ESTERS OF 1-[4,4-BIS(4-FLUOROPHENYL)BUTYL]-4-(4-CHLORO-3-TRIFLUOROMETHYLPHENYL)-4-PIPERIDINOL*

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1-[4,4-Bis(4-fluorophenyl)butyl]-4-(4-chloro-3-trifluoromethylphenyl)-4-piperidinol (*I*) was transformed by reactions with acetyl chloride, decanoyl chloride and 3,4,5-trimethoxybenzoyl chloride to the esters *II*—*IV*. The acetate *II*, administered orally, was compared with the amino alcohol *I* in the tests of antiapomorphine actions in rats and dogs and was found inactive. The decanoate *III*, which was administered intramuscularly to dogs, proved properties of an ultra-long-acting depot neuroleptic.

In connection with our studies of the syntheses of the neuroleptically active 1-[4,4-bis-(4-fluorophenyl)butyl]-4-(4-chloro-3-trifluoromethylphenyl)-4-piperidinol (*I*) (ref.[1,2]) (penfluridol[3,4]) we have prepared esters *II* – *IV* by reactions of *I* with acetyl chloride, decanoyl chloride[5] and 3,4,5-trimethoxybenzoyl chloride[6] in chloroform. The decanoate *III* exhibited effects of an ultra-long-acting neuroleptic which was not considered surprising. The present publication was induced by recent reports on the very favourable clinical results with the ester *V* (haloperidol decanoate) (ref.[7–10]), exhibiting after a single intramuscular dose of 50 – 500 mg an antipsychotic effect in schizophrenic patients lasting for four weeks.

Penfluridol acetate (*II*) and decanoate (*III*) were tested in rats and dogs for their antiapomorphine activities. The acetate *II* (in the form of hydrogen oxalate) in oral doses of 10 and 30 mg/kg did not influence with statistical significance the apomorphine stereotypies (chewing) and agitation in rats in the intervals of 4, 24 and 48 h after the administration. Further it was administered in an oral dose of 0·1 mg/kg to a group of four dogs in which emesis was elicited with apomorphine. A blockade of the apomorphine emesis was found only with one animal from the group and this only on the 2nd and 3rd day after the administration of penfluridol acetate. The 7th day after the administration, the emetic response after apomorphine appeared in all animals of the group. The same dose of penfluridol (*I*) (0·1 mg/kg orally), administered to another group of 4 dogs, blocked the apomorphine emesis in all animals of the group on the 2nd and 3rd day after the administration. Even on the 7th

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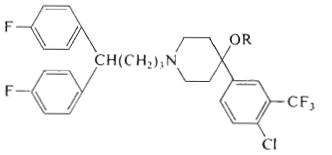
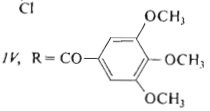
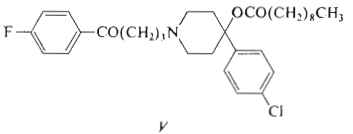
day, the emetic reaction was totally blocked in 3 animals and in the 4th one its frequency was significantly decreased. While the antiapomorphine effect of the orally administered free penfluridol (*I*) in dogs is significant and long-lasting, its acetate *II* is practically inactive in this line.



I, R = H
II, R = $COCH_3$
III, R = $CO(CH_2)_8CH_3$



IV, R = CO-



V

Penfluridol decanoate (*III*) was tested as a potential depot neuroleptic agent, *i.e.* it was administered intramuscularly. The criterion of activity was again the ability of the drug to block the emetic reaction after apomorphine in dogs. The decanoate was used in the form of a solution in Miglyol containing 25 mg in 1 ml. In a preliminary experiment, the supposed long-lasting blockade of the apomorphine emesis was confirmed. For an unambiguous evaluation, a comparison with free penfluridol (*I*) was carried out which likewise was used in the form of a solution in Miglyol (25 mg/1 ml) and administered also intramuscularly. Both compounds were administered in a single dose of 0·5 mg/kg to six-membered groups of dogs, in which in week's intervals the reaction to a standard dose of apomorphine was tested. The effect was followed for 10 weeks. Penfluridol (*I*) blocked the apomorphine reaction totally in the first three weeks, in the 5th week the blockade of emesis was less than with 50% animals and disappeared then. Penfluridol decanoate (*III*) blocked the apomorphine effects in the first two weeks only in 5 dogs of the group of six (83%), in the 3rd and 4th week the blockade of the apomorphine effect was total (100% animals protected) and even in the 7th week, 50% animals were protected. Only in the 8th week the percentage of the protected animals decreased below 50% and until the 10th

week the effects disappeared. Penfluridol decanoate (*III*) appears thus to be an ultra--long-acting depot neuroleptic agent, the action of which develops more slowly than that of penfluridol (*I*), but lasts practically twice as long. It is interesting that both of the compounds compared (*I*, *III*) did not exhibit in intramuscular doses of 1 and 5 mg/kg catalepsy in rats in the usual intervals of 1–4 h after the administration; negative findings were noted also after 48 h and on the 5th day after the administration.

EXPERIMENTAL

The melting points 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 77°C. The UV spectrum (in CH_3OH) was recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (in Nujol) with a Unicam SP 200G spectrophotometer and the ^{1}H-NMR spectra (in $CDCl_3$) with a Tesla BS 487C (80 MHz) spectrometer. The homogeneity of the compounds was checked by chromatography on thin layers of silica gel.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-(4-chloro-3-trifluoromethylphenyl)-4-piperidyl Acetate (*II*)

A solution of 2·6 g *I* (ref.[1–4]) in 3 ml chloroform was treated with a solution of 0·8 g acetyl chloride in 2 ml chloroform and the mixture was allowed to stand overnight at room temperature. It was diluted with chloroform, the solution stirred for 1 h with water and made alkaline with a solution of NaOH. The separated chloroform layer was washed with water, dried with K_2CO_3 and evaporated under reduced pressure. The residue was dissolved in 4 ml acetone and the solution treated with 0·6 g oxalic acid. A clear solution was formed by heating. Cooling and standing overnight led to crystallization of the hydrogen oxalate; 2·4 g (74%), m.p. 176–178°C (acetone). IR spectrum: 832, 886 (2 adjacent and solitary Ar–H), 1140, 1198, 1327 ($ArCF_3$, RCOOR'), 1516, 3030, 3100 (Ar), 1749 (RCOOR'), 2590, 2730 cm^{-1} (NH^+). For $C_{22}H_{31}$. .ClF_5NO_6 (656·0) calculated: 58·58% C, 4·76% H, 5·40% Cl, 14·48% F, 2·14% N; found: 58·64% C, 4·82% H, 5·03% Cl, 14·24% F, 2·47% N.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-(4-chloro-3-trifluoromethylphenyl)-4-piperidyl Decanoate (*III*)

A solution of 5·2 g *I* (ref.[1–4]) in 8 ml chloroform was stirred and slowly treated with a solution of 5·3 g decanoyl chloride[5] in 4 ml chloroform under external cooling. After standing overnight, the mixture was stirred for 3 h with 40 ml 4% NaOH, the chloroform layer was separated, washed with water, dried (K_2CO_3) and evaporated. The residue was dissolved in 20 ml acetone and the solution neutralized with 1·3 g oxalic acid. Evaporation of the solvent and addition of 50 ml ether led to crystallization of the hydrogen oxalate; 6·2 g (81%), m.p. 125–127°C (acetone–ether). IR spectrum: 832, 865 (2 adjacent and solitary Ar–H), 1122, 1185, 1328 ($ArCF_3$), 1157, 1760 (RCOOR'), 1510, 1608, 3060, 3080 (Ar), 2680, 2745 cm^{-1} (NH^+). ^{1}H-NMR spectrum: δ 6·70 to 7·60 (m, 11 H, Ar–H), 1·30–4·00 (m, 9 H, Ar_2CH, 3 NCH_2, CH_2CO), 1·28 (bs, 22 H, remaining aliphatic CH_2 groups), 0·89 (def. t, 3 H, CH_3). For $C_{40}H_{47}ClF_5NO_6$ (768·2) calculated: 62·53% C, 6·17% H, 4·61% Cl, 12·37% F, 1·82% N; found: 62·83% C, 6·18% H, 4·51% Cl, 12·37% F, 1·77% N. Decomposition of the pure salt with ice-cold 10% NaOH released the oily base *III* which was isolated by extraction with ether and used for testing.

1-[4,4-Bis(4-fluorophenyl)butyl]-4-(4-chloro-3-trifluoromethylphenyl)-4-piperidyl 3,4,5-Trimethoxybenzoate (*IV*)

The reaction of 2·6 g *I* (ref.[1-4]) and 1·9 g 3,4,5-trimethoxybenzoyl chloride[6] in 8 ml chloroform was carried out similarly like in the preceding cases. After standing overnight, the mixture was diluted with 40 ml chloroform and stirred for 1 h with a solution of 1 g NaOH in 50 ml water. The organic layer was dried (K_2CO_3) and evaporated; 3·5 g (100%) oily ester *IV*. Neutralization with oxalic acid in acetone gave the hydrogen oxalate monohydrate, m.p. 161—163°C (95% ethanol–ether). For $C_{40}H_{39}ClF_5NO_9 + H_2O$ (826·2) calculated: 58·14% C, 5·00% H, 4·29% Cl, 11·50% F, 1·70% N; found: 58·23% C, 4·98% H, 4·32% Cl, 11·31% F, 1·86% N.

Decomposition with ice-cold 10% NaOH and extraction with ether gave the oily base which was used for recording the spectra. UV spectrum: λ_{max} 266 nm (log ε 4·07), 371·5 nm (4·10). IR spectrum: 833, 870 (2 adjacent and solitary Ar—H), 1 136, 1 181, 1 343 ($ArCF_3$), 1 228 ($ArOCH_3$, ArCOOR), 1 509, 1 591, 1 615, 3 050, 3 080 (Ar), 1 719 (ArCOOR), 2 780 cm^{-1} (OCH_3, NCH_2). ^{1}H-NMR spectrum: δ 6·70—7·80 (m, 13 H, Ar—H), 3·90 (s, 3 H, 4-OCH_3), 3·85 (s, 6 H, 3,5-$[OCH_3]_2$), 1·20—3·00 (m, remaining CH and 7 CH_2).

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