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The Synthesis of (±)-Azetidine-2-carboxylic Acid and 2-Pyrrolidinone Derivatives

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(±)-Azetidine-2-carboxylic acid and 3-substituted-2-pyrrolidinones were synthesized from 2-pyrrolidinone via 3-bromo-2-methoxy-1-pyrroline (IIIa). The bromide (IIIa) was obtained by the bromination of 2-methoxy-1-pyrroline using NBS.

L-(−)-Azetidine-2-carboxylic acid (V) is an imino acid which was isolated from fresh leaves of *Convallaria majalis* by Fowden[1] who determined the structure of this imino acid and synthesised it starting from L-glutamic acid via γ-amino-α-bromobutyric acid. Later this imino acid was shown to be a useful proline analogue.[2] Recently Rodebough and Cromwell[3] synthesised (±)-azetidine-2-carboxylic acid from γ-butyrolactone in 53.4% overall yield.

In the course of investigation to introduce a functional group to 3-position of 2-alkoxy-1-pyrroline (II), we found that compound II reacts with NBS to give 3-bromo-2-alkoxy-1-pyrroline (III) whereas bromination of O-methylcaprolactim with NBS was unsuccessful. We now applied this bromide (III) to a starting material for the synthesis of (±)-azetidine-2-carboxylic acid and 3-substituted-2-pyrrolidinone derivatives. 2-Methoxy-(IIa) and 2-ethoxy-1-pyrroline (IIb) were prepared from 2-pyrrolidinone (I) by treating it with dimethyl sulfate,[4] and triethyloxonium fluoroborate respectively. These 2-alkoxy-1-pyrrolines were converted to 3-bromo-2-alkoxy-1-pyrroline (III) in 45～50% yield by refluxing them with an equivalent amount of NBS in carbontetrachloride.

Since these bromides are labile to acid, they were smoothly hydrolysed to give γ-amino-α-bromobutyric acid (IV) by treating it with diluted HCl solution. The α-bromo acid (IV) was used to the next cyclization reaction without purification. The α-bromo acid was treated with excess hot alkaline solution. When its solution was added dropwise to the refluxing alkaline solution, azetidine-2-carboxylic acid (V) was obtained in 50～58% yield. In case the α-bromo acid solution was added to the alkaline solution in one portion, the yield of azetidine-2-carboxylic acid was low

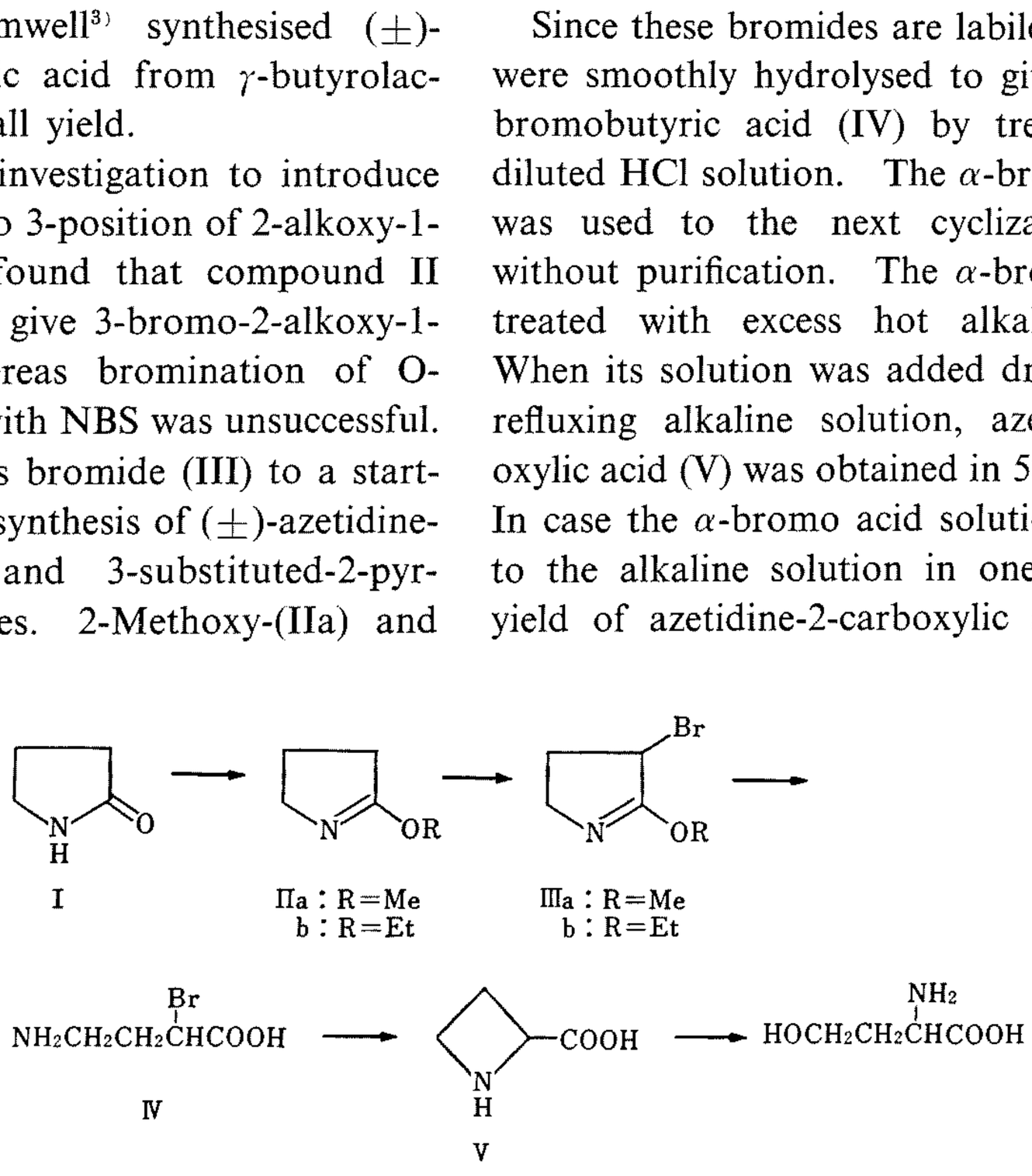

FIG. 1.

(37%). Barium hydroxide[1] and sodium hydroxide are suitable bases for the cyclization reaction. When the organic bases such as triethylamine and diethylamine are used in chloroform, no reaction was occured recovering the starting material. (±)-Azetidine-2-carboxylic acid thus obtained was identified with authentic sample synthesised by the other route. The structure of V was confirmed by transformation of it to (±)-homoserine by acid hydrolysis.

The transformation of 3-bromo-2-methoxy-1-pyrroline (IIIa) to 3-substituted-2-pyrrolidinone derivatives was carried out via route which was shown in Fig. 2.

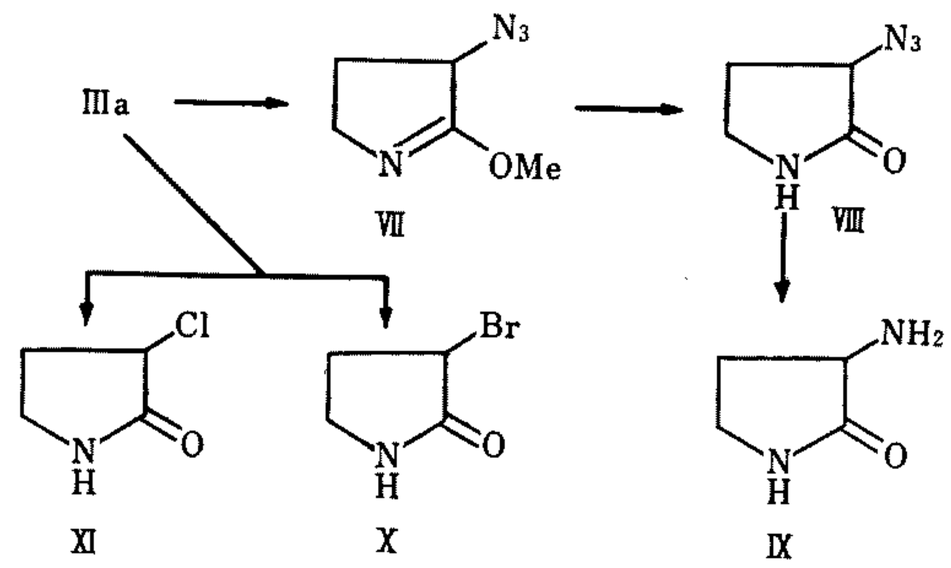

FIG. 2.

3-Bromo-2-methoxy-1-pyrroline (IIa) was converted to 3-bromo-2-pyrrolidinone (X) by treating it with HBr in methanol. The bromide (X) shows a melting point 82°C which coincides with the value of the literature.[5] When IIIa was treated with HCl in place of HBr, the mixture of 3-chloro-2-pyrrolidinone (XI) and the bromide (X) (XI: X=6: 1) was obtained. This result was confirmed by mass spectrometry. The bromide (IIIa) reacts with sodium azide in DMSO to give 3-azido-2-methoxy-1-pyrroline (VII) which is unstable at room temperature. The conversion of the azide (VII) to 3-azido-2-pyrrolidinone (VIII) which was obtained in a form of stable crystals was carried out by means of HCl in methanol. The azide (VIII) was hydrogenated under atmospheric pressure with palladium carbon to 3-amino-2-pyrrolidinone (IX) whose optically active form was already synthesised from α,γ-diaminobutyric acid by Adamson[6] and Wilkinson.[7]

Studies utilizing 3-azido-2-methoxy-1-pyrroline in the preparation of other amino acids are in progress in our laboratory.

EXPERIMENTAL

2-Methoxy-3-bromo-1-pyrroline (*IIIa*). 2-Methoxy-1-pyrroline (IIa)[4] (23 g) was refluxed with NBS (41.4g) and a small amount of benzoyl peroxide in 150ml of carbontetrachloride for one hr. The reaction mixture was cooled and was filtered to remove separated succinimide. The filtrate was washed with water and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was distilled under reduced pressure. Bp 65~70°C (10 mmHg). Yield 19.2 g. Found: C, 34.45; H, 4.54; N, 7.89. Calcd. for C_5H_8ONBr: C, 33.74; H, 4.53; N, 7.87%. IR ν_{max}^{film} cm^{-1}: 1635 (C=N), 1175, 990 (C–O).

3-Bromo-2-ethoxy-1-pyrroline (*IIIb*). 2-Ethoxy-1-pyrroline (23 g) was refluxed with NBS (36 g) and a small amount of benzoyl peroxide in 150 ml of carbontetrachloride for one hr. The reaction mixture was treated as described in procedure for IIIa. Yield 23 g. Bp 70~72°C (10 mmHg). Found: C, 37.62; H, 5.39; N, 7.01. Calcd. for $C_6H_{10}ONBR$: C, 37.51; H, 5.26; N, 7.29%. IR ν_{max}^{film} cm^{-1}: 1635 (C=N), 1330, 1020. NMR (in $CDCl_3$) δ: 4.5~4.7 (1H, quartet, C3–H), 3.05~3.35 (2H, multiplet, C5–H), 2.30~2.95 (2H, multiplet, C4–H). The bromides (III) are unstable at room temperature decomposing to resinous compound.

Azetidine-2-carboxylic acid (*V*). a) 3-Bromo-2-methoxy-1-pyrroline (IIIa) (5 g) was refluxed in 3 N HCl solution (70 ml) for 2 hr. Water and hydrogen chloride was removed under reduced pressure and the residue was dissolved in 50 ml of water. This solution was added dropwise to the refluxing solution of $Ba(OH)_2 \cdot 8H_2O$ (14.7 g in 500 ml of H_2O) with stirring. The addition required 2 hr. Diluted sulfuric acid (4 N) was added to adjust pH at 6.0. The precipitate was removed by centrifugation and the supernatant was concentrated to 10 ml. Hot methanol was added and the precipitate was filtered. The filtrate was concentrated and the residue dissolved in a small amount of water. This solution was placed on the column of Dowx 50w–x8 (100 ml) and after washing with water, the imino acid was eluted with 1 N ammonia solution. The fractions which contained the imino acid was concentrated and the residue was crystallized by the addition of methanol. Yield 1.50 g (53%).

b) γ-Bromo-α-aminobutyric acid hydrochloride

solution (50 ml) which was prepared from 5 g of 3-bromo-2-methoxy-1-pyrroline (IIIa) by the method described in procedure a) was added dropwise to the refluxing solution of NaOH (4 g in 500 ml of H_2O) with stirring. The addition of the α-bromo acid took 2 hr. Azetidine-2-carboxylic acid was obtained in a crystalline form by the method described in procedure a). Yield 1.64 (58%). Found: C, 47.36; H, 7.15; N, 13.78. Calcd. for $C_4H_7NO_2$: C, 47.52; H, 6.98; N, 13.86%. IR ν_{max}^{KBr} cm^{-1}: 1580, 1415, 1315, 1100. NMR (in D_2O) δ: 2.3~2.9 (2H, multiplet) 3.8~4.2 (2H, multiplet).

c) (±)-*Homoserine*. Synthesised azetidine-2-carboxylic acid (100 mg) was dissolved in 6 N HCl solution (40 ml) and it was refluxed for 24 hr. The solution was concentrated and placed on the Dowx 50W–X80 column. After washing with water, (±)-homoserine was eluted with 2% NH_4OH solution. The fraction which contained homoserine was concentrated and the residue was crystallized from methanol. Yield 27 mg (23%). (±)-Homoserine thus obtained was identified with authentic (±)-homoserine.

3-Bromo-2-pyrrolidinone (*X*). Dry hydrogen bromide (20 g) gas was introduced in 63 g of dry methanol and 3-bromo-2-methoxy-1-pyrroline (IIIa) (6 g) was dissolved. The mixture was kept at room temperature for 20 hr. Methanol and HBr were removed under reduced pressure and dichloromethane (100 ml) was added to the residue. Sodium carbonate solution (10%) was added to the mixture to neutralize the solution. After adding saturated NaCl solution, the organic layer was separated. The aqueous layer was extracted with five 50 ml portions of dichloromethane. The dichloromethane extracts were combined and dried over calcium chloride. The solvent was removed by distillation. The residue was crystallized. Yield 4.2 g. Mp 82°C (Recrystallized from ether.) Found: C, 29.30; H, 3.75; N, 8.46. Calcd. for C_4H_6ONBr: C, 29.23; H, 3.69; N, 8.54%. IR ν_{max}^{Nujol} cm^{-1}: 3175 (N–H), 1695 (C=O), 1284. NMR (in $CDCl_3$) δ: 8.0 (1H, broad, N–H), 4.31~4.43 (1H, multiplet, C3–H), 3.31~3.70 (2H, multiplet, C5–H), 2.25~2.90 (2H, multiplet, C4–H).

3-Azido-2-pyrrolidinone (*VIII*). 3-Bromo-2-methoxy-1-pyrroline (5 g) in 10 ml of dimethylsulfoxide was added dropwise to the suspension of sodium azide (2 g) in 20 ml of dimethylsulfoxide with vigorous stirring. During the addition, the temperature of the reaction mixture was kept under 30°C by cooling in an ice bath. After the addition the mixture was stirred for 4 hr at room temperature. The solution was poured into water and it was extracted with dichloromethane. The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure at 40°C. The crude 3-azido-2-methoxy-1-pyrroline (VII) was obtained as a light brownish oil which was unstable at room temperature. Yield 4.1 g. IR ν_{max}^{Film} cm^{-1}: 2100 (N_3), 1660 (C=N), 1450, 1340, 1260, 1000.

3-Azido-2-methoxy-1-pyrroline (4.0 g) was dissolved in 30 g of dry methanol and 10 g of dry hydrogen chloride. The mixture was kept for 15 hr at room temperature. Methanol and hydrogenchloride was evaporated under reduced pressure and 100 ml of saturated sodium carbonate solution was added to the residue. The solution was extracted with dichloromethane. After drying over anhydrous sodium sulfate the solvent was evaporated to give crystalline product (VIII). Yield 3.2 g (89%). Mp 72~73°C (Recrystallized from ether). Found: C, 38.34; H, 4.67; N, 44.44. Calcd. for $C_4H_6N_4O$: C, 38.88; H, 4.80; N, 44.43%. IR ν_{max}^{Nujol} cm^{-1}: 3200 (N–H), 2100 (N_3), 1700 (C=O). 1300, 1260. NMR (in d-DMSO): 7.9 (N–H), 4.22 (1H, triplet, C3–H), 3.12~3.36 (2H, multiplet, C5–H), 2.06~2.40 (1H, multiplet, C4–H), 1.72~1.92 (1H, multiplet, C4–H).

3-Amino-2-pyrrolidinone (*IX*). 3-Azido-2-pyrrolidinone (VIII) (2 g) was dissolved in 100 ml of methanol with 300 mg of palladium carbon (5%). The solution was hydrogenated under atmospheric pressure for 3 hr at room temperature. The catalyst was removed by filtration and the solvent was evaporated to give very hygroscopic white crystals. Yield 1.53 g (97%). Mp 99°C (Recrystallized from tetrahydrofurane). IR ν_{max}^{Nujol} cm^{-1}: 3500~3000 (N–H), 1660, 1280, 1000, 900. NMR (in $CDCl_3$) δ: 7.3 (N–H), 3.28~3.62 (3H, multiplet), 2.38~2.68 (1H, multiplet, C4–H), 2.75~2.09 (1H, multiplet, C4–H).

3-Acetoamido-2-pyrrolidinone. 3-Amino-2-pyrrolidinone was acetylated with acetic anhydride in pyridine at room temperature. Mp 174~5°C. Found: C, 50.38; H, 7.13; N, 19.87. Calcd. for $C_6H_{10}N_2O_2$: C, 50.38; H, 7.09; N, 19.87%. IR ν_{max}^{Nujol} cm^{-1}: 3260, 3100 (s) (N–H), 1690, 1630 (C=O).

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