Synthesis of a Non-Flexible Analog of Chlorpromazine

Arthur J. Elliott and Henry Guzik*

Chemical Research Department, Medicinals, Schering-Plough Pharmaceutical Research Division, Bloomfield, New Jersey 07003

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9-Chloro-2-dimethylaminomethyl-1,2-dihydropyrrolo[3,2,1-*kl*]phenothiazine (*3b*), a conformationally restricted analog of chlorpromazine, has been synthesised and has been found to be devoid of neuroleptic activity.

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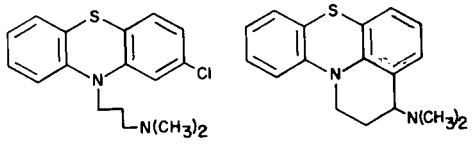
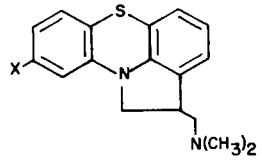
The phenothiazines, exemplified by chlorpromazine (**1**) are the largest and most widely investigated class of neuroleptic agents. The important feature of these compounds is the basic amino group attached to the nitrogen atom of the phenothiazine nucleus and separated from it by a three carbon chain (1). A degree of flexibility in the side-chain appears to be necessary since formation of a six-membered ring, as in **2**, gives a compound with only minimal neuroleptic activity (2).



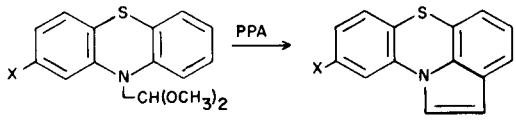
1 **2**



3a, X=H
3b, X=Cl

The incorporation of the side-chain into a five-membered ring, as in **3**, has not been reported. While such a structure would also limit the flexibility of the side-chain, it does incorporate the elements of a phenethylamine pharmacophore. We therefore decided to synthesise these tied-back analogs of promazine **3a** and chlorpromazine **3b** for evaluation as neuroleptic agents.

The pyrrolo[3,2,1-*kl*]phenothiazine ring-system (**5a**) has been reported from the polyphosphoric acid cyclisation of the acetal **4a** (3).

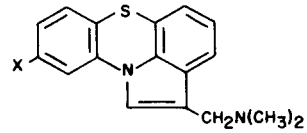


4a, X=H
4b, X=Cl

5a, X=H
5b, X=Cl

Application of this reaction to the acetal **4b**, obtained from the sodium salt of 2-chlorophenothiazine and chloroacetaldehyde dimethylacetal, gave **5b** as the only isolable product. That the cyclisation had occurred on the unsubstituted ring was shown by the pmr spectrum which showed the *peri*-proton adjacent to the chlorine as a *meta*-coupled doublet at δ 8.11 (J = 3 Hz).

Compound **5a** underwent the Mannich reaction as reported (3) to give **6a**, but **5b** required a much longer reaction time to yield **6b**. Both compounds were reduced with borane to give **3a** and **3b**, neither of which exhibited



6a, X=H
6b, X=Cl

any neuroleptic activity as measured by antagonism of methamphetamine toxicity in mice (4).

Chlorpromazine exists in the crystal form with the basic side-chain on the same side as the ring bearing the chlorine substituent (5). Thus, **3b** might represent the wrong isomer for direct comparison with chlorpormazine. However, the unknown configuration of **1** at the receptor site, coupled with the lack of activity of **3a**, which represents a tied-back version of promazine, a known neuroleptic, make this explanation unlikely.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H Nmr spectra were recorded on a Varian CFT-20 spectrometer, ir spectra were recorded on a Perkin-elmer 221 spectrophotometer, and mass spectra were determined with a Varian MAT CH5. Microanalyses were performed by the Physical Analytical Services Department of the Schering-Plough Corp.

2-Chlorophenothiazine-10-acetaldehyde Dimethylacetal (**4b**).

Sodium hydride (15.0 g, 0.625 mole) was added to anhydrous dioxane (1 *l*) under nitrogen and the well-stirred mixture was heated under reflux with 2-chlorophenothiazine (100 g, 0.43 mole) for 4 hours. To this mixture was added dropwise chloroacetaldehyde dimethylacetal (75.0 g, 0.61 mole) and then the heating was continued for 17 hours. The mixture was allowed to cool and the excess sodium hydride was destroyed by the careful addition of methanol. The mixture was filtered through celite and the solvent was evaporated *in vacuo*. The residue was partitioned between ethyl acetate (1.2 *l*) and water (700 ml), the organic layer was separated, dried (magnesium sulfate) and evaporated *in vacuo*. The

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residue was distilled *via* a kugelrohr apparatus to yield a pale yellow oil (102.1 g, 74%) distilling between 130-170° (2mm). On standing the oil solidified and was crystallised from methanol as colorless neeedles, mp 48-50°; pmr (deuteriochloroform): δ 3.31 (s, 6H), 3.92 (d, 2H, J = 5Hz), 3.66 (t, 1H, J = 5Hz), 6.8-7.2 (m, 7H), ms: m/e (% relative intensity): 321 (19).

Anal. Calcd. for $C_{16}H_{14}ClNO_2S$: C, 59.71; H, 5.01; N, 4.35. Found: C, 59.91; H, 5.29; N, 4.14.

9-Chloropyrrolo[3,2,1-*kl*]phenothiazine (**5b**).

The acetal **4b** (100 g, 0.31 mole) was dissolved in chloroform (2 ℓ) and, with rapid stirring, polyphosphoric acid (450 g) was added. The mixture was stirred rapidly for 17 hours. The organic layer was decanted, the PPA extracted with chloroform (1 ℓ) and the combined organic solutions were washed with water (2 x 1 ℓ), dried (sodium sulfate) and evaporated *in vacuo*. The residue was distilled *via* a kugelrohr apparatus to give 53.2 g (66%) of product distilling at 190-210° (2 mm). A sample was recrystallised from 1-chlorobutane to give colorless needles, mp 154-155°; pmr (DMSO-d_6): δ 6.58 (d, H-2, J = 3Hz), 6.6-7.3 (m, 5H), 7.72 (d, H-10, J = 2Hz), 7.96 (d, H-1, J = 3Hz); ms: m/e (% relative intensity) 257 (100).

Anal. Calcd. for $C_{14}H_8ClNS$: C, 65.24; H, 3.13; N, 5.43. Found: C, 65.42; H, 2.97; N, 5.20.

9-Chloro-2-Dimethylaminomethylpyrrolo[3,2,1-*kl*]phenothiazine (**6b**).

Compound **5b** (20.0 g, 0.078 mole), dioxane (200 m), acetic acid (50 m), 40% aqueous dimethylamine (50 ml) and 40% formaldehyde solution (7.5 ml) were stirred together and boiled under reflux for 8 hours with an additional 3 ml of formaldehyde solution being added every 30 minutes. The mixture was allowed to cool, acidified with concentrated hydrochloric acid and extracted with ether (2 x 400 ml). The combined extracts yielded 8.1 g of recovered **5b**. The aqueous solution was basified and extracted with ethyl acetate (2 x 400 ml), the combined extracts dried magnesium sulfate and evaporated *in vacuo*. The residue crystallised from 1-chlorobutane-hexane to yield 5.8 g (34%) of colorless prisms, mp 107-108°; pmr (DMSO-d_6): $_d$ 2.15 (s, 6H), 3.42 (s, 2H), 6.6-7.2 (m, 5H), 7.87 (d, H-10, J = 2Hz), 7.92 (d, H-1, J = 3Hz); ms: m/e (% relative intensity) 314 (34).

Anal. Calcd. for $C_{17}H_{15}ClN_2S$: C, 64.85; H, 4.80; N, 8.90. Found: C, 64.80; H, 4.53; N, 8.68.

2-Dimethylaminomethyl-1,2-dihydropyrrolo[3,2,1-*kl*]phenothiazine (**3a**).

1-Dimethylaminomethylpyrrolo[3,2,1-*kl*]phenothiazine (3) (7.0 g, 0.025 mole) in tetrahydrofuran (50 ml) was added to a 1 *M* solution of borane in tetrahydrofuran (30 ml, 0.03 mole) dropwise with stirring. The mixture was stirred for 5 minutes, then cautiously diluted with water (600 ml). The colorless solid was filtered, washed with water and dried. The product was added to a mixture of ethanol (120 ml) and 6*N* hydrochloric acid (50 ml) and the mixture was stirred and heated under reflux for 2.5 hours then allowed to cool. The mixture was concentrated *in vacuo*, basified with 2*N* sodium hydroxide solution and extracted with ethyl acetate (2 x 200 ml). The combined, dried magnesium sulfate extracts were evaporated *in vacuo* to yield an oil which was chromatographed on silica gel (220 g) using chloroform-ethyl acetate as eluent. The product was collected and obtained as a brown oil which formed 3.1 g (31%) of a maleate salt which crystallised from methanol as colorless needles, mp 181-183°; pmr (DMSO-d_6): δ 2.81 (s, 6H), 3.0-4.0 (m, 5H), 6.04 (s, 2H), 6.3-7.2 (m, 7H); ms: m/e (% relative intensity) 282 (57).

Anal. Calcd. for $C_{17}H_{18}N_2S{\cdot}C_4H_4O_4$: C, 63.31; H, 5.57; N, 7.03. Found: C, 63.49; H, 5.53; N, 6.89.

9-Chloro-2-dimethylaminomethyl-1,2-dihydropyrrolo[3,2,1-*kl*]phenothiazine (**3b**).

This compound was obtained in an analogous manner to that described for 3a above and yielded a maleate salt (17%) which crystallised from methanol-ehtyl acetate as off-white prisms, mp 169-170°; pmr (DMSO-d_6): δ 2.81 (s, 6H), 3.0-4.0 (m, 5H), 6.04 (s, 2H), 6.52 (d, H-10, J = 3Hz), 6.7-7.1 (m, 5H); ms: m/e (relative intensity) 316 (4).

Anal. Calcd. for $C_{17}H_{17}ClN_2S{\cdot}C_4H_4O_4$: C, 58.27; H, 4.89; N, 6.47. Found: C, 58.31; H, 4.62; N, 6.48.

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