[Chem. Pharm. Bull. 22(5)1003—1007(1974)]

UDC 547.822.3'592.1.04 : 547.897.057

Studies on 1-Azabicyclo Compounds. XIX.[1] Synthesis of Ten-membered Ring Amine Derivatives from 5-Methyl-10-nitromethyloctahydroquinolizinium Iodide and Its Derivatives[2]

Yoshio Arata, Tetuo Kikuti, Mineo Takahashi, and Tadashi Aoki

Faculty of Pharmaceutical Sciences, Kanazawa University[3]

(Received June 25, 1973)

Reaction of $\Delta^{1,10}$-hexahydroquinolizine (VI) with a combination of nitromethane and methyl iodide gave 5-methyl-10-nitromethyloctahydroquinolizinium iodide (VII), which, on treatment with lithium–liquid ammonia, gave the ten-membered ring amines, XIV and XV. Similar reduction of the N-acetyl methiodide (X) and the betaine (XI) derived from VII gave XVIII and XIX, respectively.

Several methods for synthesis of ten-membered ring amine system from $\Delta^{1,10}$-hexahydroquinolizine[4] (VI) *via* 10-cyano-, 10-semicarbazino-, 10-hydroxy-, and 10-methoxyoctahydroquinolizine (I, II, III, IV), and 6-chloro-1-azabicyclo[4.4.1]undecan-11-one (V) have been developed in our laboratory, such as by (a) quaternization of I[5] with methyl iodide followed by the Birch reduction, (b) reaction of II[6] with methyl iodide, (c) reaction of III[7] with methyl iodide or acid hydrolysis of the methiodide[6-8] (VIII) of IV, and (d) acid hydrolysis of V[9] followed by catalytic hydrogenation.

Now we report the synthesis of ten-membered ring amine derivatives from 10-nitromethyloctahydroquinolizine (XIII) by the method (a). $\Delta^{1,10}$-Hexahydroquinolizine (VI) was treated with a combination of nitromethane and methyl iodide in methanol to give the methiodide (VII), $C_{11}H_{21}O_2N_2I$, mp 224—225° (decomp.), along with the known methoxy methiodide (VIII), mp 260—261° (decomp.). The infrared (IR) spectrum of the former showed a band at 1560 cm^{-1} due to a nitro group and its nuclear magnetic resonance (NMR) spectrum exhibited signals at 4.75 (2H, broad, $>C-C\underline{H}_2NO_2$) and 6.82 τ (3H, singlet, $N^+-C\underline{H}_3$). Based on these evidences, the methiodide (VII) was characterized as 5-methyl-10-nitromethyloctahydroquinolizinium iodide. When the reaction was carried out in a small amount of methanol, the yield of VII increased and that of VIII decreased. In the absence of methanol as a solvent, the reaction afforded VII as a sole product in 65% yield. A mechanism for the reaction of VI with nitromethane and methyl iodide producing VII might be postulated as follows: The enamine (VI) underwent preliminary condensation with nitromethane *via* the formation of the iminium-type intermediate (XII) and the resulting product (XIII) further reacted with methyl iodide to yield the methiodide (VII) (Chart 2). The reaction using nitroethane in place of nitromethane did not progress and only the methiodide of VI was obtained, probably because of the steric hindrance of XII'.

1) Part XVIII: Y. Arata, Y. Nakagawa, Y. Arakawa, and M. Hanaoka, *Chem. Pharm. Bull.* (Tokyo), **22**, 157 (1974).
2) Reported at the 36th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, June, 1973, Kanazawa.
3) Location: *13-1 Takara-machi, Kanazawa, 920, Japan.*
4) N.J. Leonard and A.S. Hay, *J. Am. Chem. Soc.*, **78**, 1984 (1956).
5) Y. Arata, S. Yoshifuji, and Y. Yasuda, *Chem. Pharm. Bull.* (Tokyo), **17**, 1363 (1969).
6) Y. Arata, S. Yoshifuji, and T. Shioda, *Yakugaku Zasshi*, **92**, 69 (1972).
7) Y. Arata and Y. Oda, *Chem. Pharm. Bull.* (Tokyo), **21**, 752 (1973).
8) Y. Arata and T. Shioda, *Chem. Pharm. Bull.* (Tokyo), **20**, 783 (1972).
9) Y. Arata and T. Kobayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 325 (1972).

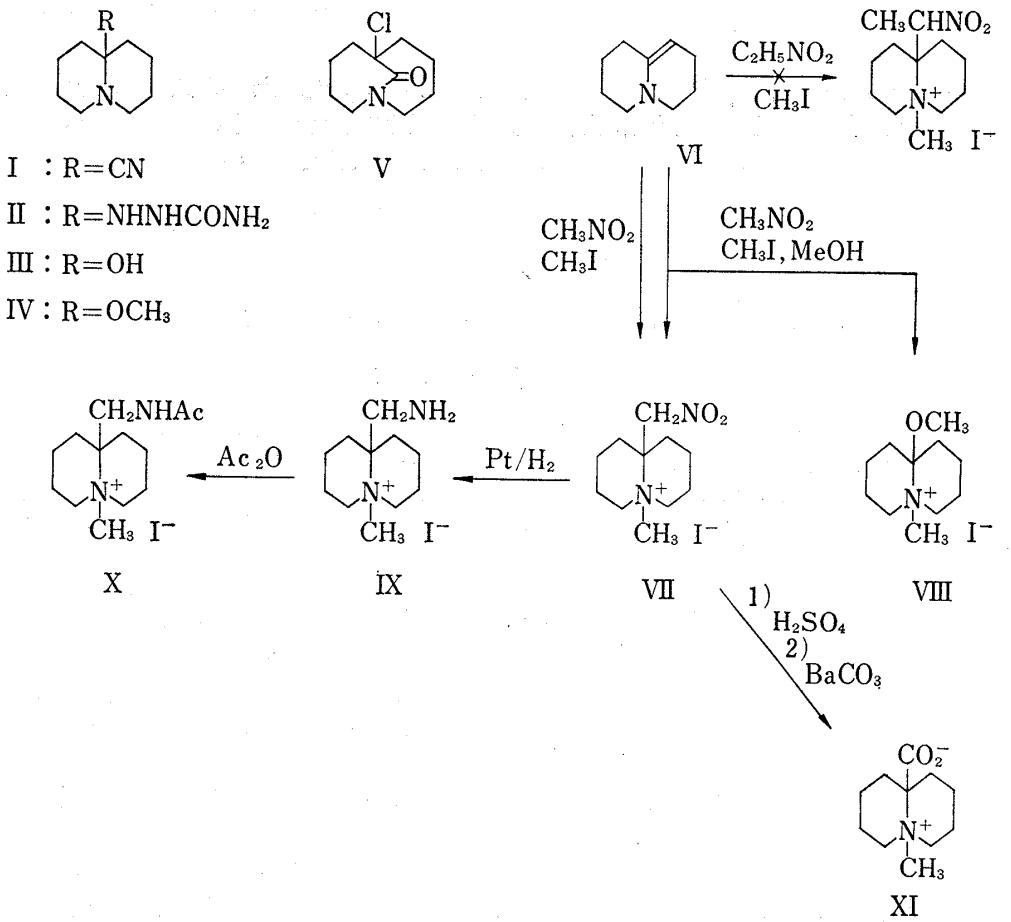

Chart 1

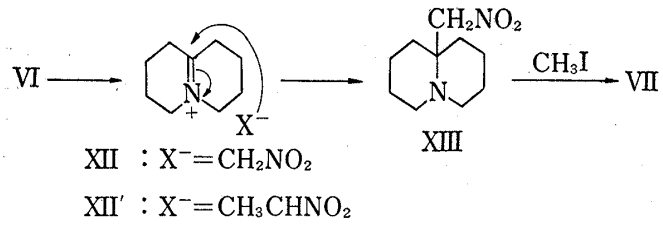

Chart 2

Catalytic hydrogenation of VII over the Adams catalyst afforded the aminomethyl methiodide (IX), mp 256—258° (decomp.), which, on heating with acetic anhydride, gave the N-acetyl derivative (X), mp 229—230°. The IR spectrum of X indicated bands at 3250, 1670, and 1528 cm^{-1} due to a secondary amide.

On the other hand, heating of VII with 85% sulfuric acid and then treatment with barium carbonate gave a syrupy product (XI), which was assumed to be 5-methyloctahydroquinolizinium-10-carboxylate because of the appearance of a band at 1550 cm^{-1} ascribable to a carboxylate in its IR spectrum and the formation of 6-carbamoyl-1-methyldecahydroazecine[5] (XIX) by its Birch reduction, as will be described later.

Finally, attempts were made to produce the ten-membered ring amines from the methiodides, VII, X, and XI. Reduction of the methiodide (VII) with lithium-liquid ammonia afforded a colorless liquid which was separated by the preparative thin-layer chromatography (TLC) into two products; XIV, bp 110—115° (bath temperature)/18 mmHg in 22% yield, and XV, bp 150° (bath temperature)/3 mmHg in 6% yield. The former fraction, IR $\nu_{max}^{liq.}$ cm^{-1}: 2800 (NCH_3), 1693 (CO) was identified as 1-methyldecahydroazecin-6-one[5-8,10] by the IR spectral comparison with the authentic sample. The IR spectrum of the latter, on the other hand, showed a band at 1730 cm^{-1} attributable to an aldehyde, while, that of its picrate

10) N.J. Leonard and M. Oki, *J. Am. Chem. Soc.*, **76**, 3463 (1954).

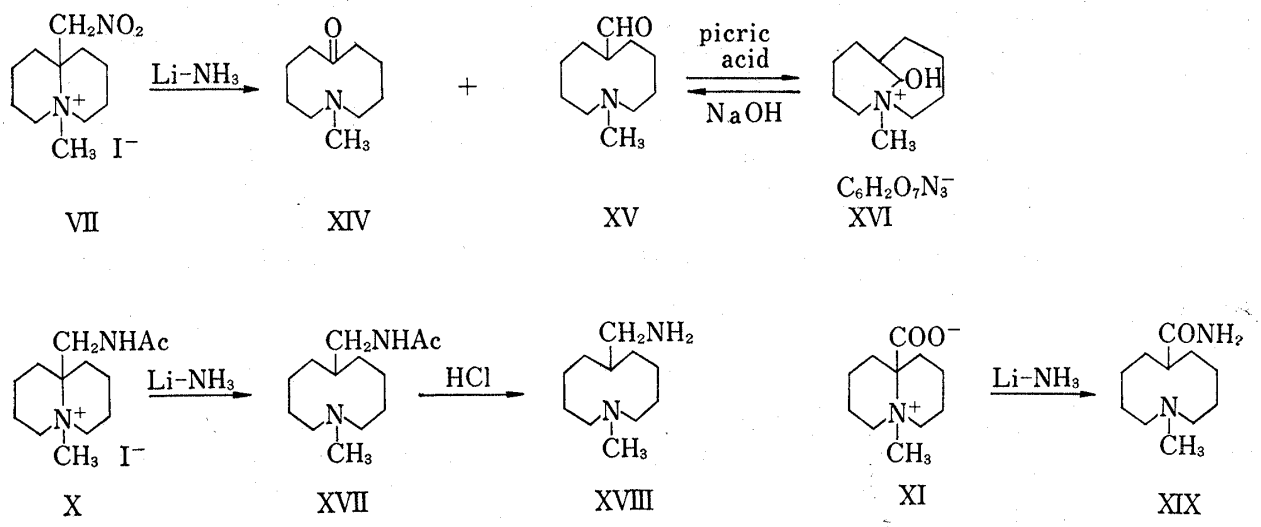

Chart 3

(XVI), mp 162—162.5°, $C_{17}H_{24}O_8N_4$, indicated a hydroxyl band at 3370 cm^{-1} and no carbonyl band. The NMR spectrum of the picrate in dimethyl-d_6 sulfoxide exhibited signals at 1.94 (1H, doublet, J=7 Hz, O<u>H</u>, disappeared by addition of D_2O), 5.05 (1H, doublet, J=7 Hz, $>C\langle^{OH}_{\underline{H}}$ appeared as a singlet by addition of D_2O) and 7.02 τ (3H, singlet, N^+–C<u>H</u>$_3$). Thus, the structure of the product (XV) was elucidated as 6-formyl-1-methyldecahydroazecine. Neutralization of XV with picric acid resulted in transannular cyclization to yield the α-hydroxy ammonium salt (XVI), which, on treatment with alkali, reverted to XV. As shown in Chart 4, the reaction of VII to XIV and XV may proceed through the intermediate (XX) which was produced by the Hofmann degradation of VII with amide anion.

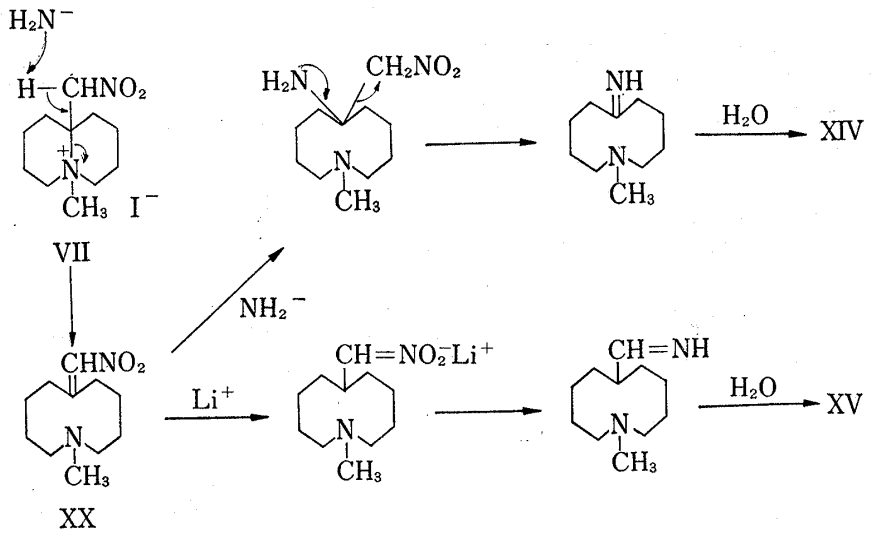

Chart 4

Reduction of the N-acetyl methiodide (X) with lithium in liquid ammonia effected selective cleavage of the central C–N bond to give in 44% yield 6-acetamidomethyloctahydroazecine (XVII), IR $\nu_{max}^{liq.}$ cm^{-1}: 3300, 3090, 1650, 1560, 1290 (NHCO), 2800 (NCH_3). Acid hydrolysis of XVII furnished the aminomethyl derivative (XVIII) which formed a crystalline picrate of mp 175—177°. No depression of the melting point was observed by admixture of this picrate with that of the authentic 6-aminomethyl-1-methyldecahydroazecine.[5] Treat-

ment of the betaine (XI) with lithium-liquid ammonia gave the carbamoyl compound (XIX), mp 177—179°, whose IR spectrum indicated carbamoyl bands at 3380, 3180, and 1655 cm^{-1} and N-methyl band at 2780 cm^{-1}. The product did not show any melting point depression on admixture with the sample of 6-carbamoyl-1-methyldecahydroazecine[5,9] and the IR spectra of both compounds were completely identical. Thus, ten-membered ring amines were successfully synthesized from nitromethyloctahydroquinolizine methiodide and its derivatives.

The application of these synthetic methods might allow the production of complex medium-sized ring amines from readily available 1-azabicyclic system.

Experimental[11]

5-Methyl-10-nitromethyloctahydroquinolizinium Iodide (VII)——A solution of $\Delta^{1,10}$-hexahydroquinolizine[4] (VI) (1.0 g) and nitromethane (1.0 g) in MeOH (5.0 ml) was kept standing in N_2 atmosphere for 40 hr and then CH_3I (2.0 g) was added to it. The solution was kept in an ice chest for 48 hr to deposit precipitates, which were collected by filtration. The precipitates were recrystallized from 95% EtOH to give colorless prisms (VII), mp 224—225° (decomp.) in 22% yield (0.55 g). IR ν_{max}^{KBr} cm^{-1}: 1560 ($-NO_2$). NMR (3% solution in D_2O at 75°) τ: 4.75 (2H, broad, $-C\underline{H}_2NO_2$), 6.82 (3H, singlet, $N^+C\underline{H}_3$). *Anal.* Calcd. for $C_{11}H_{21}O_2N_2I$: C, 38.80; H, 6.22; N, 8.23. Found: C, 38.59; H, 6.18; N, 8.35.

The filtrate was evaporated *in vacuo* to dryness and the residue was recrystallized from EtOH to give colorless cubic crystals (VIII), mp 260—261° (decomp.) (lit.[7] mp 256—258° (decomp.)) in 22% yield (0.5 g). IR ν_{max}^{Nujol} cm^{-1}: 1085 (ether). Its IR spectrum was identical with that of the authentic 10-methoxy-5-methyloctahydroquinolizinium iodide.[7]

The reaction was carried out using VI (1.0 g), nitromethane (1.0 g), CH_3I (2.0 g) and MeOH (1.0 ml) to give VII in 57% yield (1.4 g) and VIII in 4.4% yield (0.1 g). The reaction of VI (1.0 g) with nitromethane (1.0 g) and CH_3I (2.0 g) gave VII in 65% yield (1.5 g).

10-Aminomethyl-5-methyloctahydroquinolizinium Iodide (IX)——A solution of VII (2.0 g) in H_2O (100 ml) was hydrogenated over platinic oxide (100 mg) at room temperature for 5 hr; 400 ml of H_2 was taken up within 5 hr. The catalyst was filtered off, and the filtrate was evaporated *in vacuo* to dryness. Recrystallization of the residue from H_2O gave colorless prisms (IX), mp 256—258° (decomp.). Yield, 1.5 g. IR ν_{max}^{KBr} cm^{-1}: 3360, 1590 ($-NH_2$). *Anal.* Calcd. for $C_{11}H_{23}N_2I$: C, 42.58; H, 7.47; N, 9.03. Found: C, 42.17; H, 7.29; N, 8.71.

Dipicrate: Recrystallization from acetone afforded yellow needles, mp 229—232° (decomp.). *Anal.* Calcd. for $C_{23}H_{28}O_{14}N_8$: C, 43.11; H, 4.41; N, 17.49. Found: C, 42.89; H, 4.54; N, 17.24.

10-Acetamidomethyl-5-methyloctahydroquinolizinium Iodide (X)——The amino methiodide (IX) (1.4 g) was heated with Ac_2O (10 ml) at 90—100° for 1 hr. The solution was evaporated *in vacuo* to dryness leaving the crude X. Recrystallization from EtOH–AcOEt (1:1) afforded colorless needles (X), mp 229—230°. Yield, 1.0 g. IR ν_{max}^{KBr} cm^{-1}: 3250, 1670, 1528 (–CONH–). *Anal.* Calcd. for $C_{13}H_{25}ON_2I$: C, 44.32; H, 7.15; N, 7.95. Found: C, 44.56; H, 7.23; N, 7.67.

5-Methyloctahydroquinolizinium-10-carboxylate (XI)——The nitromethyl methiodide (VII) (0.5 g) was heated with 85% H_2SO_4 (1 g) at 110—120° for 8 hr. The solution was shaken with $CHCl_3$. The aqueous layer was treated with excess $BaCO_3$ with stirring and then filtered. The filtrate was evaporated *in vacuo* to dryness to leave a syrupy product (XI). IR $\nu_{max}^{liq.}$ cm^{-1}: 1550 ($-COO^-$).

Reduction of VII with Li in Liquid NH_3 [Formation of 1-Methyldecahydroazecin-6-one (XIV) and 6-Formyl-1-methyldecahydroazecine (XV)]——To a solution of VII (2.77 g) in liquid NH_3 (200 ml) was added Li (500 mg) in small portions with stirring. The solution was kept standing for 1 hr. After evaporation of NH_3, the residue was shaken with H_2O and ether. The ether layer was dried over Na_2SO_4 and then evaporated. The oily residue was fractionally distilled to give a colorless liquid (XIV) (100 mg), bp 110—120° (bath temperature)/18 mmHg, *Rf*[11] 0.13, and a colorless liquid (100 mg), bp 120—200° (bath temperature)/3 mmHg, *Rf*[11] 0.13 and 0.38. The latter fraction was developed over plate-TLC and eluted successively with MeOH. XIV and XV were fractionated.

XIV: A colorless liquid, bp 110—115° (bath temperature)/18 mmHg. Yield, 300 mg. IR ν_{max}^{liq} cm^{-1}: 2800 (NCH_3), 1693 (CO). Its IR spectrum was identical with that of the authentic specimen[7] (XIV). Picrate: Recrystallization from EtOH gave yellow prisms, mp 254–256° (decomp.) [lit.[7] mp 258–260°

11) All the melting points were measured with a Yanagimoto Micro-Melting Point Apparatus and are uncorrected. IR spectra were measured with a Spectrophotometer-G and -S, Japan Spectroscopic Co., Ltd., and NMR spectra with a Spectrometer H-60-C, Japan Electron Lab. Co., using tetramethylsilane as an internal standard. The *Rf* values of TLC were determined on Al_2O_3 GF_{254} (Merck) using $CHCl_3$ as a developer and spots were detected by I_2.

(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, 5.59; N, 13.92.

XV: A colorless liquid, bp 150° (bath temperature)/3 mmHg. Yield, 90 mg. IR $\nu_{max}^{liq.}$ cm^{-1}: 1720 (CO), 2800 (NCH_3). NMR (5% solution in $CDCl_3$) τ: 7.14 (3H, singlet, $NC\underline{H}_3$). Picrate (XVI): Recrystallization from EtOH gave yellow needles, mp 162—162.5°. *Anal.* Calcd. for $C_{17}H_{24}O_8N_4$: C, 49.51; H, 5.86; N, 13.59. Found: C, 49.35; H, 5.66; N, 13.28. NMR (4% solution in DMSO-d_6) τ: 1.94 (1H, doublet, J=7 Hz, O$\underline{H}$, disapeared by treatment with D_2O), 5.05 (1H, doublet, J=7 Hz, $>C<^{OH}_{\underline{H}}$ appeared as a singlet by addition of D_2O), 7.02 (3H, singlet, $NC\underline{H}_3$).

6-Acetamidomethyl-1-methyldecahydroazecine (XVII)——To a solution of X (640 mg) in liquid NH_3 (150 ml), Li (150 mg) was added in small portions with stirring and the reaction solution was allowed to stand for 1 hr. After evaporation of NH_3, ether and H_2O were added to the residue with stirring. The ether layer was dried over Na_2SO_4 and the solvent was evaporated. The residue was distilled to give a colorless viscos liquid (XVII), bp 150° (bath temperature)/3 mmHg in 44% (180 mg) yield. IR $\nu_{max}^{liq.}$ cm^{-1}: 3300, 3090, 1560, 1290 (–CONH–), 2800 (N–CH_3).

6-Aminomethyl-1-methyldecahydroazecine (XVIII)——XVII (160 mg) was refluxed with 10% HCl (5 ml) for 2 hr. The solution was made alkaline with aqueous NaOH and then shaken with ether. The ether layer was washed with H_2O, dried over Na_2SO_4 and then evaporated. The residue was distilled to give a colorless liquid (XVIII), bp 95° (bath temperature)/3 mmHg. Yield, 115 mg. IR $\nu_{max}^{liq.}$ cm^{-1}: 3370, 3320 (–NH_2), 2800 (NCH_3). Its IR spectrum was identical with that of the authentic 6-aminomethyl-1-methyldecahydroazecine[5] (XVIII).

Picrate: Recrystallization from EtOH gave yellow prisms, mp 178—179° (lit.[5] mp 178—179°). This picrate did not show any melting point depression on admixture with that of the sample[5] (XVIII).

6-Carbamoyl-1-methyloctahydroazecine (XIX)——To a solution of the crude XI derived from VII (0.5 g) in liquid NH_3 (200 ml), Li (120 mg) was added in small portions with stirring. The solution was kept standing for 1 hr and then evaporated. To the residue ether and H_2O were added with stirring. The ether layer was dried over Na_2SO_4 and the solvent was evaporated. The residue was recrystallized from AcOEt to give colorless needles (XIX), mp 177—179° (lit.[9] mp 177—178°). Yield, 150 mg. *Anal.* Calcd. for $C_{11}H_{22}ON_2$: C, 66.62; H, 11.18; N, 14.13. Found: C, 66.26; H, 11.13; N, 14.01. IR ν_{max}^{KBr} cm^{-1}: 3380, 3180, 1650 (–$CONH_2$), 2780 (NCH_3). No melting point depression was observed by admixture of this product with the sample[9] of XIX, and the IR spectra of both compounds were in accordance.

Acknowledgement The authors are indebted to Mr. Y. Itatani, Misses T. Tsuji and S. Toyoshima for microanalyses and NMR and mass spectral data.