

three wave lengths. These measurements resulted in a value of 1.25 ± 0.08 l. mole⁻¹ for the equilibrium constant, and the extinction coefficients were 78 at 450 m μ , 38 at 460 m μ , and 16 at 470 m μ .

This demonstration of the large uncertainties introduced in the values of the equilibrium constants by the presence in the solutions of small amounts of 2:1 or 1:2-complexes led us to question some of our previous results. In particular, there was an unexplained discrepancy between our value of 0.257 ± 0.005 l. mole⁻¹ for the equilibrium constant for formation of the 1,3,5-trinitrobenzene-aniline complex⁹ in chloroform and the value of 5.1 ± 0.7 mole fraction⁻¹ (approximately 0.41 ± 0.06 l. mole⁻¹) reported by Landauer and McConnell.¹⁰

(10) J. Landauer and H. McConnell, *THIS JOURNAL*, **74**, 1221 (1952).

We repeated our measurements starting with the crystalline complex, but this gave erratic results, which we attribute to an instability of the 1:1-complex. By mixing the two components in solution in exactly 1:1 molar ratios we obtained satisfactory measurements. These resulted in a value of 0.51 ± 0.03 l. mole⁻¹ for the equilibrium constant. This suggests that all of our previously reported results on this complex may be in error because of the presence of 1:2-complex. We hope to be able to repeat some of these measurements in the future.

Acknowledgment.—We are indebted to Miss Kathryn Church and Mr. Kurt Schoeni for assistance with the calculations.

NORTH ADAMS, MASS.

[CONTRIBUTION NO. 2106 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

The Formation and Reactions of Certain Oxazolonium Ions

BY JOSEPH L. O'BRIEN¹ AND CARL NIEMANN²

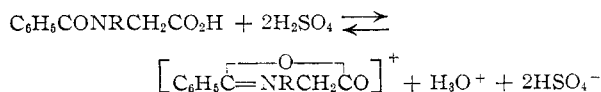
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A cryoscopic investigation has shown that α -acylamino acids may undergo complex ionization in sulfuric acid to form the corresponding oxazolonium ions. The structural requirements for this acid-catalyzed cyclization have been considered and a mechanism consistent with the facts is presented. Auxiliary experiments have not only confirmed the cryoscopic evidence but also indicate that the azlactonization of α -acylamino acids in acetic anhydride is catalyzed by sulfuric acid. A sulfuric acid catalyzed Erlenmeyer synthesis is described which gives an excellent yield of 2-phenyl-4-benzal-5-oxazolone, obtained as a mixture of the geometrical isomers. The stereochemistry of this condensation is discussed and it is suggested that sulfuric acid inhibits the mutarotation of the intermediate addition product. An improved preparation of α -(N-methylbenzamido)-cinnamic acid from benzoylsarcosine by the new method provides further evidence for an oxazolonium ion intermediate.

It has been shown^{3,4} that amino acids ionize normally in sulfuric acid, behaving to a varying extent as di-acid bases. For the simplest α -amino acid, glycine, the van't Hoff factor of 2.2 indicates that the second ionization is only about 20% complete. The lack of extensive protonation of the carboxyl group of the glycine cation in sulfuric acid may be attributed to the influence of the positively charged α -ammonium group.^{3,4}

In the present investigation the cryoscopic behavior in sulfuric acid of several derivatives of glycine has been determined. Of particular interest are the results obtained for the α -acylamino acids, cf. Table I. While the data for acetyl-glycine are inconclusive, it is clear that the ioniza-

tion of benzoylglycine and benzoylsarcosine to give i factors of nearly 4 cannot be explained on the basis of simple protonation. Rather, it appears that these latter α -acylamino acids undergo complex ionization⁵ in sulfuric acid with the formation of the corresponding oxazolonium ions.⁶ A possible mechanism for this dehydrative cyclization is presented in Fig. 1. Although the theoretical value of the i factor for the over-all reaction



is 4 and the observed value is 3.6 for benzoylglycine and 3.8 for benzoylsarcosine, it is not unreasonable to conclude that with both of the above compounds cyclization is nearly complete.⁷⁻¹⁰ The conclusion that cyclization of the above benzoyl compounds is essentially complete when R is either H or CH₃ is entirely consistent with the mechanism suggested in Fig. 1 but it is contrary to the notion that enoli-

TABLE I

i -FACTORS FOR SEVERAL α -ACYLAMINO ACIDS IN SULFURIC ACID

Compound	
Acetyl-glycine	2.5
Benzoylglycine	3.6
Benzoylsarcosine	3.8
Phthalylglycine	1.8
Benzenesulfonylglycine	2.2
Benzoylglycine ethyl ester	2.5

(1) Rohm and Haas Co., Inc., Philadelphia, Pa.

(2) To whom inquiries regarding this article should be sent.

(3) J. L. O'Brien and C. Niemann, *THIS JOURNAL*, **73**, 4264 (1951).

(4) G. Williams and M. L. Hardy, *J. Chem. Soc.*, 2560 (1953).

(5) M. S. Newman, H. G. Kuivila and A. B. Garrett, *THIS JOURNAL*, **67**, 704 (1945).

(6) J. L. O'Brien and C. Niemann, *ibid.*, **72**, 5348 (1950).

(7) R. J. Gillespie, E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 2473 (1950).

(8) R. J. Gillespie, *ibid.*, 2493 (1950).

(9) R. J. Gillespie, J. Graham, E. D. Hughes, C. K. Ingold and E. R. A. Peeling, *ibid.*, 2504 (1950).

(10) R. J. Gillespie, *ibid.*, 1851 (1954).

zation (lactam to lactim) necessarily precedes such ring closures.^{11,12}

Although it is possible that acetylglutamine may undergo limited cyclization, the available cryoscopic data are inconclusive. The value of the observed *i* factor, *i.e.*, 2.5, may be due either to further protonation of the acyclic structures II and III (with CH₃, replacing C₆H₅), to partial cyclization to the oxazolonium ion, or to hydrogen bonding to one of the solvent species.¹³ On the other hand, the *i* factors obtained for phthalylglycine and benzenesulfonylglycine, *i.e.*, 1.8 and 2.2, indicate that these compounds do not cyclize in sulfuric acid. The phthalyl compound appears to be incompletely ionized, while the benzenesulfonyl derivative gives results which are not significantly different from those given by the parent glycine.^{3,4} The failure of phthalylglycine to cyclize may be attributed to steric factors; for benzenesulfonylglycine one must postulate that the cyclic compound is unstable for some other reason. The *i* factor of 2.5 for benzoylglycine ethyl ester may be explained in terms of simple protonation if one takes into account the greater basicity of the ester group as compared to the carboxylic acid group.¹⁴ The possibility that a small amount of cyclization occurs cannot be excluded, but this seems unlikely since it has been found⁵ that the normal methyl ester of *o*-benzoylbenzoic acid does not give rise to a cyclic carbonium ion in sulfuric acid. The protonated ester group appears to be too weakly electronegative for the nucleophilic displacement on the carboxyl carbon (III → IV) to occur.

It is known that azlactones derived from α -*p*-nitrobenzamido acids give an intense red-violet color with aqueous alkali.^{15,16} We have found that a sulfuric acid solution of *p*-nitrobenzoylalanine when treated with an excess of aqueous potassium hydroxide gives the same red-violet color as that obtained under the same conditions with 2-(*p*-nitrophenyl)-4-methyl-5-oxazolone. That sulfuric acid can cause the cyclization of an α -acetamido acid was shown when a small amount of 2-methyl-4-benzal-5-oxazolone was isolated from a sulfuric acid solution of α -acetamidocinnamic acid which had been allowed to stand overnight at room temperature.

The above results suggested that the azlactonization of α -acylamino acids in acetic anhydride might be catalyzed by sulfuric acid. A simple qualitative test with *p*-nitrobenzoyl-DL-alanine showed this to be true. It was also found that the addition of a few drops of sulfuric acid to a suspension of α -acetamidocinnamic acid in acetic anhydride caused an exothermic reaction and produced a yellow solution which, on pouring into ice-water, gave a 38% yield of the azlactone. Although it is possible that some direct acid-catalyzed cyclization, *cf.* Fig. 1, occurs in acetic anhydride alone, the catalytic function of sulfuric acid in the

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 (14) R. A. Craig, A. B. Garrett and M. S. Newman, *ibid.*, **72**, 163 (1950).
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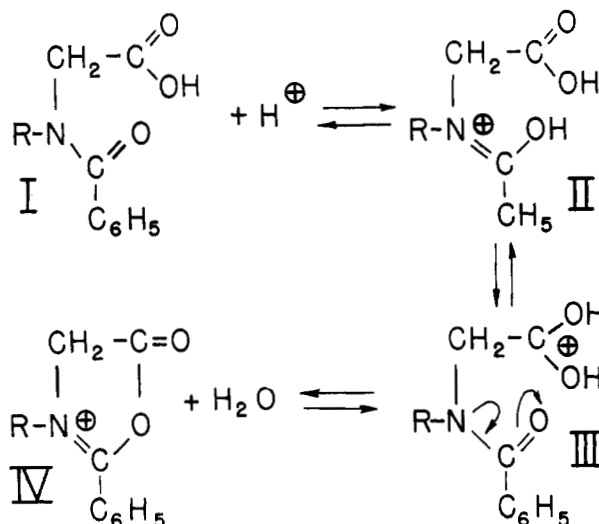


Fig. 1.—Mechanism of oxazolonium ion formation in sulfuric acid.

case at hand is probably associated with a prior reaction of sulfuric acid with acetic anhydride to give products¹⁷⁻²³ which promote the formation of the mixed anhydride of the α -acylamino acid and acetic acid. This latter mixed anhydride has been considered to be the most likely intermediate in the usual azlactonization with acetic anhydride alone.¹⁸

With evidence that benzoylglycine in sulfuric acid may be present as the oxazolonium ion and with the knowledge that sulfuric acid appears to be a favorable medium for an acid-catalyzed Perkin reaction^{24,25} benzaldehyde was allowed to react with a sulfuric acid solution of benzoylglycine. There was obtained a 35% yield of a yellow product, m.p. 120–151°, which was converted nearly quantitatively to 2-phenyl-4-benzal-5-oxazolone, m.p. 164–165.5°, by subsequent treatment with pyridine at room temperature. Carter and Risser²⁷ report that a mixture of the geometrical isomers of 2-phenyl-4-benzal-5-oxazolone melted at 125–135° and further that the lower melting (146–148°), labile isomer can be converted to the higher melting (163–165°), stable isomer by treatment with pyridine at room temperature. We are thus led to believe that our sulfuric acid catalyzed reaction product is a mixture of the geometrical isomers of the azlactone. It was thought that the above reaction could be made of preparative interest by effecting the condensation in ordinary concentrated sulfuric acid. However, even when a large excess of 96% acid was used only a small amount of product could be isolated.

Since it had been found that the azlactonization

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 (18) W. Baker, W. D. Ollis and V. D. Poole, *ibid.*, 1542 (1950).
 (19) R. J. Gillespie, *ibid.*, 2997 (1950).
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 (25) C. R. Hauser and D. S. Breslow, *ibid.*, **62**, 2389 (1940).
 (26) H. B. Gillespie and H. R. Snyder, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 489.
 (27) H. E. Carter and W. C. Risser, *J. Biol. Chem.*, **139**, 255 (1941).

of α -acylamino acids in acetic anhydride is catalyzed by sulfuric acid, the condensation of benzaldehyde with benzoylglycine in mixtures of these solvents was examined. It was observed that heating such mixtures to 100° caused considerable tar formation and that the reaction was incomplete unless two moles of sulfuric acid per mole of benzaldehyde and of benzoylglycine were used. The optimum conditions were obtained when one mole of benzaldehyde was treated with one mole of benzoylglycine in a mixture of two moles of sulfuric acid and three moles of acetic anhydride for 24 hours at room temperature. The products from several runs, obtained in 85–86% yield, were yellow solids which melted over an approximately 20° range within the limits 119–152°. Recrystallization from acetic anhydride did not substantially improve the melting points. However, treatment with pyridine at room temperature²⁷ gave in all cases an essentially quantitative yield of 2-phenyl-4-benzal-5-oxazolone, m.p. 163.5–164.5°.

Reduction of a typical reaction product melting at 130–152° by the method of Lamb and Robson²⁸ gave a 75% yield of benzoyl-DL-phenylalanine. The formation in good yield of a homogeneous reduction product confirms the above conclusion that the product of the acid-catalyzed condensation is a mixture of geometrical isomers. However, our attempts to separate these mixtures by the method of Carter and Risser²⁷ were unsuccessful.

The acid-catalyzed condensation of benzaldehyde with benzoylsarcosine gave a 66% yield of α -(N-methylbenzamido)-cinnamic acid, m.p. 116–117.5°. The satisfactory yield in this reaction conducted at room temperature may be contrasted with the results of Heard,¹¹ who reported that no product was formed in the sodium acetate catalyzed reaction conducted in acetic anhydride at 100°. However, Deulofeu²⁹ obtained a 40% yield of a product, m.p. 110–111°, by conducting the base-catalyzed reaction at 130–135°. The fact that the acid-catalyzed reaction proceeds without external heating suggests that benzoylsarcosine *per se* is not the reactive component, but is first cyclized to the more reactive oxazolonium ion. The concept of an oxazolonium ion intermediate in reactions of the acylsarcosines also has been advanced by Cornforth and Elliott.³⁰ In addition to the examples cited by these authors,³⁰ the above concept also appears to be capable of explaining the racemization of several α -N-methylamino acids in the presence of certain acetylating agents.^{31,32}

The behavior of several substituted benzaldehydes in the acid-catalyzed condensation reaction has been investigated. While anisaldehyde gave with benzoylglycine a 41% yield of the azlactone, *o*-chlorobenzaldehyde and *m*-nitrobenzaldehyde gave only 10 and 13%, respectively. These results are in contrast with those observed in the usual base-catalyzed Perkin³³ and Erlenmeyer³⁴

reactions where negatively substituted benzaldehydes give better yields than does benzaldehyde itself. However, the present results are in accord with the probable mechanism of the sulfuric acid catalyzed reaction where activation of the aldehyde group by protonation might be expected to occur to a lesser extent in the presence of electronegative substituents.³⁵ Salicylaldehyde yielded no condensation product, but gave instead a 76% yield of the triacetate.³⁶ This anomalous behavior is probably due to the very rapid formation in the reaction mixture of disalicylaldehyde,³⁷ which on standing is slowly converted into the triacetate.^{36,37}

It has been noted above that the sulfuric acid and the sulfuric acid-acetic anhydride catalyzed condensations of benzaldehyde with benzoylglycine give a mixture of the geometrical isomers of 2-phenyl-4-benzal-5-oxazolone. The only product observed in the acetic anhydride and acetic anhydride-sodium acetate catalyzed reactions is the higher melting (165–166°) isomer.^{26,34} However, there are several reports in the literature^{38–41} of instances where the base-catalyzed reaction has yielded a mixture. Thus, it appears that the formation of geometrical isomers in the Erlenmeyer synthesis is dependent both upon the catalytic system and upon the particular pair of reactants. It has been found in this investigation that these effects are not due to isomerization of the unsaturated azlactones in the reaction media. Instead it appears that the geometrical course of the Erlenmeyer reaction may be determined by the interconversion of stereoisomeric forms of the intermediate addition product, *viz.*, by the mutarotation of the intermediate.

If it is assumed that the condensation reaction *per se* leads to a mixture of all four of the possible stereoisomeric forms of the intermediate addition product, *i.e.*, 2-phenyl-4-(α -hydroxybenzyl)-5-oxazolone, we may postulate an orientation by rotation about the central carbon-carbon bond so that the α -hydrogen atom and the β -hydroxy group are in a *trans* position before the β -elimination reaction can occur.^{42,43} The *threo* isomers will then give rise to one geometrical isomer of the unsaturated azlactone, whereas the *erythro* isomers will yield the other. In the absence of mutarotation, and with the assumption of equal rates for the β -elimination reactions, one would expect the over-all condensation reaction to yield an equimolar mixture of the two geometrical isomers. Our results with the sulfuric acid catalyzed reaction of benzaldehyde with benzoylglycine are in general agreement with this concept.

It is logical to assume that the oxazolonium ion

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(33) J. R. Johnson, "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., 1942, p. 210.

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(41) S. Larsen and J. Bernstein, *ibid.*, **72**, 4447 (1950).

(42) E. R. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, New York, N. Y., 1950, pp. 118, 119.

(43) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 467, 468.

derived from benzoylglycine first loses a proton before reacting with the conjugate acid of benzaldehyde. In the case of benzoylsarcosine, the N-methyloxazonium ion itself must react and it is observed that the yield of the condensation product is somewhat lower. Another difference with the N-methyl compound is the fairly sharp melting point of the product, indicating a practically pure geometrical isomer. The steric influence of the N-methyl group may be responsible.

Independent support for the postulate that sulfuric acid can inhibit the mutarotation of the intermediate condensation product of benzaldehyde and benzoylglycine is given by some polarimetric studies on the rate of racemization of benzoyl-D-alanine. It was found that this compound, although completely racemized in acetic anhydride solutions in less than 10 hours at room temperature, retains an appreciable amount of optical activity after 24 hours in an acetic anhydride solution containing sulfuric acid, cf. Fig. 2. A solution of benzoyl-D-alanine in 100% sulfuric acid lost but one-third of its rotatory power in one week. There can be no doubt that azlactone formation was both rapid and almost complete in these instances. The conclusion that sulfuric acid inhibits the racemization of the optically active azlactone is therefore inescapable. On the other hand, it is known that many optically active azlactones are rapidly racemized in acetic anhydride,⁴⁴ and that racemization is increased by the presence of a basic catalyst such as sodium acetate.⁴⁵ Furthermore, it is not unlikely that the mutarotation of the intermediate condensation product can lead to an equilibrium mixture consisting largely of one diastereomer.^{46,47} Hence, if mutarotation is rapid enough, the final reaction product may be an essentially pure geometrical isomer of the unsaturated azlactone. This appears to be the situation in the usual, base-catalyzed Erlenmeyer synthesis with benzaldehyde and benzoylglycine. In other instances, where the rate and position of equilibrium associated with mutarotation are less favorable, both geometrical isomers appear to be obtained.

Recently Stefanovic and Stefanovic⁴⁸ have reported several observations which are pertinent to the subject just discussed. These investigators obtained a 61% yield of the saturated azlactone of α -benzamido- β -acetamido- β -phenylpropionic acid (A) from the reaction of benzylidenbisacetamide with benzoylglycine in a mixture of acetic acid and acetic anhydride. They also isolated from this reaction a small amount of an acid which was converted by acetic anhydride to a saturated azlactone (B) which was isomeric with A. Prolonged heating with acetic anhydride converted A to the stable, high-melting (165–166°) isomer of 2-phenyl-4-benzal-5-oxazolone, while similar treatment of B afforded the labile, low-melting (143–145°) isomer of the same unsaturated azlactone. These experi-

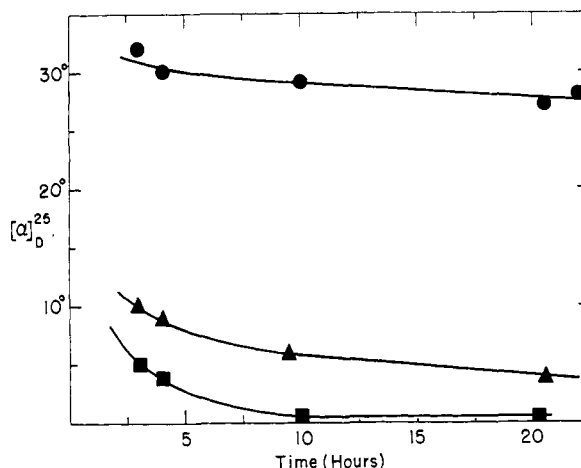


Fig. 2.—Racemization of benzoyl-D-alanine in sulfuric acid and in acetic anhydride: ●, 100% sulfuric acid; ■, acetic anhydride; ▲, mixture of 100% sulfuric acid and acetic anhydride.

ments appear to provide additional support for the present interpretation of the stereochemistry of the condensation of benzaldehyde with 2-phenyl-5-oxazolone. However, it should be noted that the above investigators⁴⁸ appear to have incorrectly related the diastereoisomeric saturated azlactones and the corresponding unsaturated azlactones derived from the former compounds. Thus, on the basis of the *trans*-elimination mechanism^{42,43} the racemic pair having the *threo* configuration should yield the isomer of the unsaturated azlactone in which the β -phenyl group and the nitrogen atom in the oxazolone ring are *cis* to each other. There is as yet no experimental evidence to show whether this *cis*-azlactone is the high-melting or the low-melting isomer.

Experimental^{49,50}

Cryoscopic Studies.—The apparatus and technique have been described previously.³ The solutes were prepared according to recognized procedures, with the exception of benzoylsarcosine. An improved preparation of this compound is given below. The cryoscopic data are summarized in Table II where T is the initial freezing point of the sulfuric acid, Δm , the increment in molality of the solution; ΔT , the corrected resultant freezing point depression; and i , the van't Hoff factor calculated from the relation $i = \Delta T / \Delta m \times 6.154 (i - 0.0047t)$ where t is the mean depression.⁵ It will be noted that in this study⁵¹ a value of 6.154 was taken as the cryoscopic constant of sulfuric acid. In 1950 Gillespie, Hughes and Ingold⁷ suggested that a value of 5.98 was more nearly correct and this latter value was used by Williams and Hardy.⁴ However, in 1954 Gillespie¹⁰ concluded that a value of 6.12 was to be preferred to the value of 5.98. As the difference between this latest value, *i.e.*, 6.12, and the value employed in this study, *i.e.*, 6.15, is not significant insofar as this investigation is concerned we have not re-evaluated the primary data which are given in Table II. The factors responsible for the usual increase in the value of i with increasing solute concentration have already been referred to.³ Of the compounds listed in Table II, benzenesulfonylglycine and benzoylglycine ethyl ester show this latter effect the most clearly. However, with acetylglycine the reverse relationship is clearly indicated, there being a definite decrease in i with increasing concentration. Perhaps this may be taken as evidence for partial oxazonium ion formation, since Treffers and

(44) J. W. Cornforth, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, pp. 732, 738 and 733.

(45) H. B. Carter and C. M. Stevens, *J. Biol. Chem.*, **133**, 117 (1940).

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(48) G. Stefanovic and M. Stefanovic, *J. Org. Chem.*, **21**, 161 (1956).

(49) All melting points are corrected.

(50) Microanalyses by Dr. A. Elek.

(51) J. L. O'Brien, Ph.D. Thesis, Calif. Inst. Tech., Pasadena, 1952.

TABLE II
PRIMARY CRYSCOPIC DATA

<i>T</i>	Δm	ΔT	
Acetylglycine			
10.0	0.0318	0.501	2.57
	.0386	.586	2.48
	.0444	.653	2.41
Benzoylglycine			
10.1	0.0364	0.825	3.70
	.0335	.692	3.38
	.0304	.675	3.65
Benzoylsarcosine			
9.9	0.0340	0.781	3.75
	.0299	.703	3.85
	.0373	.878	3.87
Phthalylglycine			
9.7	0.0364	0.395	1.77
	.0382	.404	1.73
	.0421	.473	1.84
Benzenesulfonylglycine			
9.9	0.0276	0.333	1.97
	.0513	.648	2.06
	.0369	.492	2.19
	.0389	.529	2.23
Benzoylglycine ethyl ester			
9.5	0.0362	0.504	2.28
	.0332	.501	2.47
	.0315	.496	2.59

Hammett⁵² observed a similar behavior for certain substituted benzoic acids whose complex ionization is incomplete. Finally it should be noted that with none of the compounds considered in this study was there a drift of *i*-values with time.

Benzoylsarcosine.—To a cooled solution of 12.3 g. (0.138 mole) of sarcosine, m.p. 209–210° with dec.,⁵³ and 12 g. (0.3 mole) of sodium hydroxide in 108 ml. of water was added 17.4 ml. (0.15 mole) of benzoyl chloride in the course of 20 minutes. The mixture was warmed briefly, cooled and filtered. The filtrate was acidified with concd. hydrochloric acid to give a colorless oil which was extracted in three stages with a total of 150 ml. of chloroform. The extract was dried over anhydrous calcium sulfate and filtered. When 250 ml. of petroleum ether (60–70°) was added to the filtrate a colorless oil separated. The mixture was placed in an ice-bath for several hours whereupon the oil solidified. The white solid was collected, washed with petroleum ether and dried to give 23.2 g. (87%) of product, m.p. 104–105°. This product was recrystallized from three volumes of ethyl acetate to give benzoylsarcosine, m.p. 104–105°. Cocker and Lapworth⁵³ report 50% yield of product melting at 103.5–104° dec. but their method was found to be less satisfactory than that described above.

2-(*p*-Nitrophenyl)-4-methyl-5-oxazolone.—Ten g. of *p*-nitrobenzoyl-DL-alanine⁵⁴ was warmed briefly on the steam-bath with 100 ml. of acetic anhydride. The solvent was removed under reduced pressure, the residue taken up in 50 ml. of benzene, 150 ml. of petroleum ether (60–70°) added to the solution and the latter cooled in an ice-bath. After 3 hours the pale yellow solid was collected, washed with petroleum ether and dried to give 6.6 g. (71%) of the azlactone. Recrystallization from a mixture of benzene and petroleum ether gave a product, m.p. 127–129°.

Anal. Calcd. for C₁₀H₈O₄N₂: C, 54.6; H, 3.4; N, 12.7. Found: C, 54.7; H, 3.9; N, 12.7.

The azlactone gave an intense red-violet color with aqueous alkali, a reaction characteristic of azlactones derived from the *p*-nitrobenzoylamino acids.^{15,16} When a small amount of *p*-nitrobenzoyl-DL-alanine was dissolved in a few ml. of sulfuric acid and the solution quickly poured

into an excess of cold aqueous potassium hydroxide, the intense red-violet color characteristic of the azlactone was observed. A small amount of *p*-nitrobenzoyl-DL-alanine was suspended in a few ml. of acetic anhydride in duplicate test-tubes. When a few drops of concd. sulfuric acid was added to the second tube, a clear solution formed almost immediately. The contents of both tubes were then poured into separate beakers containing an excess of aqueous potassium hydroxide. Whereas the first mixture gave only a faint pink color, the second mixture, containing the sulfuric acid, gave an intense red-violet color.

2-Methyl-4-benzal-5-oxazolone.—(A) One g. of α -acetamidocinnamic acid was dissolved in 5 ml. of 100% sulfuric acid and the orange solution allowed to stand overnight at room temperature. It was then poured into 50 ml. of ice-water, the mixture filtered and the yellow solid triturated with aqueous sodium bicarbonate to give 0.15 g. of the azlactone, m.p. 146.5–149.5°. Recrystallization of this latter product from carbon tetrachloride gave a 2-methyl-4-benzal-5-oxazolone, m.p. 150–152°. Upon admixture with an authentic sample of the azlactone, m.p. 152–153°, the m.p. was not depressed. (B) One g. of α -acetamidocinnamic acid was covered with 3 ml. of acetic anhydride. When 0.25 ml. of 100% sulfuric acid was added, the mixture evolved heat as most of the solid dissolved. The mixture was then poured into ice-water, the yellow solid collected and triturated with aqueous sodium bicarbonate to give 0.35 g. (38%) of 2-methyl-4-benzal-5-oxazolone, m.p. 149–151°.

Condensation of Benzaldehyde with Benzoylglycine in 100% Sulfuric Acid.—To 5 g. of benzoylglycine dissolved in 18 ml. of 100% sulfuric acid was added 3 ml. of benzaldehyde and the resulting red solution maintained at 50° for 24 hours. The solution was then poured into 200 ml. of ice-water. The pale yellow precipitate was collected, triturated with aqueous sodium bicarbonate and dried to give 2.4 g. of product, m.p. 120–151° (35% yield of the azlactone mixture). The product was dissolved in 40 ml. of pyridine at room temperature. After 10 minutes the solution was poured into a mixture of ice, water and 50 ml. of concd. hydrochloric acid. The yellow precipitate was collected, washed with water and dried to give 2.3 g. of 2-phenyl-4-benzal-5-oxazolone, m.p. 164–165.5°. The mixed m.p. with an authentic sample of 2-phenyl-4-benzal-5-oxazolone, m.p. 163–164°, was 163–165°.

Condensation of Benzaldehyde with Benzoylglycine in a Mixture of Sulfuric Acid and Acetic Anhydride.—(A) To 10 g. of finely powdered benzoylglycine covered with 18 ml. of acetic anhydride was added 6 ml. of concd. sulfuric acid. Shaking gave a golden yellow solution as the temperature of the mixture rose to 60°. Six ml. of benzaldehyde was then added whereupon the reaction mixture turned a deep orange-red color. The reaction mixture was allowed to stand 24 hours at room temperature, the solid mass broken up with a spatula and poured into 100 ml. of ice-water. The yellow precipitate was collected, triturated with aqueous sodium bicarbonate and dried to give 12.0 g. of product, m.p. 130–152° (86% yield of the azlactone mixture). (B) In a second experiment using 100% sulfuric acid, there was obtained 11.8 g. (85%) of a product, m.p. 119–131°. Crystallization of 10 g. of this product from 75 ml. of acetic anhydride gave 7 g. of yellow needles, m.p. 123–129°. A second crystallization gave yellow needles of m.p. 124–141°. (C) The product from a third experiment, m.p. 121–143°, was dissolved in 185 ml. of pyridine at room temperature and the azlactone isolated in the usual manner to give 11.1 g. (80%) of 2-phenyl-4-benzal-5-oxazolone, m.p. 163.5–165°. The mixed melting point with an authentic sample was 164–165.5°. (D) A fourth experiment was conducted in a 500-ml., 3-necked flask equipped with thermometer, stirrer and dropping funnel. The reagents were added dropwise and with external cooling so that at no time did the temperature of the reaction mixture exceed 30°. From 100 g. of benzoylglycine, 180 ml. of acetic anhydride, 60 ml. of 100% sulfuric acid and 60 ml. of benzaldehyde there was obtained 118 g. (85%) of yellow product. This product was crystallized from 750 ml. of acetic anhydride to give 104 g. of yellow needles, m.p. 124–141°. Five g. of this recrystallized product was treated with 70 ml. of pyridine in the usual manner to give 5 g. of 2-phenyl-4-benzal-5-oxazolone, m.p. 163–164.5°, mixed m.p. 162–164°.

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(53) W. Cocker and A. Lapworth, *J. Chem. Soc.*, 1894 (1931).

(54) W. M. Colles and C. S. Gibson, *ibid.*, 99 (1928).

(55) M. Bergmann and F. Stern, *Ann.*, **448**, 20 (1926).

Reduction of Azlactone Mixture to Benzoyl-DL-phenylalanine.—(A) A mixture of 10 g. of the above azlactone, m.p. 130–152°, 1.6 ml. of constant-boiling hydriodic acid, 3 g. of red phosphorus and 70 ml. of glacial acetic acid was heated under refluxing conditions for one hour. The hot reaction mixture was filtered, poured into 1 liter of water, the precipitate collected and dried to give 8.1 g. (75%) of benzoyl-DL-phenylalanine, m.p. 181–182.5° (lit.²⁸ yield 72%, m.p. 181°). (B) In a second experiment a mixture of isomers melting at 124–141° gave a 64% yield of recrystallized benzoyl-DL-phenylalanine, m.p. 181–183°, which was not depressed on admixture with an authentic sample of benzoyl-DL-phenylalanine, m.p. 183.5–185°, prepared by the benzoylation of the amino acid.

Condensation of Benzaldehyde with Benzoylsarcosine.—Benzoylsarcosine, 5.4 g., was allowed to react with 3 ml. of benzaldehyde in a mixture of 3 ml. of 100% sulfuric acid and 9 ml. of acetic anhydride. The reaction mixture was allowed to stand for 24 hours at room temperature, the orange solution poured into 50 ml. of ice-water, the pale tan taffy collected, triturated with aqueous sodium carbonate solution, the alkaline solution extracted with ether and the ethereal extract discarded. The alkaline aqueous phase was acidified with concd. hydrochloric acid to give a pale yellow oil which was taken up in 65 ml. of chloroform and the chloroform solution was dried and filtered. The addition of 150 ml. of petroleum ether (60–70°) to the above solution precipitated a colorless oil, which solidified when the mixture was cooled in an ice-bath. The colorless solid was collected and dried to give 5.2 g. (66%) of α -(N-methylbenzamido)-cinnamic acid, m.p. 116–117.5° (lit.²⁹ m.p. 110–111°).

Anal. Calcd. for $C_{17}H_{15}O_3N$: C, 72.6; H, 5.4; N, 5.0. Found: C, 72.5; H, 5.3; N, 4.9.

Reaction of Benzoylglycine with Substituted Benzaldehydes.—The following aldehydes were condensed with

benzoylglycine in a mixture of sulfuric acid and acetic anhydride essentially as described above. The crude products were treated with pyridine in the manner previously described. The yields and melting points of the corresponding azlactones were: anisaldehyde, 41%; m.p. 155.5–157.5° (lit.⁵⁶ m.p. 156.5°); *o*-chlorobenzaldehyde, 10%; m.p. 160–161° (lit.⁵⁷ m.p. 158–159°); *m*-nitrobenzaldehyde, 13%; m.p. 176–177° (lit.⁵⁸ m.p. 178°). Salicylaldehyde gave a 76% yield of the triacetate, m.p. 98.5–100° (lit.⁵⁶ m.p. 101–102°).

Attempted Isomerization Reactions.—When 5 g. of 2-phenyl-4-benzal-5-oxazolone, m.p. 164–166°, was treated with 3 ml. of sulfuric acid and 9 ml. of acetic anhydride for 24 hours at room temperature 4.9 g. (98%) of the azlactone, m.p. 160–163°, was recovered. When 0.3 g. of an azlactone mixture, m.p. 123–129°, was heated for one-half hour at 100° with 5 ml. of acetic anhydride and 1 g. of sodium acetate, 0.3 g. (100%) of an azlactone mixture, m.p. 125–155°, was recovered.

Racemization of Benzoyl-D-alanine.—Benzoyl-D-alanine, large, glistening plates, m.p. 147–148°, $[\alpha]_D^{25} -36.0^\circ$ (0.9576 g. in 5 ml. aqueous sodium hydroxide), lit.⁵⁹ m.p. 148°, $[\alpha]_D^{25} -36.9^\circ$ (in an equivalent amount of aqueous potassium hydroxide) was used to prepare three solutions, *i.e.*, (A) 0.1429 g. in 5 ml. of 100% sulfuric acid; (B) 0.9426 g. and 1.25 ml. of 100% sulfuric acid made up to 5 ml. with acetic anhydride; and (C) 0.4382 g. in 10 ml. of acetic anhydride. The rotations of these three solutions as a function of time of standing at 25° are given in Fig. 2.

(56) E. Erlenmeyer, Jr., and F. Wittenberg, *Ann.*, **337**, 294 (1904).

(57) F. Mauthner, *J. prakt. Chem.*, **95**, 55 (1917).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE PENNSYLVANIA STATE UNIVERSITY]

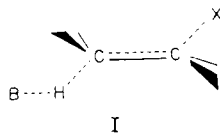
Mechanism of E2 Elimination Reactions. Stereospecificity of Elimination Reactions in the 2-Benzenesulfonyl-3-iodobutane System

By PHILIP S. SKELL AND JAMES H. MCNAMARA

RECEIVED JULY 16, 1956

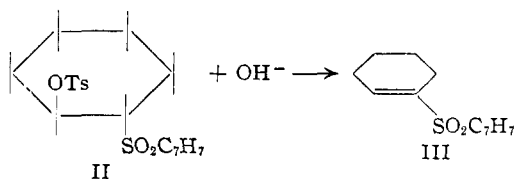
The base-catalyzed dehydrohalogenation of the two diastereoisomeric 2-benzenesulfonyl-3-iodobutanes is stereospecific. Thus, the presence of the powerful electron-withdrawing group, $C_6H_5SO_2$, does not activate the H sufficiently to change the mechanism of E2 elimination (simultaneous loss of H and X) to one involving a carbanion intermediate.

The mechanism of base-catalyzed elimination reactions, E2, is generally considered to involve simultaneous loss of H and X and a planar transition state whose geometry corresponds to *trans* elimination.



Bordwell and Kern¹ have presented convincing evidence for E2 *cis*-elimination in the reaction of hydroxide ions with *trans*-2-(*p*-tolylsulfonyl)-cyclohexyl *p*-toluenesulfonate and the corresponding *trans*-cyclopentyl compound.

(1) F. G. Bordwell and R. J. Kern, *THIS JOURNAL*, **77**, 1141 (1955). This reference succinctly summarizes recent theoretical developments in this field. See also J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., N. Y., 1956, Chap. 7; D. J. Cram and F. A. Abd Elhafez, *THIS JOURNAL*, **74**, 5851 (1952); D. Y. Curtin and D. B. Kellom, *ibid.*, **75**, 6011 (1953).



It was established that 3-*p*-tolylsulfonyl-1-cyclohexene (IV) was not an intermediate in the reaction which produces III. Thus II undergoes *cis*-elimination of *p*-toluenesulfonic acid to produce III in preference to the stereochemically favorable *trans*-elimination to produce IV. This enhancement of rate for *cis*-elimination was attributed to the acid-strengthening character of the sulfone substituent.

Two mechanistic sequences should be considered, (2) involving a carbanion intermediate, or (3) which

