1-METHYL-, 1-PHENYL-, AND 1-(2-(2-DIMETHYLAMINOETHOXY)-PHENYL)-2,3,4,9-TETRAHYDRO-1*H*-PYRIDO[3,4-*b*]INDOLE AND THEIR 2-SUBSTITUTED DERIVATIVES: SYNTHESIS AND PHARMACOLOGICAL SCREENING

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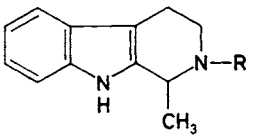
1-Methyl- and 1-phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (*I* and *IV*) were transformed via the chloroacetyl derivatives *II* and *V* to the 4-methylpiperazinoacetyl compounds *III* and *VI*; compound *VI* inhibits effectively the formation of the indomethacin-induced gastric ulcers in rats but is devoid of anticholinergic activity and does not inhibit the gastric secretion in rats. Reaction of tryptamine with 2-(2-dimethylaminoethoxy)benzaldehyde afforded compound *IX* which proved inactive in tests for antidepressant activity. Compounds *IV* and *IX* were treated with ethyl chloroformate and gave carbamates *VII* and *X*; compound *VII* does not show anticonvulsant activity.

Derivatives of 9*H*-pyrido[3,4-*b*]indole (β-carboline, norharman) and its 1,2,3,4-tetrahydro derivative occur in plants as alkaloids[1], and are presumed to be formed in animals as mammalian alkaloids[2,3]. They exert many important and useful pharmacodynamic activities, e.g. they interact with the benzodiazepine receptors in the brain and behave like their antagnists[4], act as serotonin uptake inhibitors in the brain[5], increase the prolactin level in the blood serum[6] and have antidopaminergic[7], antidepressant[8], and anticonvulsant activities[9]. Our team attempted to search in the series after antihypertensive agents as reserpine models[10–12] and in 1-benzyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole we found a strong central depressant which could be used to bring about model depressive states in humans[13]. In the present contribution we are describing several 2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indole derivatives which have been tested for antiulcer, anticonvulsant, and antidepressant activities.

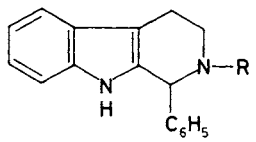
Tryptamine[14,15] was reacted with acetic anhydride to give the N-acetyl derivative[16] which was cyclized by the Bischler–Napieralski reaction[17] with phosphorus pentoxide in xylene to the crude 1-methyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole[16]. This was not isolated in pure state and characterized but diretly subjected to reduction with sodium borohydride in aqueous ethanol in the presence of sodium hydroxide (method[13]); *I* was obtained in moderate yield (the same compound was prepared previously[18–20] by the Pictet–Spengler synthesis[21]). Reaction of *I* with chloroacetyl

chloride by the known method[22] gave *II* which was treated with excessive 1-methylpiperazine at room temperature and gave 56% *III*.



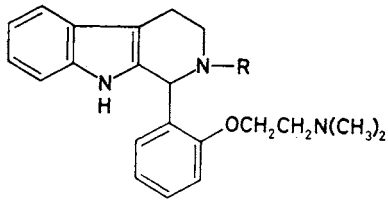
I, R = H
II, R = $COCH_2Cl$
III, R = $COCH_2N\bigcirc NCH_3$

Reaction of tryptamine[14,15] with benzoyl chloride was carried out using the known method[23] and resulted in N-benzoyltryptamine (cf. refs[24,25]) which was cyclized with phosphorus oxychloride in refluxing toluene, and the crude 1-phenyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole (cf. ref.[25]) was reduced with sodium borohydride in aqueous ethanol containing sodium hydroxide to *IV* (yield 56%) (method[13]). Compound *IV* was also prepared by the Pictet–Spengler synthesis[21] by reacting tryptamine hydrochloride[15] with benzaldehyde in a boiling mixture of ethanol and benzene in the presence of a small amount of dilute hydrochloric acid using the described procedure[26] (cf. also ref.[27] and for different procedures refs[10,28]). Reaction of *IV* with chloroacetyl chloride in chloroform in the presence of triethylamine at room temperature gave the not homogeneous *V* (characterized by the mass spectrum) which reacted similarly like in the preceding case with 1-methylpiperazine and gave *VI* in a good yield. Treatment of *IV* with a slight excess of ethyl chloroformate in boiling benzene gave the carbamate *VII* together with the hydrochloride of the starting *IV* (ref.[26]). The structure of *VII* was confirmed by spectra and the compound was reduced with lithium aluminium hydride in ether to the known *VIII* (ref.[27]).



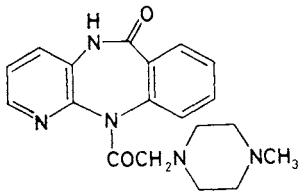
IV, R = H
V, R = $COCH_2Cl$
VI, R = $COCH_2N\bigcirc NCH_3$
VII, R = $COOC_2H_5$
VIII, R = CH_3

Refluxing a mixture of tryptamine hydrochloride[15] with 2-(2-dimethylaminoethoxy)benzaldehyde[29], ethanol, benzene, and a small amount of dilute hydrochloric acid afforded the hydrochloride of *IX*. The released base was characterized by spectra confirming structure *IX*. Treatment of *IX* with ethyl chloroformate in boiling benzene afforded the hydrochloride of *X* (monohydrate).



IX, R = H
X, R = $COOC_2H_5$

Compound *VI* was considered an analogue of the antiulcer and antisecretory agent pirenzepine (*XI*) (refs[30–33]) and was, therefore, tested in this line. Its acute toxicity in mice, LD_{50} = 906 mg/kg orally (for *XI*, LD_{50} > 2 500 mg/kg p.o.). The testing of the antiulcer effect used the indomethacin-induced gastric lesions in rats (method[34]); *VI* inhibited very effectively the formation of these lesions; ED_{50} = = 26·3 mg/kg p.o. (for *XI*, ED_{50} = 32·7 mg/kg p.o.). Our compound was thus more active than pirenzepine. Pyloric ligated rats were used to evaluate the effect of *VI* on gastric secretion (method[35]). The dose of 50 mg/kg p.o. of *VI* did not inhibit the parameters investigated; on the contrary there was a clear indication of raising these parameters (*XI* in the same dose had very high antisecretory effect). Because the anticholinergic activity appears very often as a typical effect of antiulcer and antisecretory agents, it was also investigated with *VI*. This activity was assessed in the first line by means of the mouse mydriasis test[36]. Pirenzepine (*XI*) as a standard had significant mydriatic effect in doses of 10 and 100 mg/kg p.o. and the effect was dose-dependent. *VI* in the oral dose of 100 mg/kg was inactive. A further criterion of anticholinergic activity used was the evaluation of the affinity of *VI* to muscarinic receptors in the rat brain using 0·5 nmol l^{-1} [^{3}H]quinuclidinyl benzilate as the ligand; IC_{50} = 22 052 nmol l^{-1} (for *XI*, IC_{50} = 275·5 nmol l^{-1}). Pirenzepine (*XI*) is thus a rather strong anticholinergic compound and *VI* is very weak. The results mentioned do not warrant any more detailed testing of *VI*.



XI

Compound *VII* was considered a possible anticonvulsant. Its acute toxicity in mice, LD_{50} > 1 000 mg/kg p.o. In the dose of 10 mg/kg p.o. in the electroshock test in mice it did not show anticonvulsant activity and did not influence the lethality

rate. In the test of inhibition of the spontaneous motor activity of mice (Dews), its $ED_{50} > 10$ mg/kg p.o. in the intervals of 1 and 3 h after the administration.

Compound *IX* was submitted to tests for antidepressant activity. Acute toxicity in mice, $LD_{50} > 500$ mg/kg p.o. In the test of reserpine-induced hypothermia in mice, the dose of 10 mg/kg p.o. was without effect. The oral dose of 25 mg/kg had not significant effect towards the reserpine ptosis in mice. In the test of reserpine--induced gastric ulcers in rats, the oral dose of 50 mg/kg was ineffective. The oral dose of 10 mg/kg did not influence the locomotor activity in mice (test of Dews). In concentrations of 100 nmol l^{-1} *IX* did not significantly inhibit the binding of 4 nmol l^{-1} [^{3}H]imipramine and 4 nmol l^{-1} [^{3}H]desipramine to the binding sites in rat hypothalamus. Compound *IX* lacks completely the character of a potential antidepressant.

EXPERIMENTAL

The melting points were determined in a Kofler block and they are not corrected; the samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at suitably elevated temperature. The UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded with a Unicam SP 8 000 spectrophotometer, the IR spectra (in Nujol, ν in cm^{-1}) with a Perkin–Elmer spectrophotometer, ^{1}H NMR spectra (in C^2HCl_3 unless stated otherwise, δ, J in Hz) with a Tesla BS 487C (80 MHz) spectrometer, and finally the mass spectra (m/z and % given) with MCH 1 320 and Varian MAT 44S spectrometers. The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The solutions were dried with $MgSO_4$ and evaporated on a rotating evaporator under reduced pressure.

1-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (*I*)

A stirred solution of 3·85 g N-acetyltryptamine[16] (m.p. 75°C) in 250 ml xylene was treated with 15 g P_2O_5, the mixture was refluxed for 2 h, after cooling treated with further 15 g P_2O_5, and the refluxing was continued for 1 h. After cooling the solid was filtered, washed with ether, decomposed with 150 ml water and 100 ml dilute hydrochloric acid, and the suspension was heated until dissolution. After cooling the solution was washed with ether, the aqueous layer was made alkaline with 10% NaOH, and extracted with ether. Evaporation of the extract gave the crude 1-methyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole[16] which was dissolved in 100 ml ethanol, the stirred solution was treated with 30 ml 10% NaOH, and then slowly at 45—50°C with 1·7 g $NaBH_4$. The mixture was stirred for 30 min at 50—55°C, diluted with water, and extracted with dichloromethane. Processing of the extract gave 1·0 g (28%) *I*, m.p. 176—177°C. Refs[18–20], m.p. 179—180 and 178—180°C, respectively.

1-Phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (*IV*)

A) N-Benzoyltryptamine[23] (4·2 g, m.p. 143°C) was added over 5 min to a refluxing mixture of 50 ml toluene and 7·5 ml $POCl_3$, the mixture was stirred and refluxed for 1 h, treated with further 5·0 ml $POCl_3$ and the refluxing was continued for 1 h. Volatile components were evaporated in vacuo, the residue (the crude 1-phenyl-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole[25]) was dissolved in 100 ml ethanol, the solution was treated with 40 ml 10% NaOH, and under stirring

slowly with 1·7 g $NaBH_4$. The mixture was stirred for 30 min at room temperature and allowed to stand overnight. The separated product was filtered and crystallized from ether; 2·2 g (56%), m.p. 166–168°C. Ref.[28], m.p. 167–168°C.

B) Refluxing a mixture of 78·6 g tryptamine hydrochloride[15], 42·4 g benzaldehyde, 1 000 ml ethanol, 400 ml benzene, 20 ml water, and 3 ml hydrochloric acid for 8 h, and processing the mixture[26] gave 65·5 g (58%) hydrochloride of *IV*, m.p. 265–270°C. Ref.[26], m.p. 267–270°C. Treatment of this salt with 10% NaOH and extraction with ether gave the base *IV*, m.p. 168 to 170°C (aqueous ethanol), identical with the product obtained under *A*).

1-(2-(2-Dimethylaminoethoxy)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (*IX*)

A mixture of 9·65 g 2-(2-dimethylaminoethoxy)benzaldehyde[29], 9·87 g tryptamine hydrochloride[15], 125 ml ethanol, 50 ml benzene, 2·5 ml water, and 5 drops hydrochloric acid was stirred and refluxed for 12 h. After standing overnight, the hydrochloride of *IX* was filtered; 15·8 g, m.p. 250–258°C. Processing of the mother liquor gave further 1·2 g *IX*.HCl, the total yield being 17·0 g (92%). Crystallization from ethanol gave the homogeneous compound, m.p. 254–258°C. For $C_{21}H_{26}ClN_3O$ (371·9) calculated: 67·82% C, 7·05% H, 9·53% Cl, 11·30% N; found: 67·68% C, 7·20% H, 9·56% Cl, 11·02% N.

IX. HCl (15·0 g) was decomposed by shaking with 300 ml 10% NaOH and the base *IX* was isolated by extraction with ether; 10·2 g, m.p. 130–131°C (benzene). IR spectrum: 740, 753 (4 adjacent Ar—H); 1 235, 1 252 (ArOR); 1 490, 1 586, 1 595, 3 050 (Ar); 2 720 (N—CH_3); 3 320 (NH). ^{1}H NMR spectrum: 2·20 bs, 1 H (NH); 2·30 s, 6 H ($N(CH_3)_2$); 2·40–4·40 m, 8 H (OCH_2CH_2N, 2 H-3, and 2 H-4); 5·60 bs, 1 H (H-1); 6·70–7·60 m, 8 H (8 ArH); 9·65 bs, 1 H (H-9). For $C_{21}H_{25}N_3O$ (335·5) calculated: 75·19% C, 7·51% H, 12·53% N; found: 75·30% C, 7·55% H, 12·25% N.

2-(Chloroacetyl)-1-phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (*V*)

A solution of 6·5 g *IV* in 120 ml warm chloroform was cooled, 8 ml triethylamine were added, and the stirred mixture was treated at room temperature with 5·0 ml chloroacetyl chloride, added dropwise. The mixture was stirred for 2 h at room temperature, diluted with chloroform, the solution was washed with water, 2% hydrochloric acid, water, and 10% K_2CO_3, dried, evaporated, and allowed to crystallize; 4·7 g (55%) product which could not be obtained homogeneous even after repeated crystallization from chloroform or a mixture of dioxane and toluene, m.p. 244–245°C. Mass spectrum: 324 (M^+, $C_{19}H_{17}ClN_2O$, 10), 289 (30), 247 (17), 246 (19), 245 (21), 218 (75), 217 (69), 185 (100), 169 (40), 144 (59), 115 (79). For $C_{19}H_{17}ClN_2O$ (324·8) calculated: 70·26% C, 5·28% H, 10·92% Cl, 8·62% N; found: 69·46% C, 5·28% H, 11·50% Cl, 8·29% N.

1-Methyl-2-(4-methyl-1-piperazinyl)acetyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (*III*)

A mixture of 1·0 g *II* (ref.[22], m.p. 168–171·5°C) and 7·0 ml 1-methylpiperazine was stirred for 4 h at room temperature, diluted with benzene, the solution was washed with water, dilute NH_4OH, and water, dried, and evaporated; 0·7 g (56%) *III*, m.p. 203–205°C (chloroform–ether). IR spectrum: 753, 761 (4 adjacent Ar—H); 1 580, 3 030 (Ar); 1 628 (>NCOR); 2 790 (N—CH_3); 3 175 (NH). ^{1}H NMR spectrum: 1·50 d, 3 H (C—CH_3, J = 6·5); 2·25 s, 3 H (NCH_3); 2·52 bs, 8 H ($4CH_2N$ of piperazine); 2·70–4·30 m, 6 H ($CH_2CH_2NCOCH_2N$); 5·75 bq, 1 H (H-1, J = 6·5); 7·00–7·50 m, 4 H (4 ArH); 9·18 bs, 1 H (H-9). For $C_{19}H_{26}N_4O$ (326·4) calculated: 69·91% C, 8·03% H, 17·16% N; found: 69·68% C, 7·93% H, 16·96% N.

2-(4-Methyl-1-piperazinyl)acetyl-1-phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (*VI*)

A mixture of 4·7 g *V* and 20 ml 1-methylpiperazine was stirred for 2 h at room temperature, diluted with benzene, the solution was washed with dilute NH_4OH and water, dried, and evaporated. The residue was crystallized from a mixture of ethanol and ether; 4·3 g (72%) 2 : 1 solvate of *VI* with ethanol, m.p. 148–151·5°C. Mass spectrum: 388 (M^+, $C_{24}H_{28}N_4O$, 2), 288 (4), 287 (5·5), 247 (4·5), 245 (4·2), 218 (10), 113 (99), 70 (100), 42 (41). IR spectrum: 704, 742, 751 (5 and 4 adjacent Ar—H); 1 489, 1 590, 3 050 (Ar); 1 640 (>NCOR); 3 250 (NH, OH). ^{1}H NMR spectrum: 2·18 s, 3 H (NCH_3); 2·40 bs, 8 H (4 CH_2N of piperazine); 2·70–3·50 m, 6 H (CH_2CH_2.$NCOCH_2N$); 4·10 m, 1 H (H-1); 6·80–7·60 m, 9 H (9 ArH); 8·75 bs, 1 H (H-9). For $C_{24}H_{28}N_4O$ + 0·5 C_2H_6O (411·6) calculated: 72·96% C, 7·59% H, 13·61% N; found: 72·74% C, 7·36% H, 13·26% N.

Dihydrochloride, 1 : 1 solvate with ethanol, m.p. 198–202°C (ethanol–ether). For $C_{24}H_{30}Cl_2$.N_4O + C_2H_6O (507·5) calculated: 61·57% C, 7·15% H, 13·97% Cl, 11·04% N; found: 61·48% C, 7·05% H, 14·19% Cl, 11·27% N.

2-(Ethoxycarbonyl)-1-phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (*VII*)

A warm solution of 6·2 g *IV* in 100 ml benzene was added dropwise to a stirred and refluxed solution of 3·25 g ethyl chloroformate in 40 ml benzene, the mixture was refluxed for 2 h and cooled. The precipitated *IV*.HCl (3·3 g, 42%, m.p. 264–268°C) was filtered off, the filtrate was washed with 10% H_2SO_4, dried, and evaporated; 3·8 g (47%) *VII*, m.p. 192–193°C (benzene). UV spectrum: 224 (4·62), 273 (3·93), 280 (3·93), 290 (3·81). IR spectrum: 700, 735, 765 (5 and 4 adjacent Ar—H); 1 105, 1 115, 1 230, 1 258, 1 665 (>NCOOR); 1 489, 1 590, 1 618, 3 010, 3 020, 3 050, 3 080 (Ar); 3·310 (NH). ^{1}H NMR spectrum: 1·22 t, 3 H (CH_3 of ethyl, J = 7·0); 2·70–3·30 m, 3 H and 4·30 m, 1 H (CH_2CH_2N); 4·13 q, 2 H (CH_2O, J = 7·0); 6·39 bs, 1 H (H-1); 7·20 m, 3 H (H-6, H-7, H-8); 7·25 s, 5 H (C_6H_5); 7·50 m, 1 H (H-5); 7·90 bs, 1 H (H-9). For $C_{20}H_{20}N_2O_2$ (320·4) calculated: 74·97% C, 6·29% H, 8·74% N; found: 74·89% C, 6·34% H, 8·44% N.

2-(Ethoxycarbonyl)-1-(2-(2-dimethylaminoethoxy)phenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (*X*)

A solution of 5·0 g *IX* in 60 ml benzene was added dropwise to a stirred and refluxing solution of 1·95 g ethyl chloroformate in 40 ml benzene, the mixture was refluxed for 4 h, and cooled. The precipitated *X*.HCl was filtered and crystallized from benzene; 5·5 g (91%), m.p. 231–234°C. Crystallization of the analytical sample was carried out from a mixture of aqueous ethanol and ether which was accompanied by formation of the monohydrate, m.p. 155–160°C. Mass spectrum: 407 (M^+, $C_{24}H_{29}N_3O_3$, 30), 335 ($C_{20}H_{19}N_2O_3$, 6), 307 ($C_{18}H_{15}N_2O_3$, 2), 247 ($C_{17}H_{15}N_2$, 7), 72 ($C_4H_{10}N$, 77), 58 (C_3H_8N, 100). UV spectrum: 272 (4·05), 278 (4·04), 290 (3·86). IR spectrum: 744 (4 adjacent Ar—H); 1 100, 1 230 (ArOR, C—O in NCOOR); 1 589, 1 600 (Ar); 1 660 (>NCOOR); 2 470, 2 640, 2 680, 2 720 (NH^+); 3 190, 3 370 (NH and H_2O). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): 1·25 t, 3 H (CH_3 in ethyl, J = 7·0); 2·50–3·70 m, 5 H (CH_2CH_2NCHAr); 2·98 s, 6 H ($N(CH_3)_2$); 3·60 bm, 2 H (CH_2N); 4·19 q, 2 H ($COOCH_2$, J = 7·0); 4·52 bm, 2 H ($ArOCH_2$); 6·80–7·60 m, 8 H (8 ArH). For $C_{24}H_{30}ClN_3O_3$ + H_2O (462·0) calculated: 62·39% C, 7·00% H, 7·67% Cl, 9·09% N; found: 62·23% C, 6·90% H, 7·93% Cl, 9·09% N.

2-Methyl-1-phenyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (*VIII*)

A solution of 4·8 g *VII* in 250 ml ether was added dropwise over 1 h to a stirred solution of 1·8 g $LiAlH_4$ in 20 ml ether. The mixture was refluxed for 3 h, under cooling decomposed by a slow addition of 2 ml water, 2 ml 15% NaOH, and 6 ml water, stirred for 30 min, and the solid was filtered off. The filtrate was dried, evaporated, and the residue was crystallized from 8 ml benzene; 2·8 g (72%) *VIII*, m.p. 94–95°C. Ref.[27] (methylation of *IV* with formaldehyde and formic acid), m.p. 95°C.

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