Notes

Synthesis of the Isoquino[1,2-*c*][1,4]benzothiazine Ring System

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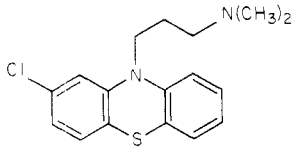
The phenothiazine molecules, of which chlorpromazine (1) is a prototype, have proven useful as medicinal agents.[2]



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We report here a synthesis of the related, novel isoquino[1,2-*c*][1,4]benzothiazine ring system with the appropriate substitution for future elaboration of aminoalkyl side chains. These compounds represent analogues of phenothiazines with a displaced benzo group and a potentially restricted side chain.

Our strategy for synthesis of the target canted phenothiazine is displayed pictorially in Figure 1. The first step in this plan called for alkylation of an anilino nitrogen with an appropriate substrate which could later be converted to the desired side chains. Unfortunately, initial attempts at this type of reaction where R = CN and X = OTs or I led to either elimination of phenylacrylonitrile or alkylation at sulfur. Alternatively, methyl 3,4-dimethoxyphenylacetate (**2**) was condensed with the anion of acetonitrile by using a modified procedure of Takano.[3] Reaction of the resultant ketone **3** with 2-aminothiophenol in the presence of catalytic amounts of tosic acid gave the benzothiazoline **4**.

The key step in the sequence centered around the observation that cyano thiazoline **4** readily underwent β elimination of thiophenoxide (see Scheme I). Subsequent sulfur alkylation with methyl bromoacetate gave enamine **5** which contained all the necessary functionality for completion of the synthesis. The ^{1}H NMR spectrum of **5** showed only one sharp singlet (δ 4.6) for the olefinic proton, thus indicating the formation of only one isomer. The *E* configuration seems most likely in light of the lack of allylic coupling between the olefinic and benzylic protons. β-Amino-[4] and β-anilinocrotonitriles[5] of the *E* configuration have coupling constants of 0 and <0.2 Hz, respectively, whereas the corresponding *Z* compounds have *J* values of 0.8 and 0.5 Hz.

Reduction of cyanoenamine **5** was accomplished in 98% yield with sodium cyanoborohydride in the weakly acidic medium of 2,2,2-trifluoroethanol and methanol. Resultant

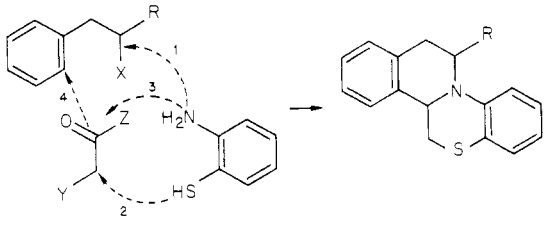

Figure 1.

amino ester **6** was readily cyclized to lactam **7** by reflux in a 3:1 mixture of methanol and 10% aqueous hydrochloric acid.

The final step in construction of the tetracyclic ring system required a Bischler–Napieralski condensation of the lactam carbonyl on the activated dimethoxyphenyl ring. Although not described herein, we carried out the synthesis of the analogue of lactam **7** without 3,4-dimethoxy substitution on the phenyl ring. It was completely resistant to cyclization under numerous conditions which included phosphorus oxychloride, polyphosphoric acid, and anhydrous hydrogen fluoride. In the cyclization of **7**, a minimal amount of polyphosphoric acid was used and the resultant azinium ion was isolated as the perchlorate salt **8**.[6] As a result of the aqueous acid medium, the nitrile was simultaneously converted to a primary amide. Reduction of the intermediate salt **8** with sodium borohydride led to a 1:1 mixture of cis and trans isomers.[7]

This novel tetracyclic ring structure should be readily convertible to a variety of phenothiazine analogues by trivial modification of the 12-acetamido substituent into amino alkyl side chains.

Experimental Section

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were obtained on either a Varian T-60 or A-60A spectrometer.

3,4-Dimethoxy-β-oxobenzenebutanenitrile (3). Sodium hydride (12 g, 0.5 mol) was freed of mineral oil by washing three times with heptane under nitrogen. It was then suspended in 500 mL of dioxane before the addition of acetonitrile (20.5 g, 0.5 mol) followed by 3 mL of absolute ethanol. The mixture was stirred for 30 min before the addition of ester **2** (99.3 g, 0.45 mol) in 300 mL of dioxane. It was then heated under reflux for 1.5 h. There was a large amount of gas evolved during the first 30 min of heating. The mixture was poured into ice–water and further diluted to 3 L with water. It was extracted with 100 mL of Et_2O to remove an oily film before acidification with concentrated sulfuric acid and extraction three times with ethyl acetate (1.5 L total). These organic extracts were combined, washed with saturated sodium bicarbonate solution (700 mL) and brine, dried with magnesium sulfate, and concentrated to yield 65.18 g of orange-yellow oil: ^{1}H NMR (δ, $CDCl_3$, Me_4Si) 3.55 (s, 2 H, PhCH_2), 3.75 (s, 2 H, CH_2CN), 3.8 (s, 6 H, methoxyls), 6.6–7.0 (m, 4 H, aromatics); IR (neat film) 1720 (C=O), 2200 and 2230 (C=N) cm^{-1}. This material was used without further purification.

2-[(3,4-Dimethoxyphenyl)methyl]-2-benzothiazoleacetonitrile (4). Ketone **3** (65.1 g, 0.3 mol) and 2-aminothiophenol (37 g, 0.3 mol) were admixed in 500 mL of benzene. A small

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(2) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics", 5th ed., Macmillan, New York, 1975, p 152.
(3) T. Takano, *Yakugaku Zasshi*, **79**, 1449 (1959).
(4) E. Bullock and B. Gregory, *Can. J. Chem.* **43**, 332 (1965).
(5) J. Dedina, J. Kuthan, J. Palecek, and J. Schrame, *Collect. Czech. Chem. Commun.*, **40**, 3476 (1975).
(6) R. E. Lyle and G. A. Heavner, *J. Org. Chem.*, **40**, 50 (1975).
(7) Recrystallization of this compound in methanol slightly fractionated one pair of diastereomers from the other but these were not characterized further.

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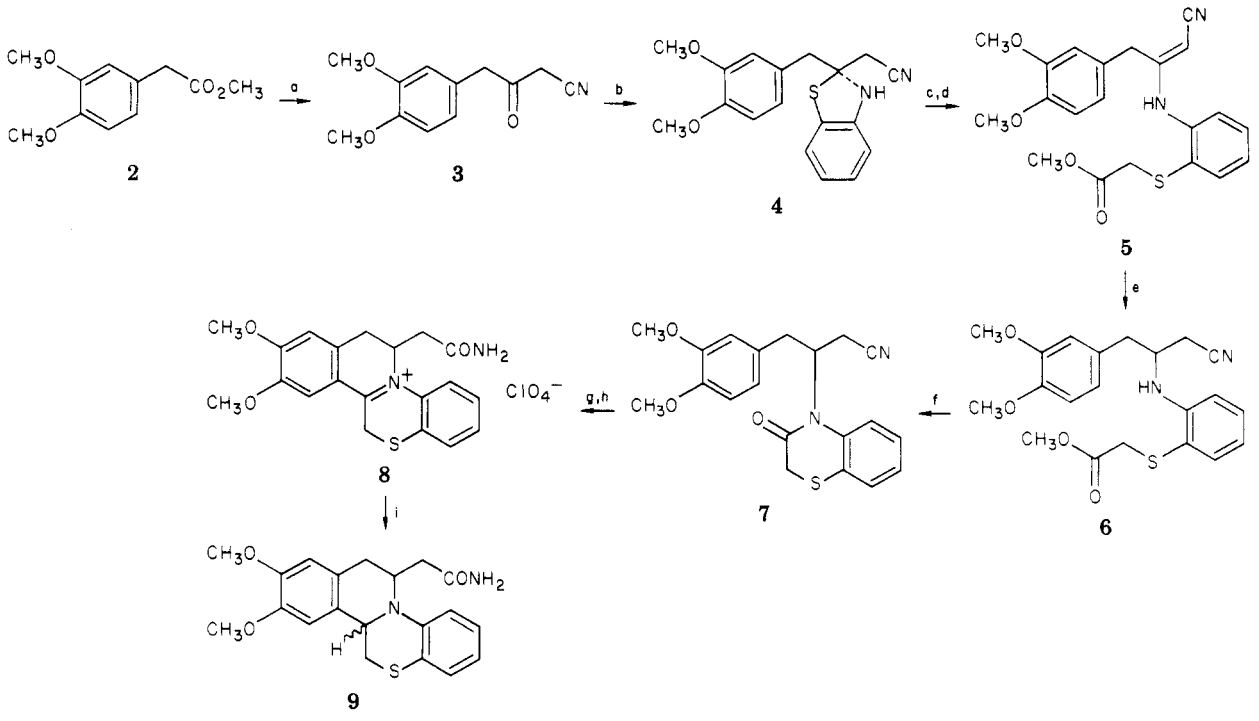
Scheme I[a]



[a] Conditions: (a) CH_3CN, NaOEt, dioxane; (b) 2-aminothiophenol, TsOH, C_6H_6; (c) NaH, THF; (d) $BrCH_2CO_2CH_3$; (e) $NaCNBH_3$, CF_3CH_2OH, CH_3OH; (f) HCl, H_2O–CH_3OH; (g) PPA; (h) $HClO_4$(aq); (i) $NaBH_4$, CH_3OH.

amount (300 mg) of tosic acid monohydrate was added. The flask was equipped with a Dean–Stark trap and the mixture was heated under reflux for 27 h. It was then washed with saturated sodium bicarbonate solution four times and 10% sodium carbonate solution three times to remove as much unreacted 2-aminothiophenol as possible. It was then dried with brine and $MgSO_4$ and concentrated in vacuo to yield 89 g of viscous yellow oil. This material was chromatographed on a Waters LPLC unit with Woelm GF silica gel as the absorbant. Elution was done with 2% ethyl acetate–benzene. The pure fractions were combined to yield 22.5 g. Rechromatography of the cruder fractions yielded an additional 20 g of pure product. The oil, which crystallized on standing, was digested with diisopropyl ether, filtered, and washed with ethyl ether to give thiazoline **4**: mp 95–99 °C; ^1H NMR (δ, $CDCl_3$, Me_4Si) 2.8 (bs, 2 H, $PhCH_2$), 3.4 (s, 2 H, CH_2CN), 3.82 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.4 (bs, 1 H, NH), 6.5–7.4 (m, 7 H, aromatics).

Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58; S, 9.82. Found: C, 66.28; H, 5.34; N, 8.63; S, 9.93.

Methyl [2-[[1-(Cyanomethylene)-2-(3,4-dimethoxyphenyl)ethyl]amino]phenylthio]acetate (5). Thiazoline **4** (1.0 g, 3.1 mmol) in THF (10 mL) was added dropwise over 3 min to a stirred, cooled (ice bath) suspension of sodium hydride (89 mg, 3.7 mmol) in THF (4 mL) under nitrogen. The mixture was stirred at 0 °C for 45 min. Initially, after the evolution of hydrogen had ceased, it was a clear red solution. Later a white solid precipitated. To this was added methyl bromoacetate (0.47 g, 3.1 mmol) in THF (3 mL). The color was immediately dissipated. The mixture was allowed to warm to room temperature and stirred for 75 min before it was partitioned between water–ether. The organic layer was separated, washed with water twice and brine, dried with $MgSO_4$, and concentrated to yield 1.14 g (93.4%) of yellow oil which was analytically pure: ^1H NMR (δ, $CDCl_3$, Me_4Si) 3.3 (s, 2 H, $PhCH_2$), 3.6 (s, 3 H, CO_2CH_3), 3.8–4.0 (s's, 8 H, SCH_2 and methoxyls), 4.6 (s, 1 H, olefinic), 6.7–7.7 (m, 8 H, NH and aromatics).

Anal. Calcd for $C_{21}H_{22}N_2O_4S$: C, 63.30; H, 5.56; N, 7.03. Found: C, 63.24; H, 5.81; N, 7.09.

Methyl [2-[[1-(Cyanomethyl)-2-(3,4-dimethoxyphenyl)ethyl]amino]phenylthio]acetate (6). Sodium cyanoborohydride (0.35 g, 5.52 mmol) in methanol (5 mL) was added to a stirred solution of enamino nitrile **5** (1.1 g, 2.76 mmol) in trifluoroethanol (15 mL). The yellow solution was heated at 70 °C under nitrogen for 24 h. It was then cooled with an ice bath before the addition of 5 mL of 1 N KOH (aqueous). After a few minutes the reaction was further diluted with water and ether. The ether layer was separated and the aqueous layer was extracted with two additional portions of ether. The combined organic extracts were washed three times with water and once with brine, dried with $MgSO_4$, and concentrated to yield 1.08 (97.7%) of clear yellow oil. In order to remove any transesterification impurities for analysis, the oil was dissolved in methanol (50 mL) with 3 drops of glacial acetic acid. It was refluxed for 27 h, concentrated, neutralized with dilute NaOH, and extracted into ether. This was dried and concentrated to yield a quantitative return of yellow oil of analytical purity: ^1H NMR (δ, $CDCl_3$, Me_4Si) 2.55 (bd, J = 5 Hz, 2 H, $PhCH_2$), 3.0 (bd, J = 6 Hz, 2 H, CH_2CN), 3.35 (s, 2 H, CH_2S), 3.6 (s, 3 H, CO_2CH_3), 3.8 (s, 7 H, methoxyls and buried methine), 5.5 (d, J = 8 Hz, NH), 6.4–7.6 (m, 7 H, aromatics).

Anal. Calcd for $C_{21}H_{24}N_2O_4S$: C, 62.98; H, 6.04; N, 6.99. Found: C, 63.13; H, 6.16; N, 6.90.

β-[(3,4-Dimethoxyphenyl)methyl]-3-oxo-2*H*-1,4-benzothiazine-4-propanenitrile (7). The amino ester **6** (16.6 g) was dissolved in 300 mL of methanol before the addition of 100 mL of aqueous 10% hydrochloric acid solution. The cloudy mixture was heated under gentle reflux for 48 h before it was poured into water and extracted three times with methylene chloride. The organic extracts were combined, dried, and concentrated to yield ca. 13 g of viscous yellow gum. This material was chromatographed (LPLC) on 500 g of Woelm silica gel. Elution with 5% ethyl acetate–chloroform yielded 8 g of pure product as a foam. A small sample was recrystallized from 2-propanol to yield colorless prisms: mp 120–121 °C; ^1H NMR (δ, $CDCl_3$, Me_4Si) 3.3 (s, 2 H, CH_2S), 3.75, 3.80 (s's, 6 H, methoxyls), 2.7–5.8 (m, 5 H), 6.5–7.5 (m, 7 H, aromatics).

Anal. Calcd for $C_{20}H_{20}N_2O_3S$: C, 65.19; H, 5.47; N, 7.60; S, 8.70. Found: C, 65.00; H, 5.49; N, 7.60; S, 8.65.

4b,5,12,13-Tetrahydro-2,3-dimethoxyisoquino[1,2-*c*]-[1,4]benzothiazine-12-acetamide (9). Lactam **7** (1.0 g) was suspended in 15 g of commercial polyphosphoric acid and heated on a steam bath with occasional stirring for 5.5 h. Although there were some undissolved chunks of solid which were presumably starting material, the mixture was diluted to 100 mL with water and filtered to remove that material (0.35 g). To the filtrate was slowly added ca. 10 mL of 10% perchloric acid solution (aqueous). The mixture was stored in a refrigerator overnight before the yellow precipitated solid was isolated by vacuum filtration. This

was dried at 50 °C under vacuum to yield 0.6 g of perchlorate salt 8: IR (KBr) 1680 (C=O) cm^{-1}.

The yellow solid was suspended in methanol (25 mL) and cooled with an ice bath under nitrogen before the careful addition of sodium borohydride. The resultant mixture was stirred at 0 °C for 30 min and at ambient temperature for 1.5 h. The pale tan solution was quenched with the addition of 25 mL of saturated sodium bicarbonate solution. It was stirred for 2 h before it was partitioned between water–methylene chloride. The aqueous layer was extracted with a second portion of methylene chloride. The combined organic extracts were dried and concentrated to yield 0.58 g of clear tan oil which crystallized on sitting. Recrystallization from methanol yielded fine white needles, mp 184–190 °C. Except for a methoxyl singlet at δ 3.8, the ^1H NMR spectrum consisted of a series of unresolved humps from 2.0 to 7.4.

Anal. Calcd for $C_{20}H_{22}N_2O_3S$: C, 64.84; H, 5.99; N, 7.56; S, 8.66. Found: C, 65.02; H, 6.20; N, 7.38; S, 9.06.

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Registry No. 2, 15964-79-1; 3, 70456-63-2; 4, 70456-64-3; 5, 70456-65-4; 6, 70456-66-5; 7, 70456-67-6; 8, 70456-69-8; 9, 70456-70-1; acetonitrile, 75-05-8; 2-aminothiophenol, 137-07-5; methyl bromoacetate, 96-32-2.

A Convenient Synthetic Sequence for the Deuterium Labeling of Olefins in the Allylic Position

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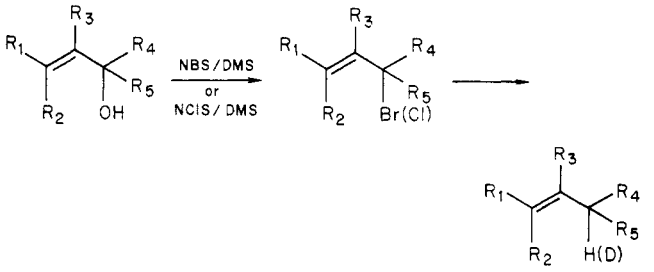
During the course of our studies of the mechanism of allylic functionalization[1] we have developed a convenient, high-yield, synthetic sequence which produces olefins isotopically labeled at the allylic positions. The established reaction sequence for such labeling generally involves synthesis of a mesylate or tosylate,[2] followed by lithium aluminum hydride (deuteride) reduction. This sequence proved to be impractical in the case of allylic alcohols due to the instability of these intermediates at temperatures required for the reduction reaction. By replacing the mesylates and tosylates with chlorides and/or bromides produced by Corey's method,[3] we have been able to produce labeled olefins in good yield.

Results and Discussion

The generalized reaction sequence employed is



The application of this technique to several olefins is summarized in Table I.

For primary allylic alcohols (R_4 = R_5 = H or D) the resulting allylic bromides or chlorides are both sufficiently stable to be handled conveniently and characterized by NMR (see Table I, entries 1 and 2). In the reduction of secondary allylic alcohols (R_4 = alkyl, R_5 = H or D), however, it is preferable to employ chlorides since the bromides undergo decomposition (see entries 5–7). The chlorides are also preferred for styrene derivatives (see entries 3 and 4). Only for primary allylic alcohols could the more traditional mesylate intermediate be employed, and here only if low temperatures were maintained through the workup and reduction. The mesylates of the secondary or styryl alcohols and of the diols (entries 8–10) were unstable[4] even at low temperatures and no olefin products could be isolated.

The solvent used in the second step of this sequence is chosen relative to the boiling point of the product olefin, diglyme being preferred for low-boiling olefins which can easily be distilled out of this solvent.

In the sequences which convert primary alcohols to the corresponding hydrocarbons, no evidence of cis–trans or allylic rearrangement could be detected in either step in the reaction sequence. This point could be examined with particular care for entries 2–4 and 10. For entries 2–4, careful examination of NMR spectra showed no evidence of rearrangement product. This point is strengthened by entry 10, where VPC analysis of the product olefin showed no evidence of rearrangement to *trans*-2-butene or to the allylic rearrangement isomer 1-butene.

Conversions involving secondary alcohols were somewhat less clean. For entries 5–7, conversion of the alcohols to the chlorides was accompanied by a few percent of allylic rearranged chloride (as revealed by NMR examination). Conversion of these chlorides to hydrocarbons showed a consistent 5–10% allylic rearrangement isomer, some of which apparently occurred in the reduction step. Thus, while this method appears to be suitable for secondary systems, it is not as unambiguously regiospecific as for the primary substrates.

In an attempt to assess the limits of applicability of this method, we have carried out these reactions on the benzylic/allylic alcohol shown in Scheme I. Both *E* and *Z* alcohols gave an allyl chloride whose structure is assigned by NMR as the rearrangement product. This is clearly the result of complete allylic rearrangement to the more stable species. Reduction of this compound gave the indicated mixture of olefins.

In summary this sequence offers the advantage of high regiospecificity for primary alcohols and represents a significant improvement in yield and convenience over the more traditional methods. With simple aliphatic secondary systems only small quantities of rearranged products were found. Materials labeled with deuterium and, in particular, methyl-labeled compounds are thus more generally

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(4) Reaction mixtures turned black almost immediately even during careful low-temperature workups.

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