

## N-Alkyl-3-piperidyl Phenothiazine-10-carboxylates

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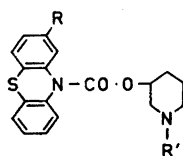
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A number of N-alkyl-3-piperidyl esters of some phenothiazine-10-carboxylic acids have been synthesised.

N-Alkyl-3-piperidyl esters have recently aroused great pharmacological interest. For example N-ethyl-3-piperidyl diphenylacetate and N-ethyl-3-piperidyl benzilate methobromide have found clinical use as spasmolytic agents<sup>1,2</sup> and N-alkyl-3-piperidyl esters of benzoic acid and phenylcycloalkylglycolic acids have been reported to exert strange hallucinogenic effects<sup>3,4</sup>.

In an earlier paper from these laboratories the synthesis of a number of  $\beta$ -dialkylaminoalkyl phenothiazine-10-carboxylates with pronounced antispasmodic and nicotolytic properties was described<sup>5</sup>, one of which,  $\beta$ -diethylaminoethyl phenothiazine-10-carboxylate (Transergan<sup>®</sup>) has found use as an antispasmodic<sup>6</sup> and antiparkinsonism<sup>7</sup> drug.

The present paper deals with the synthesis of a series of N-alkyl-3-piperidyl phenothiazine-10-carboxylates of the general formula shown below.



R = H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, CH<sub>3</sub>O, Cl, CH<sub>3</sub>CO

R' = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>

The preparation of these esters seemed worth while, not only because of their potential spasmolytic properties, but also owing to the combination in one molecule of two structural elements of psychopharmacological interest, *viz.* an N-alkyl-3-piperidyl and a phenothiazine residue, which in most cases is substituted in the important 2-position.

The new compounds were readily obtained by the reaction of a phenothiazine-10-carbonyl chloride with N-methyl-, and N-ethyl-3-hydroxypiperidine in the presence of triethylamine.

The 2-substituted phenothiazine-10-carbonyl chlorides used as starting materials were prepared from the appropriate 2-substituted phenothiazine and phosgene with the exception of 2-acetylphenothiazine-10-carbonyl chloride, which was obtained from phenothiazine-10-carbonyl chloride and acetyl chloride by the Friedel–Crafts reaction.

That the acetyl group had entered the 2-position in the phenothiazine nucleus was proved by the treatment of the reaction product with alcoholic potassium hydroxide which yielded 2-acetylphenothiazine.

Results from the pharmacological tests will be published elsewhere.

## EXPERIMENTAL

2-Methyl-, 2-ethyl-, 2-methoxy- and 2-chlorophenothiazine were obtained from Société des Usines Chimiques Rhône-Poulenc, France. N-Methyl- and N-ethyl-3-hydroxypiperidine were obtained from Lakeside Laboratories, Inc., U.S.A.

### Phenothiazine-10-carbonyl chlorides

*2-Methylphenothiazine-10-carbonyl chloride.* 2-Methylphenothiazine (42.4 g, 0.2 mole) was dissolved in toluene (750 ml) and a solution of phosgene in toluene (330 ml containing 10 % v/v) was added. The mixture was heated at 90° under efficient reflux for 4 h. After cooling, ethanol (50 ml) was added to destroy excess of phosgene. The solvent was evaporated *in vacuo* and the residue, a dark oil which soon crystallised, was recrystallised from ethyl acetate giving light grey crystals (54 g, 98 %) of m.p. 120–121°. Further recrystallisation from the same solvent raised the m.p. to 122–122.5°. (Found: C 60.5; H 3.66; N 4.95. Calc. for  $C_{14}H_{10}ClNOS$ : C 61.0; H 3.66; N 5.08).

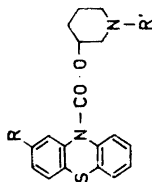
*2-Ethylphenothiazine-10-carbonyl chloride* was prepared by the same method. As it was impossible to get the product in crystalline form, it was used as starting material for syntheses without further purification.

*2-Methoxyphenothiazine-10-carbonyl chloride* was obtained in 88 % yield in the same way. This compound has earlier been prepared<sup>8</sup> by heating 2-methoxyphenothiazine and phosgene in a sealed vessel. M.p. 94–95° (from methanol), (lit.<sup>8</sup> 96–97°).

*2-Chlorophenothiazine-10-carbonyl chloride.* 2-Chlorophenothiazine reacted with phosgene more sluggishly than the foregoing 2-substituted phenothiazines. The reaction mixture (46.5 g of 2-chlorophenothiazine in 750 ml of toluene and 330 ml of 10 % phosgene in toluene) was heated at 140° in an oil bath for 6 h under effective reflux. A further quantity (130 ml) of phosgene in toluene was then added and the reaction mixture was heated at 140° for further 8 h. The solvent was removed *in vacuo* and the solid residue was extracted with benzene to remove the unreacted 2-chlorophenothiazine which is sparingly soluble in this solvent. After evaporation of the benzene the residue was crystallised from ethyl acetate to give crystals (35.0 g, 59 %) melting at 100–101°. (Found: C 52.9; H 2.36; N 4.70. Calc. for  $C_{13}H_7Cl_2NOS$ : C 52.7; H 2.38; N 4.73).

*2-Acetylphenothiazine-10-carbonyl chloride.* To a suspension of phenothiazine-10-carbonyl chloride (131 g, 0.5 mole) in carbon disulphide (800 ml) was added with stirring anhydrous aluminium chloride (200 g, 1.5 mole), and the mixture was heated to reflux to dissolve the phenothiazine compound. After cooling to room temperature acetyl chloride (54.9 g, 0.7 mole) was added in portions and the reaction mixture was heated slowly. At 30° a vigorous reaction started and external heating was stopped. The colour of the mixture changed from pink to green and hydrogen chloride was evolved. The reaction subsided in one hour and the reaction mixture was then refluxed for 3 h. A dark viscous oil was gradually formed at the bottom of the reaction flask. After cooling the bottom layer was separated and poured on *ca.* 1 kg of crushed ice and 25 ml of conc. hydrochloric acid. A greyish precipitate separated which was collected by filtration and dried to give 150 g of product (99 %) melting at 108–110°. Two recrystallisations from ethyl acetate raised the m.p. to 120–122°. This compound has been prepared from 2-

Table 1.



| No. | R               | R'                            | Yield <sup>a</sup><br>% | Deriva-<br>tive   | M.p.<br>°C | Recryst.<br>Solvent <sup>b</sup> | Formula   | Calc. % |      |      | Found % |      |      |
|-----|-----------------|-------------------------------|-------------------------|---|------------|----------------------------------|---|---------|------|------|---------|------|------|
|     |                 |                               |                         |   |            |                                  |   | C       | H    | N    | C       | H    | N    |
| 1   | H               | CH <sub>3</sub>               | 72                      | Base<br>HCl   | 88-90      | P                                | C <sub>19</sub> H <sub>30</sub> N <sub>2</sub> O <sub>2</sub> S                                   | 67.0    | 5.92 | 8.23 | 66.7    | 5.98 | 8.17 |
| 2   | H               | C <sub>2</sub> H <sub>5</sub> | 86                      | CH <sub>3</sub> Br  | 230-232 d. | M-E                              | C <sub>19</sub> H <sub>30</sub> N <sub>2</sub> O <sub>2</sub> S · HCl                             | 60.5    | 5.02 | 7.43 | 60.5    | 6.06 | 7.18 |
|     |                 |                               | 55                      | HCl   | 273-274 d. | M                                | C <sub>19</sub> H <sub>30</sub> N <sub>2</sub> O <sub>2</sub> S · CH <sub>3</sub> Br              | 55.2    | 5.32 | 6.44 | 54.8    | 5.41 | 6.17 |
| 3   | CH <sub>3</sub> | CH <sub>3</sub>               | 67                      | CH <sub>3</sub> Br  | 222-223 d. | A-E                              | C <sub>20</sub> H <sub>32</sub> N <sub>2</sub> O <sub>2</sub> S · HCl                             | 61.4    | 5.93 | 7.17 | 61.3    | 6.18 | 7.20 |
|     |                 |                               | 71                      | C <sub>2</sub> H <sub>5</sub> I                                       | 232-233 d. | A-E                              | C <sub>20</sub> H <sub>32</sub> N <sub>2</sub> O <sub>2</sub> S · CH <sub>3</sub> Br              | 56.1    | 5.61 | 6.24 | 56.0    | 5.72 | 6.20 |
|     |                 |                               | 92                      | HCl   | 220-221 d. | A-E                              | C <sub>20</sub> H <sub>32</sub> N <sub>2</sub> O <sub>2</sub> S · C <sub>2</sub> H <sub>5</sub> I | 51.8    | 5.33 | 5.49 | 51.9    | 5.49 | 5.12 |
|     |                 |                               | 69                      | HCl   | 242-244 d. | A-E                              | C <sub>20</sub> H <sub>32</sub> N <sub>2</sub> O <sub>2</sub> S · HCl                             | 61.4    | 5.93 | 7.17 | 61.3    | 6.11 | 6.91 |
|     |                 |                               | 80                      | HCl   | 223-224 d. | A-E                              | C <sub>21</sub> H <sub>34</sub> N <sub>2</sub> O <sub>2</sub> S · HCl                             | 62.3    | 6.22 | 6.92 | 62.3    | 6.31 | 6.65 |
|     |                 |                               | 57                      | HCl   | 240-242 d. | M                                | C <sub>21</sub> H <sub>34</sub> N <sub>2</sub> O <sub>2</sub> S · HCl                             | 62.3    | 6.22 | 6.92 | 61.7    | 6.31 | 7.01 |
|     |                 |                               | 80                      | HCl   | 202-203 d. | A-E                              | C <sub>22</sub> H <sub>36</sub> N <sub>2</sub> O <sub>2</sub> S · HCl                             | 63.1    | 6.50 | 6.69 | 62.5    | 6.80 | 6.42 |
|     |                 |                               | 66                      | HCl   | 242-244 d. | M-E                              | C <sub>20</sub> H <sub>32</sub> N <sub>2</sub> O <sub>2</sub> S · HCl                             | 59.0    | 5.70 | 6.89 | 59.3    | 6.23 | 6.66 |
|     |                 |                               | 77                      | HCl   | 230-231 d. | M-E                              | C <sub>21</sub> H <sub>34</sub> N <sub>2</sub> O <sub>2</sub> S · HCl                             | 59.9    | 5.99 | 6.66 | 59.9    | 6.18 | 6.59 |
|     |                 |                               | 64                      | HCl   | 235-237 d. | M-E                              | C <sub>19</sub> H <sub>30</sub> ClN <sub>2</sub> O <sub>2</sub> S · HCl                           | 55.5    | 4.90 | 6.81 | 56.0    | 5.09 | 6.57 |
|     |                 |                               | 80                      | Base <sup>c</sup>   | 220-222 d. | A-E                              | C <sub>20</sub> H <sub>31</sub> ClN <sub>2</sub> O <sub>2</sub> S · HCl                           | 56.5    | 5.21 | 6.59 | 56.7    | 5.44 | 6.28 |
|     |                 |                               | 49                      | HCl   | 112-114    | A                                | C <sub>21</sub> H <sub>32</sub> N <sub>2</sub> O <sub>2</sub> S                                   | 65.9    | 5.80 | 7.33 | 66.2    | 5.66 | 7.22 |
| 49  | HCl             | 236-238 d.                    | A                       | C <sub>21</sub> H <sub>32</sub> N <sub>2</sub> O <sub>2</sub> S · HCl | 60.2       | 5.53                             | 6.69  | 60.3    | 5.68 | 6.38 |         |      |      |
| 49  | HCl             | 188-189 d.                    | A-E                     | C <sub>22</sub> H <sub>34</sub> N <sub>2</sub> O <sub>2</sub> S · HCl | 61.0       | 5.82                             | 6.47  | 61.0    | 5.70 | 6.23 |         |      |      |

<sup>a</sup> Calculated on the recrystallised products.

<sup>b</sup> A, ethanol; E, ether; M, methanol; P, petroleum ether.

acetylphenothiazine and phosgene by Schmitt *et al.*, who report the m.p. 116–117°. (Found: C 58.8; H 3.28; N 4.57. Calc. for  $C_{15}H_{10}ClNOS$ : C 59.3; H 3.32; N 4.61).

Treatment of this compound with potassium hydroxide in ethanol yielded 2-acetylphenothiazine, m.p. 188–189° undepressed on admixture with an authentic specimen.

### N-Alkyl-3-piperidyl phenothiazines-10-carboxylates

A solution of the appropriate phenothiazine-10-carbonyl chloride (0.05 mole), N-alkyl-3-hydroxypiperidine (0.05 mole) and triethylamine (0.075 mole) in toluene (50 ml) was heated under reflux. The reflux times were 4 h in syntheses using N-methyl-3-hydroxypiperidine and 8 h with the N-ethyl homologue. After cooling the triethylamine hydrochloride was removed by filtration and the toluene solution was washed thoroughly with water and then extracted with N hydrochloric acid. The slightly soluble hydrochloride of the reaction product usually separated as a semi-crystalline oil. The hydrochloride was separated, dissolved in water and combined with the acid water extract. The extract was made alkaline with sodium carbonate solution. The reaction product usually separated as a viscous oil which in two cases (compounds 1 and 11) crystallised. When it was impossible to obtain the base in crystalline form it was dissolved in ether and converted to the hydrochloride by the addition of ethereal hydrogen chloride. Some of the bases were quaternised with alkyl halides according to the method earlier described for  $\beta$ -dialkylaminoalkyl phenothiazine-10-carboxylates<sup>5</sup>.

Physical constants and analytical data are collected in Table 1.

Before analysis the compounds were dried at 50° and 0.05 mm. The elemental analyses were performed by Dr. A. Bernhardt, Mülheim, Germany.

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