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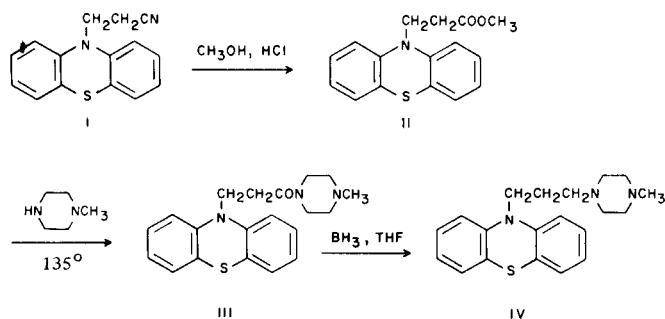
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A novel synthesis of perazine (10-(4-methylpiperazinyl-3-propyl)phenothiazine), likely to be applicable to 10-dialkylaminopropyl phenothiazines generally, is described.

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Piperazinopropylphenothiazines are substances of considerable medicinal interest and quite a number of them have been described. Some have other uses also. 10-(4-Methylpiperazinyl-3-propyl)phenothiazine (perazine, IV), for example, is a useful reagent for the spectrophotometric assay of platinum [1].

Having need of a quantity of perazine and finding reported procedures [2,3] for its preparation problematical we have developed a simple three-step route to it.



Key is the conversion of methyl ester II into piperazide III. Godefroi and Wittle [4] reported the ester function of II to be "remarkably inert". To prepare amides, they found it necessary to hydrolyze nitrile I with base, a procedure attended by considerable β-elimination and reversion to phenothiazine, and to subject the acid to an erratic and uncertain [4,5] conversion to the acid chloride; from which, subsequently, piperazide III was prepared by Hromatka *et al.* [6]. We find, however, that *N*-methylpiperazine reacts smoothly with methyl phenothiazinepropionate (II) at a temperature just below the boiling point of the amine to give piperazide III near-quantitatively and pure enough for reduction directly to the amine IV. Like disubstituted amides in general [7], III is reduced in high yield by diborane. Yield of target compound IV, as malonate salt, is 64% overall from phenothiazine.

The facile amidation is by no means unique to piperazines. Preliminary experiments show that morpholine and piperidine react just as readily, the ester carbonyl group (ir) disappearing and being replaced by amide during 15-30 hours at 120-130°. The crude products exhibit the expected nmr characteristics. It seems likely, therefore,

that the sequence may be generally applicable as a route to dialkylamides of phenothiazinepropionic acid and thence to dialkylaminopropyl phenothiazines.

#### EXPERIMENTAL

The proton nmr data were obtained on a Varian EM 360 (chemical shifts, δ, ppm downfield from internal TMS). The melting points were determined on a Fisher-Johns apparatus with baffled block and are uncorrected.

Methyl β-(10-Phenothiazinyl)propionate (II).

β-(10-Phenothiazinyl)propionitrile (I) was prepared (90%) as described by Godefroi and Wittle [4]; nmr (deuteriochloroform): 7.3-6.6 (m, 8H, aromatic), 4.1 (t, 2H, NCH<sub>2</sub>-), 2.8 (t, 2H, -CH<sub>2</sub>CN); and was converted into the ester by reaction with water in methanol-dioxane-hydrogen chloride as described by them for the 2-chloro analog. It is imperative, we find, that the solvent be saturated with hydrogen chloride *before* the nitrile is introduced, else considerable amounts of phenothiazine and methyl β-methoxypropionate are produced. The yield of crystallized ester (from methanol) was 82% based on phenothiazine, mp 64-65° (lit [4] 64-65°); nmr (deuteriochloroform): 7.3-6.7 (m, 8H, aromatic), 4.2 (t, 2H, NCH<sub>2</sub>-), 3.6 (s, 3H, OCH<sub>3</sub>), 2.8 (t, 2H, -CH<sub>2</sub>CO).

β-(10-Phenothiazinyl)propion-4-methylpiperazide (III).

*N*-Methylpiperazine (8 g, 80 mmoles) and methyl β-(10-phenothiazinyl)propionate (II) (20 g, 70 mmoles) in a large test tube, loosely stoppered, were heated (a transient vivid royal blue color quickly faded) in an oil bath at 132-135° until the ester carbonyl group (ir 1720 cm<sup>-1</sup>) disappeared completely (18 hours), appearance of amide carbonyl (1610 cm<sup>-1</sup>) being observed. Dissolution of the warm crude product in ether (50 ml) followed by chilling in ice afforded a white crystalline cake of piperazide III, (18 g, 73%), mp 72-74° (lit [6] 73-75°); nmr (deuteriochloroform): 7.3-6.7 (m, 8H, aromatic), 4.2 (t, 2H, arNCH<sub>2</sub>), 3.7-2.1 (m contg NCH<sub>3</sub> spike at 2.2, 13H, CH<sub>2</sub>CON(CH<sub>2</sub>)<sub>2</sub>NCH<sub>3</sub>).

10-(4-Methylpiperazinyl-3-propyl)phenothiazine (IV) Dimalonate.

The crude liquid product from reaction of *N*-methylpiperazine (6 g, 60 mmoles) with II (15 g, 52.5 mmoles) was taken up in dry THF (30 ml). The solution, chilled in ice, under nitrogen, was treated with diborane in THF (180 ml, 1 *M* BH<sub>3</sub>), stirred at 25° for 1 hour, and finally heated under reflux for 6 hours. Dilute hydrochloric acid (200 ml, 1 *M*) was added cautiously, solvent (200 ml) was distilled off, water (300 ml) was added, and the mixture was boiled and allowed to cool. The clear pale blue aqueous solution was decanted from a pale yellow gum (crude 10-(3-hydroxypropyl)phenothiazine), made basic with potassium hydroxide (14 g), the oil isolated in dichloromethane, the dichloromethane solution dried (potassium carbonate) and evaporated. The thick clear oil (13.9 g, 78%) was dissolved in diethyl ether-methanol (30:1) mixture (50 ml) and a solution of malonic acid (9 g, 86.5 mmoles) in methanol (15 ml) was slowly stirred in. Crystallization commenced part-way through the addition and became copious. Chilled, filtered, and washed with diethyl ether-methanol (8:1) mixture, the crystals of perazine (IV) dimalonate (22.5 g, 78%)

had mp 116-117° (lit [3] 113-115°); nmr (free base, deuteriochloroform): 7.3-6.7 (m, 8H, aromatic), 3.9 (t, 2H, arNCH<sub>2</sub>-), 2.4 (br s, 10H, piperazine CH<sub>2</sub> and piperazinomethylene CH<sub>2</sub>), 2.2 (s, 3H, NCH<sub>3</sub>), 2.1-1.8 (m, 2H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-).

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