Monatshefte für Chemie 124, 953–957 (1993)

*Monatshefte für Chemie*
*Chemical Monthly*

Printed in Austria

# Reaction of (*Z*)-Narceine Imide with 1,2-Epoxypropane

**B. Proksa**

Department of Biochemical Technology, Faculty of Chemistry, Technical University, 812 37 Bratislava, Slovakia

**Summary.** (*Z*)-Narceine imide (**1**) reacted with 1,2-epoxypropane to narceone imide (**2**) and with an excess of epoxide to N-(2-hydroxypropyl)narceone imide (**3**). Cyclization of **3** in acidic media afforded two isomers of 8,14-dimethyl-11,12-methylenedioxy-3,4,10-trimethoxyindano[1′,2′:2,3]morpholino-[3,4-a]isoindolin-5-ones **16** and **17** which differed in the spatial orientation of the C-8–$CH_3$. Narceonic acid (**18**) cyclized into the isochroman-3-spiro-3′-phthalide derivative **19**.

**Keywords.** (*Z*)-Narceine imide; 1,2-Epoxypropane; Narceonic acid; Acid cyclization.

**Reaktion des (*Z*)-Narceinimid mit 1,2-Epoxypropan**

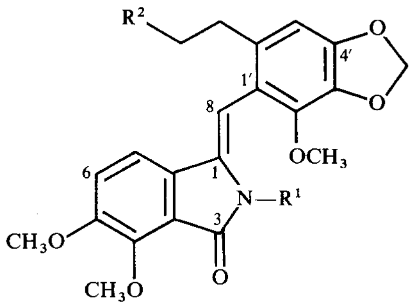
**Zusammenfassung.** (*Z*)-Narceinimid (**1**) reagierte mit 1,2-Epoxypropan zu Narceonimid (**2**) und bei Überschuß von Epoxid zu N-(2-Hydroxypropyl)narceonimid (**3**). Cyclisierung der letztgenannten Verbindung in Anwesenheit von Mineralsäuren führte zu zwei Indano[1′,2′:2,3]morpholino[3,4-a]isoindol-5-on-Isomeren **16** und **17**. Narceonsäure (**18**) wurde zu dem Isochroman-3-spiro-1′-phthalid **19** umgewandelt.

## Introduction

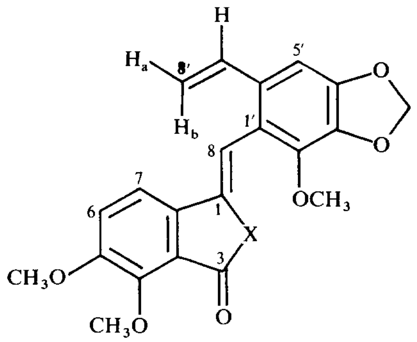
In previous studies was observed, that some secophthalideisoquinoline alkaloids were deaminomethylated by reaction with epoxides more efficiently than by Hofmann degradation of their iodomethylates [1]. In this work the reaction of (*Z*)-narceine imide and its derivatives with 1,2-epoxypropane was studied and the products of this reaction were used for construction of new heterocycles.

## Results and Discussion

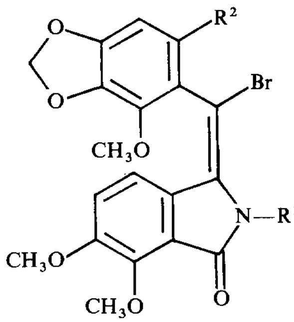
(*Z*)-Narceine imide (**1**), an artifact of isolation of poppy alkaloids [2], refluxed with an equimolar amount of 1,2-epoxypropane in methanol gave narceone imide (**2**); when an excess of epoxide was used, 2-hydroxypropyl derivative **3** was isolated. NMR spectra of compound **3** and its acetate **4** showed duplication of proton and carbon signals of the hydroxy/acetoxypropyl chain as well as of some adjacent atoms in the benzylideneisoindoline skeleton. This duplication indicates the presence of two distinct conformers due to hindered rotation about the C-8–C-1′



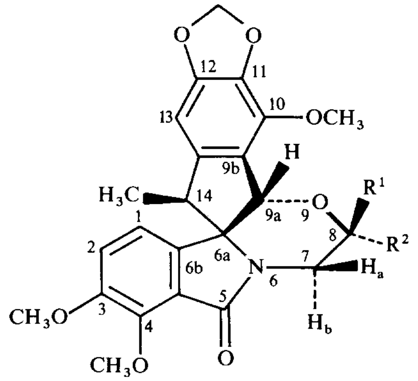
**1** $R^1 = H$ $R^2 = N(CH_3)_2$
**7** $R^1 = H$ $R^2 = N(CH_3)_2$ 1,8-dihydro
**9** $R^1 = H$ $R^2 = N^+(CH_3)_2O^-$
**10** $R^1 = H$ $R^2 = N^+(CH_3)_3I^-$
**11** $R^1 = CH_3$ $R^2 = N(CH_3)_2$



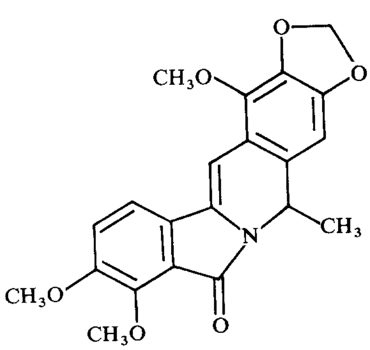
**2** $X = NH$
**3** $X = NCH_2CH(CH_3)OH$
**4** $X = NCH_2CH(CH_3)OCOCH_3$
**8** $X = NH$ 1,8-dihydro
**18** $X = O$



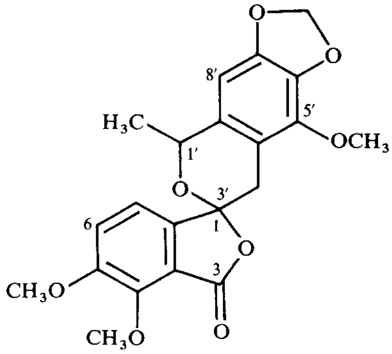
**5** $R^1 = H$ $R^2 = CH_2CH_2N(CH_3)_2$
**6** $R^1 = CH_2CH(CH_3)OH$ $R^2 = CH{=\!=}CH_2$



**16** $R^1 = CH_3$ $R^2 = H$
**17** $R^1 = H$ $R^2 = CH_3$



**12**



**19**

bond. (Z)-α-Bromo narceine imide (**5**) [3] reacted with an excess of 1,2-epoxypropane to the 2-hydroxypropyl derivative **6**. Dihydronarceine imide (**7**) [4] was easily deaminomethylated to **8** but no subsequent reaction of 1,2-epoxypropane with imide nitrogen was observed. Neither N-oxide [5] nor iodomethylate of (Z)-narceine imide [4], **9** and **10**, respectively, reacted with epoxide at the isoindolinone nitrogen and the narceine N-methylimide (**11**) was not deaminomethylated with 1,2-epoxypropane. According to these findings we suppose that the isoindolinone NH group is involved in the elimination reaction at the dimethylaminoethyl chain of narceine imide. The subsequent addition of epoxide at the heterocyclic NH group occurs when its proton is sufficiently reactive, e.g. due to extended conjugation as in narceone imide (**2**), α-bromo narceone imide (**6**), but not in dihydro narceone imide (**8**) where the conjugation is interrupted.

Narceone imide (**2**) heated in methanolic hydrochloric acid cyclized into 5*H*-isondolo[1,2-b]isoquinol-5-one **12** and isoindoline-3-spiro-2′-indan-1-one **13** [4]; in ethanol this cyclization afforded the ethoxyderivative **14** as the major product together with a small amount of **11** [3]. Refluxing of imide **2** in a mixture of acetic and hydrochloric acids furnished the hydroxy compound **15** only. N-(2-hydroxypropyl)narceone imide (**3**) heated in methanolic hydrochloric acid or in toluene/toluene sulfonic acid gave compounds **16** and **17**. According to UV spectra with bands at 213 and 296 nm both new compounds have a similar chromophor as the spiro indanoindoles **13**–**15**. This assumption was confirmed also by the $^{13}$C-NMR; the signals at 39.3 (C-14), 70.9 (C-6a), 73.1 (C-9a) as well as the signal of the methyl carbon (10.9, C-14–$CH_3$) in the spectrum of compound **16** confirmed the presence of an indane moiety with one quaternary alicyclic carbon and this compound was ascribed the structure of 8,14-dimethyl-11,12-methylene-dioxy-3,4,10-trimethoxy-indano[1′,2′:2,3]morpholino[3,4-a]isoindolin-5-one. The spatial arrangement of the alicyclic moiety was derived from an NOE experiment; intensity enhancement of the H-1 signal after irradiation of H-9a and C-14–$CH_3$ indicate that the methyl group and the H-9a proton are mutually *cis* orientated. The isomeric compounds **16** and **17** differ in arrangement of the methyl group in the methylmorpholine moiety. This group is axially bound in **16** and in equatorial position in structure **17**.

An analogue of compound **15** was synthesized from narceonic acid (**18**) prepared from narceine ethylate [6]. Heating of **18** in a mixture of acetic and hydrochloric acids afforded compound **19**. According to NMR data compared with those measured for the above mentioned compounds as well as the ones published for various isoquinoline alkaloids [7] and 5H-isoindolo[1,2-b][3]benzazepines [8], compound **19** was ascribed the structure of 1-methyl-6,7-methylenedioxy-5,6′,7′-trimethoxyisochroman-3-spiro-3′-phthalide.

## Experimental Part

Melting points were determined on a Kofler micro hot-stage, the $^1$H- and $^{13}$C-NMR spectra of $CDCl_3$ solutions were measured with a Bruker AM-300 operating at 300 and 75 MHz, respectively (δ relative to *TMS*). Silica gel 60 $PF_{254}$ was used for preparative TLC.

*(Z)-4,5-Dimethoxy-1-(6′-ethenyl-3′,4′-methylenedioxy)benzylideneisoindolin-3-one* (**2**)

(Z)-Narceine imide (2.5 g, 5.87 mmol) and 1,2-epoxypropane (350 mg, 6.02 mmol) in methanol (100 ml) were refluxed for 3 h. The mixture was concentrated and the residue crystallized from methanol–water (3:1) affording compound **2** (2.12 g), identical with an authentic sample prepared according to [4].

### *(Z)-2-(2-Hydroxypropyl)-4,5-dimethoxy-1-(6'-ethenyl-3',4'-methylenedioxy)-benzylideneisoindolin-3-one* (**3**)

Compound **1** (10.0 g, 23.5 mmol) with 1,2-epoxypropane (5.8 g, 100 mmol) dissolved in methanol (150 ml) refluxed for 4 h afforded 1-benzylideneisoindolin-3-one **3** (8.6 g, 19.6 mmol) [1].

### *(Z)-2-(2-Acetoxypropyl)-4,5-dimethoxy-1-(6'-ethenyl-3',4'-methylenedioxy)-benzylideneisoindolin-3-one* (**4**)

Compound **3** (500 mg) in acetic anhydride (2 ml) and pyridine (23 ml) was heated for 1 h. Solvents were removed in vacuo, the residue crystallized from ethanol affording acetate **4** (420 mg), m.p. 165–166 °C. For $C_{26}H_{27}NO_8$ (481.5) calc. 64.86 C, 5.65 H, 26.58 N; found 64.81 C, 5.72 H, 26.55 N. $^1$H-NMR ($CDCl_3$), $\delta$/ppm: 7.47, 7.46 (1H, ABq, $J_{6,7} = 8.3$ Hz, H-7), 7.15 (1H, ABq, H-6), 6.82 (1H, s, H-5'), 6.76, 6.58 (1H, dd, $J_{7',8'a} = 11.0$ Hz, $J_{7',8'b} = 17.4$ Hz, H-7'), 6.31, 6.25 (1H, s, H-8), 5.96 (2H, s, $OCH_2O$), 5.60, 5.59 (1H, d, H-8''b), 5.20, 5.14 (1H, d, H-8'a), 4.69 (1H, m, H-2''), 4.10 (3H, s, C-4–$OCH_3$), 4.07, 3.99 (3H, s, C-2'–$OCH_3$), 3.90 (3H, s, C-5–$OCH_3$), 3.76 (1H, dd, $J_{1''a,1''b} = 14.6$ Hz, $J_{1''a,2''} = 7.6$ Hz, H-1''a), 3.58, 3.21 (1H, dd, $J_{1''a,1''b} = 14.6$ Hz, $J_{1''b,2''} = 3.2$ Hz), 1.84, 1.83 (3H, s, $COCH_3$), 0.84, 0.79 (3H, d, $J_{2'',3''} = 6.4$ Hz, H-3''). $^{13}$C-NMR ($CDCl_3$) $\delta$/ppm: 17.58 (C-3''), 20.97, 21.10 ($COCH_3$), 44.55, 44.68 (C-1''), 56.80 (C-5–$OCH_3$), 59.32, 59.53 (C-2'–$OCH_3$), 62.41 (C-4–$OCH_3$), 68.64, 68.84 (C-2''), 98.24, 98.36 (C-8), 98.79 (C-5'), 101.06 ($OCH_2O$), 114.68, 114.89 (C-8'), C-115.01 (C-7), 119.22 (C-6), 120.12 (C-1'), 126.00 (C-3a), 131.58 (C-6'), 132.29 (C-7a), 134.26 (C-7'), 135.80 (C-1), 141.00 (C-2'), 146.64 (C-4), 149.38 (C-4'), 153.03 (C-5), 166.29 (C-3), 170.29 ($COCH_3$).

### *(Z)-8-Bromo-2-(2''-hydroxypropyl)-4,5-dimethoxy-1-(6'-ethenyl-3',4'-methylenedioxy)-benzylideneisoindolin-3-one* (**6**)

(*Z*)-$\alpha$-Bromonarceine imide (**5**, 1.5 g, 3.0 mmol) with 1,2-epoxypropane (2.0 g, 34.4 mmol) in ethanol (50 ml) was refluxed for 4 h. The solvent was evaporated and the residue was chromatographed on silica gel eluted with benzene:methanol (9:1). Crystallization of the appropriate fraction from acetone – *n*-heptane afforded compound **6** (580 mg, 1.12 mmol), m.p. 142–143 °C. For $C_{24}H_{24}BrNO_7$ (518.4) calc. 55.61 C, 4.67 H, 2.70 N; found 55.55 C, 4.55 H, 2.68 N. $^1$H-NMR ($CDCl_3$) $\delta$/ppm: 6.90 (1H, s, H-5'), 6.80 (1H, ABq, $J_{6,7} = 8.6$ Hz, H-7), 6.72 (1H, dd, $J_{7',8'a} = 18.5$, $J_{7',8'b} = 10.9$ Hz, H-7'), 6.03 (2H, ABq, $J = 1.6$ Hz, $OCH_2O$), 5.99 (1H, ABq, H-6), 5.59 (1H, d, H-8'a), 5.19 (1H, d, H-8'b), 4.59 (1H, dd, $J_{1''a,1''b} = 14.1$ Hz, $J_{1''a,2''} = 2.1$ Hz, H-1''a), 4.32 (1H, m, H-2''), 4.28 (1H, dd, $J_{1''b,2''} = 8.8$ Hz, H-1''b), 4.02 (3H, s, C-4–$OCH_3$), 3.95 (3H, s, C-5–$OCH_3$), 3.81 (3H, s, C-2'–$OCH_3$), 1.34 (3H, d, $J_{2'',3''} = 6.1$ Hz, H-3''). $^{13}$C-NMR ($CDCl_3$) $\delta$/ppm: 20.9 (C-3''), 49.3 (C-1''), 56.3 (C-5–$OCH_3$), 59.9 (C-2'–$OCH_3$), 62.1 (C-4–$OCH_3$), 68.9 (C-2''), 95.4 (C-8), 99.8 (C-5'), 101.5 ($OCH_2O$), 115.4 (C-8'), 116.6 (C-7), 118.4 (C-6), 120.7 (C-3a), 125.0 (C-1'), 130.2 (C-6'), 131.5 (C-1), 132.6 (C-7a), 135.7 (C-7'), 136.6 (C-3'), 140.8 (C-2'), 146.3 (C-4), 125.0 (C-7'a), 134.6 (C-6'), 140.2 (C-7a), 140.4 (C-7'a) 140.6 (C-3'a), 147.0 (C-4), 150.9 (C-5'), 152.2 (C-5), 169.2 (C-3).

### *Cyclization of 2-(2'-Hydroxypropyl)narceone Imide* (**3**)

Compound **3** (0.80 g, 1.82 mmol) dissolved in ethanol (15 ml) and acidified with hydrochloric acid (1 ml) was refluxed for 4 h. Ethanol was evaporated in vacuo, water (20 ml) was added to the residue and the precipitate was filtered off and dried. Crystallization from acetone furnished pure compound **16** (320 mg, 0.73 mmol), m.p. 238–239 °C. For $C_{24}H_{25}NO_7$ (439.5) calc. 65.59 C, 5.73 H, 3.19 N; found 65.52 C, 5.75 H, 3.18 N. $^1$H-NMR ($CDCl_3$) $\delta$/ppm 6.83 (1H, ABq, $J_{1,2} = 7.3$ Hz, H-2), 6.47 (1H, s, H-13), 6.11 (1H, ABq, H-1), 6.00 (2H, ABq, $J = 1.6$ Hz, $OCH_2O$), 4.56 (1H, s, H-9A), 4.38 (1H, dd, $J_{7a,7b} = 13.5$ Hz, $J_{7b,8} = 2.5$ Hz, H-7b), 4.09 (3H, s, C-4–$OCH_3$), 4.04 (3H, s, C-10–$OCH_3$), 3.89 (1H, q, $J_{14,CH_3} = 7.1$ Hz, H-14), 3.83 (3H, s, C-3–$OCH_3$), 3.51 (1H, m, H-8), 2.91 (1H, dd, $J_{7a,8} = 10.6$ Hz, H-7a), 1.27 (3H, d, C-8–$CH_3$), 0.79 (3H, d, C-14–$CH_3$). $^{13}C$ ($CDCl_3$) $\delta$/ppm: 10.8 (C-14–$CH_3$), 18.4 (C-8–$CH_3$), 39.2 (C-14), 43.7 (C-7), 56.5 (C-3–$OCH_3$), 59.9 (C-10–$OCH_3$), 62.4 (C-4–$OCH_3$), 70.8 (C-8), 69.9 (C-6a), 80.0 (C-9a), 99.1 (C-13), 101.1 ($OCH_2O$), 115.6 (C-1), 117.3 (C-2), 123.2 (C-4a), 124.0 (C-9b), 134.9 (C-11), 138.2 (C-13a), 140.9 (C-6b), 141.8 (C-10), 148.3 (C-4), 151.1 (C-12), 152.6 (C-3), 165.8 (C-5).

The liquid after crystallization of compound **16** was concentrated and chromatography of the residue on silica gel thin layer plates in chloroform:benzene:methanol (10:10:1) afforded amorphous compound **17** (248 mg). For $C_{24}H_{25}NO_7$ (439.5) calc. 65.59 C, 5.73 H, 3.19 N; found 65.56 C, 5.69 H, 3.16 N. $^1$H-NMR ($CDCl_3$) $\delta$/ppm: 6.86 (1H, ABq, $J_{1,2} = 8.3$ Hz, H-2), 6.47 (1H, s, H-13), 6.19 (1H, ABq, H-1), 6.00 (2H, ABq, $J = 1.6$, $OCH_2O$), 4.84 (1H, s, H-9a), 4.20 (1H, m, H-8), 4.19 (1H, d, $J_{7a,7b} = 13.5$ Hz, H-7b), 4.11 (3H, s, C-4–$OCH_3$) 4.04 (3H, s, C-10–$OCH_3$), 3.94 (1H, q, $J_{14,CH_3} = 6.2$ Hz, H-14), 3.84 (3H, s, C-3–$OCH_3$), 3.48 (1H, dd, $J_{7a,8} = 4.0$ Hz, H-7a), 1.23 (3H, d, C-8–$CH_3$), 0.80 (3H, d, C-14–$CH_3$). $^{13}$C-NMR ($CDCl_3$), $\delta$/ppm: 10.9 (C-14–$CH_3$), 15.4 (C-8–$CH_3$), 39.3 (C-14), 41.3 (C-7), 56.6 (C-3–$OCH_3$), 60.0 (C-10–$OCH_3$), 62.5 (C-4–$OCH_3$), 68.0 (C-8), 70.8 (C-6a), 73.1 (C-9a), 98.8 (C-13), 101.2 ($OCH_2O$), 115.6 (C-1), 117.2 (C-2), 123.0 (C-4a), 124.0 (C-9b), 135.0 (C-11), 138.5 (C-13a), 140.9 (C-6b), 141.8 (C-10), 147.6 (C-4), 151.5 (C-12), 152.7 (C-3), 165.8 (C-5).

*1-Methyl-6,7-methylenedioxy-5,6,7'-trimethoxyisochroman-3-spiro-3'-phthalide* (**19**)

Narceonic acid (**18**, 1.0 g, 2.61 mmol) dissolved in acetic acid:hydrochloric acid (25 ml, 10:1) was heated at 80 °C for 2 h; then the solution was poured into water (150 ml). The precipitate was filtered off and dried; crystallization from benzene afforded compound **19**, m.p. 195–196 °C. For $C_{21}H_{20}O_8$ (400.4) calc. 63.00 C, 5.02 H; found 62.91 C, 4.96 H. $^1$H-NMR ($CDCl_3$) $\delta$/ppm: 7.23 (1H, ABq, $J_{4',5'} = 8.2$, H-4'). 7.14 (1H, ABq, H-5'), 6.38 (1H, s, H-8), 5.90 (2H, ABq, $J = 1.6$, $OCH_2O$), 5.19 (1H, q, $J_{1,CH_3} = 6.5$ Hz, H-1), 4.12 (3H, s, C-7'–$OCH_3$), 3.98 (3H, s, C-5–$OCH_3$), 3.92 (3H, s, C-6'–$OCH_3$), 3.23 (1H, ABq, $J_{4a,4b} = 17.1$ Hz, H-4a), 3.02 (1H, ABq, H-4b), 1.54 (3H, d, C-1–$CH_3$). $^{13}$C-NMR ($CDCl_3$) $\delta$/ppm: 21.5 (C-1–$CH_3$), 31.8 (C-4), 56.8 (C-6'–$OCH_3$), 59.4 (C-5–$OCH_3$), 62.3 (C-7'–$OCH_3$), 70.9 (C-1), 98.5 (C-3), 100.8 ($OCH_2O$), 103.8 (C-8), 113.2 (C-4a), 115.1 (C-5'), 117.0 (C-4'), 119.1 (C-7'a), 131.4 (C-8a), 134.5 (C-6), 140.3 (C-3'a), 142.6 (C-5), 146.2 (C-7'), 148.6 (C-7), 153.8 (C-6'), 166.8 (C-1').

## References

[1] Proksa B., Steiner B., Uhrínová S., Koóš M. (1992) Coll. Czech. Chem. Commun. **57**: 1516
[2] Hodková J., Veselý Z., Koblicová Z., Holubek J., Trojánek J. (1971) Lloydia **35**: 61
[3] Proksa B., Bobál M., Kováč Š. (1982) Chem. Papers **36**: 559
[4] Trojánek J., Koblicová Z., Veselý Z., Suchan V., Holubek J. (1975) Coll. Czech. Chem. Commun. **40**: 681
[5] Proksa B., Votický Z. (1980) Coll. Czech. Chem. Commun. **45**: 2125
[6] Freund M., Frankforter G. B. (1893) Ann. Chem. **277**: 20
[7] Hughes D. W., MacLean D. B. (1981) In: Manske R. H. F., Rodrigo, R. G. A. (eds) The Alkaloids, Vol. 18. Academic Press, New York, p. 217
[8] Uhrínová S., Uhrín D., Hricovíni M., Proksa B. (1992) Chem. Papers **46**: 339

*Received December 7, 1992. Accepted February 18, 1993*