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

The Action of Sodium Ethoxide in Absolute Ethanol on Epimeric DL-2-Benzamidocyclohexyl *p*-Toluenesulfonates[1]

BY TANEZO TAGUCHI AND MASAHARU KOJIMA

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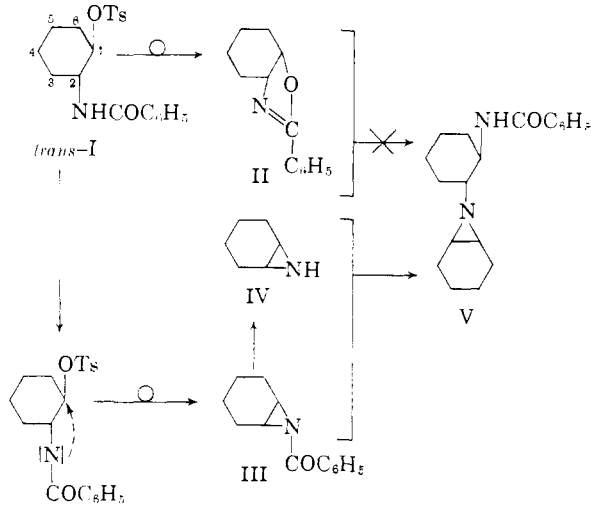
DL-*trans*-2-Benzamidocyclohexyl *p*-toluenesulfonate (*trans*-I) was treated with sodium ethoxide in absolute ethanol to give DL-*cis*-2-phenyl-4,5-cyclohexanoöxazoline (II), *meso-cis*-cyclohexenimine (IV) and DL-*trans*-2-benzamido-1-cyclohexeniminocyclohexane (V); the *cis* epimer yielded cyclohexanone (VIII) and 3-benzamidocyclohexene (IX). A mechanism is proposed which explains the formation of these products.

Solvolyses of DL-*trans*[2-5] (*trans*-I) and DL-*cis*[6]-2-benzamidocyclohexyl *p*-toluenesulfonates (*cis*-I) have been investigated. However little information is available on base-catalyzed reactions of these compounds, particularly catalysis by alkali alkoxide which may influence the mode of participation of the benzamido group by altering the distribution of electrons. This prompted us to undertake the current study. *trans*-I was boiled in absolute ethanol containing sodium ethoxide for five hours to give DL - *cis* - 2 - phenyl - 4, 5 - cyclohexanoöxazoline (II), *meso-cis*-cyclohexenimine (IV), ethyl benzoate, sodium *p*-toluenesulfonate and DL-*trans*-2-benzamido - 1 - cyclohexeniminocyclohexane (V). The structure of V was established by elemental analyses, determination of molecular weight, infrared spectrum and the fact that IV reacted with *meso-cis*-benzoylcyclohexenimine[7] (III) to give V.

The reactions may be explained mechanistically as follows: the steric requirement of *trans*-I favors internal displacement of the tosyloxy group by the benzoyl group, by which the *cis*-oxazoline II is formed with inversion under our reaction conditions as well as in solvolysis.[2-5] On the other hand, ethoxide ion facilitates ionization of the hydrogen attached to the amide nitrogen and accordingly increases the electron density of the nitrogen atom. This leads to the formation of the imine products IV and V, a result which shows the relative anchimeric nature of the amide nitrogen. Presumably *cis*-cyclohexenimine (IV) is formed *via* the intermediate *meso-cis*-benzoylcyclohexenimine (III) which subsequently reacts with IV to give V. Although we were unable to detect the intermediate III, treatment of synthetic III under the same conditions gave IV and V; V was also obtained by boiling III and IV in absolute alcohol. The alternate pathway to V through the possible interaction of II and IV was ruled out, since both reactants remained unchanged when boiled in absolute alcohol in the presence or absence of sodium ethoxide. The *trans* assignment for V was based on the known *trans* opening[8] of the imine ring, a cleavage which occurs in its formation from III and IV.



The yields of the products II, IV and V, were 7.2, 14.7 and 14.6% respectively, the ratio of II to IV plus V being about 1:4. This ratio represents roughly the relative participation of the amidocarbonyl group and of the amide nitrogen in the reaction; for according to the above mechanism, II arises from the reaction of the amidocarbonyl group, while the formation of IV and V is due to the reaction of the amide nitrogen to give the intermediate III. Although this ratio is only a rough approximation, it is evident that the participation of the amide nitrogen is considerably greater than that of the amidocarbonyl group under these conditions, in contrast to the results obtained under solvolytic conditions.[2-5]

cis-I was treated in the same way as the *trans* epimer except that a longer reaction time (15 hours) was required. The products were cyclohexanone (VIII), 3-benzamidocyclohexene (IX) and benzamide; IX was identified by derivation to 2,3-dibromo-1-benzamidocyclohexane[9] (X) which was also obtained by benzoylation of 3-aminocyclohexene[10] (XII) followed by bromination. Presumably the elimination of *p*-toluenesulfonic acid from *cis*-I occurred by two pathways which yielded VIII and IX, respectively: one proceeded through the diaxial elimination of α-H_2 and *p*-toluenesulfonate ion to give VIII *via* VI and VII, and the other through the elimination of α-H_6 and *p*-toluenesulfonate ion to give IX. This indicates that a conformation containing an *e*-benzamido group and an α-tosyloxy

(1) Studies in Stereochemistry, XXI; paper XX, *Chem. Pharm. Bull. (Tokyo)*, **6**, 824 (1958).

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

(3) S. Winstein, L. Goodman and R. Boschan, *ibid.*, **72**, 2311 (1950).

(4) S. Winstein and R. Boschan, *ibid.*, **72**, 4669 (1950).

(5) T. Taguchi and M. Nakayama, *ibid.*, **73**, 5679 (1951).

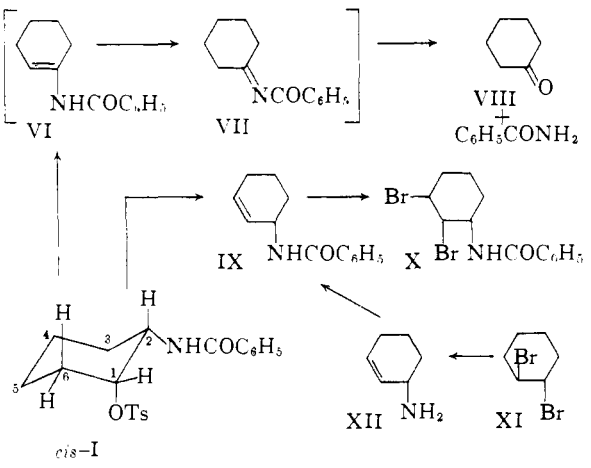
(6) T. Taguchi and M. Kojima, *Pharm. Bull. (Tokyo)*, **3**, 351 (1955).

(7) M. Svoboda, J. Sicher, J. Farkaš and M. Pánková, *Collection Czechoslov. Chem. Communs.*, **20**, 1426 (1955).

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

(9) Compound X is identical with dibromide-(A), m.p. 189–190° dec., prepared by S. Winstein, R. Boshan and L. Goodman, personal communication, THIS JOURNAL, **80**, 4312 (1958).

(10) F. Hofmann and P. Dann, *Chem. Zentr.*, **50**, 2342 (1926)I.



group was preferentially involved. The products formed and the longer reaction time required are in accord with the accepted fact that the participation of the benzamido group in the reaction is less important for *cis*-I than for the *trans* epimer. In view of the fact that the solvolysis of *cis*-I[6] gave partly the DL-*cis*-oxazoline (II) and II was not formed with sodium ethoxide, it seems probable that sodium ethoxide depresses the anchimeric property of the amidocarbonyl group, because the formation of the *cis*-oxazoline (II) arises from the attack of the group at C_1, even though the formation of II is not energetically assisted by the attack.

Experimental[11]

DL-*trans*-**2-Benzamidocyclohexyl** *p*-**toluenesulfonate** (*trans*-I) was prepared by the author's procedure,[5] m.p. 123°.

DL-*cis*-**2-Benzamidocyclohexyl** *p*-**toluenesulfonate** (*cis*-I) was prepared by the author's procedure,[6] m.p. 174–175°.

Treatment of *trans*-I with Sodium Ethoxide in Absolute Ethanol. Isolation of DL-*cis*-2-Phenyl-4,5-cyclohexanooxazoline (II), *meso*-*cis*-Cyclohexenimine (IV), DL-*trans*-2-Benzamido-1-cyclohexeniminocyclohexane (V), Ethyl Benzoate and Sodium *p*-Toluenesulfonate.—To 30 ml. of anhydrous ethanol containing 0.22 g. of sodium was added 3.0 g. of *trans*-I, and the mixture was boiled for 5 hours. After cooling, the precipitated sodium tosylate was filtered, yield 1.38 g., and the filtrate was evaporated. The residue was steam distilled after the addition of 10 ml. of water. The distillation residue was filtered (m.p. 215–217°, yield 0.35 g.) and recrystallized from ethanol to give colorless needles, m.p. 220–221°, which were identical with V prepared by the method described below; infrared λ_{max}^{Nujol} 3.04, 6.13, 6.51 μ (–NHCO–R).

Anal. Calcd. for $C_{19}H_{28}N_2O$ (V): C, 76.46; H, 8.78; N, 9.38; equiv. wt., 298.4. Found: C, 76.82; H, 8.69; N, 9.35; equiv. wt., 298.7.

The distillate was extracted with ether and washed with water. The combined aqueous solution was saturated with solid sodium hydroxide under cooling. The resulting oil was extracted with ether, dried over sodium hydroxide and evaporated to dryness. The residual oil, which had an ethyleniimine-like odor, was distilled over an oil-bath heated to 170–190°, and the distillate converted to a picrate by the usual method; m.p. 120–121°, yield 0.37 g. Recrystallization from ethanol gave yellow prisms, m.p. 120–121°, which were identified as IV-picrate by a mixed m.p. determination.

Anal. Calcd. for $C_{12}H_{14}N_4O_7$: C, 44.17; H, 4.32; N, 17.17. Found: C, 44.12; H, 4.30; N, 17.11.

The ether layer was extracted with 10% hydrochloric acid, washed with water and evaporated to dryness. The residue, which had odor of ethyl benzoate (weight 0.35 g.), gave benzoic acid upon alkaline hydrolysis. The hydrochloric acid solution was combined with the wash water and neutralized with 10% aqueous sodium hydroxide and extracted with ether. The ethereal solution yielded a picrate (0.26 g., m.p. 153–156°) which was recrystallized from ethanol to give yellow plates, m.p. 155–156° alone and on admixture with the II-picrate.

meso-*cis*-**Cyclohexenimine (IV).**—The procedure of Paris and Fanta[12] was used, m.p. 20°; picrate, m.p. 120–121°.

meso-*cis*-**Benzoylcyclohexenimine (III).**—The procedure of M. Svoboda, *et al.*,[7] was adapted, m.p. 75–77°.

DL-*trans*-**2-Benzamido-1-cyclohexeniminocyclohexane (V).** (**a**).—A mixture of 0.30 g. of III and 0.15 g. of IV in 2 ml. of ethanol was boiled for 2.5 hours. After removal of the ethanol, a small amount of ether was added to the residue which was then filtered; yield 0.25 g., m.p. 215–217°. Recrystallization from ethanol gave colorless needles of V, m.p. 220–221°.

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.46; H, 8.78; N, 9.38. Found: C, 76.45; H, 8.80; N, 9.47.

(**b**).—A mixture of 0.20 g. of III and 0.10 g. of IV in 2 ml. of ether was allowed to stand at room temperature for 3 weeks. The colorless silky needles which separated (yield 50 mg., m.p. 220–221°) were found to be identical with V, prepared according to (a), by a mixed m.p. determination.

(**c**).—To a solution of 0.017 g. of sodium dissolved in 4 ml. of absolute ethanol was added 0.30 g. of III, and the mixture was boiled for 4 hours. After cooling and filtration the ethanolic mother liquor was evaporated to dryness. The amorphous residue crystallized upon treatment with a mixture of 5 ml. of water and a small amount of ether. The crude product (yield 30 mg., m.p. 216–221°) was recrystallized from ethanol to give colorless needles, m.p. 220–221° alone and on admixture with a sample of V obtained under (a).

The ether–water solution obtained above was separated. The ether layer was washed with water several times. The combined aqueous solution after saturation with sodium hydroxide was extracted with ether. This ether extract was dried and treated with a saturated ethereal solution of picric acid. The resulting precipitate upon recrystallization from ethanol gave yellow prisms which melted at 120–121° alone and on admixture with a sample of IV-picrate.

Treatment of *cis*-I with Sodium Ethoxide in Absolute Ethanol.—*cis*-I (6 g.) in 60 ml. of absolute ethanol containing 0.44 g. of sodium was boiled for 15 hours. The reaction mixture was treated essentially as described for *trans*-I. The distillate gave a 2,4-dinitrophenylhydrazone (yield 2.35 g., m.p. 157–158°) which was identical with the cyclohexanone derivative.

The aqueous solution remaining after the steam distillation was evaporated to dryness *in vacuo*, extracted with ether and evaporated to dryness. When the residue was dissolved in 8 ml. of carbon tetrachloride, crystals separated (yield 0.44 g., m.p. 125–127°) which were recrystallized from ethanol to give colorless plates melting at 126–127° alone and on admixture with a sample of benzamide.

Anal. Calcd. for C_7H_7NO: N, 11.56. Found: N, 11.52.

On evaporation, the carbon tetrachloride solution gave a gummy product which could not be crystallized. Treatment of the gum, redissolved in carbon tetrachloride, with a carbon tetrachloride solution of bromine under cooling gave an oil from which the solvent was decanted. On the addition of ethanol and ether, this oil gave crystals (yield 0.62 g., m.p. 190–192° dec.) which were recrystallized from ethanol as colorless needles, m.p. 192–193° dec., identical with DL-2,3-dibromo-1-benzamidocyclohexane prepared as described below.

Anal. Calcd. for $C_{13}H_{15}NOBr_2$ (X): C, 43.24; H, 4.18; N, 3.37; Br, 44.26; equiv. wt., 361.1. Found: C, 43.35; H, 4.50; N, 3.56; Br, 44.60; equiv. wt., 344.

DL-**3-Aminocyclohexene (XII)** was prepared by an adaptation of Hofmann's procedure,[10] b.p. 138°.

DL-**3-Benzamidocyclohexene (IX).**—Treatment of 0.5 g. of XII, 0.8 g. of benzoyl chloride and 5 ml. of 20% sodium hydroxide by the Schotten–Baumann procedure gave 1.01 g. of a solid, m.p. 97–99°. Recrystallization from ether–petroleum ether yielded colorless needles, m.p. 102–104°.

(11) All melting points are uncorrected.

(12) E. Paris and P. E. Fanta, THIS JOURNAL, **74**, 3007 (1952).

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]

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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

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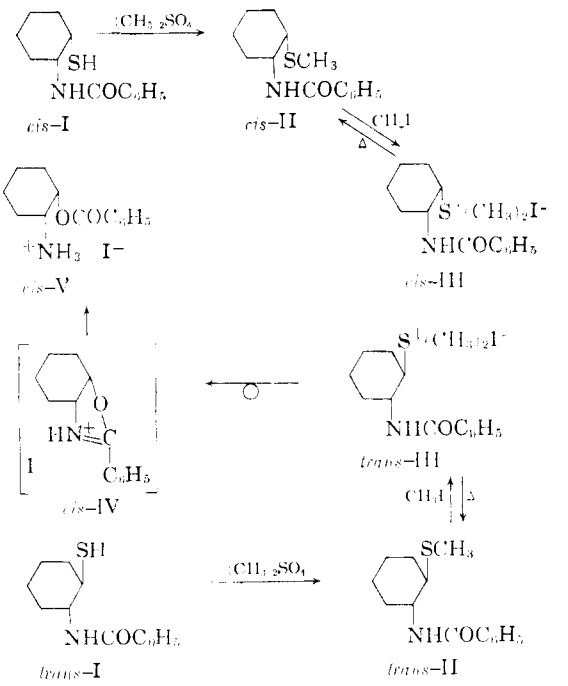
DL-*trans*- and DL-*cis*-2-benzamidocyclohexyl-S,S-dimethylsulfonium iodides (III) were prepared by successive methylation of the corresponding thiol derivatives (I) with retention. Upon the same treatment, DL-*threo*-1-phenyl-2-benzamidopropane thiol (*threo*-X) gave the S-dimethylsulfonium iodide (*threo*-XII) 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).