[Chem. Pharm. Bull. 23(7)1561—1564(1975)] UDC 547.94.04 : 547.567.04

Utilization of Protopine and Related Alkaloids. IX.[1] Formation of 4b,6-Epidioxybenzo[*c*]phenanthridine Derivative and Its Reaction with 2,3-Dichloro-5,6-dicyanobenzoquinone

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(Received December 16, 1974)

The carbinolamine **2** is oxidized with oxygen to give the peroxide **6** whose structure is established on the basis of the spectral properties and the structure of the hexahydrochelerythrine **7** obtained on the sodium borohydride reduction. Formation pathway of the peroxide **6** is examined. Treatment of the peroxide **6** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) affords the keto amide **10**, two nitriles **11** and **12**, and keto aldehyde **13**. Structures for these compounds are mainly proved by the spectral data. Further, it is examined that these compounds are probably formed by oxidation and reduction of the peroxide **6** with DDQ and 2,3-dichloro-5,6-dicyanohydroquinone resulted from DDQ during reaction.

We previously reported the synthesis of an analogue of corynoline, *trans*-11-hydroxy-10b-methyl-4b,5,6,10b,11,12-hexahydrochelerythrine, in which the important steps were conversion of the dihydroisoquinoline **1** into the carbinolamine **2** and subsequently dehydrogenation of the lactam **3** to the didehydrolactam **4**.[1,3] While attempts to obtain the ether **5** from **2** were enormously carried out, it was found that **2** was extremely sensitive to oxidation, giving unidentified products. This paper is concerned with a product which was obtained by the oxygen oxidation of **2** and its reaction with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

On oxidation with air or molecular oxygen at room temperature **2** gave the peroxide **6**. The presence of the 4b,6-epidioxy group in **6** is confirmed by the spectral properties which

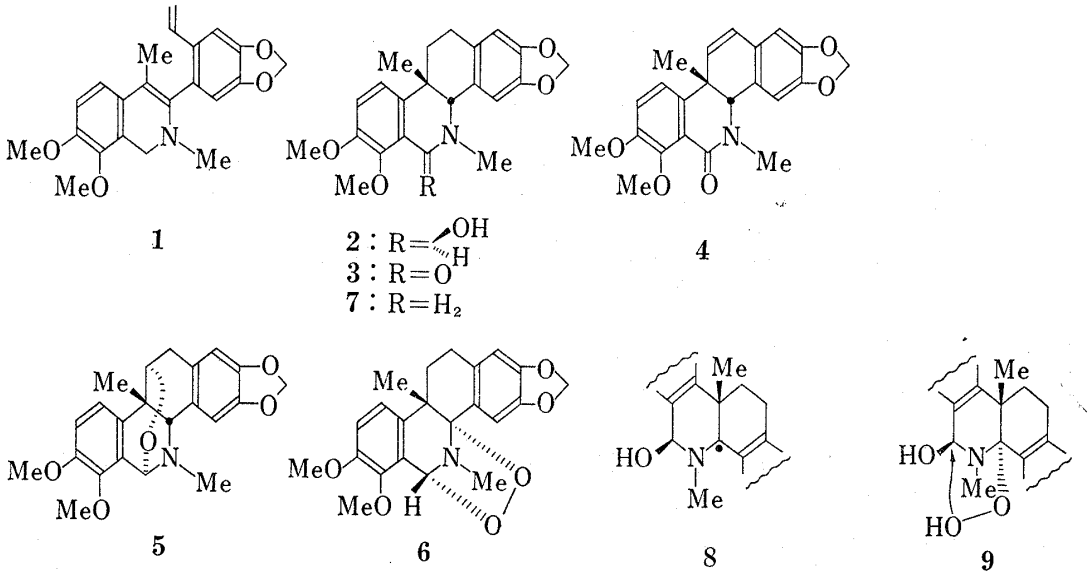
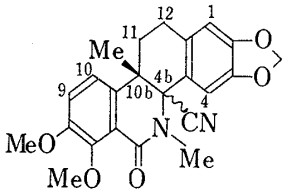


Chart 1

1) Part VIII: M. Onda, K. Yuasa, and J. Okada, *Chem. Pharm. Bull.* (Tokyo), **22**, 2365 (1974).
2) Location: *Minato-ku, Tokyo 108, Japan.*
3) M. Onda, K. Yuasa, J. Okada, K. Kataoka (née Yonezawa), and K. Abe, *Chem. Pharm. Bull.* (Tokyo), **21**, 1333 (1973).

displays no signal for the 4b-H in the nuclear magnetic resonance (NMR) spectrum and an intense band due to the O-O group (870 cm^{-1}) instead of that of the OH group in the infrared (IR) spectrum (CCl_4). The fact that **6** was reduced with sodium borohydride to give the hexahydrochelerythrine **7** is in accord with the above observations. 4b-Epicorynoline, whose B/C configuration is *trans*, shows the NMR signals for the 4-H and N-Me group at δ 7.17 and 2.47, respectively.[4a] Corynoline[4] and other analogs,[1,3] whose B/C configuration is *cis*, exhibit signals for the corresponding protons at δ *ca.* 6.7 and *ca.* 2.25, respectively. The *trans* configuration suffers from steric repulsion between the 4-H and N-Me group. The *cis* one with the axial 10b-Me group to C ring is released from the above-mentioned repulsion. Differences in the chemical shifts of these protons in the *cis* and *trans* isomers are mainly attributed to such a steric situation. Hence, **6** showing the NMR signals for the 4-H and N-Me group at δ 7.33 and 2.40, respectively, can be assigned to be *trans*. A likely formation pathway of **6** would be considered as follows. The radical **8**, which is formed from **2** by the hydrogen abstraction, affords the hydroperoxide **9** by stereoselective attack of the HOO radical from the less hindered side. Subsequently, the back side attack of the hydroperoxy group at C-6 converts **9** into **6** by intramolecular dehydration. If **6** is formed *via* the above-mentioned pathway, since the B/C configuration in **6** is *trans*, the 6-OH group should be *cis* to the 10b-Me group in **9** and, also, in **2**. This may be confirmed on the basis of the NMR examination. The *cis* B/C configuration with the axial 10b-Me group to C ring in **7** was proved by the presence of the nuclear Overhauser effect between the 4b-H and 10b-Me group and the chemical shifts of these protons.[3] Since **7** was derived by the sodium borohydride reduction of **2**,[3] the stereochemistry of B/C in **2** is the same as that in **7**. The NMR signals for the 4b-H in **2** and **7** appear at δ 3.84 and 3.08, respectively. Down-field shift of the 4b-H in **2** can be explained by the *cis* 6-OH group to the 4b-H (1,3-diaxial interaction). Accordingly, these facts support the *cis* 6-OH group to the 10b-Me group.

TABLE I. NMR Data of the Nitriles **11** and **12**[a]



	1-H	4-H	9-H	10-H	11- and 12-H_2	OCH_2O	OMe	NMe	10b-Me
11, *trans*[b]	6.65	6.95	6.99,d *J* 9	7.05,d *J* 9	3.12—1.80	6.00[c]	4.02 3.88	3.14	1.18
12, *cis*[d]	6.62	7.55	6.95,d *J* 9	7.11,d *J* 9	3.13—1.74	6.00[c]	3.95 3.88	3.23	1.60

a) chemical shift (δ); coupling constant (Hz)
b) 100 MHz
c) fine splitting
d) 60 MHz

The peroxide **6** was treated with DDQ for the purpose of inserting the double bond at C-11 and C-12. On the contrary to expectation, the keto amide **10** (20%), two nitriles **11** (12%) and **12** (24%), and keto aldehyde **13** (19%) were obtained. The keto amide **10** and keto aldehyde **13** were identified as 2,3-dimethoxy-6-(1′,2′,3′,4′-tetrahydro-2′-methyl-6′,7′-methylenedioxy-1′-oxo-2′-naphthyl)-N-methylbenzamide and -benzaldehyde, respectively, by the IR and NMR spectra (see Experimental). The nitriles **11** and **12** exhibit bands due

4) *a*) N. Takao, H.-W. Bersch, and S. Takao, *Chem. Pharm. Bull.* (Tokyo), **21**, 1096 (1973); *b*) N. Takao, *Chem. Pharm. Bull.* (Tokyo), **11**, 1312 (1963); M.H. Benn and R.E. Michell, *Can. J. Chem.*, **47**, 3701 (1969).

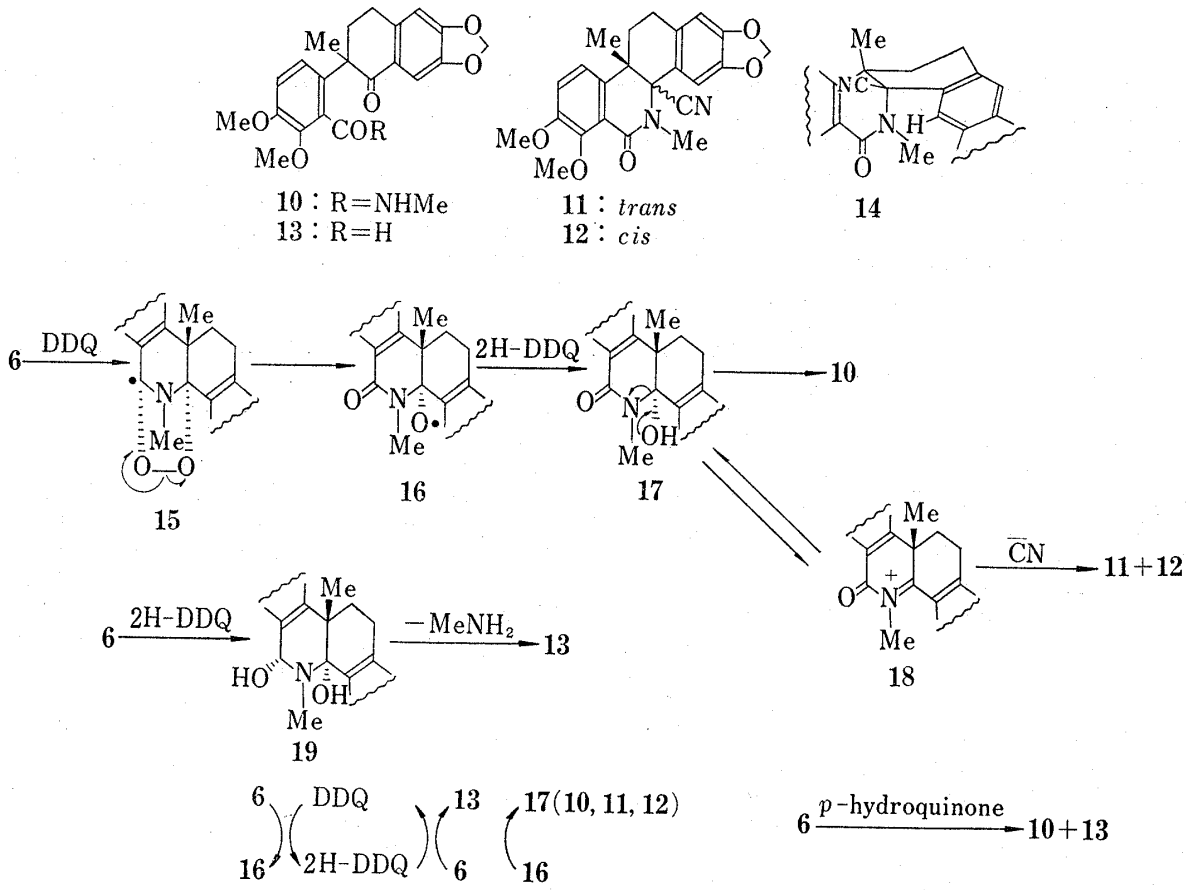


Chart 2

to the CN (2210 cm^{-1}) and lactam groups (**11**: 1650 and **12**: 1655 cm^{-1}) in the IR spectra ($CHCl_3$). Since **11** and **12** afforded **7** on reduction with lithium aluminum hydride, both compounds are considered to be the stereoisomers. The position of the CN group is deduced to be C-4b on the basis of the NMR spectra showing the absence of the 4b-H signal. The NMR data of **11** and **12** are recorded in Table I. The conformation of the *cis* isomer with the axial 10b-Me group to C ring is more stable than another one because of release from the steric repulsion between the 4-H and N-Me group. Hence, the 4-H and 10b-Me group in the *cis* isomer locate in the deshielding regions of the CN group as depicted in the stereostructure **14**. Such a steric situation is probably responsible for the large deshielding of these protons in **12**. Thus, **12** can be assigned to be *cis*-4b-cyano-10b-methyl-6-oxo-4b,5,6,10b,11,12-hexahydrochelerythrine.

Finally, we briefly examine formation pathway of the above reaction products. The first step of oxidation would be the hydrogen abstraction at C-6 in **6** by DDQ, giving the radical **15** and 2,3-dichloro-5,6-dicyanohydroquinone (2H-DDQ). The radical **15** rearranges to the radical **16** which is converted into the carbinolamide **17** by the hydrogen transfer from 2H-DDQ. Subsequent bond fission affords **10**. Another pathway, dehydroxylation, from **17** gives the iminium salt **18**, from which **11** and **12** may be formed by attack of the CN ion originated from DDQ or 2H-DDQ. The predominant formation of **12** would be ascribed to the difference in the steric stability of the isomers (product development control). On the other hand, **6** would give the dicarbinolamine **19** by reduction with 2H-DDQ, from which elimination of methylamine affords **13**. This deduction is supported by the fact that treatment of **6** with *p*-hydroquinone gave **10** and **13**.

The keto aldehyde **13** was obtained on oxidation of **2** with lead tetraacetate. This reaction, also, is considered to pass through the similar intermediate containing the 4b-OAc group to **19** which was derived from **2** by attack of lead tetraacetate at C-4b.

Experimental

Melting points were determined on a micro hot-stage and are not corrected. IR spectra were recorded on a JASCO IR-G. NMR spectra were measured with a Varian T-60 and a JNM-4H-100 in a chloroform-*d* solution. Mass spectra were taken on a JEOL JMS-OlS.

***trans*-4b,6-Epidioxy-10b-methyl-4b,5,6,10b,11,12-hexahydrochelerythrine 6**——a) A solution of **2** (110 mg) in benzene (10 ml) was allowed to stand at room temperature for 2 weeks. After removal of solvent *in vacuo*, the remaining residue was chromatographed on neutral Al_2O_3 (grade III, 10 g) by using benzene as eluent to give **6** (70 mg) as plates of mp 143—145° (from benzene–ether). NMR: δ 7.33 (s, 4-H), 6.99 (d, J 8 Hz, 10-H), 6.88 (d, J 8 Hz, 9-H), 6.60 (s, 1-H), 5.83 (s, OCH_2O), 3.88 (s, OMe), 3.85 (s, OMe), 2.78 (m, 12-H_2), 2.40 (s, NMe), 2.37 (m, hidden in the NMe signal ,11-H_A), 1.80 (dq, J 14, 5, and 3 Hz, 11-H_B), 1.27 (s, 10b-Me). Mass Spectrum *m/e*: M^+, 397.1528. Calcd. for $C_{22}H_{23}O_6N$: 397.1525. *Anal.* Calcd. for $C_{22}H_{23}O_6N$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.55; H, 5.79; N, 3.54.

b) Into a solution of **2** (584 mg) in benzene (10 ml) was introduced O_2 at room temperature for 33 hr. After work-up as mentioned above, **6** (332 mg) was obtained as plates of mp 143—145°.

Reduction of 6 with $NaBH_4$——To a solution of **6** (85 mg) in benzene–methanol (1: 1, v/v) (16 ml) was added $NaBH_4$ (50 mg). The reaction mixture was refluxed for 12 hr. After work-up, the remaining residue (85 mg) was chromatographed on neutral Al_2O_3 (grade III, 9 g) by using benzene as eluent to give **7** (50 mg) as plates of mp 134—137° which was identified with an authentic sample[3] by mixed mp and comparisons of the IR and NMR spectra.

Reaction of 6 with DDQ——To a solution of **6** (85 mg) in chloroform (3 ml) was added a solution of DDQ (60 mg) in chloroform (7 ml). The reaction mixture was stirred at room temperature for 24 hr and then filtered to remove off the precipitates. After removal of solvent *in vacuo*, the residue was taken in benzene and washed with 5% aq. NaOH and H_2O. Work-up gave an oil whose preparative thin-layer chromatography (TLC) on silica gel plates (0.5 mm) using benzene–ethyl acetate (5: 1, v/v) gave the following four compounds. The zone with *Rf* 0.14 afforded **10** (18 mg, 20%) as a syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1660 (CO), 1650 (CON). NMR: δ 7.45 (s, 8′-H), 7.00 (d, J 8 Hz, 5-H), 6.80 (d, J 8 Hz, 4-H), 6.60 (s, 5′-H), 5.98 (s, OCH_2O), 5.80 (q, J 5 Hz, NH),[5] 3.83 (s, OMe), 3.80 (s, OMe), 3.17—2.56 (m, 3H), 2.73 (d, J 5 Hz, NMe),[6] 1.83 (m, 1H), 1.58 (s, 2′-Me). Mass Spectrum *m/e*: M^+, 397.1526. Calcd. for $C_{22}H_{23}O_6N$: 397.1525. The zone with *Rf* 0.24 gave **11** (12 mg, 12%) which on recrystallization from benzene–ether gave plates of mp 194.5—195.5°. Mass Spectrum *m/e*: M^+, 406.1528. Calcd. for $C_{23}H_{22}O_5N_2$: 406.1528. The zone with *Rf* 0.47 afforded **13** (15 mg, 19%) which on recrystallization from chloroform–*n*-hexane gave plates of mp 207—210°. IR ν_{max}^{KBr} cm^{-1}: 2750 (CHO), 1700 (CHO), 1660 (CO). NMR: δ 10.4 (CHO), 7.51 (s, 8′-H), 7.24 (d, J 8 Hz, 5-H), 7.09 (d, J 8 Hz, 4-H), 6.65 (s, 5′-H), 5.97 (s, OCH_2O), 3.93 (s, OMe), 3.90 (s, OMe), 3.20—2.50 (m, 3H), 1.78 (m, 1H), 1.61 (s, 2′-Me). Mass Spectrum *m/e*: M^+, 368.1258. Calcd. for $C_{21}H_{20}O_6$: 368.1259. *Anal.* Calcd. for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.42; H, 5.38. The zone with *Rf* 0.54 gave **12** (21 mg, 24%) which on recrystallization from chloroform–*n*-hexane gave plates of mp 173.5—177.5°. Mass Spectrum *m/e*: M^+, 406.1483. Calcd. for $C_{23}H_{22}O_5N_2$: 406.1528. *Anal.* Calcd. for $C_{23}H_{22}O_5N_2$: C, 67.97; H, 5.46; N, 6.89. Found: C, 67.62; H, 5.42; N, 6.75.

Reductions of 11 and 12 with $LiAlH_4$——a) A mixture of **12** (40 mg) and $LiAlH_4$ (19 mg) in dioxane (3 ml) was refluxed for 5 hr. Work-up gave a solid (31 mg) which showed a single spot on TLC. Recrystallization from ether afforded **7** (12 mg) as plates of mp 134.5—137° which was identified with an authentic sample[3] by mixed mp and comparisons of the IR and NMR spectra.

b) A mixture of **11** (18 mg) and $LiAlH_4$ (5 mg) in dioxane (1 ml) was treated as mentioned above. The remaining residue was purified by preparative TLC as mentioned above to give **7** (8 mg) which on recrystallization from ether gave plates of mp 130—131° and identified with an authentic sample[3] by mixed mp and comparison of the IR spectrum.

Reaction of 6 with *p*-Hydroquinone——A solution of **6** (7 mg) and *p*-hydroquinone (2.4 mg) in ethanol (4 ml) was refluxed for 16 hr. After work-up, the remaining residue was purified by preparative TLC as mentioned above to give **10** (2.4 mg) and **13** (2.8 mg) whose structures were established by TLC and comparisons of the IR spectra.

Oxidation of 2 with $Pb(OAc)_4$——A mixture of **2** (358 mg), $Pb(OAc)_4$ (830 mg), and I_2 (150 mg) in benzene (30 ml) was refluxed for 1 hr. The reaction mixture was washed with H_2O, 10% aq. $Na_2S_2O_3$, and then H_2O. After drying over Na_2SO_4, work-up gave an oil (340 mg) whose chromatography on silica gel (35 g) using benzene–ethyl acetate (4: 1, v/v) as eluent gave **13** (100 mg) as plates of mp 207—210° (from chloroform–ether).

5) On addition of D_2O this signal disappeared.
6) On addition of D_2O this signal changed to a singlet.