[Chem. Pharm. Bull. 21(4) 752—756 (1973)]

UDC 547.834.2.04 : 547.897.057

# Studies on 1-Azabicyclo Compounds. XIII.[1] Synthesis of 1-Methyl-6-decahydroazecinone by the Reaction of 3,4,6,7,8,9-Hexahydro-2*H*-quinolizine with Methyl Iodide[2]

Yoshio Arata and Yukio Oda

*Faculty of Pharmaceutical Sciences, Kanazawa University*[3]

(Received July 10, 1972)

Reaction of $\Delta^{1,10}$-hexahydroquinolizine (I) with methyl iodide in various solvents were carried out. The reaction in the presence of methanol or ethanol proceeded at low temperature to give 10-methoxy-5-methyloctahydroquinolizinium iodide (IIIa) or the corresponding 10-ethoxy methiodide (IIIb), respectively, besides the methiodide (II). Using 70% aqueous methanol as a solvent, the reaction gave 1-methyl-6-decahydroazecinone (IV) accompanied with IIIa and II. The reaction in 70% aqueous tetrahydrofuran or aqueous acetone led to the formation of V besides II. Methiodides, IIIa and IIIb, were respectively converted into IV by heating with hydrobromic acid.

Recent papers of this series have described the synthesis of ten-membered ring amine derivatives from the condensation products obtained by the nucleophilic reaction of $\Delta^{1,10}$ hexahydroquinolizine(I) with hydrocyanic acid,[4,5] $RNH_2$ derivatives[6] and trichloroacetic acid.[7] As further extension of our study in these areas, we examined reaction of I with methyl iodide in various solvents.

At first, the reaction of I with methyl iodide at low temperature was carried out to afford the corresponding methiodide[8] (II), mp 248—250°(decomp.), NMR $\tau$: 4.22(1H, broad, $-C=C-\underline{H}$); 6.72(3H, singlet, $N-C\underline{H}_3$) as a sole product. The reaction in the presence of a small amount of methanol was effected to give 10-methoxy methiodide[9] (IIIa), mp 256—258°(decomp.) albeit in a poor yield besides the normal methiodide(II) as the predominant product. When the reaction was carried out in a large amount of methanol, the yield of IIIa much increased, whereas that of II decreased.

In the previous study,[9] we have already obtained the methiodide(IIIa) as the reaction product of di(10-octahydroquinolizinyl)hydroxylamine[4] with methyl iodide in methanol and proposed the formula as depicted, on the basis of its spectral data and elemental analytical values. Further, by heating in hydrobromic acid, the methiodide(IIIa) was converted into 1-methyl-6-decahydroazecinone[4,10] (IV), IR $cm^{-1}$: 2800(N-methyl), 1693(carbonyl) in a good yield. Thus, the structure of IIIa was now confirmed to be correct. On the other hand, the methiodide(II) afforded only a small amount of I, when heated in hydrobromic acid; most of the starting material was recovered unchanged. The reaction using ethanol in place of methanol yielded a product of mp 248—252°(decomp.) which was deduced to be a mixture

---

[1] Part XII: Y. Arata, S. Sakai, and S. Yasuda, *Chem. Pharm. Bull.* (Tokyo), 20, 1745 (1972).
[2] Reported at the 33rd Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, November, 1971, Toyama.
[3] Location: *13-1 Takara-machi, Kanazawa, 920, Japan.*
[4] Y. Arata, S. Yoshifuji, and Y. Yasuda, *Chem. Pharm. Bull.* (Tokyo), 17, 1363 (1969).
[5] N.J. Leonard and A.S. Hay, *J. Am. Chem. Soc.*, 78, 1984 (1956).
[6] Y. Arata, S. Yoshifuji, and T. Shioda, *Yakugaku Zasshi*, 92, 69 (1972).
[7] Y. Arata and T. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), 20, 325 (1972).
[8] N.J. Leonard, A.S. Hay, R.W. Fulwer, and V.W. Grash, *J. Am. Chem. Soc.*, 77, 439 (1955).
[9] Y. Arata and T. Shioda, *Chem. Pharm. Bull.* (Tokyo), 20, 783 (1972).
[10] N.J. Leonard and M. Oki, *J. Am. Chem. Soc.*, 76, 3463 (1954).

of II and 10-ethoxy methiodide(IIIb), judging from its nuclear magnetic resonance(NMR) spectrum. The NMR spectrum in deuterium oxide exhibited an N-methyl signal at $\tau$ 6.83 (singlet) and an O-ethyl signals at $\tau$ 6.61(quartet, $J$=7.5 cps, $OC\underline{H}_2CH_3$) and 8.67(triplet, $J$=7.5 cps, $OCH_2C\underline{H}_3$) attributable to IIIb besides an N-methyl signal at $\tau$ 6.72(singlet) and a vinyl signal at $\tau$ 4.22(broad) owing to II. The measurement of the areas of the signals for the N-methyl protons of IIIb and II indicated that both methiodides exist approximately in the ratio of 1: 1.

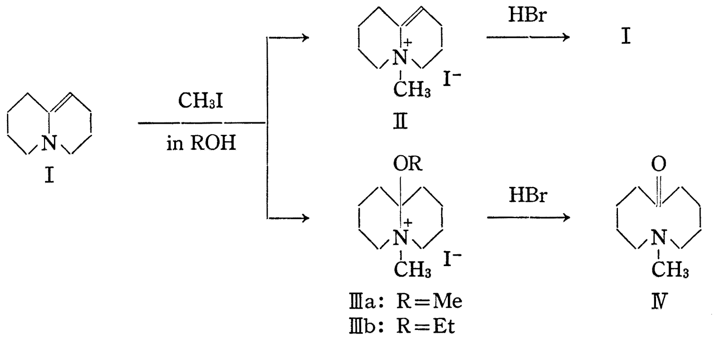

Chart 1

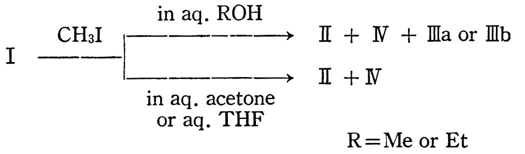

Chart 2

Since it was difficult to separate IIIb from II by fractional recrystallization, the mixture was subjected to heating with hydrobromic acid to give a considerable amount of IV and a small amount of I, recovering the unchanged methiodide(II). Based on the above evidences, the mixture was clarified to be, as expected, composed of IIIb and II.

Next, the reactions of I with methyl iodide in some aqueous solvents were performed. In 70% aqueous methanol or 70% aqueous ethanol, the reaction proceeded at low temperature and the expected IV was produced in 38—46% yield along with II and IIIa or II and IIIb, respectively.

Finally, using 70% aqueous acetone or 70% aqueous tetrahydrofuran(THF) as a solvent, the reaction gave the compounds, IV and II in 40—46% and in 30—35% yields, respectively. Thus, the one-step synthesis of IV from I was successfully achieved. The above-mentioned results are summerized in Table I. A mechanism for the reaction of I with methyl iodide

Table I. Effect of Solvent on Reaction of I with Methyl Iodide

| Solvent | Reagent, g | | | Product, % | | | |
|---|---|---|---|---|---|---|---|
| | I | $CH_3I$ | solvent | II | IIIb | IIIa | IV |
| None | 4 | 10 | 0 | 55 | | | |
| Methanol | 4.1 | 10 | 4 | 45 | | trace | |
| Methanol | 4 | 7 | 12 | 26 | | 26 | |
| Ethanol | 4 | 7 | 12 | 45—50 | | | |
| Methanol–water (7:3) | 3 | 7 | 15 | 15 | | 15 | 38 |
| Ethanol–water (7:3) | 4.2 | 9 | 20 | 15—20 | | | 46 |
| Acetone–water (7:3) | 4.4 | 8.5 | 30 | 30 | | | 40 |
| THF–water (7:3) | 4.8 | 9 | 40 | 35 | | | 46 |

condition: The reactions were carried out in the ice chest for 90—96 hr.

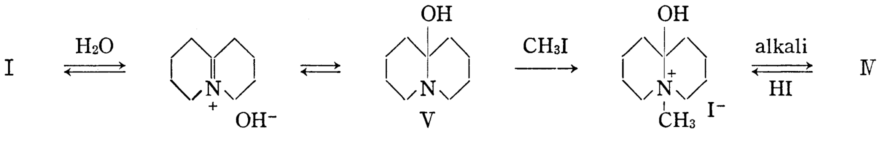

Chart 3

producing IV might be postulated as follows: the enamine(I) was precedently condensed with water through the formation of the iminium type intermediate and the resulting product(V) further reacted with methyl iodide to give 10-hydroxy-5-methyloctahydroquinolizinium iodide(VI), which, on neutralization with alkali, yielded IV(Chart 3). Hereupon, an atempt to obtain the intermediate(V) from I was successfully carried out. On treatment of I with an ether solution saturated with water, a labile product of mp 38—40° was readily afforded. Recrystallization of the product from petroleum ether resulted in decomposition leading to I and water. From the facts, the product might be deduced as 10-hydroxyoctahydroquinolizine(V). On the viewpoint of above experiment, it would be assumed that the medium-sized ring alkaloids such as cryptopine, protopine and otenecine are biologically derived from the corresponding 1-azabicycloalkane alkaloids through their enamine derivatives proceeding along the presumed route mentioned above, in which formaldehyde participates in place of methyl iodide. The conversion of the latter alkaloids into the former is now in progress.

## Experimental[11]

**3,4,6,7,8,9-Hexahydro-5-methyl-2*H*-quinolizinium Iodide[4–6] (II)**——To 4 g of 3,4,6,7,8,9-hexahydro-2*H*-quinolizine[5] (I) was added methyl iodide (4 g) under cooling in a small portion. The solution was allowed to stand in an ice chest for 4 days. The reaction solution was evaporated *in vacuo* and the residue was recrystallized from methanol–ether (3: 1) to give colorless scales of mp 248—250° (decomp.). Yield: 4.4 g (55%). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 3010, 1640 (C=C–H). NMR (10% solution in $CDCl_3$) τ: 4.22 (1H, broad, $C=\dot{C}-\underline{H}$), 6.72 (3H, singlet, $N-C\underline{H}_3$).

**Reaction of I with Methyl Iodide in Methanol [Formation of 10-Methoxy-5-methyloctahydroquinolizinium Iodide (IIIa) and II]**——To a solution of 4 g of I in methanol (12 g) was added methyl iodide (7 g) under cooling in small portions. The solution was kept standing in an ice chest for 4 days. The reaction solution was filtered to obtain the precipitates deposited and the mother liquor. IIIa: The precipitates were recrystallized from ethanol to give colorless plates, mp 256—258° (decomp.). Yield: 2.3 g (26%). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1085 (ether). Its infrared (IR) spectrum was coincident with that of the authentic sample[9] (IIIa). Picrate: recrystallized from ethanol to afford yellow needles, mp 262—263°. *Anal.* Calcd. for $C_{17}H_{24}O_8N_4$: C, 49.51; H, 5.86; N, 13.59. Found: C, 49.40; H, 5.90; N, 13.57. No depression of melting point was observed by the admixture of the picrate with that of the authentic sample[9] (IIIa). II: The mother liquor was evaporated *in vacuo* and the residue was recrystallized from methanol–ether (3: 1) giving colorless scales, mp 247—249° (decomp.). Yield: 1.6 g. Its IR spectrum was in accordance with that of II.[8]

**Reaction of I with Methyl Iodide in Ethanol [Formation of 10-Ethoxy-5-methyloctahydroquinolizinium Iodide (IIIb) and II]**——This reaction was carried out in the same condition as the case mentioned above, using 4 g of I, 7 g of methyl iodide and 12 g of ethanol. The reaction solution was filtered to obtain the precipitates deposited and the mother liquor. The precipitates were recrystallized from ethanol to yield colorless sands of mp 248—252° (decomp.). Yield: 2.4 g. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1070 (ether). NMR (10% solution in $D_2O$) τ: 6.72 (singlet, $N-C\underline{H}_3$), 4.22 (broad, $C=\dot{C}-\underline{H}$), 6.83 (singlet, $N-C\underline{H}_3$), 6.61 (quartet, $J=7.5$ cps, $OC\underline{H}_2CH_3$), 8.67 (triplet, $J=7.5$ cps, $OCH_2C\underline{H}_3$). Based on these data, the product was deduced to be a mixture of IIIb and II in the approximate ratio 1: 1. The mother liquor of the reaction was evaporated to dryness *in vacuo*. The residue was recrystallized from ethanol to give colorless sands, mp 248—250° (decomp.). Yield: 1.9 g. The product was a mixture of IIIb and II.

**1-Methyl-6-decahydroazecinone (IV)**——i) Heating of IIIa with hydrobromic acid. A solution of 0.85 g of IIIa in 7 g of 47% hydrobromic acid was heated in a sealed tube at 160° for 16 hr. The reaction solution was evaporated *in vacuo*. The residue was made alkaline with aqueous sodium hydroxide to deposit the oily product. The product was extracted with ether and the ether layer was washed with water, de-

---

[11] All melting points were measured with a Yanagimoto Micro Melting Point Apparatus and uncorrected. IR spectra were measured with a Spectrophotometer G, Japan Spectroscopic Co., Ltd., and NMR with a H-60-C of Japan Electron Lab. Co., Ltd., using tetramethylsilane as a internal standard.

siccated and then evaporated. The residue was distilled at 110—125° (bath temperature)/18 mmHg to collect a colorless liquid. Yield: 0.33 g (71%). IR $\nu_{\max}^{\text{liq.}}$ cm$^{-1}$: 2800 (N–CH$_3$), 1693 (C–O). Its IR spectrum was completely coincident with that of the sample of 1-methyl-6-decahydroazecinone[4,10] (IV). Picrate: recrystallized from ethanol giving yellow needles, mp 258—260° (decomp.). *Anal.* Calcd. for $C_{16}H_{22}O_8N_4$: C, 48.24; H, 5.57; N, 13.72. Found: C, 48.35; H, 5.54; N, 13.72.

ii) Heating of a mixture of IIIb and II with hydrobromic acid. A mixture (0.54 g) of IIIb and II was heated with 47% hydrobromic acid (7 g) in a sealed tube at 160° for 16 hr. The reaction solution was evaporated *in vacuo*. The residue was made alkaline with aqueous sodium carbonate and the solution was shaken with ether. The ether layer was washed with water, desiccated and then evaporated. The residue was distilled at 110—125° (bath temperature)/18 mmHg to give a colorless liquid. Yield: 0.12 g (43%). Its IR spectrum was coincident with that of IV.[4,10] Picrate: recrystallized from ethanol to give yellow needles, mp 260—261° (decomp.). *Anal.* Calcd. for $C_{16}H_{22}O_8N_4$: C, 48.24; H, 5.57; N, 13.72. Found: C, 48.35; H, 5.54; N, 14.08.

The mother liquor of the recrystallization was evaporated *in vacuo* and the residue was recrystallized from ethanol affording needles, mp 106—107°. The picrate did not show any melting point depression by the admixture with that of 3,4,6,7,8,9-hexahydro-2*H*-quinolizine (I). The aqueous layer was extracted with chloroform and the chloroform layer was desiccated and then evaporated. The residue was recrystallized from methanol–ether (3: 1) giving colorless scales, mp 248—250° (decomp.). Yield: 85 mg. Its IR spectorum was coincident with that of 3,4,6,7,8,9-hexahydro-5-methyl-2*H*-quiniloizinium iodide[8] (II).

**Heating of II with Hydrobromic Acid (Formation of I)**——Heating of 0.5 g of II with hydrobromic acid was carried out in the same conditions as the case of the reaction of IIIa with hydrobromic acid leading to IV. The reaction solution was made alkaline with aqueous sodium carbonate and shaken with ether. The ether layer was washed with water, desiccated and then evaporated. The residue was distilled at 80—85° (bath temperature)/18 mmHg to collect a colorless liquid. Yield: 60 mg. Its IR spectrum was in accordance with that of I. The alkaline solution was extracted several times with chloroform. The chloroform layer was desiccated and evaporated. The residue (0.34 g) was recrystallized from methanol–ether to afford II as colorless scales of mp 247—249° (decomp.).

**Reaction of I with Methyl Iodide in Aqueous Methanol (Formation of IV, IIIa, and II)**——To a solution of 4.3 g of I in 70% aqueous methanol (15 g) was added methyl iodide (7 g). The solution was kept standing in an ice chest under nitrogen atmosphere for 4 hr and then evaporated *in vacuo*. The residue was made alkaline with aqueous sodium hydroxide and then shaken with ether. The ether layer was washed with water and desiccated. After the evaporation of the solvent, the residue was subjected to fractional distillation to give two fractions of bp 80—85°/18 mmHg and bp 108—115°/18 mmHg. The IR spectrum of the former distillate (250 mg) was coincident with that of I. Its picrate, mp 105—106°, did not show any melting point depression by the admixture with that of I.

IV: The IR spectrum of the latter (1.45 g) was in accordance with that of IV. IR $\nu_{\max}^{\text{liq.}}$ cm$^{-1}$: 2800 (N–CH$_3$), 1693 (C=O). Picrate: recrystallized from ethanol giving yellow needles, mp 260—262° (decomp.). *Anal.* Calcd. for $C_{16}H_{22}O_8N_4$: C, 48.24; H, 5.57; N, 13.72. Found: C, 48.18; H, 5.41; N, 13.75.

IIIa: The aqueous layer was extracted several times with chloroform. The chloroform layer was desiccated followed by the evaporation of the solvent. The residue was recrystallized from ethanol to give colorless plates, mp 256—258° (decomp.). Yield: 1.02 g. The IR spectra of this product and 10-methoxy-5-methyloctahydroquinolizinium iodide (IIIa) were completely coincident.

II: The mother liquor of recrystallization was evaporated to dryness *in vacuo* and the residue was recrystallized from methanol–ether (3: 1) to give colorless scales, mp 247—249° (decomp.). Yield: 0.91 g. Its IR spectrum was coincident with that of II.

**Reaction of I with Methyl Iodide in Aqueous Ethanol (Formation of IV,IIIb, and II)**——Reaction of 4.2 g of I with methyl iodide (9 g) in 70% aqueous ethanol (20 g) was carried out in the same condition as the case of the reaction in aqueous methanol. The reaction solution was evaporated *in vacuo*. The residue was made alkaline with sodium hydroxide and the solution was shaken with ether.

IV: The ether layer was washed with water, desiccated, and then evaporated. The residue was distilled at 110—115° (bath temperature) /18mmHg to obtain a colorless liquid. Yield: 2.5 g. IR $\nu_{\max}^{\text{liq.}}$ cm$^{-1}$: 2800 (N–CH$_3$), 1693 (C=O). The IR spectra of this compound and IV[4] were completely coincident. Picrate: recrystallized from ethanol to give yellow needles, mp 259—261° (decomp.). *Anal.* Calcd. for $C_{16}H_{22}O_8N_4$: C, 48.24; H, 5.57; N, 13.72. Found: C, 48.35; H, 5.54; N, 14.08.

IIIb and II: The aqueous layer was shaken with chloroform several times. The chloroform layer was desiccated followed by the evaporation of the solvent. The residue was recrystallized from ethanol to afford colorless sands, mp 248—251° (decomp.). Yield: 1.5 g. IR $\nu_{\max}^{\text{liq.}}$ cm$^{-1}$: 1070 (ether). The product was deduced to be a mixture of IIIb and II by the infrared spectral comparison.

**Reaction of I with Methyl Iodide in Aqueous Acetone or Aqueous Tetrahydrofuran (Formation of VI and II)**——i) The reaction in aqueous acetone. To a solution of 2.2 g of I in aqueous acetone (15 g) was added methyl iodide (4.3 g). The mixture was kept standing in an ice chest for 4 days. The reaction solution was evaporated to dryness *in vacuo*. The residue was made alkaline with aqueous sodium hydroxide and then shaken with ether. The ether layer was washed with water and desiccated followed by the evaporation of the solvent. The residue was subjected to fractional distillation to collect 2 fractions boiling at 80—90° (bath temperature)/18 mmHg (yield: 200 mg) and at 115—125°/18 mmHg (yield: 1.1 g). The IR spectrum of the former fraction was coincident with that of I.

IV: The IR spectrum of the latter was coincident with that of IV. IR $\nu_{\max}^{\text{liq.}}$ cm$^{-1}$: 2800 (N–$CH_3$), 1693 (C=O). Picrate: recrystallized from ethanol giving yellow needles, mp 260—262° (decomp.). *Anal.* Calcd. for $C_{16}H_{22}O_8N_4$: C, 48.24; H, 5.57; N, 13.72. Found: C, 48.44; H, 5.52; N, 13.94.

II: The aqueous layer was extracted with chloroform. The chloroform layer was desiccated followed by the evaporation of the solvent. The residue was recrystallized from methanol–ether (3: 1) to give colorless scales, mp 248—250° (decomp.). Yield: 1.3 g. Its IR spectrum was coincident with that of II.

ii) The reaction in aqueous THF. This reaction was carried out in the same way as the case of the reaction in aqueous acetone, using 2.4 g of I, 4.3 g of methyl iodide and 20 g of 70% aqueous THF.

IV: Colorless liquid (1.35 g). Picrate: yellow needles, mp 260—262° (decomp.). II: colorless scales (1.5 g). mp 248—250° (decomp.).

**10-Hydroxyoctahydroquinolizine (V)**——The enamine (I) (0.5 g) was dissolved in a saturated solution (10 ml) of water in ether. The solution was at once evaporated *in vacuo*, to leave colorless needles (V), mp 38—40°. Attempt to recrystallization of the product from petroleum ether was carried out to deposit water. The petroleum ether layer was evaporated *in vacuo* to give only the starting material (I).

**Acknowledgement** The authors are grateful to Mr. Y. Itatani for elemental analyses and NMR measurement.