Studies on Seven-membered Heterocyclic Compounds Containing Nitrogen. I. Synthesis of 1-Azacycloheptan-4-one Hydrochloride

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As to azacycloheptanones, syntheses of 1-methyl-1-azacycloheptan-3-one[1], 1-methyl-2-ethyl-1-azacycloheptan-3-one[2], 1, 2-dimethyl-1-azacycloheptan-3-one[3], and 1-alkyl-5-phenyl-1-azacycloheptan-4-ones[4] have been reported, but no such compound as one that has no side-chain is obtained except a lactam-type 1-azacycloheptan-2-one.

The present authors obtained 1-benzyl-1-azacycloheptan-4-one (II) (b.p. 137–139°C/2 mmHg.; hydrochloride, m.p. 186–187°C (decomp.); 2, 4-dinitrophenylhydrazone hydrochloride, m.p. 206°C (decomp.)) by the Dieckmann condensation of ethyl N-benzyl-γ-(β-carbethoxyethylamino) butyrate[5] (I), using the methods of Prill and McElvain[1], and of Leonard and Barthel[2]. Reduction of II hydrochloride by palladous oxide as a catalyst afforded 1-azacycloheptan-4-one hydrochloride (III), m.p. 171°C (decomp.). 2, 4-Dinitrophenylhydrazone hydrocholoride of III was formed in two kinds of crystal; one melted at 155°C (decomp.) and the other at 211°C (decomp.). The formed could be converted into the latter.

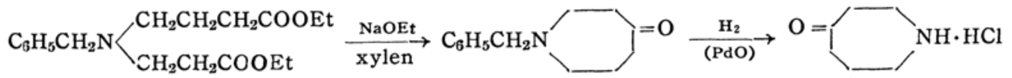
The action of diazomethane on 1-benzoyl-1-azacyclohexan-4-one yielded an oil, b. p. 172–179°C/0. 01 mmHg. likely to be 1-benzoyl-1-azacycloheptan-4-one from the analytical value and also from that of 2, 4-dinitrophenylhydrazone, m. p. 175–6°C. An attempt was made to obtain III by hydrolysis of the oil with hydrochloric acid, but the resultant oily substance did not crystallize. 2, 4-Dinitrophenylhydrazone derived from the oily substance, however, was, though in poor yield, found to be identical with the one, m.p. 155°C (decomp.) from III by mixed fusion. Further detailed study on these experiments will be described in subsequent papers.

The Dieckmann condensation of ethyl N-benzoyl-γ-(β-carbethoxyethylamino) butyrate[5] was unsuccessful.

The present study was carried out as a part of the general research on the azulenoid compounds (the representative, Prof. Tetsuo Nozoe). The authors take this opportunity to extend their deep gratitude to the members of the Department of Organic Chemistry of Tokyo Institute of Technology for their carrying out the carbon and hydrogen microanalyses and also to Mr. Kameji Yamane (this laboratory) for his cooperation in the present experiments.

Experimental

1-Benzyl-1-azacycloheptan-4-one (II).—In a 1 l. three-necked, round-bottomed flask fitted with a Hershberg stirrer, a dropping funnel and a fractionating column which had a thermometer on its head and a side arm attached to a condenser set for downward distillation, were placed sodium ethoxide, prepared from 2. 3 g. of sodium[6] and 400 cc. of dry xylene. The reaction flask was heated under stirring in an oil-bath sufficiently to cause gentle refluxing from the column, and a solution of 32.1 g. of ethyl N-benzyl-γ-(β-carbethoxyethylamino) butyrate in 200 cc. of dry xylene was added dropwise during sixteen hours. The heating was then continued until the mixture of alcohol and xylene distilled out and the thermometer registered the boiling point of xylene. The reaction mixture was extracted with four 30 cc. portions of water and three 40 cc. portions 2N hydrochloric acid. The extracts were united and refluxed with 240 cc. of concentrated hydrochloric acid for five hours. The hydrochloric acid was expelled by heating on a water-bath under reduced pressure as completely as possible and 50% potassium hydroxide solution was added to the residue to make pH 8 and extracted with five 50 cc. portions of ether. The aqueous solution was then made strongly alkaline and further extracted with seven 30 cc. portions of ether. These ether extracts were all combined and dried over magnesium sulfate. Dry hydrogen chloride was passed through to give hydrochloride of II as a precipitate. The precipitate was dried in a desiccator and dissolved in 12 cc. of methanol



(I) (II) (III)

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[1] E.A. Prill and S.M. McElvain, *J. Am. Chem. Soc.*, **55**, 1233 (1933).

[2] N.J. Leonard and E. Barthel, ibid., **71**, 3098 (1949).

[3] N.J. Leonard and S. Gelfand, ibid., **77**, 3269 (1955).

[4] R.E. Lyle and G.G. Lyle, *C.A.*, **49**, 9047 (1955).

[5] A. Yokoo and S. Morosawa, *J. Chem. Soc. Japan*, **77**, 599 (1956).

[6] "Organic Reacticn", Vol. I, p. 278.

and crystallized by adding ether. This crystal was recrystallized from methanol-ether solution as white needles, m.p. 186–187°C (decomp.), yield 5.2 g. (Found: N, 5.74. Calcd. for $C_{13}H_{17}ON \cdot HCl$: N, 5.85%).

2, 4-Dinitrophenylhydrazone Hydrochloride.—The mixture of II hydrochloride (0.1 g.), 2, 4-dinitrophenylhydrazine (0.2 g.), alcohol (10 cc.) and concentrated hydrochloric acid (0.2 cc.) was heated for two minutes. The crystals formed were recrystallized from water to yield 0.2 g. of yellow crystals, m.p. 206°C (decomp.). (Found: N, 16.87. Calcd. for $C_{19}H_{21}O_4N_5 \cdot HCl$: N, 16.65%).

The above-mentioned hydrochloride was made alkaline by adding 50% potassium hydroxide solution and taken up in ether. After drying over magnesium sulfate, the ether was removed and vacuum distillation of the residue gave II, b.p. 115–118°C/0.01 mm. (Found: N, 7.17. Calcd. for $C_{13}H_{17}ON$: N, 6.89%).

1-Azacycloheptan-4-one Hydrochloride (III).—A solution of 4 g. of II hydrochloride in 150 cc. water was shaken with 0.3 g. of PdO under hydrogen atomosphere at room temperature until the theoretical amount of hydrogen had been absorbed. After separation of the catalyst by filteration, water was removed under reduced pressure and the residue was crystallized from alcohol and ether to yield 2.1 g. (84%) of colorless needles, m.p. 171°C (decomp.).

Anal. Found: C, 48.51; H, 7.98; N, 9.29. Calcd. for $C_6H_{11}ON \cdot HCl$: C, 48.83; H, 8.08; N, 9.36%.

2, 4-Dinitrophenylhydrazone hydrochloride was obtained in yellow needles, m.p. 212°C (decomp.) (Found: N, 21.61. Calcd. for $C_{12}H_{15}O_4N_5 \cdot HCl$: N, 21.24%). Another kind of crystal was also obtained in orange scales, m.p. 152–155°C (decomp.), which was not depressed on admixture with the specimen derived from 1-benzoyl-1-azacycloheptan-4-one by hydrolysis and was also able to be converted into the modification in yellow needles by boiling with hydrochloric acid in methanol.

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