Anal. Calcd. for $C_{13}H_{15}NO$: N, 6.95. Found: N, 6.90.

DL-**2,3-Dibromo-1-benzamidocyclohexane (X).**—To a solution of 0.5 g. of IX in 8 ml. of carbon tetrachloride was added a solution of 0.4 g. of bromine in 4 ml. of carbon tetrachloride under cooling. The resulting precipitate, yield 0.57 g., m.p. 181–185° dec., was recrystallized from ethanol; m.p. 193° dec. alone and on admixture with a sample of X derived from *cis*-I; infrared λ_{max}^{Nujol} 2.98, 6.10, 6.51 μ (–NHCO–R). The addition of an aqueous silver nitrate solution to an acetone solution of the product caused no precipitation. The product was identified as the dibromide-(A) of Winstein, *et al.*, by a mixed m.p. determination and comparison of infrared spectra.[9]

Acknowledgment.—We are very grateful to Prof. S. Winstein and Dr. R. Boschan for their assistance in the identification of X. We are indebted to Mr. A. Horai and Miss O. Tada for the microanalyses, and also to Mr. H. Shindo of the Sankyo Co. Ltd. for the determination of the infrared spectra.

KATAKASU, FUKUOKA, JAPAN

[CONTRIBUTION FROM THE PHARMACEUTICAL INSTITUTE, MEDICAL FACULTY, UNIVERSITY OF KYUSHU]

Thermal, Solvolytic and Base-catalyzed Decomposition of 2-Acylaminoalkyl-S,S-dimethylsulfonium Iodides[1]

BY TANEZO TAGUCHI AND MASAHARU KOJIMA

RECEIVED AUGUST 11, 1958

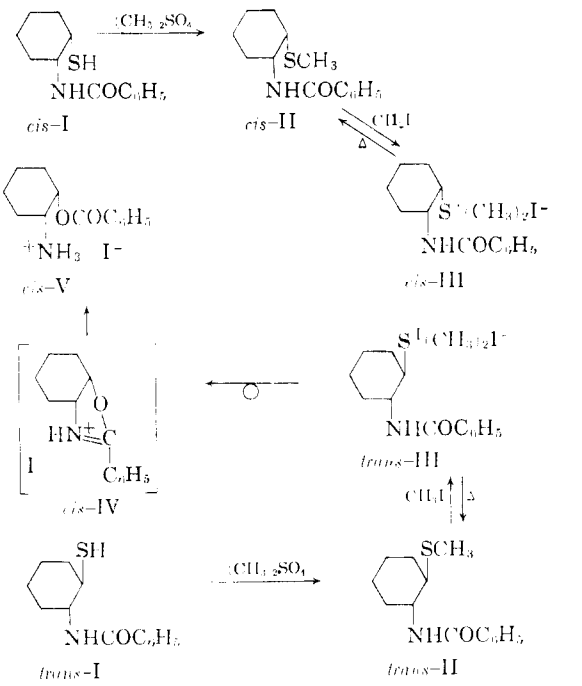
DL-*trans*- and DL-*cis*-2-benzamidocyclohexyl-S,S-dimethylsulfonium iodides (III) were prepared by successive methylation of the corresponding thiol derivatives (I) with retention. Upon the same treatment, DL-*threo*-1-phenyl-2-benzamidopropane thiol (*threo*-X) gave the S-dimethylsulfonium iodide (*threo*-XII) with retention, while *erythro*-X was converted to DL-*threo*-O-benzoyl norephedrine hydroiodide (*threo*-XIV·HI) with inversion. *trans*- and *cis*-III were decomposed by heat to the S-methyl derivatives of the same configuration. Upon solvolysis of III in water, *cis*-III yielded the corresponding S-methyl derivative, while *trans*-III gave DL-*cis*-2-aminocyclohexyl benzoate (*cis*-V) hydroiodide with inversion. On treatment of III with aqueous alkali hydroxide, both epimers decomposed to DL-*cis*-2-phenyl-4,5-cyclohexanoöxazoline (*cis*-IV), *meso-cis*-cyclohexenimine (*cis*-VII) and DL-*trans*-2-benzamido-1-cyclohexeniminocyclohexane (VIII). The base-catalyzed decomposition of *threo*-XII gave *threo*-XIII with retention. The mechanisms of these reactions are discussed.

Little information[2,3] is available concerning the participation of neighboring groups in reactions of 2-acylaminoalkyl-S,S-dimethylsulfonium iodides. In this work we have studied several reactions of these compounds and discussed the participation of neighboring groups on the basis of the products formed. The *trans* and *cis* isomers of DL-2-benzamidocyclohexyl-S,S-dimethylsulfonium iodide (III) were prepared from DL-*trans*- and DL-*cis*-2-benzamidocyclohexane thiol[4,5] (I), respectively, in two steps: methylation with dimethyl sulfate to give the corresponding S-methyl derivatives (II) which were treated with methyl iodide. The configuration of the original thiol was retained, because the reactions do not involve fission of bonds at asymmetric centers.

Thermal treatment of *trans*- and *cis*-III resulted in decomposition to the corresponding S-methyl derivatives (II) with retention. Solvolysis of *cis*-III in water gave only *cis*-II, while that of *trans*-III yielded DL-*cis*-2-aminocyclohexyl benzoate (*cis*-V) hydroiodide and a small amount of *trans*-II. Participation of the benzamido group, which is sterically permitted only in *trans*-III, facilitated the removal of the dimethylsulfonium group to afford *cis*-V with inversion persumably *via* DL-*cis*-2-phenyl-4,5-cyclohexanoöxazolinium iodide (*cis*-IV·HI); see Chart 1. The solvolyses of diastereomeric 2-benzamidocyclohexyl *p*-toluenesulfonate[3,6,7] had been found to proceed similarly.

Heating of *trans*-III in aqueous sodium hydroxide gave DL-*cis*-2-phenyl-4,5-cyclohexanoöxazoline (*cis*-IV), *meso-cis*-cyclohexenimine (*cis*-VII), DL-*trans*-2-benzamido-1-cyclohexeniminocyclohexane

CHART 1



(VIII) and *trans*-II; with the exception of *trans*-II, these products are the same as those obtained on treatment of DL-*trans*-2-benazmidocyclohexyl tosylate with sodium ethoxide.[8] There-

(1) Studies in Stereochemistry, XXIII; paper XXII, *Chem. Pharm. Bull.* (*Tokyo*), **7**, 103 (1959).

(2) C. W. Crane and H. N. Rydon, *J. Chem. Soc.*, 766 (1947).

(3) S. Winstein and R. Boschan, THIS JOURNAL, **72**, 4669 (1950).

(4) T. Taguchi and M. Kojima, *ibid.*, **78**, 1469 (1956).

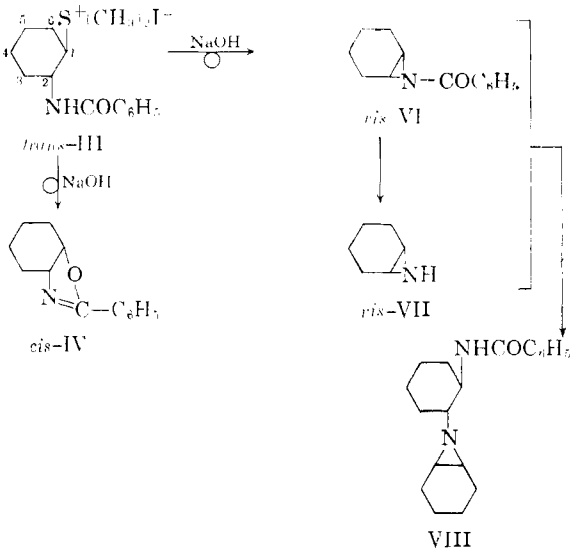
(5) M. Kojima, *Yakugaku Zasshi*, **79**, 1 (1959).

(6) G. E. McCasland, R. K. Clark, Jr., and H. E. Carter, THIS JOURNAL, **71**, 637 (1949).

(7) T. Taguchi and M. Kojima, *Pharm. Bull.* (*Tokyo*), **3**, 351 (1955).

(8) T. Taguchi and M. Kojima, THIS JOURNAL **81**, 4316 (1959).

CHART 2



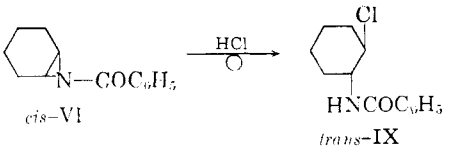
VIII

for, the mechanistic explanation given for the latter case should be applicable here. Accordingly the formation of *cis*-IV is attributable to the participation of the amidocarbonyl group. Formation of *cis*-VII and VIII can be explained as a consequence of the anchimeric property of the amido nitrogen in the presence of hydroxyl ion[8]; this would bring about the formation of *cis*-VII *via* the intermediate, *cis*-VI. Presumably *cis*-VI and *cis*-VII condensed to give VIII.

Treatment of *cis*-III with sodium hydroxide gave the same products as *trans*-III including a small amount of *trans*-II. This was unexpected, as participation of the benzamido group of the *cis*-isomer in the reaction is not permitted, and therefore one would anticipate the formation of cyclohexanone and 3-benzamidocyclohexene, the products obtained in the reaction of DL-*cis*-2-benzamidocyclohexyl tosylate with sodium ethoxide.[8]

This result may be explained by epimerization of *cis*-III to *trans*-III which then underwent decomposition. Probably the epimerization was prompted by the +I effect of the dimethylsulfonium group and the proton-withdrawing effect of hydroxyl ion on H_1. This assumption is supported by the isolation of *trans*-II from the reaction mixture.

When aqueous solutions of DL-*cis*- and *trans*-2-benzamidocyclohexyl-S,S-dimethylsulfonium hydroxide, obtained by the reaction of *cis*- and *trans*-III with silver oxide, were concentrated under reduced pressure, both of them gave *cis*-IV, *cis*-VII and VIII, the products obtained by the treatment of III with sodium hydroxide; this suggests that the reaction mechanism was the same in both cases; see Chart 2. Besides DL-*trans*-2-benzamidocyclohexyl chloride (*trans*-IX) resulted from the above treatment of the epimeric sulfonium hydroxide, being due to the use of hydrochloric acid during the separation of products. When the *cis*-oxazoline (*cis*-IV) and the N-benzoylimine (*cis*-VI) were treated independently with hydrochloric acid under similar reaction conditions, only the latter[9] gave *trans*-IX. These findings indicate that *cis*-VI is concerned as an intermediate in the reaction shown in Chart 2.



To extend this work to the acyclic series, the DL-1-phenyl-2-benzamidopropyl-S,S-dimethylsulfonium iodides (XII) were investigated. Both epimers of DL-1-phenyl-2-benzamidopropane thiol[10] (X) were methylated with dimethyl sulfate to give the corresponding propyl methyl sulfides (XI) with retention. Further methylation of *threo*-XI gave a trace of trimethylsulfonium iodide (XVI), but mainly *threo*-XII with retention. However, the same treatment of *erythro*-XI did not yield the expected *erythro*-XII but DL-*threo*-O-benzoylnorephedrine hydroiodide (*threo*-XIV·HI) with inversion, and XVI.

These results may be mechanistically explained as follows: *erythro*- and *threo*-XI react with methyl iodide to give initially the corresponding dimethyl derivative XII. Then *erythro*-XII, due to participation of the benzamido group, goes over to *threo*-XIV·HI *via* *threo*-oxazolinium iodide (*threo*-XIII·HI) with inversion, and dimethyl sulfide which is further methylated to XVI. The difference between the behavior of *erythro*- and *threo*-XII depends upon the steric compression in their transition states of oxazoline ring formation; in *erythro*-XII there would be strong steric repulsion due to eclipsed phenyl and methyl groups. This is not the case with *threo*-XIII; see Chart 4. Thus the steric repulsion of the phenyl and methyl groups prevents the formation of *erythro*-XIII from *threo*-XII; whereas *threo*-XIII is formed from *erythro*-XII in which the phenyl and methyl groups are not eclipsed in the transition state, a situation which has been discussed by Barton and Curtin.[11,12]

threo-XII was subjected to the following reactions: heating resulted in the formation of *threo*-XI. Solvolysis in water yielded a small amount of *threo*-XI and a large amount of *erythro*-XIV probably *via* *erythro*-XIII. Heating of *threo*-XII in aqueous sodium hydroxide and heating of the hydroxide obtained by the treatment of *threo*-XII with silver oxide both resulted in the formation of *threo*-XIII with retention. The retention of configuration in the formation of the oxazoline (*threo*-XIII) from *threo*-XII is presumably due to primary epimerization of *threo*-XII to *erythro*-XII which then underwent oxazoline cyclization with inversion; this epimerization is probably analogous to that of *cis*-III to *trans*-III.

Experimental[13]

DL-*cis*-2-Benzamidocyclohexane thiol[5] (*cis*-I), m.p. 128–129°.

DL-*trans*-2-Benzamidocyclohexane thiol[4] (*trans*-I), m.p. 161–162°.

(9) F. Winternitz, M. Mousseron, R. Dennilauler, *Bull. soc. chim. France*, 382 (1956).

(10) M. Kojima, *Yakugaku Zasshi*, **79**, 11 (1959).

(11) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (*London*), **10**, 54 (1956).

(12) D. Y. Curtin, *Rec. Chem. Progr.*, **15**, 111 (1954).

(13) Melting points were uncorrected.

CHART 3

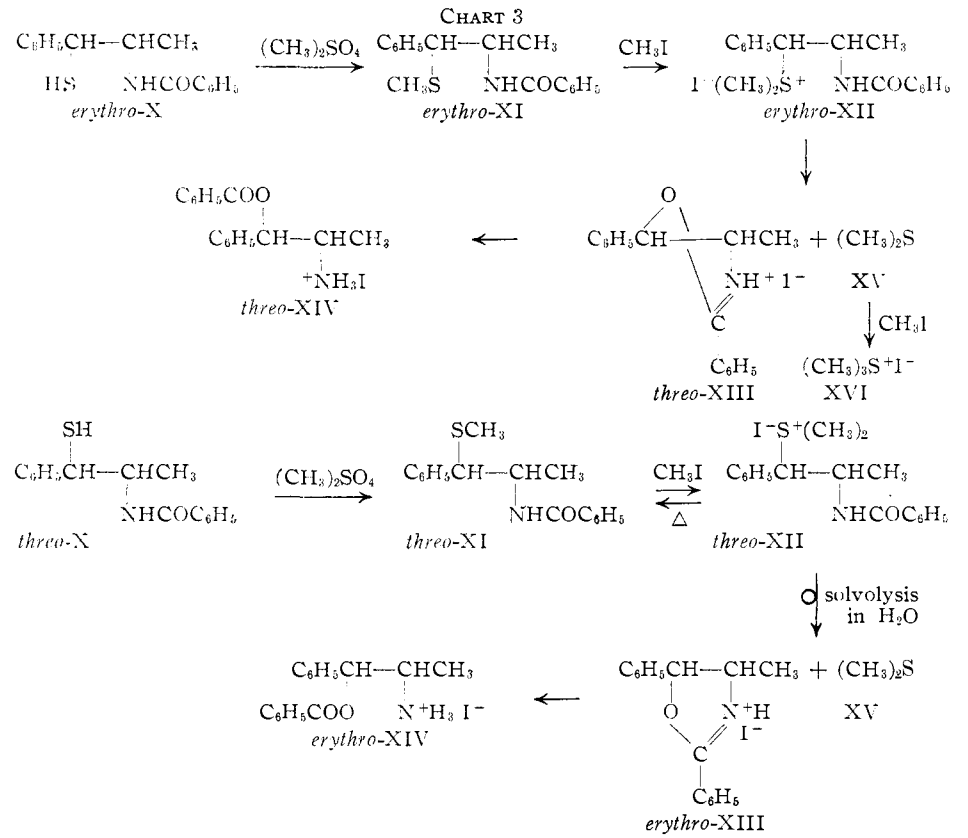


CHART 4

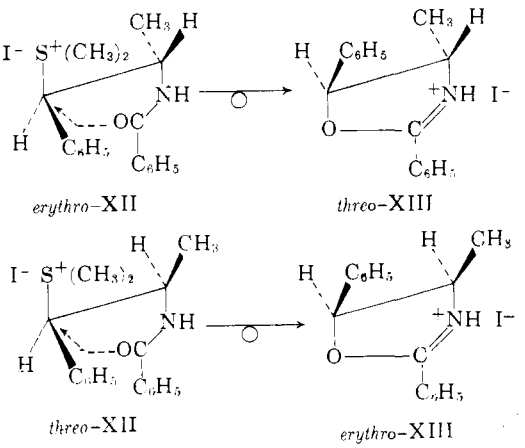
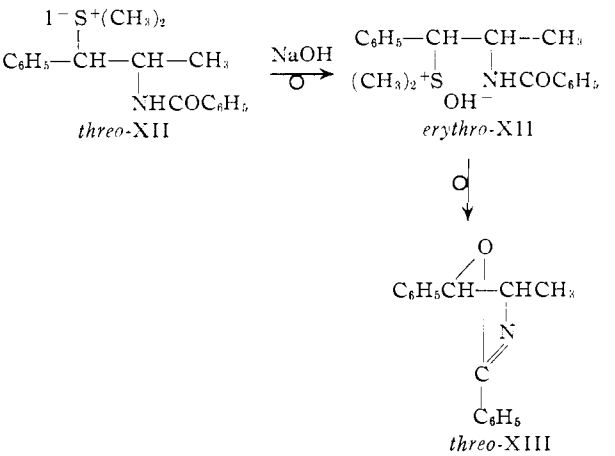


CHART 5



DL-*cis*-**2-Benzamidocyclohexyl Methyl Sulfide** (*cis*-II).—To 2 g. of *cis*-I dissolved in 10% aqueous sodium hydroxide was added dimethyl sulfate with stirring until the sodium nitroprusside test for mercaptan became negative. The resulting crystals (yield 1.5 g.) were recrystallized from 50% ethanol as colorless needles, m.p. 110–111°.

Anal. Calcd. for $C_{14}H_{19}NOS$: C, 67.41; H, 7.68; N, 5.62. Found: C, 67.31; H, 7.47; N, 5.61.

DL-*trans*-**2-Benzamidocyclohexyl Methyl Sulfide** (*trans*-II).—*trans*-I was methylated as described for *cis*-I, m.p. 155–156°.

Anal. Calcd. for $C_{14}H_{19}NOS$: C, 67.41; H, 7.68; N, 5.62. Found: C, 67.35; H, 7.24; N, 5.64.

DL-*cis*-**2-Benzamidocyclohexyl-S,S-dimethylsulfonium Iodide** (*cis*-III).—A solution of 1.5 g. of *cis*-II in 10 g. of methyl iodide was allowed to stand at room temperature overnight. The resulting crystals were filtered after the addition of benzene (yield 2.2 g.), and recrystallized from ethanol as colorless needles or rods which decomposed at 133° with the evolution of methyl iodide to give *cis*-II.

Anal. Calcd. for $C_{15}H_{22}NOSI$: C, 46.01; H, 5.66; N, 3.58. Found: C, 46.29; H, 5.80; N, 3.50.

DL-*trans*-**2-Benzamidocyclohexyl-S,S-dimethylsulfonium Iodide** (*trans*-III).—The iodomethylation of 1.2 g. of *trans*-II yielded 1.8 g. of crude *trans*-III which was recrystallized from ethanol–ether as colorless rods. They turned light yellow on standing and decomposed at 125° with the evolution of methyl iodide to give *trans*-II.

Anal. Calcd. for $C_{15}H_{22}NOSI$: C, 46.01; H, 5.66; N, 3.58. Found: C, 45.77; H, 5.65; N, 3.76.

Solvolysis of *cis*-III in Water.—*cis*-III (0.5 g.) in 20 ml. of water was boiled for 25 hours. After cooling, the precipitate was filtered, m.p. 109–110°; it showed no depression of m.p. on admixture with a sample of *cis*-II. Evaporation of the mother liquor to dryness gave 80 mg. of crystals which

were recrystallized from ethanol–ether. They were identified as *cis*-III by a mixed m.p. determination.

Solvolysis of *trans*-III in water.—*trans*-II (1.5 g., m.p. 155°) was obtained from 0.5 g. of *trans*-III treated as above. The filtrate on concentration to 2 ml. yielded additional *trans*-II, weight 10 mg., m.p. 154–155°. The mother liquor was concentrated to dryness. The oily residue, which crystallized after the addition of ethanol–ether and scratching (yield 0.13 g.), was recrystallized from ethanol–ether as colorless needles, m.p. 196–197° dec. The picrate melted at 223–224°, alone and on admixture with DL-*cis*-2-aminocyclohexyl benzoate (*cis*-V)·picrate.[14]

Anal. Calcd. for $C_{13}H_{18}NO_2I$ (*cis*-V·HI): C, 44.97; H, 5.22; N, 4.03. Found: C, 44.61; H, 5.36; N, 3.96.

The addition of alkali to an aqueous solution of the hydroiodide yielded DL-*cis*-2-benzamidocyclohexanol,[3,6] m.p. 184°.

Decomposition of *trans*-III in Aqueous Sodium Hydroxide.—To 2 g. of *trans*-III dissolved in 20 ml. of warm water was added 10 ml. of 10% aqueous sodium hydroxide. The mixture was boiled for an hour and then steam distilled. The residue which contained crystals was extracted with ether to which the crystals were transferred undissolving. The ether layer was washed with water, then with 5% aqueous hydrochloric acid repeatedly till the crystals disappeared, and with water again. Evaporation of the ether layer to dryness gave 50 mg. of crystals which were recrystallized from 50% ethanol; m.p. 155–156° alone and on admixture with a sample of *trans*-II. When the hydrochloric acid solution was made alkaline with 10% sodium hydroxide, crystals separated (yield 5 mg.) which were recrystallized from ethanol; m.p. 220–221° alone and on admixture with an authentic sample of VIII.[8]

The steam distillate was extracted with ether. The extract was washed with water and evaporated to dryness to give an oil from which a picrate was prepared, yield 0.21 g. After recrystallization from ethanol, it melted at 155–156° alone and on admixture with a sample of DL-*cis*-2-phenyl-4,5-cyclohexanoöxazoline (*cis*-IV) picrate.[3]

When the combined aqueous layer was saturated with sodium hydroxide, an oil appeared which was extracted with ether. The extract was evaporated to dryness and distilled over an oil-bath at 170–180° to give a small quantity of an oil from which a picrate was prepared; yield 0.36 g., m.p. 120–121° alone and on admixture with a sample of *meso-cis*-cyclohexenimine (*cis*-VII) picrate. When the alkaline aqueous layer was acidified with hydrochloric acid, benzoic acid (yield 0.27 g.) was obtained.

Decomposition of *cis*-III in Aqueous Sodium Hydroxide.—*cis*-III (2 g.) treated as above, yielded the same products as *trans*-III: *viz.*, *trans*-II, yield 30 mg.,[15] m.p. 155–156°; VIII, yield 10 mg.,[15] m.p. 219–220°; *cis*-IV picrate, yield 0.26 g.,[15] m.p. 155–156°; *cis*-VII picrate, yield 0.52 g.,[15] m.p. 120°; benzoic acid, yield 0.47 g.,[15] m.p. 120–121°. The crude *trans*-II required two recrystallizations. Evaporation of the recrystallization filtrate to dryness gave a solid which could not be purified by recrystallization from 50% ethanol (m.p. 86–93°) and which showed no depression of m.p. on admixture with either *trans*-II or *cis*-II.

Decomposition of *trans*-III in an Aqueous Silver Oxide Suspension.—To 3 g. of *trans*-III dissolved in 50 ml. of water was added about the mole equivalent of silver oxide with stirring, and the precipitated silver iodide filtered. The filtrate was distilled under reduced pressure to give a small quantity of residue which became turbid. The distillate was saturated with sodium hydroxide to separate an oil which was extracted with ether. The extract was dried over sodium hydroxide and evaporated to dryness. The picrate prepared from the residue, yield 60 mg., was recrystallized from ethanol as yellow needles; m.p. 120° alone and on admixture with a sample of *cis*-VII picrate. The distillation residue, to which 20 ml. of water had been added, was steam distilled. The picrate of *cis*-IV was prepared from the distillate as described under the alkaline decomposition of *trans*-III; yield 0.15 g., m.p. and mixed m.p. 154–155°.

Ether was added to the steam distillation residue. After the removal of a brownish solid, the ether layer was separated, washed three times with 5-ml. portions of 5% hydrochloric acid, washed with water and evaporated to give crystals, yield 20 mg. Recrystallization from ethanol yielded colorless plates which gave a positive Beilstein test for halogen; m.p. 163–164° alone and on admixture with DL-*trans*-2-benzamidocyclohexyl chloride (*trans*-IX).[16]

Anal. Calcd. for $C_{13}H_{16}NOCl$: N, 5.89. Found: N, 5.40.

When the combined hydrochloric washings was made alkaline, crystals separated, yield 7 mg., which were recrystallized from ethanol; m.p. 219–220° alone and on admixture with a sample of VIII.

Decomposition of *cis*-III in an Aqueous Silver Oxide Suspension.—*cis*-III (3 g.), treated with silver oxide as above, afforded the same products as *trans*-III: *cis*-VII picrate, yield 0.10 g.,[15] m.p. 120°; *cis*-IV picrate, yield 0.11 g.,[15] m.p. 155–156°; *trans*-IX, yield 35 mg.,[15] m.p. 163–164°; VIII, yield 30 mg.,[15] m.p. 219–220°.

DL-*erythro*-1-**Phenyl-2-benzamidopropane thiol**[10] (*erythro*-**X**), m.p. 119–120°.

DL-*threo*-1-**Phenyl-2-benzamidopropane thiol**[10] (*threo*-**X**) m.p. 144–145°.

DL-*erythro*-1-**Phenyl-2-benzamidopropyl methyl sulfide** (*erythro*-**XI**) was prepared from a solution containing 0.45 g. of *erythro*-X in 10 ml. of 10% aqueous sodium hydroxide, from which the insoluble material had been removed, by the method described for the preparation of *cis*-II; yield 0.45 g.,[15] m.p. 130–131°.

Anal. Calcd. for $C_{17}H_{19}NOS$: C, 71.52; H, 6.71; N, 4.91. Found: C, 71.23; H, 6.49; N, 5.35.

DL-*threo*-1-**Phenyl-2-benzamidopropyl methyl sulfide** (*threo*-**XI**) was prepared from *threo*-X (220 mg.) as above; yield 0.22 g.,[15] m.p. 153–154°.

Anal. Calcd. for $C_{17}H_{19}NOS$: C, 71.52; H, 6.71; N, 4.91. Found: C, 71.24; H, 6.29; N, 5.03.

Action of Methyl Iodide on *erythro*-XI. The Formation of DL-*threo*-O-Benzoyl-norephedrine Hydroiodide (*threo*-XIV·HI) and Trimethylsulfonium Iodide (XVI).—*erythro*-XI (1 g.) dissolved in 25 g. of methyl iodide was set aside at room temperature for three days. The precipitate, weight 1.35 g., was recrystallized from 20 ml. of ethanol to give cubes or rods which decomposed at 207–210°.

Anal. Calcd. for C_3H_9SI (XVI): C, 17.65; H, 4.44. Found: C, 17.90; H, 4.76.

The recrystallization filtrate was evaporated to dryness and the residue was recrystallized from ethanol–ether to give silky needles, yield 0.45 g., m.p. 206–207° dec. The methyl iodide solution on evaporation to dryness yielded an additional crop, weight 0.37 g.

Anal. Calcd. for $C_{16}H_{18}NO_2I$ (*threo*-XIV·HI): C, 50.14; H, 4.94; N, 3.65. Found: C, 50.07; H, 4.89; N, 3.38.

The picrate melted at 184–185° alone and on admixture with *threo*-XIV·picrate.[17] When *threo*-XIV·HI was treated with alkali, DL-*threo*-N-benzoyl-norephedrine[17] (m.p. 127–128°) was obtained.

DL-*threo*-1-**Phenyl-2-benzamidopropyl-S,S-dimethylsulfonium Iodide** (*threo*-**XII**).—The iodomethylation, as above, of 1 g. of *threo*-XI yielded 20 mg. of XVI which decomposed at 207–210°.

Anal. Calcd. for C_3H_9SI (XVI): C, 17.65; H, 4.44. Found: C, 18.12; H, 4.60.

After the removal of XVI, evaporation of the filtrate to dryness gave an oil which solidified upon the addition of ether, yield 1.17 g. Recrystallization from ethanol–ether gave colorless needles of *threo*-XII which decomposed at 118° to give *threo*-XI.

Anal. Calcd. for $C_{18}H_{22}NOSI$ (*threo*-XII): C, 50.56; H, 5.12; N, 3.27. Found: C, 51.12; H, 5.42; N, 3.33.

Solvolysis of *threo*-XII in Water.—A solution of 0.2 g. of *threo*-XII in 10 ml. of water was boiled for 1 hour. After cooling, colorless plates were filtered (yield 10 mg.) which melted at 153–154° alone and on admixture with *threo*-XI. Evaporation of the filtrate to dryness gave an oil, which crystallized upon the addition of ether, yield 0.15 g. Recrystallization from ethanol–ether gave colorless needles, m.p. 197–198° dec.

(14) T. Taguchi and M. Nakayama, THIS JOURNAL, **73**, 5679 (1951).

(15) Crude product.

(16) W. S. Johnson and E. N. Schubert, THIS JOURNAL, **72**, 2189 (1950).

(17) N. Nagai and S. Kanao, *Ann.*, **470**, 157 (1929).

Anal. Calcd. for $C_{16}H_{18}NO_2I$ (*erythro*-XIV·HI): C, 50.14; H, 4.94; N, 3.65. Found: C, 49.79; H, 4.91; N, 3.59.

The picrate melted at 188–189° alone and on admixture with *erythro*-XIV·picrate.[18] When solution of the hydroiodide was made alkaline, DL-*erythro*-N-benzoyl-norephedrine[17] (m.p. 143–144°) was obtained.

Decomposition of *threo*-XII in Aqueous Sodium Hydroxide.—A solution of 0.20 g. of *threo*-XII in 10 ml. of water was boiled until it became turbid; an oily layer appeared after ten minutes. After cooling, the mixture was extracted with ether. The extract was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness to give an oil, yield 0.12 g., which was converted to the picrate, yield 0.18 g. Recrystallization from absolute ethanol gave colorless plates; m.p. 142–143° alone and on admixture with *threo*-XIII·picrate.[17]

(18) T. Taguchi and M. Kojima, *Pharm. Bull.* (*Tokyo*), **3**, 4 (1955).

Anal. Calcd. for $C_{22}H_{18}N_4O_8$: C, 56.62; H, 3.89; N, 12.01. Found: C, 56.79; H, 3.89; N, 11.97.

Decomposition of *threo*-XII in an Aqueous Silver Oxide Suspension.—To a solution of 0.20 g. of *threo*-XII was added about the mole equivalent of silver oxide. The silver iodide was filtered and the filtrate boiled for 10 minutes until an oil appeared. After cooling, the mixture was extracted with ether. The extract was dried over anhydrous sodium sulfate and evaporated to dryness to leave 0.10 g. of an oil from which a picrate was prepared; yield 0.14 g. m.p. 141–142° alone and on admixture with *threo*-XIII·picrate.

Acknowledgments.—The authors are indebted to the Microanalytical Section of this Institute and the Center of Microanalyses of this University for microanalyses.

KATAKASU, FUKUOKA, JAPAN

[CONTRIBUTION FROM THE PHARMACEUTICAL INSTITUTE, MEDICAL FACULTY, UNIVERSITY OF KYUSHU]

Reaction of 2-Aminoalkyl Sulfates or Halides with Sodium Disulfide in the Presence of Cyclohexanone. A New Synthesis of Thiazolidines and 2-Aminoalkane Thiols[1]

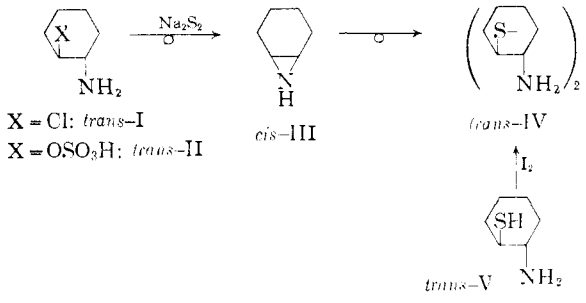
BY TANEZO TAGUCHI, MASAHARU KOJIMA AND TOMIO MURO

RECEIVED AUGUST 11, 1958

DL-*trans*-2-Aminocyclohexyl chloride (*trans*-I) or sulfate (*trans*-II) reacted with sodium disulfide to yield a compensated *trans-trans*-bis-(2-aminocyclohexyl) disulfide (IV). The *cis* epimer (*cis*-I) gave cyclohexanone (VI), *trans*-IV and DL-*trans*-spiro[cyclohexane-1,2′-(4′,5′-cyclohexano)-thiazolidine] (VII). Compound VII, which yielded VI and DL-*trans*-2-aminocyclohexane thiol (*trans*-V) upon hydrolysis, was also prepared by the condensation of VI and *trans*-V. Thus, the formation of VII was probably due to the secondary condensation of VI and *trans*-V formed in the disulfide reaction. This finding suggested a new method for the synthesis of thiazolidines by the reaction of 2-aminoalkyl halides or sulfates with sodium disulfide in the presence of aldehydes or ketones.

Mousseron and his co-workers[2] have reported the preparation of a compensated bis-(2-aminocyclohexyl) disulfide by the treatment of DL-2-aminocyclohexyl chloride (I) with sodium disulfide. The present work was undertaken to determine the configuration of this compound. DL-*trans*-2-Aminocyclohexyl chloride (*trans*-I) was treated with sodium disulfide to yield an oil which was converted to the hydrochloride. This hydrochloride was identical with a compensated *trans-trans*-bis-(2-aminocyclohexyl) disulfide (*trans*-IV) hydrochloride[3] obtained by the oxidation of DL-*trans*-2-amino-cyclohexane thiol[4] (*trans*-V) with iodine, followed by salt formation. The *trans* configuration was assigned to IV because its formation by the oxidation of *trans*-V does not involve the breaking of bonds at asymmetric centers. Therefore, it is presumed that the disulfide reaction first gave the intermediate *meso-cis*-cyclohexenimine (*cis*-III) from which *trans*-IV was formed; thus the reaction as a whole involved double inversion; see Chart 1.

CHART 1



cis-I reacted with sodium disulfide to yield cyclohexanone (VI), *trans*-IV and a basic substance which was shown to be *trans*-VII. The hydrochloride of this basic substance was hydrolyzed to give cyclohexanone (VI) and the *trans*-aminothiol (*trans*-V) hydrochloride. We then prepared the epimers of DL-spiro[cyclohexane-1,2′-(4′,5′-cyclohexano)-thiazolidine] (VII) hydrochloride by the condensation of cyclohexanone (VI) and the *trans*- or *cis*-aminothiol V; the *trans* epimer (*trans*-VII) hydrochloride was identical with the hydrochloride under consideration.

The results of the treatment of *cis*-I with sodium disulfide may be interpreted as follows: since the reaction medium becomes alkaline due to hydrolysis of sodium disulfide,[5] some of the *cis*-I undergoes elimination of hydrochloric acid to give cyclohexanone (VI) *via* 1-aminocyclohex-2-ene. Also *cis*-I gives *trans*-IV *via* *Sn*2 reaction at C_1; participation of the amino group in a reaction at C_1 is not favored by the *cis*-relationship. Then the reduction of *trans*-IV in the reaction medium gives *trans*-V which condenses with VI to yield *trans*-VII; see Chart 2. Since *trans*-IV was not reduced by sodium disulfide under similar conditions in the

(1) Studies in Stereochemistry, XXIV; paper XXIII, THIS JOURNAL, **81**, 4318 (1959).

(2) M. Mousseron, H. Bousquet and G. Marret, *Bull. soc. chim. France*, 84, (1948).

(3) There are theoretically two compensated *trans-trans* diastereoisomers, one of which is racemic and the other *meso*, but it is not clear which is the product (*trans*-IV).

(4) T. Taguchi and M. Kojima, THIS JOURNAL, **78**, 1684 (1956).

(5) O. E. Paris and P. E. Fanta, *ibid.*, **74**, 3007 (1952).