

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

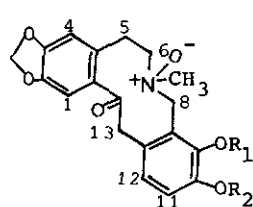
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Abstract — The pyrolysis of the N-oxides of the protopine-type alkaloids afforded three products, one of which was converted to the naturally occurring secoberbines. The photolysis of the N-oxides of the protopines supplied the benzo[c]phenanthridines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

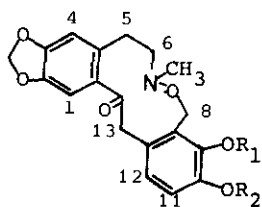
A number of the protopine and benzo[c]phenanthridine type alkaloids have been isolated from intact plants and cell cultures of Papaveraceae plants.¹ It has been proved that the benzo[c]phenanthridines are formed from the protopines in nature.² The characterization of a naturally occurring protopine N-oxide 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); $\nu_{\text{max}}^{\text{CHCl}_3}$ 1688 (CO) cm^{-1}] which was converted to the hydrochloride [mp 190-210°C (dec.), $\nu_{\text{max}}^{\text{nujol}}$ 2450-2100 (\ddagger NH), 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) δ 2.51 (3H, s, N-CH₃), 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) δ 28.70 (C-5), 44.92 (N-CH₃), 46.83 (C-13), 62.19 (C-6), 64.60 (C-8), 202.23 (CO). This reaction is analogous to the



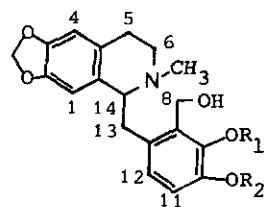
1 $R_1 + R_2 = CH_2$

8 $R_1 = R_2 = CH_3$



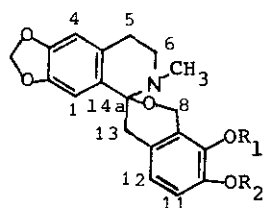
2 $R_1 + R_2 = CH_2$

9 $R_1 = R_2 = CH_3$



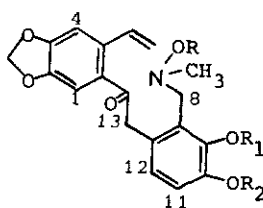
3 $R_1 + R_2 = CH_2$

12 $R_1 = R_2 = CH_3$



4 $R_1 + R_2 = CH_2$

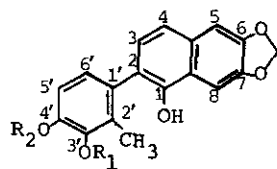
13 $R_1 = R_2 = CH_3$



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

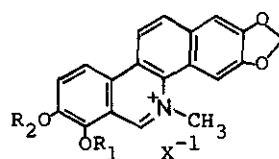
6 $R_1 + R_2 = CH_2$ $R = COCH_3$

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



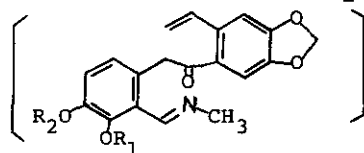
7 $R_1 + R_2 = CH_2$

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 Meisenheimer⁴ 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 (\pm)-corydalisol (3) identified by comparison of the ir and nmr spectra with those of the natural authentic sample⁶ [19.8% yield; mp 147-148°C; $\nu_{\max}^{\text{nujol}}$ 3150(OH) cm^{-1} ; CI mass m/z 356 ($M^+ + 1$); ^1H nmr (CDCl_3) δ 2.24 (3H, s, N-CH₃), 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) δ 24.46 (C-5), 41.10 (C-13), 42.97 (N-CH₃), 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) δ 2.33 (3H, s, N-CH₃), 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) δ 23.45 (C-5), 35.84 (N-CH₃), 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 [δ 5.22 (1H, d, $J_{\text{AX}} = 10.9$ Hz, $\text{CH}_X = \text{CH}_A\text{H}_B$), 5.52 (1H, d, $J_{\text{BX}} = 17.3$ Hz, $\text{CH}_X = \text{CH}_A\text{H}_B$), 7.10 (1H, dd, J_{BX} and $J_{\text{AX}} = 17.3$ and 10.9 Hz, $\text{CH}_X = \text{CH}_A\text{H}_B$)] as well as the other signals [δ 2.54 (3H, s, N-CH₃), 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 δ 45.63 (C-13), 47.62 (N-CH₃), 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); $\nu_{\max}^{\text{CHCl}_3}$ 1760 and 1685 (CO) cm^{-1} ; m/z 411 (M^+), m/z 352 ($M^+ - \text{OAc}$), m/z 175 (base peak); ^1H nmr (CDCl_3) δ 1.94 (3H, s, COCH_3).

The third product [4.6% yield; mp 159-162°C] had the following spectral data [$\nu_{\max}^{\text{nujol}}$ 3500 (OH) cm^{-1} ; m/z 322 (M^+ , base peak); ^1H nmr (CDCl_3) δ 2.02 (3H, s, C-CH₃), 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) δ 12.43 (C-CH₃) 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 (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 [$\nu_{\text{max}}^{\text{CHCl}_3}$ 3400-3100 (OH) cm⁻¹; CI mass m/z 372 (M⁺+1); ¹H nmr (CDCl₃) δ 2.20 (3H, s, N-CH₃), 3.60 (1H, dd, J=7.0 and 3.5 Hz, H-14), 4.47 and 4.76 (each 1H, d, J=11.4 Hz, H-8); ¹³C nmr (CDCl₃) δ 24.69 (C-5), 41.10 (C-13), 43.11 (N-CH₃), 47.53 (C-6), 55.10 (C-8), 66.39 (C-14)] and was identified by comparison with an authentic sample⁸. The mass spectrum of 13 had m/z 369 (M⁺) and m/z 164 (base peak). Its ¹H nmr (CDCl₃) showed an N-methyl group at δ 2.39 and the C-8 protons at δ 4.92.

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 (M⁺) and m/z 175 (base peak).

Compound (11) [5.1% yield; mp 202-204 °C; m/z 338 (M⁺, base peak)] showed a hydroxyl band at 3545 cm⁻¹ in its ir spectrum and had a C-methyl group at δ 2.80 in the ¹H nmr (CDCl₃) and at δ 13.19 in the ¹³C nmr (CDCl₃).

Irradiation of a methanolic solution of protopine N-oxide under a nitrogen atmosphere 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.

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