

## Studies on Seven-Membered Heterocyclic Compounds Containing Nitrogen. II. An Improved Synthesis of 1-Azacycloheptan-4-one and Its Related Compounds

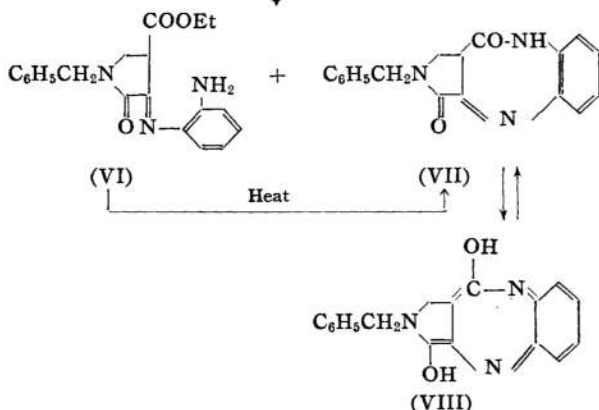
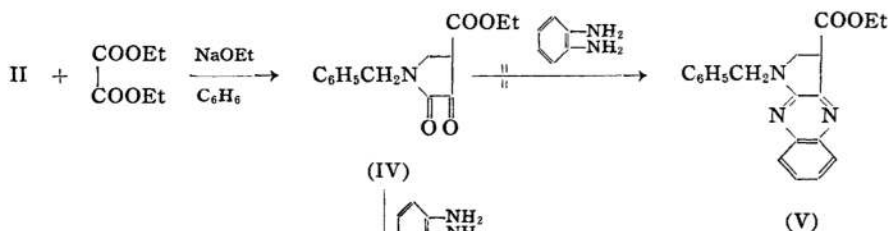
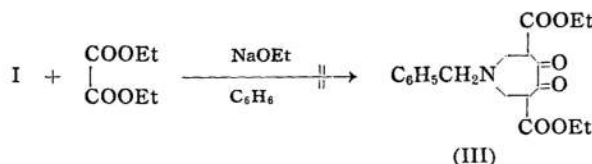
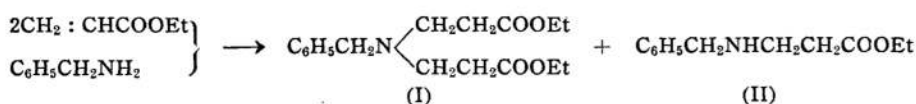
By Shiro MOROSAWA

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It was reported in the former paper<sup>1)</sup> that 1-azacycloheptan-4-one (XI) was synthesized from ethyl *N*-benzyl- $\gamma$ -( $\beta$ -carbethoxyethylamino)-butyrate<sup>2)</sup> by the Dieckmann condensation. The preparation of the butyrate, however, was so troublesome that the author tried to obtain XI by ring enlargement of 1-benzyl-4-piperidone (X)

which prepared from *N,N*-bis-( $\beta$ -carbethoxyethyl)-benzylamine (I) by the Dieckmann condensation.

The method of G. Stork and S. M. McElvain<sup>3)</sup> was applied to the preparation of I, and a fraction of b. p. 200~210°C/0.5 mm. was obtained. The author tried at first to prepare azacycloheptane dione (III)

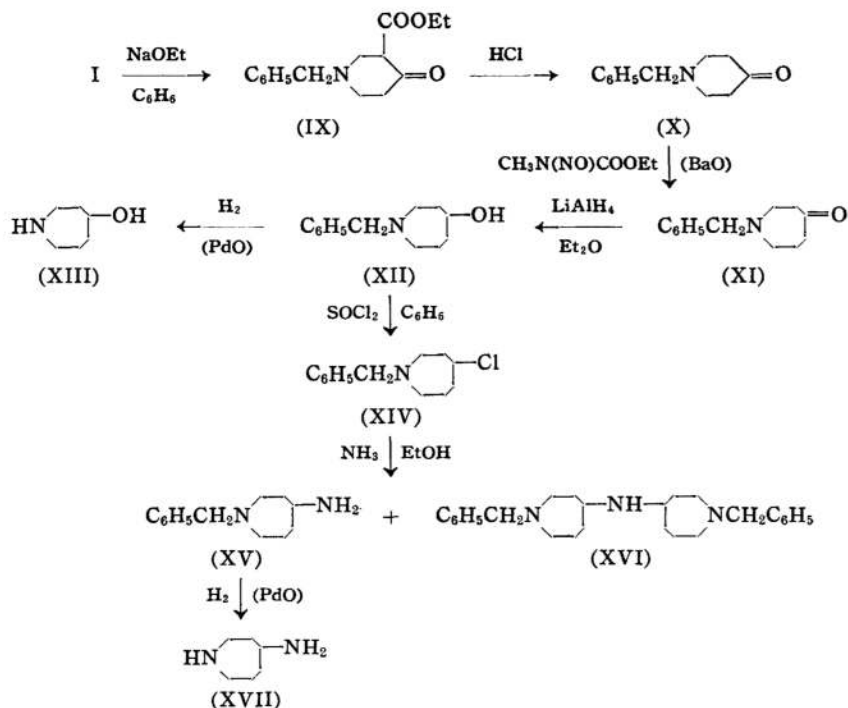


1) A. Yokoo and S. Morosawa, *This Bulletin*, **29**, 631 (1956).

2) A. Yokoo and S. Morosawa, *J. Chem. Soc. Japan*,

*Pure Chem. Sec. (Nippon Kagaku Zasshi)*, **77**, 599 (1956).

3) G. Stork and S. M. McElvain, *J. Am. Chem. Soc.*, **69**, 971 (1947).



from I and ethyl oxalate, and the fraction was heated with ethyl oxalate in the presence of sodium ethoxide in benzene. But unexpectedly, azacyclopentane dione (IV) was formed. IV was also obtained from ethyl oxalate and pure ethyl  $\beta$ -benzylaminopropionate (II)<sup>3</sup> which was prepared by the Stork and McElvain's method. It was assumed that possibly ethyl oxalate condensed with II which was previously contained in the fraction, or formed by decomposition of I during the heating. With *o*-phenylenediamine IV did not afford a compound of phenazine type (V) but two kinds of crystal; one was light yellow of m. p. 127~8°C and the other orange of m. p. 265~270°C (decomp.). They were revealed from their elementary analyses to have formulae VI and VII (or VIII), respectively. Infrared absorption spectrum of the latter crystals showed the absence of an ester and the primary amine, but because of a wide absorption band (1630~1680 cm.<sup>-1</sup>) near the carbonyl and enol, it was not clearly determined which structure, VII or VIII, is preferable. VI was converted into VII by heating.

Some different boiling points have been reported for I<sup>3,4</sup>, but as a result of the present study it was distilled out at 200~

210°C/0.5 mm. along with ethyl acrylate which was detected by its faint odor; nitrosoation test with sodium nitrite for the distillate indicated the presence of a secondary amine II. On pyrolysis, the distillate began to decompose at about 197°C to yield ethanol and ethyl acrylate, leaving a residue which was distilled out at 165~210°C/0.65 mm. without indicating a constant boiling point.

From these experiments, it is obvious that I is apt to be affected by heating and can not be refined even by vacuum distillation. In the present study, therefore, the tertiary amine I was separated from the reaction mixture by removing the secondary amine II as a nitroso compound, in 65.5% yield. I thus obtained was possibly considered to be pure from its nitrogen analysis, and was also decomposed at about 197°C on pyrolysis. On heating with an equivalent amount of sodium ethoxide in dry benzene, I was converted into hydrochloride of 1-benzyl-3-carbomethoxy-piperid-4-one (IX)<sup>4</sup> of m. p. 175°C (decomp.) as colorless prisms in 82.5% yield, which by decarboxylation with hydrochloric acid gave 1-benzylpiperid-4-one (X)<sup>5</sup> as a colorless oil of b. p. 143~6°C/5 mm.

The ring enlargement of X was performed by the C. G. Overberger and A.

4) J. R. Thayer and S. M. McElvain, *ibid.*, **49**, 2862 (1927).

5) G. Stork and S. M. McElvain, *ibid.*, **68**, 1053 (1946).

Katchmann's method<sup>6)</sup> who prepared 4-oxo-thiaepane from tetrahydro-1,4-thiapyrone and nitrosomethylurethane in the presence of barium oxide. In order to purify the crude product, this was dissolved in dry ether, and dry hydrogen chloride was passed through to precipitate it as a hydrochloride, which was recrystallized from methanol and ether. The melting point of the hydrochloride was not depressed on admixture with the one described in the former paper. Free base XI was regenerated from the hydrochloride with potassium carbonate, and gave 2,4-dinitrophenylhydrazone hydrochloride, which was also identified as the former one by mixed fusion.

Lithium aluminum hydride reduction of XI afforded 1-benzyl-1-azacycloheptan-4-ol (XII) as a colorless oil of b.p. 129°C/0.5 mm. in 95.5% yield, which on catalytic reduction with palladous oxide yielded 1-azacycloheptan-4-ol (XIII) as a hygroscopic colorless viscous oil of b.p. 82°C/0.5 mm. in 56.2% yield. XIII gave a picrolonate of m.p. 225°C (decomp.). With thionyl chloride, XII afforded 1-benzyl-4-chloro-1-azacycloheptane (XIV) as a hygroscopic colorless liquid of b.p. 104~5°C/0.3 mm. in 67.3% yield, which on standing gradually crystallized. Heating a mixture of XIV and absolute ethanol, saturated with ammonia at 0°C, in a sealed tube gave 4-amino-1-benzyl-1-azacycloheptane (XV) as a colorless oil of b.p. 105~6°C/0.4 mm. in 71% yield. Bis-(4-benzyl-4-azacycloheptyl)-amine (XVI) was also thereby obtained as a higher-boiling, light yellow viscous oil of b.p. 219~221°C/0.3 mm., which gave a picrolonate of m.p. 213°C (decomp.). XV gave a chloroaurate as yellow micro plates of m.p. 194°C (decomp.). Catalytic reduction of XV in the presence of palladous oxide as a catalyst afforded 4-amino-1-azacycloheptane (XVII) as a hygroscopic colorless oil of b.p. 80°C/10 mm., which on standing in the atmosphere gradually deposited white crystalline precipitates under fuming. XVII gave a chloroaurate of m.p. 209°C (decomp.) and a picrate of m.p. 224°C (decomp.).

### Experimental

***N,N*-Bis-( $\beta$ -carbethoxyethyl)-benzylamine (I).**—A mixture of 80 g. of benzylamine and 190 g.

of ethyl acrylate was refluxed in an oil bath for 20 hr. After cooling, a mixture of 200 cc. of concentrated hydrochloric acid and 300 cc. of water was added and cooled to below 5°C in an ice-water bath, followed by the addition of 90 g. of solid sodium nitrite in small portions under agitation. After further agitation for 30 min., the mixture was extracted with a mixture of 200 cc. of benzene and 100 cc. of ether. The organic layer was extracted 8 times with each 200 cc. portion of 3N hydrochloric acid and discarded. Aqueous layers were united and made alkaline by adding 650 g. of anhydrous sodium carbonate and extracted with a mixture of 200 cc. of benzene and 200 cc. of ether, then with that of 100 cc. of benzene and 100 cc. of ether. The extracts were united and washed with a diluted solution of sodium carbonate, and water and dried over calcium chloride. The solvent was distilled off on a water bath; the residue is further heated under reduced pressure until nothing had been distilled out. After that, the reduced pressure was held under heating on a water bath for another one hour, leaving 150 g. (65.5%) of an oily substance. (Found: N, 4.63%).

**1-Benzyl-4-carbethoxy-1-azacyclopentane-2,3-dione (IV).**—To a suspension of 3.1 g. of powdered sodium in 150 cc. of dry benzene was added 6 g. of absolute ethanol and heated with stirring to convert the sodium into sodium ethoxide. After cooling, a mixture of 13.8 g. of II (b.p. 133~5°C/2 mm.) and 10 g. of ethyl oxalate was added and allowed to stand overnight. In order to distill out 100 cc. of the azeotropic mixture of ethanol and benzene, the resulting mixture was heated in a water bath with stirring. The mixture in the reaction flask was washed with water and 2N hydrochloric acid until the washing became acidic. The benzene solution was evaporated to a small volume. Crystals formed on standing were filtered, washed with water and recrystallized from ethanol to give 8 g. (46%) of colorless crystals, m.p. 133~4°C.

*Anal.* Found: C, 64.13; H, 5.86; N, 5.19. Calcd. for  $C_{14}H_{15}O_4N$ : C, 64.3; H, 5.76; N, 5.37%.

**Compounds VI and VII.**—A mixture of 1 g. of IV, 1 g. of *o*-phenylenediamine and 10 cc. of ethanol was refluxed on a water bath for 7 hr. Orange crystals formed were filtered and recrystallized from a large amount of ethanol to give 0.2 g. of orange plates (VII), m.p. 265~270°C (decomp.).

*Anal.* Found: C, 70.85; H, 5.19; N, 13.49. Calcd. for  $C_{18}H_{15}O_2N_3$ : C, 70.8; H, 4.93; N, 13.76%.

The filtrate of VII was evaporated and allowed to stand. Crystals formed were recrystallized twice from ethanol to yield 1.2 g. of light yellow crystals (VI), m.p. 127~8°C.

*Anal.* Found: C, 68.28; H, 6.27; N, 11.81. Calcd. for  $C_{20}H_{21}O_3N_3$ : C, 68.3; H, 5.98; N, 11.95%.

**VII by heating VI.**—After heating 0.5 g. of VI at 155~165°C in an oil bath for 5 hr., a small amount of ethanol was added, heated and decanted repeatedly. Remaining crystals were recrystallized from a large amount of benzene to

6) C. G. Overberger and A. Katchmann, *ibid.*, **78**, 1967 (1956).

give 0.3 g. of orange crystals (VII).

**1-Benzyl-3-carbethoxypiperid-4-one (IX) hydrochloride.**—To a suspension of 7.5 g. of powdered sodium in 30 cc. of dry xylene were added 300 cc. of dry benzene and 17 cc. of absolute ethanol, and heated under stirring to convert the sodium into sodium ethoxide. After cooling, a solution of 100 g. of I in 180 cc. of dry benzene was added within 5 min. with stirring. After about 10–20 min., the resulting mixture became gel-like and could not be stirred; it was allowed to stand overnight. About 200 cc. of the solvent was distilled out by heating the mixture for 4 hr. After cooling, 100 cc. of water and 100 cc. of concentrated hydrochloric acid were added to deposit an oily matter, which gradually crystallized. After standing for 2 hr., the crystals were filtered, recrystallized from 40 cc. of ethanol and washed with a mixture of 25 cc. of ethanol and 25 cc. of ether to give 80 g. (82.5%) of IX hydrochloride as colorless prisms, m. p. 175°C (decomp.). (Found: C, 60.77; H, 7.02; N, 4.33%).

**1-Benzylpiperid-4-one (X).**—A mixture of 120 g. of IX hydrochloride, 400 cc. of concentrated hydrochloric acid and 350 cc. of water was refluxed for 3 hr. After cooling, the solution was evaporated to dryness under reduced pressure. The residue was dissolved in 50 cc. of water, and 100 g. of anhydrous potassium carbonate was added. Liberated oil was extracted 4 times with ether (100 cc., 100 cc., 50 cc. and 50 cc. respectively), and the combined ether extract was dried over potassium carbonate. Ether was removed and vacuum distillation gave 61 g. (70%) of a colorless oil, b. p. 143–6°C/5 mm. (Found: N, 7.24%).

X gave 2,4-dinitrophenylhydrazone hydrochloride as yellow prisms of m. p. 223°C (decomp.).

*Anal.* Found: N, 17.26. Calcd. for  $C_{15}H_{19}O_4N_5 \cdot HCl$ : N, 17.63%.

**1-Benzyl-1-azacycloheptan-4-one (XI) by ring enlargement.**—In a three-necked, round-bottomed flask, fitted with a Hershberg stirrer and a dropping funnel, 61 g. of X and 100 cc. of methanol were placed and cooled to –15°C in an ice-salt mixture. The stirring was started, and 45 g. of nitrosomethylurethane was added dropwise within 9 hr. During that time, 2 g. of barium oxide was added in small portions, and the temperature in the flask indicated about –5°C. After being kept overnight in the ice-salt mixture, the reaction mixture was filtered from any solid present, and the methanol was expelled under reduced pressure. The residue was dissolved in 400 cc. of ether and the undissolved polymethylene polymers were filtered off. Dry hydrogen chloride was passed through the ether to give a precipitate, which was separated by decantation, dried, recrystallized from 40 cc. of methanol and 20 cc. of ether and washed thrice with a mixture of 15 cc. of methanol and 15 cc. of ether to yield 28.3 g. of XI hydrochloride, m. p. 184–5°C (decomp.). Evaporation of the filtrate gave a further crop of crystals, which was recrystallized as before to give 3 g. of the substance, m. p. 184–5°C (decomp.). The total yield

was 43.6%. The melting point of this hydrochloride was not depressed on admixture with that described in the former paper.

The hydrochloride was dissolved in 15 cc. of water and 40 g. of potassium carbonate was added. Oil thereby liberated was taken up in ether and dried over potassium carbonate. After removal of ether, vacuum distillation gave 24.8 g. (37.8%, based on X) of free base as a colorless oil, b. p. 129°C/0.5 mm.

2,4-Dinitrophenylhydrazone hydrochloride of m. p. 214°C (decomp.) derived from XI did not either depress the m. p. of the former one on mixed fusion. (Found: N, 16.60%).

**1-Benzyl-1-azacycloheptan-4-ol (XII).**—A solution of 11.1 g. of XI in 150 cc. of dry ether was added dropwise to 1.05 g. of lithium aluminum hydride suspended in 100 cc. of dry ether without cooling during 1 hr. under stirring, which was continued for 15 min. The excessive hydride was then decomposed by adding dropwise 19 cc. of water with stirring. Ether was decanted, dried over magnesium sulfate and removed by distillation. The residue was distilled to yield 10.7 g. (95.5%) of a colorless oil, b. p. 129°C/0.5 mm.

*Anal.* Found: C, 74.90; H, 9.46; N, 6.70. Calcd. for  $C_{13}H_{19}ON$ : C, 76.05; H, 9.33; N, 6.82%.

**1-Azacycloheptan-4-ol (XIII).**—A solution of 4.6 g. of XII in 150 cc. of water containing 2 cc. (a slight excess) of concentrated hydrochloric acid was shaken with 0.2 g. of palladous oxide under an atmosphere of hydrogen at room temperature until the theoretical amount of hydrogen had been absorbed. After removal of the catalyst by filtration, water was evaporated under reduced pressure. To the remainder was added 2 cc. of 50% of potassium carbonate solution, followed by further addition of solid potassium carbonate. This mixture was well agitated to remove water. Ether was then added, agitated well and decanted. This procedure was repeated several times. Ethereal portions were collected and, after drying over potassium carbonate, ether was removed on a water bath to leave a residue. Vacuum distillation of the residue gave 1.45 g. (56.2%) of a quite hygroscopic colorless viscous oil, b. p. 82°C/0.5 mm.

*Anal.* Found: C, 62.13; H, 11.80; N, 11.64. Calcd. for  $C_6H_{13}ON$ : C, 62.57; H, 11.38; N, 12.16%.

**Picrolonate.**—A mixture of 0.1 g. of XIII and 1 g. of picrolonic acid in 40 cc. of ethanol was heated on a water bath for a few min. and allowed to cool. The crystals were recrystallized from ethanol to brownish yellow prisms of m. p. 225°C (decomp.), 0.26 g.

*Anal.* Found: N, 18.33. Calcd. for  $C_6H_{13}ON \cdot C_{10}H_9O_5N_4$ : N, 18.46%.

**1-Benzyl-4-chloro-1-azacycloheptane (XIV).**—To a solution of 5.3 g. of XII in 50 cc. of dry benzene, was added dropwise under cooling in an ice-water bath a solution of 4 cc. of thionyl chloride in 5 cc. of dry benzene with stirring. The solvent was removed under reduced pressure, leaving a dark red residue. The residue was dissolved in a little water and

made alkaline with solid potassium carbonate. The oily substance was taken up in benzene and dried over potassium carbonate. After removal of benzene, vacuum distillation yielded 3.9 g. (67.3%) of a highly hygroscopic colorless liquid, b. p. 104~5°C/0.3 mm. which, on standing, gradually crystallized and showed the presence of halogen by Beilstein test.

*Anal.* Found: N, 6.10. Calcd. for  $C_{13}H_{19}NCl$ : N, 6.26%.

**4-Amino-1-benzyl-1-azacycloheptane (XV) and bis-(4-benzyl-4-azacycloheptyl)-amine (XVI).**—A mixture of 3.4 g. of XIV and 20 cc. of absolute ethanol saturated with ammonia at 0°C was heated in a sealed tube at 100°C for 3 hr. After cooling, the solvent was removed under reduced pressure, and the residue was dissolved in a little water and made alkaline with solid potassium carbonate. The liberated oil was extracted with benzene and dried over potassium carbonate. After removal of benzene, the residue was vacuum-distilled to yield 2.2 g. (71%) of a hygroscopic colorless oil (XV) of b. p. 105~6°C/0.4 mm. and 0.6 g. of a light yellow viscous oil (XVI) of b. p. 219~221°C/0.3 mm.

*Anal.* Found: N, 13.56. Calcd. for  $C_{13}H_{20}N_2$  (XV): N, 13.71%. Found: C, 79.71; H, 9.46; N, 10.46. Calcd for  $C_{26}H_{37}N_3$  (XVI): C, 79.74; H, 9.52; N, 10.73%.

XV on mixing with chloroauric acid produced a chloroaurate, which was recrystallized from water to give yellow micro plates, m. p. 194°C (decomp.).

*Anal.* Found: N, 3.13. Calcd. for  $C_{13}H_{20}N_2 \cdot (HAuCl_4)_2$ : N, 3.17%.

XVI gave a picrolonate by adding an ethanolic solution of picrolonic acid, which was recrystallized from a large amount of water to give yellow crystals, m. p. 213°C (decomp.).

*Anal.* Found: N, 16.45. Calcd. for  $C_{26}H_{37}N_3 \cdot (C_{10}H_8O_5N_4)_2$ : N, 16.75%.

**4-Amino-1-azacycloheptane (XVII).**—A solution of 2 g. of XV in 80 cc. of water was

shaken with hydrogen in the presence of 0.2 g. of palladous oxide at room temperature until the theoretical amount of hydrogen had been absorbed. The catalyst was filtered off, and water was evaporated under reduced pressure. Vacuum distillation of the residue gave 0.55 g. (50%) of a highly hygroscopic colorless oil, b. p. 79~80°C/10 mm. When the distillate is allowed to stand in the atmosphere, white crystalline precipitates appeared in the oil under fuming, possibly because of absorption of carbon dioxide in the atmosphere. So the nitrogen content could not be determined.

On mixing with chloroauric acid, XVII gave a chloroaurate, which was recrystallized from water to yield yellow prisms, m. p. 209°C (decomp.).

*Anal.* Found: C, 9.18; H, 2.46; N, 3.47; Au, 48.9. Calcd. for  $C_6H_{14}O_2 \cdot (HAuCl_4)_2$ : C, 9.08; H, 2.03; N, 3.53; Au, 49.63%.

XVII and a saturated ethanolic solution of picric acid formed a picrate, which was recrystallized from ethanol to yield yellow prisms, m. p. 224°C (decomp.).

*Anal.* Found: N, 19.35. Calcd. for  $C_6H_{14}N_2 \cdot (C_6H_3O_7N_3)_2$ : N, 19.57%.

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*Chemical Institute, Faculty of Science  
Okayama University  
Tsushima, Okayama*