HETEROCYCLES, Vol. 5, 1976

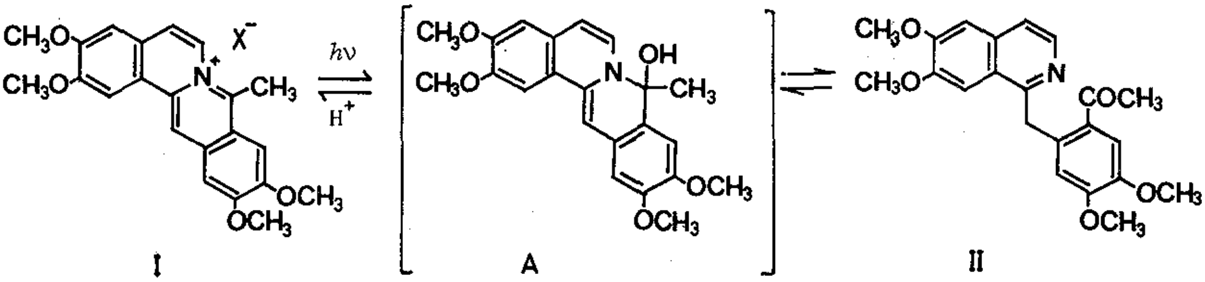
OXIDATIVE TRANSFORMATION OF DIHYDROCORALYNE TO 6'-ACETYLPAPAVERALDINE

Jiro Imai and Yoshikazu Kondo*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

Dihydrocoralyne III, obtained by partial reduction of coralynium salts in 86% yield, was autoxidized in solution at pH 8 to phenolbetaine IV in quantitative yield. Treatment of IV with *m*-chloroperbenzoic acid gave 6'-acetylpapaveraldine in 65% yield. Irradiation of III in the presence of air gave V in quantitative yield. The oxidative cleavage of IV was satisfactorily explained *via* the oxaziridine intermediate.

The antileukemic coralyne salts[1] underwent hydration across the N-C double bond under the photo-exciting or strong basic conditions[2], the resultant carbinolamine (A) proceeding concominant cleavage to acetylpapaverine II. The reaction I → II was reversible in solution and II was readily converted

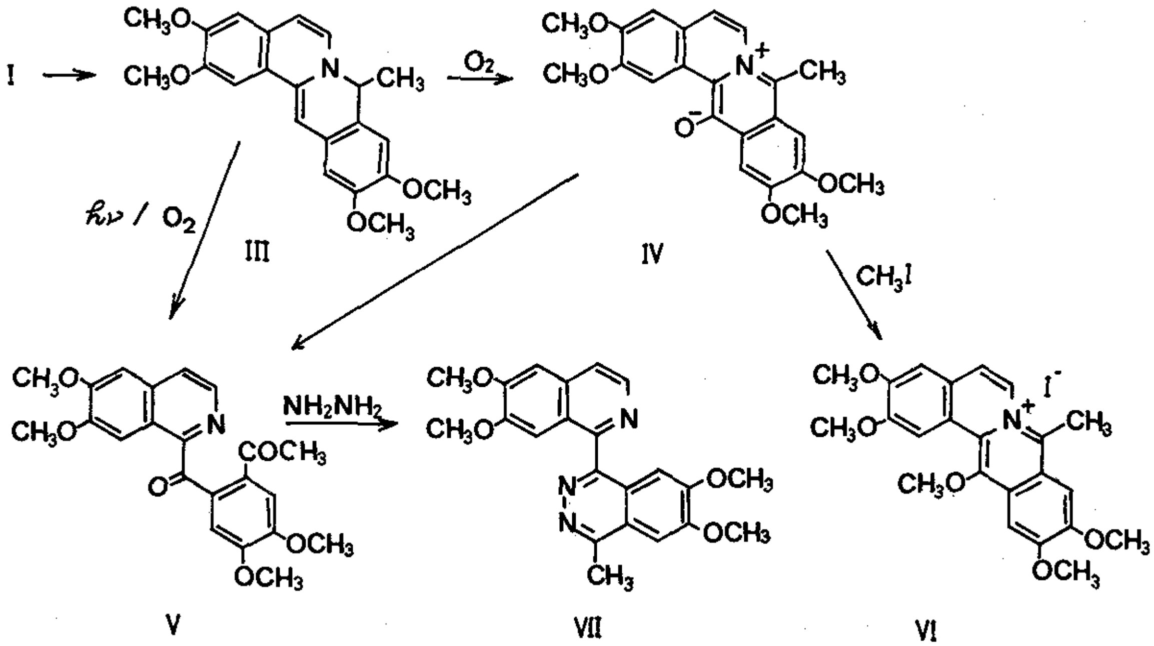


Scheme I

to I *even* at physiological pH (Scheme 1).

In this communication we wish to report the conversion of coralyne to *6'-acetylpapaveraldine*, in which a facile formation of phenolbetaine IV is shown.

Treatment of coralynium salt[3] (I, X=SO_3CH_2COOH) with zinc powder in 30% acetic acid led to dihydrocoralyne III, $C_{22}H_{23}NO_4$ mp 175-177°, nmr (δ) benzene-d_6; 1.27 (3H, d, J=7Hz, >CH-C$\underline{H}_3$), 3.44, 3.54, 3.56 and 3.62 (3H×4, each s, -OC$\underline{H}_3$), 4.49 (1H, q, J=7Hz, >C$\underline{H}$-CH_3), 5.68 (1H, d, J=8Hz, -C$\underline{H}$=CH-N<), 6.13 (1H, d, J=8Hz, -CH=C$\underline{H}$N<), 5.96, 6.35, 6.38 and 6.55 (1H×4, each s, Ar-$\underline{H}$); mass (m/e): 365 (M^+), in 85.9% yield. When formic acid was used in the place of acetic acid, the reduction of I gave coralydine, $C_{22}H_{27}NO_4$, mp 146-148°, in 88% yield[4].

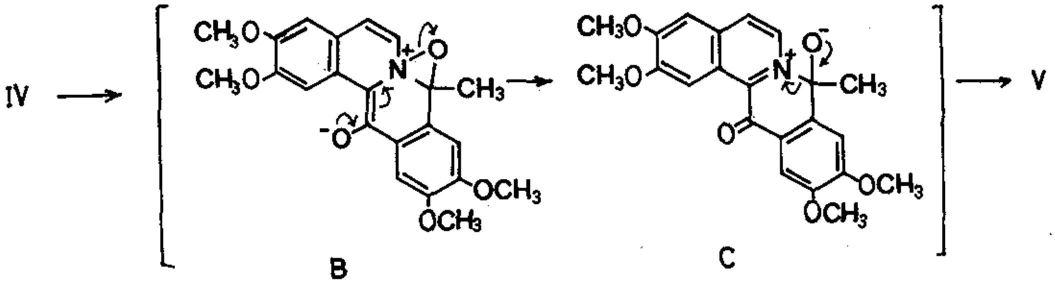


Scheme 2

III when kept in hot ethanol at pH 8 led to smooth autoxidation to the phenolbetaine IV, $C_{22}H_{21}NO_5$, mp 191-193°, nmr (δ) $CDCl_3$: 2.80 (3H, s, Ar-C$\underline{H}_3$), 3.98 (6H, s, -OC$\underline{H}_3$), 4.17 and 4.22 (3H×2, each s, -OC$\underline{H}_3$), 6.83 (1H, s, Ar-$\underline{H}$), 6.96 (1H, s, Ar-$\underline{H}$), 7.14 (1H, d, J=9Hz, -C$\underline{H}$=CH-N<), 7.82 (1H, d, J=9Hz, -CH=C$\underline{H}$-N<), 8.17 (1H, s, Ar-$\underline{H}$), 10.83 (1H, s, Ar-$\underline{H}$); ms (m/e): 379 (M^+), in quantitative yield. The structure of IV was unequivocally confirmed by its conversion to 13-methoxycoralynium iodide VI, $C_{23}H_{24}NO_5I$, mp 182-184° (dec), nmr (δ) d_6-DMSO: 2.50 (3H, s, Ar-C$\underline{H}_3$), 3.96 (6H, s, -OC$\underline{H}_3$), 4.06, 4.13 and 4.18 (3H×3, each s, -OC$\underline{H}_3$), 7.57 (2H, s, Ar-$\underline{H}$), 7.81 (1H, s, Ar-$\underline{H}$), 7.90 (1H, d, J=8Hz, -C$\underline{H}$=CH-N<), 8.86 (1H, d, J=8Hz, -CH=C$\underline{H}$-N<), 8.97 (1H, s, Ar-$\underline{H}$). As previously reported[5], berberinium phenolbetaine showed to be stable to perbenzoic acid. In contrast to it, treatment of IV with 1.2 equivalents of *m*-chloroperbenzoic acid in dichloromethane showed rapid fading of the solution to provide 6'-acetylpapaveraldine V, $C_{22}H_{21}NO_6$, mp 199-200°, nmr (δ) $CDCl_3$: 2.31 (3H, s, Ar-COC$\underline{H}_3$), 3.93, 3.96, 4.00 and 4.08 (3H×4, each s, -OC$\underline{H}_3$), 7.01, 7.11 and 7.15 (1H×3, each s, Ar-$\underline{H}$), 7.50 (1H, d, J=6Hz, -C$\underline{H}$=CH-N<), 8.17 (1H, d, J=6Hz, -CH=C$\underline{H}$-N<), 8.45 (1H, s, Ar-$\underline{H}$); ms (m/e): 395 (M^+), 352 (M^+-$COCH_3$); ir (cm^{-1}): 1670, 1355, in 65.0% yield. Remarkable acceleration of the reaction III→V was observed when a solution of III in chloroform was irradiated with a 375w photoflood lamp in the presence of air. The yield of V was quantitative.

The oxidative cleavage would be initiated by the formation of the oxaziridine intermediate and proceed by the sequence of steps IV→B→C→V shown in Scheme 3.

The oxidation of II to V either with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in methanol or with oxygen in chloroform gave unsatisfactory results



Scheme 3

in our hand.

Treatment of V with hydrazine hydrate gave the phthalazine derivative VII, $C_{22}H_{21}N_3O_4$, mp 229-231°, nmr (δ) $CDCl_3$: 3.02 (3H, s, Ar-C$\underline{H}_3$), 3.77 (6H, s, -OC$\underline{H}_3$), 3.99 and 4.03 (3H×2, each s, -OC$\underline{H}_3$), 7.09 and 7.23 (2H×2, each s, Ar-$\underline{H}$), 7.56 (1H, d, J=6Hz, -C$\underline{H}$=CH-N<), 8.45 (1H, d, J=6Hz, -CH=C$\underline{H}$-N<); ms (m/e): 391 (M^+), 376, 360; ir (cm^{-1}): no ν_{CO}, 1620, 1610.

REFERENCES

1 K. Y. Zee-Cheng, K. D. Paull, and C. C. Cheng, *J. Med. Chem., 1974,* **17**, *347.*

2 M. J. Cho, A. J. Repta, C. C. Cheng, K. Y. Zee-Cheng, T. Higuchi, and I. H. Pitman, *J. Pharm. Sci., 1975,* **64**, *1825* and references cited therein.

3 W. Schneider and K. Schroeter, *Ber., 1920,* **53**, *1459;* W. Wiegrebe, *Deutsche Apotheker-Zeitung, 1966,* **106**, *1546;* K. Y. Zee-Cheng and C. C. Cheng, *J. Pharm. Sci., 1972,* **61**, *969.*

4 W. Awe, J. Thum, and H. Wichmann, *Arch. Pharm., 1960,* **293**, *907.*

5 P. W. Jeffs and J. D. Scharver, *J. Org. Chem., 1975,* **40**, *644.*

Received, 12th July, 1976