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# Fluorocompounds Related to the Reversed Esters of Pethidine

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## Introduction

The effect of the introduction of fluorine into certain synthetic analgesics is being studied in these laboratories. One aspect has involved the preparation and pharmacological testing of compounds related to the reversed esters of pethidine, namely N-substituted-4-fluorobenzyl-4-piperidinols and their acyloxy esters (Table I).

The N-substituted-4-fluorobenzyl-4-piperidinols were prepared by the addition of the appropriate fluorobenzyl Grignard reagent to the corresponding N-substituted piperidones. The piperidinols were converted to the esters by refluxing the alcohol with the acid anhydride in the presence of pyridine, or by treating the piperdinol–Grignard complex with the corresponding acid anhydride. In the preparation of N-2′-phenylethyl-3-methyl-4-*p*-fluorobenzyl-4-piperidinol only one of the two theoretically possible diastereoisomers could be isolated.

## Results and Discussion

*Pharmacological testing.* The tertiary alcohols and their esters were tested for analgesic activity by subcutaneous injection in mice using an adaptation of the hot-plate method as described by Janssen and Jagenau;[1] the ED50 values (mg/kg) are shown in Table I. Of the compounds tested, only two, namely N-2′-phenylethyl-4-*p*-fluorobenzyl-4-piperidinol (ED50; 22·5) and N-2′-phenylethyl-4-*o*-fluorobenzyl-4-piperidinol (ED50; 16), appeared to have significant 'analgesic activity'. However, the hot-plate method does not distinguish between morphine-type analgesics and other compounds which may increase the reaction time. The compounds were also tested for mydriatic activity in mice as described by Janssen and his co-workers,[2-4] and in no case was

significant mydriatic activity noted (see Table I). Since Janssen and Jagenau[1,5] have shown that in many morphine-like analgesics there is a significant positive correlation between analgesic activity and mydriatic activity in mice, it is therefore assumed that the pharmacological effect indicated by the hot-plate test results from a general central nervous depression rather than morphine-like analgesia.

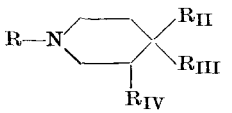
N-2′-phenylethyl-4-*p*-fluorobenzyl-4-piperidinol (Table I, No. 6) was also tested for 'analgesic activity' in mice by the Haffner-tail pinch method as modified by Bianchi and Franceschini[6] and David, Leith-Ross and Vallance.[7] The ED50 by the subcutaneous route was 27 mg/kg compared with 8 mg/kg for pethidine hydrochloride. The behaviour of the mice again suggested that the compound caused general central nervous depression rather than true analgesia.

In preliminary tests on N-2′-phenylethyl-4-*p*-fluorobenzyl-4-piperidinol, the oral and subcutaneous LD50's were of the order of 250 mg/kg and 190 mg/kg respectively. Clonic convulsions were observed only at lethal dose levels when the compound was administered orally, but subcutaneous injection of 60 mg/kg caused convulsions. It was found to possess no anti-histamine or parasympatholytic activity when tested by the usual *in vitro* procedures. Anti-electroshock and anti-metrazol activity was found to be absent (the test procedures were based on the maximal electroshock seizure and maximal metrazol seizure tests described by Goodman, Singh Grewal, Brown and Swinyard[8]). An anti-tremorine test based on a report of Everett,[9] gave negative results.

*Chemical structure and pharmacological activity.* The depressant effect of N-2′-phenylethyl-4-benzyl-4-piperidinol is enhanced by the presence of an electronegative fluorine atom in the *ortho* and *para* positions of the benzyl group (Table I, *cf.* Nos. 6, 8 and 19). Its activity is similar to that of N-2′-phenylethyl-4-phenyl-4-piperidinol (Table I, *cf.* Nos. 19 and 20). Substitution of the piperidinol with a *m*-fluorobenzyl group produces an inactive compound (Table I, No. 7).

Esterification of the active piperidinols to give the acetoxy and propionoxy esters resulted in a loss of pharmacological activity (Table I, *cf.* Nos. 6, 8, 12, 13, 16 and 17). This is in contrast to

Table 1. N-substituted-4-fluorobenzyl-4-piperidinols and their esters




| No. | R | $R_{II}$ | $R_{III}$ | $R_{IV}$ | Formula | m.p. | Carbon, % | | Hydrogen, % | | Nitrogen, % | | Halogen, % (Cl or Br) | | Equivalent | | Hot-plate test ED50, mg/kg | Mydriatic activity ED50, mg/kg |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Calc. | Found | Calc. | Found | Calc. | Found | Calc. | Found | Calc. | Found | | |
| 1 | $CH_3$ | $CH_2.C_6H_4F(p)$ | OH | H | $C_{13}H_{18}FNO$ | 118° | 70·0 | 69·9 | 8·1 | 8·3 | 6·3 | 5·8 | | | 223 | 216 | >40 | >40 |
| 2 | $CH_3$ | $CH_2.C_6H_4F(o)$ | OH | H | $C_{13}H_{18}FNO$ | 99° | 70·0 | 70·5 | 8·1 | 8·2 | 6·3 | 5·9 | | | 223 | 215 | >40 | >40 |
| 3 | $C_2H_5$ | $CH_2.C_6H_4F(p)$ | OH | H | $C_{14}H_{20}FNO$ | 113·5° | 70·8 | 69·8 | 8·5 | 8·4 | 5·9 | 5·9 | | | 237 | 231 | >40 | >40 |
| 4 | $C_2H_5$ | $CH_2.C_6H_4F(o)$ | OH | H | $C_{14}H_{20}FNO$ | 95° | 70·8 | 71·1 | 8·5 | 8·8 | 5·9 | 6·2 | | | 237 | 228 | >40 | >40 |
| 5 | $C_2H_5$ | $CH_2.C_6H_4F(m)$ | OH | H | $C_{14}H_{20}FNO$ | 59° | | | | | 5·9 | 5·6 | | | 237 | 246 | >40 | >40 |
| 6 | $C_6H_5CH_2CH_2$ | $CH_2.C_6H_4F(p)$ | OH | H | $C_{20}H_{24}FNO,HCl$ | 247°(dec) | 68·6 | 68·5 | 6·9 | 7·5 | 4·0 | 4·1 | 10·1 | 9·7 | 350 | 356 | 22·5 | ⩾40 |
| 7 | $C_6H_5CH_2CH_2$ | $CH_2.C_6H_4F(m)$ | OH | H | $C_{20}H_{24}FNO,HCl$ | 211° | 68·6 | 68·3 | 6·9 | 7·1 | 4·0 | 4·0 | 10·1 | 10·1 | 350 | 350 | ⩾40 | >40 |
| 8 | $C_6H_5CH_2CH_2$ | $CH_2.C_6H_4F(o)$ | OH | H | $C_{20}H_{24}FNO,HBr$ | 199° | 60·9 | 61·4 | 6·4 | 6·8 | 3·6 | 3·8 | 20·3 | 20·2 | 394 | 393 | 16·0 | >40 |
| 9 | $C_6H_5CH_2CH_2$ | $CH_2.C_6H_4F(p)$ | OH‡ | $CH_3$ | $C_{21}H_{26}FNO,HBr$ | 248·5° | 61·8 | 61·9 | 6·7 | 6·5 | 3·4 | 3·4 | 19·6 | 19·4 | 408 | 403 | >40 | >40 |
| 10 | $CH_3$ | $CH_2.C_6H_4F(p)$ | $OCOC_2H_5$* | H | $C_{16}H_{22}FNO_2,HBr$ | 182° | 53·3 | 54·0 | 6·4 | 6·7 | 3·9 | 3·8 | | | 360 | 365 | >40 | >40 |
| 11 | $C_2H_5$ | $CH_2.C_6H_4F(p)$ | $OCOC_2H_5$* | H | $C_{17}H_{24}FNO_2,HBr$ | 213° | 54·6 | 55·1 | 6·7 | 7·3 | 3·7 | 3·7 | | | 374 | 366 | >40 | >40 |
| 12 | $C_6H_5CH_2CH_2$ | $CH_2.C_6H_4F(p)$ | $OCOCH_3$* | H | $C_{22}H_{26}FNO_2,HBr$ | 241° | | | | | 3·2 | 3·2 | 18·3 | 18·3 | 436 | 429 | >40 | >40 |
| 13 | $C_6H_5CH_2CH_2$ | $CH_2.C_6H_4F(p)$ | $OCOC_2H_5$* | H | $C_{23}H_{28}FNO_2,HBr$ | 219° | 61·3 | 61·4 | 6·5 | 6·3 | | | 17·7 | 18·1 | 450 | 458 | >40 | >40 |
| 14 | $C_6H_5CH_2CH_2$ | $CH_2.C_6H_4F(m)$ | $OCOCH_3$* | H | $C_{22}H_{26}FNO_2,HBr$ | 246·5° | 60·5 | 61·2 | 6·2 | 6·6 | 3·2 | 3·2 | 18·3 | 18·2 | 436 | 423 | >40 | >40 |
| 15 | $C_6H_5CH_2CH_2$ | $CH_2.C_6H_4F(m)$ | $OCOC_2H_5$* | H | $C_{23}H_{28}FNO_2,HBr$ | 196·5° | 61·3 | 61·6 | 6·5 | 6·0 | 3·1 | 3·1 | 17·7 | 17·6 | 450 | 444 | >40 | >40 |
| 16 | $C_6H_5CH_2CH_2$ | $CH_2.C_6H_4F(o)$ | $OCOCH_3$† | H | $C_{22}H_{26}FNO_2,HBr$ | 245° | 60·5 | 61·3 | 6·2 | 6·3 | 3·2 | 3·3 | 18·3 | 18·6 | 436 | 429 | >40 | >40 |
| 17 | $C_6H_5CH_2CH_2$ | $CH_2.C_6H_4F(o)$ | $OCOC_2H_5$† | H | $C_{23}H_{28}FNO_2,HBr$ | 214° | 61·3 | 61·5 | 6·5 | 6·4 | 3·1 | 3·5 | 17·8 | 17·7 | 450 | 445 | >40 | >40 |
| 18 | $C_6H_5CH_2CH_2$ | $CH_2.C_6H_4F(p)$ | $OCOCH_3$* | $CH_3$ | $C_{23}H_{28}FNO_2,HBr$ | 198° | 61·3 | 61·9 | 6·5 | 6·6 | 3·1 | 3·2 | 17·8 | 17·6 | 450 | 453 | >40 | >40 |
| 19 | $C_6H_5CH_2CH_2$ | $CH_2.C_6H_5$ | OH | H | | | | | | | | | | | | | 30 | >40‖§ |
| 20 | $C_6H_5CH_2CH_2$ | $C_6H_5$ | OH | H | | | | | | | | | | | | | 34 | 36·5¶ |
| 21 | $CH_3$ | $C_6H_5$ | $OCOC_2H_5$ | $CH_3$ | β-prodine | | | | | | | | | | | | 5·6 | 11·3 |
| 22 | $CH_3$ | $C_6H_5$ | $OCOC_2H_5$ | H | pethidine HCl | | | | | | | | | | | | 28 | 21·5** |
| 23 | | | | | Morphine HCl | | | | | | | | | | | | 12·0 | 13·1** |

* Prepared by pyridine and anhydride method.
‡ Prepared by hydrolysis of ester.
‖ Reference 17.
† Prepared by decomposition of Grignard complex with anhydride.
§ Compounds Nos. 19–23 included for comparison.
¶ Reference 11.
** Reference 1.

morphine-like analgesics of the $\alpha$- and $\beta$-prodine type, in which the parent alcohols are less active.[10,11]

The replacement of the $N.CH_2CH_2C_6H_5$ group by $N.CH_3$ or $N.C_2H_5$ gave inactive compounds (Table I, *cf.* Nos. 1, 2, 3, 4, 6 and 8). Similar changes in the prodine type compounds exhibiting morphine-like analgesic activity leads to a reduction in activity.[11]

Substitution in the 3-position of the piperidine ring resulted in a loss of activity (*cf.* analgesics of the reversed esters of pethidine-type in which such substitution enhances the analgesic effect).[11,12]

In view of the convulsions caused by the N-2′-phenylethyl-4-*p*-fluorobenzyl-4-piperidinol at 60 mg/kg when administered subcutaneously, further work in this area was discontinued.

## Experimental

*N-Substituted-4-fluorobenzyl-4-piperidinols.* The following general method was used for the preparation of the piperidinols. An ethereal solution of the appropriate piperidone[11,13-15] was added dropwise to a stirred solution of the fluorobenzyl magnesum chloride in ether. The mixture was stirred for 2 h, allowed to stand overnight, and then decomposed by pouring on to crushed ice and acidifying with hydrochloric acid. The ethereal layer was washed with dilute acid and the combined acidic solutions made alkaline with ammonia and the piperidinols extracted with ether. In some cases the piperidinols were crystallized from petroleum (40–60°), in others they were converted into the hydrochlorides or hydrobromides which were crystallized from ethanol.

*Acyloxy esters. Method (a)*—To the Grignard complex, prepared as above, an anhydride was added and the mixture stirred for 2 h and then allowed to stand overnight. Water was added, the mixture acidified, and the ethereal layer separated. The acidic layer was made alkaline and the ester extracted with ether and isolated as the hydrobromide which was crystallized from ethanol.

*Method (b)*—A mixture of the piperidinol, pyridine and acid anhydride was refluxed for 3 h, at the end of which time the solvent was evaporated under reduced pressure. The residue was converted to the hydrobromide which was crystallized from ethanol.

Equivalent weights of the bases were determined by titration

with 0·02N—perchloric acid in acetic acid with Oracet blue as indicator. Titrations of salts were carried out in the same solvent in the presence of mercuric acetate by the method of Pifer and Wollish.[16]

*Summary.* The preparation of some N-substituted-4-fluorobenzyl-4-piperidinols and their acyloxy esters is reported. These have been tested for analgesic activity (hot-plate method) and for mydriatic activity. Two of the compounds, namely N-2′-phenylethyl-4-*o*-fluorobenzyl-4-piperidinol and N-2′-phenylethyl-4-*p*-fluorobenzyl-4-piperidinol appeared to possess 'analgesic activity' as assessed by the hot-plate method. True morphine-like analgesic activity is probably absent.

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