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

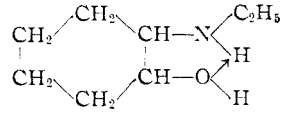
The 2-Aminocyclohexanols. I. N-Ethylation. II. A New Detosylation Product from the *trans*-N-Benzoyl O-Tosylate[1]

BY TANEZO TAGUCHI[2] AND MIWAKO NAKAYAMA

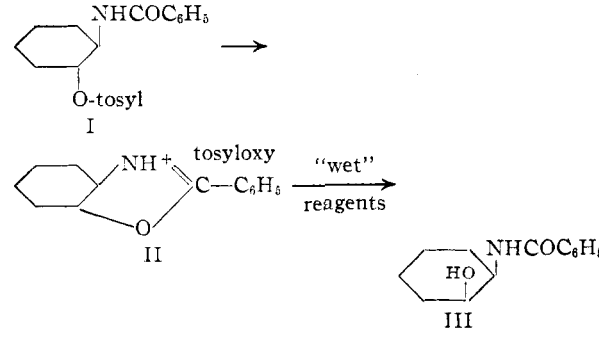
The ethylation of *trans*- and *cis*-2-aminocyclohexanol was carried out. The result showed that 2-diethylaminocyclohexanol obtained by the action of diethylamine on cyclohexene oxide or *trans*-2-chlorocyclohexanol was not the *cis*-form as previously reported but the *trans*-form, and *cis*-2-aminocyclohexanol gave only the monoethyl derivative which resisted further ethylation. On treating *dl-trans*-2-benzoylaminocyclohexyl *p*-toluenesulfonate with neutral ethanol a new substance, $C_{13}H_{17}O_2N \cdot C_7H_8O_3S$ (*dl-cis*-2-phenyl-2-hydroxy-4,5-cyclohexanoöxazolidine tosylate or *dl-cis*-2-benzoyloxycyclohexylamine tosylate) was obtained.

A few years ago Asano and co-workers[3] reported that acridine derivatives substituted by 4-dialkylaminocyclohexyl groups exhibited antimalarial activity comparable to that of Atebrine. These results prompted us to investigate other series of compounds derived from 2-dialkylaminocyclohexanol. In the course of this work, the stereochemistry of 2-diethylaminocyclohexanol has been investigated. The *cis* configuration[4] had been assigned previously to the product obtained by the action of diethylamine on cyclohexene oxide[5] or on *dl-trans*-2-chlorocyclohexanol.[6] In view of the recent studies on the stereochemistry of the 2-aminocyclohexanols it seemed more probable that this isomer was actually the *trans* form.[7] In order to establish this point *dl-cis*- and *dl-trans*-2-aminocyclohexanol were prepared and subjected to ethylation with ethyl bromide and ethyl *p*-toluenesulfonate. With ethyl bromide the *trans* form gave an N-monoethyl derivative which on further treatment gave 2-diethylaminocyclohexanol. With ethyl *p*-toluenesulfonate the diethyl derivative was obtained directly. This substance was identical with the cyclohexene-oxide–diethylamine reaction product, thus establishing the *trans* configuration of the latter compound.

dl-cis-2-Aminocyclohexanol gave only the monoethyl derivative with either ethyl bromide or ethyl *p*-toluenesulfonate. On treatment with phenyl isocyanate the *cis*-monoethyl compound gave N-phenylcarbamyl O-phenylcarbamate, m.p. 205°, and was, therefore, proven as the N-monoethyl derivative. It is suggested that the resistance of the *cis*-N-monoethyl compound to further ethylation may be due to the presence of a hydrogen bond as shown in the formula.

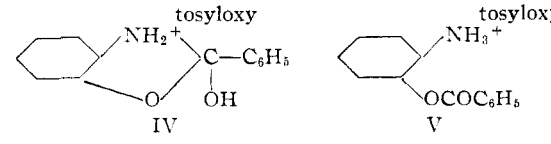


The preparation of *dl-cis*-2-benzoylaminocyclohexanol by the solvolysis of *dl-trans*-2-benzoylaminocyclohexanol tosylate (I) has been described by several authors.[7-10]



Under absolutely anhydrous conditions the *cis*-oxazolinium tosylate (II)[9] is obtained as an intermediate. The *cis*-oxazoline is readily hydrolyzed to the *cis*-benzoylaminocyclohexanol (m.p. 187°) (III) by moist reagents. On treating *trans*-2-benzoylaminocyclohexyl tosylate either with neutral aqueous ethanol or with dry ethanol under pressure a new substance, "Product A" tosylate, was obtained.

"Product A" tosylate (in contrast to the oxazoline) gives only *dl-cis*-2-benzoylaminocyclohexanol on treatment with either moist or dry basic reagents and *dl-cis*-2-aminocyclohexanol in the reaction with hydrochloric acid as expected. Elemental analyses indicated the empirical formula $C_{13}H_{17}O_2N \cdot C_7H_8O_3S$ (oxazoline tosylate, $C_{13}H_{15}ON \cdot C_7H_8O_3S$).[9] It seems probable that "Product A" tosylate is either *dl-cis*-2-hydroxy-2-phenyl-4,5-cyclohexanooxazolidine tosylate (IV) (which has been postulated as an unstable intermediate in the solvolysis of the *cis*-oxazoline)[7-10] or *dl-cis*-2-benzoyloxycyclohexylamine tosylate (V). Accordingly the basic solvolyses may involve O → N migrations of the benzoyl group.



A substance of formula $C_{13}H_{17}O_2N \cdot HCl$ has been previously obtained either by permitting the oxazoline hydrochloride to stand in air[8] or on treating the *dl-cis*-2-benzoylaminocyclohexanol with dry

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(2) Pharmaceutical Institute, University of Kyushu, Katakasu, Fukuoka, Japan.

(3) M. Asano and co-workers, *J. Pharm. Soc. Japan*, **68**, 218 (1948).

(4) "Beilstein," Vol. XIII, p. 348.

(5) Brunel, *Ann. chim.*, [8] **6**, 259 (1905).

(6) A. E. Osterberg and E. C. Kendall, THIS JOURNAL, **43**, 1370 (1921).

(7) G. E. McCasland and co-workers, *ibid.*, **71**, 637 (1949).

(8) W. S. Johnson and E. N. Schubert, *ibid.*, **72**, 2187 (1950).

(9) S. Winstein and R. Boschan, *ibid.*, **72**, 4669 (1950); *ibid.*, **72**, 2311 (1950).

(10) G. E. McCasland and D. A. Smith, *ibid.*, **72**, 2190 (1950).

ethanolic hydrochloric acid.[11] For the structure of this substance *dl-cis*-2-benzoyloxycyclohexylamine hydrochloride was proposed by both of the authors, but its melting point is listed as 212–213° by Johnson and 228° by Fodor and the identification of the structure was neglected. On repeating the two different procedures the same compound of m.p. 218° was obtained. Its picrate melted at 223° and was identical with the picrate of "Product A." Thus it may be more probable that "Product A" tosylate is represented as the tosylate of O-benzoylaminocyclohexanol. Also if this assumed structure is correct, the formation of the oxazolidine intermediate(IV) in the course of the detosylation reaction explains satisfactorily how the acyl group may migrate from nitrogen to oxygen. On treating "Product A" tosylate with excess cold aqueous sodium hydroxide or sodium carbonate, mainly an ether-soluble oily product was obtained, the picrate of which was identical with "Product A" picrate. But after removing the ether the oily product solidified gradually and was finally identified as *dl-cis*-2-benzoylaminocyclohexanol, which was no longer soluble in ether. On the other hand "Product A" tosylate was quite soluble in excess aqueous sodium bicarbonate and began to change to water-insoluble *dl-cis*-2-benzoylaminocyclohexanol after standing half an hour. Thus "Product A" is fairly stable for a short time in cold alkaline solution, but unstable on exposure to air. These results support the oxazolidine structure (IV) but cannot be accepted as conclusive proof.

The synthesis of *dl-trans*-2-benzoylaminocyclohexyl *p*-toluenesulfonate has been improved considerably, giving a yield of 79% as compared with previous reports of 30% and its melting point showed 123° (McCasland,[7] 113–114°).

Experimental[12,13]

***dl-trans*-2-Aminocyclohexanol.**—Prepared by usual methods, b.p. 105° (10 mm.), m.p. 66–68°, its hydrochloride m.p. 173°.

***dl-trans*-2-Benzoylaminocyclohexyl *p*-Toluenesulfonate.**—To 7 g. of *dl-trans*-2-benzoylaminocyclohexanol (m.p. 169°) suspended in 15 ml. of dry pyridine (redistilled) at 0° was added in portions 6.8 g. of *p*-toluenesulfonyl chloride (recrystallized from carbon tetrachloride) and shaken. The resulting clear yellow solution was allowed to stand at room temperature for 24 hours. The solution was chilled to 0°, 15 ml. of 10% hydrochloric acid added and the precipitate was filtered, washed with water and dried. The crude product melted at 121–122° and weighed 10.7 g. Recrystallization[14] from acetone gave 9.5 g. (79.8%) of colorless brilliant needles, m.p. 123°.[15]

Anal. Calcd. for $C_{20}H_{23}O_4NS$: C, 64.34; H, 6.16; N, 3.70. Found: C, 64.15; H, 6.41; N, 3.74.

Formation of "Product A" (*dl-cis*-2-Benzoyloxycyclohexylamine or *dl-cis*-2-Phenyl-2-hydroxy-4,5-cyclohexanooxazolidine). Tosylate (a).—To a solution containing 10 g. of *dl-trans*-2-benzoylaminocyclohexyl *p*-toluenesulfonate in 50 ml. of warm ethanol was added 50 ml. of water, and the solution boiled on a steam-bath for five minutes. After removing ethanol on a boiling water-bath, the solution was chilled, water added and there appeared a crystalline precipitate when scratched. After filtering, washing with water and drying, the yield was 10 g., m.p. 169–171°. Recrystallization from ethyl acetate gave 9.5 g. of colorless needles (90.5%), m.p. 173°. The resulting product is stable to water and nearly insoluble in water.

Anal. Calcd. for $C_{13}H_{17}O_2N \cdot C_7H_8O_3S$: C, 61.38; H, 6.39; N, 3.58. Found: C, 61.11; H, 6.34; N, 3.63.

To generate "Product A" from its tosylate, the latter was added to a mixture of ether and 10% aqueous sodium hydroxide solution, with stirring, in an ice-water-bath. The ether layer was separated, washed well with water and dried over fused sodium sulfate. By adding a saturated ether solution of picric acid to one part of the ether layer, the resulting precipitate was identical with "Product A" picrate. After evaporating ether in vacuum, at room temperature, from the remaining ether layer, the oily residue solidified gradually and finally changed to *dl-cis*-2-benzoylaminocyclohexanol (over-all), which was no longer soluble in ether. The same result was obtained when excess 10% aqueous sodium carbonate solution was used instead of sodium hydroxide. "Product A" tosylate was quite soluble in excess 10% aqueous sodium bicarbonate solution. After the solution was allowed to stand for half an hour, the precipitate began to appear and was identical with *dl-cis*-2-benzoylaminocyclohexanol.

(b).—One gram of *dl-trans*-2-benzoylaminocyclohexyl *p*-toluenesulfonate dissolved in 10 ml. of dry ethanol was heated at 120° in a sealed tube for two hours. After evaporating the ethanol under reduced pressure, there remained nearly colorless solid of m.p. 167°. After recrystallizing from ethyl acetate, it melted at 173°, and showed no depression, when admixed with a sample obtained by the method (a).

Hydrochloride.—By an adaption of Johnson's[8] and Fodor's[11] methods so-called *dl-cis*-2-benzoyloxycyclohexylamine hydrochloride was obtained. The products resulting by the both methods were recrystallized from dry chloroform–dry ether or dry ethanol–dry ether and melted at 218° (212–213° by Johnson and 228° by Fodor) and were proven as the same substance by a mixed m.p. determination.

Picrate (a).—The tosylate dissolved in water with a small amount of ethanol was converted to the picrate by addition of a saturated aqueous solution of sodium picrate. Recrystallization from ethanol gave yellow needles which then changed slowly to orange yellow plates; m.p. 223–224° (dec.).

Anal. Calcd. for $C_{13}H_{17}O_2N \cdot C_6H_3O_7N_3$: C, 50.89; H, 4.46; N, 12.50. Found: C, 51.18; H, 4.31; N, 12.55.

(b).—To a water solution of the hydrochloride was added a saturated aqueous solution of sodium picrate to yield material, m.p. 223° (dec.), mixed m.p. with the picrate from the tosylate, 223–224° (dec.).

Reactions of "Product A." Reaction with Sodium Acetate–Dry Ethanol to give *dl-cis*-2-Benzoylaminocyclohexanol.—A mixture of 9.5 g. of fused sodium acetate, 200 ml. of dry ethanol and 10 g. of "Product A" *p*-toluenesulfonate was refluxed for 49 hours. After cooling the resulting precipitate was separated by filtration. The filtrate was evaporated to dryness, 50 ml. of water added and the precipitate filtered, washed with 100 ml. of water and dried; m.p. 178–180°, weight 4.7 g. Recrystallization from ethyl acetate gave 4.4 g. (74.9%) of *dl-cis*-2-benzoylaminocyclohexanol, m.p. 184°.

Reaction with Sodium Carbonate to Give *dl-cis*-2-Benzoylaminocyclohexanol.—Ten grams of "Product A" *p*-toluenesulfonate in 100 ml. of 10% sodium carbonate was heated in a boiling water-bath for ten minutes and allowed to stand at room temperature until crystals had ceased to precipitate. After filtering, washing with water and drying, the crystalline precipitate weighed 5.1 g. (92.8%) and melted at 183–184°, which did not need recrystallization.

Reaction with Hydrochloric Acid to Give *dl-cis*-2-Aminocyclohexanol.—One gram of "Product A" *p*-toluenesulfonate in 15 ml. of 10% hydrochloric acid was refluxed for two hours and after cooling the precipitate (benzoic acid) separated by filtration. The filtrate was concentrated to dryness, a small amount of water added and while cooling in an ice-bath, made alkaline with gradual addition of concd. aqueous sodium hydroxide. The resulting oil layer was extracted with ether, dried over fused sodium sulfate and evaporated to dryness. The residue was dissolved again in dry ether, saturated with dry hydrochloric acid and the

(11) G. Fodor and J. Kiss, THIS JOURNAL, **72**, 3495 (1950).

(12) All melting points were uncorrected.

(13) We are indebted to Misses Yamamoto, Ota and Kondo, and Messrs. Ohata, Kurihara, Nagase, Kajima and Tani for the microanalyses.

(14) The use of aqueous ethanol for recrystallization lowered the yield by detosylation.

(15) Reported as 113–114° by McCasland (footnote (7)).

resulting precipitate recrystallized from ethyl acetate–ethanol, giving 0.23 g. of the hydrochloride (60.5%), m.p. 184°.

Reaction with Dry Acetic Acid–Sodium Acetate to Give *dl-cis*-2-Aminocyclohexanol.—The resulting solution by refluxing 5 g. of glacial acetic acid, 1 g. of acetic anhydride and 1 g. of fused sodium acetate was added to 2 g. of "Product A" *p*-toluenesulfonate and the mixture refluxed for four hours with exclusion of moisture. After cooling, the reaction mixture was poured into water, causing the separation of an oily product which could not successfully be crystallized. After extracting with ether, washing with water, 5% sodium carbonate solution and water and evaporating to dryness, the oily residue was added to 20 ml. of 10% hydrochloric acid and refluxed for two hours. After cooling, separated benzoic acid was filtered off and the filtrate was evaporated to dryness on a steam-bath. The solid residue so obtained weighed 0.7 g. (90.9%) and was recrystallized from ethyl acetate–ethanol, giving 0.55 g. (71.4%) of colorless crystals, m.p. 184–185°. A mixed m.p. with *dl-cis*-2-aminocyclohexanol hydrochloride showed no depression.

Reaction with Acetic Anhydride to Give *dl-cis*-2-Aminocyclohexanol.—A mixture of 2 g. of "Product A" *p*-toluenesulfonate and 4 g. of acetic anhydride was refluxed. After cooling, and pouring of the reaction mixture into water the resulting oily product was extracted with ether and treated as previously described with dry AcOH–AcONa, giving 0.5 g. (65%) of *dl-cis*-2-aminocyclohexanol hydrochloride.

N-Ethylation of the 2-Aminocyclohexanols. ***dl-trans*-2-Ethylaminocyclohexanol.**—A mixture of 7.0 g. (1.3 mols) of ethyl bromide, 2.1 g. (1 mol) of sodium carbonate, 50 ml. of ethanol and 6 g. (1 mol) of *dl-trans*-2-aminocyclohexanol was refluxed on a steam-bath and after cooling the insoluble solid separated. The filtrate was concentrated to dryness, a small amount of water added and made alkaline with concd. sodium hydroxide. The resulting oil layer was extracted with ether, dried over fused sodium sulfate and distilled under reduced pressure; b.p. 104–105° (12 mm.) weight 5.5 g. (73%). Its hydrochloride melted at 155°, which was identified with a sample obtained from ethylamine and cyclohexene oxide.[5]

Anal. Calcd. for $C_8H_{17}ON\cdot HCl$: N, 7.82. Found: N, 7.62.

***dl-trans*-2-Diethylaminocyclohexanol (a).**—A mixture of 5 g. of ethyl bromide, 4 g. of potassium carbonate, 50 ml. of ethanol and 5 g. of *dl-trans*-2-ethylaminocyclohexanol was refluxed on a steam-bath for five hours and after cooling the precipitate filtered off. The filtrate was made alkaline with concd. sodium hydroxide and the resulting oil layer was extracted with ether, dried over fused sodium sulfate, evaporated to dryness and distilled under reduced pressure; the yield was 4 g. (67%), b.p. 111° (15 mm.), hydrochloride m.p. 173°. A mixed melting point with the diethyl compound obtained from cyclohexene oxide and diethylamine did not depress.

(b).—To one gram (1 mol) of *dl-trans*-2-aminocyclohexanol dissolved in warm dried nitrobenzene was added 4.2 g. (2 mols) of ethyl *p*-toluenesulfonate and the mixture heated at boiling point in an oil-bath for ten minutes. After cooling, excess of hydrochloric acid was added and the nitrobenzene removed by steam distillation. After filtering, the mother solution was made alkaline with sodium carbonate. The resulting oil layer was extracted with ether, dried over fused sodium sulfate, evaporated to dryness and distilled under reduced pressure, giving *dl-trans*-2-diethylaminocyclohexanol in lower yield.

***dl-cis*-2-Ethylaminocyclohexanol**[16] **(a).**—*dl-cis*-2-Aminocyclohexanol was treated analogously with the *trans* isomer, giving *dl-cis*-2-ethylaminocyclohexanol; yield 42%, b.p. 111–112° (18 mm.), m.p. 63–65°; melting points of the hydrochloride and picrate were 189° and 169°, respectively.

Anal. Calcd. for $C_8H_{17}ON\cdot C_6H_3O_7N_3$: C, 45.20; H, 5.37; N, 15.05. Found: C, 44.99; H, 5.76; N, 14.98.

dl-cis-2-(Phenylcarbamyl)-ethylaminocyclohexyl phenylcarbamate was prepared from phenyl isocyanate and *dl-cis*-2-ethylaminocyclohexanol. Recrystallization from ethanol gave colorless needles, m.p. 205°.

Anal. Calcd. for $C_{28}H_{27}N_3O_3$: C, 69.29; H, 7.09; N, 11.02. Found: C, 69.34; H, 6.97; N, 11.32.

(b).—To 1 g. (1 mol) of the *dl-cis*-2-aminocyclohexanol dissolved in 10 ml. of warm dried nitrobenzene, was added 4 g. (2 mols) of ethyl *p*-toluenesulfonate and the mixture was heated at 230° in an oil-bath for three minutes. The crystalline precipitate was collected, washed with ether, water added and the aqueous solution made alkaline with concd. sodium hydroxide on cooling in ice. The resulting oil layer was extracted with ether, dried over fused sodium sulfate, evaporated to dryness and distilled under reduced pressure, giving 0.9 g. (78.3%) of *dl-cis*-2-ethylaminocyclohexanol.

(16) This product could not be converted to the diethyl compound by ethyl bromide and potassium carbonate.

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[CONTRIBUTION FROM THE RESEARCH DIVISION, SMITH, KLINE AND FRENCH LABORATORIES]

Adrenergic Blocking Agents. IV. β-Haloethylammonium Compounds[1]

BY JAMES F. KERWIN, GRISELLA C. HALL, EDWARD MACKO, RICHARD A. MCLEAN, EDWIN J. FELLOWS AND GLENN E. ULLYOT

The reported adrenergic blocking action of several β-haloethylammonium compounds is difficult to account for on the basis of a probable accepted mode of production of adrenergic blockade. This apparent discrepancy is explained by the presence of tertiary β-haloethylamines in the "quaternary" compounds tested by other investigators. A series of nine β-haloethylammonium salts were prepared; all failed to reverse the pressor effect of epinephrine. The inactivity of these compounds as compared with tertiary β-haloethylamines can be correlated with the chemical reactivities of the two types.

In considering structure activity relationships of drugs which block a normal function of the autonomic nervous system, attention is usually focused on the geometry of the molecule. The presence of certain appropriately situated atoms or groups provides a means for a loose attachment to cellular surfaces through operation of electrostatic or van der Waals forces. It is assumed that the continued adherence of the blocking drug prevents the approach of stimulant molecules.[2]

In contrast to this passive mode of action, the β-haloethylamines may block the excitatory effects of epinephrine by entering into a definite chemical reaction.[3] In adrenergic blockade there is an initial phase during which the drug competitively inhibits epinephrine.[3,4] This competitive antagonism may well be dependent solely upon the stereochemistry and physical properties of the molecule. However, the prolonged, non-competitive blockage which follows the initial effect is thought to be caused by alkylation of some tissue constituent of sympathetic receptors. Furthermore, there is considerable

(1) Presented before the Division of Medicinal Chemistry at the 118th Meeting of the American Chemical Society in Chicago, Illinois, September, 1950. A preliminary communication describing this work appeared in *Science*, **113**, 315 (1951).

(2) (a) A. J. Clark, "Mode of Action of Drugs on Cells," Arnold, London, 1933; (b) C. C. Pfeiffer, *Science*, **107**, 94 (1948).

(3) M. Nickerson, *J. Pharmacol. Exptl. Therap.*, Part II, **95**, 27 (1949).

(4) G. Chen and D. Russell, *ibid.*, **99**, 401 (1950).