Studies on Seven-Membered Heterocyclic Compounds Containing Nitrogen. III. Reactions of 5-Benzyl-1-oxa-5-azaspiro(5, 2)octane

By Shiro MOROSAWA

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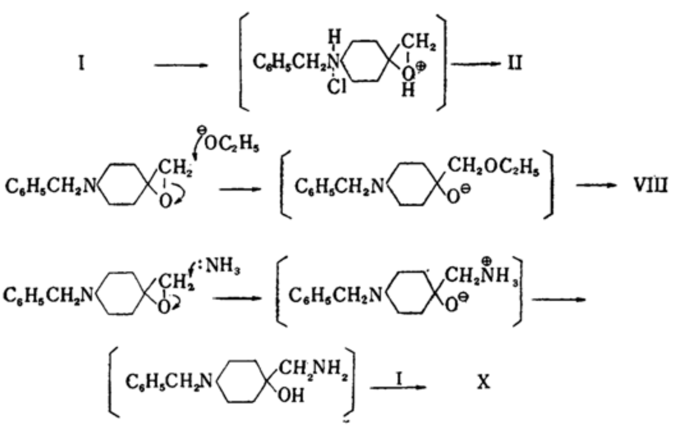
Previously[1] the author reported that 1-benzyl-1-azacycloheptan-4-one was obtained from 1-benzyl-1-azacyclohexan-4-one by ring enlargement and recrystallization as a hydrochloride, followed by the addition of alkali. The present study was undertaken in order to investigate an acidic resinous matter left in a considerable amount on evaporation of mother liquor of the recrystallization, and an epoxy compound was found out. Behaviors of the epoxy group to acid and base were examined.

After treatment of the resinous matter with alkaline water while hot, extraction with benzene yielded an oil, boiling at 119~121°C/0.45 mmHg (I). Infrared absorption spectrum showed that the oil was contaminated with a little ketonic substance even after several recrystallizations as a hydrochloride (II) and liberation by alkali. The oil afforded a sulfonic acid derivative[2] with sodium bisulfite, while 1-benzyl-1-azacycloheptan-4-one a normal addition product. The oil, if necessary, was further treated with 2, 4-dinitrophenylhydrazine and chromatographed on alumina, decolorizing carbon and magnesium sulfate[3]. The infrared absorption spectrum of the purified oil indicated characteristic two bands at 790 $\mathrm{cm^{-1}}$ and 895 $\mathrm{cm^{-1}}$, which is presumably ascribed to the epoxy group. These two bands disappeared in the infrared absorption spectrum of such compounds derived by opening the epoxy group of I as VIII, X and XII. Judging from the nitrogen analysis and the infrared absorption spectrum, the purified oil, b. p. 114°C/0.43 mmHg, was considered as an epoxy compound, 5-benzyl-1-oxa-5-azaspiro(5, 2)octane, being isomeric with 1-benzyl-1-azacycloheptan-4-one[1].

Reduction of both the resinous matter and



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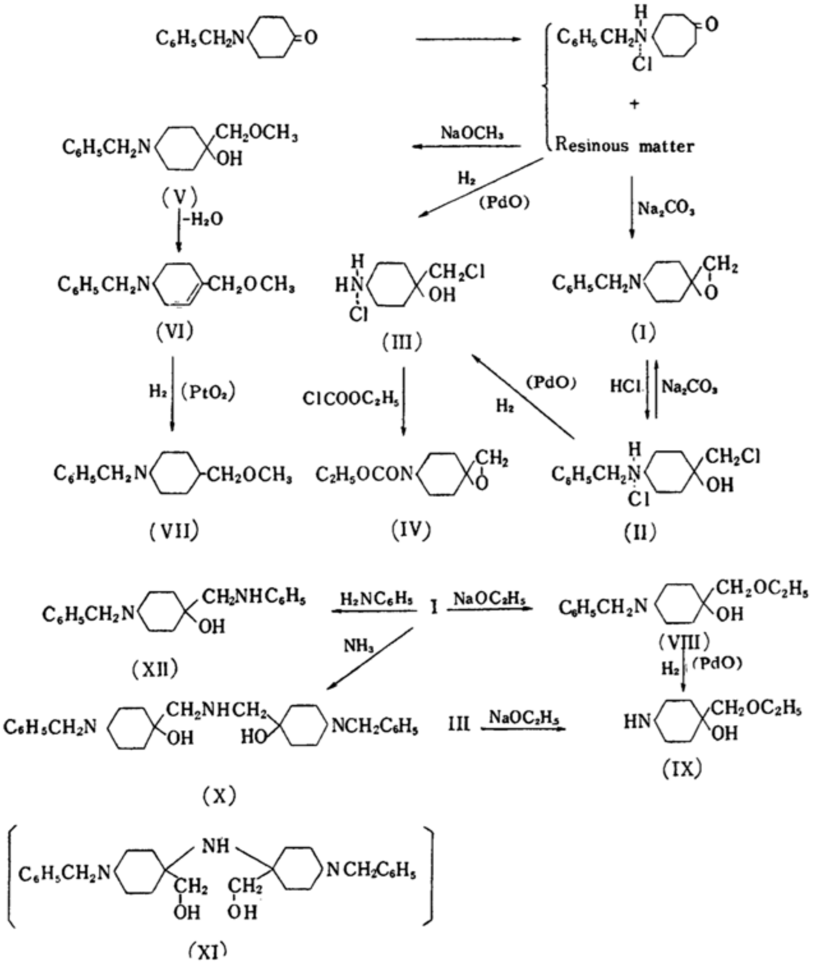
[1] S. Morosawa, This Bulletin, 31, 418 (1958).

[2] W. M. Lauer and A. Hill, *J. Am. Chem. Soc.*, 58, 1873 (1936).

[3] R. P. Linstead, J. A. Elvidge and M. Whalley, "A Course in Modern Techniques of Organic Chemistry", Butterworths Scientific Publications, London, (1955), p. 6.



II in the presence of palladous oxide produced an identical substance, m. p. 183~184°C, which was assumed to be III. III afforded a picrolonate, m. p. 228~229°C (decomp.). III and ethyl chlorocarbonate in alkali medium gave an *N*-carbethoxy epoxy compound, b. p. 94~95°C/1 mmHg (IV). The resinous matter and sodium methoxide in absolute methanol gave an oil, b. p. 146~147°C/1 mmHg (V), which was readily dehydrated to an ethylenic compound, b. p. 126°C/0.5 mmHg (VI). VI was then reduced in the presence of platinum oxide to a saturated compound, b. p. 118~120°C/4.5 mmHg (VII). In the formations of II, III and V isomeric abnormal products[4] were not detected.

In view of these facts, it was clear that II was not a primary hydroxy type but a tertiary one, and that the epoxy group of I was opened, when made acidic, and thus I might exist in the resinous matter in the form of II. Ring opening of the epoxide group by the addition of hydrogen chloride was probably due to the normal way.

I and sodium ethoxide in absolute ethanol gave an oil, b. p. 143~144°C/5 mmHg (VIII), which on reduction in the presence of palladous oxide yielded an oil, b. p. 92~93°C/7.5 mmHg (IX). On the one hand, III also gave an oil, b. p. 94°C/7.5 mmHg by the action of sodium ethoxide, which was assumed to accord with IX. This was confirmed by mixed fusion of their picrolonates. It seemed reasonable, therefore, to assume that the addition of ethanol to the epoxy group would proceed as shown below. That the ethoxide anion attacked the methylene carbon and not the spiro carbon is probably due to the steric effect.

I and ammonia in ethanolic solution yielded a crystal, m. p. 142.5°C. Among possible structures corresponding to the crystal, formula X was most probable and the other, for instance XI, could not be constructed in practice into the molecular model owing to the steric interference. The reaction might proceed in the manner like above.

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[4] R. E. Parker and N. S. Isaacs, *Chem. Revs.*, **59**, 737 (1959).

I and aniline gave a yellow oil, b. p. 202~203°C/0.2 mmHg (m. p. 79.5°C) (XII). This additional reaction also appeared to be the same as in the case of ammonia.

The infrared absorption spectra of VIII, X and XII exhibited characteristic peaks of the tertiary νOH at 1115 cm^{-1}[5].

Experimental

5-Benzyl-1-oxa-5-azaspiro(5, 2)octane (I). — A mixture of 52 g. of the resinous matter, 100 g. of sodium carbonate and 100 cc. of water was stirred for 5 hr. under heating at 70°C. An oily liberated substance was taken up in benzene and dried over potassium carbonate. Evaporation of benzene and rapid vacuum distillation in three batches gave 23 g. of crude epoxide, a colorless oil, b.p. 119~121°C/0.45 mmHg, and when not, much of the substance remained undistilled. (Found: N, 6.99%).

A mixture of 3 g. of the crude epoxide and an excessive saturated solution of sodium bisulfite was shaken vigorously for a short time. Crystals formed were filtered and recrystallized from dilute ethanol to yield 2.3 g. of colorless hexagonal prisms, m. p. 251.5°C (decomp.). It was very soluble in water and did not liberate any oil with acid or alkali.

Found: N, 4.36. Calcd. for $C_{13}H_{17}ON \cdot NaHSO_3$: N, 4.56%.

On the contrary, 1-benzyl-1-azacycloheptan-4-one gave a normal addition product, m.p. 155°C (decomp.). (Found: N, 4.40%).

A mixture of 2.7 g. of the crude epoxide, 0.8 g. of 2,4-dinitrophenylhydrazine, 0.5 cc. of concentrated hydrochloric acid and 30 cc. of ethanol was boiled on a water bath for two minutes and let stand overnight. Crystals formed were filtered and washed with a little amount of ethanol. The ethanolic solution was passed through Amberlite IRA-400 to remove the hydrochloric acid and evaporated to dryness under reduced pressure. The residual oil was chromatographed on a column packed (from top) with alumina, decolorizing carbon and magnesium sulfate[3] and eluted with dry benzene. The eluate was evaporated and vacuum distillation of the residue yielded 1.7 g. of a colorless oil, b. p. 114°C/0.43 mmHg. Infrared absorption spectrum of the oil showed no carbonyl band.

Found: N, 7.02. Calcd. for $C_{13}H_{17}ON$: N, 6.89%.

1-Benzyl-4-chloromethyl-4-hydroxy-1-azacyclohexane Hydrochloride (II).—Through a solution of the crude epoxide in absolute ether was passed dry hydrogen chloride to precipitate a white amorphous hydrochloride. Ether was decanted and the hydrochloride was recrystallized from methanol and ether to give a white crystalline powder. Because of its highly hygroscopic property, it could not be analyzed, but was assumed to be 1-benzyl-4-chloromethyl-4-hydroxy-1-azacyclohexane hydrochloride from the experiment described later. Treatment of the powder with alkaline water as above reformed the epoxide, but not pure.

4-Chloromethyl-4-hydroxy-1-azacyclohexane Hydrochloride (III).—(a) A solution of 5 g. of the acidic resinous matter in 70 cc. of water was reduced under normal temperature and pressure with 0.2 g. of palladous oxide as a catalyst until the theoretical amount of hydrogen had been absorbed. The catalyst was filtered off, and evaporation of water under reduced pressure left light yellow crystals, which were recrystallized from methanol and ether to yield 2 g. of colorless prisms, m. p. 183~184°C.

Found: C, 38.97; H, 7.13; N, 7.52. Calcd. for $C_6H_{13}ONCl_2$: C, 38.73; H, 7.04; N, 7.53%.

III formed a *picrolonate* by heating with a saturated ethanolic solution of picrolonic acid, which was recrystallized from ethanol to give yellow micro prisms, m. p. 228~229°C (decomp.).

Found: N, 15.61. Calcd. for $C_{16}H_{21}O_6N_5Cl_2$: N, 15.55%.

(b) A solution of 10 g. of II in 200 cc. of water was shaken in the hydrogen atmosphere with heating in the presence of 0.2 g. of palladous oxide as a catalyst until the theoretical amount of hydrogen had been absorbed. Light yellow needles were obtained after separation of the catalyst by filtration, followed by evaporation of water. The needles were recrystallized five times from methanol to give 2 g. of colorless prisms, m. p. 183.5~184°C in 30.7% yield, and this did not depress the melting point on admixture with the colorless prisms described above. (Found: N, 7.16%).

A *picrolonate* which derived from the prisms was also not depressed by mixing with the picrolonate mentioned above, m. p. and mixed m. p. 229°C (decomp.). (Found: N, 15.73%).

5-Carbethoxy-1-oxa-5-azaspiro(5, 2)octane (IV).—To a solution of 2 g. of III in 10 cc. of water, under stirring and cooling at below 5°C, a solution of 1.3 g. of ethyl chlorocarbonate in 10 cc. of ether and 5 cc. of 30% sodium hydroxide solution were gradually added during 1.5 hr., at such a rate that the two solutions were added simultaneously. After stirring for 15 min. the water layer was separated and extracted three times with a portion of 30 cc. ether each. Combined ethereal solution was dried over potassium carbonate. After evaporation of ether, the vacuum distillation gave 1.4 g. of a colorless oil, b. p. 94~95°C/1 mmHg in 58% yield.

Found: N, 7.29. Calcd. for $C_9H_{15}O_3N$: N, 7.56%.

1-Benzyl-4-methoxymethyl-4-hydroxy-1-azacyclohexane (V).—A solution of 14 g. of the resinous matter in 40 cc. of absolute methanol was mixed with a solution of 7 g. of sodium dissolved in 100 cc. of absolute methanol. The resultant mixture was boiled under reflux for 8 hr. After that, 5 cc. of water was added and filtered from the sodium chloride present. The sodium chloride was washed with methanol. Combined methanolic solution was evaporated to leave an oily substance, which was taken up in ether, washed twice with a 10% solution of potassium carbonate and dried over potassium carbonate. Ether was removed and the residual oil was distilled in vacuo to give 7.8 g. of a colorless oil, b. p. 146~147°C/1 mmHg.

Found: N, 5.94. Calcd. for $C_{14}H_{21}O_2N$: N, 5.95%.

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[5] 1-Methylcyclohexane-1-ol gives the peak of the tertiary νOH at 1117 cm^{-1}. H. H. Zeiss and M. Tsutsui, *J. Am. Chem. Soc.*, 75, 897 (1953).

1-Benzyl-4-methoxymethyl-1-azacyclohex-3-ene (VI).—A mixture of 4.3 g. of V and 6.1 g. of β-naphthalenesulfonic acid was heated for 15 min. on a water bath under reduced pressure (water pump), and then for 1 hr. at 170°C. After cooling, 100 cc. of 10% sodium hydroxide solution was added, extracted in ether and dried over potassium carbonate. Ether was expelled and the vacuum distillation yielded 2.2 g. of a colorless oil, b. p. 126°C/0.5 mmHg. in 56.7% yield, which on standing turned pink immediately.

Found: C, 76.75; H, 8.62; N, 6.55. Calcd. for $C_{14}H_{19}ON$: C, 77.38; H, 8.81; N, 6.45%.

1-Benzyl-4-methoxymethyl-1-azacyclohexane (VII).—A solution of 1.1 g. of freshly distilled VI in 50 cc. of methanol containing 0.6 cc. of concentrated hydrochloric acid was reduced in the presence of platinum oxide as a catalyst and the theoretical amount of hydrogen was consumed. After removal of the catalyst by filtration, methanol was distilled off and the residue was made alkaline. Oil thereby liberated was taken up in ether and dried over potassium carbonate. The ether was removed to leave an oil, which on vacuum distillation gave 0.25 g. of a colorless, fluid oil, b. p. 118~120°C/4.5 mmHg.

Found: C, 76.23; H, 9.94; N, 6.31. Calcd. for $C_{14}H_{21}ON$: C, 76.67; H, 9.65; N, 6.39%.

1-Benzyl-4-ethoxymethyl-4-hydroxy-1-azacyclohexane (VIII).—A solution of 4 g. of I in 10 cc. of absolute ethanol was mixed with a separately prepared solution of 1.5 g. of sodium in 30 cc. of absolute ethanol and the whole was boiled under reflux for 8 hr. After cooling, 2 cc. of water was added and evaporated under reduced pressure to leave an oil, which was taken up in ether, washed twice with a dilute potassium carbonate solution and dried over potassium carbonate. Oil left on evaporation of ether was distilled in vacuo to yield a colorless oil boiling at 128~136°C/0.5 mmHg, which was redistilled to give 2.5 g. of the oil, b. p. 143~144°C/5 mmHg, in 50.3% yield.

Found: N, 5.77. Calcd. for $C_{15}H_{23}O_2N$: N, 5.62%.

4-Ethoxymethyl-4-hydroxy-1-azacyclohexane (IX).—(a) A solution of 2.5 g. of VIII in 50 cc. of water containing 1 cc. of concentrated hydrochloric acid was reduced with heating and in the presence of 0.1 g. of palladous oxide as a catalyst until the theoretical amount of hydrogen had been absorbed. After separation of the catalyst by filtration, a residue left on evaporation of water was dissolved in 10 cc. of water and neutralized with potassium carbonate. A further addition of 2 g. of sodium hydroxide liberated an oil, which was extracted in ether and dried over potassium carbonate. Evaporation of ether and distillation in vacuo gave 0.5 g. of an oil, b. p. 92~93°C/7.5 mmHg in 31% yield.

Found: N, 8.77. Calcd. for $C_8H_{17}O_2N$: N, 8.82%.

IX formed a *picrolonate*, m. p. 209°C (decomp.), which was recrystallized twice from ethanol to yield yellow micro prisms, m. p. 216~217°C (decomp.).

Found: N, 16.31. Calcd. for $C_{18}H_{25}O_7N_5$: N, 16.54%.

(b) A solution of 1 g. of III in 5 cc. of absolute ethanol was mixed with a separately prepared solution of 1 g. of sodium dissolved in 15 cc. of absolute ethanol and the whole was boiled under reflux for 8 hr. After cooling, 2 cc. of water was added and filtered from any solid, which was washed with ethanol. A tan oily substance left on evaporation of ethanol was treated as before to give 0.5 g. of an oil, b. p. 94°C/7.5 mmHg (Found: N, 8.73%).

A *picrolonate* of the oil, m. p. 216~217°C (decomp.) was not depressed on admixture with that described before. (Found: N, 16.37%).

4-Anilinomethyl-1-benzyl-4-hydroxy-1-azacyclohexane (XII).—A mixture of 4.2 g. of I and 3.3 g. of freshly distilled aniline was boiled under reflux for 1.5 hr. Excessive aniline was removed under reduced pressure to leave a colored residue. Vacuum distillation of the residue gave 3.7 g. of a light yellow viscous oil boiling at 202~203°C/0.2 mmHg in a 60.5% yield. The oil gradually crystallized on standing and was recrystallized from cyclohexane and benzene in light creamy plates, m. p. 79.5°C.

Found: C, 76.70; H, 8.29; N, 9.44. Calcd. for $C_{19}H_{24}ON_2$: C, 76.99; H, 8.16; N, 9.45%.

XII afforded a *picrate*, m. p. 177.5°C (from ethanol).

Found: N, 14.55. Calcd. for $C_{19}H_{24}ON_2 \cdot (C_6H_3O_7N_3)_2$: N, 14.85%.

Bis-(4-benzyl-1-hydroxy-4-azacyclohexylmethyl)-amine (X).—A solution of 2 g. of I in 10 cc. of 99% ethanol was saturated with ammonia at 0°C and let stand for a week at room temperature. An ether insoluble substance left on evaporation of ethanol was recrystallized from dilute ethanol after treating with decolorizing carbon to give 0.6 g. of colorless scales, m. p. 142.5°C in a 30% yield.

Found: C, 73.50; H, 8.96; N, 9.99. Calcd. for $C_{26}H_{37}O_2N_3$: C, 73.72; H, 8.80; N, 9.92%.

Both *picrate*, m. p. 225°C (decomp.) and *picrolonate*, m. p. 247°C (decomp.) were insoluble and difficult to recrystallize from any common solvent.

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Chemical Institute
Faculty of Science
Okayama University
Tsushima, Okayama