with a mixture of the sample and the inert substance of known heat of transition. The heat of polymorphic transition of potassium nitrate at 128~129° was found to be 1.20 kcal./mol. by using benzoic acid as an internal standard. It is thought that the method will have wide application, especially to organic materials. Also, discrimination of pyrabital from the corresponding mixture of aminopyrine and barbital was successfully done by DTA. The curve of the former shows two peaks which is due to the stable eutectic liquefaction and to melting, while that of the latter exhibits in addition to these peaks, one pair of endothermic and exothermic ones which is attributed to the metastable eutectic liquefaction and to the molecular compound formation, respectively. These results will suggest that DTA is generally applicable to the detection of molecular compound between organic medicinals.

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138. Haruki Nishimura, Osamu Yamauchi, and Hideji Takamatsu : Studies on Phenylalkanethiolamine. VI.*1 Synthesis and Configuration of 2-Phenyl-3,4-dimethylthiomorpholine.

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In the previous papers of this series the authors reported studies on synthesis of various derivatives of 1-phenyl-2-aminoethanethiol[1] and the configuration of 1-phenyl-2-dimethylaminopropanethiol.[2] The present paper deals with synthesis of N-(2-mercaptoethyl)ephedrines and *erythro*- and *threo*-2-phenyl-3,4-dimethyltetrahydro-4*H*-1,4-thiazines, which appear to be of interest from a pharmacological point of view.

In an attempt to obtain N-(2-mercaptoethyl)-*l*-ephedrine (Ⅲ), N-chloroacetyl-*l*-ephedrine (Ⅰ), prepared by the reaction of *l*-ephedrine (L-*erythro*-series) with chloroacetyl chloride in benzene, was converted to N-thioglycoloyl-*l*-ephedrine (Ⅱ) by potassium hydrosulfide in ethanol. On reduction with lithium aluminum hydride Ⅱ gave a crude product (Ⅲ), but the infrared spectrum showed no clear SH absorption band. Since it was difficult to purify the crude product as will be mentioned, other synthetic methods were investigated.

When *l*-ephedrine was caused to react with ethylene sulfide, *l*-ephedrine was recovered unchanged, and no product was obtained.

However, when N,N'-dithiodiacetyl-bis-*l*-ephedrine (Ⅳ), obtained by the reaction of *l*-ephedrine with dithiodiacetyl chloride in chloroform, was reduced with lithium aluminum hydride, Ⅲ was obtained in a nearly pure state. The N-(2-mercaptoethyl) derivatives (Ⅶ) and (Ⅷ) were analogously prepared from *d*-*ψ*-ephedrine (L-*threo*-series) and *dl*-ephedrine(DL-*erythro*-series) through the corresponding intermediates (Ⅴ) and (Ⅵ). In their infrared spectra all these compounds showed the SH absorption band near 2550 cm^{-1} and no amide I band that was present in the spectra of the amides (Ⅳ), (Ⅴ), and (Ⅵ).

*1 Part Ⅴ : Yakugaku Zasshi, 84, 824 (1964).
*2 Ebie-kami-2-chome, Fukushima-ku, Osaka (西村温樹, 山内 脩, 高松秀二).
1) Part Ⅰ : Yakugaku Zasshi, 84, 797 (1964).
2) *a*) Part Ⅱ : *Ibid.*, 84, 806 (1964). *b*) Part Ⅲ : *Ibid.*, 84, 811 (1964).

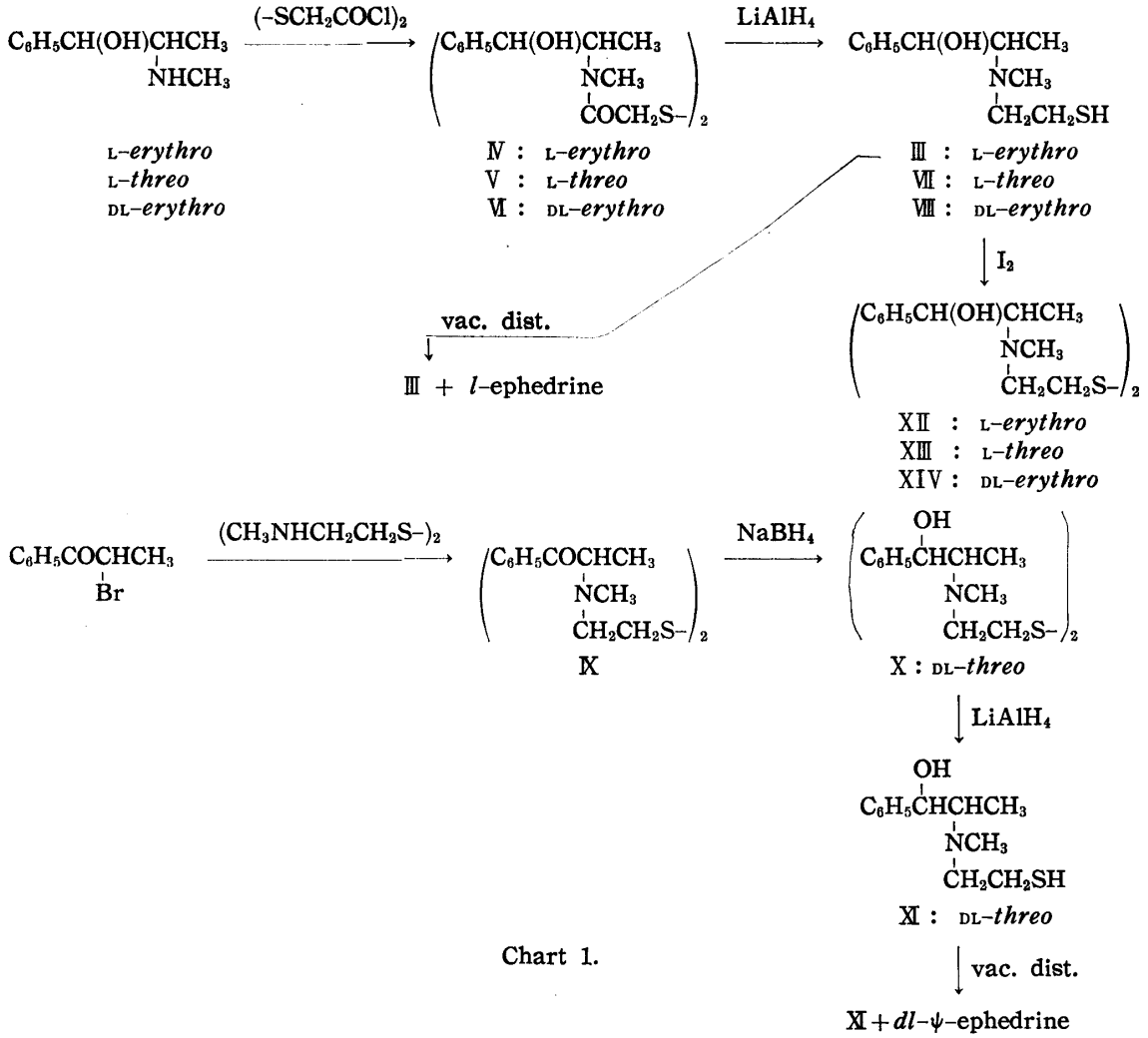


Chart 1.

The spectrum of the reduction product from II was identical with that of III and of VIII, except SH absorption band. The N-(2-mercaptoethyl) derivative (III), when distilled for purification under reduced pressure, partially decomposed to give *l*-ephedrine and furthermore attempted crystallization by salt formation with an acid was not successful.

For comparison with the thiols obtained above, a diastereomer (XI) was prepared from α-bromopropiophenone and bis(methylaminoethyl)disulfide through bis[2-(N-methyl-α-methylphenacylamino)ethyl] disulfide (IX). When IX was treated with sodium borohydride, reduction occurred only on the keto group, and further reduction of the dithio group with lithium aluminum hydride was necessary.

The infrared spectrum of the thiol (XI) thus obtained corresponded with that of the L-*threo*-compound (VII). Takamatsu[3] reported that *threo*-series compounds were obtained on reduction of propiophenone derivatives having a bulky substituent, such as benzylmethylamino group on the α-carbon, with lithium aluminum hydride or sodium borohydride.

As the situation appears to be similar on reduction of IX, exclusive formation of the *threo*-compound is comprehensible.

The thiols (III), (VII), and (VIII) were readily oxidized with iodine in ethanol to yield the corresponding disulfides (XII), (XIII), and (XIV).

3) H. Takamatsu : Yakugaku Zasshi, **76**, 1227 (1956).

The observation that ephedrine was formed as a by-product on distillation of III under reduced pressure was confirmed by the fact that XI, which is to be free from contamination by ψ-ephedrine, also yields ψ-ephedrine under the same condition. To investigate this docomposition reaction in some detail, the authors chose 2-(N-methylbenzylamino)ethanethiol as a model compound and heated it to ca. 200°, when distillation took place and N-methylbenzylamine, one of the decomposition products, was detected in the distillate. In the course of a few days a colorless substance separated from the distillate, and the analysis of the substance suggests that it can be formulated approximately as $(C_2H_4S)_n$. The existence of N-methylbenzylamine and ethylene sulfide along with 2-(N-methylbenzylamino)ethanethiol in the distillate was substantiated by gas chromatography.

Since 2-(N-methylbenzylamino)ethanol and N-(2-hydroxyethyl)-*l*-ephedrine (XV)[4] suffer no such decomposition under the same condition described above, the reaction is considered to be unique to 2-mercaptoethylamino derivatives.

The authors then investigated synthesis of 2-phenyl-3,4-dimethylthiomorpholine. Otto[4,5] synthesized an analogous compound, 2-phenyl-3,4-dimethylmorpholine, by cyclization of XV with concentrated sulfuric acid.

Haberl[6] obtained 2-phenyl-3,4-dimethylpiperazine derivatives by the reaction of primary amines with the chlorination product of N-(2-hydroxyethyl)-*dl*-ephedrine. However, the conformations of the compounds were investigated in neither case.

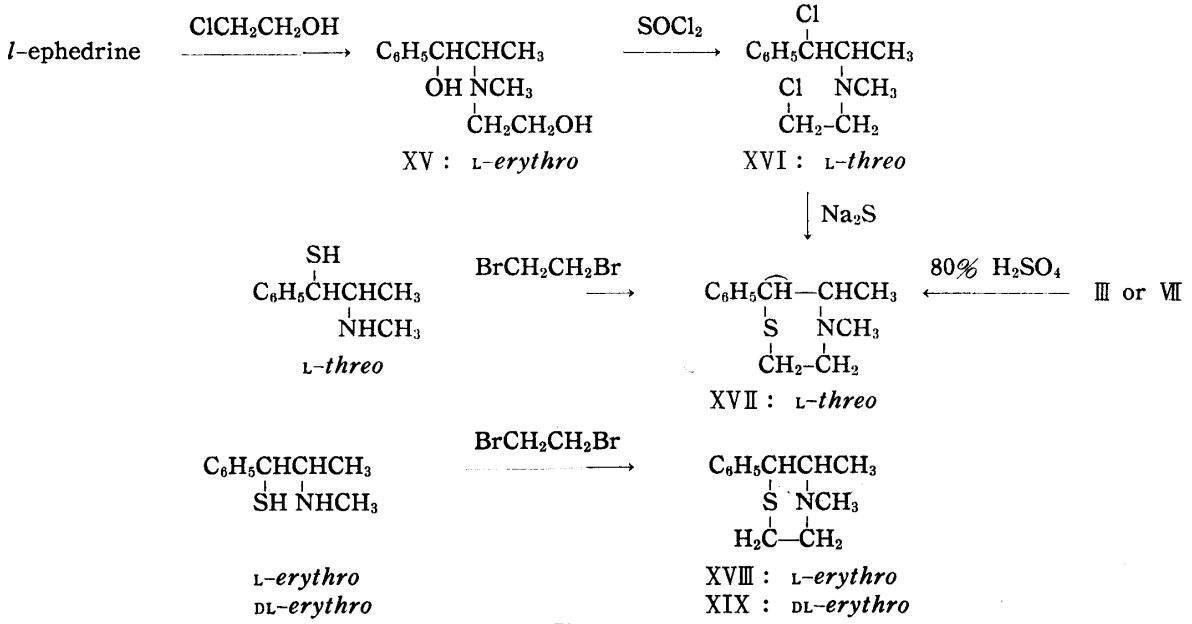


Chart 2.

2-Phenyl-3,4-dimethyltetrahydro-4*H*-1,4-thiazine (XVII) was obtained first by the reaction of the dichloride (XVI), prepared from XV and thionyl chloride, with sodium sulfide (Chart 2). The fact that chlorination of *l*-ephedrine with thionyl chloride results in formation of the *threo*-derivative suggests that XVI is also a compound of the *threo*-series, and when a nucleophilic reagent, such as sodium sulfide, attacks XVI under the condition of hydrogen chloride-elimination, it is expected to suffer Walden inversion (an internal S_N2 reaction) twice[7] yielding the *threo*-compound (XVII), which was identified by

4) W.G. Otto : Angew. Chem., **68**, 181 (1956).
5) *Idem* : Gergely. Austrian Pat., 202940 (C. A., **53**, 15102 (1959)).
6) R. Haberl : Monatsh. Chem. **89**, 798 (1958).
7) Part V : Yakugaku Zasshi, **84**, 824 (1964).

comparison with the sample obtained from L-*threo*-1-phenyl-2-methylaminopropanethiol[2a] and ethylene bromide. L- and DL-*erythro*-Tetrahydro-4*H*-1,4-thiazine derivatives (XVIII) and (XIX) were also prepared from the corresponding *erythro*-1-phenyl-2-methylaminopropanethiols.

The authors attempted the cyclization of III, VII, and XI by dehydration with sulfuric acid. The product obtained from the L-*erythro*-isomer (III) was identical with that obtained from the L-*threo*-isomer (VII) and was found to be the L-*threo*-tetrahydro-4*H*-1,4-thiazine derivative (XVII). From the DL-*threo*-isomer (XI) there was obtained the DL-*threo*-derivative (XX), whose infrared spectrum corresponded with that of XVII. It is apparent, therefore, that the *threo*-compounds are the exclusive products of the dehydration reaction with sulfuric acid.

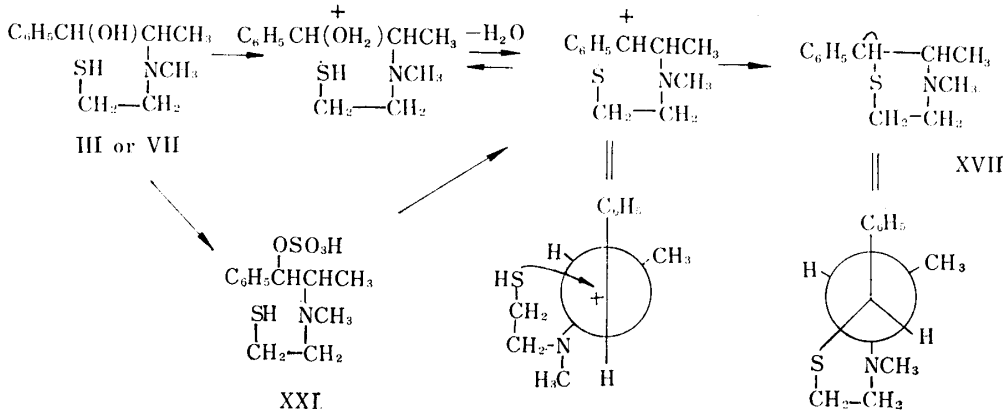


Chart 3.

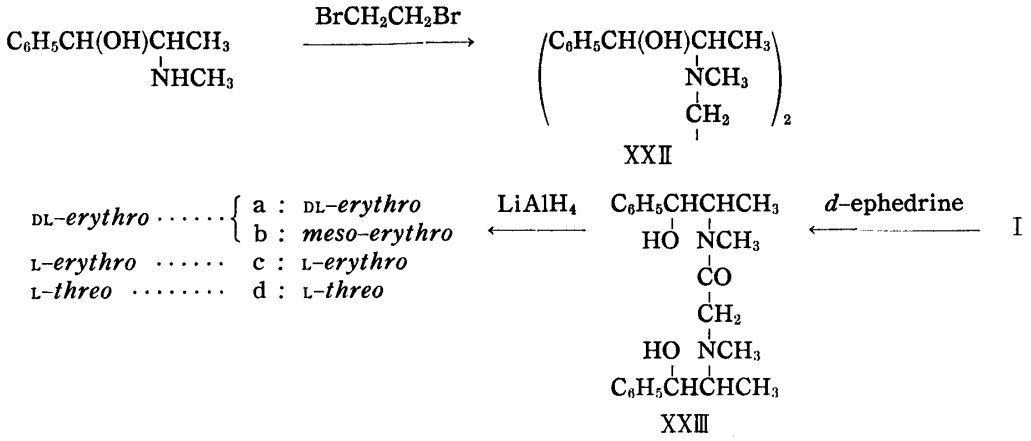
The process of ring formation can be explained by the so-called "Carbonium Ion Mechanism."[8] The carbon atom adjacent to the phenyl group first changes into a carbonium ion, which is then attacked by the mercapto group to form a thiomorpholine ring (Chart 3). The exclusive formation of XVII (*threo*-form) can be understood easily if we consider that III (*erythro*-form) and VII (*threo*-form) give rise to the corresponding carbonium ions with the same stable conformation and that ring formation occurs through the path with the least steric hindrance. As to ephedrine, on the other hand, the presence of the sulfuric acid ester is reported,[9~11] and it is already known that both *l*-ephedrine and *d*-ψ-ephedrine form the *threo*-ester. If ring formation by the S_N2 reaction is assumed to occur through the analogous ester (XXI), it leads to the *erythro*-tetrahydro-4*H*-1,4-triazine derivative, which is incompatible with the result obtained. Accordingly the carbonium ion mechanism is preferable.

As part of synthetic studies on N-(2-mercaptoethyl)ephedrine, the authors tried to obtain N-(2-bromoethyl)ephedrine as an intermediate by the reaction of ephedrine with ethylene dibromide, but even when an excessive amount of ethylene dibromide was used, N,N'-ethylenebisephedrine (XXII) only was obtained. Thus *l*-ephedrine and ethylene dibromide gave the corresponding *l*-*erythro*-derivative (XXII-c).

When *dl*-ephedrine was used, however, two kinds of crystals were obtained: the one (XXII-a) melts at 123~124° and the other (XXII-b), at 90~92°. The infrared spectrum

8) P. H. Emmett: Catalysis, vol. 7, p. 116 (1960); T. Taguchi, M. Tomoeda, T. Koga: This Bulletin, **5**, 189 (1957).
9) E. Schmidt: Arch. Pharm., **252**, 89 (1914).
10) H. Takamatsu: Yakugaku Zasshi, **76**, 1224 (1956).
11) T. Taguchi, M. Kojima: This Bulletin, **7**, 103 (1959).

of XXII-a in chloroform was identical with that of XXII-c. XXII-b was found to be identical with *meso*-N,N'-ethylenebisephedrine prepared by reduction of the amide, obtained from I and *d*-ephedrine, with lithium aluminum hydride. *d*-*ψ*-Ephedrine and ethylene dibromide gave N,N'-ethylenebis(*d*-*ψ*-ephedrine) (XXII-d).



Experimental*3

N-Chloroacetyl-*l*-ephedrine (I)——To a solution of *l*-ephedrine (56.2 g.) in benzene was added a solution of $ClCH_2COCl$ (19.3 g.) in benzene in 40 min., and the mixture was stirred for 2 hr. and filtered from *l*-ephedrine-HCl which separated in the course of the reaction. The filtrate was washed successively with dil. HCl, aq. $NaHCO_3$, and H_2O, and dried over anhyd. Na_2SO_4. After evaporation of benzene (37 g.) of a yellow oil was obtained. IR ν_{max}^{liquid} cm^{-1} : 3400 (OH); 1635 (CO); Cl (+).

N,N'-Dithiodiacetylbis(*l*-ephedrine) (IV)——A solution of $(-SCH_2COCl)_2$ (5.5 g.) in $CHCl_3$ was added to a stirred solution of *l*-ephedrine (13.8 g.) in $CHCl_3$ under cooling in ca. 30 min. The mixture was stirred at room temperature, allowed to stand overnight and filtered from *l*-ephedrine-HCl. The filtrate was washed successively with aq. Na_2CO_3, dil. HCl, and H_2O, and dried over anhyd. Na_2SO_4. After evaporation of $CHCl_3$, 7.0 g. (67%) of IV was obtained as a red brown solid, m.p. 63~70°, $[\alpha]_D^{18}$ −13° (c=0.5, EtOH). IR ν_{max}^{KBr} cm^{-1} : 3400 (OH); 1620 (CO) (the spectrum was identical with that of VI). IV is soluble in EtOH, $CHCl_3$, and tetrahydrofuran, and sparingly soluble in petr. ether, petr. benzin, and Et_2O.

N,N'-Dithiodiacetylbis(*d*-*ψ*-ephedrine) (V)——*d*-*ψ*-Ephedrine (6.9 g.) and $(-SCH_2COCl)_2$ (2.8 g.) were treated just as described above to give 3.5 g. (67%) of V as a red brown solid, m.p. 45~50°, $[\alpha]_D^{18}$ +56° (c=1, EtOH). IR ν_{max}^{KBr} cm^{-1} : 3400 (OH); 1625 (CO).

N,N'-Dithiodiacetylbis(*dl*-ephedrine) (VI)——This was analogously prepared from *dl*-ephedrine (13.8 g.) and $(-SCH_2COCl)_2$ (5.2 g.) as a red brown solid, m.p. 45°. Yield, 7.4 g. (71%). IR ν_{max}^{KBr} cm^{-1} : 3400 (OH); 1620 (CO). Since IV, V, and VI could hardly be purified by recrystallization or reprecipitation, they were employed without purification in the subsequent reactions.

N-(2-Mercaptoethyl)-*l*-ephedrine (III)——IV (7.0 g.) was dissolved in 25 ml. of tetrahydrofuran-Et_2O (1:2), and the solution was added dropwise into a stirred solution of $LiAlH_4$ (3.0 g.) in 130 ml. of tetrahydrofuran-Et_2O (1:1.5). The mixture was stirred at 30~35° for 4 hr., H_2O added, and the precipitate filtered. The filtrate was dried over anhyd. Na_2SO_4, and the solvent was evaporated to give 3.0 g. (45%) of III as a pale yellow oil. The precipitate was dissolved in dil. HCl, the solution made alkaline with Na_2CO_3 and extracted with Et_2O. The extract was washed with H_2O, dried over anhyd. Na_2SO_4, and Et_2O removed to give 1.9 g. (28%) of III as a pink oil, $[\alpha]_D^{25}$ −10° (c=1, EtOH). IR ν_{max}^{liquid} cm^{-1} : 2550 (SH) (the amide I band was not observed). The spectra of the two products were superimposable. *Anal.* Calcd. for $C_{12}H_{19}ONS$: N, 6.21; S, 14.23. Found : N, 6.19; S, 14.85. When III was submitted to vacuum distillation at 118~120°/0.06 mm. Hg, there was obtained a pale yellow distillate, from which *l*-ephedrine HCl was separated as crystals by treatment with EtOH-HCl.

N-(2-Mercaptoethyl)-*d*-*ψ*-ephedrine (VII)——To 2.5 g. of $LiAlH_4$ in 100 ml. of tetrahydrofuran-Et_2O (1:1), 6.0 g. of V in 25 ml. of tetrahydrofuran-Et_2O (2:1) was added with stirring, and the mixture was stirred at 30~35° for 4 hr. After treatment of the precipitate according to the procedure described above, 2.3 g. (41%) of VII was obtained as a yellow oil, $[\alpha]_D^{21}$ +88° (c=1, EtOH). IR ν_{max}^{liquid} cm^{-1} : 2550

*3 All melting points are uncorrected.

(SH) (no amide I band was observed). *Anal.* Calcd. for $C_{12}H_{19}ONS$: N, 6.21; S, 14.23. Found : N, 6.59; S, 14.53.

N-(2-Mercaptoethyl)-*dl*-ephedrine (VIII)——Ⅵ (6.5 g.) was treated, as described for Ⅲ and Ⅷ was obtained as a pale yellow oil. Yield, 4.4 g. (72%) (3.2 g. from the filtrate and 1.2 g. from the precipitate). The IR spectrum corresponded with that of Ⅲ. *Anal.* Calcd. for $C_{12}H_{19}ONS$: N, 6.21; S, 14.23. Found : N, 5.77; S, 15.04.

Bis[2-(N-methyl-α-methylphenacylamino)ethyl]disulfide (IX)——A solution of 2-bromopropiophenone (55.5 g.) in benzene was added dropwise to a stirred solution of $(CH_3NHCH_2CH_2S-)_2$ (47.0 g.) in benzene at room temperature in ca. 1.5 hr. The mixture was warmed for 40 min. and filtered from the precipitate, which was washed with benzene. The filtrate and the washings were combined and extracted with dil. HCl. The aq. acidic layer was made alkaline with NaOH, extracted with Et_2O, the extract washed with H_2O, dried over anhyd. Na_2SO_4, and Et_2O removed to give 39 g. (64%) of Ⅸ as a brown oil. IR ν_{max}^{liquid} cm^{-1} : 1680 (CO) (no NH absorption band was observed).

***dl-threo*-Bis[2-(N-methyl-α-methyl-β-hydroxyphenethylamino)ethyl] disulfide (X)**——A solution of $NaBH_4$ (13 g.) in MeOH was added to a stirred solution of Ⅸ (37 g.) in MeOH at 20~30° in ca. 1 hr., and stirring was continued for 1 hr. longer. The reaction mixture was poured into a large volume of H_2O, and extracted with Et_2O. The extract was washed with H_2O, dried over anhyd. Na_2SO_4, and Et_2O evaporated to yield 31.4 g. (84%) of X as a red brown oil. IR ν_{max}^{liquid} cm^{-1} : 3400 (OH) (no SH and CO absorptions were observed).

N-(2-Mercaptoethyl)-*dl*-ψ-ephedrine (XI)——A solution of X (10.0 g.) in Et_2O was added to a stirred solution of $LiAlH_4$ (5.0 g.) in Et_2O 1 hr., and the mixture was refluxed on water bath for 1 hr., decomposed with H_2O, and the precipitate collected.

The filtrate exhibited no SH reaction with sodium nitroprusside. The precipitate was dissolved in dil. HCl, the solution made alkaline with Na_2CO_3 and extracted with Et_2O. The extract was washed with H_2O and dried over anhyd. Na_2SO_4. Et_2O was evaporated to give 9.2 g. (92%) of Ⅺ as a pink oil. IR ν_{max}^{liquid} cm^{-1} : 2550 (SH) (the spectrum was identical with that of Ⅶ). *Anal.* Calcd. for $C_{12}H_{19}ONS$: C, 63.96; H, 8.50; N, 6.21; S, 14.23. Found : C, 63.76; H, 8.23; N, 6.13; S, 13.86. On distillation at 129°/0.22 mm. Hg Ⅸ gave *dl*-ψ-ephedrine, which was detected as described for *l*-ephedrine.

N,N′-Dithiodiethylbis(*l*-ephedrine) (XII)——To a solution of Ⅲ (1.6 g.) in EtOH, I_2 in EtOH was added until there appeared the color of I_2. After evaporation of EtOH the mixture was made alkaline, extracted with $CHCl_3$, the extract washed with H_2O and dried over anhyd. Na_2SO_4. Evaporation of $CHCl_3$ gave 1.5 g. of Ⅻ as a red brown oil, $[\alpha]_D^{21}$ −18° (c=1, EtOH). The IR spectrum showed no SH absorption.

N,N′-Dithiodiethylbis(*d*-ψ-ephedrine) (XIII)——Ⅶ (0.6 g.) was treated as described above, and 0.55 g. of XIII was obtained as a red brown oil, $[\alpha]_D^{22}$ +102° (c=0.5, EtOH).

N,N′-Dithiodiethylbis(*dl*-ephedrine) (XIV)——This was similarly obtained from 1.7 g. of Ⅷ as a red brown oil. Yield, 1.55 g.

N-(2-Hydroxyethyl)-*l*-ephedrine (XV)[4]——This was obtained as a colorless oil, $b.p_{0.005}$ 115~118°. Hydrochloride : m.p. 113~114°, $[\alpha]_D^{32}$ −17.0° (c=1, H_2O).

L-*threo*-1-Chloro-1-phenyl-2-(N-methyl-2-chloroethylamino)propane (XVI) Hydrochloride——To 11.6 g. of XV-HCl was added 28 g. of $SOCl_2$, and the mixture was warmed on a water bath at 50~58° for 40 min. and condensed to dryness under reduced pressure.

The residue was washed with acetone and recrystallized from acetone-EtOH to give colorless prisms, m.p. 167°, $[\alpha]_D^{32}$ +95.4° (c=1, H_2O). Yield, 10 g. *Anal.* Calcd. for $C_{12}H_{18}NCl_3$: C, 50.99; H, 6.42; N, 4.96; Cl, 37.63. Found : C, 51.08; H, 6.66; N, 4.84; Cl, 37.68.

L-*threo*-2-Phenyl-3,4-dimethyltetrahydro-4*H*-1,4-thiazine (XVII)——i) XVI-HCl (6.50 g.) was added to a mixture of NaOH (0.92 g.) and Na_2S (8.3 g.) in EtOH-H_2O, and the mixture was refluxed on a water bath for 7 hr., poured into H_2O and extracted with Et_2O. The extract was washed with H_2O, dried over anhyd. Na_2SO_4, Et_2O evaporated, and the residue distilled to give 1.05 g. (22.1%) of a colorless oil, $b.p_3$ 116~118°. It solidified on standing. Recrystallization from petr. ether gave XVII as colorless prisms, m.p. 63~64°, $[\alpha]_D^{32}$ +75.5° (c=1, EtOH). *Anal.* Calcd. for $C_{12}H_{17}NS$: C, 69.53; H, 8.27; N, 6.76. Found : C, 69.68; H, 8.47; N, 6.57. Hydrochloride : Colorless prisms (from acetone-EtOH), m.p. 151~155°, $[\alpha]_D^{20}$ +51.4 (c=1, H_2O). *Anal.* Calcd. for $C_{12}H_{18}NClS$: C, 59.13; H, 7.43; N, 5.75. Found : C, 59.28; H, 7.62; N, 5.88.

ii) A solution of $BrCH_2CH_2Br$ (1.30 g.) in EtOH was added with stirring to a mixture of L(+)-*threo*-1-phenyl-2-methylaminopropanethiol (1.50 g.) and KOH (1.24 g.) in EtOH, and the mixture was refluxed on a water bath for 1 hr., poured into H_2O and extracted with Et_2O. The extract was washed with H_2O, dried, and Et_2O removed. Vacuum distillation of the residue gave 0.53 g. (37.1%) of XVII.

iii) Ⅲ (0.4 g.) was dissolved in 80% H_2SO_4, and the solution was heated on water bath for 30 min., allowed to stand at room temperature for 2 days, made alkaline with NaOH and extracted with Et_2O.

The extract was washed with H_2O, dried, Et_2O evaporated, and the residue submitted to vacuum distillation to give 0.1 g. (27%) of XVII.

iv) Ⅶ (0.5 g.) was treated with 80% H_2SO_4 as described above, and 0.15 g. (33%) of XVII was obtained.

A mixed melting point of the product obtained by the procedure (i) with any of the other products showed no depression, and the IR spectra were superimposable.

L-*erythro*-2-Phenyl-3,4-dimethyltetrahydro-4*H*-1,4-thiazine (XVIII)——L(−)-*erythro*-1-Phenyl-2-methylaminopropanethiol-HCl (2.18 g.) was treated with KOH (1.80 g.) and $BrCH_2CH_2Br$ (1.88 g.) as described above (procedure (ii)) to yield 0.74 g. (35.8%) of XVIII as a colorless oil, b.p_4 123～124°, $[\alpha]_D^{21}$ −82.0° (c=1, EtOH). *Anal.* Calcd. for $C_{12}H_{17}NS$: C, 69.53; H, 8.27; N, 6.76. Found : C, 69.79; H, 8.26; N, 6.87. Hydrochloride : Colorless prisms (from acetone-EtOH), m.p. 243° (decomp.), $[\alpha]_D^{31}$ −79.8° (c=1, EtOH). *Anal.* Calcd, for $C_{12}H_{18}NClS$: C, 59.13; H, 7.43; N, 5.75. Found : C, 59.26; H, 7.59; N, 5.56.

DL-*erythro*-2-Phenyl-3,4-dimethyltetrahydro-4*H*-1,4-thiazine (XIX)——DL-*erythro*-1-Phenyl-2-methylaminopropanethiol (1.6 g.) was treated with KOH (1.0 g.) and $BrCH_2CH_2Br$ (1.7 g.) as described above to yield 0.55 g. (30%) of XIX as a colorless oil, b.p_4 121～122°. *Anal.* Calcd. for $C_{12}H_{17}NS$: C, 69.53; H, 8.27; N, 6.76. Found : C, 69.09; H, 8.23; N, 6.75. Hydrochloride : Colorless prisms (from acetone-EtOH), m.p. 224～225° (decomp.). *Anal.* Calcd. for $C_{12}H_{18}NClS$: C, 59.13; H, 7.43; N, 5.75. Found : C, 59.48; H, 7.34; N, 6.04.

DL-*threo*-2-Phenyl-3,4-dimethyltetrahydro-4*H*-1,4-thiazine(XX)——XI (3.2 g.) was treated with 80% H_2SO_4 according to the procedure (iii) described for XVII, and 0.65 g. (22%) of XX was obtained as a colorless oil, b.p_5 139～140°.

It solidified on standing. Recrystallization from petr. benzine gave XX of m.p. 40～42. *Anal.* Calcd. for $C_{12}H_{17}NS$: C, 69.53; H, 8.27; N, 6.76. Found : C, 69.44; H, 8.13; N, 6.48.

N,N′-Ethylenebis(*dl*-ephedrine) (XXII-a) and *meso*-N,N′-Ethylenebis(ephedrine) (XXII-b)——A mixture of 13.2 g. of *dl*-ephedrine, 3.8 g. of $BrCH_2CH_2Br$ and 30 ml. of xylene was refluxed for 5 hr., filtered from *dl*-ephedrine-HBr which separated in the course of the reaction, and the filtrate was washed with H_2O and dried over anhyd. Na_2SO_4. Xylene was evaporated under reduced pressure, petr. ether added to the residue, and the mixture scratched, when colorless crystals separated. The crystals were filtered, washed with petr. ether, and recrystallized from EtOH to give 2 g. of colorless prisms (XXII-a), m.p. 123～124°. *Anal.* Calcd. for $C_{22}H_{32}O_2N_2$: C, 74.12; H, 9.05; N, 7.86. Found : C, 73.81; H. 8.99; N, 7.75. Hydrochloride : Colorless needles (from petr. benzin-MeOH), m.p. 222～223° (decomp.). *Anal.* Calcd. for $C_{22}H_{34}O_2N_2Cl_2$: C, 61.53; H, 7.98; N, 6.52; Cl, 16.51. Found : C, 61.32; H, 7.96; N, 6.60; Cl, 16.55.

On the other hand, the filtrate was condensed, and the residue was scratched until crystallization was complete. The crystals were recrystallized from petr. benzin-EtOH to give 1.8 g. of colorless prisms (XXII-b), m.p. 90～92°; $[\alpha]_D^{22} \fallingdotseq 0$ (c≒1, EtOH). *Anal.* Calcd. for $C_{22}H_{32}O_2N_2$: C, 74.12; H, 9.05; N, 7.86. Found. C, 74.24; H, 9.11; N, 7.57.

N,N′-Ethylenebis(*l*-ephedrine) (XXII-c)——*l*-Ephedrine (13.2 g.) and $BrCH_2CH_2Br$ (3.8 g.) were dissolved in 30 ml. of xylene, and the mixture was treated as described above.

The residue was recrystallized from petr. benzin-EtOH to give 2.9 g. of XXII-c as colorless prisms, m.p. 73～75°, $[\alpha]_D^{19}$ −28.6° (c=1, EtOH). *Anal.* Calcd. for $C_{22}H_{32}O_2N_2$: C, 74.12; H, 9.05; N, 7.86. Found : C, 73.78; H, 9.17; N, 7.52. Hydrochloride : Colorless prisms (from EtOH-MeOH), m.p. 225° (decomp.), $[\alpha]_D^{20}$ −22.0° (c=1, H_2O). *Anal.* Calcd. for $C_{22}H_{34}O_2N_2Cl_2$: C, 61.53; H, 7.98; N, 6.51; Cl, 16.51. Found : C, 61.61; H, 7.82; N, 6.45; Cl, 16.31. When 10.0 g. (0.0606 mol.) of *l*-ephedrine was treated with 6.2 g. (0.033 mol.) of $BrCH_2CH_2Br$ as described above, XXII-c only was obtained. Yield, 3.2 g.

N,N′-Ethylenebis(*d*-*ψ*-ephedrine) (XXII-d)——*d*-*ψ*-Ephedrine (13.2 g.) was treated with $BrCH_2CH_2Br$ (4.0 g.) as described above. The residue was recrystallized from petr. benzin-EtOH to give 4.3 g. of XXII-d as colorless prisms, m.p. 91～92°, $[\alpha]_D^{19}$ +102° (c=1, EtOH). *Anal.* Calcd. for $C_{22}H_{32}O_2N_2$: C, 74.12; H, 9.05; N, 7.86. Found : C, 74.15; H, 9.12; N, 7.67. Hydrochloride : Colorless needles (from EtOH-MeOH), m.p. 237～239° (decomp.). *Anal.* Calcd. for $C_{22}H_{34}O_2N_2Cl_2$: C, 61.53; H, 7.93; N, 6.51; Cl, 16.51. Found C, 61.24; H, 7.87; N, 6.32; Cl, 16.99.

Synthesis of XXII-b from I——I (2.68 g.) and *d*-ephedrine (3.63 g.) were dissolved in *m*-xylene, and the mixture was refluxed for 25 min. and filtered from *d*-ephedrine-HCl. After removal of *m*-xylene from the filtrate under reduced pressure, the residue was dissolved in Et_2O, CS_2 added to the solution, and the mixture shaken vigorously with aq. NaOH. The unchanged *d*-ephedrine thus removed.

The organic layer was washed with H_2O, dried over anhyd. Na_2SO_4, and Et_2O evaporated to give 0.82 g. of crude N,N′-oxydiethylenebis(*l*-, *d*-ephedrine) (XXIII) as a yellow oil, $[\alpha]_D^{22}$ +9.4° (c=1, EtOH) (the unreasonable value is considered to be due to impurities).

A solution of 0.8 g. of XXIII in Et_2O was added with stirring to a solution of 0.34 g. of $LiAlH_4$ in Et_2O, and the mixture was stirred at room temperature for 1.5 hr. and then refluxed gently for 2.5 hr. The reaction mixture was decomposed with H_2O, and the organic layer was separated, shaken vigorously with aq. NaOH after addition of CS_2, washed with H_2O and dried over anhyd. Na_2SO_4. Et_2O was evaporated to give 0.68 g. of a yellow oil, which was chromatographed over Al_2O_3 and eluted with benzene and with acetone. The eluate with acetone gave 0.3 g. of XXII-b, m.p. 90～92°, which was confirmed to be identical with the sample of m.p. 90～92°, obtained from the mother liquor of XXII-a, by mixed melting point determination and comparison of the IR spectra.

Thermal Decomposition of 2-(N-methylbenzylamino)ethanethiol. A) Synthesis of 2-(N-methylbenzylamino)ethanethiol——A mixture of bis(chloroethyl) disulfide (10 g.) and N-methylbenzylamine (28 g.) was heated on a boiling water bath. A violent exothermal reaction took place, and the mixture turned yellow and finally red brown. After being cooled, the mixture was mixed with Et_2O, and etherinsoluble N-methylbenzylamine hydrochloride was filtered. The filtrate was extracted with dil. HCl, and the aq. acidic layer was made alkaline and extracted with Et_2O. The extract was washed with H_2O, dried over anhyd. Na_2SO_4, and Et_2O evaporated. The residue was dissolved in anhyd. benzene and dry HCl gas was passed through the solution, when the hydrochloride separated as an oil, which was separated by decantation and admixed with acetone. The acetone-insoluble substance gradually solidified and was recrystallized from iso-PrOH to give 8 g. of bis[(N-methylbenzylamino)ethyl]disulfide dihydrochloride, m.p. 190～193°. *Anal.* Calcd. for $C_{20}H_{30}N_2Cl_2S_2$: C, 55.43; H, 6.93; N, 6.47; S, 14.78; Cl, 16.40. Found : C, 55.76; H, 7.14; N, 6.13; S, 14.45; Cl, 16.02. The free base of the disulfide obtained (2.7 g.) was dissolved in Et_2O, and the solution was added dropwise to a stirred solution of $LiAlH_4$ (1.2 g.) in Et_2O. The mixture was refluxed for 30 min., decomposed with H_2O and filtered from the precipitate. The filtrate was dried, and Et_2O was evaporated. Vacuum distillation of the residue gave 1.7 g. of N-ethyl-N-methylbenzylamine, b.p_2 95～99°. *Anal.* Calcd. for $C_{10}H_{15}NS$: C, 66.30; H, 8.29; N, 7.74; S, 17.69. Found : C, 66.48; H, 8.56; N, 7.43; S, 17.41.

B) Thermal Decomposition of 2-(N-methylbenzylamino)ethanethiol——2(N-methylbenzylamino)ethanethiol was heated on an oil bath under atmospheric pressure, and fractionated into three portions distilling at (i) 200～240°(Fr. 1), (ii) 240～255°(Fr. 2), and (iii) 255～260°(Fr. 3).

1) The IR spectra showed that each fraction was mixture of 2-(N-methylbenzylamino)ethanethiol (BT) and N-methylbenzylamine (BA) and that BT was involved mainly in Fr. 1, whereas BA was involved mainly in Fr. 2 and Fr. 3. From each fraction BA was separated as the hydrochloride, m.p. 178°, whose IR spectrum was identical with that of an authentic sample.

2) In the course of several days each fraction gave a white precipitate, m.p. 98～105°, which was non-crystalline and insoluble in organic solvents. The analysis (C, 31.92, H, 5.19. S, 62.26) suggested that it consisted of polymer of ethylene sulfide (ES) (75%) and sulfur (25%), but lack of the sample made further investigation unsuccessful.

3) Each fraction was submitted to gas chromatography with the use of a Barber-Colman Model 10 Gas chromatograph (column packing 1% SE-30; length 6ft.) under the following condition : column temp. 90°, sample heater temp. 240°, detector temp. 205°, carrier gas A, 60 ml./min. The retention time 0.9, 3.6, and 29.0 (min.) observed in each fraction corresponded with those of authentic ES, BA, and BT respectively. The proportions of BA to BT were approximately 1:2 (Fr. 1), 3:1 (Fr. 2), and 15:1 (Fr. 3). The amount of ES was almost negligible in each case.

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Summary

Racemic and optically active N-(2-mercaptoethyl)ephedrines, 2-phenyl-3,4-dimethyltetrahydro-4*H*-1,4-thiazines, and their diastereomers were prepared, and their configurations were investigated. 2-Phenyl-3,4-dimethyltetrahydro-4*H*-1,4-thiazine, was obtained either by chlorination of N-(2-hydroxyethyl)ephedrine with thionyl chloride followed by cyclization with sodium sulfide, or by dehydration N-(2-mercaptoethyl)-*l*- and *d*-ψ-ephedrines with 80% sulfuric acid. Both reactions led to formation of *threo*-2-phenyl-3,4-dimethyltetrahydro-4*H*-1,4-thiazine. *erythro*-2-Phenyl-3,4-dimethyltetrahydro-4*H*-1,4-thiazine was prepared from *erythro*-1-phenyl-2-methylaminopropanethiol and ethylene dibromide.

When N-(2-mercaptoethyl)ephedrine was heated, formation of ephedrine due to partial splitting of 2-mercaptoethyl group was observed.

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