lit. 139–140°; H. von Pechmann, *Ber.*, 21, 1415 (1888); Lehr and Bloch, *Helv. Chim. Acta*, **28**, 1413 (1945).

Diacetyldi-(*m*-nitroanil), $[m\text{-}O_2NC_6H_4N{=}(CH_3)C{-}]_2$.—By procedure B: Procedure A not successful: m.p. obs. 112–113°. *Anal.* Calcd. for $C_{16}H_{14}O_4N_4$: N, 17.2. Found: N, 17.2.

Diacetyldi-(*p*-bromanil), $[p\text{-}BrC_6H_4N{=}(CH_3)C{-}]_2$.—By procedure A: m.p. 181.5–182.5°; lit. 182–183°, Lehr and Bloch, *Helv. Chim. Acta*, **28**, 1413 (1945).

Glyoxaldianil, $[C_6H_5N{=}CH{-}]_2$.—Procedure A gave resins from which crystalline products could not be obtained. Procedures B, C, and D gave non-recrystallizable amorphous powders with m.p.'s 80–81°, 105–110° and 125–126°, respectively. Its synthesis was abandoned.

Glyoxaldi-(*p*-bromanil), $[p\text{-}BrC_6H_4N{=}CH{-}]_2$.—By procedures A or D: m.p. obs. 181–181.5°; *Anal.* Calcd. for $C_{14}H_{12}N_2Br_2$: C, 45.7; H, 3.26. Found: C, 44.3; H, 2.97.

Glyoxaldi-(*p*-methoxyanil), $[p\text{-}CH_3OC_6H_4N{=}CH{-}]_2$.—By procedures A and B: m.p. obs. 155°; lit. 158°, Lehr and Bloch, *Helv. Chim. Acta*, **28**, 1413 (1945).

Glyoxaldi-(*p*-hydroxyanil), $[p\text{-}HOC_6H_4N{=}CH{-}]_2$.—By procedure A: m.p. obs. 190–191°. *Anal.* Calcd. for $C_{14}H_{12}O_2N_2$: C, 70.0; H, 5.0. Found: C, 70.2; H, 6.0.

Glyoxaldi-(*m*-nitroanil), $[m\text{-}O_2NC_6H_4N{=}CH]_2$.—By procedure D: m.p. obs. 202–203°. *Anal.* Calcd. for $C_{14}H_{10}N_4O_4$: C, 56.4; H, 3.46. Found: C, 55.86; H, 3.74.

1,4-Di-(*p*-methoxyphenyl-butadiene-1,3, $[p\text{-}CH_3OC_6H_4{-}CH{=}CH{-}]_2$.—Prepared according to some unpublished work by Fieser and Potter. Mixed one half mole of freshly distilled anisaldehyde, one-fourth mole of succinic acid, and one-half mole of litharge in 150 cc. of acetic anhydride, and heated on a hot-plate under a reflux condenser for five hours. Then was added 200 cc. of 80% HOAc, the soln. cooled overnight, and the crystals filtered and recrystallized from *n*-propanol; colorless crystals, m.p. 222.5–223.5°.

4,4-Dibromobenzaldazin, $[p\text{-}BrC_6H_4CH{=}N{-}]_2$.—By procedure A: m.p. obs. 223.5°–224.5°, lit. 221; L. Gattermann, *Ann.*, **393**, 223(1912).

4,4-Dimethoxybenzaldazin, $[p\text{-}CH_3OC_6H_4CH{=}N{-}]_2$.—By procedure A: m.p. obs. 167–168°; lit. 168°; G. Knöpfer, *loc. cit.*

Di(acetophenonal)-ethylenediamine, $[C_6H_5(CH_3)C{=}N\text{-}CH_2{-}]_2$.—By procedure A: (drop HOAc added); white crystals from ligroin, m.p. 110–111°; *Anal.* Calcd. for $C_{18}H_{20}N_2$: N, 10.6. Found: N, 10.3.

Acknowledgment.—The authors are indebted to Mr. Theodore Austin, instructor of chemistry in Howard University, for drawing the spectra.

Summary

The order of chromophoric power for the systems dianil, diene, and azine is discussed and illustrated to be decreasing in the order named. A bathochromic effect by substituting methyl groups upon the methine carbon atoms of the dianil system is noted.

HOWARD UNIVERSITY
WASHINGTON 1, D. C.

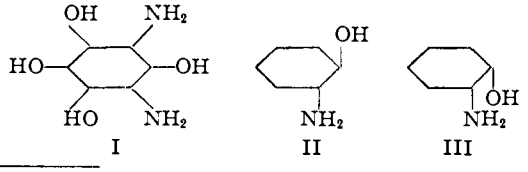
RECEIVED MAY 11, 1948

[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Stereochemistry of Cyclic Amino-alcohols. Inversion, Retention and Participation[1]

BY G. E. MCCASLAND,[2] R. K. CLARK, JR.,[3] AND HERBERT E. CARTER

The isolation of streptamine (I),[4] one of the three major degradation products of streptomycin, has stimulated interest in the stereochemistry of polysubstituted alicyclic compounds, and of cyclic aminoalcohols in particular. Streptamine is one of the twenty possible diastereoisomeric forms of 1,3-diamino-2,4,5,6-tetrahydroxycyclohexane. Of these forms, eight are *meso* and twelve racemic, and the recent synthesis[5] of streptamine from glucosamine indicates that "natural" streptamine is the all-*trans*, *meso* form. In support of stereochemical studies on streptamine, model compounds of simpler structure were investigated.



I II III

(1) The authors wish to thank the Abbott Laboratories; Eli Lilly and Company; Parke, Davis and Company; and The Upjohn Company for a generous grant in support of this work.

(2) Present address: Chemistry Department, University of Toronto.

(3) Present address: Abbott Laboratories, North Chicago.

(4) H. E. Carter, *et al.*, *Science*, **103**, 53 (1946).

(5) Wolfrom and Olin, Abstracts, Chicago Meeting, A.C.S., April, 1948, p. 5Q.

For this purpose the 2-aminocyclohexanols were selected.

Both the *cis* and *trans* forms of 2-aminocyclohexanol lack a plane of symmetry and hence are theoretically resolvable. Thus the configurations cannot be established by resolution of the *trans* isomer, as with the diol or diamine. Experimentally, two racemic forms of 2-aminocyclohexanol are known. The first, isomer "A," melts at 68°; the second, isomer "B," melts at 72°. The melting points of a number of derivatives of "A" and "B" are given in Table I.

Isomer "A" was first prepared in 1905 by Brunel[6a] by the amination of cyclohexene oxide, and also can be obtained by the amination of cyclohexene halohydrin,[6b] or by the reduction of 2-hydroxycyclohexanone oxime.[6c] The preparation of the "B" isomer was first described in a 1936 patent,[7] and few details regarding it have been published. An alternate preparation of the "B" isomer (N-benzoyl), by the tosylation and detosylation of the "A" N-benzoyl derivative, is described below.

(6) (a) Brunel, *Ann. chim.*, [8] **6**, 253 (1905); (b) Osterberg and Kendall, THIS JOURNAL, **42**, 2616 (1920); (c) Wilson and Read, *J. Chem. Soc.*, 1269 (1935).

(7) *Chem. Abs.*, **32**, 7055 (1938); *Chem. Zentr.*, **108**, I, 2260 (1937).

TABLE I

MELTING POINTS OF *trans* AND *cis* *d,l*-2-AMINOCYCLOHEXANOL DERIVATIVES

Derivative	"A" (*trans*?)	"B" (*cis*?)
Free aminoalcohol	68	72
Hydrochloride	175	185
N-Acetyl	127	147
O,N-Diacetyl	126	...
N-Benzoyl	169	193[a]
O,N-Dibenzoyl	215	153[a]
N-Benzoyl-O-acetyl	144	193[a]
O-Benzoyl-N-acetyl	199	...
N-Benzoyl-O-*p*-toluenesulfonyl	114[a]	165[a]
α-Naphthylthiourea	172[a,b]	150[a,b]
N-Benzylidene	90–92[a,b]	...

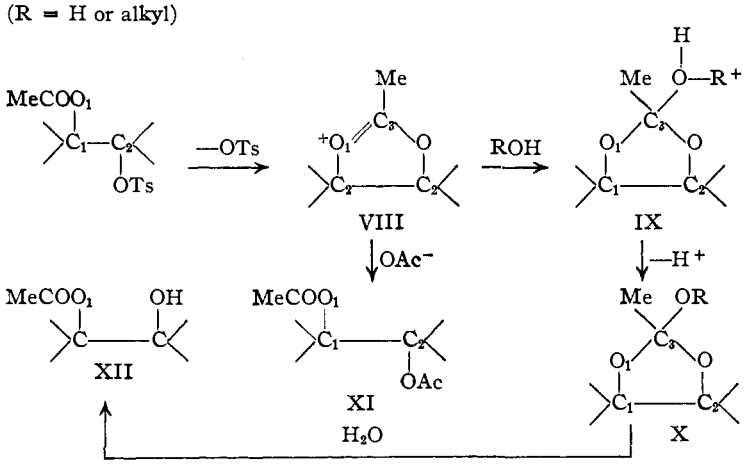
[a] Not previously reported. [b] To be described in a subsequent publication.

Isomer "A" is listed as "*cis*" in Beilstein,[8] on the basis of Brunel's designation. Certain later authors[9] favored the *trans* configuration for "A." It is now known that the oxide ring normally is opened in the *trans* manner. For this reason, and on the basis of the results described below, the "A" isomer will be designated as *trans*.

CHART I

MECHANISM OF DETOSYLATIONS

(R = H or alkyl)



For benzamidotosylate, replace —O_1— by —NH— and Me by phenyl

Although direct physical methods, such as X-ray diffraction and dipole moment, may be the most powerful approach to such questions of molecular geometry, their application at present involves well-known difficulties, which need not be considered here. An alternate approach involves a study of the inversions or retentions at each step in the formation or reactions of the aminocyclohexanols. A functional group on a neighboring carbon atom can alter the normal steric result of a displacement on carbon from inversion to retention, or *vice versa*, and the extensive recent development[10] of theories to explain this "participation" furnishes an indispensable guide to such steric studies.

The formation of *trans*-2-aminocyclohexanol by amination of either cyclohexene oxide or the *trans* halohydrin in aqueous or alcoholic ammonia is to be expected on the basis of present knowledge concerning the formation and opening of oxide rings. Supporting evidence on this point was afforded by the reaction of cyclohexene oxide with potassium amide in anhydrous liquid ammonia. In this case the high concentration of the powerfully nucleophilic amide ion should make a *trans* ring-opening more certain. From this reaction only the "A" isomer (*trans*) was obtained; the yield, however, was small.[11]

Tosylation and Detosylation

In 1942 Winstein, Hess and Buckles[12] conducted a series of experiments on the detosylation of *d,l-trans*-2-acetoxycyclohexyl-*p*-toluenesulfonate. The results obtained by these authors, and the mechanism proposed by them are shown in Chart I. Departure of tosylate ion yields the charged cyclic intermediate VIII, with inversion. In *dry* acetic acid–sodium acetate, the acetate ion attacks carbon atom C_2, with inversion, giving *trans*-diacetate XI (over-all *retention*). In *wet* acetic acid–sodium acetate, or in dry ethanol, the water or ethanol reacts more rapidly than acetate ion, to give the conjugate acid IX of the ortho ester X, which opens with retention to give the *cis*-acetoxyalcohol XII (over-all *inversion*).

It seemed probable to us that a *trans* acylamino group would participate in such detosylation reactions in the same manner as an acyloxy group. A comparison of the stereochemical behavior of the acylamino and acyloxy compounds might then provide evidence testing the validity of the *trans* assignment of configuration to "A" 2-aminocyclohexanol.

Accordingly, we prepared the N-benzoyl-O-*p*-toluenesulfonyl derivative of the "A" form of *d,l*-2-aminocyclohexanol, and solvolyzed it under Winstein's three conditions: (1) sodium acetate in dry acetic acid, (2) sodium acetate in acetic acid with a small amount of added water, (3) sodium acetate in absolute ethanol.

The results were completely analogous with those obtained by Winstein, *et al.*, for their *trans*-acyloxytosylate. In dry acetic acid the product we obtained was the "A" benzamidoacetate with

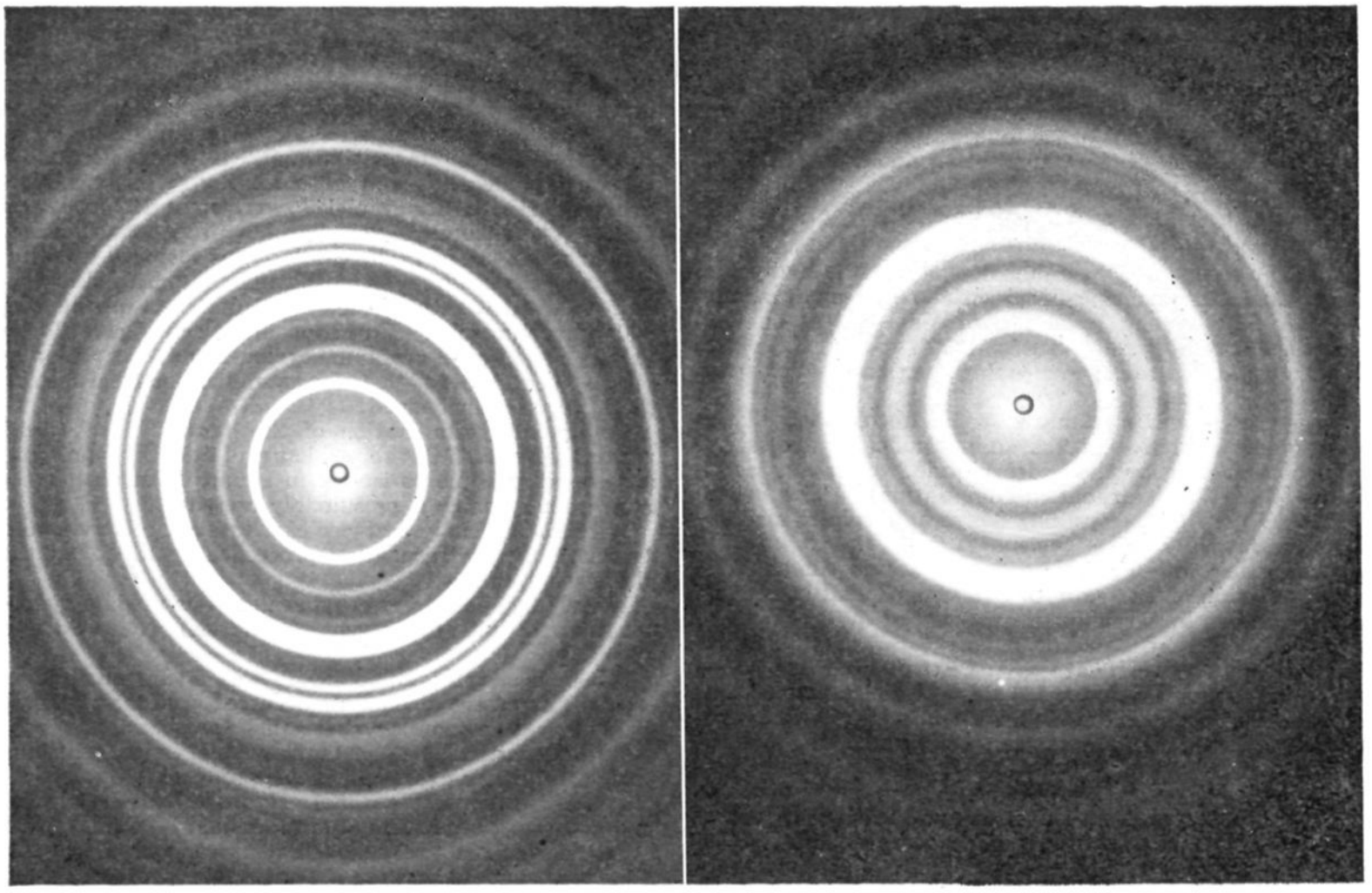
(8) Beilstein, 4th edition, Vol. XIII, p. 348.

(9) (a) Godchot and Mousseron, *Compt. rend.*, **194**, 981 (1932); (b) **198**, 2000 (1934); (c) Birckenbach, *et al.*, *Ber.*, **64**, 961, 1076 (1931); **66**, 1571 (1933).

(10) Winstein and co-workers, THIS JOURNAL, **70**, 812–846 (1948), and previous publications.

(11) The low yield with amide ion in ammonia recalls the well-known inertness of the oxide ring to hydroxide in water.

(12) Winstein, *et al.*, THIS JOURNAL, **64**, 2796 (1942); **70**, 812 (1948); *cf.* Criegee and Stanger, *Ber.*, **69B**, 2753 (1926).



cis, m. p. 147°. *trans*, m. p. 127°.

Fig. 1.—X-Ray powder spectra of *d,l*-2-acetaminocyclohexanols.

retention. In wet acetic acid, or in (dry) ethanol, the product was the "B" benzamidoalcohol with inversion.

The mechanism as modified by us for the benzamido compound is also given by Chart I if Me is replaced by phenyl and —O_1— by —NH—. Intermediate (X) in the acyloxy detosylation would be an ortho-ester; in the acylamino detosylation it would be a 2-hydroxy-2-phenyloxazolidine. While we have no direct evidence on the formation of the postulated intermediates, the striking parallelism between the results on acylamino- and acyloxytosylates strongly suggests a common mechanism. And it indicates that the "A" amino-alcohol, like the diol, has the *trans* configuration.[13]

Chlorination and Dechlorination

The treatment of a secondary alcohol with phosphorus pentachloride commonly gives the alkyl chloride with inversion. In the case of *trans*-2-aminocyclohexanol hydrochloride the normal displacement of hydroxyl by chlorine might be expected to result, since participation by the neighboring positively charge ammonium ion seems improbable.

Experimentally the reaction of *trans*-2-aminocyclohexanol hydrochloride with phosphorus pentachloride gives a high yield of a 2-chlorocyclohexylamine hydrochloride which there is good reason to regard as *cis*. Attempts to dechlorinate this compound with silver oxide were unsuccessful; only starting material could be isolated (as the N-benzoyl derivative) from the reaction mixture. The chloride and its N-benzoyl derivative failed to react appreciably even when boiled for twenty-one hours with an acetic acid solution of silver acetate.

These results are quite in accord with the findings of Winstein and co-workers[13] who reported that *cis* isomers of 2-substituted cyclohexyl chlorides show a remarkable inertness. Likewise, Leffler and Adams[14] reported that *cis*-2-*p*-nitrobenzoylaminocyclohexyl chloride was highly inert (to alkali).

X-Ray Powder Spectra.—The X-ray spectra were observed on powdered samples of *trans* and *cis*-*d,l*-2-acetaminocyclohexanol. The results are shown in Fig. 1 and are presented merely for purposes of identification.

Experimental[15,16]

Preparation of *trans*-2-Aminocyclohexanol Derivatives *d,l-trans*-2-Aminocyclohexanol.—(a) The amination pro-

(13) *dl-cis*-2-Acetoxycyclohexyltosylate reacts with dry acetic acid–acetate with inversion (Winstein, *et al.*, THIS JOURNAL, **70**, 816 (1948).

(14) Leffler and Adams, *ibid.*, **59**, 2256 (1937).

(15) Microanalyses by Clark Microanalytical Laboratory, Urbana unless otherwise credited. Semi-micro Kjeldahl analyses by Dr. Robert S. Pogrund.

(16) All melting and boiling points are corrected.

cedure of Wilson and Read[6c] was found most convenient. Redistilled, colorless *d,l-trans*-2-chlorocyclohexanol (du Pont), b.p. 92–97° (33 mm.) was used. The product, colorless stout needles, m.p. 68°, b.p. 102–107° (9 mm.), darkens on prolonged standing in air, and is best stored *in vacuo*, or in the form of its hydrochloride. Solubility of the free aminoalcohol in benzene is about 8 g./100 ml. solvent.

Anal. Calcd. for $C_6H_{13}NO$ (115.17): N, 12.17. Found: N, 12.22.

(b) To regenerate the aminoalcohol from its hydrochloride, the latter was neutralized with an equivalent amount of 0.3 *N* ethanolic sodium hydroxide. After one-half hour at 0°, sodium chloride was filtered off, and the filtrate vacuum distilled to dryness, giving colorless needles, m. p. 68–69°.

d,l-trans-2-**Aminocyclohexanol Hydrochloride.**—Evaporation of a solution of the aminoalcohol in excess hydrochloric acid gave the hydrochloride,[6a] colorless prisms, m. p. 176–177° (without decomposition). The hydrochloride can be recrystallized from absolute alcohol–benzene (1:2).

Amination with Potassium Amide–Liquid Ammonia.—To a solution of one gram of potassium metal in 100 ml. of anhydrous liquid ammonia was added 5.0 g. of cyclohexene oxide,[17] and an iron nail as catalyst. This mixture was kept overnight at −33°. Ethanol was then added to destroy potassium amide, most of the ammonia was boiled off and the residual solution neutralized with hydrochloric acid. Inorganic matter was filtered off, and the filtrate vacuum distilled to dryness. The residue was again taken up in a little ethanol, filtered and distilled. Finally, the residue was taken up in aqueous 6 *N* hydrochloric acid, and the solution distilled to dryness, giving 0.14 g. of colorless crystals, m.p. 176–178°. A mixed m. p. with the *trans* hydrochloride was not depressed.

Anal. Calcd. for $C_6H_{14}NOCl$ (151.64): N, 9.24. Found: N, 9.30 (Kjeldahl).

Liquid ammonia alone failed to react with the oxide.

d,l-trans-2-**Acetaminocyclohexyl Acetate.**—The procedure of Raiford and Mortensen[18] was used. Recrystallization of the product from benzene–ligroin (1:1) yielded long, colorless needles, m. p. 117–119°.

Anal. Calcd. for $C_{10}H_{17}NO_3$ (199.25): N, 7.03. Found: N, 7.05 (Kjeldahl).

d,l-trans-2-**Acetaminocyclohexanol.**—This compound[18] is best prepared by hydrolysis of the diacetyl derivative. Titrations of samples from the reaction mixture with standard acid showed that the hydrolysis in 1 *N* sodium hydroxide at 25° is complete in thirty minutes or less. Recrystallization of the product from benzene gives short colorless needles, m. p. 126–127°.

Anal. Calcd. for $C_8H_{15}NO_2$ (157.21): N, 8.91. Found: N, 8.78 (Kjeldahl).

d,l-trans-2-**Benzoylaminocyclohexanol.**—The general method of Leffler and Adams[14] gave a 95% yield of crude product, colorless needles, m. p. 175–176°, which did not need recrystallization.

d,l-trans-2-**Benzoylaminocyclohexyl Benzoate.**—The procedure of Raiford[18] and Mortensen was used. The product melted at 215–216°.

Anal. Calcd. for $C_{20}H_{21}O_3N$ (323.38). N, 4.33; sapon. equiv., 323.4. Found: N, 4.69; sapon. equiv. 313.

Preparation of *cis*-2-Aminocyclohexanol Derivatives

2-Acetaminophenol.—The method of Lumière and Barbier[19] was used. The alkaline solution of 2-aminophenol should be filtered (Super-Cel) to remove insoluble impurities. Recrystallization of the product from ethanol (Norit) gives colorless leaflets, m. p. 206–207°.

2-Acetaminophenyl Acetate.—The method of Meldola, *et al.*,[20] was found more satisfactory than others. The product was recrystallized from water, giving colorless needles, m. p. 74–77°. Further recrystallizations from either water or benzene–ligroin gave a maximum m. p. of 75–77°, which is that reported for the sesquihydrate.[20]

d,l-cis-2-**Acetaminocyclohexanol.**—A 22-g. portion of 2-acetaminophenol in 150 ml. of absolute ethanol was hydrogenated with Raney nickel catalyst at 100 atm. and 180°. The theoretical uptake of hydrogen was reached in four to six hours. The catalyst was removed by filtration, and the colorless or red filtrate concentrated in vacuum to a thick sirup, which crystallized on mixing with 100 ml. of acetone. Filtration and drying gave 2.5 g. (11%) of *d,l-cis*-2-acetaminocyclohexanol,[7] as colorless prisms, m. p. 146–147°. On recrystallization from acetone the m. p. was unchanged.

Fractional crystallization of the mother liquor, using various solvents, failed to yield any additional *cis* product, nor was it possible to isolate in a pure form any of the *trans* isomer, which is presumably present.

With the specially active nickel catalyst of Pavlic and Adkins,[21] the hydrogenation proceeded at 150°, but the yield was even lower.

When (dry, acid-free) ethyl acetate was used as hydrogenation solvent (to prevent alcoholysis), the yield was only 5%.

When diacetyl-2-aminophenol was hydrogenated, in ethanol, extensive alcoholysis occurred, and a very small yield of *cis*-2-acetaminocyclohexanol was obtained.

Hydrogenation of 2-acetaminophenol with platinum oxide catalyst gave an unpurifiable product.

d,l-cis-2-**Aminocyclohexanol Hydrochloride.**—A solution of 1.0 g. of the acetamino compound in excess of 6 *N* hydrochloric acid was refluxed for two hours, and distilled in vacuum to dryness. The residue was washed with a little acetone, giving 0.9 g. (94%) of colorless crystals,[7] m. p. 189–190°, with decomposition.

Attempted Preparation of *d,l-cis*-2-Acetaminocyclohexyl Acetate.—Application of the method used for the *trans* compound, and of other methods, failed to yield any crystalline product, possibly due to oxazoline formation.

d,l-cis-2-**Aminocyclohexanol.**—Treatment of the *cis* hydrochloride by the same procedure described for the *trans* isomer gives the free aminoalcohol,[7] colorless crystals, m. p. 72–73°.

d,l-cis-2-**Benzoylaminocyclohexanol.**—(a) Treatment of the aminoalcohol hydrochloride by the general procedure of Leffler and Adams[14] gave an 86% yield of crude product, colorless leaflets melting sharply at 189–190°, which did not need recrystallization. (b) This compound can be obtained by detosylation of the *trans* tosylate (see below).

d,l-cis-2-**Benzoylaminocyclohexyl Benzoate.**—Treatment of 150 mg. of the aminoalcohol hydrochloride by the Schotten–Baumann procedure, followed by benzoylation in hot pyridine, gave a product which crystallized from ethanol as colorless crystals, m. p. 152–154°.

Anal. Calcd. for $C_{20}H_{21}NO_3$ (323.38): N, 4.33; sapon. equiv. (O-benzoyl), 323.4. Found: N, 4.42 (Kjeldahl); sapon. equiv., 342.

Inversion and Retention in Detosylation Reactions

Preparation of *d,l-trans*-2-Benzoylaminocyclohexyl-*p*-toluenesulfonate.—To the benzamidoalcohol (4.4 g.) suspended in 10 ml. dry pyridine at 0° was added 4.3 g. of *p*-toluenesylfonyl chloride, and the clear yellow solution allowed to stand at 25° for twenty-four hours. The mixture was chilled to 0° and 10 ml. of 6 *N* hydrochloric acid and 20 ml. of water (both ice-cold) were successively added. The precipitate was filtered off, washed repeatedly with water and dried. The crude product (3.5 g.) was recrystallized from 15 ml. of 60–70% ethanol, giving 1.3 g. (18%) of colorless needles, m. p. 111–112°. A sample recrystallized again, for analysis, melted at 113–114°.

(17) "Organic Syntheses," Coll. Vol. I, 2nd ed., p. 185.

(18) Raiford and Mortensen, This Journal, **50**, 1201 (1928). (The m. p. of *d,l-trans*-2-acetaminocyclohexanol was incorrectly reported as 315° instead of 127°.)

(19) Lumière and Barbier, *Bull. soc. chim.*, [3] **33**, 784 (1905).

(20) Meldola, *et al.*, *J. Chem. Soc.*, **69**, 1323 (1896).

(21) Pavlic and Adkins, This Journal, **68**, 1471 (1946).

Anal. Calcd. for $C_{20}H_{23}O_4NS$ (373.45): C, 64.32; H, 6.21; N, 3.75. Found: C, 64.23; H, 5.91; N, 3.75.

The use of ethanol probably lowers the yield by detosylation, but no other satisfactory method of purification has been found.

Inversion of Configuration with Wet Acetic Acid–Sodium Acetate: Formation of *d,l-cis*-2-Benzoylaminocyclohexanol.—A mixture of 0.95 ml. of acetic acid (m. p. 16°), 0.05 ml. of water, 0.1 g. of fused sodium acetate, and 300 mg. of the *trans*-benzamidotosylate was refluxed four hours. After cooling, 10 ml. of water was added, and solid sodium carbonate added gradually until *p*H 8. The mixture was extracted with two 20-ml. portions of ether. The dried ether extract on evaporation gave an oily solid residue, which was washed with benzene–ligroin, yielding 25 mg. of colorless crystals, m. p. 179–182°. From the benzene–ligroin filtrate was obtained 15 mg. more material, of m. p. 186–188°; total yield[22] 40 mg. (22%). The product was recrystallized for analysis from benzene–ligroin, giving colorless plates, m. p. 192–193°.

Anal. Calcd. for $C_{12}H_{17}O_2N$ (219.28): N, 6.39. Found: N, 6.44.

Retention of Configuration with Dry Acetic Acid–Sodium Acetate: Formation of *d,l-trans*-2-Benzoylaminocyclohexyl Acetate.—An anhydrous acetic acid solution was prepared by refluxing 9.5 ml. of glacial acetic acid (m. p. 16°) with 0.53 ml. of acetic anhydride and 1.0 g. of fused sodium acetate. A 1.0-ml. aliquot of the resulting solution was added to 300 mg. of the *trans*-benzamidotosylate, and the mixture refluxed for four hours, with exclusion of moisture. After cooling, the reaction mixture was diluted with 4 ml. of water, causing the separation of 170 mg. (dry weight) of precipitate, m. p. 115–130°. The material was recrystallized from 50% ethanol, giving 80 mg. (38%)[22] of *trans*-2-benzoylaminocyclohexyl acetate,[18] colorless plates, m. p. 135–139°. A final recrystallization raised the m. p. to 143–144°.

Inversion of Configuration with (Dry) Ethanol–Sodium Acetate: Formation of *d,l-cis*-2-Benzoylaminocyclohexanol.—A mixture of 300 mg. of *trans*-benzamidotosylate, 280 mg. of fused sodium acetate, and 4.3 ml. of absolute ethanol was refluxed for forty-nine hours. After a few hours, crystals (sodium *p*-toluenesulfonate?) separated from the solution. After cooling, the filtered solution was evaporated to dryness, 1–2 ml. of water added, and the precipitate filtered off and washed with 2–3 ml. of water. The residue, after drying, was a crystalline powder, weight 157 mg., m. p. about 175°. Recrystallization from ethyl acetate gave 95 mg. (54%)[22] of *d,l-cis*-2-benzoylaminocyclohexanol, colorless plates, m. p. 184–186°.

Preparation of *d,l-cis*-2-Benzoylaminocyclohexyl *p*-Toluenesulfonate.—A 373-mg. portion of the *cis*-benzamidoalcohol was suspended in 1.0 ml. of dry pyridine. With ice-cooling, 350 mg. of *p*-toluenesulfonyl chloride was added, and the mixture left at 25° for fifty hours. At 0° there was successively added 2–3 ml. of water, 1.0 ml. of 6 *N* hydrochloric acid, and again 2–3 ml. of water. The precipitate was filtered off, washed well with water, and dried *in vacuo*. The colorless crystalline solid so obtained weighed 339 mg. and melted at 145–175°.

Between crossed Nicol prisms the crystals appeared as colorless needles, with a smaller amount of colored leaflets. By successive crystallizations from dilute ethanol or absolute methanol, an analytic sample of m. p. 163–165° was obtained which appeared nearly homogeneous (needles) under the polarizing microscope. The yield at this stage was very small, however, and has not yet been improved.

Anal. Calcd. for $C_{20}H_{23}O_4NS$ (373.45): C, 64.32; H, 6.21; N, 3.75. Found: C, 64.36; H, 6.20; N, 3.66.

Chlorination and Dechlorination

***d,l-cis*-2-Chlorocyclohexylamine Hydrochloride.**—A 6.0-g. portion of the *trans* aminoalcohol hydrochloride was treated with 11.9 g. of finely powdered phosphorus pentachloride in 100 ml. of dry benzene at 10°, and the mixture stirred for two hours at 25°. The product was collected on a sintered glass filter and washed repeatedly with dry carbon tetrachloride. After drying, the product[6b] weighed 5.0 g., m. p. 179–181°, with decomposition. The product was recrystallized from benzene–alcohol (5:1) yielding 3.5 g. of colorless needles, m. p. 185–186°, with decomposition. A mixed m. p. with the starting material was depressed to 143–153°.

The free chloro-amine was obtained by neutralizing the hydrochloride with concentrated aqueous alkali at 0° in the presence of ether. The crude liquid chloro-amine obtained by evaporating the dried ether extract was used directly for further operations.

***d,l-cis*-2-Benzoylaminocyclohexyl Chloride.**—A 0.4-g. portion of the chloro-amine hydrochloride was treated by the Schotten–Baumann procedure at 0–10° with 2.0 equivalents of benzoyl chloride, and 4.0 equivalents of 1 *N* aqueous sodium hydroxide. The precipitate was washed with water, and recrystallized from ethanol, yielding 0.3 g. of colorless rectangular leaflets, m. p. 153–154°. A sample recrystallized again, for analysis, showed no change in m. p.

Anal. Calcd. for $C_{13}H_{16}NOCl$ (237.73): C, 65.68; H, 6.79; Cl, 14.92. Found: C, 66.27; H, 7.15; Cl, 15.12.

A mixed m. p. with the dibenzoyl derivative (m. p. 153°) was depressed. The compound gave a positive Beilstein test for halogen, but was totally inert to hot alcoholic silver nitrate, and when it was boiled for twenty-one hours with silver acetate–acetic acid, hardly any silver chloride was formed.

Reaction of the *cis*-Chloro-amine with Silver Oxide or Carbonate.—Silver nitrate solution was treated with excess sodium carbonate solution, and the precipitate was washed, and suspended in water. To an excess of the resulting suspension the *d,l*-chloro-amine (or its hydrochloride) was added in portions. (If added all at once, a gummy ball forms.) The mixture was stirred at 40° for two hours. The product was mainly unchanged starting material, even when the temperature was increased from 40 to 70°, or the reaction time increased, or sodium hydroxide used in place of sodium carbonate. This was verified by benzoylation of the product, giving a 54% yield of *d,l-cis*-2-benzoylaminocyclohexyl chloride, m. p. 150–153°; mixed m. p. with an authentic sample not depressed. (A mixed m. p. with the dibenzoyl derivative was depressed.) These results indicate that the *d,l*-chloro-amine very largely fails to react under these conditions.

X-Ray Power Spectra

Patterns on powdered samples of *trans*- and *cis*-*d,l*-2-acetaminocyclohexanol were obtained using a flat cassette at 5 cm. from the sample and copper Kα radiation. The results are shown as positive prints in Fig. 1.[23]

Summary

1. Detosylation of *d,l-trans*-2-benzoylaminocyclohexyl-*p*-toluenesulfonate in dry acetic acid–sodium acetate gives the benzamidoacetate with retention. The reaction in wet acetic acid or (dry) ethanol gives the benzamidoalcohol with inversion. Thus, a neighboring acylamino group can participate in the same manner as a neighboring acyloxy group to determine the steric result of a detosylation reaction.

2. The steric results are consistent with the viewpoint that the 2-aminocyclohexanol of m. p. 68°, originally designated as *cis*, is actually the *trans* isomer.

3. The *cis* and *trans* forms of *d,l*-2-aminocyclo-

(22) It is reasonable to expect that the amount of each detosylation product actually present in its reaction mixture may be considerably greater than the reported yield based on material actually isolated and purified.

(23) We are indebted to Dr. R. T. Miller and Dr. N. N. Hellman of the Northern Regional Research Laboratory, Peoria, for these observations.

hexanol have been characterized by the preparation of various new derivatives and by X-ray powder spectra.

4. The chloro-amine obtained by phosphorus pentachloride treatment of *d,l-trans*-2-aminocyclohexanol hydrochloride has a very inert halogen characteristic of its *cis* structure.

RECEIVED JULY 82, 1948

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Sulfur-containing Amines. VI.[1] Antispasmodics

BY GEORGE M. FOHLEN,[2] WOLFGANG HUBER,[3] S. C. LASKOWSKI AND R. O. CLINTON

In previous communications[4,5] from these laboratories there have been described a number of sulfur-containing amines, which are of pharmacological interest as ester and amide precursors in local anesthetic types[1] and as side chains in antimalarial types.[6] In the present work we have extended the investigation to include derivatives of the sulfur-containing amines with a number of disubstituted acetic acid types, with the expectation that the sulfide linkage might provide favorable toxicity indices.[1]

The acids used were of the type which previous investigators have shown to form spasmolytically active esters, *viz.*: diphenylacetic, benzilic, fluorene-9-carboxylic, dibenzylacetic, α-cyclohexylphenylacetic and 9,10-dihydroanthracene-9-carboxylic acids.

The esters were prepared by either of two general methods. The first of these, reaction of an acid chloride with the alcohol or amine in cold benzene, is the preferable method. As has been previously indicated,[1] the reaction of the sulfur-containing amines with an acid chloride must be carefully controlled to avoid decomposition of the heat-labile sulfur compound. Only in two cases were satisfactorily stable hydrochlorides isolated; in general it was found preferable to isolate the free bases and convert them to the citrate salts.

The second method of preparing the basic esters utilized transesterification, in the presence of sodium alkoxide as catalyst. This method gave excellent results with both methyl benzilate[7] and methyl fluorene-9-carboxylate.

In Table I there are listed the esters prepared from straight and branched chain sulfur-containing amino alcohols. In addition, there was prepared one ester of an alcohol containing two sulfide linkages and a single example of an amide. These compounds, with other examples, are described in the experimental section.

(1) Paper V: Clinton, Salvador, Laskowski and Suter, THIS JOURNAL, **70**, 950 (1948).

(2) Present address: Barrett Division, Allied Chemical and Dye Corp., Philadelphia 6, Pennsylvania.

(3) Present address: Electronized Chemicals Corporation, New York, N. Y.

(4) Clinton, Suter, Laskowski, Jackman and Huber, THIS JOURNAL, **67**, 594 (1945).

(5) Laskowski and Clinton, *ibid.*, **69**, 519 (1947).

(6) Huber, Bair, Boehme, Laskowski, Jackman and Clinton, *ibid.*, **67**, 1849 (1945); **68**, 322 (1946).

(7) *Cf.* Holmes, U. S. Patent 2,399,736.

This series of compounds has been tested for antispasmodic activity *in vitro* against barium chloride and acetylcholine-induced spasms on rabbit intestinal strips and against histamine-induced spasms on strips of guinea pig ileum.[8] None of the compounds exhibited a high degree of activity against the acetylcholine-induced spasms. The activity against histamine-induced spasms was considerably less than that of papaverine, with the exception of 3-(3-(1-piperidyl)propylmercapto)-2-propyl fluorene-9-carboxylate citrate which was of the same order of magnitude. The compounds did not differ greatly in their musculotropic activity, *i. e.*, against barium chloride-induced spasms, all being equal to or slightly more active than papaverine.

Experimental[9]

The following examples will serve to illustrate the various procedures used. The yields of the compounds varied from 24 to 87%, the lower yields being chiefly ascribable to isolation difficulties.

2-(2-Diethylaminoethylmercapto)-ethyl Diphenylacetate Hydrochloride.—To an ice-cooled solution of 13.0 g. of diphenylacetyl chloride in 100 ml. of dry benzene was added during a five-minute period, with shaking, a cold solution of 10.0 g. of 2-(2-diethylaminoethylmercapto)-ethanol[4] in 50 ml. of dry benzene. The clear solution was warmed for fifteen minutes on the steam-bath and then cooled. Five hundred milliliters of Skellysolve A was then added; the precipitated oil crystallized on cooling and scratching. After three recrystallizations from ethyl acetate there was obtained 15.8 g. (67%) of large white prisms.

With the other sulfur-containing amines it was necessary to convert the oily or low-melting hydrochlorides to the free bases by means of ethyl acetate–ammonia, and thence to the citrate through the use of citric acid monohydrate in acetone or absolute alcohol solution.

3-(2-Diethylaminoethylmercapto)-propyl Benzilate Citrate.—A mixture of 5 g. of methyl benzilate, 4 g. of 3-(2-diethylaminoethylmercapto)-propanol,[4] and 0.15 g. of sodium metal in 50 ml. of Skellysolve E was refluxed under a pressure of about 30 mm. for four hours. An equal volume of benzene was then added and the mixture was washed several times with water and dried. The oily residue remaining after removal of the solvents *in vacuo* was taken up in dry acetone and treated with a solution of 4.2 g. of citric acid monohydrate in acetone. The white crystalline product was then repeatedly recrystallized from acetone.

(8) We are indebted to Dr. T. J. Becker (deceased) and his staff for the pharmacological testing of these compounds. A more detailed report of these tests will be published elsewhere.

(9) All melting points are uncorrected. We are indebted to Mr. Morris E. Auerbach and his staff for the analyses.