[CONTRIBUTION FROM THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY, DEPARTMENT OF CHEMISTRY]

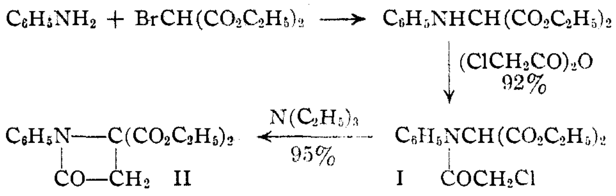
A New Synthesis of β-Lactams

BY JOHN C. SHEEHAN AND AJAY KUMAR BOSE[1]

The fused β-lactam-thiazolidine structure proposed for penicillin has focused the attention of chemists on β-lactams. A recent discussion of the chemistry of β-lactams[2] lists the compounds which had been prepared through 1947, including those made during the collaborative British–American project on the chemistry of penicillin. No new methods for the synthesis of β-lactams were discovered in the course of the very intensive effort made to synthesize penicillin and other β-lactams.[3] Recently a new method for the preparation of β-lactams was reported from this Laboratory.[4]

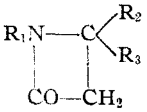
We have now developed a second new synthesis of β-lactams. In the conventional methods for preparing 2-azetidinones by cyclization procedures, attempts are made to close a carboxyl function against an amino group. In our synthesis the amide linkage is formed first and the four-membered β-lactam ring is then made by establishing a carbon-to-carbon bond.

Primary amines react with bromomalonic ester to give substituted aminomalonic esters, which can be chloroacetylated readily by treatment with chloroacetic anhydride. The chloroacetylated products undergo ring closure to β-lactams in high yields with the elimination of the elements of hydrogen chloride when treated with triethylamine at room temperature. This series of reactions may be illustrated by using anilinomalonic ester as a specific example.



Ring closure could also be brought about by refluxing for a few hours an ethereal solution of diethyl chloroacetanilidomalonate (I) with a suspension of potassium carbonate.

The following β-lactams have been prepared and characterized by us.



II, R_1 = phenyl, $R_2 = R_3 = CO_2C_2H_5$
III, R_1 = phenyl, $R_2 = CO_2K$, $R_3 = CO_2C_2H_5$
IV, R_1 = phenyl, R_2 = H, $R_3 = CO_2C_2H_5$
V, R_1 = phenyl, R_2 = H, $R_3 = CO_2H$
VI, R_1 = phenyl, $R_2 = R_3 = CO_2CH_2C_6H_5$
VII, R_1 = phenyl, $R_2 = R_3 = CO_2H$
VIII, R_1 = β-naphthyl, $R_2 = R_3 = CO_2C_2H_5$

It is interesting to note that in this facile cyclization to a four-membered ring in high yields, no product corresponding to the formation of larger rings or linear polymerization was isolated. Analyses and molecular weight determinations are in accord with the β-lactam formulation.

During the penicillin project[2] it was noted that in infrared spectra the carbonyl stretching band of an open-chain disubstituted amide occurs near 6 μ (1667 cm.$^{-1}$), but the corresponding band in a monocyclic β-lactam is observed at about 5.74 μ (1742 cm.$^{-1}$). Thus 1-phenyl-2-azetidinone (XII), curve A, shows a strong absorption at 5.68–5.72 μ (1760–1748 cm.$^{-1}$) The carbonyl group in an ester is usually found to give a band at 5.7–5.8 μ (1755–1725 cm.$^{-1}$). From curve B it will be observed that I has a strong double peak at 5.7 and 5.76 μ (1754 cm.$^{-1}$ and 1736 cm.$^{-1}$) evidently due to the ester groups, and another strong band at 5.96 μ (1678 cm.$^{-1}$), which can be assigned to the carbonyl of the amide function. In compound II, one should expect contributions from the ester and amide groups in the same region. The bands, 5.62 μ (1779 cm.$^{-1}$) and 5.74 μ (1742 cm.$^{-1}$) shown by II in curve C, can be explained in this way. The compound VIII has strong absorption bands at 5.64 μ (1773 cm.$^{-1}$) and at 5.68 μ (1761 cm.$^{-1}$), in curve D. Compound IV shows a broad band from 5.62–5.72 μ (1779 to 1748 cm.$^{-1}$). Compound V, curve E, shows a broad peak at 5.73 μ (1745 cm.$^{-1}$) and a narrow-peak at 5.86 μ (1706 cm.$^{-1}$). The former can be assigned to the β-lactam carbonyl and the latter to the carbonyl of the carboxy function. It should be noted that in II, IV, and VIII, the β-lactam carbonyl absorbs at a somewhat lower wave length than that reported for other β-lactams, all of which, however, were without carboxy substituents. The observed infrared spectra are, therefore, compatible with the β-lactam formulation.

As a further proof of structure, 1-phenyl-4,4-dicarbethoxy-2-azetidinone (II) was converted to the dibenzylamide of anilinosuccinic acid. Hydrolysis of II with strong alkali gave a potassium salt which, on heating with hydrochloric acid, underwent decarboxylation to yield the crystalline hydrochloride of anilinosuccinic acid

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(1) Overseas scholar of the Government of India.

(2) Clarke, Johnson and Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 973.

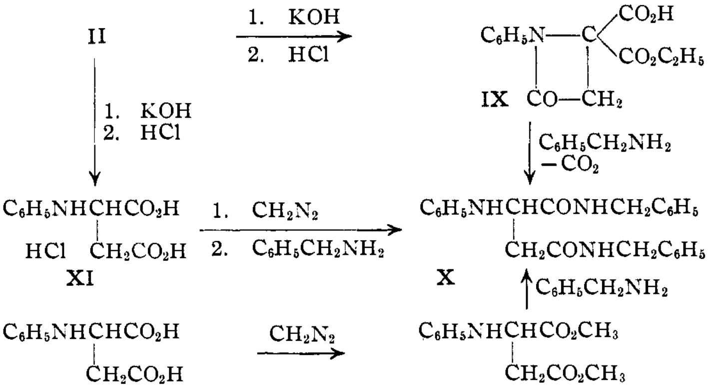
(3) The cyclization of β-amino acid esters to β-lactams by means of Grignard reagents, ascribed in ref. 2 to the Pfizer group (P. 10, 1), was discovered by Breckpot (Breckpot, *Bull. Soc. Chim. Belgique*, **32**, 412 (1923)). The method has recently been extended to the preparation of the simplest β-lactam, 2-azetidinone (Holley and Holley, THIS JOURNAL, **71**, 2129 (1949)).

(4) Sheehan and Izzo, THIS JOURNAL, **70**, 1985 (1948); **71**, 4059 (1949).

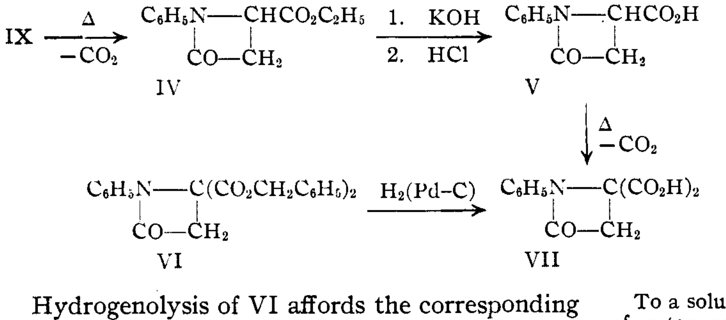
(XI). By treatment of XI successively with diazomethane and benzylamine, the dibenzylamide of anilinosuccinic acid (X) was obtained.

The interaction of II with one equivalent of potassium hydroxide at room temperature yielded a monopotassium salt. The corresponding free acid IX was converted to X on treatment with benzylamine.

Compound X was also obtained independently by interaction of anilinosuccinic acid and diazomethane followed by treatment of the resulting ester with benzylamine. A sample of X obtained in this manner, when mixed with samples obtained from II by degradation, showed no depression in melting point. The reaction sequence may be illustrated



On treating II with an equivalent of potassium hydroxide in alcoholic solution at room temperature, one ester group is saponified and the potassium salt III is obtained in 99% yield. The acid IX corresponding to III undergoes decarboxylation, on heating with a drop of pyridine as a catalyst, to give IV in good yield. In its turn IV can be saponified with one equivalent of alcoholic potassium hydroxide to V. This series of reactions is illustrated



Hydrogenolysis of VI affords the corresponding dicarboxylic acid VII, which undergoes decarboxylation on heating in presence of pyridine as a catalyst to give V. A mixture of samples of V obtained from the saponification of IV and the decarboxylation of VI shows no depression in melting point. That V has the β-lactam ring intact is further corroborated by the infrared spectrum (curve E) which shows the characteristic absorption band at 5.73 μ (1745 cm.$^{-1}$), besides a band at 5.86 μ (1706 cm.$^{-1}$) due to the carboxy function.

The stepwise hydrolysis of II to V without affecting the β-lactam structure is worthy of note because many β-lactams are known to be very susceptible to hydrolysis. Thus 1-phenyl-2-azetidinone, XII, which differs from II and IV in the absence of the ester substituents, is readily hydrolyzed by dilute alkali.[4]

Experimental[5]

Diethyl Chloroacetanilidomalonate (I).—Diethyl anilinomalonate (28 g.), obtained from diethyl bromomalonate and aniline,[6] was heated on a steam cone for 1.5 hours with chloroacetic anhydride (22 g.). The cooled melt was poured into water, and the diethyl chloroacetanilidomalonate, which separated as a colorless solid, was purified by recrystallization from ligroin. The yield was 42.5 g. (92%); m. p. 94–95°.

Anal. Calcd. for $C_{15}H_{18}O_5NCl$: C, 54.96; H, 5.53; N, 4.27. Found: C, 54.98; H, 5.84; N, 4.54.

1-Phenyl-4,4-dicarbethoxy-2-azetidinone (**II**).—To 20 g. of diethyl chloroacetanilidomalonate (I) dissolved in 50 ml. of benzene was added 8 g. of triethylamine. The mixture warmed spontaneously; triethylamine hydrochloride started to separate in a few minutes. The reaction mixture was allowed to stand for two days. Triethylamine hydrochloride (8.15 g., 97%) was removed by filtration, and the filtrate was washed with dilute hydrochloric acid and then with water. After drying over sodium sulfate, the solvent was removed, leaving 17 g. (95.5%) of viscous, amber-colored oil. By distillation of 16 g. of this oil, 14.8 g. (88.3% over-all yield) of a golden yellow liquid boiling at 160–165° (1.2 mm.) was collected, $n^{25}\text{D}$ 1.5180, d^{25}_4 1.1787. On standing for three months, this oil crystallized. After recrystallization from ether-petroleum ether, colorless rectangular prisms, m. p. 38.5–39.5°, were obtained.

Anal. Calcd. for $C_{15}H_{17}O_5N$: C, 61.84; H, 5.88; N, 4.88; mol. wt., 291.3. Found: C, 61.78; H, 5.97; N, 5.16; mol. wt. (Rast, using camphor), 287.

Hydrolysis of 1-Phenyl-4,4-dicarbethoxy-2-azetidinone (II).—On adding 0.95 g. (0.017 mole) of potassium hydroxide dissolved in 10 ml. of alcohol to a solution of 5.66 g. (0.0195 mole) of II in 10 ml. of alcohol, a crystalline solid began to separate. After two hours, about 40 ml. of ether was added to the reaction mixture. By filtration 5.05 g. (99%) of the potassium salt of 1-phenyl-4-carboxy-4-carbethoxy-2-azetidinone (III) was obtained. The crude salt was recrystallized from water and dried at 105° to a constant weight, but it was not obtained quite analytically pure.

Anal. Calcd. for $C_{13}H_{12}O_5NK$: C, 51.81; H, 4.015; N, 4.68. Found: C, 52.46; H, 4.38; N, 4.65.

To a solution of 5 g. of the potassium salt, III, in 5 ml. of water was added with cooling excess concentrated hydrochloric acid. The oily layer which separated was extracted with ether and the ethereal solution was dried over sodium sulfate. On removing the solvent, 3.6 g. (82.5%) of a viscous, colorless oil was obtained which solidified on scratching. The solid 1-phenyl-4-carboxy-4-carbethoxy-

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[5] All melting points are corrected. We are indebted to Mr. S. M. Nagy and his associates for the micro-analyses.

[6] Blank, *Ber.*, **31**, 1815 (1898).

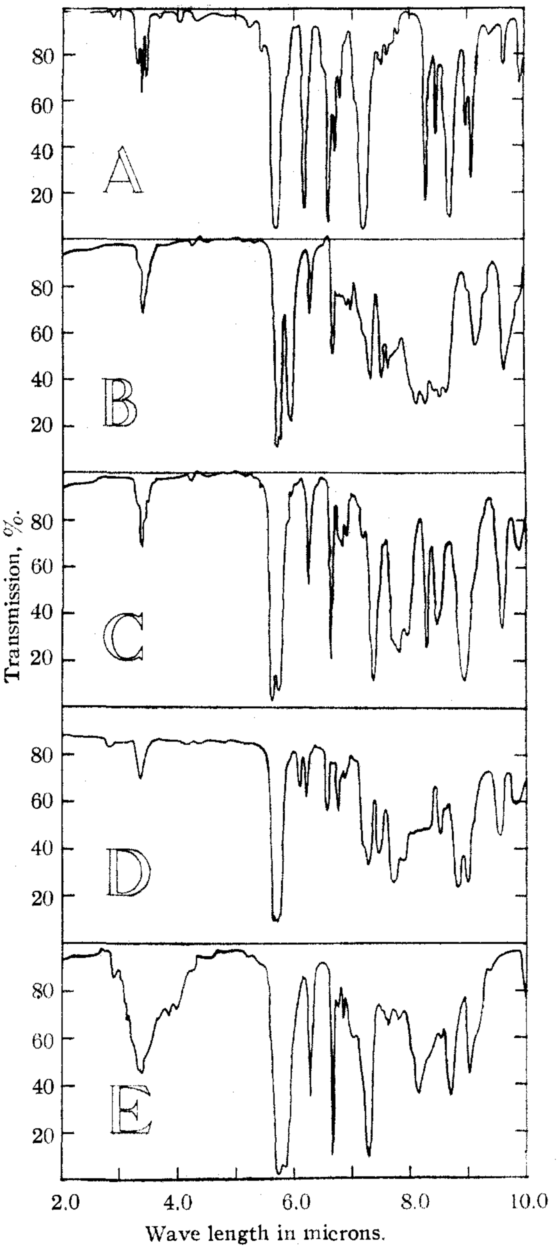

Fig. 1.—Infrared absorption spectrum: A, 1-phenyl-2-azetidinone; B, diethyl chloroacetanilidomalonate (I); C, 1-phenyl-4,4-dicarbethoxy-2-azetidinone (II); D, 1-(β)naphthyl-4,4-dicarbethoxy-2-azetidinone (VIII); E, 1-phenyl-4-carboxy-2-azetidinone (V).

2-azetidinone melted at 100–104° and evolved a gas when heated to about 160°.

To 0.5 g. of the crude acid in ether solution was added 0.61 g. of benzylamine, and the solution was protected from carbon dioxide with a soda-lime tube. After two days the crystalline material which separated was recrystallized from alcohol, m. p. 156–157°, 0.21 g. (30%). An analysis corresponded to the dibenzylamide of anilinosuccinic acid.

Anal. Calcd. for $C_{24}H_{25}O_2N_3$: C, 74.38; H, 6.50; N, 10.84. Found: C, 74.37; H, 6.71; N, 10.84.

When a solution of 1.7 g. of potassium hydroxide in 5 ml. of water and 2 g. of II were heated together on a steam cone for five hours, a crystalline potassium salt was formed. Decarboxylation was achieved by heating the salt with 5 ml. of 6 *N* hydrochloric acid. After concentration a mass of crystals was obtained which, by recrystallization from water, gave 1.25 g. (74%) of colorless rectangular plates. An analytical sample, prepared by several crystallizations from water, melted at 139° with decomposition. An analysis corresponded to the hydrochloride of anilinosuccinic acid.

Anal. Calcd. for $C_{10}H_{12}O_4NCl$: C, 48.88; H, 4.92; N, 5.70. Found: C, 48.56; H, 5.40; N, 5.75.

A sample of anilinosuccinic acid hydrochloride, prepared from II, was treated with excess diazomethane to yield dimethyl anilinosuccinate, which was not isolated but was treated directly with benzylamine in ether solution. The reaction product was crystalline, m. p. 152–154°; recrystallization from alcohol raised the melting point to 156–157°. When a sample of this product was mixed with dibenzylamide of anilinosuccinic acid prepared from an authentic sample of anilinosuccinic acid, no depression in melting point was observed.

Dibenzylamide of Anilinosuccinic Acid (X).—To an ethereal solution of 0.85 g. of anilinosuccinic acid prepared from aniline and bromosuccinic acid[7] was added an ethereal solution of diazomethane until a slight yellow color persisted. The excess diazomethane was removed by evaporation under reduced pressure and 1.5 g. of benzylamine was added. The mixture, protected by a soda-lime tube, was heated for several hours on a steam cone. The cooled solution deposited the crystalline dibenzylamide of anilinosuccinic acid (0.36 g., 23%), m. p. 154°; after one recrystallization from alcohol the melting point was constant at 156–157°. When this product was mixed with a sample of dibenzylamide of anilinosuccinic acid obtained by either of the two aforementioned reactions, the melting point was undepressed.

1-Phenyl-4-carbethoxy-2-azetidinone (IV).—On heating in an oil-bath 1-phenyl-4-carboxy-4-carbethoxy-2-azetidinone (1 g.) with a few drops of pyridine as a catalyst, decarboxylation started at 120° and was complete in thirty minutes at 160°. The residue was washed successively with a solution of sodium bicarbonate, dilute hydrochloric acid, and water, and then diluted with ether. After drying the ethereal solution over sodium sulfate, the solvent was removed, leaving a light brown oil (0.7 g., 84%). Evaporative distillation at 120–130° (0.2 mm.) yielded a golden yellow, viscous liquid; the recovery was 89%. Samples prepared by this and other runs had a constant refractive index and density; $n^{25}\text{D}$ 1.5405, d^{25}_4 1.1822.

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.96; N, 6.39; *MR*, 57.78. Found: C, 65.55; H, 6.22; N, 6.64; *MR*, 58.23.

Dibenzyl Anilinomalonate.—Dibenzyl malonate (28.4 g.) was brominated by the method described for ethyl bromomalonate.[8] The washed reaction mixture weighed 33.4 g., indicating that bromination had proceeded to 62.5%. The pure bromoester (18.2 g., 80% recovery) was obtained by distillation as a mildly lachrymatory light yellow liquid, $n^{25}\text{D}$ 1.5532, b.p. 210–213° (3 mm.).

A mixture of aniline (2.82 g.) and dibenzyl bromomalonate (5.5 g.) was stored for several days. Ether was then added and the aniline hydrobromide was removed by filtration. The filtrate solidified after removal of the solvent. By recrystallizing this solid from ligroin, 3.8 g. (67%) of dibenzyl anilinomalonate, m. p. 83–86°, was obtained. On further recrystallization the m. p. was constant at 84–85°.

Anal. Calcd. for $C_{23}H_{21}O_4N$: C, 73.58; H, 5.64; N, 3.73. Found: C, 73.91; H, 5.87; N, 3.58.

1-Phenyl-4,4-dicarbobenzoxy-2-azetidinone (VI).—Dibenzyl anilinomalonate (2 g.) and chloroacetic anhydride (1.2 g.) were heated together on a steam cone for 2.5

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(7) Volhard, *Ann.*, **242**, 141 (1887).

(8) Blatt, ed., "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 245.

hours. The molten reaction mixture was poured into water, and the heavy oily layer was thoroughly digested with water and then dissolved in benzene. After drying over sodium sulfate the solvent was removed, leaving an uncrystallizable, colorless oil which was used directly for the next step.

To a solution of the crude dibenzyl chloroacetanilidomalonate in 20 ml. of benzene was added 1 g. of triethylamine. Crystalline triethylamine hydrochloride started to separate immediately. After allowing the reaction mixture to stand overnight, a 93% yield (0.68 g.) of triethylamine hydrochloride was obtained. Removal of the solvent left a viscous, yellow oil, which solidified during storage. Recrystallization from cyclohexane afforded 1.6 g. of colorless, cubic crystals, m. p. 94–95°. The overall yield of the crystalline β-lactam from dibenzyl anilinomalonate was 88.5%.

Anal. Calcd. for $C_{25}H_{21}O_5N$: C, 72.30; H, 5.06; N, 3.38. Found: C, 72.20; H, 5.31; N, 3.52.

1-Phenyl-4,4-dicarboxy-2-azetidinone (VII).—Hydrogenolysis of 3 g. of VI was carried out at room temperature in ethyl acetate solution, using 0.25 g. of palladium on charcoal (Darco) as a catalyst. The time required was 1.75 hours. After removal of the catalyst, the solvent was evaporated, yielding an oil (1.6 g., 96%) which solidified completely. On recrystallization from a mixture of ethyl acetate and ligroin, the melting point was 171–172° with decomposition and evolution of gas.

Anal. Calcd. for $C_{11}H_9O_5N$: C, 56.17; H, 3.86; N, 5.96. Found: C, 55.77; H, 4.17; N, 6.04.

1-Phenyl-4-carboxy-2-azetidinone (V)—(a) From 1-Phenyl-4-carbethoxy-2-azetidinone (IV).—To 0.4 g. of IV in 5 ml. alcohol was added 0.104 g. of potassium hydroxide dissolved in 10 ml. of alcohol. After storing the solution overnight at room temperature, excess ether was added. A potassium salt was obtained as crystalline clusters (0.26 g., 61%). To a concentrated aqueous solution of this salt (0.15 g.) was added hydrochloric acid, the solution was extracted with ether and the extract was dried over sodium sulfate. After removing the solvent, 0.120 g. (96%) of a solid, m. p. 119–122°, was obtained. By recrystallization from ether–petroleum ether colorless needles, m. p. 123°, were obtained. On standing overnight in a drying oven, the m. p. rose to 148°. Another sample prepared in the same manner gave rhombic crystals, m. p. 148–148.5°. The melting point of a mixture of the two types of crystals melted at 148–148.5°.

Anal. Calcd. for $C_{10}H_9O_3N$: C, 62.82; H, 4.75; N, 7.33. Found: C, 63.05; H, 5.05; N, 7.18.

(b) From 1-Phenyl-4,4-dicarboxy-2-azetidinone (VII).—Decarboxylation of VII to V was achieved by heating on an oil-bath (130°) 0.2 g. of VII with a drop of pyridine as a catalyst. The residue was taken up in ether and washed with a hydrochloric acid solution. After drying the ethereal solution over sodium sulfate, the solvent was removed, leaving 0.13 g. (80%) of a colorless solid, m. p. 139–144°. Recrystallization from ether–petroleum ether raised the m. p. to 147–148°. A mixture of this material with V obtained by procedure (a) melted undepressed at 147–148°.

1-(β-Naphthyl)-4,4-dicarbethoxy-2-azetidinone (VIII).—The procedure outlined for obtaining VI from dibenzyl anilinomalonate was used with 2 g. of ethyl β-naphthylmalonate.[6] The intermediate chloroacetylated compound was obtained as 2.35 g. of viscous oil. The corresponding β-lactam VIII was isolated as 2.15 g. (95%) of a crystalline solid. Recrystallization from ligroin or cyclohexane gave a product melting at 75–76°.

Anal. Calcd. for $C_{19}H_{19}O_5N$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.87; H, 5.76; N, 4.15.

Infrared Absorption Spectra.—The infrared spectra shown in Fig. 1 were determined with a Baird Infrared Recording Spectrophotometer, Model B. Five per cent. solutions in carbon tetrachloride were used for curves A, B and C. A ten per cent. solution in methylene chloride was used for D and a five per cent. solution in tetrachloroethane for E.

Summary

A series of β-lactams has been synthesized by a new method involving the cyclization of chloroacetamidomalonic esters by treatment with triethylamine at room temperature. Uniformly high yields were obtained; no tendency to form compounds containing larger rings or those resulting from linear polymerization was observed.

The stepwise saponification and decarboxylation of 1-phenyl-4,4-dicarbethoxy-2-azetidinone lead successively to 1-phenyl-4-carboxy-4-carbethoxy-2-azetidinone, and 1-phenyl-4-carboxy-2-azetidinone. The structure of the latter was proved by an independent synthesis from 1-phenyl-4,4-dicarbobenzoxy-2-azetidinone by hydrogenolysis and decarboxylation, thus demonstrating that the β-lactam ring survived the two selective alkaline hydrolyses.

CAMBRIDGE 39, MASSACHUSETTS

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE OHIO STATE UNIVERSITY]

A New Synthesis of α-Alkoxy Ketones[1]

BY MELVIN S. NEWMAN AND PHILIP F. BEAL III

Attention has previously been called to the similarity between the Curtius rearrangement of acid azides and the Wolff rearrangement of α-diazoketones.[2] Since it had recently been shown that the Curtius rearrangement was acid catalyzed[3] we were led to study the acid catalyzed reactions of diazoketones.

Inasmuch as protonic acids were known to react with diazoketones to yield unrearranged ketones containing the proton and anion of the acid attached to the carbon which originally held the diazo group, a non-protonic acid was indicated. When an ether or benzene solution of diazoacetophenone was treated with boron fluoride etherate, nitrogen was evolved immediately at room temperature. The reaction product, however, was a dark colored tar. When methanol was the solvent, a good yield of α-methoxyacetophenone was obtained. This reaction proved to be quite general

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[1] Presented in part at the American Chemical Society Meeting at Atlantic City, August, 1948. Taken in part from the Ph.D. thesis of P. F. B., Ohio State, 1949.

[2] B. Eistert, *Ber.*, **68**, 208 (1935).

[3] M. S. Newman and H. Gildenhorn, THIS JOURNAL, **70**, 317 (1948).