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Azetidines. II. Some Functional Derivatives of Azetidines[1]

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The sodium methoxide-catalyzed cyclization of methyl α-tosylamino-γ-chlorobutyrate gave methyl 1-tosylazetidine-2-carboxylate, which was then converted to the corresponding carboxylic acid and carbinol. 1-Acetyl-2, 2, 4, 4-tetramethylazetidine-3-carboxylic acid was prepared by the photolysis of 1-acetyl-4-diazo-2, 2, 5, 5-tetramethylpyrrolidin-3-one. The formation of 1-acetyl-2, 2, 4, 4-tetramethyl-3-azetidinone was confirmed.

The azetidine derivatives have not been extensively investigated; there have been particularly few reports on those derivatives which have functional groups directly attached to the ring. Although a number of β-lactams and *N*-acyl derivatives are known,[3] the only other such derivatives known until very recently were condensed 3-azetidinones,[4] 1-acetyl-3-hydroxytetramethylazetidine-3-carboxylic acid,[5] and azetidine-2-carboxylic acid. The last-named acid was prepared by treating α-bromo-γ-aminobutyric acid with barium hydroxide, and it was separated from other amino acid by-products by paper chromatography.[6] Recently, however, elegant syntheses of 3-acylazetidines[7] and 3-azetidinols[8] have been reported.

We have been interested in the preparation of azetidine carboxylic acid derivatives which may be adopted for a preparative-scale experiments, and so have attempted to prepare methyl 1-tosylazetidine-2-carboxylate (I) by the ring closure of methyl α-tosyl-amino-γ-bromobutyrate (II) by a base. The treatment of methyl α, γ-dibromobutyrate with tosylamide under a variety of conditions (MeOH/NaOMe, *t*-BuOH/*t*-BuOK, MeOH/NaOH, DMF/NaH, Et_2O/NaH) failed to give the tosylamino derivative, and so this approach was abandoned.

We next tried to prepare I by a base-catalyzed cyclization of methyl α-tosylamino-γ-halobutyrate. The treatment of methyl α-amino-γ-iodobutyrate (III) with tosyl chloride in pyridine afforded methyl α-tosylamino-γ-chlorobutyrate (IV), resulting from the *N*-tosylation, accompanied by the replacement of the iodine atom of III by chlorine. The cyclization of IV to I was effected in 60% yield by the use of sodium methoxide in methanol. Support for the structure I is obtained by correct analyses, a molecular-weight determination, and spectroscopic data. The NMR spectrum of the ester I (Fig. 1) shows a one-proton triplet at τ 5.43 for the methine proton, two two-proton multiplets at *ca.* 6.2 and 7.7 for the ring methylene protons of the 3 and 4 positions, two methyl singlets at τ 6.29 and 7.56, and an aromatic multiplet between 2.1—2.7. The ester I was hydrolyzed by sodium hydroxide to the corresponding carboxylic acid V and was reduced by lithium aluminum hydride to 1-tosylazetidine-2-methanol VI.

We attempted the reaction of *N*-tosylaspartic anhydride, VII, and methylmagnesium iodide in order to find out if the carboxyl group in VII may be attacked internally by the nitrogen atom to give a rearrangement product, VIII. This reaction did not give the expected compound, VIII; instead, a substance of an unknown structure and with a composition of $C_{11}H_{15}NO_3S$ was isolated in a low yield.

The only azetidine-3-carboxylic acid derivative so far reported is 1-acetyl-3-hydroxy-2, 2, 4, 4-tetramethylazetidine-3-carboxylic acid (IX), which was prepared by Sandris and Ourisson by the benzylic-acid rearrangement of 1-acetyl-2, 2, 5, 5-tetramethylpyrrolidine-3, 4-dione (X).[5] This diketone, X, seemed to be an ideal starting material for the preparation of azetidine-3-carboxylic acid unsubstituted by the hydroxyl group. The treatment of the diketone X with *p*-toluenesulfonhydrazide gave the corresponding monotosyl hydrazone, XI, which was then converted to the stable diazoketone, XII, by elution through an alumina column. The photolysis of the diazoketone XII in aqueous tetrahydrofuran caused a contraction of

1) Part I: T. Chen, H. Kato and M. Ohta, This Bulletin, **40**, 1964 (1967).

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3) J. A. Moore, "Heterocyclic Compounds with Three- and Four-membered Rings," Part Two, ed. by A. Weissberger, Interscience Publishers, New York, N. Y. (1964), p. 885; E. Testa, A. Wittgens, G. Maffii and G. Bianchi, *Research Progress in Organic, Biological and Med. Chem.*, **1**, 477 (1964).

4) J. A. Moore and R. W. Medeiros, *J. Am. Chem. Soc.*, **81**, 6026 (1959); F. J. Marascia, J. A. Moore, R. W. Medeiros and E. Wyss, *ibid.*, **84**, 3022 (1962).

5) C. Sandris and G. Ourisson, *Bull. soc. chim. France*, **1958**, 345.

6) L. Fowden, *Biochem. J.*, **64**, 323 (1956).

7) J. L. Inbach, E. Doomes, R. P. Rebman and N. H. Cromwell, *J. Org. Chem.*, **32**, 78 (1967).

8) V. R. Gaertner, *Tetrahedron Letters*, **1966**, 4691; R. A. Clasen and S. Searles, Jr., *Chem. Commun.*, **1966**, 289.

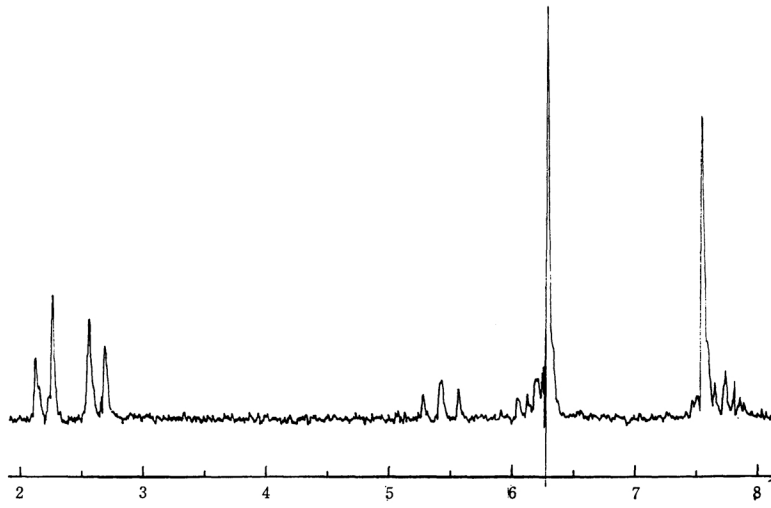
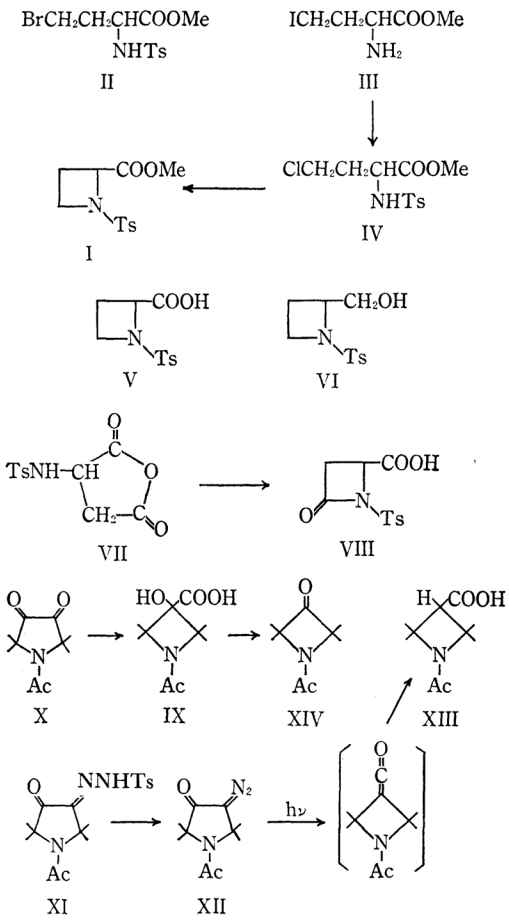


Fig. 1. The NMR spectrum of methyl 1-tosylazetidine-2-carboxylate.



the pyrrolidine ring, giving the carboxylic acid XIII in a good yield.

In order to see if such a type of the formation of azetidinecarboxylic acid is applicable to enolizable ketones, 1-benzylpyrrolidine-2, 3-dione[9] was treated with *p*-toluenesulfonhydrazide; however, this gave only an intractable viscous material which did not give the diazo derivative on treatment with alumina.

Sandris and Ourisson[5] have treated the hydroxy acid IX with lead tetraacetate and obtained a small amount of "a colorless product badly crystallized." On the basis of only the intense infrared absorption band at 1815 cm^{-1}, they assumed this substance to be 1-acetyl-2, 2, 4, 4-tetramethyl-3-azetidinone, but it has not been isolated in a pure form. We repeated their experiment because, if their assumption is correct, it is the only example of a 3-azetidinone which is not fused to another ring. We were successfull in isolating, by sublimation, pure XIV as colorless needles with a melting point of 41—42°C. This substance and its 2, 4-dinitrophenylhydrazone gave correct analyses, and XIV showed an intense infrared absorption band at 1820 cm^{-1} due to the strained carbonyl group. The NMR spectrum of this substance shows only two sharp singlets of the *N*-acetyl group and the four methyl groups on the ring at τ 8.1 and 8.46 corresponding to three and twelve protons respectively. From the information described above, it is now evident that the compound isolated is indeed 1-acetyl-2, 2, 4, 4-tetramethyl-3-azetidinone (XIV).

Experimental[10]

Methyl α-Tosylamino-γ-chlorobutyrate (IV). To a solution of 7.4 g of methyl-amino α-γ-iodobutyrate

9) P. L. Southwick and R. T. Crouch, *J. Am. Chem. Soc.*, **75**, 3413 (1953).

10) The general conditions for the measurements of physical constants and spectra were the same as described in Part I.[1]

hydrochloride in 10 g of dry pyridine, there was slowly added, with cooling, 7.6 g of tosyl chloride. After being allowed to stand overnight in a refrigerator, the mixture was poured onto ice, acidified with hydrochloric acid, and extracted with ether. The extract was dried over magnesium sulfate and then concentrated to give 7.2 g of crystals melting at 55—60°C. Recrystallization from aqueous ethanol afforded 4 g of yellow crystals melting at 77—79°C. This substance was positive to Beilstein's halogen test, but at room temperature it did not readily precipitate silver chloride from an ethanolic solution of silver nitrate. IR: 3200, 1720, 1160 cm^{-1}.

Found: C, 47.23; H, 5.18; N, 4.63%. Calcd for $C_{12}H_{16}O_4NSCl$: C, 47.14; H, 5.24; N, 4.58%.

Methyl 1-Tosylazetidine-2-carboxylate (I). A methanolic solution of sodium methoxide (prepared from 0.18 g of sodium and 15 m*l* of methanol) was slowly added, with cooling, to a solution of 2.4 g of the butyrate IV in 30 m*l* of methanol. After being stirred for two hours, the mixture was refluxed for another ten hours. A white precipitate was separated by filtration after cooling. Recrystallization from methanol afforded 1.25 g (yield 60%) of colorless needles melting at 102—103°C. IR: 1730, 1160 cm^{-1}. No absorption due to an imino hydrogen atom was observed. NMR: see Fig. 1.

Found: C, 53.80; H, 5.72; N, 5.40%; mol wt (Rast), 309. Calcd for $C_{12}H_{15}NO_4S$: C, 53.53; H, 5.58; N, 5.20%; mol wt, 269.

1-Tosylazetidine-2-carboxylic Acid (V). A solution of 0.54 g of the ester I and 0.08 g of sodium hydroxide in 60 m*l* of ethanol was allowed to stand at room temperature for four hours. The mixture was then poured onto ice, and neutralized with hydrochloric acid; the crystals which separated out were collected to give 0.48 g (yield 96%) of white needles melting at 137—139°C. Recrystallization from benzene raised the melting point to 140—141°C. IR: 1710, 1165 cm^{-1}.

Found: C, 52.00; H, 5.48; N, 5.70%. Calcd for $C_{11}H_{13}NO_4S$: C, 51.76; H, 5.13; N, 5.49%.

1-Tosylazetidine-2-methanol (VI). To a suspension of 0.76 g of lithium aluminum hydride in 50 m*l* of ether, 2.1 g of the ester I were added in small portions with stirring and cooling; the mixture was then stirred for another two hours and subsequently allowed to stand overnight. The mixture was decomposed with water and extracted with ether, and the ether extract was dried over magnesium sulfate. On the evaporation of the solvent, 0.7 g of colorless needles was isolated (mp 96—100°C). Recrystallization from benzene-hexane raised the melting point to 104—105°C. IR: 3520 cm^{-1}.

Found: C, 55.00; H, 6.21; N, 6.04%. Calcd for $C_{11}H_{15}NO_3S$: C, 54.76; H, 6.27; N, 5.81%.

Reaction of *N*-Tosylaspartic Anhydride (VII) and Methylmagnesium Iodide. The anhydride VII (6.9 g) was added gradually, with ice cooling, to an ether solution of methylmagnesium iodide which had been prepared from 2.4 g of magnesium and 14.2 g of methyl iodide in 100 m*l* of ether. The reaction mixture was stirred for two hours with ice cooling and was then left to stand overnight. The resultant mixture was hydrolyzed by the addition of water and extracted with ether. The ether extract was dried over magnesium sulfate, and the ether was removed to give 0.7 g of yellow crystals melting at 172—176°C. Recrystallization from xylene gave colorless needles melting at 176—177°C. IR: 3300, 3160, 1770, 1740, 1600, 1165, 1158, 810 cm^{-1}.

Found: C, 55.10; H, 6.07; N, 5.66%; mol wt (Rest), 210. Calcd for $C_{11}H_{15}NO_3S$: C, 54.76; H, 6.27; N, 5.81%; mol wt, 241.

1-Acetyl-2, 2, 5, 5-tetramethylpyrrolidine-3, 4-dione-monotosylhydrazone (XI). A solution of 2 g of 1-acetyl-2, 2, 5, 5-tetramethylpyrrolidine-3, 4-dione, 2 g of *p*-toluenesulfonhydrazide, and three droplets of concentrated hydrochloric acid in 50 m*l* of ethanol was refluxed for an hour. The concentration of the solvent afforded 3.2 g of pale yellow needles melting at 142—143°C. Recrystallization from aqueous ethanol gave colorless needles, melting at 145—146°C. IR: 3150, 1710, 1635, 1576 cm^{-1}.

Found: C, 55.92; H, 6.33; N, 11.69%. Calcd for $C_{17}H_{23}N_3O_4S$: C, 55.88; H, 6.35; N, 11.50%.

1-Acetyl-4-diazo-2, 2, 5, 5-tetramethylpyrrolidin-3-one (XII). A chloroform solution of 0.5 g of the tosylhydrazone XI was passed through a column of alumina, and the eluate was concentrated to give 0.25 g of yellow needles, melting at 109—110°C. IR: 2100, 1670, 1635 cm^{-1}.

Found: C, 57.05; H, 7.01; N, 20.06%. Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08%.

1-Acetyl-2, 2, 4, 4-tetramethylazetidine-3-carboxylic Acid (XIII). A solution of 0.45 g of the diazoketone XII in a mixture of 100 m*l* of tetrahydrofuran and 10 m*l* of water was illuminated through a Pyrex filter with an immersion-type 100-W high-pressure mercury lamp under an atmosphere of nitrogen and with water cooling. After five hours, the evolution of nitrogen was no longer observed. The solvent was dried over sodium sulfate, and the residue which remained after the evaporation of the solvent was recrystallized from tetrahydrofuran-hexane to give 0.25 g of white fine needles, mp 229—230°C. This substance is soluble in aqueous sodium bicarbonate, whereupon carbon dioxide is evolved. IR: broad absorption between 3000—2400 cm^{-1}, 1725, 1580 cm^{-1}.

Found: C, 60.68; H, 8.77; N, 7.42%. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03%.

1-Acetyl-2, 2, 4, 4-tetramethyl-3-azetidinone (XIV). To a refluxing solution of 0.5 g of 1-acetyl-3-hydroxy-2, 2, 4, 4-tetramethylazetidine-3-carboxylic acid in 20 m*l* of chloroform, there was added a solution of 1.5 g of lead tetraacetate in 20 m*l* of chloroform. After an hour's refluxing, the mixture was filtered, and the filtrate was neutralized with aqueous sodium bicarbonate and was extracted with chloroform. The extract was dried over calcium chloride, and the solvent was evaporated to give a colorless residual liquid which slowly solidified. Sublimation afforded 0.15 g of colorless needles melting at 41—42°C. IR: 1820, 1640 cm^{-1}. NMR (τ): 8.1 (3H, singlet); 8.46 (12H, singlet).

Found: C, 63.69; H, 8.77; N, 8.24%. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28%.

2, 4-Dinitrophenylhydrazone: Orange-yellow needles, mp above 300°C.

Found: C, 51.38; H, 5.25; N, 20.18%. Calcd for $C_{15}H_{19}N_5O_5$: C, 51.57; H, 5.48; N, 20.05%.

The Reaction of 1-Benzylpyrrolidine-2, 3-dione and *p*-Toluenesulfonhydrazide. (a) A pale yellow

viscous material was formed when a solution of the pyrrolidinedione (0.5 g), *p*-toluenesulfonhydrazide (0.5 g), and a droplet of ethanol was allowed to stand overnight at room temperature, or when it was refluxed for an hour.

(b) A solution of the pyrrolidinedione (0.5 g) and *p*-toluenesulfonhydrazide (0.5 g) in 30 m*l* of chloroform in the presence of magnesium sulfate was allowed to stand overnight in a refrigerator; then the solution was passed through an alumina column and was eluated with chloroform and then with ethanol. No yellow color, which is characteristic of the diazoketone, was observed, and no identifiable product could be isolated from the eluate.

We are indebted to Miss Mizuko Yoshida for the measurement of the NMR spectra.