lyzed by treatment with one equivalent of 1 *N* sodium hydroxide solution in 95% ethanol for two hours at reflux temperature. The β-benzohydrylaminohydrocinnamic acid, isolated by extraction of a neutralized aqueous solution with ether, was obtained in 74% yield as a powdery solid; softening point 75–80°; neutralization equivalent, 327 (calcd. 331). This was identical with a sample prepared from the amino ester.

**Reaction Rate Studies.**—Reactions were run in glass-stoppered Pyrex test-tubes. Reactants were heated (or cooled) to the proper temperature before mixing. Unless otherwise indicated, the concentration of reactants at zero time was determined experimentally. The β-lactams were distilled or recrystallized at least twice. N,N-Diethylpropionamide[21] was prepared from propionic anhydride and diethylamine; b. p. 81–85° at 20 mm.

(a) **Alkaline Hydrolyses.**—To a weighed sample of approximately 2 millimoles of the amide was added the calculated volume of an 85% ethanol solution 0.522 *N* in sodium hydroxide. Sufficient 85% ethanol was added so that the initial molarity of the reactants was essentially the same for all amides studied, irrespective of molecular weight. Samples were withdrawn with a graduated pipet, diluted 1:5 with 85% ethanol at room temperature (at 0° in the case of reactions at 0°), and titrated immediately with 0.451 *N* hydrochloric acid (in 85% ethanol) using phenolphthalein as indicator.[22]

(b) **Ethanolyses.**—To a weighed sample of approximately 1.2 millimoles of the amide was added the calculated amount of 0.495 *N* ethanolic hydrogen chloride and sufficient absolute ethanol to adjust the initial molarity of the reactants. Samples were withdrawn with a graduated pipet, diluted 1:5 with 50% ethanol, and titrated immediately with 0.510 *N* aqueous sodium hydroxide using sodium alizarinsulfonate as indicator. In the case of 1-benzyl-4-phenyl-2-azetidinone, the titration was carried out potentiometrically because of the low basicity of the amino ester.

(21) J. v. Braun, *Ber.*, **36**, 2287 (1903).

(22) F. W. Foreman, *Biochem. J.*, **14**, 451 (1920).

**Isolation of Ethyl β-Benzylaminopropionate Hydrochloride.**—A solution of 44.5 mg. (0.28 millimole) of 1 benzyl-2-azetidinone in 0.56 ml. of 0.495 *N* ethanolic hydrogen chloride (0.28 millimole of hydrogen chloride) was heated at 50° for twenty-four hours. The solution was evaporated to dryness under reduced pressure. The crystalline product was washed with absolute ether and dried; wt. 58.5 mg. (87.5%), micro m. p. 141–149° dec. After two recrystallizations from ethanol–ether 35 mg. was recovered; micro m. p. 148–153° dec.; capillary m. p. 151–153° dec.; mixed capillary melting point with an authentic sample of ethyl β-benzylaminopropionate hydrochloride was undepressed.

**Reactivity toward Diethylamine.**—A solution of 85 mg. (1.0 millimole) of 1-methyl-2-azetidinone in 1 ml. of diethylamine was heated in a glass-stoppered test-tube at 50° for four hours. The diethylamine was then removed by evaporation under reduced pressure. Titration in 50% ethanol indicated that less than 0.001 milliequivalent of basic material was present. Therefore, less than 0.1% of the β-lactam had reacted to give a basic product.

**Acknowledgment.**—The authors wish to express their appreciation to Dr. Carl M. Stevens for his many helpful suggestions.

## Summary

Four N-alkyl-β-lactams have been synthesized by treatment of the corresponding β-amino esters with one equivalent of ethylmagnesium bromide. The reaction shows promise as a method of preparation of simple N-alkyl-β-lactams.

The yield of amide does not exhibit any direct relationship to the basicity of the amino ester.

Rates of alkaline hydrolysis and rates of ethanolysis in the presence of hydrogen chloride have been determined.

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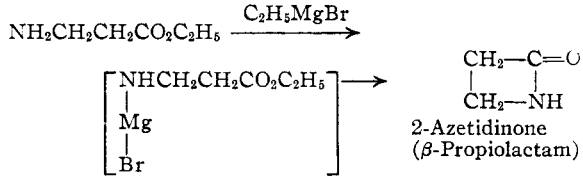
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, THE STATE COLLEGE OF WASHINGTON]

# 2-Azetidinone (β-Propiolactam)[1]

BY ROBERT W. HOLLEY[2,3] AND ANN D. HOLLEY[3]

The reaction of a β-amino ester with one equivalent of a Grignard reagent is applicable to the synthesis of a variety of N-alkyl-β-lactams.[4] It seemed possible that the reaction might be extended to the synthesis of the unsubstituted four-membered lactam, 2-azetidinone (β-propiolactam). Synthesis of the compound in very low yield has now been accomplished in this way, and the properties of this previously unknown compound have been investigated.




2-Azetidinone is a colorless solid of melting point 73–74°. It is a neutral compound, practically odorless when pure, very soluble in water, ethanol, and chloroform, and moderately soluble in ether and benzene. It has been purified by recrystallization from ether or by sublimation at moderate temperatures. Its boiling point, 106° at 15 mm., is lower than that of 2-pyrrolidone.[5]

Hydrolysis of 2-azetidinone with aqueous alkali yields β-alanine, which was isolated in 80% yield as the *p*-toluenesulfonamide. Ethanolysis in the presence of hydrogen chloride affords β-alanine ethyl ester hydrochloride.

The rates of reaction of 2-azetidinone with so-

(1) This work was supported in part by a grant from the College Committee on Research of The State College of Washington.

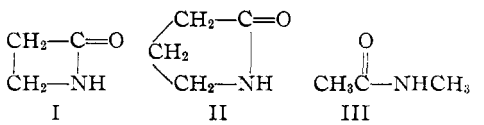
(2) American Chemical Society Postdoctoral Fellow, 1947–1948.

(3) Present address: New York State Agricultural Experiment Station, Geneva, N. Y.

(4) R. W. Holley and A. D. Holley, THIS JOURNAL, **71**, 2124 (1949).

(5) E. Fischer, *Ber.*, **34**, 444 (1901), reported for 2-pyrrolidone, b. p. 138° at 12 mm. S. S. Guha-Sircar, *J. Indian Chem. Soc.*, **5**, 549 (1928); *C. A.*, **23**, 818 (1929), reported b. p. 114° at 14 mm.

dium hydroxide in 85% ethanol and with ethanolic hydrogen chloride were determined. 2-Azetidinone (I) is much more reactive than the five-membered ring amide 2-pyrrolidone (II) and the straight-chain, N-alkylamide, N-methylacetamide (III). It is somewhat more reactive than the 1-alkyl-2-azetidinones.[4] The data are summarized in Table I.



I II III

The energy of activation for the alkaline hydrolysis of 2-azetidinone is about 16 kcal.

TABLE I

HYDROLYSES AND ETHANOLYSES

| Compound | Reaction | Initial concn., moles/l. | $T$, °C. | Time, min. | Amount reacted, % | $k \times 10$, liter moles$^{-1}$ min.$^{-1}$ |
|---|---|---|---|---|---|---|
| I | Alk. hydr. | 0.48[b] | 50 ± 1 | 15 | 48 | 1.3 |
| | | | | 20 | 56 | 1.3 |
| I | Alk. hydr. | .48[b] | 0 | 1050 | 38 | 0.012 |
| II[a,c] | Alk. hydr. | .48 | 50 ± 1 | 180 | 4 | .005 |
| | | | 50 ± 1 | 300 | 8 | .006 |
| | | | 50 ± 5 | 1390 | 36 | .008 |
| III[a] | Alk. hydr. | .49 | 50 ± 5 | 1320 | 15 | .003 |
| I | EtOH, HCl | .44[b] | 50 ± 1 | 15 | 54 | |
| | | | | 20 | 61 | |
| II[a,c] | EtOH, HCl | .46 | 50 ± 5 | 1080 | *ca.* 10 | |
| III[a] | EtOH, HCl | .45[b] | 50 ± 5 | 2600 | *ca.* 10 | |

[a] The procedures followed are those reported in the previous paper (ref. 4). [b] The initial concentration was not determined experimentally; the value was calculated from the approximate volume of the reactants. [c] Synthesized from γ-aminobutyric acid according to the procedure of S. Gabriel, *Ber.*, **22**, 3338 (1889).

Although 2-azetidinone is a reactive compound when compared with normal amides, it is relatively unreactive in comparison with the penicillins. Thus, 2-azetidinone was recovered nearly quantitatively from methanol solution after sixteen hours at 50° in the absence of catalyst. The reaction of sodium benzylpenicillinate with methanol is reported to be essentially complete in two hours at 25°.[6] Only 2% reaction, measured by the formation of non-volatile basic material, took place when 2-azetidinone was heated with diethylamine for sixteen hours at 50°. The reaction of benzylpenicillin with amines is rapid.[7]

2-Azetidinone (β-propiolactam) is not as reactive as β-propiolactone. β-Propiolactone reacts almost completely with methanol in the absence of a catalyst during sixteen hours at 45°,[8] conditions which give little or no reaction with 2-azetidinone. β-Propiolactone reacts with saturated sodium chloride solution at room temperature to give a 74% yield of sodium β-chloropropionate.[9] Under similar conditions, 2-azetidinone did not react.

2-Azetidinone showed no significant inhibition of growth of *Staph. aureus* (Oxford) in liquid medium (Difco Bacto Pen-assay broth) when tested at approximately 1000 times the concentration at which benzylpenicillin is active.[10]

## Experimental[11]

**2-Azetidinone (β-Propiolactam).**—A solution of 82 g. (0.70 mole) of distilled β-alanine ethyl ester[12] (neutralization equivalent, 120; calcd., 117) in 2.0 liters of absolute ether was placed in a flask equipped with an efficient condenser and a dropping funnel. From the dropping funnel was added 325 ml. (0.70 mole) of a 2.16 *N* ethereal solution of ethylmagnesium bromide during 35 minutes. The contents of the flask were agitated occasionally and left at room temperature (30°) for one and three-quarters hours. At this time, 220 ml. of saturated ammonium chloride solution was added, with caution. After the addition was complete, the contents of the flask were mixed thoroughly and the ether solution was decanted and dried over anhydrous magnesium sulfate. The aqueous mixture was extracted with eight 500-ml. portions of chloroform (freshly distilled).[13] After three of these extractions the aqueous mixture was diluted with 100 ml. of water. The chloroform extracts were dried over magnesium sulfate. Ether and chloroform were removed by distillation, first at atmospheric pressure and finally at water pump pressure. Titration of an aliquot of the 59.8 g. of residue gave a neutralization equivalent of 180, corresponding to the presence of 0.336 mole of basic material. A second aliquot was further evaporated to remove the last traces of chloroform (some unreacted β-alanine ethyl ester was lost during the process); titration of this indicated the presence of 11.5 g. (16% yield) of amide (—$NHCH_2CH_2CO$—) units.

The remaining 59.5 g. (neutralization equivalent 180) was diluted with 20 ml. of absolute ethanol and 81 ml. (0.33 mole) of 4.1 *N* ethanolic hydrogen chloride was added slowly with cooling of the solution. Since the resultant solution was acidic, it was brought just to the neutral point (spot test with sodium alizarinsulfonate as indicator) by the addition of 1.67 ml. (0.012 mole) of triethylamine. Ethanol was removed at water pump pressure until the weight of the residual oil was 68 g. This oil was extracted successively with 500, 400, 400 and 200 ml. of absolute ether; the last extract was left with the residue overnight. The residue partially crystallized during the extractions. Ether was distilled from the combined extracts at atmospheric pressure until the volume reached 20 ml.; the last of the ether was removed at water pump pressure. The residual oil, wt. 1.49 g., had a strong "nicotine-like" odor. The oil was distilled and the distillate, b. p. 80–100° at 2 mm., 710 mg., crystallized immediately. The solid was washed with 0.5 ml. of ether, and then dried at reduced pressure, wt. 476 mg. This was dissolved in 30 ml. of warm absolute ether and the solvent was distilled until crystals appeared (final volume approximately 8 ml.). The mixture was cooled in an ice–salt-bath and the crystalline 2-azetidinone was collected by filtration, washed with cold absolute ether, and dried. The weight of colorless, nearly odorless solid was 333 mg., m. p. 73–74°. A second crop of 46 mg. was obtained by concentration of the mother liquors to 2 ml. The total yield of pure 2-azetidinone was 379 mg. (0.76%). Fur-

(6) S. A. Ballard, D. S. Melstrom and C. W. Smith, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, Chap. XXVI.

(7) R. L. Peck and K. Folkers, *ibid.*, Chap. IV.

(8) Gresham, Jansen, Shaver, Gregory and Beears, THIS JOURNAL, **70**, 1004 (1948).

(9) Gresham, Jansen, Shaver and Gregory, *ibid.*, **70**, 999 (1948).

(10) 1-Methyl-2-azetidinone, 1-benzyl-2-azetidinone, and 1-benzyl-4-phenyl-2-azetidinone (*cf.* ref. 4) were also tested and found to be inactive at this concentration.

(11) All melting points are corrected.

(12) From β-alanine ethyl ester hydrochloride, which was prepared by esterification of β-alanine: *cf.* W. J. Hale and E. M. Honan, THIS JOURNAL, **41**, 774 (1919).

(13) A preliminary investigation of the solubility characteristics of 2-pyrrolidone had indicated that this procedure would probably be satisfactory for the isolation of 2-azetidinone.

ther recrystallization from ether, or sublimation at 70° at 2 mm., did not raise the melting point. For analysis, a sample was recrystallized twice from ether. This sample had a b. p. (micro) of 106° at 15 mm. 2-Azetidinone was protected from moist air since it was known that 1-methyl-2-azetidinone and 2-pyrrolidone are hygroscopic.

*Anal.* Calcd. for $C_3H_5NO$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.71; H, 6.97; N, 19.45.

The melting point of 2-azetidinone was unchanged by ten minutes heating in a capillary tube at 110°. However, when a sample of 2-azetidinone, sealed in a capillary tube, was heated to 180° during the course of ten minutes, it was converted to a cloudy viscous material. The instability of 2-azetidinone at high temperatures was observed during an attempt to prepare a sample for a Rast molecular weight determination in camphor. Because of this difficulty and because 2-pyrrolidone gives high molecular weight values, presumably because of association, no further attempt to determine the molecular weight was made. The fact that the boiling point of 2-azetidinone is below that of 2-pyrrolidone is considered sufficient indication of its low molecular weight.

A mixture of 2-azetidinone and acrylamide[14] (m. p. 81–83°) liquefied at room temperature.

**Alkaline Hydrolysis (a) Rate.**—In a glass-stoppered test-tube a solution of 17.5 mg. (0.246 millimole) of 2-azetidinone in 0.02 ml. of 85% ethanol was heated to 50°, and 0.473 ml. of an 85% ethanol solution which was 0.522 *N* in sodium hydroxide (0.247 millimole of sodium hydroxide) was added (at 50°). The solution was heated at 50° for fifteen minutes. The test-tube was then placed in an ice–salt-bath and 2.5 ml. of cold 85% ethanol was added. The solution was titrated with 0.451 *N* hydrochloric acid (in 85% ethanol) with phenolphthalein as indicator. It neutralized 0.286 ml. (0.129 millimole); 48% of the 2-azetidinone had reacted. In subsequent experiments 56% reacted in twenty minutes at 50°, and 38% reacted in 1050 minutes at 0°.

**(b) Isolation of the *p*-Toluenesulfonamide of β-Alanine.**—A solution of 20 mg. (0.28 millimole) of 2-azetidinone in 0.4 ml. of water and 0.15 ml. of 40% potassium hydroxide solution was heated at 75° for one-half hour. The solution was cooled and treated with 150 mg. (0.79 millimole) of finely powdered *p*-toluenesulfonyl chloride. The addition of 0.08 ml. of 40% potassium hydroxide during the reaction was required to keep the solution basic. The aqueous solution was extracted repeatedly with ether and was then acidified with 0.15 ml. of concentrated hydrochloric acid. The *p*-toluenesulfonyl derivative was extracted into ether, and the ethereal solution was washed with water and dried over anhydrous magnesium sulfate. The ether was removed at reduced pressure; 57 mg. (84%) of the *p*-toluenesulfonamide of β-alanine was obtained, m. p., sintered 106–110°, melted 116–119°. Recrystallization twice from 0.2 ml. of ethanol, 0.2 ml. of ether, plus 30–70° petroleum ether to cloudiness gave 39.5 mg. (58%); m. p. 119–121°; neutralization equivalent, 240 (calcd. 243). A mixed melting point with authentic *p*-toluenesulfonamide of β-alanine (m. p. 119.5–121°; prepared from β-alanine) showed no depression.

(14) E. H. Huntress and S. P. Mulliken, "The Identification of Pure Organic Compounds," Vol. I, John Wiley and Sons, New York, N. Y., 1941, p. 182.

**Ethanolysis in the Presence of Hydrogen Chloride (a) Rate.**—In a glass-stoppered test-tube, a solution of 15.8 mg. (0.22 millimole) of 2-azetidinone in 0.04 ml. of absolute ethanol was heated to 50°, and 0.45 ml. of a solution of 0.495 *N* hydrogen chloride (0.22 millimole) in absolute ethanol (at 50°) was added. The solution was heated at 50° for fifteen minutes. The test-tube was then placed in an ice-bath and 2.5 ml. of cold 50% ethanol was added. The solution was titrated with 0.510 *N* aqueous sodium hydroxide using sodium alizarinsulfonate as indicator. It neutralized 0.20 ml., 0.10 millimole; 54% of the 2-azetidinone had reacted. In a second experiment, 61% reacted in twenty minutes at 50°.

**(b) Isolation of β-Alanine Ethyl Ester Hydrochloride.**—A solution of 13.8 mg. (0.194 millimole) of 2-azetidinone in 0.39 ml. of 0.495 *N* hydrogen chloride in absolute ethanol was heated at 50° for one hour. The solvent was evaporated at reduced pressure and the solid residue was washed with absolute ether. The yield of β-alanine ethyl ester hydrochloride, identical with an authentic sample, was 27 mg. (91%).

**Attempted Reactions with 2-Azetidinone (a) Methanolysis in the Absence of Acid.**—A solution of 7.0 mg. of 2-azetidinone in 1 ml. of absolute methanol was heated at 50° for sixteen hours. The solution was evaporated to dryness and the solid was washed with ether; recovery, 6.0 mg.; m. p. 72–73.5°. A mixed melting point with 2-azetidinone was undepressed.

**(b) Reaction with Diethylamine.**—A solution of 16.0 mg. of 2-azetidinone in 0.3 ml. of diethylamine was heated at 50° for sixteen hours. The diethylamine was evaporated at reduced pressure. Titration of the residue indicated approximately 2% reaction (formation of basic material).

**(c) Reaction with Sodium Chloride Solution.**—A solution of 7.1 mg. of 2-azetidinone and 17.5 mg. of sodium chloride in 0.04 ml. of water was left at 30° for six hours. Titration of the solution with 0.1 *N* hydrochloric acid indicated less than 1% reaction had taken place.

**Acknowledgment**—The authors wish to thank Dr. Carl M. Stevens and Mr. R. Watanabe for the microbiological assays, and Dr. Stevens for his many helpful suggestions.

## Summary

2-Azetidinone (β-propiolactam), a previously unknown compound, has been synthesized in small yield by treatment of β-alanine ethyl ester with one equivalent of ethylmagnesium bromide. This is the first β-lactam reported having a hydrogen on the nitrogen.

2-Azetidinone is much more reactive than 2-pyrrolidone and N-methylacetamide and is somewhat more reactive than simple N-alkyl-β-lactams. Its reactivity is low in comparison with that of benzylpenicillin.

2-Azetidinone shows no significant activity against *Staph. aureus*.

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