BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 47(5), 1297—1298 (1974)

Reaction of *N*-Nitroso-1,2,3,4-tetrahydroisoquinolines with Base. A New Method for the Conversion of 1,2,3,4-Tetrahydroisoquinolines into 3,4-Dihydroisoquinolines

Kazuo SAKANE, Ken-ichi TERAYAMA, Eiichi HARUKI, Yoshio OTSUJI, and Eiji IMOTO

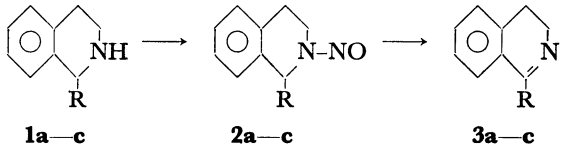
Department of Applied Chemistry, College of Engineering, University of Osaka Prefecture, Sakai-shi, Osaka 591

(Received December 27, 1973)

Synopsis. Treatment of *N*-nitroso-1,2,3,4-tetrahydroisoquinoline (**2a**) and its 1-methyl derivative (**2b**) with base gave the corresponding 3,4-dihydroisoquinolines (**3a** and **3b**). However, similar treatment of *N*-nitroso-1,2,3,4-tetrahydroisoquinoline-1-acetic acid (**2c**) gave a mixture of **3b** and 1,2,3,4-tetrahydroisoquinoline-1-(α-hydroxyimino)acetic acid (**4**).

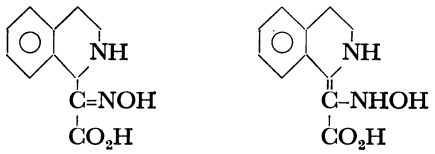
Reaction for the preparation of 3,4-dihydroisoquinolines from 1,2,3,4-tetrahydroisoquinolines can be classified into two types: direct dehydrogenation using oxidizing agents such as Hg(II)–EDTA[1] and potassium ferrate (VI),[2] and the elimination of a substituent attached to *N*-heteroatom and a hydrogen at the 1-position of tetrahydroisoquinolines, such as the base-induced elimination of hydrogen halide from *N*-halogeno-1,2,3,4-tetrahydroisoquinolines,[3,4] and the photochemically induced elimination of *p*-toluenesulfinic acid from *N*-tosyl-1,2,3,4-tetrahydroisoquinolines in the presence of base.[5] We report here a new method belonging to the latter.

N-Nitroso-1,2,3,4-tetrahydroisoquinolines derived from 1,2,3,4-tetrahydroisoquinolines were converted into 3,4-dihydroisoquinolines with base. The sequence of the reactions employed is outlined in Chart 1. The procedure is simple and the yields are generally good.



1a—c **2a—c** **3a—c**

a, R=H; b, R=CH_3; c, R=CH_2CO_2H.



4a **4b**

Chart 1.

N-Nitroso-1,2,3,4-tetrahydroisoquinolines (**2a—c**) were prepared by the nitrosation of the corresponding 1,2,3,4-tetrahydroisoquinolines (**1a, b**) or the hydrochloride (**1c**) with isoamyl nitrite or sodium nitrite in hydrochloric acid. Treatment of **2a** and **2b** with aqueous sodium hydroxide resulted in the formation of the corresponding 3,4-dihydroisoquinolines in high yields, no other products being detected in the reaction mixture. Total yields of **3a** and **3b** from **1a** and **1b** were 70 and 80%, respectively. It is almost certain that **3a** and **3b** are produced by the base-induced elimination of hydrogen hyponitrite from *N*-nitroso compounds, although the reaction of this type has scarcely been reported. Daeniker[6] noted that *N*-nitroso-*N*-benzylaniline undergoes the elimination of hydrogen hyponitrite on being treated with a base.

However, a similar treatment of **2c** with sodium hydroxide afforded two products, **3b** and 1,2,3,4-tetrahydroisoquinoline-1-(α-hydroxyimino)acetic acid (**4**). The yields of **3b** and **4** from **2c** were 20 and 70%, respectively. Compound **3b** probably arises by the decarboxylation of **3c**, a primary product of the reaction of **2c** with base. On the other hand, the base-induced migration of the nitroso group from nitrogen to the carbon adjacent to the carboxyl group in **2c** accounts for the production of **4**. The migration of nitroso group of this kind, *viz.*, migration of nitroso group from nitrogen to an active methylene, has been observed in the reaction of *N*-nitroso amino acid.[6]

The structure of the compounds were confirmed by means of analytical and spectral data or by comparison with the respective authentic samples. The spectral data suggested that **4** exists in the form of **4a** or **4b**, or in equilibrium between **4a** and **4b**.

Experimental

3,4-Dihydroisoquinoline (3a) from 1,2,3,4-Tetrahydroisoquinoline (1a). A mixture of 1.3 g (0.01 mol) of **1a** and 4.6 g (0.04 mol) of isoamyl nitrite was allowed to stand at room temperature for 1 hr, and the excess isoamyl nitrite was evaporated. The residue dissolved in benzene was passed through a column of alumina using *n*-hexane–benzene mixture as an eluent to give 1.5 g (90%) of *N*-nitroso-1,2,3,4-tetrahydroisoquinoline (**2a**) as yellow solids: IR (KBr) 2920, 1420, 1355, 1330, 1160, 1100, 1040, 920, 805, and 750 cm^{-1}; NMR ($CDCl_3$) δ 2.84 (t, J=6.4 Hz, 2/3H), 2.99 (t, J=5.9 Hz, 4/3H), 3.76 (t, J=6.4 Hz, 2/3H), 4.42 (t, J=5.9 Hz, 4/3H), 4.71 (s, 4/3H), 5.27 (s, 2/3H), and 7.10 ppm (m, 4H). The NMR spectrum exhibited the same pattern as that reported by Chow and Colon[7] for **2a** indicating that **2a** exists in a pair of *syn* and *anti* conformers along the axis of the N–N partial double bond in the ratio 2:1.

Compound **2a** thus obtained was used without further purification for the preparation of **3a**. A mixture of 1.5 g (0.009 mol) of **2a** in 20 ml of ethanol and 10 ml of 20% aqueous NaOH was refluxed for 10 hr, cooled, diluted with water and then taken up in CH_2Cl_2. The CH_2Cl_2 solution was extracted with 3 M HCl. The aqueous extract was made basic with 10% NaOH and extracted with CH_2Cl_2.

The extract was washed with water and dried over Na_2SO_4. Removal of CH_2Cl_2 left an oil, which was dissolved in benzene and passed through a column of alumina with benzene to give 0.9 g (70%) of **3a**. The IR spectrum (film) showed an absorption at 1630 cm^{-1} (C=N) and was identical with that of the authentic sample prepared by the method of Snyder and Werber.[8] The picrate, mp 172—175 °C, showed no depression in the mixed melting point test with the picrate from the authentic sample of **3a**.

1-Methyl-3,4-dihydroisoquinoline (3b) from 1-Methyl-1,2,3,4-tetrahydroisoquinoline (1b). *N*-Nitroso-1,2,3,4-tetrahydroisoquinoline (**2b**) was prepared from 1.5 g (0.01 mol) of **1b** and 4.6 g (0.04 mol) of isoamyl nitrite by a method similar to that described above. A solution of the crude product in benzene was chromatographed on alumina. Elution with *n*-hexane–benzene gave 1.5 g (85%) of **2b** as a yellow viscous oil: IR (film) 2970, 2930, 2860, 1495, 1430, 1360, 1315, 1295, 1150, 1110, and 760 cm^{-1}; NMR ($CDCl_3$) δ 1.47 (d, J=7.3 Hz, 3/2H), 1.72 (d, J=7.3 Hz, 3/2H), 2.80—3.30 (m, 2H), 3.40—5.10 (m, 2H), 5.91 (q, J=7.3 Hz, 1H), and 7.17—7.50 ppm (m, 4H, aromatic).

The oil **2b** was used without further purification for preparation of **3b**. A 1.5 g (0.0085 mol) sample of **2b** in 20 ml of ethanol was treated with 10 ml of 20% NaOH. Work-up of the reaction mixture yielded an oil, which upon distillation gave 1.1 g (92%) of **3b** as a colorless oil, bp 127—138 °C/20 mmHg: IR (film) 1630 cm^{-1} (C=N). The IR spectrum of this compound was identical with that of the authentic sample prepared by the method of Lora-Tamayo, Madronero, and Munoz.[9] The picrate, mp 187—190 °C, showed no depression in the mixed melting point test with the authentic specimen.

1,2,3,4-Tetrahydroisoquinoline-1-acetic Acid (1c) Hydrochloride. A mixture of 17 g (0.078 mol) of ethyl 1,2,3,4-tetrahydroisoquinoline-1-acetate[10-12] in 50 ml of 3 M HCl was refluxed for 1 hr. A half of water was removed under atmospheric pressure at 130—140 °C (oil bath temperature) left solids. The solids were extracted with 30 ml of boiling acetone, and the insoluble material (HCl salt of **1c**) was separated by filtration. The filtrate was evaporated to dryness, and the residue (unhydrolyzed ester) was repeatedly hydrolyzed. The solids obtained by hydrolysis were combined and recrystallized from dioxane–methanol to give 17 g (quantitative) of the hydrochloride of **1c** as white crystals; mp 183—184 °C: IR (KBr) 3500—2400 (OH), and 1720 cm^{-1} (C=O). Found: C, 58.44; H, 5.91; N, 6.42%. Calcd for $C_{11}H_{14}NO_2Cl$: C, 58.02; H, 6.15; N, 6.15%.

N-Nitroso-1,2,3,4-tetrahydroisoquinoline-1-acetic Acid (2c). To a solution of 2.0 g (0.0088 mol) of the hydrochloride of **1c** in 20 ml of 3 M HCl was added 20 ml of 10% sodium nitrite under cooling in an ice–water bath. The mixture was stirred for 1 hr under cooling. The resulting solids were filtered, and recrystallized from aqueous ethanol to give 1.7 g (90%) of **2c** as white needles, mp 167—169 °C: IR (KBr) 3100—2300 (OH) and 1720 cm^{-1}. Found: C, 59.71; H, 5.50; N, 12.48%. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72%.

Reaction of 2c with Aqueous Sodium Hydroxide. A mixture of 3.0 g (0.014 mol) of **2c**, 50 ml of ethanol and 30 ml of 20% NaOH was refluxed for 10 hr. The precipitates were occasionally filtered. Additional precipitates obtained upon cooling the mixture were separated by filtration. The filtrate was extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4, and then evaporated. The residue was chromatographed on a column of alumina. Elution with CH_2Cl_2 gave 0.4 g (20%) of **3b**. The IR spectrum of this compound was identical with the authentic sample.

The precipitates were combined and dissolved in water. The solution was acidified with concd HCl and allowed to stand for 2 hr. The resulting precipitates were filtered, and recrystallized from aqueous ethanol to give 2.1 g (70%) of 1,2,3,4-tetrahydroisoquinoline-1-(α-hydroxyimino) acetic acid (**4**) as white needles, mp 145—146 °C: IR (KBr) 3520, 3350, 2900—2200, and 1680 cm^{-1} (C=O); UV (EtOH) λ_{max} (log ε) 212 (3.90) and 294 nm (3.87); NMR (CF_3COOH) δ 3.10—3.70 (m, 4H), 4.17—5.10 (m, 2H), 6.15—6.70 (m, 1H), and 7.56 ppm (m, 4H, aromatic). Found: C, 59.90; H, 5.50; N, 12.45%. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72%.

References

1) J. Knabe and G. Grund, *Arch. Pharmz.*, **296**, 820 (1963).
2) R. J. Audette, J. W. Quail, and P. J. Smith, *Tetrahedron Lett.* **1971**, 279.
3) N. Whittaker, U. S. 3135759; *Chem. Abstr.*, **61**, 5710g (1964).
4) E. Eckhart, *Magy. Kem. Folyoirat*, **70**, 296 (1964); *Chem. Abstr.*, **61**, 13355e (1964).
5) B. Umezawa, O. Hoshino, and S. Sawaki, *Chem. Pharm. Bull.* (Tokyo), **17**, 1115 (1969).
6) von H. U. Daeniker, *Helv. Chim. Acta*, **47**, 33 (1964).
7) Y. L. Chow and C. J. Colon, *Can. J. Chem.*, **46**, 2827 (1968).
8) H. R. Snyder and F. X. Werber, *J. Amer. Chem. Soc.*, **72**, 2962 (1950).
9) M. Lora-Tamayo, R. Madronero, and G. G. Munoz, *Chem. Ber.*, **93**, 289 (1960).
10) S. G. Agbalyan, A. O. Nshanyan, and L. A. Nersesyan, *Izv. Akad. Nauk Arm. SSR, Khim. Nauki*, **16**, 77 (1963); *Chem. Abstr.*, **59**, 5132c (1964).
11) W. Sobotka, W. N. Beverung, G. G. Munoz, J. C. Sircar, and A. I. Meyers, *J. Org. Chem.*, **30**, 3667 (1965).
12) G. Van Binst and J. C. Nouls, *J. Chem. Soc. C*, **1970**, 150.