α-BENZYLDOPAMINE AND SOME RELATED COMPOUNDS: SYNTHESIS AND PHARMACOLOGICAL SCREENING

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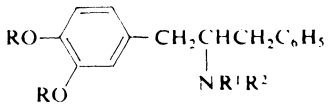
Received August 11th, 1983

Claisen reaction of 3,4-dimethoxyphenylacetonitrile with ethyl phenylacetate, the following stepwise hydrolysis and decarboxylation afforded *via* the amide *V* 1-(3,4-dimethoxyphenyl)--3-phenylpropan-2-one (*VI*). Leuckart reaction resulted in the crude formamide derivative *IIIb* which was subjected to alkaline hydrolysis to the primary amine *Ib* on the one hand, and to reduction to the secondary amine *IIb* on the other. Demethylation with hydrobromic acid gave hydrobromides of 1-(3,4-dihydroxyphenyl)-3-phenyl-2-propylamine (title compound *Ia*) and its N-methyl derivative *IIa*. The alcohol *VII*, obtained by reduction of the ketone *VI*, was transformed by treatment with thionyl chloride to the chloro compound *VIII* which afforded by substitution reaction with 1-methylpiperazine the piperazine derivative *IX*. While the methoxylated amines *Ib* and *IIb* have mild sitmulating and some antiarrhythmic effects, N-methyl-α-benzyldopamine (*IIa*) displayed a clear dopaminomimetic character.

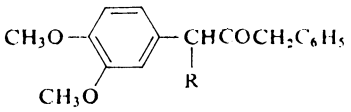
In one of the previous communications[1] we have described our first attempts to join the effort of many laboratories after developing new dopaminomimetic and antiparkinsonic agents by modification of the structure of dopamine [2-(3,4-dihydroxyphenyl)ethylamine] by introduction of hydrophobic residues in order to attain a balance between the hydrophilic and hydrophobic parts of the molecule and the ability to penetrate the blood-brain barrier which is a property being lacking with dopamine itself. In this line we introduced a 4-tolyl residue into the α-position of the dopamine molecule and prepared 2-(3,4-dihydroxyphenyl)-1-(4-tolyl)-ethylamine and some of its derivatives and analogues[1]. In the present communication we are describing the synthesis of the isomeric 1-(3,4-dihydroxyphenyl)-3-phenyl-2-propylamine (*Ia*), *i.e.* α-benzyldopamine, as well as several of its derivatives.



I, $R^1 = R^2 = H$
II, $R^1 = H$, $R^2 = CH_3$
III, $R^1 = H$, $R^2 = CHO$

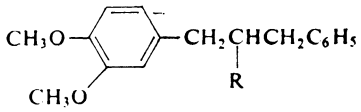
In formulae *I*–*III*: *a*, R = H, *b*, $R = CH_3$

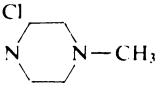
The synthesis started from a Claisen reaction of 3,4-dimethoxyphenylacetonitrile with ethyl phenylacetate in ethanol in the presence of sodium ethoxide; the reaction was carried out by using a general method leading to the synthesis of asymmetrical 1,3-diaryl-2-propanones[2]. The oily cyano ketone *IV* was obtained in a high yield. Because it was considered useful to proceed further *via* a crystalline intermediate, the nitrile was subjected to mild hydrolysis with a mixture of hydrochloric acid and acetic acid at 35–40°C (method[3]) and gave the crystalline amide *V*. The pure amide was then hydrolyzed with boiling 10% hydrochloric acid; decarboxylation took simultaneously place and 1-(3,4-dimethoxyphenyl)-3-phenylpropan-2-one (*VI*) was obtained. Its identity was confirmed by spectra. The following Leuckart reaction[4], carried out by heating with a mixture of formamide and formic acid to 180°C, afforded in an almost theoretical yield the oily formamide derivative *IIIb*. Its hydrolysis with potassium hydroxide in boiling ethanol gave the primary amine *Ib*, isolated in the form of the crystalline hydrochloride. By reduction of the oily formamide with lithium aluminium hydride in ether the secondary amine *IIb* was obtained which was isolated and characterized likewise as the hydrochloride. Demethalation of the dimethoxy amines *Ib* and *IIb* by heating with hydrobromic acid to 100°C resulted in hydrobromides of 1-(3,4-dihydroxyphenyl)-3-phenyl-2-propylamine (*Ia*) and its N-methyl derivative *IIa*.

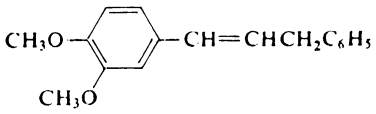


IV, R = CN
V, R = $CONH_2$
VI, R = H

Reduction of the ketone *VI* with sodium borohydride in boiling ethanol gave the oily secondary alcohol *VII* whose structure was confirmed by the ^1H NMR spectrum. Treatment with thionyl chloride in boiling benzene afforded the oily chloro derivative *VIII*. This was subjected to a substitution reaction with excessive 1-methylpiperazine in a mixture with dimethylformamide at 125–30°C. The product was separated into the neutral and basic components and it was found that the hydrogen chloride elimination was the main reaction which took place. The neutral product, obtained in a yield of 84%, consists according to the ^1H NMR spectrum, mainly of the diarylpropene *X*, and/or of its isomer with a shifted double bond, respectively. The thin-layer chromatography on silica gel showed contamination with minor quantities of the alcohol *VII*, chloride *VIII* and further two substances. The basic product was obtained in a yield of only 7·5%; it was the piperazine derivative *IX* which was identified by the analysis of the crystalline dihydrochloride.



VII. R = OH
VIII. R = Cl
IX. R = 



X

The hydrobromides of amines *Ia* and *IIa* were pharmacologically tested with regard to possible central effects; they were administered orally (the doses given were calculated for the bases). Both amines are little toxic. Compound *Ia* in a dose of 500 mg/kg has no lethal effect in mice; for compound *IIa* the LD_{50} is about 750 mg/kg. The discoordinating effect in the rotarod test in mice appears only in relatively high doses; for compound *IIa* the ED_{50} value of 75 mg/kg was determined. Both compounds in a dose of 50 mg/kg have no cataleptic effect in rats. Compound *Ia* in a dose of 25 mg/kg did not show anticataleptic effect toward perphenazine catalepsy in rats and compound *IIa* in a dose of 50 mg/kg surprisingly potentiates the cataleptic effect of perphenazine (by 20 – 30%) after simultaneous or sequential administration. Compound *IIa* was also tested with regard to the possibility of influencing the oxotremorine tremor in mice; it proved inactive in this line in a dose of 80 mg/kg and can thus be considered as lacking the central anticholinergic activity. In a dose of 100 mg/kg, however, it significantly lowers the concentrations of dopamine metabolites, *i.e.* homovanillic acid (to 82% of the control in the interval of 90 min after the administration) and 3,4-dihydroxyphenylacetic acid ,in rat brain homogenates. This result indicates a clear dopaminomimetic character of the substance.

Compounds *Ia* and *IIb* were tested by methods of the general pharmacological screening (Dr M. Bartošová, affiliated unit of this institute at Pardubice - Rosice). On intravenous administration to rats they are rather toxic; LD_{50} : Ib 37·5 mg/kg, *IIb* 35 mg/kg. Both were administered in the screening in the basic intravenous dose of 7 mg/kg. In these doses both compounds did not reveal analgetic, discoordinating, mydriatic, myorelaxant. antihistamine, antireserpine, anorectic and thiopental--potentiating effects in the usual tests in mice, rats and guinea-pigs. Compound *IIb* in the form of a 1% solution has a local anaesthetic effect in the test of corneal anaest-

hesia in rabbits but it irritates. Compound *Ib* in the basic dose displayed antiarrhythmic activity toward aconitine arrhythmias in rats (the intensity similar like with quinidine); compound *IIb* showed only an indication of this effect. Both compounds in concentrations of 10–50 μg/ml have negative inotropic and negative chronotropic activity on the isolated rabbit heart atrium. In doses higher than 7 mg/kg *i.v.* both compounds have central stimulating activity manifested by enhanced activity and reactivity of mice.

The compounds prepared were also tested for antimicrobial activity *in vitro* (Drs A. Šimek, J. Vintika and J. Turinová, bacteriological department of this institute); the microorganisms and the minimum inhibitory concentrations in μg/ml are given unless they exceed 100 μg/ml: *Streptococcus β-haemolyticus*, *IIa* 100; *Streptococcus faecalis*, *IIa* 100; *Staphylococcus pyogenes aureus*, *IIa* 100; *Proteus vulgaris*, *IIa* 50; *Mycobacterium tuberculosis* H37Rv, *IIa* 100, *IIb* 100; *Saccharomyces pasterianus*, *Ia* 100, *Ib* 100, *IIa* 100, *IIb* 100; *Trichophyton mentagrophytes*, *Ia* 50, *Ib* 50, *IIa* 100, *IIb* 50; *Candida albicans*, *Ia* 100, *Ib* 100, *IIa* 100, *IIb* 50; *Aspergillus niger*, *Ia* 100, *Ib* 100, *IIa* 100, *IIb* 100.

EXPERIMENTAL

The melting points of analytical samples 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 IR spectra (in Nujol unless stated otherwise) were recorded with a Unicam SP 200G spectrophotometer and ^1H NMR spectra (in C^2HCl_3) with a ZKR-60 (Zeiss, Jena) or with a Tesla BS 487C (80 MHz) spectrometer. The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromatography on alumina (Brockmann, activity II).

2-(3,4-Dimethoxyphenyl)-3-oxo-4-phenylbutyramide (*V*)

Sodium ethoxide was prepared by dissolving 9·2 g Na in 150 ml ethanol, 35·4 g 3,4-dimethoxyphenylacetonitrile were added and the mixture was treated with 40·0 g ethyl phenylacetate. The mixture obtained was stirred and refluxed for 3·5 h, allowed to stand overnight at room temperature and poured into a mixture of 600 g ice and water. It was stirred for 15 min and extracted with ether. The aqueous alkaline layer containing the sodium salt of the enol was separated and acidified with 75 ml 5M-HCl. The oxo nitrile *IV* was extracted with ether, the extract was dried with Na_2SO_4 and evaporated. The residue (60 g, crude *IV*) was dissolved in 600 ml acetic acid, the solution was treated with 400 ml hydrochloric acid and the mixture warmed to 35–50°C. It was then allowed to stand for 48 h at room temperature and poured into 6 l water at 10°C. After stirring for 30 min the precipitated product was filtered, washed with water and dried; 40·4 g (64%), m.p. 137–143°C. Analytical sample, m.p. 158–159°C (ethanol). IR spectrum: 706, 760, 812, 862 (5 and 2 adjacent and solitary Ar—H), 1 024, 1 141, 1 236, 1 255, 1 263 (Ar—O—CH_3), 1 522, 1 590, 1 603 (Ar), 1 650 ($CONH_2$), 1 726 (RCOR'), 3 195, 3 385 cm^{-1} (NH_2). For $C_{18}H_{19}NO_4$ (313·4) calculated: 68·99% C, 6·11% H, 4·47% N; found: 69·14% C, 6·27% H, 4·61% N.

1-(3,4-Dimethoxyphenyl)-3-phenylpropan-2-one (*VI*)

A suspension of 15·7 g *V* in 550 ml 10% hydrochloric acid was stirred and refluxed for 6 h. After cooling the mixture was extracted with ether, the extract was washed with 10% $NaHCO_3$ and water,

dried with $CaCl_2$ and evaporated. The residue was dissolved in 35 ml ethanol, the solution was filtered with charcoal and the filtrate evaporated *in vacuo*. The residue crystallized by standing overnight; 10·8 g (80%), m.p. 32—35°C. Analytical sample, m.p. 38—41°C (benzene–light petroleum). IR spectrum: 699, 704, 739, 745, 804, 859 (5 and 2 adjacent and solitary Ar—H), 1 021, 1 032, 1 142, 1 160, 1 242, 1 261 ($ArOCH_3$), 1 513, 1 591 (Ar), 1 710 cm^{-1} (RCOR'). ^1H NMR spectrum: δ 6·70—7·50 (m, 8 H, ArH), 3·80 and 3·85 (2 s, 3 + 3 H, 2 OCH_3), 3·70 and 3·64 (2 s, 2 + 2 H, $ArCH_2COCH_2Ar'$). For $C_{17}H_{18}O_3$ (270·3) calculated: 75·53% C, 6·71% H; found: 75·36% C, 6·66% H.

1-(3,4-Dimethoxyphenyl)-3-phenyl-2-propylamine (*Ib*)

A mixture of 15·5 g *VI*, 43 g formamide and 9·0 g formic acid was stirred and slowly heated to 180°C. It was maintained for 12 h at this temperature. After cooling to 90°C, there were added 150 ml water and the mixture was extracted with chloroform. The extract was washed with water, filtered with charcoal, dried with Na_2SO_4 and evaporated *in vacuo*. The oily residue (16·4 g, 100%) was considered the crude *IIIb* and was used for further work without characterization.

A mixture of 15·5 g crude *IIIb*, 20 ml ethanol and 20 g KOH was stirred and refluxed for 2·5 h. It was then diluted with 100 ml water and extracted after cooling with ether. The extract was dried with K_2CO_3 and evaporated; 12·1 g (86%) crude oily base *Ib*. It was dissolved in 25 ml ethanol and the solution was treated with a slight excess of HCl in ether. Addition of ether completed the precipitation of the hydrochloride; 11·5 g (72%), m.p. 180—181°C. Analytical sample, m.p. 184—185·5°C (ethanol–ether). For $C_{17}H_{22}ClNO_2$ (307·8) calculated: 66·33% C, 7·21% H, 11·52% Cl, 4·55% N; found: 66·40% C, 7·10% H, 11·73% Cl, 4·32% N.

N-Methyl-1-(3,4-dimethoxyphenyl)-3-phenyl-2-propylamine (*IIb*)

Oily *IIIb* (14·9 g) was dissolved in 150 ml ether and the solution was added dropwise to a stirred suspension of 10·0 g $LiAlH_4$ in 200 ml ether. The mixture was refluxed for 8 h, cooled, decomposed by a slow addition of 10 ml water, 10 ml 20% NaOH and 25 ml water, it was stirred for 1 h, 10 g K_2CO_3 were added and after 30 min stirring the solid was filtered off and washed with ether. The filtrate was evaporated *in vacuo* giving 8·4 g (59%) oily *IIb*. This crude base was purified by chromatography on 150 g neutral Al_2O_3 (activity II). Less polar impurities were removed by elution with benzene and the product was eluted with chloroform (5·4 g). It was dissolved in 6 ml 2-propanol, the solution was treated with a slight excess of HCl in ether and the mixture was diluted with ether; 3·15 g hydrochloride, m.p. 119—120°C (2-propanol–ether). IR spectrum (KBr): 695, 737, 764, 810, 885 (5 and 2 adjacent and solitary Ar—H), 1 025, 1 233, 1 261 ($ArOCH_3$), 1 511, 1 588, 1 601 (Ar), 2 415 cm^{-1} (NH_2^+). For $C_{18}H_{24}ClNO_2$ (321·8) calculated: 67·17% C, 7·52% H, 11·02% Cl, 4·35% N; found: 66·92% C, 7·36% H, 10·78% Cl, 4·23% N.

1-(3,4-Dihydroxyphenyl)-3-phenyl-2-propylamine (*Ia*)

A mixture of 4·6 g *Ib* . HCl and 20 ml 46% hydrobromic acid was stirred and heated for 1 h to 100°C. The solution formed was allowed to crystallize overnight, the precipitated solid was filtered, washed with ethanol and ether and dried; 3·15 g (65%) hydrobromide of *Ia*, m.p. 244—246°C. Analytical sample, m.p. 244—246°C (ethanol–ether). IR spectrum (KBr): 699, 746, 790, 814, 869 (5 and 2 adjacent and solitary Ar-H), 1 204, 1 252, 1 268 (ArOH), 1 488, 1 529, 1 599 (Ar), 1 616 (NH_2), 2 550 (NH_3^+), 3 280 cm^{-1} (OH, NH_2). For $C_{15}H_{18}BrNO_2$ (324·2) calculated: 55·56% C, 5·60% H, 24·65% Br, 4·32% N; found: 55·72% C, 5·62% H, 24·47% Br, 4·22% N.

N-Methyl-1-(3,4-dihydroxyphenyl)-3-phenyl-2-propylamine (*IIa*)

A mixture of 5·8 g *IIb* . HCl and 30 ml 46% hydrobromic acid was stirred and heated for 5 h to 100°C, 1 g charcoal was added and the stirring was continued for 1 h. The mixture was filtered, the filtrate was evaporated *in vacuo* and the residue crystallized from 10 ml 2-propanol (several days standing); 4·5 g (78%) hydrobromide of *IIa*, m.p. 147–154°C. Analytical sample, m.p. 155–156°C (2-propanol–ether). For $C_{16}H_{20}BrNO_2$ calculated: 56·81% C, 5·96% H, 23·63% Br, 4·14% N; found: 56·95% C, 6·12% H, 23·76% Br, 4·16% N.

1-(3,4-Dimethoxyphenyl)-3-phenylpropan-2-ol (*VII*)

A mixture of 15·0 g *VI* with 220 ml ethanol was stirred and slowly treated with 10·0 g $NaBH_4$. It was refluxed for 5 h, decomposed with 50 ml water and ethanol was distilled off. The residue was diluted with 150 ml water, acidified with 100 ml 2·5M-HCl and extracted with benzene. The extract was dried with $MgSO_4$ and evaporated; 15·3 g (100%) crude oily *VII* which was distilled, b.p. 142°C/30 Pa. ^{1}H NMR spectrum: δ 7·20 (s, 5 H, C_6H_5), 6·82 (m, 3 H, remaining ArH), 3·80 (s, 6 H, 2 OCH_3), c. 4·00 (m, 1 H, CH—O), 2·50–3·00 (m, 4 H, 2 $ArCH_2$), 1·74 (s, 1 H, OH). For $C_{17}H_{20}O_3$ (272·3) calculated: 74·97% C, 7·40% H; found: 74·97% C, 7·43% H.

1-(3,4-Dimethoxyphenyl)-3-phenyl-2-propyl Chloride (*VIII*)

A solution of 11·5 g *VII* in 50 ml benzene was stirred and treated with a solution of 9.5 g $SOCl_2$ in 10 ml benzene and the mixture was refluxed for 1·5 h. Evaporation of the volatile components *in vacuo* gave 10·8 g (89%) homogeneous oil which was distilled; b.p. 154–156°C/30 Pa. For $C_{17}H_{19}ClO_2$ (290·8) calculated: 70·22% C, 6·58% H, 12·20% Cl; found: 70·45% C, 6·67% H, 11·78% Cl.

1-[1-(3,4-Dimethoxyphenyl)-3-phenyl-2-propyl]-4-methylpiperazine (*IX*)

A mixture of 8·7 g *VIII*, 0·6 g KI, 6 ml dimethylformamide and 10 g 1-methylpiperazine was stirred and heated under reflux for 5 h to 125–130°C. The volatile components were evaporated *in vacuo* at 100°C, the residue was dissolved in 150 ml toluene and the solution was washed with water. The basic product was extracted from the toluene solution with 125 ml 5M-HCl (in two portions), the aqueous acid layer was filtered with charcoal, the filtrate was treated with 150 ml 20% NaOH and the base was extracted with toluene. The extract was dried with K_2CO_3 and evaporated; 0·8 g (7·5%) oily *IX*. It was dissolved in 8 ml ethanol and the solution was treated with a slight excess of HCl in ether; 0·8 g dihydrochloride, m.p. 171–174°C (ethanol–ether). 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: 62·06% C, 7·46% H, 16·22% Cl, 6·64% N.

The toluene layer after the extraction with hydrochloric acid was washed with water, dried and evaporated *in vacuo*; 6·4 g (84%) almost homogeneous oil. It was chromatographed on 120 g Al_2O_3 and the product obtained by elution with benzene containing 2% methanol was distilled, b.p. 146°C/30 Pa. The ^{1}H NMR spectrum indicates the identity of this neutral product as that of 1-(3,4-dimethoxyphenyl)-3-phenyl-1-propene (*X*) or the double bond position isomer: δ 7·25 (m, 5 H, C_6H_5), 6·78 (m, 3 H, remaining ArH), 6·35 (m, 2 H, ArCH=CH), 3·87 (s, 6 H, 2 OCH_3), 3·50 (m, 2 H, $ArCH_2$). The product is contaminated by minor quantities of *VII*, *VIII* and further two substances (TLC); in agreement with that the carbon content is lower than the theoretical value.

The authors are indebted to Drs J. Holubek and E. Svátek (Physico-chemical department of this institute) for recording and interpretation of spectra, and to Mrs J. Komancová, Mrs V. Šmídová, Dr Z. Volková, Mrs A. Slavíková and Mrs J. Kropáčová (Analytical department) for carrying out the analyses.

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Translated by the author (M. P.).