SYNTHESIS OF N-(1-PHENYL-2-PROPYL)-2,5-DIPHENYL-PENTYLAMINE AND SOME RELATED COMPOUNDS AS POTENTIAL NEUROTROPIC AND CARDIOVASCULAR DRUGS

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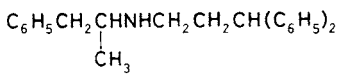
Heating of 2,5-diphenylvaleric acid with 2-phenylethylamine, 1-phenyl-2-propylamine, 1-phenyl-2-butylamine (*IX*), 1-(4-methoxyphenyl)-2-propylamine, 1-(4-methoxyphenyl)-2-butylamine (*X*) and 1-(4-dimethylaminophenyl)-2-propylamine to 200–210°C resulted in the amides *IIb*–*VIIb* which were reduced with lithium aluminium hydride in boiling dibutyl ether to give the amines *IIa*, *IIIa*, and *Va*–*VIIa*. A similar two-step sequence starting from 4-phenyl-4-(phenylthio)-butyric acid and the amine *IX* gave compound *VIIIa*. The salts of the title amines revealed some central stimulating, antireserpine, thiopental potentiating, anticonvulsant, and antiarrhythmic effects. 1-(4-Dimethylaminophenyl)-2-butylamine (*XI*), prepared in this connection, proved anorectic activity.

N-Substituted derivatives of 1-phenyl-2-propylamine (amphetamine) and related compounds with bulky N-substituents, containing aryl groups, are mostly devoid of the amphetamine-like central excitating character and reveal some other useful neurotropic and cardiovascular activities (antidepressant, sympatholytic, coronary dilating, *cf.*[1,2]). A typical example is N-(1-phenyl-2-propyl)-3,3-diphenylpropylamine (prenylamine, *I*) (ref.[3–6]) which is in practical use as a mild coronary dilator and antianginal drug. In previous investigations in a different connection we used 2,5-diphenylvaleric acid[7,8] and 4-phenyl-4-(phenylthio)butyric acid[9] as intermediates and considered now these acids to be suitable precursors of the bulky N-substituents for the amphetamine-like aralkylamines. The result was the synthesis of the amines *IIa*, *IIIa*, and *Va*–*VIIIa* which is the subject of the present communication.

The starting aralkylamines were obtained by reduction of the corresponding 1-aryl-2-nitroalkenes with lithium aluminium hydride in ether, mixture of diethyl ether and benzene or tetrahydrofuran; this method has already been described for the used 1-phenyl-2-propylamine[10], 1-(4-methoxyphenyl)-2-propylamine[11] and 1-(4-dimethylaminophenyl)-2-propylamine[12]. Preparation of further two aralkylamines – 1-phenyl-2-butylamine (*IX*) (ref.[13]) and 1-(4-methoxyphenyl)-2-butylamine (*X*) (ref.[14]) – has been described by making use of different methods; in our work they were obtained by the mentioned hydride reduction of 1-phenyl-2-nitrobutene[15] and 1-(4-methoxyphenyl)-2-nitrobutene[15]. 1-(4-Dimethylaminophenyl)-2-nitrobute-

ne[16] afforded by the same method 1-(4-dimethylaminophenyl)-2-butylamine (*XI*) which was not included in a systematic study[17] dealing with a number of similar compounds.



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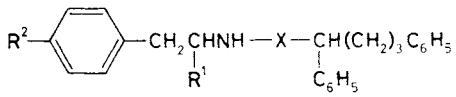
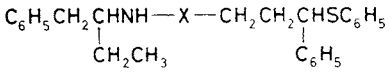
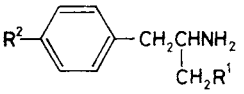


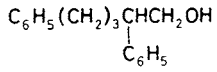
II, $R^1 = R^2 = H$ — *V*, $R^1 = CH_3$; $R^2 = OCH_3$
III, $R^1 = CH_3$; $R^2 = H$ — *VI*, $R^1 = CH_2CH_3$; $R^2 = OCH_3$
IV, $R^1 = CH_2CH_3$; $R^2 = H$ — *VII*, $R^1 = CH_3$; $R^2 = N(CH_3)_2$



VIII

In formulae *II* - *VIII* *a*, X = CH_2 *b*, X = CO





IX, $R^1 = CH_3$; $R^2 = H$
X, $R^1 = CH_3$; $R^2 = OCH_3$
XI, $R^1 = CH_3$; $R^2 = N(CH_3)_2$

XII

Heating of 2,5-diphenylvaleric acid[7] and 4-phenyl-4-(phenylthio)butyric acid[9] with the named aralkylamines (used in a slight excess) to 190–210°C (method A) resulted in the amides *IIb*–*VIIIb*. The amides *IIb*–*VIb* were crystalline, *VIIb* was oily but afforded a crystalline hydrochloride, *VIIIb* was oily and was used without further characterization. The amides were little soluble in ether and attempts to reduce them with lithium aluminium hydride in the form of suspensions in diethyl ether were unsuccessful. The method of choice was found in carrying out the reductions in refluxing dibutyl ether (method B). The obtained amines *IIa*–*VIIIa* were

oily and with the exception of *IVa* they afforded crystalline maleates. The molecules of amides *IIIb*–*VIIIb* and amines *IIIa*–*VIIIa* contain two centres of chirality: the crude products are considered mixtures of racemates. The amides and maleates of the amines, however, were crystallized until constant melting points were reached. Analytical samples, therefore, could represent homogeneous racemates. The amides and amines *II*–*VIII* are assembled in Table I with the usual experimental data. Preparations of the amide *IVb* and amine *VIa* are described as examples in the Experimental. 2,5-Diphenylpentanol (*XII*) was prepared by reduction of 2,5-diphenylvaleric acid[7] with lithium aluminium hydride in diethyl ether.

The amines *IIa*, *IIIa*, *Va*–*VIIIa*, and *XI* were subjected to the general pharmacological screening in the form of salts, described in the Experimental or in Table I. With the exception of compound *XI*, oral administration was used. Acute toxicity in mice (LD_{50} in mg/kg) and the screened doses (D in mg/kg): *IIa*, 1 500, 300; *IIIa*, 1 500, 300; *Va*, 1 500, 300; *VIa*, 2 500, 300; *VIIa*, 1 000, 200; *VIIIa*, 1 500, 300; *XI*, *i.v.* 47, 9. Compound *IIa* in doses higher than D brought about sedation in mice, in the dose D it raised the blood pressure of normotensive rats and inhibited the vasopressin spasms of coronary vessels in guinea-pigs (the effect was weaker than that of prenylamine, *I*). Compound *IIIa* at the dose D potentiated the thiopental-sleeping time in mice (to 200% of the control value), in doses higher than D there were signs of central excitation. Compound *Va* at doses D had antireserpine effects in mice in the test of ptosis as well as in the test of hypothermia; in higher doses again signs of central excitation. Compound *VIa* potentiated thiopental in mice at doses D and D/2. Compound *VIIa* (VÚFB-9965) was the most interesting one of the series: at the dose D it had incoordinating effects in the rotarod test in mice, antagonized pentetrazole convulsions in mice, had hyperthermic effect in rats, potentiated thiopental in mice, had antireserpine activity in mice in the tests of ptosis and hypothermia, and significant antiarrhythmic effect in rats (towards aconitine) and in mice (toward chloroform ventricular fibrillations); in doses higher than D signs of central excitation. Compound *VIIIa*: mild potentiation of thiopental in mice and at higher doses excitation. The amphetamine derivative *XI* (VÚFB-9966) elicited elevation of blood pressure in normotensive rats (short duration), antagonized significantly reserpine ptosis in mice and mildly the reserpine hypothermia, caused sedation at dose D but excitation at higher doses in mice. Most interesting was its significant anorectic activity in mice (an oral dose of 10 mg/kg suppressed food consumption by 50%; for comparison, the ED_{50} for dexphenmetrazine is 25 mg/kg *p.o.*). Important anorectic activity was described for the lower homologue of our compound, *i.e.* 1-(4-dimethylaminophenyl)-2-propylamine[12].

The compounds prepared were also tested for antimicrobial activity *in vitro* (microorganisms and the minimum inhibitory concentrations in μg/ml are given unless they exceed 125 μg/ml): *Streptococcus β-haemolyticus*, *IIa* 12·5, *IIIa* 12·5, *Va* 12·5, *VIa* 12·5, *VIIa* 12·5, *VIIIa* 12·5; *Staphylococcus pyogenes aureus*, *IIa* 6·25,

TABLE I

Amides *IIb*—*VIIIb* and Maleates of Amines *IIa*, *IIIa*, and *Va*—*VIIIa*

Compound[a]	Method (yield, %)	M.p., °C (solvent)	Formula (mol. wt.)	Calculated/Found		
				% C	% H	% N
IIb	*A* (70)	71—72[b] (benzene–hexane)	$C_{25}H_{27}NO$ (357·5)	83·98 83·84	7·61 7·51	3·92 3·87
IIIb	*A* (65)	106—107 (benzene–light petroleum)	$C_{26}H_{29}NO$ (371·5)	84·05 83·83	7·87 7·85	3·77 3·65
IVb[c]	*A* (65)	111—112 (benzene–light petroleum)	$C_{27}H_{31}NO$ (385·5)	84·11 83·88	8·11 8·29	3·63 3·24
Vb	*A* (67)	76—77[d] (benzene–hexane)	$C_{27}H_{31}NO_2$ (401·5)	80·76 80·59	7·78 7·89	3·49 3·62
VIb	*A* (81)	120—121 (aqueous ethanol)	$C_{28}H_{33}NO_2$ (415·6)	80·92 81·14	8·00 8·00	3·37 3·37
VIIb-HCl	*A* (86)	191—192 (ethanol–ether)	$C_{28}H_{35}ClN_2O$ (451·0)	74·55 74·39	7·83 7·98	6·21[e] 5·87
IIa-M[f]	*B* (79)	149—150 (ethanol)	$C_{29}H_{33}NO_4$ (459·6)	75·78 75·59	7·24 7·16	3·05 3·16
IIIa-M	*B* (82)	121—122 (ethanol–ether)	$C_{30}H_{35}NO_4$ (473·6)	76·08 76·08	7·45 7·60	2·96 2·82
Va-M	*B* (64)	114—115 (ethanol–ether)	$C_{31}H_{37}NO_5$ (503·6)	73·93 73·62	7·41 7·58	2·78 2·82
VIa-M[c]	B (30)	125—126 (ethanol–ether)	$C_{32}H_{39}NO_5$ (517·6)	74·23 74·24	7·60 7·57	2·71 2·68
VIIa-M	*B* (65)	127—128 (ethanol–ether)	$C_{32}H_{40}N_2O_4$ (516·7)	74·39 74·09	7·80 7·94	5·42 5·43
VIIIa-M	*B* (66)	112—113 (ethanol–ether)	$C_{30}H_{35}NO_4S$ (505·6)	71·25 71·36	6·98 7·26	2·77[g] 2·56

[a] M = hydrogen maleate. [b] IR spectrum: 695, 700, 737, 750 (C_6H_5), 1 496 (Ar), 1 536, 1 540, 1 642 (NHCO), 3 320 cm^{-1} (NH). [c] See Experimental. [d] IR spectrum: 695, 740, 750 (C_6H_5), 810 (2 adjacent Ar—H), 1 250 ($ArOCH_3$), 1 510 (Ar), 1 535, 1 640 (CONH), 3 330 cm^{-1} (NH). [e] Calculated: 7·86% Cl; found: 8·03% Cl. [f] The oily base was distilled, b.p. 220°C/70 Pa. For $C_{25}H_{29}N$ (343·5) calculated: 87·41% C, 8·51% H, 4·08% N; found: 86·75% C, 8·66% H, 3·99% N. [g] Calculated: 6·34% S; found: 6·60% S.

IIIa 12·5, *Va* 12·5, *VIa* 12·5, *VIIa* 12·5, *VIIIa* 25; *Mycobacterium tuberculosis* H37Rv, *IIa* 12·5, *IIIa* 12·5, *Va* 12·5, *VIa* 50, *VIIa* 12·5, *VIIIa* 25; *Saccharomyces pasterianus*, *VIa* 125; *Trichophyton mentagrophytes*, *Va* 125, *VIa* 125, *VIIa* 125, *VIIIa* 12·5; *Aspergillus niger*, *VIa* 125.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block and are not corrected. The samples were dried for 8 h *in vacuo* of about 25 Pa over P_2O_5 at room temperature or at 77°C. The IR spectra (in Nujol) were recorded with a Unicam SP 200 G spectrophotometer and the ^1H NMR spectra (in C^2HCl_3) with a ZKR-60 (Zeiss, Jena) spectrometer. TLC was used for checking the homogeneity of the substances and composition of the reaction mixtures (silica gel).

1-Phenyl-2-butylamine (*IX*)

A solution of 16·8 g 1-phenyl-2-nitrobutene[15] in 100 ml diethyl ether was added dropwise over 65 min to a stirred suspension of 12·0 g $LiAlH_4$ in 200 ml diethyl ether, and the mixture was refluxed for 3 h. After standing overnight it was cooled and decomposed under stirring by a slow addition of 50 ml 20% NaOH. The solid was filtered off, washed with diethyl ether, the filtrates were evaporated and the residue was distilled; 12·0 g (86%), b.p. 100–103°C/1·5 kPa, n_D^{24} 1·5122. Ref.[13], b.p. 98–99°C/1·3 kPa, n_D^{25} 1·5128.

1-(4-Methoxyphenyl)-2-butylamine (*X*)

A solution of 26·0 g 1-(4-methoxyphenyl)-2-nitrobutene[15] in 60 ml diethyl ether was added over 30 min to a stirred suspension of 20 g $LiAlH_4$ in 300 ml diethyl ether and the mixture was refluxed for 2 h. After cooling the mixture was decomposed by treatment with 80 ml 20% NaOH, the solid was filtered off and the filtrate was evaporated to a volume of about 100 ml. The base was extracted by shaking with a mixture of 25 ml conc. hydrochloric acid and 75 ml water, the separated aqueous solution was made alkaline with 20% NaOH and the base was isolated by extraction with benzene. The extract was dried with solid KOH, evaporated and the residue was distilled; 15·0 g (68%), b.p. 114–116°C/0·3 kPa. Ref.[14] disclosed only the m.p. of the hydrochloride (168°C).

1-(4-Dimethylaminophenyl)-2-butylamine (*XI*)

A solution of 25·0 g 1-(4-dimethylaminophenyl)-2-nitrobutene[15] in 70 ml benzene was slowly added to a stirred suspension of 11·0 g $LiAlH_4$ in 350 ml diethyl ether and the mixture was refluxed for 3 h. After cooling it was decomposed with 44 ml 20% NaOH, filtered and the filtrate distilled; 21·0 g (96%) crude *XI*, b.p. 130°C/0·3 kPa, n_D^{21} 1·5728. This product was transformed to the dihydrochloride by treatment with HCl in diethyl ether, m.p. 222–224°C (ethanol). For $C_{12}H_{22}Cl_2N_2$ (265·2) calculated: 54·34% C, 8·36% H, 26·74% Cl, 10·56% N; found: 54·29% C, 8·40% H, 26·48% Cl, 10·75% N.

N-(1-Phenyl-2-butyl)-2,5-diphenylvaleramide (*IVb*) (Method A)

A mixture of 10·2 g 2,5-diphenylvaleric acid[7] and 7·0 g *IX* was heated for 4 h to 195–210°C. After partial cooling it was dissolved in 80 ml benzene, the solution was washed with dilute

hydrochloric acid and 10% Na_2CO_3, dried with Na_2SO_4 and evaporated. The residue was dissolved in 10 ml warm diethyl ether and induced to crystallize by the addition of 30 ml light petroleum; 10·0 g (65%), m.p. 111–112°C (benzene–light petroleum). IR spectrum: 700, 750 (C_6H_5), 1 535, 1 545, 1 644 (CONH), 1 600 (Ar), 3 305 cm^{-1} (NH). ^1H NMR spectrum: δ 7·00–7·30 (m, 15 H, 3 C_6H_5), 5·10 (d, 1 H, NH), 4·00 (m, 1 H, CHN), 3·21 (t, J = 7·0 Hz, 1 H, CHAr), 2·64 (d, J = 6·0 Hz, 2 H, CH_2Ar in phenylbutyl), 2·55 (t, J = 7·0 Hz, 2 H, $ArCH_2$ in diphenylvaleryl), 1·00–2·30 (m, 6 H, remaining 3 CH_2), 0·70 (t, J = 7·0 Hz, 3 H, CH_3). Analysis is included in Table I.

N-[1-(4-Methoxyphenyl)-2-butyl]-2,5-diphenylpentylamine (*VIa*) (Method B)

A solution of 13·0 g *VIb* in 110 ml warm dibutyl ether was added dropwise to a stirred suspension of 5·0 g $LiAlH_4$ in 40 ml dibutyl ether and the mixture was refluxed for 6 h. After standing overnight at room temperature it was decomposed by a slow addition of 20 ml 20% NaOH, filtered, and the filtrate was evaporated *in vacuo* at 80°C. The residue (11·6 g oily base *VIa*) was dissolved in 140 ml diethyl ether and the solution was treated with a solution of 3·5 g maleic acid in 10 ml ethanol. The separated oily hydrogen maleate crystallized after 3 h standing at 4°C. It was filtered, washed with diethyl ether and dried; 4·80 g (30%), m.p. 115–118°C. Analytical sample, m.p. 125–126°C (ethanol–diethyl ether). ^1H NMR spectrum: δ 7·00–7·40 (m, 10 H, 2 C_6H_5), 6·96 (q, 2 H, 2, 6-H_2 in the remaining Ar), 6·70 (q, 2 H, 3,5-H_2 in the remaining Ar), 6·30 (s, 2 H, CH=CH of maleic acid), 3·74 (s, 3 H, OCH_3), 1·20–3·50 (m, 6 CH_2 and 2 CH), 0·91 (t, 3 H, C–CH_3). The analysis is included in Table I.

2,5-Diphenylpentanol (*XII*)

A solution of 15·0 g 2,5-diphenylvaleric acid[7] in 150 ml diethyl ether was added dropwise to a stirred suspension of 5·0 g $LiAlH_4$ in 60 ml diethyl ether, and the mixture was refluxed for 4 h. After cooling it was decomposed by addition of 20 ml 20% NaOH. It was filtered, the solid was washed with diethyl ether and the filtrate was distilled; 13·5 (96%), b.p. 168°C/70 Pa. ^1H NMR spectrum: δ 7·00–7·50 (m, 10 H, 2 C_6H_5), 3·65 (d, J = 6·0 Hz, 2 H, CH_2O), c. 2·75 (m, 1 H, CHAr), 2·55 (t, J = 6·0 Hz, $ArCH_2$), c. 1·55 (m, 4 H, CH_2CH_2), 1·45 (bs, disappears after ^2H_2O, 1 H, OH). For $C_{17}H_{20}O$ (240·3) calculated: 84·95% C, 8·39% H; found: 84·58% C, 8·37% H.

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