Data for some properties of these ketones have been collected in Table I. From these ketones were prepared semicarbazones,[9] for which melting points and analytical data are reported in Table II. Even though a much longer period of heating than usual was employed, it was difficult to obtain, even in poor yield, semicarbazones from the 1-methylbutyl and 1-ethylpropyl ketones. Purification of the semicarbazones also was difficult in these two cases.

From time to time attempts have been made in this Laboratory to regenerate ketones from semicarbazones, or similar derivatives, as a means of purification of alkoxyalkyl alkyl (or phenyl) ketones. In general, these attempts have been unsuccessful. However, by adding dropwise a saturated solution of sodium nitrite[10] to an ice-cold, glacial acetic acid solution of the semicarbazone of 1-methoxypropyl 3-methylbutyl ketone, then warming the mixture for ten minutes before pouring into ten volumes of water, there was obtained a sparingly soluble layer. The latter was dried and distilled to yield the ketone in 63% yield.

(9) Shriner and Fuson, "The Systematic Identification of Organic Compounds," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 142.

Summary

Fifteen ketones have been synthesized by interaction of appropriate Grignard reagents with 1-methoxybutyronitrile.

(10) Goldschmidt and Veer, *Rec. trav. chim.*, **65**, 796 (1946).

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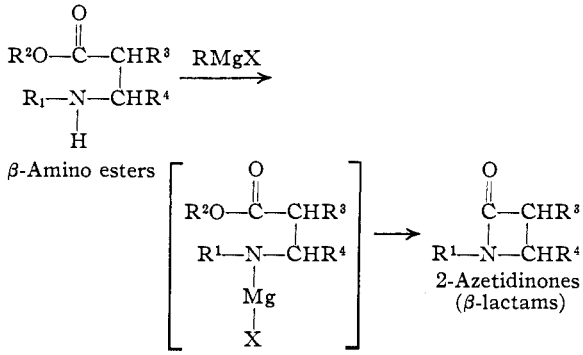
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, THE STATE COLLEGE OF WASHINGTON]

Synthesis and Reactivity of Some 1-Alkyl-2-azetidinones (N-Alkyl-β-lactams)[1]

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

The discovery that the reactive ring system present in the penicillins is probably a β-lactam[4] has greatly stimulated interest in β-lactams and has made the relation of reactivity of β-lactams to their structure a problem of considerable importance. β-Lactams known prior to the war-time penicillin work were found to be relatively resistant to hydrolysis, behavior which is characteristic of most amides. A number of different β-lactams were prepared and studied during the penicillin work and data concerning them is summarized in "The Chemistry of Penicillin."[5] The number of synthetic methods for the preparation of β-lactams is still very limited, however, and the data on their reactivity are inadequate for a conclusion to be drawn as to the reason for the reactivity of the penicillins.

The reaction of a β-amino ester with a Grignard reagent, according to the following equation, was one of the methods developed for the synthesis of β-lactams during the war-time penicillin work.[5] Presumably an intermediate aminomagnesium halide is formed; the reaction of aminomagnesium halides with esters is known to afford amides.[6] Five β-lactams, all with N-phenyl substitution ($R^1 = C_6H_5$) had been prepared by this method.[5]



The present study was undertaken to determine the applicability of this reaction to the synthesis of N-alkyl-β-lactams and, if possible, to find a relationship between the yield of β-lactam and the structure of the β-amino ester used in the reaction.

Four N-alkyl-β-lactams were subsequently synthesized: 1-methyl-2-azetidinone, I, $R^1 = CH_3$, $R^3 = R^4 = H$; 1-benzyl-2-azetidinone, II, $R^1 = C_6H_5CH_2$, $R^3 = R^4 = H$; 1-benzyl-4-phenyl-2-azetidinone, III, $R^1 = C_6H_5CH_2$, $R^3 = H$, $R^4 = C_6H_5$; 1-benzohydryl-4-phenyl-2-azetidinone, IV, $R^1 = (C_6H_5)_2CH$, $R^3 = H$, $R^4 = C_6H_5$. Some reactions of these four β-lactams were studied, and particular attention was given to the relationship of structure to reactivity.

Synthesis of N-Alkyl-β-lactams

Each of the four β-amino esters used was subjected to identical reaction conditions. An aliquot of the crude organic material from each reaction was titrated with hydrochloric acid, and from the neutralization equivalent found, the per cent. of amino ester units [$R^1NH - - - CH(R^4)CH_2CO_2C_2H_5$] remaining was calculated. By difference, the amount of amide [$-CH(R^4)CH_2CON(R^1)-$] present in the material and the percentage yield of amide were determined; the latter is given in

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

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(4) Committee on Medical Research, O. S. R. D., *Science*, **102**, 627 (1945).

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

(6) F. Bodroux, *Compt. rend.*, **138**, 1427 (1904).

Table I as "% Total amides." Since all products of intermolecular reaction, except cyclic products, would be basic, separation from the neutral β-lactams was simplified. The basic compounds present in the mixture were neutralized with hydrogen chloride, converting them to ether-insoluble salts. The material which remained soluble in ether and in petroleum ether was chiefly β-lactam. The β-lactams were purified by distillation or recrystallization; the values of "% β-Lactam" given in Table I are calculated from the amount of once distilled or once recrystallized β-lactam. The β-lactams were characterized by elementary analysis, by molecular weight determination, and by hydrolysis to the corresponding amino acids which were compared with authentic samples.

TABLE I

Starting material, Ethyl	β-Lactam	% Total amides	% β-Lactam	Ratio: % β-Lactam/% Total amides
β-Methylaminopropionate	I	48	11	0.23
β-Benzylaminopropionate	II	26	5	.19
β-Benzylaminohydrocinnamate	III	64	45	.70
β-Benzohydrylaminohydrocinnamate	IV	*ca.* 10	3.3	*ca.* .3

TABLE II[b,c]

Amine	pK_a
Benzylamine	8.7[a]
Ethyl β-methylaminopropionate	8.4
Ethyl β-aminopropionate	8.4
Benzohydrylamine	7.7
Ethyl β-aminohydrocinnamate	7.5
Ethyl β-benzylaminopropionate	7.4
Ethyl β-benzylaminohydrocinnamate	6.2
Ethyl β-benzohydrylaminohydrocinnamate	4.3
Aniline	4.2[a]

[a] W. H. Carothers, C. F. Bickford and G. J. Hurwitz, THIS JOURNAL, 49, 2908 (1927), give pK_a 9.4 for benzylamine in water, and pK_a 4.7 for aniline in water, at 25°. [b] The dissociation constants were determined at 25° by titration of a 0.07 ± 0.01 *M* solution of the amine in 95% ethanol with 1 *N* hydrochloric acid, using a Beckman Model G *p*H meter. The *p*H at the midpoint of the titration is numerically equal to pK_a. [c] The nearly equal effect on basicity which results from substitution of a hydrogen on a carbon adjacent to the nitrogen by a phenyl group and by a carboethoxymethyl group is interesting.

To investigate the relation between basicity and yield of β-lactam, relative basicities of the amino esters used were determined by potentiometric titration. The pK_a values are listed in Table II. For comparison, the pK_a values of several other amines, determined under identical conditions, are included in the Table. There is no obvious relation between the yield of total amides (Table I) and the basicity of the amino esters (Table II). It is important to note, however, that the yield of amide remains high with even the most basic amino ester, ethyl β-methylaminopropionate.

A possible side reaction in the synthesis of β-lactams by this method would be enolization of the α-hydrogen of the ester followed by self-condensation. Hauser and Walker[7] report that methylanilinomagnesium bromide reacts with ethyl propionate to give only the amide, while diethylaminomagnesium bromide causes self-condensation of the ester, though some amide is also formed.[8] This side reaction should be favored by increasing the basicity of the aminomagnesium halide. The crude reaction product from ethyl β-methylaminopropionate did give a positive enol test with ferric chloride solution; the crude reaction product from ethyl β-benzylaminohydrocinnamate did not.

Although in all experiments 80% or more of the starting amino ester was accounted for, the yield of total amide from a given amino ester varied in duplicate runs. An explanation of this may be found in the fact that the reaction mixtures were heterogeneous. The magnesium halide derivatives of the amino esters precipitated immediately on addition of ethylmagnesium bromide to the ethereal solutions of the amino esters. The precipitates were usually amorphous solids or oils which in certain instances crystallized during the course of the reaction. Such variation in the physical nature of the reaction mixtures might well result in different yields of amide from the same amino ester. When a comparison is made of the results with different amino esters, it must be considered that the reactions were run for an arbitrary length of time. As no investigation of the relative rates of reaction was made, the conditions chosen may be closer to the optimum for one amino ester than for another. These variables might be expected to influence the yield of total amides and the yield of β-lactam. They should have less influence on the ratio of the yield of β-lactam to the total yield of amide. These ratios are included in Table I.

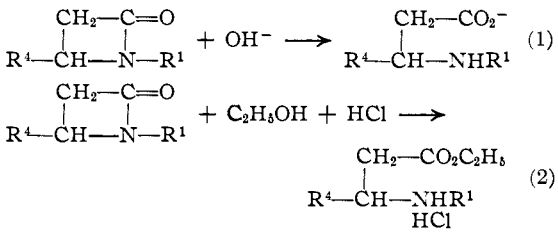
The proximity of large groups to the nitrogen atom in the amino ester molecule would be expected to make any reaction with that nitrogen less probable, and should hinder the formation of amide. This hindrance might be more effective in retarding intermolecular amide (straight-chain amide) formation than in retarding intramolecular amide (β-lactam) formation. Although the data are too limited for any conclusions to be drawn, it is nevertheless interesting to attempt to correlate the expected trend in steric hindrance with the ratio of the yield of β-lactam to the total yield of amide (Table I).

Reactivity of N-Alkyl-β-lactams

Alkaline hydrolysis of the β-lactams has been shown by isolation of the amino acids to proceed according to equation 1. The studies of the rates of hydrolysis were carried out in 85% ethanol us-

(7) C. R. Hauser and H. G. Walker, THIS JOURNAL, **69**, 295 (1947).

(8) F. C. Frostick, Jr., and C. R. Hauser, *ibid.*, **71**, 1350 (1949).



(1)

(2)

ing equimolar, approximately 0.5 *N* concentrations of sodium hydroxide and β-lactam. The alkaline hydrolysis of amides is known to be a bimolecular reaction,[9] and in the present work satisfactory constancy of the calculated second-order rate constants was found. The data obtained are summarized in Table III. Also included for comparison are the data for N,N-diethylpropionamide. The energy of activation for alkaline hydrolysis of 1-methyl-2-azetidinone was calculated as approximately 18 kcal. This energy of activation is of the same order of magnitude as that calculated from the data for the alkaline hydrolysis, in water, of simple straight-chain amides having no alkyl substituents on the nitrogen.[9a]

TABLE III

ALKALINE HYDROLYSES

Compound	Initial concn., moles/l.	*T*, °C.	Time, min.	Amount reacted, %	$k \times 10^2$, liter moles^{-1} min.$^{-1}$
1-Methyl-2-azetidinone (I)	0.48	50 ± 1	15	8.3	1.3
			60	32	1.6
			180	56	1.5
			300	66	1.4
				Av.	1.5 ± 0.2
1-Methyl-2-azetidinone (I)	.49	0	2430	9.1	0.0084
			3900	17	0.0107
				Av.	0.0095 ± 0.001
1-Benzyl-2-azetidinone (II)	.48	50 ± 1	15	11	1.7
			60	33	1.7
			180	59	1.7
			300	70	1.6
				Av.	1.7 ± 0.1
1-Benzyl-4-phenyl-2-azetidinone (III)	.44	50 ± 1	15	6.8	1.1
			60	19	0.89
			180	43	0.95
			300	55	0.93
				Av.	1.0 ± 0.1
1-Benzohydryl-4-phenyl-2-azetidinone (IV)	.23[a,b]	50 ± 1	300	19	0.3
N,N-Diethylpropionamide	.48	50 ± 5	1360	<3	<0.005

[a] The initial concentration was not determined experimentally; the value was calculated from the approximate volume of the reactants. [b] The lower concentration was necessary because of the insolubility of the β-lactam.

The reaction of the β-lactams with ethanolic hydrogen chloride was shown to proceed according to equation 2. Studies of the rate of ethanolysis in the presence of hydrogen chloride were carried out using equimolar, approximately 0.5 *N* concentrations of hydrogen chloride and β-lactam in absolute ethanol. 1-Benzohydryl-4-phenyl-2-azetidinone (IV) was omitted from this series because the product of the reaction, ethyl β-benzohydrylaminohydrocinnamate, is too weakly basic to be titrated very accurately in ethanol. For comparison, the approximate rate of reaction was also determined with N,N-diethylpropionamide. Reitz[9c] reported that the rate of methanolysis of acetamide in the presence of hydrogen chloride is independent of acid concentration. Taylor and Davis,[10] on the contrary, had reported that the ethanolysis of acetamide in the presence of hydrogen chloride shows bimolecular kinetics. Since the data obtained in the present studies were limited, calculated rate constants are not included with the data which are summarized in Table IV.

TABLE IV

ETHANOLYSES IN THE PRESENCE OF HYDROGEN CHLORIDE

Compound	Initial concn., moles/l.	*T*, °C.	Time, min.	Amount reacted, %
1-Methyl-2-azetidinone (I)	0.45	50 ± 1	15	12
			60	36.5
			120	48
1-Benzyl-2-azetidinone (II)	.44	50 ± 1	15	5.2
			60	22
			120	32.5
1-Benzyl-4-phenyl-2-azetidinone (III)	.46	50 ± 5	1350	25
N,N-Diethylpropionamide	.46[a]	50 ± 5	2610	<3

[a] The initial concentration was not determined experimentally; the value was calculated from the approximate volume of the reactants.

In both ethanolysis and alkaline hydrolysis experiments the β-lactams were much more reactive than N,N-diethylpropionamide. This indicates the importance of the four-membered ring in facilitating the hydrolysis of simple β-lactams. The β-lactams are much less reactive than the penicillins, however.[5,11]

In correlating the reactivity of the β-lactams with their structures, it is likely, as suggested by the discussion in "The Chemistry of Penicillin,"[5] that at least two factors must be considered:[12] (a) the steric effect of substituents and (b) the polarization of the amide group which is due to the presence of these substituents. The steric effect (a) might be expected to decrease the rate of both of the reactions studied here as the size and number of substituents increases. It would be predicted

(9) (a) J. C. Crocker and F. H. Lowe, *J. Chem. Soc.*, **91**, 952 (1907); (b) E. Calvet, *Compt. rend.*, **192**, 1569 (1931); (c) O. Reitz, *Z. physik. Chem.*, **A183**, 371 (1939).

(10) H. A. Taylor and T. W. Davis, *J. Phys. Chem.*, **32**, 1467 (1928).

(11) R. G. Benedict, W. H. Schmidt and R. D. Coghill, *J. Bact.*, **51**, 291 (1946).

(12) An explanation of the reactivity of β-lactams in general is given by R. B. Woodward, Chapter XV, "The Chemistry of Penicillin." Fusion of the β-lactam ring in a bicyclic system such as that present in the penicillins is also discussed by Woodward, but since this system is not present in the N-alkyl-β-lactams it will not be considered here.

from this that the rate of both reactions should decrease from I to IV. On the other hand, the polarization effect (b) of the substituents might be expected to increase the rate of alkaline hydrolysis as the basicity of the nitrogen decreases. The relative basicity of the nitrogens in the present series is known from the measurements of the dissociation constants of the corresponding amino esters (Table II); the basicity decreases from I to IV. As a result, consideration of the polarization effect leads to a prediction of increasing rate of alkaline hydrolysis in the present series from I to IV. In alkaline hydrolysis, then, the two effects (a) and (b) are opposed, and the observation of a slight increase of the reaction velocity from I to II followed by decreases to III and IV can be explained as the result of a combination of the two effects. The mechanism of ethanolysis is not as well established as is the mechanism of alkaline hydrolysis, but it might be expected that the polarization effect would decrease the rate of reaction from I to IV. If so the effects (a) and (b) would act in the same direction and the decrease in reaction velocity should be more pronounced than that observed in alkaline hydrolysis. The experimental results are in agreement with such a view.

Experimental[13]

Preparation of β-Amino Esters

Ethyl β-Methylaminopropionate.—The procedure followed was entirely analogous to that described by Morsch[14] for the synthesis of methyl β-methylaminopropionate. Ethyl acrylate[15] (1 mole) was added with cooling to a 6 *M* solution of methylamine in absolute ethanol containing 1.1 moles of methylamine. The solution was allowed to stand at room temperature for two days. The amino ester was collected at 61–72° at 17 mm. (48.5%). A sample was dissolved in 95% ethanol and titrated with standard aqueous acid using sodium alizarinsulfonate as indicator; neutralization equivalent, 129 (calcd. 131). This material was redistilled; 77% was recovered as the main fraction, b. p. 64.5–65.5° at 17 mm.; neutralization equivalent, 129; $n^{22}D$ 1.4218. A sample was again distilled; b. p. 68–68.5° at 18 mm.; $n^{22}D$ 1.4218.

Anal. Calcd. for $C_6H_{13}O_2N$: N, 10.68. Found: N, 10.43, 10.36.

Ethyl β-Aminohydrocinnamate.—To 5.0 g. (30 millimoles) of finely powdered β-aminohydrocinnamic acid,[16] 7 ml. of thionyl chloride was cautiously added. When the evolution of gases had ceased, the flask was stoppered and allowed to stand at room temperature for one-half hour. Sulfur dioxide, hydrogen chloride, and excess thionyl chloride were removed at the water pump. To the crystalline amino acid chloride hydrochloride, 10 ml. of absolute ethanol was added cautiously. The solution was allowed to stand at room temperature for one-half hour, and then it was poured into 40 ml. of absolute ether. The solid was filtered and washed with ether; the yield of unpurified ethyl β-aminohydrocinnamate hydrochloride was 6.2 g. (88%). The amino ester hydrochloride was washed several times with ether. The amino ester was liberated in 85% yield using 15% sodium carbonate solution and extracting into ether; neutralization equivalent, 195 (in 95% ethanol solution, sodium alizarinsulfonate as indicator) (calcd. 193). This material was used in subsequent syntheses without further purification.

A small sample of the amino ester hydrochloride was dissolved in absolute ethanol from which it crystallized on addition of petroleum ether–ether; m. p. 136–139° (capillary, dec.).[17]

Anal. Calcd. for $C_{11}H_{15}O_2N\cdot HCl$: N, 6.10; Cl, 15.44. Found: N, 6.13; Cl, 15.77.

Ethyl β-Benzylaminohydrocinnamate.—Attempted preparation of this amino ester by the addition of benzylamine to ethyl cinnamate and by the reaction of benzylamine with ethyl β-bromohydrocinnamate were unsuccessful; the latter gave benzylamine hydrobromide and ethyl cinnamate.

A mixture of 3.96 g. (20.5 millimoles) of ethyl β-aminohydrocinnamate and 1.30 g. (10.25 millimoles) of benzyl chloride was heated at 70° for five hours. The solution was cooled; ethyl β-aminohydrocinnamate hydrochloride crystallized. The mixture was diluted with 25 ml. of absolute ether, placed in the refrigerator for a few hours, filtered, and the solid was washed thoroughly with ether. The hydrochloride, 2.14 g., m. p. 134–139° (dec.) was converted in 97% yield to ethyl β-aminohydrocinnamate; neutralization equivalent, 193 (calcd. 193). The ether-soluble material was isolated (3.08 g.). To this oil was added an excess, 6.0 ml., of 2.4 *N* ethanolic hydrogen chloride solution. The ethanol was partially removed by evaporation under reduced pressure, and the solid mass was mixed thoroughly with 10 ml. of absolute ether, allowed to stand one hour, filtered, and the solid was washed twice with ether and dried. The weight of ethyl β-benzylaminohydrocinnamate hydrochloride was 2.65 g. (81%); m. p. 179–182°. Ethyl β-benzylaminohydrocinnamate was liberated from the hydrochloride in 97% yield; the neutralization equivalent (potentiometric titration) was 290 (calcd. 283). For analysis, the hydrochloride was recrystallized from ethanol–petroleum ether; m. p. 179–183° (dec.).

Anal. Calcd. for $C_{18}H_{21}O_2N\cdot HCl$: C, 67.59; H, 6.93; N, 4.38; Cl, 11.09. Found: C, 67.29, 67.44; H, 7.08, 6.96; N, 4.64, 4.97; Cl, 11.02, 11.14.

Ethyl β-Benzohydrylaminohydrocinnamate.—A mixture of 4.01 g. (20.75 millimoles) of ethyl β-aminohydrocinnamate and 2.10 g. (10.37 millimoles) of freshly distilled benzohydryl chloride[18] was heated at 95° for five hours. The mixture was cooled and the isolation of ethyl β-benzohydrylaminohydrocinnamate hydrochloride was carried out in a manner identical with that used for the isolation of ethyl β-benzylaminohydrocinnamate hydrochloride. The yield of ethyl β-benzohydrylaminohydrocinnamate hydrochloride was 3.65 g. (89%); micro m. p. 177–193° (melting at the edges only). For analysis, the hydrochloride was recrystallized twice from ethanol–petroleum ether; micro m. p. 180–191° (melting at the edges only); capillary m. p. 212–214°, with preliminary decomposition.

Anal. Calcd. for $C_{24}H_{25}O_2N\cdot HCl$: C, 72.80; H, 6.62; N, 3.54; Cl, 8.96. Found: C, 72.90, 72.81; H, 6.82, 7.25; N, 3.78, 3.87; Cl, 9.10, 9.27.

The amino ester was liberated quantitatively from the hydrochloride. In one preparation the amino ester crystallized slowly; m. p. 63–66°. It was recrystallized from absolute ethanol for analysis; m. p. 65–67°.

Anal. Calcd. for $C_{24}H_{25}O_2N$: N, 3.89. Found: N, 3.92, 3.93.

Preparation of β-Lactams

Modifications of the general procedure, required for the isolation of certain β-lactams, are described under headings of the β-lactams below.

General Procedure.—To a 0.4 *M* solution of the β-amino ester in sodium-dried ether was added an equimolar quantity of standard (approximately 2 *N*) ethereal ethyl-

(13) Unless otherwise specified, melting points were determined on a micro melting point block and are corrected.

(14) K. Morsch, *Monatsh.*, **63**, 220 (1933); *C. A.*, **28**, 2679 (1934).

(15) We wish to thank the Rohm and Haas Company for a generous supply of ethyl acrylate.

(16) T. B. Johnson and J. E. Livak, THIS JOURNAL, **58**, 299 (1936).

(17) E. Dyer, *ibid.*, **63**, 265 (1941), reports m. p. 137–138°.

(18) N. T. Farinacci and L. P. Hammett, *ibid.*, **59**, 2542 (1937).

magnesium bromide, as rapidly as the evolution of gases would permit. A precipitate separated while the Grignard solution was being added, and evolution of ethane was complete almost immediately. The mixture, protected from atmospheric moisture, was allowed to stand at room temperature for one and one-half hours with occasional agitation. The magnesium compounds were decomposed by the cautious addition of an excess of 10% ammonium chloride solution. The mixture was agitated until all the solid had dissolved, and the ether solution was separated and washed twice with small volumes of water. The aqueous washes were extracted with ether, and the ethereal solutions were combined and dried over magnesium sulfate. The solution was evaporated at the water pump to constant weight.

The neutralization equivalent of the residual oil was determined by titration with standard hydrochloric acid. From the neutralization equivalent, the amount of standard (approximately 4 *N*) ethanolic hydrogen chloride required to just neutralize the free amino groups was calculated and added to the oil. Most of the ethanol was removed by evaporation under reduced pressure. The residue was mixed thoroughly with absolute ether (one-third of the volume used in the reaction) and the ethereal solution was separated from the hydrochloride by filtration or decantation. The hydrochloride was washed repeatedly with ether. The ether solution was concentrated by distillation and the last traces of ether were removed at the water pump. The ether-soluble residue was extracted repeatedly with small portions of boiling ligroin. The ligroin extracts were combined, the solvent was removed by distillation under reduced pressure, and the crude β-lactam was purified by distillation or recrystallization.

Calculations.—From the neutralization equivalent of the crude organic material, the yield of amide was calculated as follows: Wt. of organic material/neutral equiv. = Number of moles of amino ester units, [NH-(R^1)- - - $CH(R^4)CH_2CO_2C_2H_5$]. Number of moles of amino ester units × mol. wt. of amino ester = wt. of amino ester units present. Wt. of organic material—wt. of amino ester units present = wt. of amide units [—$N(R^1)CH(R^4)CH_2CO$—] present. From the weight of amide units in the crude organic material, the % yield of total amide was calculated in the usual manner. Percentage yields are based on the total weight of starting material and are not corrected for recovered starting material.

1-Methyl-2-azetidinone (I).—Because of the solubility of this β-lactam in water, the magnesium compounds were decomposed with an excess of saturated ammonium chloride solution, and the aqueous phase was extracted repeatedly with portions of chloroform totaling approximately the same as the volume of ether used in the reaction. The ether and chloroform were removed by distillation through a short column. The crude reaction product gave a positive enol test with ferric chloride solution. From 35.4 g. of ethyl β-methylaminopropionate was obtained 24.9 g. of crude reaction product, neutralization equivalent, 235. Low boiling (30–55°) petroleum ether was used instead of ligroin because of the volatility of the β-lactam. The petroleum ether-soluble residue was distilled, 2.60 g. (11%); b. p. 70–75° at 20 mm. The 1-methyl-2-azetidinone was redistilled and the middle fraction, two-thirds, b. p. 69.5–70° at 18 mm., was used for analysis and in the hydrolysis experiments. It was neutral. It absorbed over three moles of water per mole when it was placed in moist air and allowed to stand for several days; because of this, analysis was difficult.

Anal. Calcd. for C_4H_7ON: C, 56.44; H, 8.30; N, 16.46; mol. wt. 85. Found: C, 56.34; H, 8.28; N, 16.54; mol. wt. (Rast), 90.

1-Benzyl-2-azetidinone (II).—From 81.5 g. of ethyl β-benzylaminopropionate[19] was obtained 60 g. of crude reaction product; neutralization equivalent, 286. The crude product, from ligroin solution, was purified by distillation; 3.2 g. (5%); b. p. 98–112° at 2 mm. For analysis and for use in the hydrolysis experiments the 1-benzyl-2-azetidinone was redistilled; b. p. 107–110° at 2 mm. It was neutral. It absorbed about one mole of water per mole in contact with moist air for several days.

Anal. Calcd. for $C_{10}H_{11}ON$: C, 74.50; H, 6.86; N, 8.69; mol. wt., 161. Found: C, 74.47, 74.23; H, 6.89, 6.75; N, 8.74, 8.67; mol. wt. (Rast), 164, 173.

1-Benzyl-4-phenyl-2-azetidinone (III).—Starting with 8.01 g. of amino ester, the yield of total amides was 63%; 83% of the starting material was accounted for. The crude reaction product gave a negative enol test with ferric chloride solution. The yield of slightly yellow 1-benzyl-4-phenyl-2-azetidinone, b. p. 145–150° at 2 mm., was 3.0 g. (45%). After redistillation, the analytical sample was colorless; micro b. p. 160–162° at 15 mm.; $n^{23}D$ 1.5799.

Anal. Calcd. for $C_{16}H_{15}ON$: N, 5.90; mol. wt., 237. Found: N, 5.97; 6.07; mol. wt. (Rast), 238.

1-Benzohydryl-4-phenyl-2-azetidinone (IV).—From 0.997 g. of ethyl β-benzohydrylaminohydrocinnamate was obtained 0.789 g. of crude reaction product of approximate neutralization equivalent 405 (by potentiometric titration, the low basicity of the amino ester making the titration inaccurate). 1-Benzohydryl-4-phenyl-2-azetidinone crystallized slowly on cooling the solution after most of the ligroin had been removed by distillation from the ligroin extracts. The solid was filtered from the ligroin and residual oil. It was washed with cold ligroin and dried. The yield of crude crystalline product thus obtained was 3.3%. It was recrystallized from ligroin (70% recovery) to give a colorless product; m. p. 98.5–100.5°. Further recrystallization from ligroin did not raise the melting point.

Anal. Calcd. for $C_{22}H_{19}ON$: C, 84.31; H, 6.11; N, 4.47; mol. wt., 313. Found: C, 84.31, 84.45; H, 6.68, 6.58; N, 4.68, 4.54; mol. wt. (Rast), 329.

For comparison, N-benzohydrylcinnamamide was synthesized from cinnamoyl chloride and benzohydrylamine; m. p., 219–221° (with sublimation).

Reactions of β-Lactams

Hydrolysis of β-Lactams.—(a) 1-Methyl-2-azetidinone was converted to *p*-toluenesulfonyl-β-methylaminopropionic acid by hydrolysis with an excess of 15% potassium hydroxide solution at 70° for one-half hour followed by treatment of the solution with *p*-toluenesulfonyl chloride. The *p*-toluenesulfonamide was obtained in 93% yield; m. p. 107–109°. Recrystallization from ethanol–water gave an 86% recovery of material; m. p. 108.5–110[20]; neutralization equivalent, 252 (calcd. 257). A mixed melting point with *p*-toluenesulfonyl-β-methylaminopropionic acid prepared from ethyl β-methylaminopropionate was undepressed.

(b) 1-Benzyl-2-azetidinone was hydrolyzed by treatment with one equivalent of 1 *N* sodium hydroxide solution in 95% ethanol for two hours at reflux temperature. The solution was evaporated, the residue, dissolved in water, was extracted with ether, neutralized, evaporated to dryness, and extracted with absolute ethanol. The β-benzylaminopropionic acid, recrystallized from 95% ethanol, was obtained in 84% yield. It was recrystallized from ethanol with 70% recovery; m. p. 184–184.5°; neutralization equivalent, 175 (titrated potentiometrically, calcd. 179). A mixed melting point with β-benzylaminopropionic acid, prepared from ethyl β-benzylaminopropionate, was undepressed.

(c) 1-Benzyl-4-phenyl-2-azetidinone was hydrolyzed by two hours refluxing with one equivalent of 1 *N* sodium hydroxide solution in 95% ethanol. The solution was evaporated and β-benzylaminohydrocinnamic acid crystallized from a small volume of water when the hydrolysis product was neutralized with hydrochloric acid; yield 75%; m. p. 187–188°; neutralization equivalent, 256 (calcd. 255). A mixed melting point with amino acid prepared from the amino ester was undepressed.

(d) 1-Benzohydryl-4-phenyl-2-azetidinone was hydro-

(19) G. Stork and S. M. McElvain, *ibid.*, **69**, 971 (1947).

(20) E. Späth, J. P. Wibaut and F. Kesztler, *Ber.*, **71B**, 100 (1938), reported 109–110.5°.

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.

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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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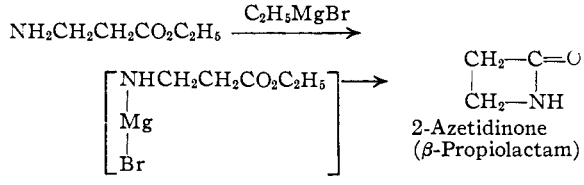
2-Azetidinone (β-Propiolactam)[1]

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-

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(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. 133° 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.