POTENTIAL ANTIDEPRESSANTS: N-PHENACYL DERIVATIVES OF (*E*)-N-METHYL-3-(6,11-DIHYDRODIBENZO[*b*, *e*]THIEPIN-11-YLIDENE)-PROPYLAMINE

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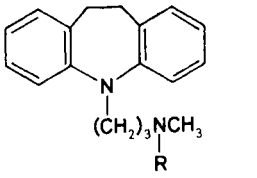
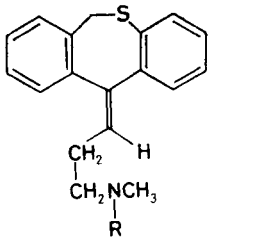
Reactions of (*E*)-N-methyl-3-(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propylamine (*V*) with phenacyl chloride and 4-chlorophenacyl bromide in chloroform in the presence of sodium or potassium carbonate afforded the title compounds *VI* and *VII*. Their hydrochlorides showed very low acute toxicity in mice but in comparison with prothiadene (*IV*), they were less effective in the common animal tests used for assessing the thymoleptic activity (inhibition of reserpine-induced hypothermia and ptosis in mice, potentiation of yohimbine toxicity in mice, anticataleptic action in rats). These activity relations are in disagreement with those published for the analogous pair of 10,11-dihydrodibenz[*b*,*f*]azepine derivatives imipramine (*I*) and lofepramine (*III*).

In the classical series of antidepressants derived from 10,11-dihydrodibenz[*b*,*f*]azepine, substitution of N-methyl in the molecule of imipramine (*I*) (ref.[1]) or of N-hydrogen in the molecule of its active metabolite desipramine (*II*) (ref.[2]) with 4-chlorophenacyl led to a further clinically useful compound *III* known as lofepramine (LEO 640, Gamonil^{R}, Amplit^{R}) (refs[3-6]). Compound *III* differs from *I* and *II* mainly by its higher lipophility, lower basicity, much lower acute toxicity, and lower anticholinergic activity. On the other hand, *III* is practically equipotent with *I* and *II* in tests for antireserpine activity in mice and rats (hypothermia, ptosis). Its lower antiadrenergic effects explain its lower cardiotoxicity[7]. Its metabolic N-dealkylation in the rat[8,9] and in human[10,11] proceeds as removal of the 4-chlorophenacyl group, the major metabolite being desipramine (*II*). In the parallel series of antidepressants derived from 6,11-dihydrodibenzo[*b*,*e*]thiepin with prothiadene (dosulepin) (*IV*) (ref.[12]) and northiadene (*V*) (ref.[13]) as leading substances, the introduction of larger groups as N-substituents led to rather disappointing results in the line of activity of these products[14]. It must be admitted, however, that molecules of the main part of these compounds contained hydroxyl or ester groups and that their lipophility was probably not much increased in comparison with that of *IV* and *V*. For this reason, the synthesis of *VI* and *VII*, analogous to lofepramine (*III*), has recently been carried out. The availability of homogeneous (*E*)-*V* (ref.[15]) formed the material basis of these preparations.

Compound *V* was reacted with phenacyl chloride and 4-chlorophenacyl bromide[16] in boiling chloroform in the presence of sodium carbonate or potassium carbonate to give *VI* and *VII*. The homogeneous oily bases were obtained by chromatography



I, R = CH_3
II, R = H
III, R = CH_2CO–C$_6$H$_4$–Cl



IV, R = CH_3
V, R = H
VI, R = $CH_2COC_6H_5$
VII, R = CH_2CO–C$_6$H$_4$–Cl

of the crude products on silica gel and were transformed to hydrochlorides. The pure bases were released from the recrystallized hydrochlorides and were used for recording the spectra. The IR spectra confirmed the unchanged (*E*)-configuration (cf. refs[14,15]). In the case of synthesis of *VI*, there was a more polar by-product which was eluted after *VI*; it was identified as the hydrochloride of the starting *V* (cf. ref.[15]).

Compounds *VI* and *VII* were pharmacologically tested in the form of hydrochlorides (the doses given were calculated per bases) as potential antidepressants and were compared with *IV* and/or *V*. In the in vivo tests, the substances were administered orally. In comparison with prothiadene (*IV*), the acute toxicity of the new compounds in mice is much lower. Doses of 1 g/kg of *VI* and *VII* did not elicit any toxic symptoms; LD_{50} of *IV* is 224 mg/kg. In the rotarod test in mice *VI* showed a clear discoordinating action in high (but still nontoxic) doses; ED_{50} = 584 mg/kg. Compound *VII* was inactive in doses of 100, 250, and 500 mg/kg; the dose of 1 000 mg/kg brought about ataxia in 20% animals. For prothiadene (*IV*), the ED_{50} is about 100 mg/kg which is already in the range of subtoxic doses. In the test of reserpine-induced hypothermia in mice[17], *VI* showed a mild antagonistic effect; D_{50} = 134 mg/kg (for comparion the D_{50} of *IV* was 9·5 and for *V* 11·5 mg/kg). Reserpine ptosis in mice was antagonized significantly with *VI* starting with the dose of 300 mg/kg; the antagonistic effect of *VII* started with the dose of 1 000 mg/kg (for *IV* the minimum effective dose with a statistically significant antagonism was 25 mg/kg). In the test of potentiation of yohimbine lethality in mice, ED_{50} of *VI* was 241 mg/kg, for *VII* about 1 000 mg/kg (it was administered in doses of 100, 250, 500, and 1 000 mg/kg; the highest dose given potentiated in 50% of the animals).

The ED_{50} in this test for *IV* and *V* were 31·5 and 39·9 mg/kg, respectively. In rats, oral doses of 100, 250, and 500 mg/kg *VI* did not antagonize the cataleptic effect of perphenazine; on the other hand, the PD_{50} doses for the anticataleptic effect of *IV* and *V* were 42·9 and 42·0 mg/kg, respectively. Compounds *VI* and *VII* inhibited mildly the binding of 4 nmol l^{-1} (^{3}H)imipramine and of 4 nmol l^{-1} (^{3}H)desipramine in rat hypothalamus. In the case of imipramine, *VI* in the concentration of 100 nmol . l^{-1} inhibited by 35%; IC_{50} values in nmol l^{-1}: *VII*, 263; *IV*, 36·4; *V*, 260·8. For desipramine binding the IC_{50} values in nmol l^{-1} were: *VI*, 355; *VII*, 581; *IV*, 299; *V*, 118. In conclusion, the N-phenacyl derivatives of northiadene *VI* and *VII* are little toxic and significantly less active in the tests for antireserpine activity than prothiadene (*IV*) and northiadene (*V*). In the affinities to the imipramine and desipramine binding sites in the rat hypothalamus, the differences were not so significant. The structural change, which led in the imipramine–desipramine series to a new antidepressant agent (lofepramine, *III*), proved unsuitable in the prothiadene–northiadene series.

EXPERIMENTAL

The melting points were determined in Kofler block and were not corrected; the samples were dried in vacuo of about 60 Pa over P_2O_5 at 100°C. The UV spectra (λ_{max} in nm (log ε)) were recorded with a Unicam SP 8 000 spectrophotometer, IR spectra (ν in cm^{-1}) with Perkin–Elmer 298 spectrophotometer, and ^{1}H NMR spectra (δ, J in Hz) with a Tesla BS 487 C (80 MHz) spectrometer. The homogeneity of the substances and fractions was checked by thin-layer chromatography on silica gel (Silufol).

(*E*)-N-Methyl-N-phenacyl-3-(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propylamine (*IV*)

A stirred mixture of 14·1 g *V* (ref.[15]), 25 ml chloroform, and 5·3 g Na_2CO_3 was treated over 15 min with a solution of 7·7 g phenacyl chloride in 15 ml chloroform. The reaction was slightly exothermic. The mixture was stirred for 2 h at room temperature and then refluxed for 30 min. After cooling it was diluted with 50 ml dichloromethane, the solid was filtered off and washed with dichloromethane, and the filtrate was evaporated under reduced pressure. The inhomogeneous residue was chromatographed on a column of 50 g silica gel (Merck). A mixture of 90% benzene and 10% chloroform eluted the unchanged phenacyl chloride. The following elution with chloroform alone gave 9·9 g (49%) oily *IV* which was dissolved in 22 ml ethanol and the solution was acidified with a solution of HCl in ether. Addition of ether led to crystallization of the hydrochloride, m.p. 189–193°C with decomposition (ethanol–ether). UV spectrum (CH_3OH): 233·5 (4·49), infl. 246 (4·40), infl. 272 (3·95), 302·5 (3·49). IR spectrum (Nujol): 684, 760 (5 adjacent Ar—H); 732, 760, 787 (4 adjacent Ar—H); 1 490, 1 585, 1 600 (Ar); 1 695 (ArCOR); 2 450, 3 285 (NH^+); in CS_2: 732, 750, 766 (indicates the (*E*)-configuration). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): 2·50 bt, 2 H (CH_2N^+ in aminopropylidene); 2·85 s, 3 H (N^+CH_3); 3·35 bt, 2 H (CH_2 in the middle of propylidene); 3·60 d, 1 H and 4·80 d, 1 H (ABq, $ArCH_2S$, J = 13·0); 5·10 s, 2 H ($COCH_2N^+$); 5·95 t, 1 H (C=CH, J = 7·0); 6·90–7·50 m, 8 H (8 ArH of the tricycle); 7·65 m, 3 H (H-3, H-4 and H-5 of benzoyl); 8·00 m, 2 H (H-2 and H-6 of benzoyl). For $C_{26}H_{26}ClNOS$ (436·0) calculated: 71·62% C, 6·01% H, 8·13% Cl, 3·21% N, 7·35% S; found 71·37% C, 6·17% H, 8·40% Cl, 3·17% N, 7·67% S.

A sample of the hydrochloride was decomposed with NH_4OH and the homogeneous oily base was isolated by extraction with ether. Its ^1H NMR spectrum was also recorded (C^2HCl_3): 2·12 m, 2 H (CH_2 in the middle of propylidene); 2·18 s, 3 H (NCH_3); 2·52 bt, 2 H (CH_2N in aminopropylidene); 3·65 s, 2 H ($COCH_2N$); 3·20 bd, 1 H and 4·82 bd, 1 H (ABq, $ArCH_2S$, J = 13·0); 5·80 t, 1 H (C=CH, J = 7·0); 6·80–7·50 m, 11 H (8 ArH of the tricycle and H-3, H-4, and H-5 of benzoyl); 7·88 m, 2 H (H-2 and H-6 of benzoyl).

The chromatography, which led to *IV*, was continued using a mixture of 95% chloroform and 5% methanol. There were eluted 2·5 g crystalline compound, m.p. 247–250°C (toluene–ethanol), which was identified as *V* hydrochloride. ^1H NMR spectrum ($C^2H_3SOC^2H_3$): 2·30 m, 2 H (CH_2 in the middle of propylidene); 2·42 s, 3 H (CH_3N^+); 2·91 bt, 2 H (CH_2N^+); 3·55 bd, 1 H and 4·78 bd, 1 H (ABq, $ArCH_2S$, J = 13·0); 5·90 t, 1 H (C=CH, J = 7·0); 6·70 to 7·50 m, 9 H (8 ArH and NH^+). Ref.[15], m.p. 244–246°C.

N-(4-Chlorophenacyl)-N-methyl-3-(6,11-dihydrodibenzo[*b*,*e*]-thiepin-11-ylidene)propylamine (*V*)

A stirred solution of 11·2 g *V* (ref.[15]) in 30 ml chloroform was treated with 5·8 g K_2CO_3, and then slowly with 9·35 g 4-chlorophenacyl bromide (it was obtained by bromination of 4-chloroacetophenone[16], cf. analogy[18], m.p. 96–98°C). The mixture was stirred for 1 h at room temperature and then refluxed for 2 h. After cooling the mixture was diluted with 50 ml chloroform and washed with 50 ml water. After drying with K_2CO_3 the chloroform solution was evaporated and the residue was chromatographed on 150 g silica gel (Merck 40). The fractions, obtained by elution with benzene, were discarded. Elution with mixtures of benzene and chloroform and with chloroform alone gave 8·4 g (48%) oily *V* which was transformed by treatment with HCl in ethanol–ether to the hydrochloride (5·7 g), m.p. 190–194°C (ethanol–ether). For $C_{26}H_{25}Cl_2NOS$ (470·5) calculated: 66·38% C, 5·36% H, 15·07% Cl, 2·98% N, 6·81% S; found: 66·41% C, 5·48% H, 14·97% Cl, 2·76% N, 6·77% S.

The base, which was released from the salt by treatment with NH_4OH and isolated by extraction with ether, was used for recording the spectra. UV spectrum (CH_3OH): 231 (4·36), 303 (3·40). IR spectrum (film): 750, 764, 832 (4 and 2 adjacent Ar—H); 1 582, 1 587, 3 015, 3 055 (Ar); 1 678 (ArCO); 1 620 (Ar_2C=C); 2 792 (N—CH_3); in CS_2: 700, 729, 747, 761 (corresponds to (*E*)-configuration). ^1H NMR spectrum (C^2HCl_3): 2·18 t, 2 H (CH_2 in the middle of propylidene, J = 6·0); 2·18 s, 3 H (NCH_3); 2·52 t, 2 H (CH_2N in aminopropylidene, J = 6·0); 3·25 bd, 1 H and 4·80 bd, 1 H (ABq, $ArCH_2S$, J = 13·0); 3·62 s, 2 H ($COCH_2N$); 5·82 t, 1 H (C=CH, J = 7·0); 6·80—7·30 m, 8 H (8 ArH in the tricycle); 7·30 d, 2 H (H-3 and H-5 in 4-chlorobenzoyl, J = 9·0); 7·90 d, 2 H (H-2 and H-6 in 4-chlorobenzoyl, J = 9·0).

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