Stereoselective Synthesis of (*E*)-11-(2-Chloroethylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin

Yoshitaka OHISHI,* Mitsuo HAYASHIDA, Teruo MUKAI, Kazuhiko KIMURA, and Michiko NAGAHARA

Central Research Institute, Kaken Pharmaceutical Co., Ltd., 14, Shinomiya Minamikawara-machi, Yamashina-ku, Kyoto 607, Japan.
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Three acidic metabolites (5—7) of 6,11-dihydro-11-(3-dimethylaminopropylidene)dibenzo[*b*,*e*]thiepin(dothiepin) were prepared. In the synthetic course, a reaction of 6,11-dihydro-11-vinyldibenzo[*b*,*e*]thiepin-11-ol (2) with $SOCl_2$ stereoselectively afforded (*E*)-11-(2-chloroethylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (3). The mechanism of this reaction is discussed.

Keywords dothiepin; drug metabolite; allyl alcohol; thionyl chloride; allyl chloride; ion pair process; sulfur; cation stabilization; stereoselectivity; olefinic chloride

6,11-Dihydro-11-(3-dimethylaminopropylidene)dibenzo-[*b*,*e*]thiepin hydrochloride (dothiepin hydrochloride)[1] displays in experiments on animals a pronounced antireserpine activity and was found to be a potent antidepressive thymoleptic in clinical practice.[2] Metabolic studies of dothiepin hydrochloride were carried out using rat, dog and human, and several acidic and basic metabolic products were isolated.[3] We prepared three acidic metabolic products (**5**—**7**) in order to examine their biological activity.

The cyclic ketone (**1**) was treated with vinyl magnesium bromide in tetrahydrofuran (THF) to give the allyl alcohol (**2**).[4] The allyl alcohol (**2**) was treated with thionyl chloride to give the allyl chloride (**3**) as a mixture of *E*/*Z* isomers. The ratio of the geometrical isomers was estimated to be 11 : 1 on the basis of the olefinic proton signal intensities in the proton nuclear magnetic resonance (^{1}H-NMR). Attempts to separate the two isomers of the chloride (**3**) were unsuccessful. The allyl alcohol (**2**) was treated with hydrogen chloride gas in chloroform to afford a single isomer of the chloride (**3**) in low yield (<50%). The isomeric mixture of the chloride (**3**) was converted to the nitrile (**4**) in 71% yield by treatment with KCN. The predominant isomer (**4a**) (mp 98.0—99.5°C) from the isomeric mixture of the nitrile (**4**) was isolated in 44% yield by fractional recrystallization. Concentration of the mother liquor yielded the nitrile (**4**) as a mixture of the two isomers.

Attempts to reduce the isomeric nitrile (**4a**) to the primary amine (**8**) with $LiAlH_4$–ether systems were unsuccessful,[5] though **4a** was converted into **8** by treatment with an $NaBH_4$–$NiCl_2$ system in a good yield.[6] The amine hydrochloride (**8**) was converted to the dimethylamino compound hydrochloride (**9**) by the Clark–Eschweiler method.[7] Physical data of **9** were identical with those of an authentic *E*-isomer of dothiepin hydrochloride, (*E*)-6,11-dihydro-11-(3-dimethylaminopropylidene)dibenzo[*b*,*e*]thiepin hydrochloride.[8] These results clearly indicated that the stereochemistry of **3a**[9] and **4a** should be assigned as *E*. The isomer (**4a**) was treated with aqueous NaOH solution to afford the

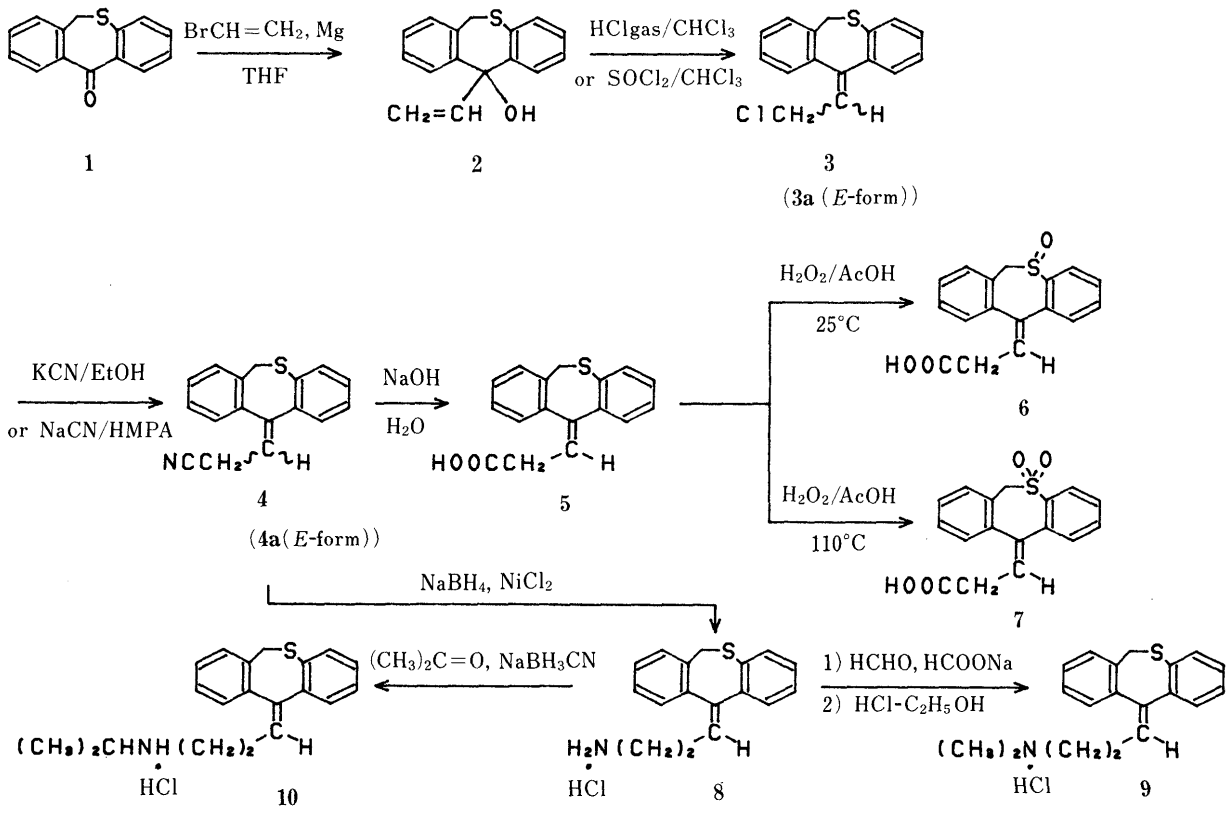

Chart 1

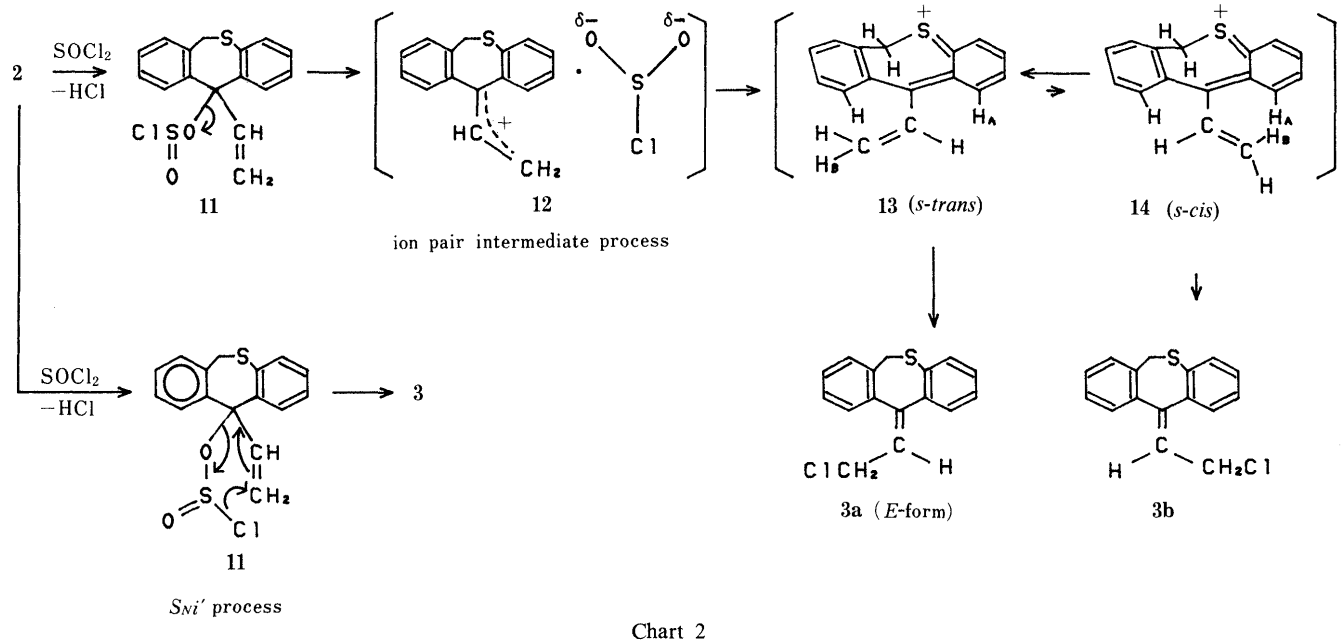

Chart 2

carboxylic acid (**5**). The carboxylic acid (**5**) was oxidized by H_2O_2 in acetic acid at 25 °C to give the sufoxide (**6**), while oxidation by H_2O_2 at 110 °C afforded the sulfone (**7**). Thus, the three acidic metabolic products (**5**—**7**) could be prepared through these reactions. The structures of the acidic metabolic products (**5**—**7**) which had been isolated in metabolic studies were confirmed by direct comparison with **5**, **6** and **7** prepared in this study. A study of their biological activity is in progress. Furthermore, reductive isopropylation of the amine (**8**) with acetone in the presence of $NaBH_3CN$ afforded the isopropylamino compound (**10**) in a good yield (Chart 1).

Young and his co-workers proposed two mechanisms, a cyclic *SNi′* process[10] and a rigid-oriented undissociated ion-pair process[11] in the reactions of several allyl alcohols with $SOCl_2$.[12]

The sulfur atom in the thiepin ring probably plays an important role in the formation of the *E*-isomer (**3a**) from the allyl alcohol (**2**) through the ion pair process in this reaction. Namely, the sulfur atom may stabilize the ion pair intermediates (**13**, **14**).[13] We presume that the stabilized intermediate (**13**) may be preferred to the intermediate (**14**) because of a considerable steric repulsion between H_A and H_B in **14**. In addition, the single isomer which was obtained from **2** by treatment with hydrogen chloride gas was identified as the *E*-isomer (**3a**) by comparison of its ^{1}H-NMR spectrum with the ^{1}H-NMR spectrum of the compound (**3a**:**3b**=11:1) produced by the reaction of **2** and $SOCl_2$. Thus, the stable allyl cation (**12**) would be formed exclusively, and the cation (**12**) might produce the *E*-isomer (**3a**) through **13**, in the reaction of **2** with hydrogen chloride gas (Chart 2).

Experimental

All melting points were measured with a Thomas Hoover capillary melting point apparatus, and are uncorrected. ^{1}H-NMR spectra were recorded with a JEOL PS-100 spectrometer. Chemical shifts are given in δ values with tetramethylsilane (TMS) as an internal standard, and the following abbreviations are used: s, singlet; d, doublet; dd, double of doublets; br s, broad singlet; br d, broad doublet. Low-resolution mass spectra (MS) were obtained with a Hitachi M-52 instrument. Infrared (IR) spectra were recorded with a Shimadzu IR-17G spectrometer.

6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-one (1) A mixture of *o*-phenylthiomethylbenzoic acid (10 g, 0.041 mol) and polyphosphoric acid (105%, 30 ml) was heated at 100 °C for 4 h. The reaction mixture was poured into ice-water, and the aqueous solution was extracted with ethyl acetate. The ethyl acetate layer was dried over Na_2SO_4 and concentrated to give the ketone (**1**) (7 g, 76%, colorless plates).[1]

6,11-Dihydro-11-vinyldibenzo[*b*,*e*]thiepin-11-ol (2) A mixture of Mg (0.294 g, 0.012 mol) and vinyl bromide (1.3 g, 0.012 mol) in anhydrous THF (20 ml) was stirred at 25 °C for 25 min. The ketone (**1**) (2.1 g, 0.0093 mol) was added to the mixture at 45 °C under stirring. The yellow mixture was stirred at 60 °C for 2.5 h, then poured into H_2O (100 ml) and the whole was extracted with ethyl acetate (150 ml). After removal of ethyl acetate, a pale yellow powder was obtained. The powder was recrystallized from petroleum benzin to give colorless prisms (**2**) (2.1 g, 89%). mp 121—124 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.48 (1H, d, J=14 Hz, one H of CH_2S), 4.76 (1H, dd, J=2, 16 Hz, *trans* H of CH_2=), 4.79 (1H, d, J=14 Hz, one H of CH_2S), 5.11 (1H, dd, J=2, 10 Hz, *cis* H of CH_2=), 6.22 (1H, dd, J=10, 16 Hz, CH=CH_2), 6.74—7.80 (8H, m, phenyl protons). MS *m/z*: 254 (M^+), 237, 195. IR ν_{max}^{KBr} cm^{-1}: 3490, 1481, 1460, 1021. *Anal.* Calcd for $C_{16}H_{14}OS$: C, 75.56; H, 5.55. Found: C, 75.32; H, 5.61.

11-(2-Chloroethylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (3) Thionyl chloride (1 ml) was added to a solution of **2** (2.55 g, 0.01 mol) in dry chloroform (120 ml) at 0 °C under vigorous stirring. Stirring was continued for 30 min, then the solvent was evaporated off to give crude **3** as plates (2.5 g, 91%). ^{1}H-NMR ($CDCl_3$) δ: 3.38 (1H, d, J=14 Hz, one H of CH_2S), 3.97 (d, J=8 Hz, CH_2Cl), 4.23 (d, J=8 Hz, CH_2Cl) {intensity of ratio of two signals (3.97:4.23) 11:1}, 4.90 (1H, d, J=14 Hz, one H of CH_2S), 5.94 (t, J=8 Hz, $CH_2C\underline{H}$), 6.19 (t, J=8 Hz, $CH_2C\underline{H}$) {intensity of ratio of two signals (5.94:6.19=1:11}, 7.01—7.45 (8H, m, phenyl protons). MS *m/z*: 272 (M^+), 273, 221. IR ν_{max}^{KBr} cm^{-1}: 3085, 2950, 1471, 1241. *Anal.* Calcd for $C_{16}H_{13}ClS$: C, 70.45; H, 4.80. Found: C, 70.39; H, 4.71. Attempts to separate the two geometric isomers were unsuccessful.

Dry hydrogen chloride gas was bubbled into a mixture of **2** (2 g, 0.0079 mol) and dry chloroform (25 ml) for 5 min at 5 °C. The reaction mixture was poured into ice-water and extracted with ether. The ether layer was washed with water and dried over Na_2SO_4. Removal of the ether gave a pale yellow oil (**3**) (1.1 g, 50%). This chloride (**3**) consisted of one geometric isomer on the basis of its ^{1}H-NMR spectrum {^{1}H-NMR ($CDCl_3$) δ: 3.38 (1H, d, J=14 Hz, one H of CH_2S), 3.97 (2H, d, J=8 Hz, CH_2Cl), 4.90 (1H, d, J=14 Hz, one H of CH_2S), 6.19 (1H, t, J=8 Hz, $CH_2C\underline{H}$), 7.01—7.45 (8H, m, phenyl protons); signals at δ 5.94 and 4.23 were not detected}.

(*E*)-11-(2-Cyanoethylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (4a) NaCN (0.74 g, 0.015 mol) was added to a mixture of the crude chloride (**3**, 2.73 g, 0.01 mol) and hexamethylphosphoamide (15 ml) and the mixture was stirred for 1 h at 70 °C, then poured into ice-water. The solution was extracted with ethyl acetate and the nitrile (**4**) was obtained as an oily residue. The residue was purified by column chromatography on silica gel (benzene:hexane=1:1) to afford **4** as a solid (1.85 g, 71%). The solid

nitrile was purified by fractional recrystallization from ether and cyclohexane (1 : 1) to give a single isomer (**4a**, 1.15 g, 44%). mp 98.0—99.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.98 (2H, d, J=7 Hz, CH_2CN), 3.41 (1H, d, J=14 Hz, one H of CH_2S), 4.82 (1H, d, J=14 Hz, one H of CH_2S), 5.93 (1H, t, J=7 Hz, CH), 7.00—7.40 (8H, m, phenyl protons). MS m/z: 263 (M^+), 223. IR ν_{max}^{KBr} cm^{-1} 2290, 1595, 1430. *Anal.* Calcd for $C_{17}H_{13}NS$: C, 77.53; H, 4.98. Found: C, 77.33; H, 5.21. Concentration and cooling of the mother liquor gave pale yellow prisms (0.7 g), consisting of approximately equal amounts of two geometric isomers (**4**). The signals of the *Z*-isomer in the ^{1}H-NMR spectrum of the *E*/*Z* mixture of the nitrile (**4**) were as follows: δ: 3.18 (d, J=7 Hz, CH_2CN), 3.40 (d, J=14 Hz, one H of CH_2S), 4.80 (d, J=14 Hz, one H of CH_2S), 5.67 (t, J=7 Hz, CH).

(*E*)-11-(2-Carboxyethylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (5) A mixture of **4a** (1.28 g, 0.0049 mol), KOH powder (0.96 g) and ethyleneglycol (15 ml) was stirred for 5 h at 175 °C. The mixture was poured into ice-water, then 12 N HCl was added to precipitate a gray powder (1.7 g). After being washed with ether and water, the powder was purified by column chromatography on silica gel (ethanol : benzene = 1 : 1), and then recrystallized from ether and petroleum benzin (1 : 1) to afford **5** as colorless prisms (0.56 g, 41%). mp 126—128 °C. ^{1}H-NMR ($CDCl_3$): δ 2.87 (2H, d, J=7.5 Hz, CH_2COOH), 3.16 (1H, d, J=14 Hz, one H of CH_2S), 4.68 (1H, d, J=14 Hz, one H of CH_2S), 5.84 (1H, t, J=7.5 Hz, =C<u>H</u>CH_2), 6.60—7.20 (8H, m, phenyl protons), 9.18 (1H, br s, COOH). MS m/z: 282 (M^+), 235, 223. IR ν_{max}^{KBr} cm^{-1}: 3070, 2950, 2400—2800, 1760. *Anal.* Calcd for $C_{17}H_{14}O_2S$: C, 72.31; H, 5.00. Found: C, 72.47; H, 4.89.

(*E*)-11-(2-Carboxyethylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin 5-Oxide (6) A mixture of **5** (0.1 g, 0.00036 mol), 30% H_2O_2 (0.3 ml) and acetic acid (2 ml) was stirred for 1 h at 25 °C, then poured into ice-water to precipitate a colorless powder. The powder was recrystallized from methanol to give **6** as colorless needles (0.072 g, 68%). mp 227—229 °C. ^{1}H-NMR (DMSO-d_6): δ 3.00 (2H, d, J=8 Hz, CH_2COOH), 3.27 (1H, br s, COOH), 4.57 (2H, br s, CH_2S), 6.21 (1H, t, J=8 Hz, =CH), 7.10—7.75 (8H, m, phenyl protons). MS m/z: 298 (M^+), 282, 235. IR ν_{max}^{KBr} cm^{-1}: 3400, 2940, 2700—2300, 1722. *Anal.* Calcd for $C_{17}H_{14}O_3S$: C, 68.44; H, 4.73. Found: C, 68.52; H, 4.98.

(*E*)-11-(2-Carboxyethylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin 5,5-Dioxide (7) A mixture of **5** (0.1 g, 0.00036 mol), 30% H_2O_2 (1.5 ml) and acetic acid (1.5 ml) was stirred for 1 h at 110 °C, then poured into ice-water to afford a colorless powder. The powder was purified by column chromatography on silica gel (5% ethanol–benzene) to afford **7** as colorless prisms (50 mg, 45%). mp 166—169 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.98 (2H, d, J=8 Hz, CH_2COOH), 3.20 (1H, br s, COOH), 4.73 (1H, d, J=15 Hz, one H of CH_2S), 5.13 (1H, d, J=15 Hz, one H of CH_2S), 6.30 (1H, t, J=8 Hz, =CH), 7.15—8.00 (8H, m, phenyl protons). MS m/z: 314 (M^+), 296, 270, 258. IR ν_{max}^{KBr} cm^{-1}: 3400, 1704, 1300. *Anal.* Calcd for $C_{17}H_{14}O_4S$: C, 64.96; H, 4.49. Found: C, 65.23; H, 4.19.

(*E*)-11-(3-Aminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin Hydrochloride (8) A 4% $NiCl_2$ ethanol solution (4 ml) was added to a mixture of **4a** (0.264 g, 0.001 mol), dioxane-isopropyl alcohol (5 ml : 25 ml) and $NaBH_4$ (0.38 g, 0.01 mol) at 25 °C under vigorous stirring. After the mixture had been stirred for 5 h at 25 °C, it was acidified with 10% HCl. The acidic aqueous solution was evaporated to afford an oily residue, which was made strongly basic to litmus with ammonium hydroxide (d=0.9) and extracted with ether. The residue from the ether solution was purified by column chromatography on silica gel (methanol chloroform : benzene = 10 : 45 : 45) to give the free amine of **8**. The crude amine was treated with hydrogen chloride–ethanol and the resultant salt (**8**) was recrystallized from ether and ethanol (1 : 1) to give colorless plates (0.14 g, 46%). mp 240—242 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.00—3.21 (4H, m, $CH_2C\underline{H}_2CH_2NH_2$), 3.65 (1H, d, J=14 Hz, one H of CH_2S), 4.70 (1H, d, J=14 Hz, one H of CH_2S), 5.95 (1H, t, J=7 Hz, =CH), 6.90—7.60 (8H, m, phenyl protons), 8.60 (3H, br s, NH_3^+). MS m/z: 267 (M^+), 204. IR ν_{max}^{KBr} cm^{-1}: 2800—2000, 1605, 1490. *Anal.* Calcd for $C_{17}H_{17}NS$: C, 76.36; H, 6.41. Found: C, 76.57; H, 6.29.

6,11-Dihydro-11-(3-dimethylaminopropylidene)dibenzo[*b*,*e*]thiepin Hydrochloride (9) A mixture of **8** (0.031 g, 0.0001 mol), sodium formate (0.068 g, 0.0001 mol), formic acid (50 μl, 0.001 mol) and formaldehyde (37% solution in water, 1 ml) was stirred for 4 h at 95 °C. The solution was made strongly basic to litmus with 15% aqueous NaOH solution and extracted with ether. The residue obtained from the ether extract was treated with hydrogen chloride–ethanol and then the solution was evaporated. The powder thus obtained was recrystallized from ethanol–ether (1 : 1) twice to afford **9** as colorless needles (0.015 g, 46%). mp 228—230 °C. ^{1}H-NMR ($CDCl_3$): δ 2.63 (3H, s, $N(C\underline{H}_3)(CH_3)$), 2.70 (3H, s, $N(CH_3)(C\underline{H}_3)$), 2.30—3.43 (4H, m, CH_2CH_2N), 3.40 (1H, d, J=14 Hz one H of CH_2S), 4.76 (1H, d, J=14 Hz, one H of CH_2S), 5.86 (1H, t, J=7 Hz, =CH), 6.90—7.40 (8H, m, phenyl protons). MS m/z: 295 (M^+), 204. IR ν_{max}^{KBr} cm^{-1}: 2800—2000, 1585, 1555, 1485. *Anal.* Calcd for $C_{19}H_{22}ClNS$: C, 68.76; H, 6.68. Found: C, 68.71; H, 6.51. These data are consistent with those of (*E*)-dothiepin HCl.

(*E*)-11-(3-Isopropylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin Hydrochloride (10) Sodium cyanoborohydride (0.063 g, 0.001 mol) was added to a mixture of **8** (0.037 g, 0.0001 mol), acetone (1 ml), dimethylsulfoxide (7 ml), methanol (1 ml), molecular sieves 4A (activated powder, 50 mg) at 0 °C and the mixture was stirred for 2 h at 25 °C. The filtrate obtained from the reaction mixture was made strongly basic to litmus with 2 N sodium hydroxide and then extracted with ether. The residue from the ether layer was treated with hydrogen chloride–ethanol and evaporated under reduced pressure. The crude HCl salt (**10**) was recrystallized from ethanol and ether (1 : 1) to give a colorless powder (0.025 g, 72%). mp 211—213 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, d, J=7 Hz, $CH_3 \times 2$), 2.21—3.23 (5H, m, $C\underline{H}NHC\underline{H}_2C\underline{H}_2$), 3.35 (1H, d, J=14 Hz, one H of CH_2S), 4.80 (1H, d, J=14 Hz, one H of CH_2S), 5.90 (1H, t, J=7 Hz, =CH), 6.90—7.40 (8H, m, benzene protons). MS m/z: 309 (M^+), 204, 72. IR ν_{max}^{KBr} cm^{-1}: 2900—2400, 1590, 1480, 1470. *Anal.* Calcd for $C_{20}H_{24}ClNOS$: C, 66.37; H, 6.68. Found: C, 66.20; H, 6.89.

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