Synthesis of Isopromethazine Hydrochloride

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Abstract □ Isopromethazine hydrochloride was synthesized in gram quantities by using a method which ensures that the isopromethazine is not contaminated with promethazine hydrochloride.

Keyphrases □ Isopromethazine hydrochloride—synthesis □ Promethazine hydrochloride—synthesis of isopromethazine □ Promethazine isomer—synthesis □ Antihistamine—isopromethazine synthesis

Promethazine (*N,N,α*-trimethyl-10*H*-phenothiazine-10-ethanamine, I) is an antihistamine that is usually synthesized by the reaction of either 2-chloro-1-dimethylaminopropane (1–7) or 1-chloro-2-dimethylaminopropane (2) with phenothiazine in the presence of bases such as sodium hydroxide, sodium amide, or phenyllithium (1), or with the Grignard derivative of phenothiazine (7). When *β*-haloamines are treated with bases, aziridinium salts are frequently formed (8, 9), and the three-membered ring can be opened by a nucleophile at either ring carbon to produce isomeric alkylation products (10) (Scheme I). Thus, in the alkylation of phenothiazine with 2-chloro-1-dimethylaminopropane, *N,N,β*-trimethyl-10*H*-phenothiazine-10-ethanamine (isopromethazine, II) is obtained in addition to the desired I[1]. These isomeric compounds can be separated by fractional crystallization (6), but small amounts of II usually remain in the purified samples of I. Therefore, a sample of pure II was needed as a reference standard for the analysis of I (13–17)[2,3].

EXPERIMENTAL

Phenothiazine[4] was recrystallized from 95% ethanol. Butyllithium[4] (1.6 *M* in hexane) and 2-chloropropionyl chloride[4] were used without further purification. Previously unopened anhydrous ethyl ether and tetrahydrofuran were used without further drying. NMR[5], MS[6], and IR spectra[7] were obtained. Melting points were uncorrected.

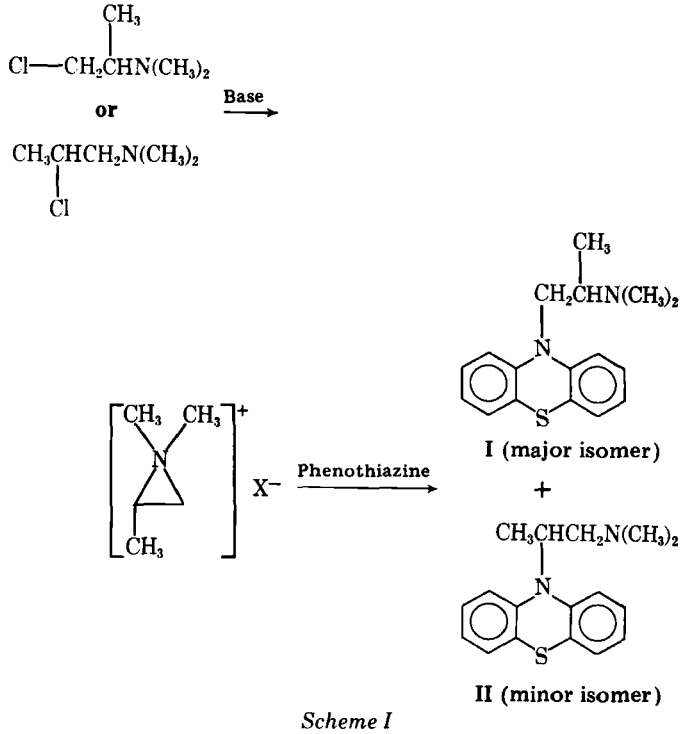
***N,N,β*-Trimethyl-10*H*-phenothiazine-10 - *α* - oxoethanamine** (V)—To a solution of phenothiazine (15.9 g, 0.08 mole) in 500 ml of dry ether under a nitrogen atmosphere and cooled to −20 to −30°, 50 ml of 1.6 *M* *n*-butyllithium in hexane was added with stirring. The resulting bright-yellow solution was stirred for 30 min, then *N,N*-dimethyl-2-chloropropionamide (18) (IV, 10.9 g, 0.08 mole) in 25 ml of ethyl ether was added over 1 hr. The solution was warmed to room temperature, the unreacted 10-lithiophenothiazine was hydrolyzed with water, the organic layer was dried over sodium sulfate, and the solvent was removed under reduced pressure to yield 21.7 g of residue, which was dissolved in toluene and transferred to a silica gel (60–200-mesh) column. Elution with toluene removed unreacted phenothiazine (6 g) and traces of highly colored impurities. Subsequent elution with toluene–ethyl acetate (85:15) afforded 11.4 g of nearly colorless amide (V, mp 161–163° [lit. (19) mp 165–167°] 76% based on unrecovered phenothiazine). ^{1}H-NMR ($CDCl_3$, 60 MHz): 1.9 (C—CH_3, 3H, d, J = 8 Hz), 2.9, 3.1 (N—CH_3, 6H, two s), 4.8 (CH, 1H, q, J = 8 Hz), 7.1 ppm (ArH, 8H, m); ^{13}C-NMR ($CDCl_3$): 15.97, 36.23, 37.37, 56.93, 116.27, 123.03, 124.35, 127.15, 127.79, 143.64, 169.84 ppm; IR: 1645 cm^{-1} (ν C=O, s); mass spectrum (80 eV, 300°): m/z 298 (M^+), 226 (M − C_3H_6NO), 198 (M − $C_5H_{10}NO$), 194 (M − C_3H_6NO − S), 154 (M − $C_5H_{10}NO$ − CS), 72 (C_3H_6NO, 100%).

Anal.—Calc. for $C_{17}H_{18}N_2OS$: C, 68.42; H, 6.08; N, 9.39; S, 10.75. Found: C, 68.41; H, 5.91; N, 9.42; S, 10.46.

***N,N,β*-Trimethyl-10*H*-phenothiazine-10-ethanamine Hydrochloride**—To a solution of lithium aluminum hydride (2 g, 0.053 mole) in 500 ml of dry tetrahydrofuran, V (5.0 g, 0.0167 mole) in 50 ml of tetrahydrofuran was added. The reaction mixture was stirred for 2 hr, then the excess hydride was destroyed with ethyl acetate and dilute sodium hydroxide solution. The reaction mixture was filtered and the solvent removed under reduced pressure. The residue was dissolved in ether and treated with hydrogen chloride gas to yield the crude hydrochloride of II. This material was recrystallized from acetonitrile to yield 3.9 g of nearly colorless prisms (72%, mp 196–198° [lit. (5) mp 193–194°]). ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.84 (C—CH_3, 3H, d, J = 8 Hz), 2.72 (N—CH_3, 6H, s), 3.2–3.8 (CH_2, 2H, m), 4.78 (CH, 1H, m), 6.9–7.2 ppm (ArH, 8H, m); ^{13}C-NMR ($CDCl_3$): 21.72, ~42 (broad), 52.53, 57.79, 117.14, 123.73, 126.40, 127.73, 127.95, 143.52 ppm; IR: 2300 cm^{-1} (ν N^+H, broad); mass spectrum (80 eV, 300°): m/z 284 (M − HCl), 226 (M − HCl − C_3H_8N), 198 (M − HCl − $C_5H_{12}N$), 194 (M − HCl − C_3H_8M − S), 58 (C_3H_8N, 100%), 36,38 (HCl).

Anal.—Calc. for $C_{17}H_{21}ClN_2S$: C, 63.62; H, 6.59; Cl, 11.05; N, 8.73. Found: C, 63.78; H, 6.83; Cl, 10.97; N, 9.02.

***N*-(2-Hydroxy-1-propyl)phthalimide**—A solution of 1-amino-2-propanol (5 g, 0.066 mole) and *N*-carboethoxyphthalimide (10 g, 0.05 mole) in 200 ml of 1,2-dichloroethane was stirred 2 hr at room temperature. An aqueous solution of potassium carbonate was added, and after stirring 15 min, the organic phase was separated, washed with water, and dried. The solvent was removed under reduced pressure, and the oily residue was recrystallized from ether–hexane to yield 1.7 g of the phthalimide, mp 86–87°.



Scheme I

[1] Under certain conditions, II has been reported as the predominant isomer (11, 12).

[2] A small sample of II (Chemical Reference Substance) may be obtained from the European Pharmacopoeia Commission, 67006 Strasbourg, Strasbourg, France.

[3] The USP (17) does not mention II in its monograph on promethazine hydrochloride.

[4] Aldrich Chemical Co.

[5] Perkin-Elmer R12B or Varian XL-200 spectrometer.

[6] Varian MAT-311A spectrometer.

[7] Perkin-Elmer 621 spectrophotometer.

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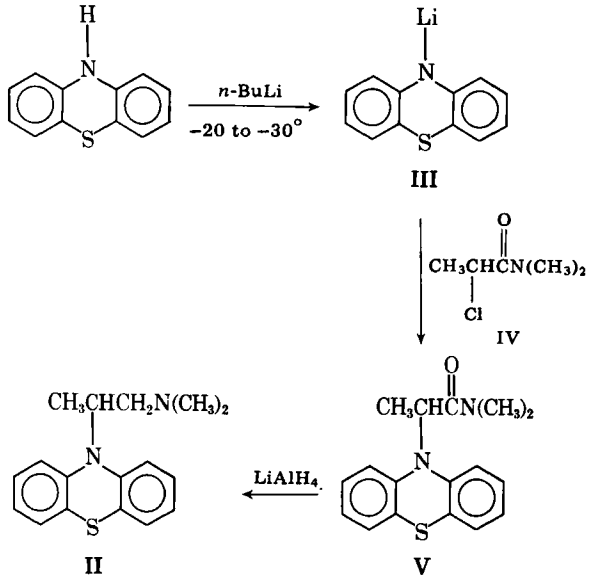

Scheme II

Anal.—Calc. for $C_{11}H_{11}NO_3$: C, 64.37; H, 5.40; N, 6.83. Found: C, 64.39; H, 5.22; N, 6.71.

The reaction of this material with phosphorus tribromide in pyridine yielded a white crystalline compound (mp 162–164°) that contained no bromine by elemental analysis; the compound was not identified.

RESULTS AND DISCUSSION

Due to the rearrangements noted with β-haloamines (8, 9), it was necessary to use an alkylating agent, which precluded the formation of isomeric products. This involved selecting a 2-halopropylamine with the amino group protected to prevent aziridine formation. The approach utilized (Scheme II) is similar to that reported previously (20). Compound III was prepared from phenothiazine and *n*-butyllithium by the procedure of Gilman and Diehl (21), and IV was prepared from dimethylamine and 2-chloropropionyl chloride by the procedure of Weaver and Whalen (18). When III was prepared at −20 to −30° and allowed to react with IV, a 76% yield of V resulted. This material was separated from unreacted phenothiazine by chromatography on silica gel. The reaction of V with lithium aluminum hydride in tetrahydrofuran afforded a 72% yield of II, which was isolated as the hydrochloride salt. The nearly colorless prisms (mp 196–198°) exhibited no loss of weight when heated in a thermal balance, indicating no solvent of crystallization.

The isopromethazine hydrochloride was shown to be identical to a European Pharmacopoeia Reference Standard[2] by UV and IR spectroscopy and by GLC on a 3% OV-101 on Chromosorb W column at 230° (retention time, 6.69 min). The GLC analyses of both prepared and standard isopromethazine hydrochloride indicated traces of phenothiazine (retention time, 3.73 min) and an unidentified compound (retention time, 3.24 min), which may have been formed by degradation on the column. The analyses indicated that no promethazine hydrochloride (retention time, 7.72 min; detection limit, ~0.1%) was present[8].

When III was prepared at room temperature and allowed to react with IV, a mixture of products including phenothiazine and V was obtained. One of the products appeared to be one of the dimers of phenothiazine (22, 23) (mass spectrum: *m/z* 396).

Another approach to the preparation of II involved the protection of the side-chain amine as a phthalimide. The reaction of 2-hydroxy-aminopropane with *N*-carboethoxyphthalimide (24) produced *N*-(2-hydroxy-1-propyl)phthalimide (mp 87–88°; elemental analysis and ^{1}H-NMR spectrum were satisfactory for this compound). However, attempts to replace the hydroxyl group with a halogen using either phosphorus tribromide in pyridine or triphenylphosphine and carbon tetrachloride were unsuccessful.

The use of a haloamide as a alkylating agent for III produced II in good yield. This method should prove useful as a general route to phenothiazine-containing compounds.

[8] Mr. Bobby R. Rader, Food and Drug Administration, Los Angeles, Calif., personal communication.

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