[Chem. Pharm. Bull. 27(10)2411—2414(1979)]

UDC 547.834.2.04 : 547.232.1.04

Stereoselective Alkylation of 1-Oxoquinolizidine

Seitaro Saeki, Ayako Yamashita, Yoko Matsukura, and Masatomo Hamana

Faculty of Pharmaceutical Sciences, Kyushu University[1]

(Received April 24, 1979)

In contrast to other nucleophilic reagents, dimethyloxosulfonium methylide and nitromethane attack 1-oxoquinolizidine (**1**) in a stereoselective manner to yield only the axially substituted products, quinolizidine-1-spirooxirane (**2**) and 1(*e*)-hydroxy-1(*a*)-nitromethylquinolizidine (**4a**). This high stereoselectivity can be explained in terms of an interaction between the lone pair on the ring nitrogen atom and the cationic center of the reagents.

Keywords——nucleophilic addition to carbonyl group; axial attack; participation of a lone pair on nitrogen atom; intramolecular hydrogen bond; dimethyloxosulfonium methylide; nitromethane; quinolizidine-1-spirooxirane; 1(*e*)-hydroxy-1(*a*)-nitromethylquinolizidine

In the course of studies on the reactions of N-benzoyloxypyridinium chloride with 1(10)-dehydroquinolizidine and 1,1-disubstituted 9-dehydroquinolizidines,[2] we investigated the reaction of 1-oxoquinolizidine with dimethyloxosulfonium methylide and nitromethane and found that nucleophilic addition occurred in a stereoselective manner to give only the axially substituted products.

A tetrahydrofuran solution of 1-oxoquinolizidine(**1**) and dimethyloxosulfonium methylide, previously prepared from trimethyloxosulfonium chloride and sodium hydride in the same solvent, was refluxed for 2 hr. Purification by chromatography on silica gel afforded a quinolizidine-1-spirooxirane (**2**), a colorless oil, bp 90—100°/0.15 mm (bath temp.), as the sole product in 50% yield. The product **2** formed a picrate, $C_{10}H_{17}NO \cdot C_6H_3N_3O_7$, yellow plates, mp 157—159°. The infrared (IR) spectrum of free **2** exhibited Bohlmann bands[3] at 2900—2720 cm^{-1} and the nuclear magnetic resonance (NMR) spectrum showed an AB-type quartet (τ 7.06, 7.54; J=5.3 Hz) centered at τ 7.30, which can be assigned to the methylene protons of the oxirane ring.[4]

Reduction of **2** with lithium aluminum hydride gave 1-hydroxy-1-methylquinolizidine (**3a**), colorless needles, mp 97—99°, which was identical with the known 1(*e*)-hydroxy-1(*a*)-methylquinolizidine obtained from **1** and methylmagnesium iodide.[2b] Thus the product **2** was identified as the isomer in which the C_1–CH_2 bond is axial, as shown in Chart 1.

The reaction of **1** with nitromethane was next examined. Upon treatment with excess nitromethane (4 eq) and diethylamine (2.5 eq) in 50% ethanol at room temperature for 4 days with stirring, 1-hydroxy-1-nitromethylquinolizine (**4**) was obtained as colorless needles, mp 165—167°, in 20% yield accompanied by 64% recovery of **1**, no other product being detected.

1) Location: *Maidashi, Higashi-ku, Fukuoka 812, Japan.*

2) *a*) S. Saeki, A. Yamashita, Y. Matsukura, and M. Hamana, *Chem. Pharm. Bull.* (Tokyo), **22**, 2341 (1974); *b*) S. Saeki, A. Yamashita, Y. Morinaka, and M. Hamana, *Yakugaku Zasshi*, **96**, 456 (1976); *c*) S. Saeki, A. Yamashita, Y. Morinaka, and M. Hamana, *Chem. Pharm. Bull.* (Tokyo), **24**, 2509 (1976); *d*) *Idem*, *ibid.*, **25**, 79 (1977).

3) *a*) F. Bohlmann, *Chem. Ber.*, **31**, 2157 (1958); *b*) J. Skolik and P.J. Krueger, *Tetrahedron*, **24**, 5439 (1968).

4) *a*) N.F. Chamberlain, "The Practice of NMR Spectroscopy," Plenum Press. Inc., London and New York, 1974, p. 225, 295; *b*) R.S. Bly, C.M. DuBose, Jr., and G.B. Bonizer, *J. Org. Chem.*, **33**, 2188 (1968).

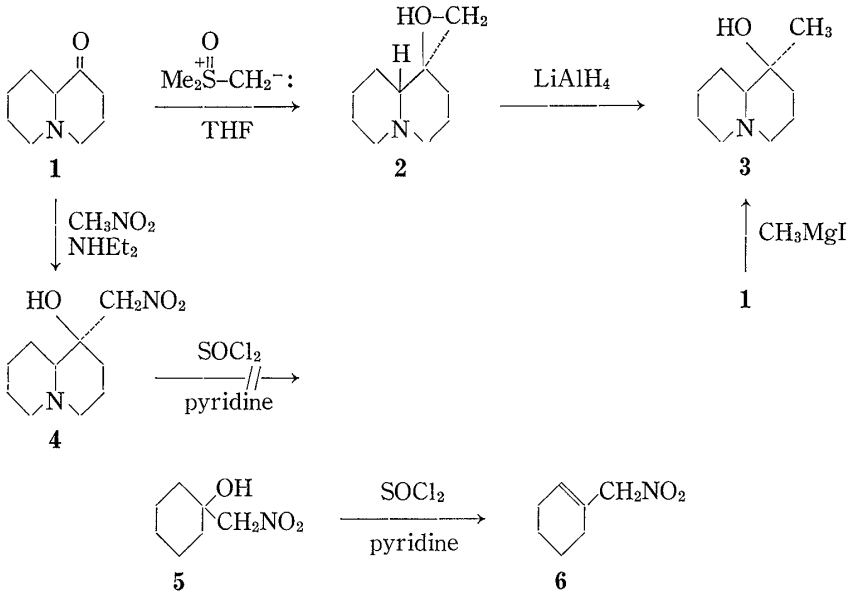
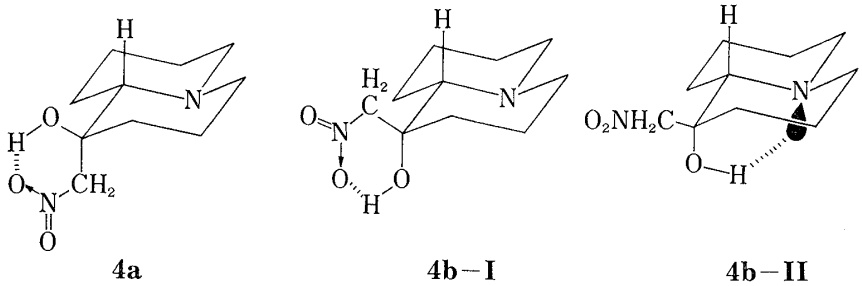


Chart 1

The analytical values were consistent with the empirical formula $C_{10}H_{18}N_2O_3$, and the NMR spectrum in deuterochloroform showed an AB-type quartet (τ 4.96, 5.55; J=12.7 Hz) centered at τ 5.26, which can be assigned to the methylene protons adjacent to the nitro group. The IR spectrum of **4** in dichloromethane displayed an OH band at 3540 cm^{-1}, Bohlmann bands at 2940—2777 cm^{-1}, and two NO_2 bands at 1550 and 1350 cm^{-1}; the OH band at 3540 cm^{-1} appeared at 3580 cm^{-1} when measured in a 0.006 M solution in carbon tetrachloride, indicating the presence of an intramolecular hydrogen bond.

With respect to the intramolecular hydrogen bond in the *trans* form of 1-hydroxy-1-nitromethylquinolizidine (**4**), three forms (**4a**, **4b-I** and **4b-II**) can be considered, as shown in Chart 2. The presence of an intramolecular hydrogen bond similar in type to **4b-II** has



4a **4b−I** **4b−II**

νOH 3580 cm^{-1} (0.006 M solution in CCl_4)

3b

νOH 3560 cm^{-1}
(0.006 M solution in CCl_4)

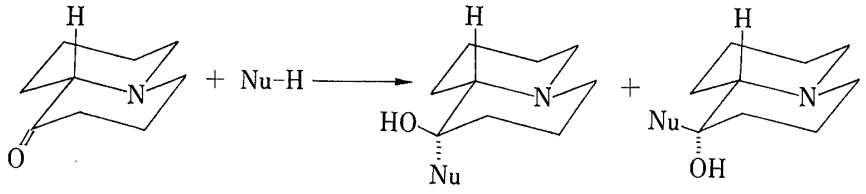
5

νOH 3563 cm^{-1}
(0.006 M solution in CCl_4)

Chart 2

already been demonstrated in 1(*a*)-hydroxy-1(*e*)-methylquinolizidine (**3b**),[2b,5] and we confirmed here that there is also an intramolecular hydrogen bond in 1-nitromethylcyclohexanol (**5**) (Chart 2). Thus, the configuration of **4** cannot be unambiguously clarified by IR spectroscopy alone.

Fraser and Kon[6] have shown that 1-nitromethylcyclohexanol (**5**) readily undergoes dehydration when treated with thionyl chloride in pyridine at room temperature for 2 hr, giving 1-nitromethylcyclohexene (**6**). In a similar way, **4** was warmed with thionyl chloride and pyridine at 70° for 30 min with stirring, but no dehydration product was isolated and the starting material was quantitatively recovered (Chart 1). This result suggests that the hydroxyl group of **4** has the equatorial configuration. From this finding, together with the following consideration of nucleophilic addition to 1-oxoquinolizidine **1**, **4** can probably be assumed to be 1(*e*)-hydroxy-1(*a*)-nitromethylquinolizidine **4a**.



Nu-H (Nucleophile)	Nu	Relative ratio A	B
$NaBH_4$	H	85	17
CH_3MgI	CH_3	64	36
PhMgBr	Ph	12	88
Me_2SOCH_2	CH_2SOMe_2	100	—
CH_3NO_2	CH_2NO_2	100	—

Chart 3

Nucleophilic addition to 1-oxoquinolizidine **1** generally affords a pair of stereoisomers; axial attack of a reagent gives a product of type A, and equatorial attack gives a type B isomer, as shown in Chart 3. In fact, reactions of **1** with sodium borohydride,[7] methylmagnesium iodide[8a] and phenylmagnesium bromide[8b] give rise to a mixture of the two isomers. Thus, it is very significant that the above-mentioned reactions are highly stereoselective and give only the product of type A in each case.

Such highly stereoselective formation of **2** and **4a** does not seem to be governed by steric factors, in view of the reactions with sodium borohydride and Grignard reagents. A more likely explanation is that the interaction between the lone pair on the ring nitrogen and the cationic center of the reagents permits only axial attack of the nucleophiles on the 1-oxo group of **1**, as shown in Chart 4.

Chart 4

5) *a*) H.S. Aaron, G.E. Wieks, Jr., and C.P. Rader, *J. Org. Chem.*, **29**, 2248 (1964); *b*) H.A. Aaron and C.P. Fergus, *Tetrahedron Lett.*, **1968**, 6191.
6) H.B. Fraser and G.A.R. Kon, *J. Chem. Soc.*, **1934**, 604.
7) C.P. Rader, G.E. Wicks, Jr., R.S. Young, and H.S. Aaron, *J. Org. Chem.*, **29**, 2252 (1964).
8) *a*) D. Temple and J. Sam, *J. Heterocycl. Chem.*, **5**, 441 (1968); *b*) *Idem*, *ibid.*, **7**, 847 (1970).

Experimental[9]

Reaction of 1-Oxoquinolizidine (1) with Dimethyloxosulfonium Methylide——A solution of NaH (120 mg, 5 mmol) and trimethyloxosulfonium chloride (640 mg, 5 mmol) in tetrahydrofuran (THF) (5 ml) was refluxed for 1 hr in a nitrogen stream, until evolution of hydrogen ceased. A THF solution (5 ml) of **1** (640 mg, 5 mmol) was then added over a period of 2 hr. The whole was refluxed for 2 hr, then concentrated under reduced pressure. Water was added and the resulting mixture was extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and evaporated down. The residue was chromatographed on silica gel with CH_2Cl_2–petr. ether (3: 1) to give 370 mg (50%) of quinolizidine-1-spirooxirane (**2**), a colorless oil, bp 90—100°/0.15 mm (bath temp.). IR ν_{max}^{Neat} cm^{-1}: 2900—2720 (Bohlmann bands). NMR ($CDCl_3$) τ: 7.06 (1H, d, J=5.3 Hz, –O–CH_2–), 7.54 (1H, d, J=5.3 Hz, –O–CH_2–). Picrate: yellow plates, mp 157—159° (EtOH). *Anal.* Calcd. for $C_{16}H_{20}N_4O_8$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.44; H, 5.11; N, 13.70.

Reduction of 2 with $LiAlH_4$——An ether solution (20 ml) of **2** (100 mg, 6 mmol) was added to a suspension of $LiAlH_4$ (10.2 mg, 0.27 mmol) in anhydrous ether (50 ml). The reactants were stirred at room temperature for 5 days, a small amount of water was added, the solvent was evaporated off and the residue was extracted with CH_2Cl_2. The crystalline residue obtained from the extract was recrystallized from petr. ether to give 42 mg (41%) of 1(*e*)-hydroxy-1(*a*)-methylquinolizidine (**3**), colorless needles, mp 97—99°. This was identical with an authentic sample prepared from **1** and methylmagnesium iodide[2b] by mixed melting poing test and by comparison of their IR spectra.

Reaction of 1 with Nitromethane——A solution of **1** (500 mg, 3.3 mmol), nitromethane (900 mg, 13.6 mmol) and diethylamine (610 mg, 8.3 mmol) in 50% EtOH (17 ml) was stirred at room temperature for 4 days. Ice water was added to the reaction mixture, the nitromethane layer was separated and the aqueous layer was extracted with a large amount of CH_2Cl_2. The residue obtained from the extract was chromatographed on silica gel. Elution with CH_2Cl_2 gave 320 mg of unreacted **1** and the fraction eluted with CH_2Cl_2–MeOH (1: 1) afforded 140 mg of 1(*e*)-hydroxy-1(*a*)-nitromethylquinolizidine (**4**), colorless needles, mp 165—167° (CH_2Cl_2-petr. ether). IR (20% solution in CH_2Cl_2) ν_{max} cm^{-1}: 3540 (OH), 2940—2777 (Bohlmann bands), 1550 and 1350 (NO_2). IR (6 mmol solution in CCl_4) ν_{max} cm^{-1}: 3580 (OH). NMR ($CDCl_3$) τ: 4.96 (1H, d, J=12.7 Hz, –CH_2–NO_2), 5.55 (1H, d, J=12.7 Hz, –CH_2–NO_2), 7.02 (1H, b.s. OH, exchangeable with D_2O). MS *m/e*: 214 (M^+). *Anal.* Calcd. for $C_{10}H_{18}N_2O_3$: C, 56.05; H, 8.47; N, 13.08. Found: C, 56.05; H, 8.69; N, 12.76.

Acknowledgement This work was supported in part by a grant from the Takeda Science Foundation, which is gratefully acknowledged.

9) All melting and boiling points are uncorrected. IR spectra were recorded on JASCO DS-301, IR-S, IR-E spectrophotometers. NMR spectra were measured with a JNM C-60H spectrophotometer at 60 MHz using TMS as an internal reference.