HETEROCYCLES, Vol 20, No 8, 1983

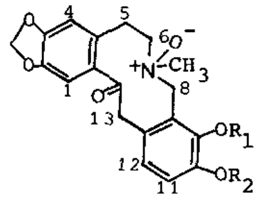
THE PYROLYSIS AND PHOTOLYSIS OF THE PROTOPINE TYPE ALKALOID N-OXIDES THE SYNTHESIS OF THE SECOBERBINES AND BENZO[C]PHENANTHRIDINES

Kinuko Iwasa* and Narao Takao
Kobe Women's College of Pharmacy, Motoyamakita-machi
Higashinada-ku, Kobe 658, Japan

Abstract — The pyrolysis of the N-oxides of the protopine-type alkaloids afforded three products, one of which was converted to the naturally occurring secoberbines. The photolysis of the N-oxides of the protopines supplied the benzo[c]phenanthridines as well as the one of the pyrolysis products.

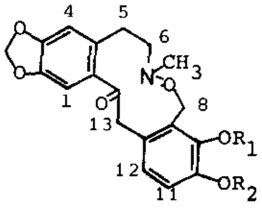
A number of the protopine and benzo[c]phenanthridine type alkaloids have been isolated from intact plants and cell cultures of Papaveraceae plants.[1] It has been proved that the benzo[c]phenanthridines are formed from the protopines in nature.[2] The characterization of a naturally occurring protopine N-oxide has previously been described.[3] This alkaloid might be an important biosynthetic intermediate between the benzo[c]phenanthridines and protopines. We now report the pyrolysis and photolysis of the N-oxides of protopine type alkaloids. We also described the preparation of the racemates of the naturally occurring secoberbines from a product of the pyrolysis.

Protopine N-oxide (1) was pyrolyzed by heating in a dry oven to 175°C. The resultant mixture of three products was separated by preparative TLC. The main product was isolated as an oil [60% yield m/z 369.1232, m/z 310 (base peak); $\nu_{max}^{CHCl_3}$ 1688 (CO) cm^{-1}] which was converted to the hydrochloride [mp 190-210°C (dec.), ν_{max}^{nujol} 2450-2100 ($\overset{+}{N}H$), 1685 (CO) cm^{-1}]. This product was regarded as the ring-enlarged compound (2) from its spectral data. ^1H nmr ($CDCl_3$, at 50°C) δ2.51 (3H, s, N-CH_3), 4.06 (2H, brs, H-13), 4.54 (2H, brs, H-8), 6.68 (1H, s, H-4), 6.89 (1H, s, H-1), 6.74 and 6.77 (each 1H, d, J = 8.0 Hz, H-11 and H-12); ^{13}C nmr ($CDCl_3$) δ28.70 (C-5), 44.92 (N-CH_3), 46.83 (C-13), 62.19 (C-6), 64.60 (C-8), 202.23 (CO). This reaction is analogous to the



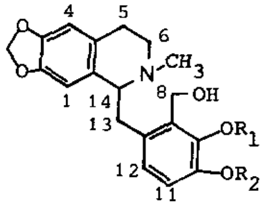
1 $R_1 + R_2 = CH_2$

8 $R_1 = R_2 = CH_3$



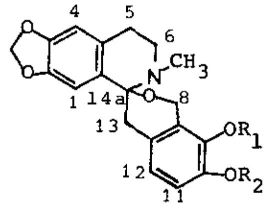
2 $R_1 + R_2 = CH_2$

9 $R_1 = R_2 = CH_3$



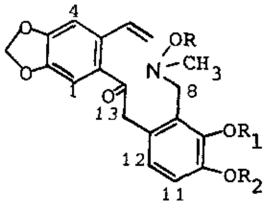
3 $R_1 + R_2 = CH_2$

12 $R_1 = R_2 = CH_3$



4 $R_1 + R_2 = CH_2$

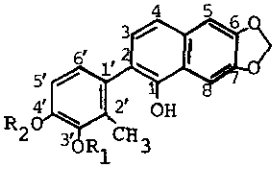
13 $R_1 = R_2 = CH_3$



5 $R_1 + R_2 = CH_2$ $R = H$

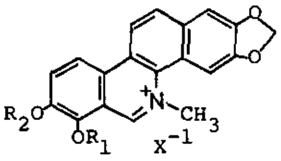
6 $R_1 + R_2 = CH_2$ $R = COCH_3$

10 $R_1 = R_2 = CH_3$ $R = H$



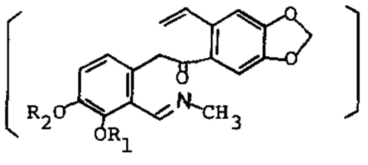
7 $R_1 + R_2 = CH_2$

11 $R_1 = R_2 = CH_3$



15 $R_1 + R_2 = CH_2$

16 $R_1 = R_2 = CH_3$



17

rearrangement of N-benzylamine oxides to O-benzylhydroxylamines, discovered by Meisenheimer[4] and studied by Cope[5]. Reduction of 2 with zinc in acetic acid afforded two products together with 32% of the starting material. The one was (±)-corydalisol (3) identified by comparison of the ir and nmr spectra with those of the natural authentic sample[6] [19.8% yield; mp 147-148°C; ν_{max}^{nujol} 3150(OH) cm^{-1}; CI mass m/z 356 (M^++1); ^1H nmr ($CDCl_3$) δ2.24 (3H, s, N-CH_3), 2.92 (1H, dd, J = 14.5 and 3.5 Hz, H-13), 2.97 (1H, dd, J = 14.5 and 7.5 Hz, H-13), 3.61 (1H, dd, J = 7.5 and 3.5 Hz, H-14), 4.50 and 4.62 (each 1H, d, J = 12.0 Hz, H-8); ^{13}C nmr ($CDCl_3$) δ24.46 (C-5), 41.10 (C-13), 42.97 (N-CH_3), 47.30 (C-6), 54.93 (C-8), 66.50 (C-14)]. The other was recognized as hypecorine (4)[7] [10% yield, mp 160-162°C] on the basis of its spectral data [m/z 353 (M^+), m/z 148 (base peak); ^1H nmr ($CDCl_3$) δ2.33 (3H, s, N-CH_3), 3.01 and 3.26 (each 1H, d, J = 16.0 Hz, H-13), 4.82 and 4.86 (each 1H, d, J = 16.0 Hz, H-8), 6.57 and 6.88 (each 1H, s, H-4 and H-1), 6.56 and 6.67 (each 1H, d, J = 8.0 Hz, H-11 and H-12); ^{13}C nmr ($CDCl_3$) δ23.45 (C-5), 35.84 (N-CH_3), 36.06 (C-13), 45.60 (C-6), 59.22 (C-8), 126.64 (C-13a)].

The second product [16% yield; mp 149-150°C; m/z 369 (M^+), m/z 175 (base peak)], isomer of compound (2), had infrared bands at 3180 (OH) and 1695 (CO) cm^{-1} and showed typical styrene-type signals [δ5.22 (1H, d, $\underline{J}_{AX}$ = 10.9 Hz, $CH_X=C\underline{H}_AH_B$), 5.52 (1H, d, $\underline{J}_{BX}$ = 17.3 Hz, $CH_X=CH_A\underline{H}_B$), 7.10 (1H, dd, $\underline{J}_{BX}$ and $\underline{J}_{AX}$ = 17.3 and 10.9 Hz, $C\underline{H}_X=CH_AH_B$)] as well as the other signals [δ2.54 (3H, s, N-CH_3), 3.73 and 4.18 (each 2H, brs, H-8 and H-13), 5.30 (1H, br, OH), 6.61 and 6.72 (each 1H, d, J = 8.0 Hz, H-11 and H-12), 7.03 and 7.22 (each 1H, s, H-1 and H-4)] in the ^1H nmr spectrum ($CDCl_3$).

The ^{13}C nmr spectrum showed the signals of δ45.63 (C-13), 47.62 (N-CH_3), 57.35 (C-8), 115.39 (C-6), 135.84 (C-5), and 200.18(CO). It was the hydroxylamine (5), formed by a Cope elimination reaction. Acetylation of 5 with Ac_2O in pyridine afforded the amorphous acetate (6); $\nu_{max}^{CHCl_3}$ 1760 and 1685 (CO) cm^{-1}; m/z 411 (M^+), m/z 352 (M^+- OAc), m/z 175 (base peak); ^1H nmr ($CDCl_3$) δ1.94 (3H, s, $COCH_3$).

The third product [4.6% yield; mp 159-162°C] had the following spectral data [ν_{max}^{nujol} 3500 (OH) cm^{-1}; m/z 322 (M^+, base peak); ^1H nmr ($CDCl_3$) δ2.02 (3H, s, C-CH_3), 5.28 (1H, s, OH), 6.79 (2H, s, H-5' and H-6'), 7.03 and 7.25 (each 1H, d, J = 8.2 Hz, H-3 and H-4), 7.10 and 7.53 (each 1H, s, H-5 and H-8); ^{13}C nmr ($CDCl_3$) δ12.43 (C-CH_3) 99.17 (C-3), 103.68 (C-8), 106.49 (C-6'), 118.83 (C-5), 123.71 (C-5'), 126.53 (C-4)] and was the phenolic compound (7) which might be formed by pyrolysis of the compound (5).

When allocryptopine N-oxide (8) was heated in a dry oven to about 129°C at 0.3-0.5

mmHg, the three products, **9**, **10**, and **11**, were also formed in analogy with protopine N-oxide. Compound (**9**) [21.9% yield; mp 148-151 °C] exhibited a carbonyl absorption band at 1695 cm^{-1} in the ir spectrum, and its mass spectrum showed *m/z* 385 ($\underline{M}^+$) and *m/z* 326 (base peak). In analogy with compound (**2**), reduction of **9** with zinc in acetic acid gave two products **12** and **13** in 60 and 1% yield, respectively. Compound (**12**), mp 105-107 °C, had the following spectral data [$\nu_{max}^{CHCl_3}$ 3400-3100 (OH) cm^{-1}; CI mass *m/z* 372 ($\underline{M}^+$+1); ^1H nmr ($CDCl_3$) δ2.20 (3H, s, N-CH_3), 3.60 (1H, dd, $\underline{J}$ = 7.0 and 3.5 Hz, H-14), 4.47 and 4.76 (each 1H, d, $\underline{J}$ = 11.4 Hz, H-8); ^{13}C nmr ($CDCl_3$) δ24.69 (C-5), 41.10 (C-13), 43.11 (N-CH_3), 47.53 (C-6), 55.10 (C-8), 66.39 (C-14)] and was identified by comparison with an authentic sample.[8] The mass spectrum of **13** had *m/z* 369 ($\underline{M}^+$) and *m/z* 164 (base peak). Its ^1H nmr ($CDCl_3$) showed an N-methyl group at δ2.39 and the C-8 protons at δ4.92.

The isomer **10** of **9** was obtained as the amorphous hydroxylamine (36.2% yield). Its ir spectrum showed a broad band in the region 3600-3300 cm^{-1} and a carbonyl absorption band at 1680 cm^{-1}. The mass spectrum had *m/z* 385 ($\underline{M}^+$) and *m/z* 175 (base peak).

Compound (**11**)[5.1% yield; mp 202-204 °C; *m/z* 338 ($\underline{M}^+$, base peak)] showed a hydroxyl band at 3545 cm^{-1} in its ir spectrum and had a C-methyl group at δ2.80 in the ^1H nmr ($CDCl_3$) and at δ13.19 in the ^{13}C nmr ($CDCl_3$).

Irradiation of a methanolic solution of protopine N-oxide under a nitrogen atomosphere furnished two products. The first product was identical with the compound (**2**) from pyrolysis of the N-oxide. The second product was proved to be the benzo[*c*]phenanthridine, sanguinarine (**15**) since it was reduced with sodium borohydride in methanol to dihydrosanguinarine which was identical with an authentic sample in the ir and ^1H nmr spectra. Compound **2** and **15** were obtained in 24 and 1% yield, respectively, along with 37% recovery of the starting N-oxide. Photolysis of allocryptopine N-oxide (**8**) also afforded **9** and chelerythrine (**16**) in 15 and 2% yield, respectively, along with 33% recovery of the starting N-oxide. Reduction of **16** with sodium borohydride in methanol led to dihydrochelerythrine identical with an authentic sample in terms of the ir and ^1H nmr spectra. The benzo[*c*]phenanthridines (**15** and **16**) would be obtained *via* the possible intermediate **17** by double cyclizations.

In conclusion, photolysis of the N-oxides of the protopine-type alkaloids was shown to supply the benzo[*c*]phenanthridines. The pyrolysis and photolysis products of the N-oxide, **2** and **9**, were converted into the secoberbines. The N-oxides of the protopines as well as the compound, **2**, **5**, **9**, and **10** may also play a role as an intermediate in the biosyntheses of various isoquinoline alkaloids.

ACKNOWLEDGMENTS The authors are grateful to Professor M. Hanaoka, Faculty of Pharmaceutical Sciences, Kanazawa University, for the generous gift of authentic sample of **12**. We also thank Dr. G. Nonaka, Faculty of Pharmaceutical Sciences, Kyushu University, for supplying the ir and nmr spectra of (+)-corydalisol.

REFERENCES

1. A. Ikuta, K. Syono, and T. Furuya, *Phytochemistry*, 1974, **13**, 2175.
   K. Iwasa and N. Takao, *Phytochemistry*, 1982, **21**, 611.
2. N. Takao, K. Iwasa, M. Kamigauchi, and M. Sugiura, *Chem. Pharm. Bull.*, 1976, **24**, 2859.
3. K. Iwasa, M. Okada, and N. Takao, *Phytochemistry*, 1983, **22**, 627.
4. J. Meisenheimer, *Ber.*, 1919, **52**, 1667; J. Meisenheimer, H. Greeske, and A. Willmersdorf, *ibid.*, 1922, **55**, 513.
5. R. F. Kleinschmidt and A. C. Cope, *J. Amer. Chem. Soc.*, 1944, **66**, 1929; A. C. Cope and P. H. Towle, *ibid.*, 1949, **71**, 3423; A. C. Cope, T. T. Foster, and P. H. Towle, *ibid.*, 1949, **71**, 3929.
6. G. Nonaka and I. Nishioka, *Chem. Pharm. Bull.*, 1975, **23**, 294; M. Shamma, A. S. Rothenberg, G. S. Jayatilake, and S. F. Hussain, *Tetrahedron*, 1978, **34**, 635. M. Shamma has described mp 127-128°C for (±)-Corydalisol different from ours.
7. M. Shamma and J. L. Moniot, “Isoquinoline Alkaloids Reseach 1972-1977,” p 263, Plenum Press, New York, 1978.
8. M. Hanaoka, K. Nagami, and T. Imanishi, *Heterocycles*, 1979, **12**, 497.

Received, 25th April, 1983