone (80 ml), 10·2 g 3-dimethylamino-2-phenylpropyl chloride

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[a] ^{1}H-NMR spectrum: δ 6·90 (s, 4 H, Ar—H), *c.* 3·80 (m, 2 H, OCH_2), 3·82 (s, 3 H, OCH_3), 2·00—2·50 (m, 3 H, $CHCH_2N$), 2·20 (s, 6 H, CH_3NCH_3), 1·10 (d, 3 H, C—CH_3). [b] Hydrogen maleate. [c] See Experimental. [d] Calculated: 10·56% Cl; found: 10·55% Cl. [e] ^{1}H-NMR spectrum: δ 7·28 (s, 5 H, C_6H_5 of the benzyloxy group), 7·20 (m, 5 H, C_6H_5 in position 2 of the propane chain), 6·82 (s, 4 H, remaining Ar—H), 4·90 (s, 2 H, OCH_2Ar), 4·15 (mcd, 2 H, OCH_2 in the propane chain), 3·28 (m, 1 H, CHAr), 2·65 (m, 2 H, CH_2N), 2·15 (s, 6 H, CH_3NCH_3). [f] ^{1}H-NMR spectrum: δ 7·20—7·50 (m, 5 H, C_6H_5), 6·90 (s, 4 H, remaining Ar—H), 5·11 (s, 2 H, OCH_2Ar), 3·98 (d, J = 7·0 Hz, 2 H, OCH_2 in the propane chain), 2·70 (m, 2 H, CH_2N), 2·35 (s, 3 H, NCH_3), 2·30 (m, 1 H, CH), 1·45 (bs, 1 H, NH), 1·08 (d, J = 7·0 Hz, 3 H, C—CH_3). [g] IR spectrum: 695, 743 (5 and 4 adjacent Ar—H), 1030, 1038, 1126, 1220, 1256 (ArOR), 1508, 1596, 3010, 3040 (Ar), 2403, 2500 cm^{-1} (NH_2^+). [h] Calculated: 11·02% Cl; found: 11·09% Cl.

and 1·5 g KI were added and the mixture was stirred and refluxed for 16 h, cooled and filtered. The filtrate was evaporated, diluted with 5% NaOH and the product extracted with benzene. The extract was dried (K_2CO_3) and distilled. The lower boiling fraction (5·1 g, b.p. 60—95°C / / 93 Pa) was redistilled, b.p. 115–120°C/0·47 kPa, dissolved in ether and transformed by treatment with HCl to the hydrochloride, m.p. 169—173°C (acetone). The product was identified as 3-dimethylamino-2-phenylpropyl acetate (*XII*) hydrochloride. Mass spectrum, *m/e*: 221·1415 (M^+, $C_{13}H_{19}NO_2$), 58 (base peak, $CH_2{=}N[CH_3]_2$). For $C_{13}H_{20}ClNO_2$ (257·8) calculated: 60·58% C, 7·82% H, 13·76% Cl, 5·43% N; found: 60·80% C, 7·92% H, 13·78% Cl, 5·52% N. The pure base was released by treatment with 40% NaOH, isolated by extraction with ether and used for recording the spectra. IR spectrum (film): 709, 767 (C_6H_5), 1042, 1235, 1743 (RCOOR'), 1500, 1608, 3033, 3063, 3088 (Ar), 2772, 2822 cm^{-1} [$N(CH_3)_2$]. ^{1}H-NMR spectrum: δ 7·20 (m, 5 H, C_6H_5), 4·30 (m, 2 H, OCH_2), 3·12 (m, 1 H, CHAr), 2·50 (m, 2 H, NCH_2), 2·20 (s, 6 H, CH_3NCH_3), 1·95 (s, 3 H, CH_3CO).

The higher boiling fraction was the desired *Vb*; 7·0 g (46%), b.p. 148°C/93 Pa. ^{1}H-NMR spectrum: δ 7·10—7·50 (m, 5 H, C_6H_5), 6·87 (s, 4 H, 4 Ar—H of the pyrocatechol residue), 4·20 (d, J = 7·0 Hz, 2 H, OCH_2 in the propylamine residue), 3·98 (q, J = 7·0 Hz, OCH_2 in ethoxyl), 3·35 (m, 1 H, CHAr), 2·70 (m, 2 H, CH_2N), 2·25 (s, 6 H, CH_3NCH_3), 1·40 (t, J = 7·0 Hz, 3 H, CH_3 in ethoxyl). The base treated with HCl in ether gave the hydrochloride, m.p. 157—159°C (acetone). Analyses in Table I.

N-Methyl-3-(2-methoxyphenoxy)-2-methylpropylamine (*VIIa*)
(Method *B*)

A solution of 11·6 g *IVa* in 40 ml benzene was refluxed and treated over 10 min with a solution of 8·4 g ethyl chloroformate in 20 ml benzene, added dropwise. The mixture was refluxed for 90 min, cooled, washed with dilute hydrochloric acid and water, dried with K_2CO_3 and evaporated *in vacuo*. The residue (14·2 g oil) was dissolved in 16 ml ethanol, 14 g KOH were added and the mixture was refluxed for 3 h in a bath of 130—140°C. It was then diluted with water and extracted with benzene. The extract was washed with water and the base re-extracted with 10% hydrochloric acid. The separated aqueous layer was made alkaline with dilute NaOH, the base extracted with benzene and the extract processed by distillation; 8·9 g (82%), b.p. 102°C/93 Pa. ^{1}H-NMR spectrum: δ 6·90 (s, 4 H, Ar–H), 3·98 (*d*, J = 7·0 Hz, 2 H, OCH_2), 3·90 (s, 3 H, OCH_3), 2·70 (m, 2 H, CH_2N), 2·48 (s, 3 H, NCH_3), 2·30 (m, 1 H, CH), 1·48 (bs, 1 H, NH), 1·09 (d, J = 7·0 Hz, 3 H, C–CH_3). Neutralization with maleic acid in a mixture of ethanol and ether gave the hydrogen maleate, m.p. 84—86°C (ethanol–ether). Analyses in Table I.

N-Methyl-2-phenylallylamine (*XIII*)

A refluxing solution of 7·9 g *Vb* in 30 ml benzene was treated dropwise over 10 min with a solution of 5·0 g ethyl chloroformate in 20 ml benzene, the mixture was refluxed for 1·5 h, cooled, washed with dilute hydrochloric acid and water, dried ($MgSO_4$) and evaporated. The remaining oil (10·0 g) was dissolved in 12 ml ethanol, 10 g KOH were added and the mixture was refluxed for 4 h (bath temperature 140°C). It was then diluted with water, extracted with benzene and the extract was washed with 10% hydrochloric acid. The separated aqueous layer was made alkaline with 20% NaOH, the base extracted with benzene, the extract dried (K_2CO_3) and evaporated; 1·5 g (39%) crude *XIII*. Treatment with HCl in ether gave 1·63 g hydrochloride, m.p. 125—140°C; analytical sample, m.p. 141—144°C (acetone–ethanol–ether) (ref.[20], m.p. 140°C). Mass spectrum, *m/e* (%): 147·1057 (M^+, $C_{10}H_{13}N$, 22), 144·0815 ($C_{10}H_{10}N$, 11), 119·0814 (100), 118·0777 (18), 104 (24), 44 (100). IR spectrum: 711, 783 (C_6H_5), 910 ($CH_2{=}CRR'$), 1501, 1509, 1579, 1600

(Ar), 1640 (C=C), 2460, 2588 cm^{-1} (NH_2^+). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 9·45 (bs, 2 H, $NH_2^{(+)}$), *c.* 7·30 (m, 5 H, C_6H_5), 5·70 and 5·58 (2 s, 2 H, CH_2=), 4·01 (s, 2 H, CH_2N), 2·55 (s, 3 H, NCH_3). For $C_{10}H_{14}ClN$ (183·7) calculated: 65·39% C, 7·68% H, 19·30% Cl, 7·63% N; found: 65·63% C, 7·70% H, 19·26% Cl, 7·61% N.

The original alkaline aqueous solution, from which the base was removed by extraction, was acidified with hydrochloric acid and extracted with ether. Processing of the extract gave 1·7 g 2-ethoxyphenol, b.p. 63°C/0·24 kPa.

N-Methyl-3-(2-benzyloxyphenoxy)-2-phenylpropylamine (*IXb*)

VIb (7·9 g) in 30 ml benzene was treated with 3·55 g ethyl chloroformate in 20 ml benzene like in the preceding cases. The crude carbamate obtained (9·2 g) was hydrolyzed with 8 g KOH in 10 ml ethanol and gave only 2·6 g of oily basic product. Treatment with HCl in ether gave 2·55 g hydrochloride which was crystallized from acetone and melted at 124–126°C. It was characterized as a molecular complex of hydrochlorides of bases *IXb* and *XIII*. The mass spectrum proved only the presence of the low-molecular weight component *XIII*, *m/e* (%): 147 (M^+, $C_{10}H_{13}N^{(+)}$ 9), 132 (M—15, 6), 118 (50), 44 (CH_2=NH—CH_3, 100), 28 (100). For $C_{23}H_{26}ClNO_2$ + + $C_{10}H_{14}ClN$ (567·6) calculated: 69·83 % C, 7·10% H, 12·49% Cl, 4·94% N; found: 69·96% C, 7·58% H, 12·29% Cl, 4·96% N. The molecular complex was decomposed with 40% NaOH, the mixture of bases was isolated by extraction with ether and used for recording the following spectra. IR spectrum (Infrascan, $CHCl_3$): 1135, 1265 (ArOR), 1510, 1605, 1645 (Ar and ArC=C). 3380 cm^{-1} (NH). ^{1}H-NMR spectrum, δ, signals of *IXb*: 7·30 (m, 5 H, C_6H_5 in position 2 of the propylamine residue), 7·21 (s, 5 H, C_6H_5 of the benzyloxy group), 6·82 (s, 4 H, remaining Ar—H), 4·99 (s, 2 H, OCH_2Ar), 4·18 (med, 2 H, OCH_2 in the propylamine residue), 3·30 (m, 1 H, CHAr), 3·00 (m, 2 H, CH_2N), 2·28 (s, 3 H, NCH_3), 1·28 (bs, 1 H, NH); signals of *XIII*: 7·30 (m, 5 H, C_6H_5), 5·32 and 5·18 (2 bs, 2 H, H_2C=C), 3·58 (bs, 2 H, CH_2N), 2·38 (s, 3 H, NCH_3), 1·28 (bs, 1 H, NH).

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REFERENCES

1. Finch N. in the book: *Industrial Pharmacology* (S. Fielding, H. Lal, Eds), Vol. 2, Antidepressants, p. 1. Futura Publishing Company, Mount Kisco, New York 1975.
2. Protiva M.: *Pokroky ve farmacii* 2, 7. Avicenum, Prague 1979.
3. Greenwood D. T., Mallion K. B., Todd A. H., Turner R. W.: J. Med. Chem. *18*, 573 (1975).
4. Playle A. C.: Med. Actual. (Drugs of Today) *11*, 69 (1975).
5. Pinder R. M., Brogden R. N., Speight T. M., Avery G. S.: Drugs *13*, 401 (1977).
6. Kabeš J., Dostál T.: Česk. Psychiat. *72*, 384 (1976).
7. Christensen J. A., Squires R. F. (A/S Ferrosan): Belg. 810 310 (Brit. Appl. 30.01.1973); Ger. Offen. 2 404 113; Fr. 2 215 233.
8. Castañer J., Chatterjee S. S.: Drugs of the Future *2*, 309 (1977); *4*, 381 (1979).
9. Lassen J. B.: Psychopharmacology *57*, 151 (1978).
10. Petersen E. N., Bechgaard E., Sortwell R. J., Wetterberg L.: Eur. J. Pharmacol. *52*, 115 (1978).

11. Lund J., Lomholt B., Fabricius J., Christensen J. A., Bechgaard E.: Acta Pharmacol. Toxicol. *44*, 289 (1979).
12. Molloy B. B., Schmiegel K. K. (Eli Lilly and Co.): U.S. 4 018 895 (Appl. 19.01.1974); Ger. Offen 2 500 110; Chem. Abstr. *87*, 134 520 (1977).
13. Castañer J., Paton D. M.: Drugs of the Future *2*, 51 (1977); *3*, 82 (1978).
14. Castañer J., Paton D. M.: Drugs of the Future *2*, 27 (1977); *3*, 81 (1978); *4*, 70 (1979); *5*, 49 (1980).
15. Traynelis V. J., Dadura J. G.: J. Org. Chem. *26*, 686 (1961).
16. Jones J. W. (Gulf Oil Corp.): U.S. 3 317 474 (Appl. 21.05.1963); Chem. Abstr. *67*, 22 566 (1967).
17. Bourquin J.-P. Schwarb G., Gamboni G., Fischer R., Ruesch L., Guldimann S., Theus V., Schenker E., Renz J.: Helv. Chim. Acta *41*, 1072 (1958).
18. Brajtburg J. (Instytut Farmaceutyczny): Pol. 56 435 (Appl. 09.02.1967); Chem. Abstr. *70*, 114 594 (1969).
19. Satzinger G.: Justus Liebigs Ann. Chem. *728*, 64 (1969).
20. Benoit G., Herzog R.: Bull. Sci. Pharmacol. *42*, 34, 102 (1935); Chem. Abstr. *33*, 6259 (1939).
21. Klarmann E., Gates L. W., Shternov V. A.: J. Amer. Chem. Soc. *54*, 1204 (1932).
22. Jones J. H., Young G. T.: J. Chem. Soc. (C) *1968*, 436.
23. Protiva M., Rajšner M., Adlerová E., Seidlová V., Vejdělek Z. J.: This Journal *29*, 2161 (1964).
24. Seidlová V., Protiva M.: This Journal *32*, 2826 (1967).
25. Rajšner M., Svátek E., Metyšová J., Protiva M.: This Journal *34*, 1963 (1969).
26. Metyšová J., Metyš J.: Int. J. Neuropharmacol. *4*, 111 (1965).

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