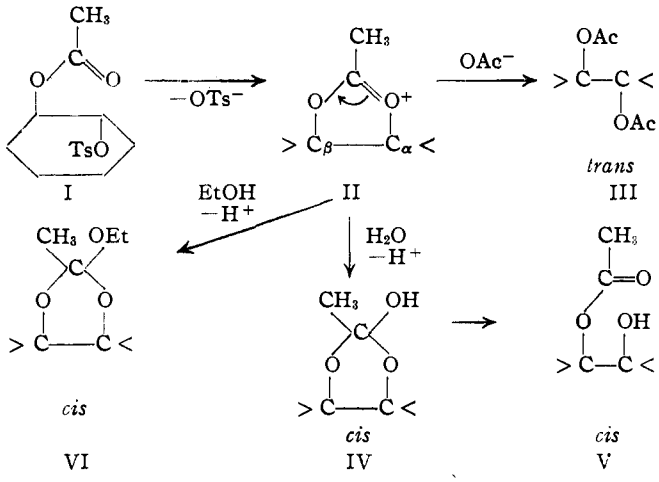
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

The Role of Neighboring Groups in Replacement Reactions. XVII. Complex Neighboring Groups. The Benzamido Group[1]

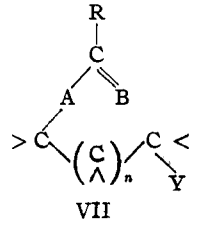
BY S. WINSTEIN AND ROBERT BOSCHAN

The participating acyloxy group is, in a sense, one of the more complex[1] neighboring groups. To illustrate, solvolysis of *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate[2] I gives rise to the intermediate II with Walden inversion at C_α. The nature of the final products depends on the conditions; in dry neutral[1,3] or basic[2] acetic acid solution II turns up as *trans*-1,2-diacetoxycyclohexane III with a second Walden inversion at either C_α or C_β. In acetic acid containing water,[2] *cis*-monoacetate V is produced by way of

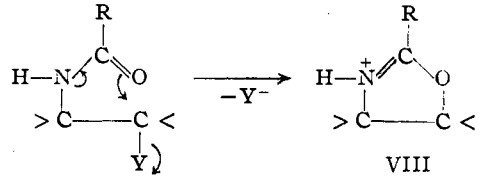


the orthomonoacetate IV, water coördinating at the acyl carbon atom. In ethanol as a solvent, there is produced orthoester[4] VI, analogous to the orthomonoacetate IV but sufficiently more stable to permit isolation. The control by the various sets of conditions of the nature and stereochemistry of the product of displacements involving a participating acyloxy group is very general.[1]

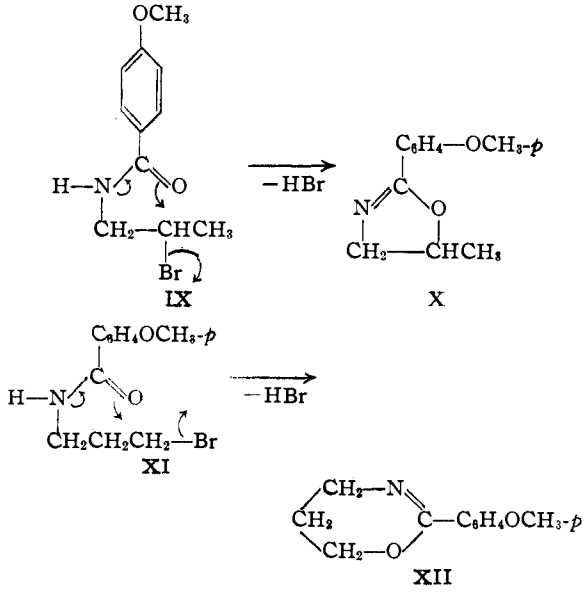
While there is considerable yet to be reported[3] in connection with the participation of the acyloxy group, it has been clear for some time that the acyloxy group is a model for similarly complex groups summarized by the general expression VII, where A and B represent oxygen, nitrogen or sulfur, and R is alkyl, aryl, alkoxyl, alkylthio, amino, etc. In this paper we report a qualitative and quantitative comparison of the benzamido with the acetoxy group.



When we began the above-mentioned considerations, there were cases in the literature which illustrated the analogy between the acylamino and the acyloxy groups. The analog of the intermediate ion II in the acylamino case is an oxazolinium ion VIII which is, in general, capable of isolation as a salt or as the free oxazoline. For



example, heating 1-*p*-methoxybenzamido-2-bromopropane IX with water yields the oxazoline[5] X. Similarly, the trimethylene analog XI yields[6] the heterocycle XII.



Recently, there has appeared stereochemical evidence with regard to the participation of the

(1) (a) Much of the material of this paper was presented in summary before the Organic Division of the American Chemical Society at (a) the St. Louis meeting of the Society, Sept., 1948, and (b) Eleventh National Organic Symposium, Madison, Wisconsin, June 21, 1949, page 65 of abstracts. Paper XVI, Winstein, Goodman and Boschan, THIS JOURNAL, **72**, 2811 (1950).

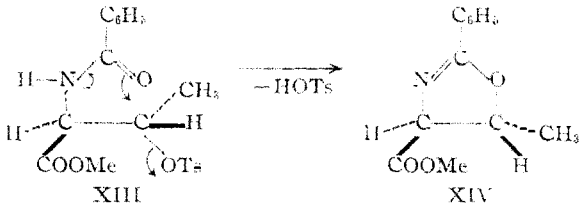
(2) Winstein, Hess and Buckles, *ibid.*, **64**, 2796 (1942).

(3) Winstein, R. Roberts and Corse, unpublished work.

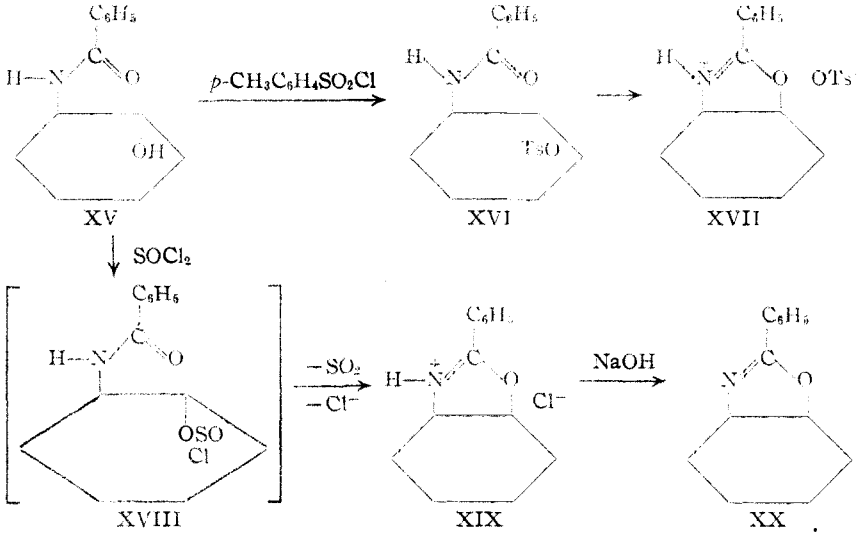
(4) Winstein and Buckles, THIS JOURNAL, **65**, 613 (1943).

(5) Rehlander, *Ber.*, **27**, 2157 (1894).

benzamido group. Attenburrow, Elliot and Penny[6] obtained the *trans*-oxazoline XIV from



solvolysis of the *p*-toluenesulfonate of N-benzoyl-allothreonine methyl ester XIII in ethanol containing potassium acetate, the expected Walden inversion occurring with participation of the benzamido group. Treatment of N-benzoyl-allothreonine methyl ester with thionyl chloride in the classical[7] method of synthesis of oxazolines gave the hydrochloride of the same oxazoline,[6,8] a steric result which could not have been anticipated with as much certainty as in the case of the toluenesulfonate XIII. Analogously, N-benzoylthreonine methyl ester gives the hydrochloride of the geometric isomer of XIV, the *cis*-



oxazoline. Treatment of the hydrochlorides with water opens the oxazolines with no further configurational changes, just as in the transformation of intermediate II to glycol monoacetate V. Thus XIV, which is derived from the allothreonine derivative gives N-benzoylthreonine.

Analogy between the reactions of *trans*-2-benzamidocyclohexyl *p*-toluenesulfonate XVI and those of the corresponding acetoxy compound I has very recently been reported by McCasland, Clark and Carter.[9] These workers solvolyzed XVI under three of the sets of conditions which had previously been employed in the case of I[2,4] and obtained analogous steric results to those we had previously reported. There was isolated *trans*-2-benzamidocyclohexyl acetate from anhydrous acetic acid containing sodium acetate, *cis*-2-benzamidocyclohexanol from wet acetic acid containing sodium acetate, and *cis*-2-benzamidocyclohexanol from dry ethanol containing sodium acetate.

In our comparison of the benzamido with the acetoxy group we also employed *trans*-2-benzamidocyclohexyl *p*-toluenesulfonate XVI, whose configuration is clear from the method of preparation, involving *trans* opening of cyclohexene oxide by ammonia, followed by benzoylation and tosylation.

The solvolysis of XVI could not be followed in glacial acetic acid by the titration of generated toluenesulfonic acid by the procedure previously[10] used for the acetoxy compound. The oxazolinium ion which is produced by ionization of XVI is relatively stable and is insufficiently acidic to be titrated with sodium acetate in glacial acetic acid. The solvolysis in absolute ethanol containing potassium acetate was, however, easily followed by titration with aqueous base to the phenolphthalein endpoint, this titration liberating free oxazoline from oxazolinium salt. Good first-order kinetics were obeyed, data for a typical run being summarized in Table I. The results of the several runs at two temperatures are summarized in Table III. The average first-order rate constant at 74.51° is 1.78×10^{-3} sec.$^{-1}$, which is nearly 200 times the value, 9.95×10^{-6} sec.$^{-1}$, previously[10] reported for *trans*-2-acetoxycyclohexyl *p*-toluenesulfonate in ethanol at 75.04°. Thus, the driving force[11] due to participation of a benzamido group is probably substantially larger than for the acetoxy group.

The *cis*-2-benzamidocyclohexyl *p*-toluenesulfonate, prepared from the *cis*-2-benzamidocyclohexanol, readily available from the *trans*-2-benzamidocyclohexanol as discussed below, solvolyzes very much more slowly than the *trans* isomer. The solubility of the material is too low in ethanol to permit kinetic measurements in the manner carried out with the *trans* isomer. On the other hand, it was possible to follow the first-order solvolysis in acetic acid because the difficulty of accumulation of a basic intermediate

(6) Attenburrow, Elliot and Penny, *J. Chem. Soc.*, 310 (1948).

(7) (a) Bergmann and Brand, *Ber.*, **56**, 1280 (1923); (b) Bergmann and Mickeley, *Z. physiol. Chem.*, **140**, 128 (1924).

(8) Pfister, Robinson, Shabica and Tishler, THIS JOURNAL, **70**, 2297 (1948); **71**, 1101 (1949).

(9) McCasland, Clark and Carter, *ibid.*, **71**, 687 (1949).

(10) Winstein, Hanson and Grunwald, *ibid.*, **70**, 812 (1948).

(11) Winstein, Grunwald and Ingraham, *ibid.*, **70**, 821 (1948).

TABLE I

SOLVOLYSIS OF *trans*-2-BENZAMIDOCYCLOHEXYL *p*-TOLUENESULFONATE IN ABSOLUTE ETHANOL AT 49.61°

Time, min.	(ROTs)(10^3 *M*)	10^4k, sec.$^{-1}$
0.0	16.00	..
10.0	14.88	1.24
21.0	13.61	1.29
47.0	11.22	1.26
62.0	10.21	1.22
82.0	8.71	1.24
102.0	7.70	1.20
127.0	6.27	1.21
152.0	5.45	1.18
178.0	4.25	1.24
204.0	3.70	1.20
	Mean	1.23 ± 0.03

TABLE II

SOLVOLYSIS OF *cis*-2-BENZAMIDOCYCLOHEXYL *p*-TOLUENESULFONATE IN GLACIAL ACETIC ACID AT 74.72°

Time, hr.	(ROTs)(10^3 *M*)	10^4k, sec.$^{-1}$
0.0	24.4	..
5.3	23.2	2.65
16.5	21.0	2.58
21.5	20.2	2.22
34.4	19.7	2.46
39.1	17.1	2.52
45.9	16.2	2.49
48.5	15.8	2.50
	Mean	2.49 ± 0.08

TABLE III

RATE CONSTANTS FOR SOLVOLYSIS OF 2-BENZAMIDOCYCLOHEXYL *p*-TOLUENESULFONATES

Compound[a]	ROTs (10^3 *M*)	Temp., °C.	Solvent[b]	KOAc (10^3 *M*)	k_1, sec.$^{-1}$
I	21.3	74.51	A	30.2	1.794×10^{-3}
I	19.5	74.61	A	43.1	1.768×10^{-3}
I	16.0	49.61	A	28.2	1.227×10^{-4}
I	22.4	49.67	A	18.2	1.258×10^{-4}
II	24.4	74.72	B	0.00	2.488×10^{-6}
II	32.6	74.74	B	0.00	2.489×10^{-6}

[a] I, *trans*-2-benzamidocyclohexyl; $\Delta H^{\pm}$ = 23.2 kcal./mole; II, *cis*-2-benzamidocyclohexyl. [b] A, Absolute alcohol; B, glacial acetic acid, containing *ca.* 0.1% acetic anhydride.

is absent in this case. Sample data are summarized in Table II and the results of two runs at 74.72° are listed in Table III. The first order constant, 2.49×10^{-6} sec.$^{-1}$ at 74.72°, would be somewhat reduced in ethanol,[12] so that the ratio of reactivities of *trans* to *cis* is of the order of 1000, similar to the ratio[13] that prevails for *trans*-2-acetoxy over *cis*-2-acetoxy. The solvolysis reaction of the *cis*-benzamidocyclohexyl *p*-toluenesulfonate is far from simple and will be dealt with in a subsequent article.

As the measurements show, the rate of ionization of *trans*-2-benzamidocyclohexyl *p*-toluenesulfonate XVI is high and brief treatments in anhydrous glacial acetic acid or ethanol are sufficient to convert XVI to its water-soluble, ether-insoluble isomer, *cis*-2-phenyl-4,5-tetramethyleneoxazolinium *p*-toluenesulfonate XVII. For example, six minutes of heating of XVI in glacial acetic acid gave the oxazolinium tosylate XVII in 95% yield. Analogously, a two-minute reflux period in glacial acetic acid containing potassium acetate gave rise to an 85% yield of product isolated as the picrate.

The relatively great tendency for XVI to ionize to XVII is evident in some of its other behavior. Even refluxing in benzene converts XVI to the water-soluble XVII. The melting point behavior of XVI is interesting in this respect. The pure substance melts at 118–119°, while the oxazolinium tosylate XVII melts at 160.5–161°. Addition of XVII to XVI gives essentially no melting point depression but instead causes the mixture to melt nearly at the higher temperature, the conversion of XVI to XVII being promoted by the addition of some of the ionic material initially.

In contrast with the results of McCasland, Clark and Carter,[9] who obtained *cis*-2-benzamidocyclohexanol as the product of long refluxing of XVI in absolute ethanol in the presence of acetate ion, we have isolated the oxazoline as the picrate in 87% yield after a 38-hour reflux period in the presence of added potassium acetate and as the *p*-toluenesulfonate in 73% yield after a 66-hour reflux period without added acetate ion. The oxazolinium tosylate is stable to water at room temperature for short periods of time, as evidenced by the fact that the picrate can be obtained on addition of picric acid to an aqueous solution of the oxazolinium tosylate. Therefore, we would guess that the result of McCasland, *et al.*, was not due to hydrolysis of the oxazoline in the course of working up the ethanolysis reaction mixture but due to the presence of sufficient water (0.43% would suffice) for this hydrolysis in the ethanol solvent during the reflux period.

Even from solvolysis of XVI in acetic acid containing water (and also potassium acetate) it is possible to isolate the intermediate oxazoline. After a 1-minute reflux period in acetic acid containing 1.81 times the theoretically required amount of water for hydrolysis of the oxazoline, a 66% yield of oxazoline picrate was obtained along with a small amount of *cis*-2-benzamidocyclohexanol.

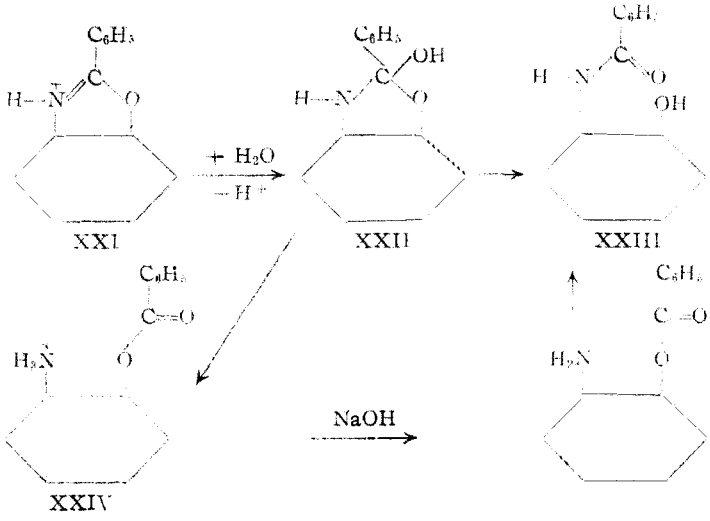
The same steric result which is obtained in the conversion of *trans*-2-benzamidocyclohexyl *p*-toluenesulfonate XVI to the *cis*-oxazoline XX accompanies the action of thionyl chloride on the *trans*-2-benzamidocyclohexanol XV. Treatment of the benzamido alcohol with thionyl chloride at room temperature gave a deliquescent oxazoline hydrochloride XIX, which was not easily handled as such but which could be converted to the

(12) Grunwald and Winstein, THIS JOURNAL, **70**, 846 (1948).

(13) Winstein, Grunwald, Buckles and Hanson, *ibid.*, **70**, 816 (1948).

oxazoline XX and then to the picrate which proved identical with the oxazoline picrate from solvolysis of XVI. Evidently the benzamido alcohol XV is converted to the chlorosulfinate[14] XVIII and it is the OSOCl group[13] which is the departing group.

From our results it is clear that the end-products from solvolysis of the type reported by McCasland, Clark and Carter[9] arise from relatively slow reactions of the oxazolinium salt XVII. Of such reactions of the oxazolinium salts reported here, the one with water is the most rapid. While,



as already stated, one minute of refluxing of XVI in acetic acid containing potassium acetate and excess water gave rise largely to oxazoline, two minutes of refluxing, this time with a larger proportion of water, gave rise to *cis*-2-benzamidocyclohexanol XXIII in 24% yield.

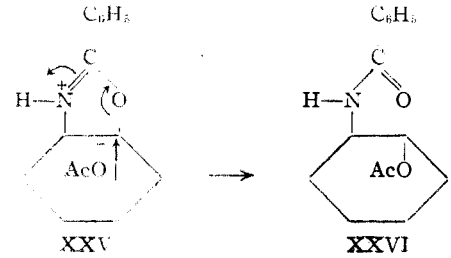
Long treatment of oxazoline *p*-toluenesulfonate XVII with moist acetic acid containing potassium acetate gave rise to *cis*-2-benzamidocyclohexanol XXIII in 27% yield, not much superior to the yield reported by McCasland, Clark and Carter[9] from analogous treatment of XVI. The conditions are conductive to complications and the reaction is being examined further.

The reaction of interest here is the reaction of oxazolinium ion XXI with water to yield the intermediate XXII (analogous to the orthomonoacetate IV or the orthoester VI), which gives rise to ordinary amide XXIII. A structure of the type XXII is an intermediate, as suggested by Bergmann,[15] for acyl migration O→N or N→O, just as IV is an intermediate for acyl migration O→O, originally suggested by Emil Fischer[16] as we have pointed out previously.[17]

The hydrolysis of oxazolinium ion XXI is very smooth in water, a high yield of *cis*-2-benzamidocyclohexanol XXIII being obtained on making alkaline the clear solution of the salt XXIV.

Hydrolysis of the reaction mixture from treatment of *trans*-2-benzamidocyclohexanol XV with thionyl chloride, without prior isolation of the oxazolinium salt, gives rise to 93% crude yield of *cis*-2-benzamidocyclohexanol XXIII, this representing the most convenient method for preparation of the latter material in quantity. Thus, here, just as in the allothreonine–threonine conversion, the treatment with thionyl chloride followed by hydrolysis, is a very convenient method for changing configuration.

The oxazolinium tosylate XVII is very stable in hot dry acetic acid, but addition of potassium acetate very markedly increases the rate of destruction of oxazolinium ion and therefore liberation of acid (which consumes acetate base). From heating oxazolinium tosylate XVII with potassium acetate in dry acetic acid, *trans*-2-benzamidocyclohexyl acetate XXVI may be isolated in 40% yield, again not much higher than the yield reported by McCasland, Clark and Carter[9] for the over-all treatment of XVI. There are here also possibilities for complications, and this reaction is being examined further. While our study of the kinetics of the reaction is not yet complete, the simplest reaction would appear to be the attack of oxazolinium ion by acetate ion as indicated in XXV.



This inversion from oxazoline to *trans*-2-benzamidocyclohexyl acetate (or, in other words, over-all retention of configuration from XVI to XXVI) parallels the steric result in the analogous acetoxy case[2,3,4,10] involving the final entry of OAc^-, Cl^- or OTs^-. The reaction of oxazolinium ion with chloride ion would be analogous to the Pinner[18] reaction. Formula XXVII symbolizes what is apt to be the most prevalent mechanism for the conversion of an iminoether hydrochloride[19] to amide and alkyl chloride and Formula XXVIII the analogous

(14) Cowdrey, Hughes, Ingold, Masterman and Scott, *J. Chem. Soc.*, 1252 (1937).

(15) Bergmann, Brand and Weinmann, *Z. physiol. Chem.*, **131**, 1 (1923).

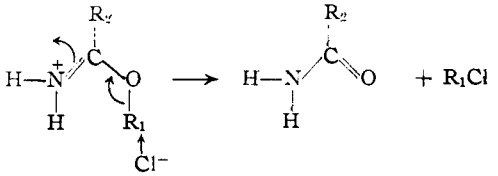
(16) Fischer, *Ber.*, **53**, 1621 (1920).

(17) Winstein and Buckles, THIS JOURNAL, **64**, 2787 (1942).

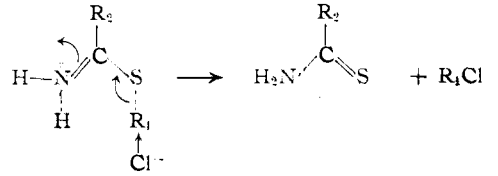
(18) Pinner, *Ber.*, **16**, 355, 1654 (1883).

(19) McElvain and Nelson, THIS JOURNAL, **64**, 1825 (1942).

reaction of a thioimino ether[20,21] hydrochloride.



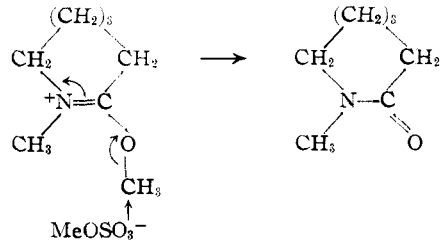
XXVII



XXVIII

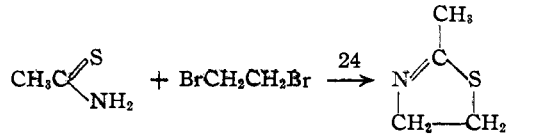
Elliott[22] reported that if the temperature was allowed to rise during the treatment of N-benzoyl allothreonine ethyl ester with thionyl chloride that chloride, $CH_3CHClCHNHBzCO_2C_2H_5$ was found in the product. He visualized a competing reaction of the chlorosulfinate which gives rise to chloro-compound, but it seems just as likely to us that oxazolinium chloride may give the chloro-compound in question.

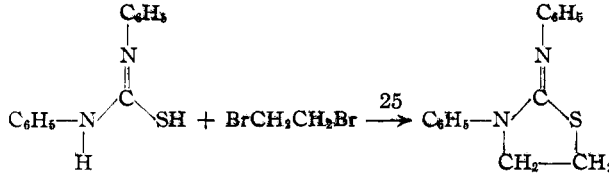
A related reaction is the one symbolized by XXIX which Benson and Cairns[23] suspected is involved in the methyl sulfate catalyzed transformation of caprolactam O-methyl ether to the N-methylcaprolactam XXX.



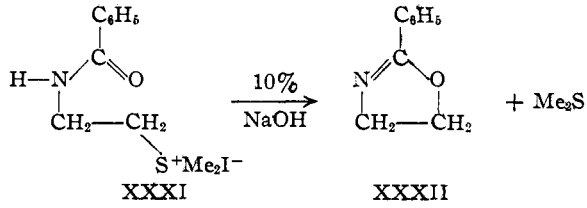
XXIX XXX

Competition between Back-side Neighboring Group Participation and Other Processes.— Internal displacement of a substituent by a neighboring group is, of course, always to be reckoned with as a competing possibility in suitable cases. For example, there are a number of recorded cases of reaction of a dihalide with a material such as a thioamide. After one halide atom is displaced, internal displacement of the second halogen competes successfully with bimolecular displacement or elimination and heterocycles are produced. Two examples[24,25] are





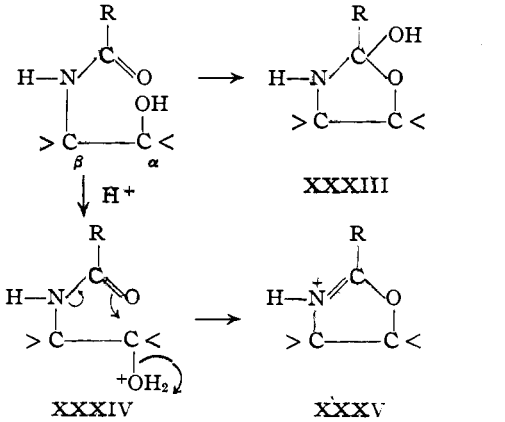
Neighboring group participation of the kind here envisioned probably accounts for the formation of oxazoline XXXII from the sulfonium salt XXXI rather than elimination to a vinyl com-



XXXI XXXII

pound which is converted to oxazoline, as supposed by Crane and Rydon.[26]

A more interesting competition is between back-side participation of the kind dealt with at length in this series of papers and what we have termed front-side participation.[1a] In the case of the neighboring acetoxy group, when the group to be replaced is OH, we have pointed out already[1a] that there are reactions which replace the OH group which proceed through an intermediate of the type IV, which is formed from materials of the type V. With the neighboring acylamino group, this same kind of competition is possible.



XXXIII XXXIV XXXV

Competing with acyl migration by way of intermediate XXXIII, which does not involve configurational change at C_α and C_β, is the possible formation of oxazolinium ion XXXV by back-side participation as symbolized in XXXIV. The formation and destruction of XXXIII may be formulated along the lines nowadays employed

(20) Hartigan and Cloke, THIS JOURNAL, **67**, 709 (1945).

(21) On this basis, it becomes easily understandable that when R_1 is C_6H_5, the other mode of decomposition is followed completely,[20] C_6H_5SH and C_6H_5CN being produced.

(22) Elliot, *J. Chem. Soc.*, 589 (1949).

(23) Benson and Cairns, THIS JOURNAL, **70**, 2115 (1948).

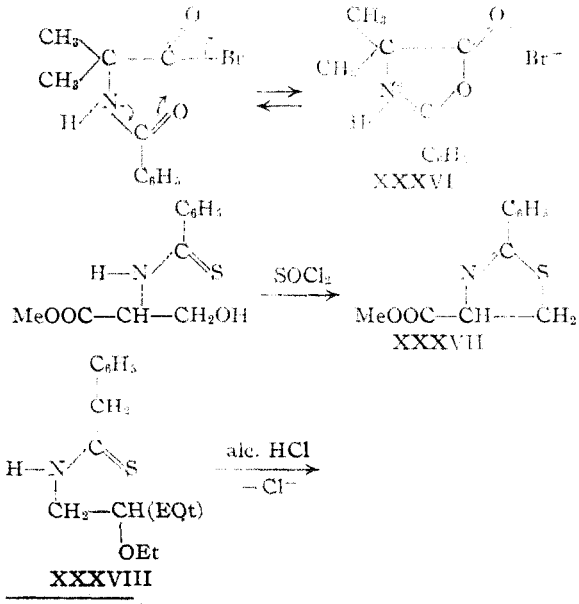
(24) Pinkus, *Ber.*, **26**, 1083 (1893).

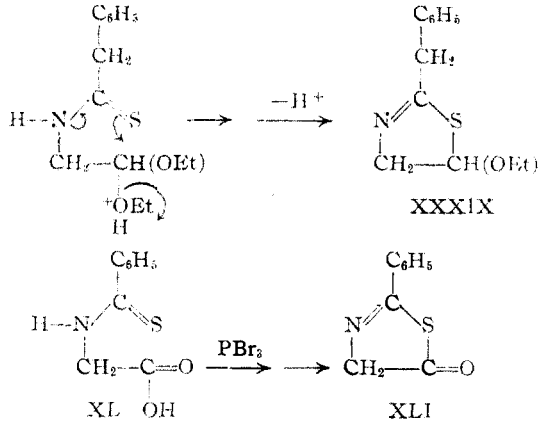
(25) (a) Will, *ibid.*, **15**, 343 (1882); (b) Gabriel, *ibid.*, **22**, 1139 (1889).

(26) Crane and Rydon, *J. Chem. Soc.*, 766 (1947).

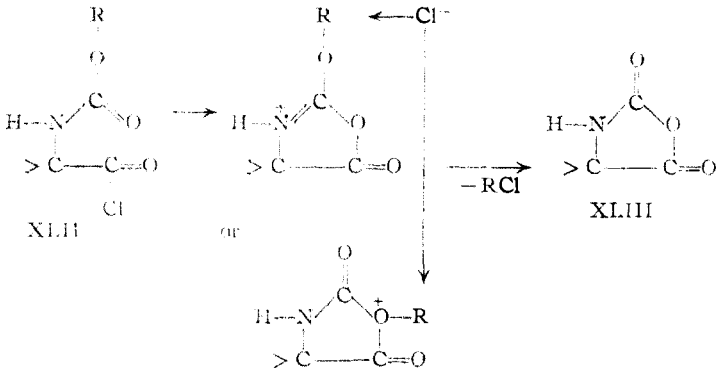
in interpreting esterification and ester hydrolysis.[27] The oxazolinium ion XXXV can under proper conditions turn up as acyl migrated material, but with a different configuration at C_α than from the more usual mechanism. Essentially this kind of competition has been called on recently[28] as a means of explaining some of the phenomena in connection with acyl migration in the ephedrine series.

Other Complex Neighboring Groups.—Regarding participation of other complex neighboring groups in displacement processes, there is considerable qualitative information already in the literature. This is especially true if we include for consideration the behavior of acid halides which actually represent but a special state of substitution of C_α and, as pointed out recently,[15] are sometimes useful for furnishing information on neighboring groups. In the case of the acylamino group itself, it is worth noting that Smith and Rasmussen[29] on the basis of infrared spectroscopic data have recently assigned the oxazolone structure XXXVI to the material prepared from N-benzoyl-α-aminoisobutyric acid and phosphorus tribromide. For the thioacylamino group, orientation is afforded by the conversion of N-thiobenzoylserine to the thiazoline[30] XXXVII, the acetal XXXVIII to the substituted thiazoline[31] XXXIX and the acid XL to the thiazolone[32] XLI.



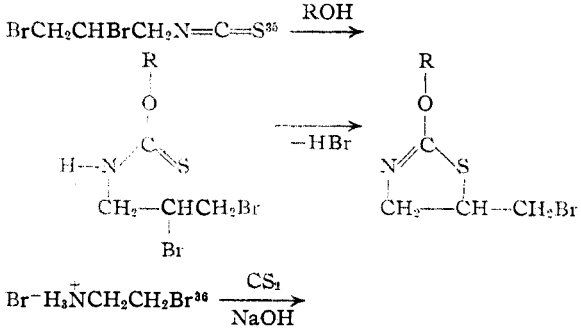


In connection with the N-carboalkoxy neighboring group one can derive some feeling for

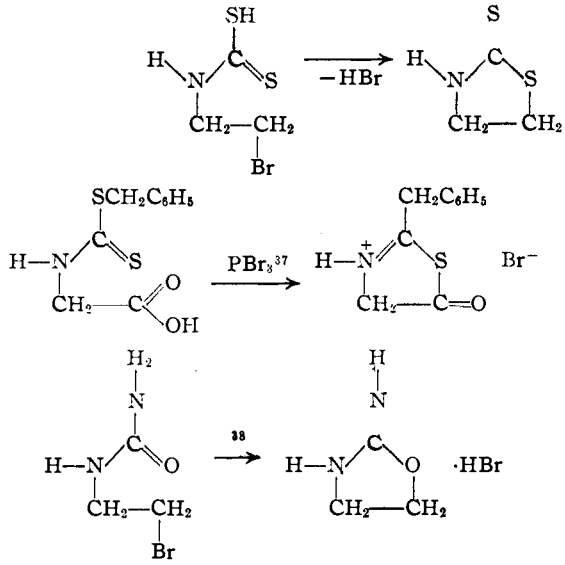


participation from the ready formation of the N-carboxy anhydrides[33] XLIII from the acid halides XLII, a plausible route being the indicated one. Also, the allothreonine to threonine isomerization[8] may be performed with the N-carbomethoxy-allothreonine ethyl ester[34] instead of the N-benzoyl derivative.

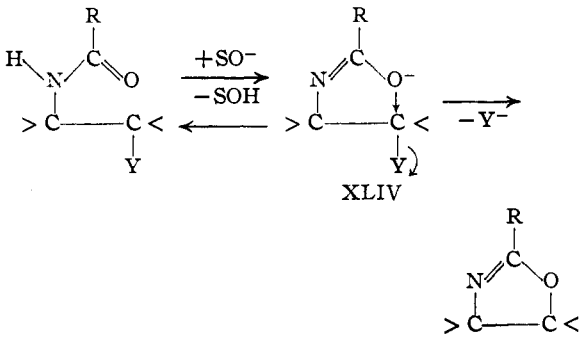
For still other neighboring groups, the following conversions illustrate participation of interest here.



(27) Day and Ingold, *Trans. Faraday Soc.*, **37**, 686 (1941).
(28) Welsh, THIS JOURNAL, **71**, 3500 (1949).
(29) Smith and Rasmussen, *ibid.*, **71**, 1080 (1949).
(30) Elliot, *Nature*, **162**, 658 (1948).
(31) Abraham, Baker, Chain and Robinson, CPS 43; Annual Reports, 1948, p. 210.
(32) J. B. Jepson, D. Phil. Thesis, Oxford, 1946; Annual Reports, 1948, p. 209.
(33) (a) Leuchs and Geiger, *Ber.*, **41**, 1721 (1908); (b) Woodward and Schramm, THIS JOURNAL, **69**, 1551 (1947).
(34) Pfister and Tishler, U. S. Patent 2,446,192; *C. A.*, **42**, 8211 (1948).
(35) (a) Dixon, *J. Chem. Soc.*, **69**, 31 (1896); (b) Gabriel and Colman, *Ber.*, **39**, 2889 (1906).
(36) Gabriel, *ibid.*, **22**, 1139 (1889).



In most cases internal reaction of a corresponding anion, *e. g.*, XLIV, is possible. In



alkaline solution especially, further kinetic analysis is necessary to evaluate the indicated second-order contribution to the total rate.

Experimental

trans-2-**Aminocyclohexanol.**—To 22.0 g. (0.224 mole) of redistilled cyclohexene oxide was added 16.0 g. of ammonium chloride (C. P.) and 90 cc. of concentrated ammonium hydroxide (*ca.* 15 molar). The mixture (in a flask bomb) was kept in a 75° thermostat overnight. After the reaction mixture was cooled and 2.88 g. of white crystalline material was filtered off, the filtrate was subjected to continuous chloroform extraction overnight. The chloroform was removed from the extract by distillation and the residue was distilled at reduced pressure to yield 16.50 g. (64%) of a water-white liquid, b. p. 111° (16 mm.), which crystallized to a white solid in the receiver, m. p. 68–69° after one recrystallization from a mixture of Skellysolve B (ligroin b. p. 60–70°) and chloroform (m. p. reported[9] 68–69°).

trans-2-**Benzamidocyclohexanol.**—To 9.04 g. (0.0785 mole) of *trans*-2-aminocyclohexanol dissolved in *ca.* 75 cc. of distilled water was added 14.6 g. (0.106 mole) of benzoyl chloride and a solution of 4.15 g. (0.107 mole) of sodium hydroxide in 40 cc. of water. After several minutes of swirling, 15.9 g. (93%), of material, m. p. 171–172° after recrystallization from either a Skellysolve B–chloroform mixture or water (reported[9] m. p. 169°), was obtained.

Action of Thionyl Chloride on *trans*-2-**Benzamidocyclohexanol. Isolation of 2-Phenyl-4,5-tetramethyleneoxazoline.**—To 15 cc. of purified thionyl chloride (cooled to 0°) was added in small portions 3.16 g. (0.0145 mole) of *trans*-2-benzamidocyclohexanol. The mixture was allowed to stand at room temperature for two and one-half hours. Then it was poured into 150 ml. of anhydrous ether (cooled to 0°), at which time an oil separated out. This material, 2-phenyl-4,5-tetramethyleneoxazoline hydrochloride, appeared to crystallize at low temperatures, but was deliquescent when exposed to air.

The ether suspension was shaken with a solution of 20 g. of sodium hydroxide in 150 cc. of water (cooled to 0°). Then the ether layer was separated and dried over anhydrous potassium carbonate for four hours. On addition of this ether solution to a solution of 3.5 g. of picric acid in 150 ml. of anhydrous ether, 4.30 g. (69%) of a yellow precipitate appeared almost immediately, m. p. 154–155°, m. p. 155.5° after two recrystallizations from a mixture of chloroform and Skellysolve B.

Anal. Calcd. for $C_{19}H_{16}O_8N_4$: C, 53.02; H, 4.216; N, 13.02. Found: C, 52.95; H, 4.33; N, 13.09.

trans-2-**Benzamidocyclohexyl** *p*-**Toluenesulfonate.**—Fourteen cc. of anhydrous pyridine was added to a mixture of 8.21 g. (0.0375 mole) of *trans*-2-benzamidocyclohexanol and 8.21 g. (0.0432 mole) of purified *p*-toluenesulfonyl chloride. The solution was allowed to stand overnight at room temperature and worked up in the usual way, the product being taken up in benzene. The benzene solution was dried over anhydrous potassium carbonate and cooled to yield 3.87 g. (28%) of material, m. p. 118–119° (reported[9] m. p. 114°).

Isomerization of *trans*-2-**Benzamidocyclohexyl Tosylate in Dry Benzene to 2-Phenyl-4,5-tetramethyleneoxazoline Tosylate.**—Four grams (0.0107 mole) of *trans*-2-benzamidocyclohexyl tosylate was dissolved in 100 cc. of dry benzene (dried over sodium) and the solution was refluxed for 17 hours. When the solution was cooled and the sides of the flask were scratched, a white precipitate appeared. Filtration of the precipitate yielded 2.62 g. of a white, water-soluble, ether-insoluble solid, m. p. 159°. When one part of this material was mixed with *ca.* 4 parts of *trans*-2-benzamidocyclohexyl tosylate, the melting point was 155°, after softening at 152°.

Anal. Calcd. for $C_{20}H_{23}O_4N$: C, 64.32; H, 6.21; N, 3.75. Found: C, 64.49; H, 6.25; N, 4.15.

To a pinch of the material in *ca.* 5 cc. of water was added 3 cc. of a saturated solution of picric acid in water. An immediate yellow precipitate appeared. Reprecipitation of this material from chloroform with Skellysolve B gave a material, m. p. 151–154.5°, mixed m. p. with oxazoline picrate from *trans*-benzamidocyclohexanol and thionyl chloride, 154–155.5°.

Solvolysis of *trans*-2-**Benzamidocyclohexyl Tosylate in Dry Acetic Acid. Isolation of 2-Phenyl-4,5-tetramethyleneoxazoline Tosylate.**—Three grams of *trans*-2-benzamido cyclohexyl tosylate was dissolved in *ca.* 25 cc. of glacial acetic acid (0.1% acetic anhydride), and the solution was refluxed for six minutes, then cooled in an ice-bath. To the mixture was added *ca.* 300 cc. of anhydrous ether, which precipitated 2.86 g. (95%) of white crystals, m. p. 160.5–161°, mixed m. p. with oxazoline tosylate prepared from *trans*-2-benzamidocyclohexyl tosylate and hot benzene, 159.5–160.5°.

Solvolysis of *trans*-2-**Benzamidocyclohexyl Tosylate in Acetic Acid in the Presence of Potassium Acetate. Isolation of 2-Phenyl-4,5-tetramethyleneoxazoline Picrate.**—A mixture of 1.00 g. (0.00268 mole) of *trans*-2-benzamidocyclohexyl tosylate, 0.98 g. (0.0100 mole) of potassium acetate, 25 cc. of dry acetic acid (*ca.* 0.1% Ac_2O) and 1 cc. of redistilled acetic anhydride was refluxed for 2 minutes, then poured into a solution containing 20 g. of NaOH in 100 cc. of water, and cooled to room temperature. The aqueous suspension was extracted with 3 portions of ether totalling about 250 cc. The ether extract was dried for

(37) Cook, Harris, Heilbron and Shaw, *J. Chem. Soc.*, 1056 (1948).

(38) Gabriel, *Ber.*, **50**, 826 (1916).

10 minutes over anhydrous potassium carbonate, then filtered. To the dried ether extract was added a solution of 1 g. of recrystallized picric acid in 250 cc. of anhydrous ether to yield 0.98 g. (85%) of a yellow solid, m. p. 154.5–155°, mixed m. p. with material from treatment of *trans*-2-benzamidocyclohexanol with thionyl chloride, 155.5–156°.

Solvolysis of *trans*-2-Benzamidocyclohexyl Tosylate in Absolute Ethanol. Isolation of 2-Phenyl-4,5-tetramethyleneoxazoline Picrate.—To a mixture of 0.87 g. (0.00233 mole) of *trans*-2-benzamidocyclohexyl tosylate and 0.72 g. (0.0074 mole) of potassium acetate (dried at 140°) was added *ca.* 50 cc. of high-grade absolute alcohol. The mixture was refluxed, taking precautions to exclude moisture, for 38 hours. Then the mixture was cooled to room temperature and filtered. The filtrate was evaporated under vacuum and the residue, a white solid, was shaken with anhydrous ether, filtered, and washed once with anhydrous ether. A total of *ca.* 75 cc. of anhydrous ether was used for this. To the ether extract was added a solution of 0.8 g. (0.0035 mole) of picric acid in *ca.* 40 ml. of dry ether to yield 0.87 g. (86.5%) of material, m. p. 154.0–155.5°, mixed m. p., with oxazoline picrate (from *trans*-benzamidocyclohexanol and thionyl chloride) 155–156°.

Solvolysis of *trans*-2-Benzamidocyclohexyl Tosylate in Absolute Ethanol. Isolation of 2-Phenyl-4,5-tetramethyleneoxazoline Tosylate.—A solution of 1.00 g. (0.00268 mole) of *trans*-2-benzamidocyclohexyl tosylate in *ca.* 45 cc. of absolute ethanol was refluxed for 66 hours. Most of the ethanol was removed by distillation and *ca.* 50 cc. of anhydrous ethyl ether was added to the remainder. Filtration yielded 0.73 g. of white crystals, m. p. 161–161.5°, mixed m. p. with a sample of oxazoline tosylate from treatment of *trans*-benzamide tosylate with hot benzene, 160–160.5°. A small pinch of the material was dissolved in *ca.* 1 cc. of water, about 2 cc. of 6 *N* NaOH was added, and the solution was extracted with 1 cc. of ether. To the ether extract was added a solution of picric acid in ether to yield material, m. p. 154–155°, mixed m. p. with oxazoline picrate from *trans*-benzamidocyclohexanol and thionyl chloride, 154.5–155°.

Solvolysis of *trans*-2-Benzamidocyclohexyl *p*-Toluenesulfonate in Moist Acetic Acid.—To a mixture of 0.41 g. (0.0042 mole) of anhydrous potassium acetate and 1.00 g. (0.00268 mole) of *trans*-2-benzamidocyclohexyl tosylate was added 23 cc. of glacial acetic acid (m. p. 16.48°) and 0.2665 g. of water (total water content, 0.0157 mole). The solution was refluxed for two minutes, cooled, and poured into a cold solution of 20 g. of sodium hydroxide in 100 cc. of water. The precipitate, m. p. 135–165°, weighed 0.51 g. After one recrystallization from a mixture of Skellysolve B and chloroform, there was obtained 0.14 g. of material, m. p. 184–185°, mixed m. p. with *cis*-2-benzamidocyclohexanol showing no depression. The aqueous filtrate from above was extracted with 100 cc. of ether. No precipitate appeared when ethereal picric acid was added to this ether solution.

To 1.00 g. (0.00268 mole) of *trans*-2-benzamidocyclohexyl tosylate and 0.41 g. (0.0042 mole) of anhydrous potassium acetate was added 20 cc. of glacial acetic acid (m. p. 16.48°) and 0.0724 g. of water (total water content 0.00484 mole). The mixture was refluxed for one minute, cooled, and poured into a cold solution of 20 g. of NaOH in 100 cc. of water. The suspension thus obtained was extracted with three portions of ether (total 125 cc.). A small amount of solid material, m. p. 183–184°, mixed m. p. with *cis*-2-benzamidocyclohexanol 184–186°, was filtered out and the ether was dried over anhydrous potassium carbonate. To the ether extract was added a solution of 0.70 g. of picric acid in 10 cc. of ether, and there was obtained 0.76 g. (66%) of material, m. p. 154–155.5°, mixed m. p. with 2-phenyl-4,5-tetramethyleneoxazoline picrate 155–156°.

2-Phenyl-4,5-tetramethyleneoxazoline.—1.00 g. of 2-phenyl-4,5-tetramethyleneoxazolinium tosylate was dissolved in 40 cc. of water. Sodium hydroxide (6 *N*) was added until a drop of the solution imparted a blue color to litmus paper. The resultant suspension was extracted with two 20-cc. portions of ether, and the ether extract was dried over anhydrous potassium carbonate. Evaporation of the ether extract left an oil which crystallized readily. Recrystallization from petroleum ether gave 0.53 g. (98%) of material, m. p. 45–46°, analytical sample, m. p. 46.0–46.6°.

Anal. Calcd. for $C_{13}H_{15}ON$: C, 77.58; H, 7.51. Found: C, 77.21; H, 7.50.

Hydrolysis of Oxazolinium Tosylate. Isolation of *cis*-2-Benzamidocyclohexanol.—A solution of 0.60 g. (0.0016 mole) of oxazolinium tosylate in 30 cc. of water was boiled for 20 minutes. Then 10 cc. of water was added and the boiling was continued for an additional 15 minutes. The solution was cooled in ice and 6 *N* KOH was added dropwise. A precipitate appeared as the KOH was added. This was a water-white oil which appeared to go partially into solution upon shaking. Suddenly a large amount of white precipitate appeared. Filtration yielded 0.45 g. of material, m. p. 182–184°, m. p. after two recrystallizations from a mixture of 95% ethanol and Skellysolve (ligroin, b. p. 30–60°), 187° (reported[9] 189–190°).

Anal. Calcd. for $C_{13}H_{17}O_2N$: C, 71.20; H, 7.82; N, 6.39. Found: C, 70.88; H, 7.80; N, 6.71.

Opening of Oxazolinium Tosylate in Dry Acetic Acid in the Presence of Excess Acetate Ion. Isolation of *trans*-2-Benzamidocyclohexyl Acetate.—To 1.00 g. of oxazolinium tosylate (0.00268 mole) and 0.40 g. (0.00408 mole) of anhydrous potassium acetate was added 43 cc. of anhydrous acetic acid (*ca.* 0.1% acetic anhydride) and 1 cc. of redistilled acetic anhydride. The solution was refluxed for 75 hours. Then the solution was cooled to room temperature and carefully poured into saturated sodium bicarbonate solution. The precipitate was filtered, washed with water, taken up in chloroform (*ca.* 50 cc.), and the chloroform solution was dried over anhydrous potassium carbonate. The chloroform solution was evaporated to 20–25 cc. and Skellysolve F was added to precipitate the material. This solid and a small amount of residue from evaporation of the filtrate totalled 0.28 g. (40% on the basis of *trans*-2-benzamidocyclohexyl acetate), m. p. 139–141°, m. p. after one recrystallization from a mixture of chloroform and Skellysolve B, 140–141°, mixed m. p. with a sample of benzamido-acetate from *trans*-benzamidocyclohexanol and acetic anhydride, 142–143°. The aqueous solution from which the benzamido-acetate was precipitated was extracted with *ca.* 100 cc. of ether, and the ether extract was dried over potassium carbonate, and distilled to remove the ether. The residue was a paste-like material, amounting to 0.20 g., which sublimed nearly completely at 1 mm., the sublimate also being a paste. The sublimate contained nitrogen and is being studied further.

Solvolysis of 2-Phenyl-4,5-tetramethyleneoxazoline Tosylate in Wet Acetic Acid. Isolation of *cis*-2-Benzamidocyclohexanol.—To 1.00 g. (0.00268 mole) of 2-phenyl-4,5-tetramethyleneoxazoline tosylate was added 0.38 g. (0.0037 mole) of anhydrous potassium acetate and 43 cc. of glacial acetic acid (m. p. 16.39°). 0.1635 g. (0.0091 mole) of water was then added and the mixture was refluxed for 66 hours. The solution, after cooling, was poured into saturated sodium bicarbonate solution. The bicarbonate solution was extracted with ether on a continuous extractor for two days. Evaporation of the ether extract left a gummy residue. All attempts to crystallize the gum failed. The gum dissolved slowly in dilute sulfuric acid (1–2 *N*). The first acid extract was neutralized with sodium hydroxide solution and 0.12 g. of a white precipitate was obtained, m. p. 179–180°, mixed m. p. with *cis*-2-benzamidocyclohexanol, 182–184°, mixed m. p. with *trans*-2-benzamidocyclohexanol, 148–151°. An additional 0.04 g. of material with the same m. p. as above was obtained when the gummy residue was heated to boiling in dilute acid and the filtered acid solution neutralized with sodium hydroxide to bring the total yield of *cis*-2-benzamidocyclohexanol to 0.16 g. (27%).

***trans*-2-Benzamidocyclohexyl Acetate.**—To 1.00 g. (0.00487 mole) of *trans*-2-benzamidocyclohexanol was

added 1 cc. (1.08 g., 0.0106 mole) of redistilled acetic anhydride and 3 cc. of anhydrous pyridine. The mixture was warmed on the steam-bath for about ten minutes, and set aside. Filtration after one day yielded 0.44 g. of crystals, m. p. 144–144.5° (reported[9] 144°). The filtrate was poured onto ice and the pyridine was neutralized with concentrated hydrochloric acid to yield an additional 0.68 g. of material, m. p. 141–142°, for a total yield of 1.12 g. (88%).

cis-2-Benzamidocyclohexanol.—16.12 g. (0.0735 mole) of *trans*-2-benzamidocyclohexanol (powdered in a mortar) was added in small portions to 15 cc. of thionyl chloride (cooled to 0°). Five cc. of thionyl chloride was added to bring a small amount of undissolved material into solution. The mixture was allowed to warm to room temperature and left for three hours. Then the mixture was carefully poured into *ca.* 400 cc. of distilled water. The resulting aqueous solution was filtered and the filtrate was refluxed for 10 minutes. After refluxing, the solution was cooled in an ice–salt-bath, filtered, and potassium hydroxide (6 *N*) was added to the filtrate to yield (after drying at 1 mm. over phosphorus pentoxide) 15.08 g. (93.5%) of material, m. p. 180–182°.

cis-2-Benzamidocyclohexyl Tosylate.—Ten grams (0.0457 mole) of *cis*-2-benzamidocyclohexanol, 10.0 g. (0.0527 mole) of *p*-toluenesulfonyl chloride, and 100 cc. of anhydrous pyridine were warmed on a hot-plate until all the solid material went into solution. The solution was set aside for a day. Then the pyridine solution was poured into ice, and the pyridine was neutralized by adding concentrated hydrochloric acid until the solution imparted a red color to methyl orange. The precipitate was filtered and taken up in benzene. The benzene layer was dried over potassium carbonate, and cooled to yield 7.92 g. (46.5%) of material, m. p. 162–163° (reported[9] m. p. 163–165°).

Rate Measurements in Absolute Ethanol.—The stock solution for a run was made up in a 100-cc. volumetric flask and distributed among 13 or 14 ampoules. The ampoules were sealed and inserted in the thermostat. At specified times, ampoules were removed from the thermostat, cooled for one minute in water at room temperature, and opened. A sample (4.723 cc.) was pipetted into 25 cc. of distilled water, and titrated with standard aqueous sodium hydroxide solution, using phenolphthalein as indicator. A blank was run to determine the titration correction. The absolute alcohol used in the rate runs and in all solvolyses in ethanol contained less than 0.01% water as shown by the paraffin oil test of Robertson.[39]

Rate Measurements in Glacial Acetic Acid.—These were performed according to the procedure of Winstein, Grunwald and Ingraham.[1]

Acknowledgment.—We are grateful to the Research Corporation for a grant-in-aid in support of this work.

Summary

Participation of certain so-called neighboring groups in nucleophilic replacement processes is briefly discussed, and qualitative and quantitative comparison between the neighboring benzamido and acetoxy groups is reported.

The rate of ionization of *trans*-2-benzamidocyclohexyl *p*-toluenesulfonate is *ca.* 200 times that of the corresponding acetoxy compound, brief treatment in glacial acetic acid or ethanol sufficing for nearly quantitative conversion to *cis*-2-phenyl-4,5-tetramethyleneoxazoline, which can be isolated as the *p*-toluenesulfonate, picrate or free base. The same steric result attends the conversion of *trans*-2-benzamidocyclohexanol to oxazoline by thionyl chloride.

Opening of the oxazolinium salt by aqueous acid or glacial acetic acid solutions gives the same stereochemical results previously observed with neighboring acetoxy. The opening by water, together with the treatment of *trans*-2-benzamidocyclohexanol with thionyl chloride make up a convenient method of preparation of *cis*-2-benzamidocyclohexanol.

(39) Robertson, "Laboratory Practice of Organic Chemistry," The Macmillan Co., New York, N. Y., 1943, p. 178.

LOS ANGELES 24, CALIF. RECEIVED APRIL 25, 1950

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF CALIFORNIA]

The Interaction of Bromine with Benzene and Certain of its Derivatives

BY R. M. KEEFER AND L. J. ANDREWS

Two interesting examples of the basic nature of the aromatic nucleus have been considered in recent publications concerning complex formation of certain aromatic substances with iodine[1] and with silver ion.[2] Recently it has been reported that the ultraviolet absorption spectra of solutions of bromine[3] in certain aromatic compounds display maxima very similar to those described[1a,b] for the interaction of iodine and benzenoid systems. The present investigation was undertaken to see whether the absorption spectra reported by Bayliss[3] could be explained by bromine–aromatic complex formation. Spectrophotometric methods similar to those used by Benesi and Hildebrand[1a,b] have been employed to evaluate the equilibrium constants for the formation of bromine addition complexes of benzene and several of its derivatives in carbon tetrachloride solution. The results are of interest not only because of their relationship to the findings of the studies with iodine and silver ion but are also potentially useful in connection with proposed experiments concerning the mechanism of substitution of bromine in the aromatic nucleus.[4]

Experimental

Materials.—All organic compounds were of the best grade available from Eastman Kodak Co. The carbon tetrachloride was dried over calcium chloride and distilled.

(1) (a) Benesi and Hildebrand, THIS JOURNAL, **70**, 3978 (1948); (b) Benesi and Hildebrand, *ibid.*, **71**, 2703 (1949); (c) Fairbrother, *Nature*, **160**, 87 (1947); (d) Fairbrother, *J. Chem. Soc.*, 1051 (1948).

(2) (a) Andrews and Keefer, THIS JOURNAL, **71**, 3644 (1949); (b) Andrews and Keefer, *ibid.*, **72**, 3113 (1950).

(3) Bayliss, *Nature*, **163**, 764 (1949).

(4) Robertson, *J. Chem. Soc.*, 933 (1949), has postulated a bromine–mesitylene addition compound as an intermediate in the formation of bromomesitylene.