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

Neighboring Groups in Addition. VI.[1] The Benzamido Group in 3-Benzamidocyclohexene. Stereospecific Synthesis of Trisubstituted Cyclohexane Derivatives[2]

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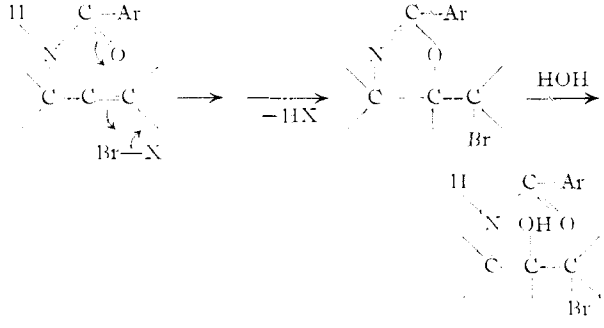
The previously demonstrated pronounced tendency for a neighboring benzamido group to participate in electrophilic olefin addition makes such addition reactions of 3-benzamidocyclohexene interesting for stereospecific synthesis of vicinally trisubstituted cyclohexane derivatives. Thus, from addition of bromine to 3-benzamidocyclohexene in methanol is obtained a mixture of bromo-ether, dibromide and *cis*-oxazolinium bromide. The latter substance is obtained more conveniently and in excellent yield from the reaction of 3-benzamidocyclohexene with N-bromosuccinimide in the less nucleophilic solvent, acetic acid. Hydrolysis of the *cis*-oxazolinium bromide gives rise to the 2-bromo-6-benzamidocyclohexanol with the bromine atom in a *trans* and the benzamido group in a *cis* relationship to the hydroxyl group. Treatment of the benzamido-bromohydrin with dilute alkali leads to *cis*-1,2-epoxy-3-benzamidocyclohexane. Addition of bromine to 3-benzamidocyclohexene in acetic acid in the presence of a high concentration of lithium bromide leads almost exclusively to a mixture of two isomeric dibromides. These dibromides isomerize during acetolysis and also lead to a bromo-oxazine. The most straightforward tentative assumption regarding the dibromides is that they represent the two possible *trans*-dibromides from normal *trans*-addition to 3-benzamidocyclohexene. Conformational considerations rationalize oxazine rather than oxazoline formation in acetolysis of the dibromides.

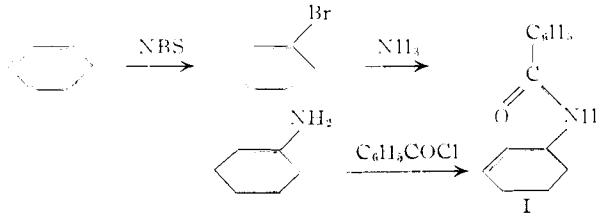
The pronounced tendency of the acylamino group to participate in the additions of bromine and N-bromosuccinimide (NBS) to 3-benzamido- and 3-*p*-methoxybenzamidopropenes was illustrated in the previous article in this series.[1] Excellent yields of bromomethyloxazolines could be isolated from these reactions, and the oxazolines represented a source of the corresponding β-amino-alcohols.



As pointed out previously,[2a] such conversions with cyclohexenyl derivatives yield polysubstituted alicyclic compounds whose substituents possess definite stereochemical relationships; the detailed results of the study of some pertinent addition reactions involving bromine or NBS and 3-benzamidocyclohexene (I) are reported in the present article.

3-Benzamidocyclohexene and its Addition Reactions in Methanol and Acetic Acid.—A convenient route to 3-benzamidocyclohexene (I) involved ammonolysis of 3-bromocyclohexene in liquid ammonia, followed by Schotten–Baumann benzoylation of the 3-aminocyclohexene.

Just as in the case of 3-benzamidopropene,[1] addition of bromine to 3-benzamidocyclohexene in methanol led to a mixture of oxazolinium bromide II, dibromide III and bromoether (Table I). While the dibromide fraction of the product obtained in methanol as a solvent was not characterized fully, it was easily distinguished from the oxazolinium bromide II by its failure to consume



dilute base or silver nitrate in titration. Toward both of these reagents, the oxazolinium bromide *II* displayed satisfactory equivalent weights. The oxazolinium bromide was converted easily to the free oxazoline IV and the oxazolinium picrate, both of which were obtained as analytically pure materials.

As summarized in Table I, a much superior route to the oxazolinium bromide II involved the use of NBS as the positive bromine donor and the less nucleophilic acetic acid as solvent.[1] Yields of 84-86% of oxazolinium bromide II easily were achieved from treatment of 3-benzamidocyclohexene with NBS in glacial acetic acid followed by isolation of the oxazoline IV as the hydrobromide II. The reaction between 3-benzamidocyclohexene and NBS also was carried out in aqueous dioxane, the free oxazoline IV being isolated as a distillable liquid.

TABLE I

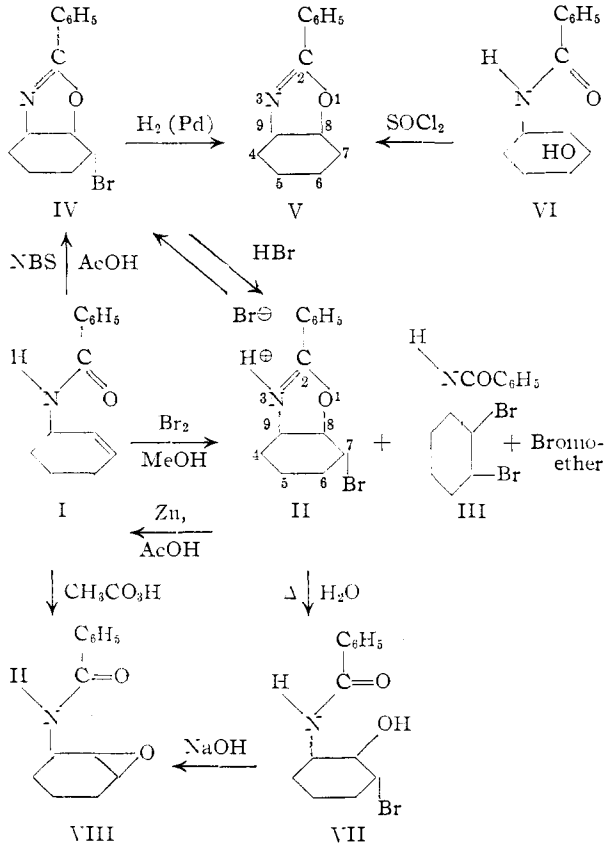
SUMMARY OF PRODUCTS OF ADDITION REACTIONS OF 3-BENZAMIDOCYCLOHEXENE (I)

Reagent	Solvent	Yields, % Oxazoline or oxazoline·HBr	Dibromides	Bromoethers
Br_2	MeOH	40	32	23
NBS	HOAc	85		
Br_2 + LiBr (large excess)	HOAc	6	87	

Structure, Configuration and Transformations of the Oxazoline.—In a reaction analogous to the regeneration of olefins from vicinal dihalides, haloethers, etc., the oxazolinium salt II readily was

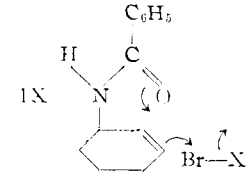
(1) Paper V, L. Goodman and S. Winstein, THIS JOURNAL, **79**, 4788 (1957).

(2) Some of the material of this paper was presented in summary form: (a) S. Winstein, L. Goodman and R. Boschan, *ibid.*, **72**, 2811 (1950); (b) S. Winstein, L. Goodman and R. Boschan, p. 436 of Abstracts, XIIth International Congress of Pure and Applied Chemistry, New York, N. Y., Sept., 1951.



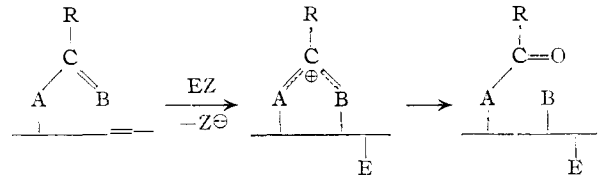
reconverted in high yield to 3-benzamidocyclohexene with zinc in acetic acid. The same reaction proceeds less smoothly with the free oxazoline IV.

The presence of an oxazoline rather than an oxazine ring in the heterocyclic product from bromine addition to benzamidocyclohexene was confirmed by hydrogenolysis over a palladium catalyst. This gave rise to 2-phenyl-*cis*-cyclohexoxazoline-8,9 (V), the picrate of which proved to be identical with that of authentic material prepared from *trans*-2-benzamidocyclohexanol (VI) and thionyl chloride.[3] The *cis* configuration of the oxazoline rather than *trans* is, of course, the one predicted from the mechanism of formation of the oxazolinium salt during halogen addition to benzamidocyclohexene (see IX).



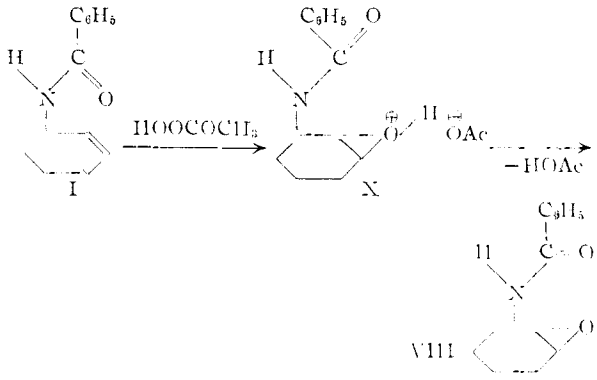
When an aqueous solution of the oxazolinium bromide II was heated at 100° and then neutralized, the benzamido-bromohydrin VII was formed. A *trans* relationship of the bromine atom and hydroxyl group of the bromohydrin VII can be anticipated from the expected *trans* nature of the addition to the double bond of benzamidocyclohexene (I) as portrayed in formula IX and the known retention of configuration[3,4] in the hydrolysis of a *cis*-oxazoline to a *cis*-benzamido-alcohol. The anticipated *trans* relationship of the bromine and oxygen atoms in the bromohydrin VII, and therefore the bromo-oxazoline IV, was confirmed by the rapid, quantitative conversion with dilute aqueous base[5] to the epoxide VIII, identical with material prepared from 3-benzamidocyclohexene (I) with peracetic acid.[6] An equivalent weight fairly close to theoretical could be obtained by determination of base consumption by bromohydrin VII, but a slow, continuing consumption of base, probably resulting from amide hydrolysis, reduced the accuracy of the determination.

Summarizing the stereochemical relationships among the three adjacent groups in the benzamido-bromohydrin VII, the benzamido group is *cis* to hydroxyl, while the bromine atom is *trans*. It may be instructive to regard formation of the benzamido-bromohydrin VII as only one example of possible stereospecific syntheses of trisubstituted alicyclic derivatives which depend on participation of complex neighboring groups in electrophilic olefin addition reactions. Some of the general possibilities may be better appreciated from the generalized scheme



the complex neighboring group[3] being represented as —A—C(R)=B and the electrophilic reagent[7] as EZ.

Two features of the preparation of epoxide VIII from 3-benzamidocyclohexene (I) deserve comment. It is interesting that the reaction of I with peracetic acid, another example of an electrophilic olefin addition, proceeds without neighboring benzamido group participation. From such participation, an hydroxyoxazoline would be expected. However, donation of positive hydroxyl to the olefinic group apparently occurs without back-side benzamido group intervention, followed by proton loss from the epoxide conjugate acid X.

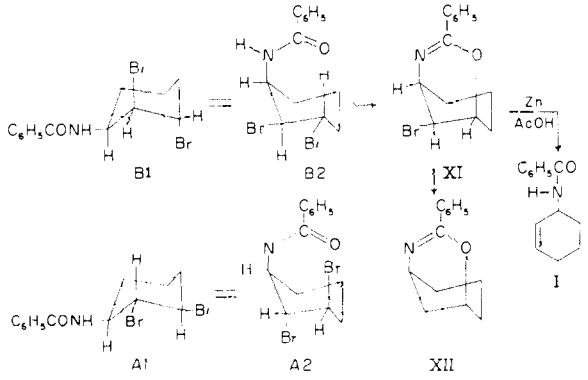


The second feature of the preparation of epoxide VIII from 3-benzamidocyclohexene (I) and perace-

(3) S. Winstein and R. Boschan, THIS JOURNAL, **72**, 4669 (1950).
(4) G. E. McCasland, H. E. Carter and R. K. Clark, Jr., *ibid.*, **71**, 637 1949).
(5) P. D. Bartlett, *ibid.*, **57**, 224 (1935).
(6) D. Swern, *ibid.*, **69**, 1692 (1947).
(7) S. Winstein and L. Goodman, *ibid.*, **76**, 4368 (1954).

tic acid which deserves comment is that the *cis*-epoxide VIII was the only one observed. Henbest and Wilson[8] have reported recently that epoxidation of cyclic allylic alcohols occurs on the side of the ring *cis* to the hydroxyl group and it is apparent that the benzamido group exerts a similar *cis*-directing effect in the epoxidation leading to VIII.

The Dibromides and their Transformations.—Developing bromide ion competes with neighboring group intervention in addition of bromine to a substituted olefin.[1,7] This is responsible for the formation of dibromide III from treatment of 3-benzamidocyclohexene (I) with bromine in methanol. Dibromide formation was made dominant by the addition of bromine to benzamidocyclohexene in acetic acid containing a large quantity of lithium bromide. Under these conditions, the oxazolinium bromide II constituted only *ca.* 6% of the product. The dibromide fraction contained a high-melting isomer (A) and a low-melting one (B) in approximate 30:70 proportions, and these could be obtained by fractional crystallization as analytically pure materials containing no ionic halogen. Both dibromides A and B regenerated 3-benzamidocyclohexene (I) smoothly on treatment with zinc in ethanol. The behavior of the dibromides in solvolysis was of potential interest because of the possibilities for anchimeric effects due to neighboring bromine or benzamido. However, the solvolytic behavior of dibromides A and B was examined only briefly, and the work was interrupted before matters were fully clarified. When either of the dibromides A or B was heated in refluxing glacial acetic acid, there was formed a mixture of A and B accompanied by a new basic nitrogen compound XI isomeric with oxazoline IV. When silver acetate was included in the refluxing acetic acid, good yields of the new basic nitrogen compound were obtained and none of the



dibromides A or B was recovered. Under these conditions, B appeared to react substantially more rapidly than did A. Hydrogenolysis of the new basic nitrogen compound XI over a palladium catalyst to remove the bromine atom gave rise to a bromine-free base, m.p. 102–103°, isomeric with the *cis*-oxazoline V. Two attempts to hydrolyze the bromo-base XI were unsuccessful; mild conditions gave back the starting base, and the use of 6 *N* perchloric acid at 160–170° yielded only tars accompanied by some of the starting material.

(8) H. B. Henbest and R. A. Wilson, *J. Chem. Soc.*, 1958 (1957).

The hydrolytic stability of the bromo-base XI rules out a *trans*-oxazoline structure.[9,10] On treatment with zinc in acetic acid, the hydrochloride of XI gave an excellent yield of 3-benzamidocyclohexene (I), and this rules out any deep-seated rearrangements in the formation of XI. Thus, the facts point to a bromo-oxazine structure XI for the bromo-base from the dibromides A and B. The parent oxazine XII recently has been reported by Burford, Hewgill and Jefferies[11] as a crystalline material, m.p. 102°, in agreement with that of the product of hydrogenolysis of the bromo-base XI.

The most straightforward tentative assumption regarding the dibromides A and B is that they are the two *trans*-dibromides from normal *trans* addition of bromine to 3-benzamidocyclohexene (I). With this assumption, and the additional one that oxazine ring closure involves O–6[12] participation of the benzamido group in the rate-determining step, one can interpret further the behavior of the dibromides A and B. Dibromide A would be disposed toward oxazoline formation only as a very unfavorable conformation (A2) with *cis*-axial bromine and benzamido groups. Dibromide B, in a not so unfavorable conformation (B2), leads to oxazine XI. Considering model compounds, *trans*-3-benzamidocyclohexyl toluenesulfonate[13] gives oxazine in ethanol somewhat more rapidly than *trans*-2-benzamidocyclohexyl toluenesulfonate[3] leads to oxazoline. Therefore, it is easy to understand the formation of oxazine XI, rather than an oxazoline, from the dibromides. The most straightforward tentative mechanism of isomerization of the two dibromides A and B is the one employed for mutarotation of cholestene dibromides.[13] Other mechanisms and configurational assignments to the bromine atoms in the dibromides and the bromo-oxazine XI are conceivable so the remarks regarding configurations and mechanisms of reaction of the dibromides A and B are admittedly speculative.

Experimental[14]

3-Aminocyclohexene.—To a mixture of 20.11 g. (0.37 mole) of ammonium chloride in about 500 ml. of liquid ammonia was added, with stirring, 60.5 g. (0.38 mole) of bromocyclohexene[15] over a period of 75 minutes. The ammonia was allowed to evaporate, and the residue was dissolved in a solution of 31.0 g. (0.77 mole) of sodium hydroxide in 150 ml. of water. The resulting solution was continuously extracted with ether for 4 hours, and the extract was dried over potassium carbonate. The ether was distilled using a 12-inch center-rod column and the residue distilled through the same column to give 24.4 g. (66.7%) of material, b.p. 73–75.4° (87 mm.), $n^{25}D$ 1.4816–1.4821. A second preparation gave a 55% yield of material, b.p. 139–140° (756 mm.), $n^{25}D$ 1.4822 (reported[16] b.p. 137–138°).

Anal. Calcd. for $C_6H_{11}N$: C, 74.17; H, 11.41. Found: C, 73.84; H, 11.56.

(9) W. S. Johnson and E. N. Schubert, THIS JOURNAL, **72**, 2187 (1950).

(10) R. Boschan and R. Glick, unpublished work.

(11) R. R. Burford, F. R. Hewgill and P. R. Jefferies, *J. Chem. Soc.*, 2037 (1957).

(12) F. L. Scott, R. E. Glick and S. Winstein, *Experientia*, **13**, 183 (1957).

(13) C. A. Grob and S. Winstein, *Helv. Chim. Acta*, **35**, 782 (1952).

(14) Melting and boiling points are uncorrected.

(15) K. Ziegler, A. Späth, E. Schaaf, W. Schumann and E. Winkelmann, *Ann.*, **551**, 80 (1942).

(16) F. Hofmann and P. Danum, *Mitt. schles. Kohlenforsch. Inst. Kaiser-Wilhelm Ges.*, **2**, 97 (1925); *C. A.*, **22**, 1249 (1928).

The picrate of the amine was prepared in dry ether and recrystallized from water several times; m.p. 151–154.5°.

Anal. Calcd. for $C_{12}H_{14}N_4O_7$: C, 44.17; H, 4.32. Found: C, 44.24; H, 4.57.

3-Benzamidocyclohexene (I).—A solution of 23.4 g. (0.24 mole) of 3-aminocyclohexene, 36.6 g. (0.92 mole) of sodium hydroxide and 200 ml. of water was chilled in ice and to it was added, rapidly and with stirring, 35.2 g. (0.25 mole) of benzoyl chloride. The resulting precipitate was filtered and washed with dilute sodium hydroxide and water. After being dried the material was recrystallized from benzene–petroleum ether to give 31.0 g. (64%) of solid, m.p. 98–100°. An analytical sample had m.p. 100–101.2° (a m.p. of 101.8–102.8° has been achieved and an isomorphous form, m.p. 95–97°, has been isolated in this work).

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.48; H, 7.58.

Addition of Bromine to 3-Benzamidocyclohexene (I) **in Dry Methanol.**—A solution of 5.03 g. (0.025 mole) of I in 75 ml. of dry methanol was cooled to −3°, and 4.80 g. (0.025 mole) of bromine was added, with stirring, over a period of 10 minutes. The solution was stirred for 1.5 hours more while it warmed to 20°, and it was then filtered to remove 5.31 g. of material, m.p. 184–185° dec. Volhard titration indicated the presence of 64% of 2-phenyl-7-*trans*-bromo-*cis*-cyclohexoxazolinium-8,9-bromide (II) and titration with standard base to the phenolphthalein end-point indicated the presence of 53% of II (these titrations were run before it was discovered that the removal of the free oxazoline IV by the use of chloroform made it possible to obtain accurate, rapid titrations by the Volhard method). A portion of the precipitate was recrystallized from dry methanol to yield a solid, m.p. 192–192.5° dec.

Anal. Calcd. for $C_{13}H_{15}NOBr_2$: C, 43.24; H, 4.19. Found: C, 43.17; H, 4.22; titration of the recrystallized salt by the Volhard method gave equivalent weights of 377 and 370 (theory for II, 361.1).

A portion of the original precipitate was suspended in dilute sodium hydroxide solution, and the resulting mixture was extracted with ether. The ether extract was dried and added to a solution of picric acid in dry ether. The picrate which precipitated on long standing, m.p. 167–192° dec., still contained dibromide III. Two recrystallizations from methanol gave the analytical sample, m.p. 167–169°.

Anal. Calcd. for $C_{19}H_{17}N_4O_8Br$: C, 44.81; H, 3.37; N, 11.00. Found: C, 44.76; H, 3.45; N, 11.31.

The filtrate from the original precipitate yielded 0.13 g. of material, mainly oxazolinium bromide II, m.p. 179–182° dec., m.p. 189.5–190° dec., after solution in methanol and reprecipitation with ether.

The filtrate and washings from the above solid were evaporated, *in vacuo*, to a volume of about 25 ml. Dry ether, 250 ml., was added and 0.70 g. of a white solid, mainly oxazolinium bromide II, precipitated; m.p. 189–189.5° dec., equivalent weight 379 by Volhard titration. A portion of the precipitate was heated, in a water suspension, on the steam-bath for 30 minutes. All but a trace of oil went into solution. The solution was decanted from the oil and neutralized with sodium bicarbonate solution. This yielded a gummy solid which was recrystallized from methanol and again from ethyl acetate to obtain an analytical sample of *trans*-2-bromo-*cis*-6-benzamidocyclohexanol (VII), m.p. 125–126°.

Anal. Calcd. for $C_{13}H_{16}NO_2Br$: C, 52.36; H, 5.41. Found: C, 52.23; H, 5.52.

Evaporation of the filtrates from the 0.70 g. of solid (above) to a small volume gave 0.35 g. of white solid, m.p. 176–180° dec., which appeared to be dibromide III.

Evaporation of the final filtrate to dryness left 1.78 g. of an uncrystallizable oil considered to be bromo-ether.

Reaction with NBS in Glacial Acetic Acid.—A mixture of 3.60 g. (0.0178 mole) of I, 3.15 g. (0.0178 mole) of NBS and 16 ml. of glacial acetic acid was stirred at room temperature for 3 hours. The acetic acid was evaporated with the aid of the water aspirator, and the residue was taken up in 100 ml. of dry ether, the precipitated succinimide being removed by filtration. The filtrate was added to 250 g. of dry ether which had been saturated with hydrogen bromide gas, and 5.42 g. (84%) of II precipitated, equivalent weight by the Volhard titration (using chloroform) 363.6 (theory 361.1). Another identical preparation gave an 86.4% yield of II. The oxazolinium chloride was also prepared by addition of ethereal hydrogen chloride; m.p. 169–170.5° dec.

2-Phenyl-7-*trans*-bromo-*cis*-cyclohexoxazoline (IV).—A mixture of 1.20 g. (0.0059 mole) of I, 1.06 g. (0.0059 mole) of NBS, 10 ml. of dioxane and 7 ml. of water was allowed to stand at room temperature for two days. About 100 ml. of water was added, and the solution was extracted with three 35-ml. portions of ether. The ether and dioxane were evaporated with air, and the residue was distilled from a Hickman still at 0.005 mm. to yield a colorless oil.

Anal. Calcd. for $C_{13}H_{14}NOBr$: C, 55.73; H, 5.04. Found: C, 55.83; H, 5.10.

The oxazoline IV also was prepared by shaking the oxazolinium bromide II with aqueous sodium acetate solution and extracting the resulting mixture with ether. The oil remaining after removal of the ether, could be evaporatively distilled at 0.1 mm. (bath temperature, 135–140°) to yield a viscous liquid which analyzed satisfactorily for IV, but which became discolored on standing.

Reaction of Oxazolinium Bromide II with Zinc.—To a hot solution of 1.00 g. (0.0028 mole) of oxazoline salt II in 20 ml. of dry acetic acid was added 1.00 g. of zinc dust. The solution was allowed to stand for 1.5 hours, and then it was heated to boiling and filtered. The acetic acid was removed *in vacuo* from the filtrate, and the oily residue crystallized when 30 ml. of water was added. The crystalline product, 0.49 g. (88%), had m.p. 91–93°, mixed m.p. with authentic 3-benzamidocyclohexene 99–100°. One recrystallization gave material of melting point 97°, which appeared to be an isomorphous form of 3-benzamidocyclohexene (I).

When the free oxazoline IV was treated with zinc in acetic acid it was not possible to obtain crystalline I from the reaction residue after filtration and evaporation. The residue, however, was not basic and it was clear that elimination had taken place. Treatment of this residue with NBS in acetic acid gave rise to 56% of oxazoline IV isolated as the picrate, m.p. 166–167°.

Hydrogenolysis of Oxazolinium Bromide II.—A mixture of 1.08 g. (0.003 mole) of II, 2.0 g. of 2% palladium-on-calcium carbonate catalyst, 0.60 g. (0.015 mole) of sodium hydroxide and 30 ml. of dry methanol was shaken with hydrogen at 23 lb. for 7.5 hours, during which time the theoretical quantity of hydrogen was absorbed (90% of it in the final 1.5 hour period). The solution was neutralized with Dry Ice and filtered. Methanol was evaporated from the filtrate, and the residual salts were extracted with boiling chloroform. The chloroform solution was evaporated, and the residue was taken up in dry ether. Addition of a dry ether solution of picric acid gave 0.48 g. of a picrate, m.p. 141–190° dec. Recrystallization from methanol gave material with m.p. 141–146° and further recrystallization from chloroform–petroleum ether gave 0.19 g., m.p. 151–155.4°. A final recrystallization gave material, m.p. 154–156°, m.p. 155–157° when mixed with an authentic sample[3] of the picrate of 2-phenyl-*cis*-cyclohexoxazoline-8,9 (V), m.p. 155–157°. The yield of hydrogenation product was estimated to be 20%.

***trans*-2-Bromo-*cis*-6-benzamidocyclohexanol** (VII).—A mixture of 2.0 g. of II and 15 ml. of water was heated on the steam-bath for 30 minutes, complete solution resulting. The solution was neutralized by the addition of a solution of 0.50 g. of sodium bicarbonate in a small volume of water. A gummy solid precipitated which was recrystallized from ethyl acetate to yield fractions of 0.62 g., m.p. 123.5–126°, and 0.34 g., m.p. 124.5–126°, for a 52.1% yield. Titration with standard base gave equivalent weights 308.8 (immediate back-titration of excess base), 306.1 (with excess base 5 minutes) and 290.5 (with excess base 20 minutes). The calculated equivalent weight for VII is 298.2, and the overconsumption of base may be due to slow hydrolysis of the amide linkage.

***cis*-3-Benzamido-1,2-epoxycyclohexane** (VIII). (a) **From VII.**—To a solution of 1.00 g. (0.0034 mole) of VII in 10 ml. of 95% ethanol was added a solution of 0.30 g. (0.0045 mole) of potassium hydroxide in 10 ml. of 95% ethanol. A white precipitate appeared almost immediately. The solution was shaken at room temperature for 15 minutes and filtered. To the filtrate was added 30 ml. of water, and the solution was extracted with three 15-ml. portions of chloroform. The chloroform was evaporated *in vacuo*, leaving 0.66 g. (91%) of solid, m.p. 103–112°, mixed m.p. with authentic VIII, 110–114°. After one recrystallization from benzene–petroleum ether, the material had m.p. 115–116°.

(b) **From I.**—The amide I (0.93 g., 0.0048 mole) was dissolved in 30 ml. of chloroform and 1.10 g. (0.0052 mole) of a commercial 40% peracetic acid solution in glacial acetic acid was added. The solution was stored at 0° for 48 hours and at room temperature for 24 hours, and then the excess acid was neutralized with a solution of 1.5 g. of sodium bicarbonate in 30 ml. of water. The chloroform layer was dried over potassium carbonate, and the chloroform was evaporated *in vacuo*. Addition of petroleum ether (20–40°) to the residue and chilling yielded 0.76 g. (76%) of white solid, m.p. 112–115°. Two recrystallizations gave the analytical sample, m.p. 115–116°.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96. Found: C, 71.95; H, 7.03.

The material did not give a precipitate with picric acid in dry ether.

The epoxide VIII also was prepared in 81% yield by allowing I to react with a mixture of 30% hydrogen peroxide and acetic anhydride.

Reaction of I with Bromine and Lithium Bromide.—A solution of 48.0 g. (0.55 mole) of dry lithium bromide and 20.0 g. (0.0995 mole) of I in 100 ml. of glacial acetic acid was stirred in an ice-bath while 15.9 g. (0.0997 mole) of bromine was added over a period of 10–15 minutes. The mixture was stirred for 7 hours more and allowed to stand overnight at room temperature. Ether, 500 ml., was added and 2.01 g. (5.6%) of the oxazoline salt II, m.p. 191–192° dec., precipitated.

Ether was evaporated from the filtrate over the steam-bath and 700 ml. of water was added to the residue, causing separation of an oil which rapidly crystallized. The crystalline precipitate was filtered and was extracted with three 350-ml. portions of boiling ether, each extract being filtered. Evaporation of the ether extract left 22.0 g. (61.3%) of dibromide B, m.p. 118–123°, m.p. 125–127° after a single recrystallization from aqueous acetone.

Anal. Calcd. for $C_{13}H_{15}NOBr_2$: C, 43.24; H, 4.19. Found: C, 43.28; H, 4.30.

The residue from the ether extraction was refluxed with 250 ml. of acetone, the mixture was filtered and the filtrate chilled, yielding 4.15 g. of the high melting dibromide A, m.p. 188° dec. Recrystallization of the residue from the acetone extraction plus material recovered from the mother liquors of the acetone recrystallization gave rise to two more crops of A, 4.08 g., m.p. 188.5–189° dec., and 1.09 g., m.p. 188.5–190° dec., for a total yield of 9.32 g. (26.0%) of A. An analytical sample had m.p. 189–190° dec.

Anal. Found: C, 43.40; H, 4.19.

Both dibromides A and B, when suspended in water, gave a pink color to phenolphthalein on addition of one drop of 0.08 *N* sodium hydroxide. Also, they showed negligible consumption of 0.069 *N* silver nitrate in Volhard titration in water or methanol.

Debromination of Dibromides A and B.—A suspension of 0.60 g. (0.0016 mole) of A, 25 ml. of 95% ethanol and 0.49 g. (0.0082 mole) of zinc dust was heated under reflux for 2 hours with frequent shaking. After the mixture had stood overnight the zinc was filtered and washed with ethanol. The filtrate was diluted with 200 ml. of water and 0.27 g. (81%) of a fluffy precipitate was collected, m.p. 101–102.1°, mixed melting point with authentic I, 101.8–102.8°.

When 0.57 g. of B was similarly treated, there was obtained 0.22 g. (69%) of material, m.p. 94–100°, m.p. after one recrystallization 101.8–102.8°.

Acetolysis of Dibromides A and B.—A solution of 2.0 g. (0.0055 mole) of the high-melting dibromide A in 20 ml. of dry acetic acid was heated under reflux for 24 hours. The acetic acid was removed *in vacuo* and the residue was extracted with hot ether. The ether was evaporated to yield 0.17 g. of material, m.p. 116–122° after recrystallization from aqueous acetone, m.p. 118–121° after another recrystallization, mixed m.p. with dibromide B 122–124°. The residue from the ether extraction was dissolved in chloroform, decolorized with Norite and filtered. The chloroform was evaporated and the residue triturated with ether and filtered. The crystalline material weighed 0.70 g., m.p. 155–160°. The solid was added to water and the resulting aqueous suspension was filtered, leaving 0.18 g., m.p. 168–171° dec., m.p. 182–183° dec. after recrystallization from chloroform, mixed m.p. with authentic A 185–186°. The aqueous filtrate from the recovery of A was made basic with 10–15 ml. of 6 *N* potassium hydroxide. A precipitate was formed, and 0.20 g. of the precipitate was dissolved in dry ether and the solution added to a solution of picric acid in ether. The picrate, 0.36 g., m.p. 197–201°, was recrystallized from acetone to give material with m.p. 202–203°, mixed m.p. with authentic oxazine XI picrate (see below), 203–205°.

A solution of 1.0 g. (0.0028 mole) of the low-melting dibromide B in 10 ml. of dry acetic acid was refluxed for 45 minutes, then cooled to room temperature. Addition of 100 ml. of dry ether caused the formation of a gum which crystallized readily. Filtration yielded 0.25 g. (25%) of a water-soluble solid, m.p. 166–168°. The solid, in aqueous solution, was mixed with an aqueous solution of picric acid and the picrate was produced in essentially quantitative yield, m.p. 201–205°, m.p. 205° after recrystallization.

Anal. Calcd. for $C_{19}H_{17}N_4O_8Br$: C, 44.81; H, 3.37; N, 11.00. Found: C, 44.77; H, 3.35; N, 11.11.

Evaporation of the ether from the original precipitation and addition of water produced an emulsion. The mixture was extracted with chloroform and the extract was dried over sodium sulfate. The chloroform was evaporated and the gummy residue was taken up in hot, anhydrous ether. On standing at room temperature the ether solution deposited 0.06 g. (6%) of crystals of A, m.p. 182–184° dec. Evaporation of the filtrate left 0.51 g. (51%) of B, m.p. 117–119°, m.p. 128° after recrystallization, mixed m.p. with authentic B 125–127°.

Acetolysis of Dibromides A and B in the Presence of Silver Acetate.—A solution of 1.0 g. (0.0028 mole) of A in 15 ml. of dry acetic acid which contained 0.46 g. (0.0028 mole) of dry silver acetate was heated under reflux for 4.3 hours. After filtering the silver salts, the filtrate was evaporated *in vacuo* and the residue was taken up in ether, only a trace of solid remaining undissolved. Addition of ethereal picric acid precipitated 0.75 g. (53%) of a solid, m.p. 157–175°. Three recrystallizations from chloroform raised the m.p. to 199–202° and a fourth crystallization to 203–204°, mixed m.p. with authentic oxazine XI picrate, 204–206°.

When 0.50 g. (0.0014 mole) of B in 20 ml. of dry acetic acid containing 0.23 g. (0.0014 mole) of dry silver acetate was refluxed for 2.2 hours and worked up as described above, there was isolated 0.53 g. (75%) of picrate, m.p. 196–202°, m.p. 207° after recrystallization from chloroform, mixed m.p. with authentic oxazine XI picrate, 207°.

Preparation of Bromoöxazine XI.—A quantity of dibromide B was solvolyzed in dry acetic acid as described above. The ether-insoluble residue after evaporation of the acetic acid was collected and added to water. The aqueous suspension was filtered, and the filtrate was made strongly basic with 6 *N* potassium hydroxide, yielding an oil which crystallized readily. The solid, m.p. 115–116°, was purified by sublimation; m.p. 118–119°.

Anal. Calcd. for $C_{13}H_{13}NOBr$: C, 55.73; H, 5.04. Found: C, 56.04; H, 5.00.

In a more recent experiment by Dr. F. Gadient, 539 mg. of dibromide B was treated with 248 mg. of silver acetate in 15 ml. of acetic acid. Working up the reaction mixture gave rise to 303 mg. (70%) of bromoöxazine XI, m.p. 121–122° after crystallization from ether–pentane.

Hydrogenolysis of Bromoöxazine XI.—A solution of 1.0 g. (0.0028 mole) of dibromide B in 15 ml. of dry acetic acid which contained 0.46 g. (0.0028 mole) of dry silver acetate was refluxed for 2 hours. The mixture was filtered and the solvent was evaporated *in vacuo*. Methanol (30 ml.) was added to the residue and the solution was filtered. Sodium hydroxide (0.30 g.) and 1.0 g. of palladium-on-charcoal catalyst were added to the filtrate and the mixture was shaken with hydrogen at 30 lb. pressure for two hours. The catalyst was filtered and washed with 10 ml. of methanol. A second 1.0 g. of catalyst was added and hydrogenation was continued at 30 lb. pressure for one hour. The catalyst was filtered and the filtrate was evaporated *in vacuo*. The residue was taken up in ether, and the solution was filtered and added to an ethereal picric acid solution. A precipitate, 0.1 g., m.p. 178–179°, slowly formed. The melting point of the picrate was unchanged by recrystallization from chloroform–petroleum ether.

Anal. Calcd. for $C_{19}H_{18}N_4O_8$: C, 53.02; H, 4.22. Found: C, 52.94; H, 4.23.

In a more recent experiment by Dr. F. Gadient, hydrogenation of 243 mg. of bromoöxazine XI in 15 ml. of methanol over palladium on charcoal at atmospheric pressure gave rise to 117 mg. (60.5%) of oxazine XII, m.p. 102–103°, m.p. of picrate 178–179°, and 65 mg. of N-cyclohexylbenzamide, m.p. 150–151°, mixed m.p. with an authentic specimen, 150–151°.

Reaction of Bromoöxazine Hydrochloride with Zinc.—The bromoöxazine XI, 0.50 g., was dissolved in 10 ml. of ether, and an excess of ethereal hydrogen chloride solution was added dropwise. The ether was decanted from the precipitate and 10 ml. of glacial acetic acid and 1.0 g. of zinc dust were added. The mixture was shaken until the white solid dissolved, and then it was allowed to stand at room temperature for 1.5 hours. The zinc was removed by filtration and the filtrate was evaporated *in vacuo*. Water was added to the residue which readily crystallized, yielding 0.25 g. (70%) of 3-benzamidocyclohexene (I), m.p. 91–92°, mixed m.p. with authentic I 99–101°, m.p. 94–95° after one recrystallization.

Attempted Hydrolysis of Bromoöxazine XI.—To 0.25 g. of bromoöxazine was added 2 ml. of water and 4 ml. of 60% perchloric acid. The solution was boiled 15 minutes and allowed to stand overnight. The solution was heated on the steam-bath for 2 hours and neutralized with excess sodium bicarbonate solution, yielding 0.20 g. of a solid, m.p. 90–110°. This material was dissolved in 5 ml. of absolute ethanol and to it was added a solution of 0.1 g. of potassium hydroxide in 6 ml. of absolute ethanol. The alcohol was removed *in vacuo* and ether was added to the residue. The ethereal solution was filtered, and the filtrate was divided into two equal parts. To one part was added ethereal picric acid solution, yielding 0.10 g. of bromoöxazine XI picrate, m.p. and mixed m.p. 204–205°. The other portion of the ether filtrate was evaporated to yield 0.09 g. of material, m.p. 118–119°, m.p. 120–121° when mixed with the starting material. The recovery of starting material was 56%.

To 0.61 g. of bromoöxazine XI was added 6 ml. of 60% perchloric acid and 3 ml. of water. The solution was sealed in a bomb tube and was heated at 160–170° for 1.25 hours. The tube was cooled, opened, and the contents filtered from a small amount of tar. To the nearly colorless filtrate was added excess sodium bicarbonate solution, 0.21 g. (34%) of a white solid precipitating, m.p. and mixed m.p. with starting material, 118–120°.

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LOS ANGELES 24, CALIF.

[CONTRIBUTION FROM ABBOTT LABORATORIES]

The Amidomethylation Reaction. Preparation of *m*- and *p*-Aminomethylphenylacetic Acids

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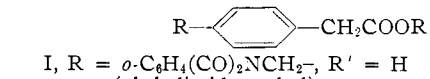
Condensation of phenylacetic acid with N-hydroxymethylphthalimide in concentrated sulfuric acid gives a mixture of *m*-(X) and *p*-(I)-phthalimidomethylphenylacetic acids, the latter in preponderant quantity. The *p*-isomer I can also be isolated from the zinc chloride-catalyzed reaction of phenylacetic acid with N-bromomethylphthalimide. The reaction of phenylacetic acid with N-hydroxymethylchloroacetamide in concentrated sulfuric acid likewise gives *p*-chloroacetylaminomethylphenylacetic acid (II) in 35–40% yields. *p*-Aminomethylphenylacetic acid hydrochloride (III) and the corresponding *m*-isomer XI are obtained readily from these condensation products. Their structures have been established by conversion to *p*-tolyl(V)- and *m*-tolyl(XII)-acetic acids, respectively.

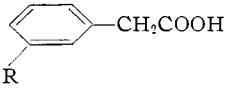
In connection with the study of basically substituted phenylacetic acids for use as penicillin precursors, the aminomethyl derivatives seemed to offer appropriate possibilities. However, *o*-aminomethylphenylacetic acid, prepared by a circuitous route,[1] appeared to be the sole isomer of this series described in the literature.

A direct aromatic substitution reaction by certain N-hydroxymethylamides, originally reported by Tscherniac[2] and later extended by Einhorn, seemed to offer the most direct route to the desired compounds. Thus Einhorn and co-workers[3] found that both benzoic and cinnamic acids, with N-hydroxymethylchloroacetamide in concentrated sulfuric acid, yielded the ring substituted chloroacetylaminomethyl derivatives, the former giving only the *m*-isomer, but the latter, both *m*- and *p*-substituted cinnamic acids. This paper reports the extension of this amidomethylation reaction to the direct substitution of phenylacetic acid.

Treatment of phenylacetic acid with N-hydroxymethylphthalimide in concentrated sulfuric acid led to a mixture of the *m*-(X) and *p*-(I) phthalimidomethylphenylacetic acids with the latter predominating. Removal of the phthaloyl groups by means of hydrazine and hydrochloric acid gave, respectively, the hydrochlorides of *m*-aminomethylphenylacetic acid (XI), m.p. 193–195°, and *p*-aminomethylphenylacetic acid (III), m.p. 232–233°. The third isomer, *o*-aminomethylphenylacetic acid hydrochloride, reportedly[1] melts at 154°. Orientations of the two isomers were established by catalytic reductive methylation ($CH_2O + H_2 + Pd$) to the corresponding dimethylamino derivatives



I, R = *o*-$C_6H_4(CO)_2NCH_2$–, R′ = H (phthalimidomethyl)
II, R = $ClCH_2CONHCH_2$–, R′ = H
III, R = $-CH_2NH_2 \cdot HCl$, R′ = H
IV, R = $-CH_2N(CH_3)_2 \cdot HCl$, R′ = H
V, R = CH_3, R′ = H
VI, R = $ClCH_2CONHCH_2$–, R′ = C_2H_5
VII, R = $ClCH_2CONHCH_2$–, R′ = CH
VIII, R = $(C_2H_5)_2NCH_2CONHCH_2$–, R′ = C_2H_5
IX, R = $-CH_2NH_2 \cdot HCl$, R′ = CH_3



X, R = *o*-$C_6H_4(CO)_2NCH_2$–, (phthalimidomethyl)
XI, R = $-CH_2NH_2 \cdot HCl$
XII, R = CH_3

(1) J. v. Braun and H. Reich, *Ann.*, **445**, 243 (1925).
(2) J. Tscherniac, German Patent 134,979 (1902); P. Friedlaender, *Fortschr. Teerfarb.*, **6**, 143 (1900–1902).
(3) (a) A. Einhorn and T. Mauermayer, *Ann.*, **343**, 295 (1905). (b) A. Einhorn and M. Göttler, *Ber.*, **42**, 4837 (1909).