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Dehydration of 4-Oximino-carboxylic Acids with Dicyclohexylcarbodiimide

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Treatment of 4-oximino-4-phenylbutyric acid with dicyclohexylcarbodiimide gave 6*H*-3-phenyl-4,5-dihydro-6-oxo-1,2-oxazine (IId), which was characterized by its infrared spectrum and some reactions. Ring cleavage of IId was easily accomplished by acid or base such as hydrochloric acid, alcohol or amines. The treatment of 4-oximino-valeric acid with dicyclohexylcarbodiimide was also studied.

The investigation of keto dihydro-1,2-oxazines has received only scant attention. Maeder (2) reported the preparation of 6*H*-3-benzyl-4-phenyl-4,5-dihydro-6-oxo-1,2-oxazine (IIa) by heating 4-oximino-3,5-diphenylvaleric acid with acetic anhydride containing sulfuric acid. Errera (3) described the reaction of succinohydroxamic acid with acetyl chloride which gave a product believed to be a 3-acetoxy derivative (IIb). Hurd and Botteron (4) stated the product obtained by the reaction of succinohydroxamic acid with benzoyl chloride to be the 3-benzoyloxy derivative (IIc). However, neither the structures of these two products nor their reactivities have been characterized. On the other hand, some attempts have been made to cyclize 4-oximino-4-phenylbutyric acid (I) to the keto dihydro-1,2-oxazines by Dollfus (5), who obtained only an acetyl derivative of I by reacting I with acetic anhydride or acetyl chloride and observed only the formation of an unstable *anti* form of I by treatment with sulfuric acid, thereby failing to obtain the oxazine ring.

This paper describes the dehydration of 4-oximino-carboxylic acids with dicyclohexylcarbodiimide to form the corresponding 6*H*-4,5-dihydro-6-oxo-1,2-oxazines and to record some reactions of the latter.

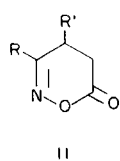
Treatment of 4-oximino-4-phenylbutyric acid (I) with an equimolar amount of dicyclohexylcarbodiimide in tetrahydrofuran at room temperature gave a crystalline product with the theoretical amount of *N,N'*-dicyclohexylurea. The elementary analysis of the product indicated the empirical formula, $C_{10}H_9NO_2$, corresponding to the cyclic structure IId. Its infrared spectrum showed the absorption bands at 1765 (C=O) and 1610 cm^{-1} (C=N) and no absorption band in the hydroxyl region. It has been shown that 4*H*-isoxazoline-5-ones which are five membered analogs of 6*H*-4,5-dihydro-6-oxo-1,2-oxazine (II) show absorption bands at 1813-1750 cm^{-1} (=C=O) and 1624-1550 cm^{-1} (=C=N) (6). Thus, the absorption bands of IId at 1765 and 1610 cm^{-1} could be ascribed to the =C=O and the =C=N groups of ring system II, respectively. From an observation of the infrared spectrum as well as the following reactivities, the product (IId) was assigned the structure, 6*H*-3-phenyl-4,5-dihydro-6-oxo-1,2-oxazine.

Compound IId, on treatment with aqueous alkali gave the parent oximino acid (I) and alcoholysis of IId gave the ester (III). Hydrolysis of IId with 3*N* hydrochloric acid yielded 3-benzoylpropionic acid. Reaction of IId with aniline, hydroxylamine and *O*-benzylhydroxylamine gave the corresponding anilide (IV), hydroxamic acid (V) and *O*-benzylhydroxamate (VI), respectively in good yield. The structure of IV and VI was established by the comparisons (m. p., mixed m. p. and infrared spectra) with an authentic sample prepared by the oximation of 3-benzoylpropionanilide (VII) and *N*-(3-benzoylpropionyl)-*O*-benzylhydroxylamine (VIII), respectively. Furthermore, VI on treatment with hydrochloric acid and formaldehyde gave also VIII.

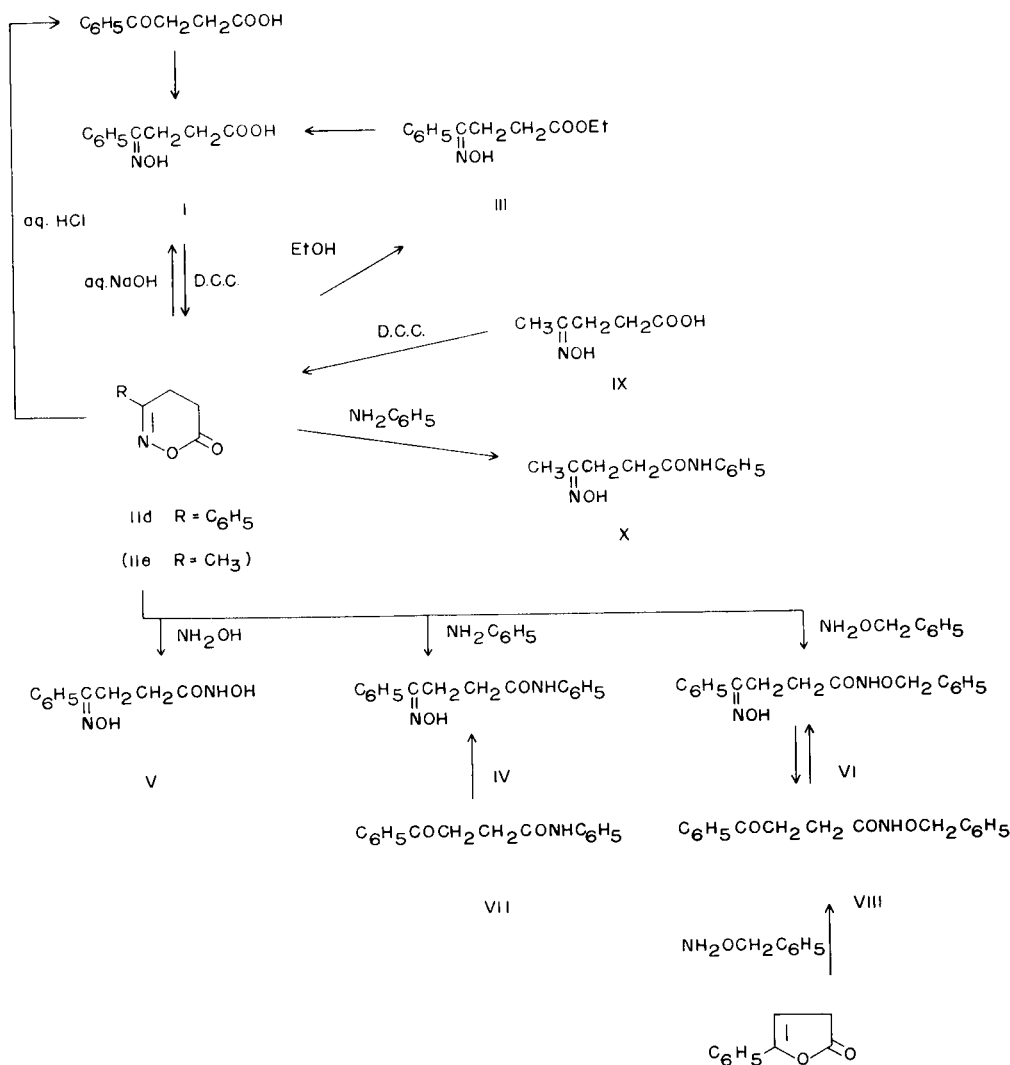
The easy cleavage of IId may be due to the lack of enolization. This was indicated by the lack of absorption in the OH region in the infrared spectrum of IId and by a negative ferric reaction. On the other hand the five membered analog of IId, 4*H*-isoxazoline-5-ones, are known to be stabilized by a contribution of a conjugated double bond due to enolization, and are unchanged on heating with acid or alkali and give a positive ferric chloride reaction (7).

Rischbieth (8) reported the treatment of 4-oximino-valeric acid (IX) with sulfuric acid to give 6*H*-3-methyl-4,5-dihydro-6-oxo-1,2-oxazine (IIe), however, Bredt and Boedinghous (9) later reexamined this reaction and found that the product is not the oxazine derivative but *N*-methylsuccinimide.

When IX was treated with dicyclohexylcarbodiimide in a similar manner as in the case of IId, a pale yellow, oily product was obtained with the theoretical amount of *N,N'*-dicyclohexylurea. The infrared spectrum of the product showed a strong absorption band at 1785 cm^{-1} which might indicate the cyclic structure IIe. The reaction of the oily product with aniline gave 4-oximinovaleranilide (X), which showed no depression in mixed melting point with an authentic sample. These facts indicate that the oily product obtained in the reaction of IX with dicyclohexylcarbodiimide is 6*H*-3-methyl-4,5-dihydro-6-oxo-1,2-oxazine (IIe).



	R	R'
a	C ₆ H ₅ CH ₂	C ₆ H ₅
b	CH ₃ COO	H
c	C ₆ H ₅ COO	H



EXPERIMENTAL

6H-3-Phenyl-4,5-dihydro-6-oxo-1,2-oxazine (II d).

To a solution of 10 g. of 4-oximino-4-phenylbutyric acid (5) in 100 ml. of absolute tetrahydrofuran was added 11 g. of dicyclohexylcarbodiimide and the mixture was allowed to stand at room temperature overnight. After removal of the precipitated dicyclohexylurea, the solution was concentrated under reduced pressure to give a crystalline

residue. Rapid recrystallization from 1-butanol afforded 7 g. of colorless leaflets, m.p. 99.5-100.5°. The infrared spectrum showed absorption bands at 1765 and 1610 cm⁻¹.

Anal. Calcd. for C₁₆H₁₃NO₂: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.41; H, 5.19; N, 8.03.

Treatment of II d with aqueous sodium hydroxide.

In 20 ml. of aqueous sodium hydroxide solution (4%) was suspended

0.5 g. of IId, and the mixture was allowed to stand at room temperature. After 10 minutes, the mixture became a clear solution. It was treated with activated charcoal and acidified with 3 *N* hydrochloric acid to afford 0.4 g. of colorless crystals, m.p. 133–135°. The product was shown to be I by mixed melting point and the infrared spectrum.

Treatment of IId with hydrochloric acid.

A suspension of 0.5 g. of IId in 20 ml. of 3 *N* hydrochloric acid was heated on a boiling water bath for 1 hour after which a clear solution was obtained. On cooling the solution, 0.45 g. of colorless needles, m.p. 115–116° separated. The product was identified as 3-benzoylpropionic acid by comparison with an authentic sample (10).

Treatment of IId with ethanol.

A suspension of 1 g. of IId in 20 ml. of ethanol was allowed to stand at room temperature for 3 days. The resultant red solution was concentrated under reduced pressure to give a red brown oil, which was established to be ethyl 4-oximino-4-phenyl butyrate (III) by comparison of the infrared spectrum with that of authentic sample. The oil was hydrolyzed by warming with 5% aqueous sodium hydroxide followed by neutralization with 3 *N* hydrochloric acid to give I (m.p. 130–132°).

4-Oximino-4-phenylbutylanilide (IV).

(a) By reaction of IId with aniline.

To a solution of 1 g. of IId in 30 ml. of benzene was added 0.56 g. of aniline and the mixture was refluxed for 2 hours. The solution was concentrated under reduced pressure and the residue was recrystallized from benzene to afford 0.5 g. (32.6%) of colorless needles (IV), m.p. 173–174°, dec. IV was soluble in ethanol and ether. The infrared spectrum showed absorption bands at 3250, 1660 and 1605 cm^{-1} .

Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.63; H, 6.22; N, 10.65.

(b) By oximation of 3-benzoylpropionanilide.

To a solution of 0.4 g. of 3-benzoylpropionanilide (11) in 42 ml. of ethanol was added an aqueous solution of 0.13 g. of hydroxylamine hydrochloride and 0.1 g. of potassium hydroxide. The mixture was refluxed for 10.5 hours. Then it was concentrated under reduced pressure and the residue was recrystallized from benzene to yield 0.25 g. of colorless needles, m.p. 171–172°. The product showed no depression in melting point when mixed with the specimen obtained by method (a).

4-Oximino-4-phenylbutyrylhydroxamic acid (V).

To a solution of 3 g. of IId in 40 ml. of dioxane was added 0.6 g. of hydroxylamine, and the mixture was heated under reflux for 4 hours. The dioxane was evaporated under reduced pressure and the residue crystallized upon addition of benzene. Recrystallization from 1-butanol yielded 2.2 g. of crystals, m.p. 138–139°. The product is soluble in ethanol and ether, insoluble in benzene, and gives a wine red color with a methanolic solution of ferric chloride. The infrared spectrum showed absorption bands at 3200, 3050, 1655 and 1635 cm^{-1} .

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_3$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.39; H, 5.83; N, 13.61.

N-(4-Oximino-4-phenylbutyryl)-*O*-benzylhydroxylamine (VI).

(a) By reaction of IId with *O*-benzylhydroxylamine.

To a solution of 1.7 g. of IId in 25 ml. of dioxane was added 1.2 g. of *O*-benzylhydroxylamine, and the mixture refluxed for 4 hours, and worked up as described above for V. Recrystallization from benzene yielded 1.7 g. of colorless leaflets, m.p. 117–118°. It was soluble in alcohol and chloroform. The infrared spectrum showed absorption bands at 3160, 1655 and 1635 cm^{-1} .

Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_3$: C, 68.44; H, 6.08; N, 9.19. Found: C, 68.19; H, 5.88; N, 9.46.

(b) By oximation of VIII.

To a solution of 0.45 g. of VIII in 40 ml. of methanol was added an aqueous solution of 0.15 g. of hydroxylamine hydrochloride and 0.13 g. of potassium hydroxide, and the mixture was refluxed for 8 hours. The solution was concentrated under reduced pressure, and the residue was washed with water and benzene added. It gradually solidified. Recrystallization from benzene afforded 0.35 g. of leaflets, m.p. 117.5–119°. The identity of this product with the specimen prepared by method (a) was established by a mixed melting point and a comparison of the infrared spectra.

N-(3-Benzoylpropionyl)-*O*-benzylhydroxylamine (VIII).

(a) By reaction of 5-phenyl-2,3-dihydro-2-furanone with *O*-benzylhydroxylamine.

To a suspension of 3 g. of 5-phenyl-2,3-dihydro-2-furanone (12) was added 2.3 g. of *O*-benzylhydroxylamine, and the mixture was refluxed for 1 hour. The resultant clear solution was concentrated under reduced pressure to give a residue, which on addition of di-*n*-butyl ether solidified gradually. By recrystallization from di-*n*-butyl ether, 3 g. of colorless needles, m.p. 98–99°, was obtained. The infrared spectrum showed strong absorption bands at 3125, 1690 and 1665 cm^{-1} .

Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{NO}_3$: C, 72.01; H, 6.05; N, 4.94. Found: C, 71.91; H, 5.75; N, 5.01.

2,4-Dinitrophenylhydrazone of VIII.

Orange needles from 1-butanol, m.p. 173–175°.

Anal. Calcd. for $\text{C}_{23}\text{H}_{21}\text{N}_5\text{O}_6$: N, 15.11. Found: N, 15.10.

(b) By hydrolysis of VI.

To a solution of 1.0 g. of VI in 5 ml. of ethanol were added 2 ml. of concentrated hydrochloric acid and 2 ml. of formaldehyde (40% aqueous solution), and the resultant clear solution was allowed to stand at room temperature overnight. The solution was then poured into water to separate an oil, which was extracted with ether. After being washed with water and dried over anhydrous sodium sulfate, the extract was concentrated to afford a pale brown oil. The infrared spectrum showed that the oil was crude VIII. The oil was converted into the 2,4-dinitrophenylhydrazone, which melted at 175–177° and showed no depression by mixed melting point with the specimen obtained by method (a).

Treatment of IX with dicyclohexylcarbodiimide.

To a solution of 10.5 g. of 4-oximinovaleic acid in 200 ml. of tetrahydrofuran was added 16.1 g. of dicyclohexylcarbodiimide, and the mixture was allowed to stand at room temperature overnight. After removal of the precipitated dicyclohexylurea, the solution was concentrated under reduced pressure to yield 12 g. of a yellow jelly. The infrared spectrum showed a strong absorption band at 1785 cm^{-1} similar to that of IId, and thus might indicate that the product was 6*H*-3-methyl-4,5-dihydro-6-oxo-1,2-oxazine (IIe). Attempts to purify the product by crystallization or chromatography were unsuccessful. The product gave a violet color with a methanolic solution of ferric chloride, but it may be due to an impurity.

Treatment of crude IIe with aniline.

A solution of 2.3 g. of the crude jelly obtained in the reaction of IX with dicyclohexylcarbodiimide and 1.86 g. of aniline in 20 ml. of benzene was refluxed for 2 hours. On cooling the resultant solution deposited a white solid, which was recrystallized from ethyl acetate to give 1.7 g. of colorless needles, m.p. 146–147°. The product was identified with authentic 4-oximinovaleeranilide (X) (13) (lit. m.p. 144–146°) both by a mixed melting point and by a comparison of the infrared spectrum (3270, 1655 and 1600 cm^{-1}).

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