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Halogen compounds related to the reversed esters of pethidine

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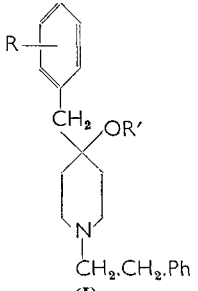
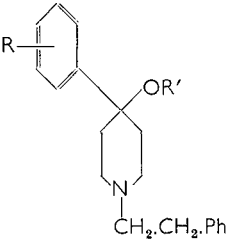
Some 1-phenethyl-4-piperidinols and their acyl esters have been prepared and investigated in a preliminary screening procedure as potential morphine-like analgesics or CNS depressants. 4-*p*-Fluorophenyl-1-phenethyl-4-propionoxypiperidine on oral administration to mice was found to be a potent morphine-like analgesic.

HARPER and Simmonds (1959) reported on a series of fluoro-compounds, namely *N*-substituted 4-fluorobenzyl-4-piperidinols and their acyl esters, which were structurally related to the prodine-type analgesics. Two of these compounds, 4-*o*-fluorobenzyl-1-phenethyl-4-piperidinol (I; R = *o*-F: R′ = H) and 4-*p*-fluorobenzyl-1-phenethyl-4-piperidinol (I; R = *p*-F: R′ = H), although devoid of morphine-like activity, appeared to possess some central nervous system depressant effect. It was therefore of interest to prepare the corresponding chloro-compounds (I; R = *o*- or *p*-Cl; R′ = H).



(I)



(II)

Since prodine-type compounds having a halogen substituent in the 4-phenyl group had not been prepared previously, it was also considered of interest to synthesise and assess pharmacologically, compounds of the type II (R = F, Cl, or CF_3, and R′ = H, CO·Me or CO·Et). Compounds with a 1-phenethyl group were chosen since prodine analgesics of this type have been shown to be potent morphine-like analgesics (Janssen & Eddy, 1960).

Chemistry

The piperidinols (I; R = *o*-Cl, or *p*-Cl and R′ = H; II: R = *p*-F, or *p*-CF_3 and R′ = H) were prepared by the addition of the appropriate Grignard reagent to 1-phenethyl-4-piperidone. The compound (II; R = *p*-Cl, R′ = H) was prepared by the aralkylation of 4-*p*-chlorophenyl-4-piperidinol, which was obtained from 4-*p*-chlorophenyl-1,2,3,6-tetrahydropyridine. The latter was prepared from *p*-chloro-α-methyl-

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styrene by the method of Schmidle & Mansfield (1956). The piperidinol (II; R = *m*-CF_3, R′ = H) was obtained by hydrolysis of the propionic ester.

The piperidinols were converted into their esters by refluxing with the appropriate acid anhydride in the presence of pyridine, or by treating the piperidinol-metallic complex with an acid anhydride.

4-*p*-Fluorophenyl-1-phenethyl-4-piperidinol and 4-*p*-chlorophenyl-1-phenethyl-4-piperidinol on refluxing with hydrobromic acid in aqueous methanol gave the corresponding tetrahydropyridine derivatives. 4-*p*-Chlorophenyl-1,2,3,6-tetrahydro-1-phenethylpyridine was also obtained by aralkylation of the corresponding secondary base.

Pharmacology

The piperidinols and their esters of type I (R = *o*- or *p*-Cl, R′ = H, CO·Me or CO·Et) (in the form of salts) were tested for analgesic activity by subcutaneous injection in mice using an adaptation of the hot-plate test as described by Janssen & Jageneau (1957). Significant activity was found only in one case, namely 4-*p*-chlorobenzyl-1-phenethyl-4-piperidinol (I; R = *p*-Cl, R′ = H), which had an ED50 of 27 mg/kg, comparable to that of the *p*-fluoro-analogue (I; R = *p*-F; R′ = H, ED50 22·5 mg/kg), previously prepared by Harper & Simmonds (1959). It was, however, less active than the *o*-fluoro-compound (I; R = *o*-F, R′ = H, ED50 16 mg/kg). Since the hot-plate test does not distinguish between morphine-type analgesics and other compounds which may increase the reaction time, mydriatic activity in mice was also determined as described by Jageneau & Janssen (1956). Janssen & Jageneau (1956, 1957) have shown that in many morphine-like analgesics there is a correlation between analgesic and mydriatic activities in mice. None of the above compounds had significant mydriatic activity.

In the case of the piperidinols of type II, only the compounds (II; R = *p*-F, R′ = H) (ED50 = 26 mg/kg) and (II; R = *p*-CF_3, R′ = H, ED50 = 30 mg/kg) had significant activity in the hot-plate test. In neither case did they appear to be morphine-like in character, since the compounds were devoid of mydriatic activity.

In the case of the esters of the type (II; R = *p*-F, *p*-Cl, *p*-CF_3 and *m*-CF_3 and R′ = CO·Me and CO·Et) which were tested by a hot-plate method as described by Beckett, Casy, Hall & Vallance (1961) only one (II; R = *p*-F, R′ = CO·Et) had morphine-like analgesic activity. (The Straub tail effect was noted at 32 mg/kg on oral administration.) This compound on subcutaneous administration to mice had an ED50 of 12 mg/kg (approximately four times the activity of pethidine), and on oral administration to mice had an ED50 of 41 mg/kg (three times the activity of codeine). This oral analgesic activity appeared to be associated with the *p*-fluoro-atom, since similar activity was not found in the *m*- or *p*-trifluoromethyl or *p*-chloro-analogues. A comparison with the unsubstituted analogues (II; R = H, R′ = CO·Et) is obviously of interest. Some preliminary investigations on the available acetoxy and

butyroxy compounds (II; R = H, R′ = CO·Me or CO·Pr^n) were carried out. In the hot-plate test these on oral administration to mice had ED50's of 71 and 62 mg/kg respectively, being 1·5 and 1·7 times, respectively, the activity of codeine and were thus less active than the *p*-fluoro-compound. Introduction of the *p*-fluoro-substituent also reduces toxicity, the LD50's in mice of the compounds (II; R = *p*-F, R′ = CO·Et) and (II; R = H, R′ = CO·Me) on oral administration being 500 and 125 mg/kg respectively.

The tetrahydropyridine derivatives prepared during this investigation did not have significant activity in the hot-plate test or mydriatic activity.

Experimental

4-p-*Fluorophenyl*-1-*phenethyl*-4-*piperidinol.* 1-Phenethyl-4-piperidone (6·8 g) in ether was added to a cooled, stirred, ethereal solution of *p*-fluorophenylmagnesium bromide prepared from *p*-bromofluorobenzene (11·7 g) and magnesium (1·75 g). The mixture was stirred for 2 hr, allowed to stand overnight and then decomposed by pouring on to crushed ice and acidifying with hydrochloric acid. The precipitated hydrochloride (9·5 g) was collected, dissolved in water and made alkaline with ammonia solution. Extraction with ether gave an oil which on treatment with ethanolic hydrogen chloride gave 4-p-*fluorophenyl*-1-*phenethyl*-4-*piperidinol hydrochloride*, m.p. 198° (from ethanol). Found: C, 67·2; H, 6·9; N, 4·3; Equiv. wt 344. $C_{19}H_{23}ClFNO$ requires: C, 67·9; H, 6·9; N, 4·2% Equiv. wt 336.

The ethereal layer from the decomposed reaction mixture was extracted with dilute hydrochloric acid and the combined acidic extracts made alkaline with ammonia solution. Extraction with ether gave an oil (3·1 g) which on treatment with ethanolic hydrogen bromide gave 4-p-*fluorophenyl*-1-*phenethyl*-4-*piperidinol hydrobromide*, m.p. 168° (from ethanol). Found: C, 59·4; H, 6·3; N, 3·6; Br, 21·1; Equiv. wt 383. $C_{19}H_{23}BrFNO$ requires: C, 60·0; H, 6·1; N, 3·7; Br, 21·0%. Equiv. wt 380.

In a similar manner, *p*-bromo-ααα-trifluorotoluene (18 g), magnesium (2·0 g) and 1-phenethyl-4-piperidone (10 g) gave 1-*phenethyl*-4-p-ααα-*trifluorotolyl*-4-*piperidinol hydrochloride* m.p. 178° (from ethanol). Found: C, 62·4; H, 6·3; N, 3·6; Equiv. wt 375. $C_{20}H_{23}ClF_3NO$ requires: C, 62·2; H, 6·0; N, 3·6%. Equiv. wt 386.

p-Chlorobenzyl chloride (10·7 g), magnesium (1·6 g) and 1-phenethyl-4-piperidone (6·8 g) gave 4-p-*chlorobenzyl*-1-*phenethyl*-4-*piperidinol hydrochloride* (10·4 g), m.p. 249° (from ethanol). Found: C, 65·6; H, 7·1; N, 3·9; Equiv. wt 366. 366. $C_{20}H_{25}Cl_2NO$ requires: C, 65·6; H, 6·9; N, 3·8%. Equiv. wt 366.

o-Chlorobenzyl chloride (36·0 g), magnesium (5·9 g) and 1-phenethyl-4-piperidone (15·5 g) gave 4-o-*chlorobenzyl*-1-*phenethyl*-4-*piperidinol hydrochloride* (20·7 g), m.p. 202° (from ethanol). Found: C, 65·6; H, 6·9; N, 3·9; Cl, 19·8; Equiv. wt 363. $C_{20}H_{25}Cl_2NO$ requires: C, 65·6; H, 6·9; N, 3·8; Cl, 19·4%. Equiv. wt 366.

1-*Phenethyl*-4-m-ααα-*trifluorotolyl*-4-*piperidinol.* 1-Phenethyl-4-piperidone (20·3 g) in ether (60 ml) was added dropwise to a stirred cooled solution of the lithium aryl prepared by radical exchange from *m*-bromo-ααα-trifluorotoluene (36 g) and butyl-lithium in ether (100 ml). The butyl-lithium was prepared by the addition of butyl bromide (23·3 g) in ether (25 ml) to lithium (1·8 g) in ether (50 ml), cooled to −30° in an acetone/carbon dioxide bath. To the clear solution, propionic anhydride (14·3 g) in dry ether was added dropwise with stirring. The mixture became turbid and was stirred for a further 6 hr and then added to crushed ice and an excess of acetic acid. Some crystalline solid (the ester hydrobromide) was precipitated at this stage, and was collected and crystallised from ethanol to give 1-*phenethyl*-4-*propionyloxy*-4-m-ααα-*trifluorotolylpiperidine hydrobromide* (1 g), m.p. 224°. Found: C, 57·4; H, 5·5; N, 3·0; Equiv. wt 486. $C_{23}H_{27}BrF_3NO_2$ requires: C, 56·8; H, 5·6; N, 2·9%. Equiv. wt 486. The ether solution was washed with dilute acid, the combined acidic solutions were made alkaline with ammonia solution and extracted with ether. On evaporation an oil was obtained which on treatment with ethanolic hydrogen chloride gave 1-*phenethyl*-4-*propionyloxy*-4-m-ααα-*trifluorotolylpiperidine hydrochloride*, m.p. 229° (from ethanol). Found: C, 62·3; H, 6·4; N, 3·1; Equiv. wt 442. $C_{23}H_{27}ClF_3NO_2$ requires: C, 62·5; H, 6·2; N, 3·2%. Equiv. wt 422. 1-Phenethyl-4-propionyloxy-4-*m*-ααα-trifluorotolylpiperidine hydrochloride (2·8 g) was refluxed with a solution of potassium hydroxide (1·6 g) in 96% ethanol (50 ml) for 15 hr. The residue obtained by ether extraction of the diluted mixture gave an oil which on treatment with ethanolic hydrogen chloride gave 1-*phenethyl*-4-m-ααα-*trifluorotolyl*-4-*piperidinol hydrochloride*, m.p. 235° (from ethanol). Found: C, 62·2; H, 6·4; N, 3·5; Equiv. wt 389. $C_{20}H_{23}ClF_3NO$ requires: C, 62·2; H, 6·0; N, 3·6%. Equiv. wt 386.

4-p-*Chlorophenyl*-1-*phenethyl*-4-*piperidinol.* *p*-Chloro-α-methylstyrene (305 g) was stirred and heated at 40–60° with a solution of ammonium chloride (214 g) in formaldehyde solution (40%, 730 ml) for 4 hr. The mixture was then stirred with methanol for 2 days, evaporated under reduced pressure (15 mm), and stirred and heated with hydrochloric acid (600 ml), on a steam-bath for 4 hr. The mixture was diluted with water (250 ml), cooled in ice water, and made alkaline with concentrated potassium hydroxide solution. Toluene extraction gave an oil which on distillation gave 4-*p*-chlorophenyl-1,2,3,6-tetrahydropyridine, b.p. 164°/6 mm. This base on treatment with hydrochloric acid, followed by evaporation with benzene and ethanol, gave 4-p-*chlorophenyl*-1,2,3,6-*tetrahydropyridine hydrochloride*, m.p. 206° (from ethanol). Found: C, 57·9; H, 5·7; N, 5·8; Equiv. wt 231. $C_{11}H_{13}Cl_2N$ requires: C, 57·4; H, 5·7; N, 6·1%. Equiv. wt 230.

4-*p*-Chlorophenyl-1,2,3,6-tetrahydropyridine hydrochloride (10 g), suspended in acetic acid (30 ml), was shaken with 25% hydrogen bromide in acetic acid (30 ml) and on standing overnight gave 4-bromo-4-*p*-chlorophenylpiperidine hydrobromide (11·5 g), m.p. 216° (Janssen, 1959, 213–215°). This solid on crystallisation from ethanol-ether gave

4-p-*chlorophenyl*-1,2,3,6-*tetrahydropyridine hydrobromide*, m.p. 211°. Found: C, 48·3; H, 4·9; N, 4·8; Equiv. wt 271; E_{max} 16,530 at 249 mμ. $C_{11}H_{13}BrClN$ requires: C, 48·1; H, 4·8; N, 5·1%. Equiv. wt 275.

The addition of an excess of sodium hydroxide solution to a solution in water of 4-bromo-4-*p*-chlorophenylpiperidine hydrobromide gave 4-*p*-chlorophenyl-4-piperidinol, m.p. 136° (from toluene) (Janssen, 1959).

A mixture of 4-*p*-chlorophenyl-4-piperidinol (4·5 g), phenethyl bromide (5 g), sodium bicarbonate (3·5 g) and toluene was refluxed for 3 days. The mixture was filtered, and the filtrate on concentration gave the free base 4-p-*chlorophenyl*-1-*phenethyl*-4-*piperidinol* (1·5 g), m.p. 128° (from ethanol). Found: C, 72·4; H, 7·0; N, 4·2; Equiv. wt 318. $C_{19}H_{22}ClNO$ requires: C, 72·3; H, 7·0; N, 4·4%. Equiv. wt 316. Further concentration gave the salt, 4-p-*chlorophenyl*-1-*phenethyl*-4-*piperidinol hydrobromide* (4·3 g), m.p. 199° (from ethanol). Found: C, 57·3; H, 5·8; N, 3·5; Equiv. wt 401. $C_{19}H_{22}BrClNO$ requires: C, 57·5; H, 5·8; N, 3·5%. Equiv. wt 397.

PREPARATION OF ACYL ESTERS

4-p-*Chlorophenyl*-1-*phenethyl*-4-*propionyloxypiperidine*. A mixture of the piperidinol (2 g), propionic anhydride (3 ml) and piperidine (3 ml) were refluxed together for 3 hr. Evaporation of the solvent gave an oil which on treatment with ethanolic hydrogen chloride gave 4-p-*chlorophenyl*-1-*phenethyl*-4-*propionyloxypiperidine hydrochloride*, m.p. 208° (from ethanol). Found: C, 64·3; H, 6·8; N, 3·5; Equiv. wt 413. $C_{22}H_{27}Cl_2NO_2$ requires: C, 64·7; H, 6·7; N, 3·4%. Equiv. wt 408.

In a similar manner the following were prepared:

1-*Phenethyl*-4-*propionyloxy*-4-p-*ααα-trifluorotolylpiperidine hydrochloride*, m.p. 230° (from ethanol). Found: C, 62·4; H, 6·3; N, 3·3; Equiv. wt 449. $C_{23}H_{27}ClF_3NO_2$ requires: C, 62·5; H, 6·2; N, 3·2%. Equiv. wt 442.

4-*Acetoxy*-1-*phenethyl*-4-m-*ααα-trifluorotolylpiperidine hydrochloride*, m.p. 231° (from ethanol). Found: C, 61·3; H, 6·1; N, 3·3; Equiv. wt 427. $C_{22}H_{25}ClF_3NO_2$ requires: C, 61·8; H, 5·9; N, 3·3%. Equiv. wt 428.

4-*Acetoxy*-4-o-*chlorobenzyl*-1-*phenethylpiperidine hydrochloride*, m.p. 221° (from ethanol). Found: C, 63·9; H, 6·8; N, 3·3; Equiv. wt 407. $C_{22}H_{27}Cl_2NO$ requires: C, 64·7; H, 6·7; N, 3·4%. Equiv. wt 408.

4-o-*Chlorobenzyl*-1-*phenethyl*-4-*propionyloxypiperidine hydrochloride monohydrate*, m.p. 129° (from ethanol). Found: C, 62·8; H, 7·4; N, 3·2; Equiv. wt 435. $C_{23}H_{31}Cl_2NO$ requires: C, 62·7; H, 7·1; N, 3·2%. Equiv. wt 440.

4-p-*Chlorobenzyl*-1-*phenethyl*-4-*propionyloxypiperidine hydrochloride monohydrate*, m.p. 200° (from ethanol). Found: C, 63·1; H, 7·3; N, 3·3; Equiv. wt 420. $C_{23}H_{31}Cl_2NO$ requires: C, 62·7; H, 7·1; N, 3·3%. Equiv. wt 440.

4-p-*Fluorophenyl*-1-*phenethyl*-4-*propionyloxypiperidine*. The Grignard complex obtained from *p*-bromofluorobenzene (16 g), magnesium (2·4 g) and 1-phenethyl-4-piperidone (10·2 g) was treated with propionic anhydride (9·1 g.) in ether, and gave p-*fluorophenyl*-1-*phenethyl*-4-*propionyl*-

oxypiperidine hydrochloride, m.p. 210° (from isopropanol). Found: C, 67·6; H, 6·9; N, 3·4; Equiv. wt 391. $C_{22}H_{27}ClFNO_2$ requires: C, 67·4; H, 6·9; N, 3·6. Equiv. wt 391.

4-p-*Fluorophenyl*-1-*phenethyl*-4-*propionyloxypiperidine hydrobromide*, m.p. 185° (from ethanol). Found: C, 60·7; H, 6·3; N, 3·4; Equiv. wt 440. $C_{22}H_{27}BrFNO_2$ requires: C, 60·6; H, 6·2; N, 3·2%. Equiv. wt 436.

4-*Acetoxy*-1-*phenethyl*-4-p-ααα-*trifluorotolylpiperidine*. This compound was prepared in a manner similar to that described for 1-phenethyl-4-propionyloxy-4-*m*-ααα-trifluorotolylpiperidine. Butyl-lithium was prepared from butyl bromide (16·4 g) and lithium (1·25 g). The butyl-lithium was treated with *p*-bromo-ααα-trifluorotoluene (25 g), 1-phenethyl-4-piperidone (14·2 g) and acetic anhydride (20 g). The addition of ice water gave a precipitate (35 g) which on recrystallisation from ethanol gave 4-*acetoxy*-1-*phenethyl*-4-p-ααα-*trifluorotolylpiperidine hydrobromide*, m.p. 259°. Found: C, 55·9; H, 5·5; N, 2·7; Equiv. wt 463. $C_{22}H_{25}BrF_3NO_2$ requires: C, 55·9; H, 5·3; N, 2·9%. Equiv. wt 472.

4-p-*Chlorophenyl*-1-*phenethyl*-1,2,3,6-*tetrahydropyridine*. (*a*) 4-*p*-Chlorophenyl-1,2,3,6-tetrahydropyridine (5·8 g), phenethyl bromide (7·6 g), sodium bicarbonate (3·5 g) and toluene (200 ml) were refluxed together for 3 days. The filtered solution on evaporation gave 4-p-*chlorophenyl*-1-*phenethyl*-1,2,3,6-*tetrahydropyridine*, m.p. 132° (from ethanol) (1·9 g). Found: C, 76·1; H, 6·7; N, 4·8; Equiv. wt 295; E_{max} = 18,500 at 253 mμ. $C_{19}H_{20}ClN$ requires: C, 76·6; H, 6·8; N, 4·7%. Equiv. wt 298.

(*b*) 4-*p*-Chlorophenyl-1-phenethyl-4-piperidinol hydrobromide (1 g) refluxed in a mixture of methanol (200 ml) and hydrobromic acid (60%, 50 ml) for 3 hr, gave on cooling 4-p-*chlorophenyl*-1-*phenethyl*-1,2,3,6-*tetrahydropyridine hydrobromide*, m.p. 231° (from methanol). Found: C, 59·8; H, 5·7; N, 3·5; Equiv. wt 389; E_{max} = 19,400 at 251 mμ. $C_{19}H_{21}BrClN$ requires: C, 60·2; H, 5·6; N, 3·7%. Equiv. wt 379.

Similarly, dehydration of the piperidinol gave 4-p-*fluorophenyl*-1-*phenethyl*-1,2,3,6-*tetrahydropyridine hydrobromide*, m.p. 201° (from ethanol). Found: C, 62·1; H, 5·9; N, 4·0; Equiv. wt 353; E_{max} = 17,500 at 241 mμ. $C_{19}H_{21}BrFN$ requires: C, 63·0; H, 5·9; N, 3·9%. Equiv. wt 362.

Equivalent weights of the bases were determined by titration with 0·02N perchloric acid in glacial acetic acid using Oracet Blue B as indicator. Titration of salts was carried out in the same solvent in the presence of mercuric acetate by the method of Pifer & Wollish (1951).

The ultra-violet absorption measurements were made on solutions in ethanol.

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