[Chem. Pharm. Bull.
32(3) 909—912 (1984)]

Utilization of Protopine and Related Alkaloids. XV.[1] Photolysis of 4-Methyl-1-oxoanhydroberberine

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(Received June 28, 1983)

Photolysis of 4-methyl-1-oxoanhydroberberine (**9**) in the presence of nitrosobenzene gives two isomeric photoadducts (**11**) and (**12**). In the presence of diethyl azodicarboxylate, **9** affords two different types of photoadduct (**13**) and (**14**). These photoadducts are considered to be formed by the photochemically allowed $[2_s+2_s+2_a]$ cycloaddition reactions.

Keywords——benzo[*c*]phenanthridine; photolysis; $[2_s+2_s+2_a]$ cycloaddition reaction; mechanism; ^{1}H-NMR

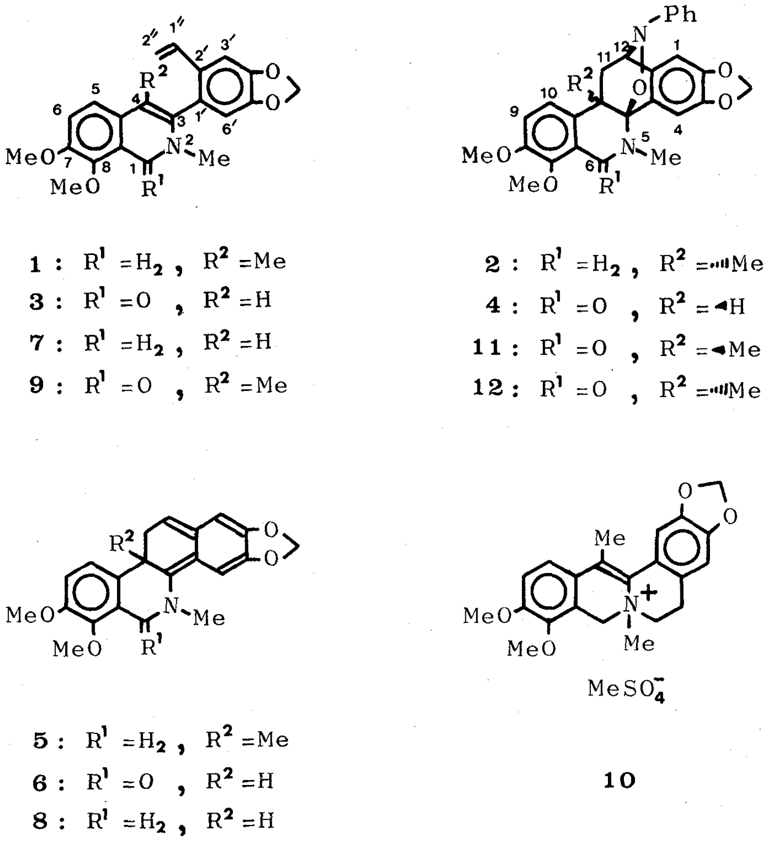
Photolysis of 4-methylanhydroberberine (**1**) in the presence of nitrosobenzene gave the 10bα-methyl-4bβ,12β-epoxyimine (**2**),[2] and 1-oxoanhydroberberine (**3**) afforded the 10bβ-hydro-4bβ,12β-epoxyimine (**4**).[3] The Diels–Alder reactions of the initial photoproducts (**5**) and (**6**), formed by the electrocyclic reactions of "hexatrienes," with nitrosobenzene were thought to afford **2** and **4**, respectively. The exclusive and stereoselective formation of these compounds can be rationalized in terms of the transition states in the Diels–Alder reactions. On the other hand, in spite of the formation of the initial photoproduct (**8**),[4] photolysis of anhydroberberine (**7**) gave no photoadduct with nitrosobenzene. As a continuation of this work, we now report the photolysis of 4-methyl-1-oxoanhydroberberine (**9**).

13-Methyldihydroberberine methosulfate (**10**), derived from α-allocryptopine or berberinum chloride, gave **1** on Hofmann degradation,[5] and **1** was oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and then potassium ferricyanide to give **9** (overall 69%).

Photolysis of **9** in the presence of nitrosobenzene afforded the 10bβ-methyl-4bβ,12β-epoxyimine (**11**) (32%) and the 10bα-methyl isomer (**12**) (29%). Distinction between the two isomers was based on the 10b-methyl chemical shifts in the proton magnetic resonance (^{1}H-NMR) spectra (**11**, δ 1.62; **12**, δ 0.70; **2**, δ 0.68[2]). On the other hand, photolysis of **9** in the absence of nitrosobenzene gave no photoproduct, showing that the electrocyclic reaction of "hexatriene" did not occur.

From the results obtained above, it is clear that **11** and **12** were formed by two $[2_s+2_s+2_a]$ cycloaddition reactions (photochemically allowed). Owing to nonbonded interaction between the 4-hydrogen and the 5-methyl group in **12**, **11** is thought to be more stable than **12**. If "product-like" control is operative in the photolysis, **11** would be stereoselectively formed.[3] When nitrosobenzene suprafacially approaches the 3- and 1″-carbons and its phenyl group points to the 3-benzene moiety in **9**, the *supra* and *antara* faces of the 4- and 2″-carbons are sterically uncrowded and are available for two *supra*–*antara* combinations of the two carbons. Thus, the nonstereoselective formation of **11** and **12** would be conducted by "reactant-like" control *via* two $[2_s+2_s+2_a]$ paths, in contrast to the exclusively stereoselective formation of **2**.[2]

Photolysis of **9** in the presence of diethyl azodicarboxylate gave the 10bβ-methyl-4bβ,12β-hydrazine (**13**) (16%) and the α-tetralone (**14**) (13.5%). The structure of **13** was established on the basis of the 10b-methyl chemical shift (δ 1.44) in the ^{1}H-NMR spectrum.



1 : $R^1 = H_2$, $R^2 = Me$
3 : $R^1 = O$, $R^2 = H$
7 : $R^1 = H_2$, $R^2 = H$
9 : $R^1 = O$, $R^2 = Me$

2 : $R^1 = H_2$, $R^2 = $ ···Me
4 : $R^1 = O$, $R^2 = $ ◂H
11 : $R^1 = O$, $R^2 = $ ◂Me
12 : $R^1 = O$, $R^2 = $ ···Me

5 : $R^1 = H_2$, $R^2 = Me$
6 : $R^1 = O$, $R^2 = H$
8 : $R^1 = H_2$, $R^2 = H$

10

Chart 1

The infrared (IR) and ^{1}H-NMR spectra of **14** showed a ketonic carbonyl group (1710 cm^{-1}) and an N-methylcarbamoyl function [δ 5.78 (1H, q, $J=5$ Hz, N$\underline{H}$Me) and 2.63 (3H, d, $J=5$ Hz, NH$\underline{Me}$)], respectively.

The formation of **13** as a sole photoadduct (as in the cases of **11** and **12**) reveals that the photolysis proceeded *via* a $[2_s+2_s+2_a]$ path. Owing to nonbonded interaction between the inner N-ethoxycarbonyl function and the 5- or 10b-methyl group, **13** is expected to be less stable than the 10bα-methyl isomer. Thus, the exclusive and stereoselective formation of **13** cannot be explained by "product-like" control. When diethyl azodicarboxylate suprafacially approaches the 3- and 1$''$-carbons, the inner N-ethoxycarbonyl function would be directed toward the 4-methyl group in order to avoid nonbonded interaction with the 2-methyl group in **9**, as shown in Chart 2 (A). As a result, the *supra* face of the 4-carbon is sterically crowded, and the 2$''$-carbon approaches the 4-carbon from the *antara* face.[6] Thus, the formation of **13** is likely to be conducted by "reactant-like" control *via* a $[2_s+2_s+2_a]$ path.

The α-tetralone (**14**) was not formed on irradiation of **13** in benzene under the same conditions as above. A possible pathway to **14** may be as follows. Photo-hydrolysis[7] of **9** would partly give a ketone (**15**), which would isomerize to an enol (**16**). Photolysis of **16** with diethyl azodicarboxylate would afford a photoadduct (**17**) *via* either of two possible $[2_s+2_s+2_a]$ paths and subsequently, **17** would isomerize to **14**.

Reduction of **12** with lithium aluminium hydride stereoselectively afforded the aniline (**18**) (89%),[2] from which the corynoline analog (**19**) was easily derived.[2] In contrast, **11** was inert to the reducing agent, giving no product.

The stereochemistry of the photoadducts obtained above will be discussed in detail on the basis of the ^{1}H- and ^{13}C-NMR spectral data in a separate paper.

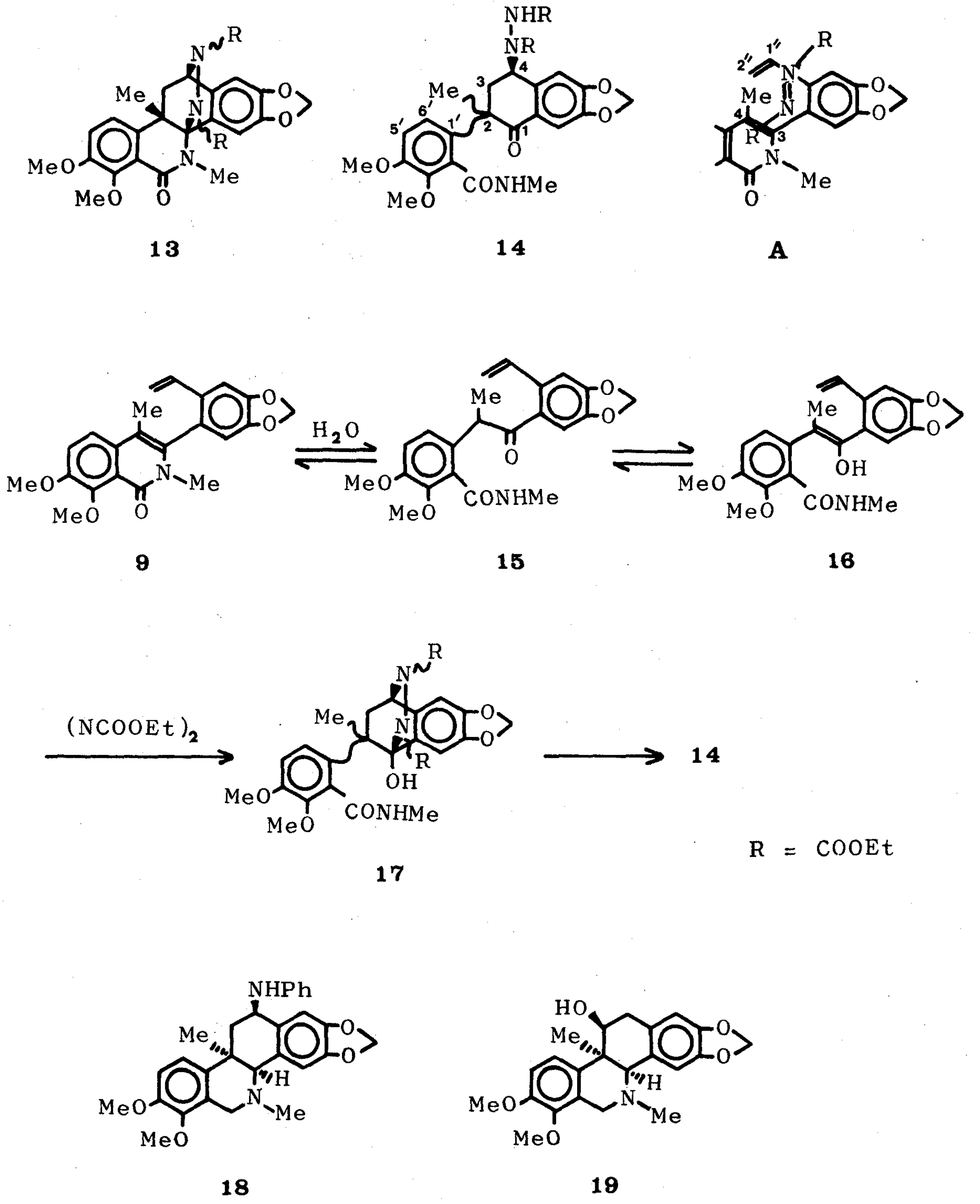


Chart 2

Experimental

Melting points were determined on a micro hot-stage apparatus and are uncorrected. Spectral data were recorded on the following spectrometers: IR—Hitachi 260-30 (chloroform); ^{1}H-NMR—Varian EM-390 (90 MHz) (deuteriochloroform); mass (MS)—JEOL JMS-01S.

4-Methyl-1-oxoanhydroberberine (9)——A solution of **10**$^{5)}$ (500 mg) in 25% methanolic KOH (3.6 ml) was refluxed for 10 min. The reaction mixture was then poured onto ice-water, and the precipitate (**1**) was collected by filtration and dissolved in chloroform.

A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (200 mg) in chloroform (30 ml) was added to a solution of **1** (obtained from the above chloroform solution) in chloroform (5 ml), and the mixture was stirred at room temperature for 1.5 h. After removal of the solvent *in vacuo*, the residue was dissolved in methanol (10 ml) and a solution of $K_3Fe(CN)_6$ (1 g) in 25% aqueous KOH (20 ml) was added, then the whole was refluxed for 2 h. The reaction mixture was filtered and concentrated *in vacuo*, then extracted with ethyl acetate. Work-up gave brown crystals (390 mg), which were recrystallized from ethanol to yield **9** (275 mg, 69%) as light yellow prisms of mp 184—185 °C. IR ν_{max} cm^{-1}: 1642 (NC=O). ^{1}H-NMR δ: 7.38 (2H, s, 5- and 6-H's), 7.15 (1H, s, 6′-H), 6.60 (1H, s, 3′-H), 6.35 (1H, dd, $J=17$ and 11 Hz, 1″-H), 6.03 (2H, s, 4′,5′-OCH_2O–), 5.56 (1H, dd, $J=17$ and 1 Hz, 2″-H), 5.07 (1H, dd, $J=11$ and 1 Hz, 2″-H), 4.01 (3H, s, 8-OMe), 3.95 (3H, s, 7-OMe), 3.17 (3H, s, 2-Me), 1.94 (3H, s, 4-Me). MS Calcd for $C_{22}H_{21}NO_5$: M, 379.142. Found *m/z*: M^+, 379.142.

10bβ-Methyl-4bβ,12β-(*N*-phenylepoxyimino)-4b,10b,11,12-tetrahydrooxychelerythrine (11) and the 10bα-Methyl Isomer (12)——A solution of **9** (108.9 mg) and nitrosobenzene (33.8 mg) in benzene (280 ml) was irradiated with a 100 W medium pressure mercury lamp under N_2 for 30 min. Removal of the solvent *in vacuo* gave an oil (140 mg), which was purified by prep. TLC[8] (Al_2O_3; benzene/ethyl acetate = 2/1, v/v) to yield **11** (44.1 mg, 32%), *Rf* 0.53, and **12** (40.5 mg, 29%), *Rf* 0.47.

The 10bβ-Methyl-4bβ,12β-epoxyimine (**11**): Colorless prisms of mp 249.5—251 °C (from ethanol). IR ν_{max} cm^{-1}: 1650 (NC=O). ^{1}H-NMR δ: 7.12—6.70 (6H, m, aromatic H's), 6.66 (1H, d, $J=9$ Hz, 9- or 10-H), 6.52 (1H, s, 4-H), 6.30 (1H, s, 1-H), 5.69, 5.65 (2H, AB-q, $J=1$ Hz, 2,3-OCH_2O–), 4.64 (1H, dd, $J=4$ and 2 Hz, 12-H), 3.96 (3H, s, 7-OMe), 3.73 (3H, s, 8-OMe), 3.39 (3H, s, 5-Me), 2.68 (1H, dd, $J=13$ and 4 Hz, 11-H), 2.28 (1H, dd, $J=13$ and 2 Hz, 11-H), 1.62 (3H, s, 10b-Me). MS Calcd for $C_{28}H_{26}N_2O_6$: M, 486.179. Found *m/z*: M^+, 486.180.

The 10bα-Methyl Isomer (**12**): Light yellow prisms of mp 235—235.5 °C (from ethanol). IR ν_{max} cm^{-1}: 1660 (NC=O). ^{1}H-NMR δ: 7.07 (2H, s, 9- and 10-H's), 7.03—6.67 (6H, m, aromatic H's), 6.64 (1H, s, 1-H), 5.88 (2H, s, 2,3-OCH_2O–), 4.84 (1H, dd, $J=4$ and 2.5 Hz, 12-H), 3.95 (3H, s, 7-OMe), 3.83 (3H, s, 8-OMe), 3.47 (3H, s, 5-Me), 3.08 (1H, dd, $J=13$ and 2.5 Hz, 11-H), 2.04 (1H, dd, $J=13$ and 4 Hz, 11-H), 0.70 (3H, s, 10b-Me). NOE: δ: 6.64 (1-H)→δ 4.84 (11.5%, 12-H). MS Calcd for $C_{28}H_{26}N_2O_6$: M, 486.179. Found *m/z*: M^+, 486.178.

4bβ,12β-[*N*,*N*′-Bis(carboethoxy)hydrazo]-10bβ-methyl-4b,10b,11,12-tetrahydrooxychelerythrine (13) and 4β-1″,2″-Bis(carboethoxy)hydrazo-2ξ-3′,4′-dimethoxy-2′-methylcarbamoylphenyl-2ξ-methyl-6,7-methylenedioxy-1-oxo-1,2,3,4-tetrahydronaphthalene (14)——A solution of **9** (50.0 mg) and diethyl azodicarboxylate (22.7 mg) in benzene (120 ml) was irradiated with a 100 W medium pressure mercury lamp under N_2 for 15 min. Work-up of the reaction mixture gave an oil (73 mg), which was purified by prep. TLC (Al_2O_3; benzene/ethyl acetate = 2/1, v/v) to yield **13** (11.5 mg, 16%), *Rf* 0.24, and **14** (10.1 mg, 13.5%), *Rf* 0.14.

The 10bβ-Methyl-4bβ,12β-hydrazine (**13**): Colorless granules of mp 126—129 °C (from ether/petr. ether). IR ν_{max} cm^{-1}: 1710 (OC=O), 1650 (NC=O). ^{1}H-NMR δ: 6.75, 6.50 (1H each, d, $J=9$ Hz, 9- and 10-H's), 6.58 (1H, s, 1-H), 6.38 (1H, s, 4-H), 5.79, 5.76 (2H, AB-q, $J=1$ Hz, 2,3-OCH_2O–), 5.17 (1H, t, $J=3$ Hz, 12-H), 4.32—3.90 (4H, m, $COOC\underline{H}_2Me$), 3.89 (3H, s, 7-OMe), 3.73 (3H, s, 8-OMe), 3.42 (3H, br s, $W_H=8$ Hz, 5-Me), 2.57 (1H, dd, $J=15$ and 3 Hz, 11-H), 2.35 (1H, dd, $J=15$ and 3 Hz, 11-H), 1.44 (3H, s, 10b-Me), 1.35—0.91 (6H, m, $COOCH_2\underline{Me}$). NOE: δ 6.58 (1-H)→δ 5.17 (6%, 12-H). MS Calcd for $C_{28}H_{31}N_3O_9$: M, 553.206. Found *m/z*: M^+, 553.204.

The α-Tetralone (**14**): Colorless granules of mp 240—241.5 °C (from ethanol). IR ν_{max} cm^{-1}: 1750 (OC=O), 1710 (C=O), 1660 (NC=O). ^{1}H-NMR δ: 7.48 (1H, s, 8-H), 7.25 (1H, s, 5-H), 7.14, 6.88 (1H each, d, $J=9$ Hz, 5′- and 6′-H's), 6.57 (1H, s, $N\underline{H}COOEt$, exchangeable with D_2O), 6.00 (2H, s, 6,7-OCH_2O–), 5.78 (1H, q, $J=5$ Hz, 2′-$CON\underline{H}Me$), 4.16, 4.12 (2H each, q, $J=7$ Hz, $COOC\underline{H}_2Me$), 3.83 (3H, s, 3′-OMe), 3.74 (3H, s, 4′-OMe), 3.27 (1H, t, $J=12$ Hz, 3-H), 2.63 (3H, d, $J=5$ Hz, 2′-$CONH\underline{Me}$), 2.06 (1H, dd, $J=12$ and 5 Hz, 3-H), 1.64 (3H, s, 2-Me), 1.27, 1.20 (3H each, t, $J=7$ Hz, $COOCH_2\underline{Me}$), 12-H signal overlapped with the signal at δ 4.16. Decoupling: δ 5.78 (2′-$CON\underline{H}Me$)→δ 2.63 (2′-$CONH\underline{Me}$, d→s); 2.63→5.78 (q→s). MS Calcd for $C_{28}H_{33}N_3O_{10}$: M, 571.217. Found *m/z*: M^+, 571.218.

12β-Anilino-10bα-methyl-4bα,5,6,10b,11,12-hexahydrochelerythrine (18)——A mixture of **12** (20.2 mg) and $LiAlH_4$ (8.5 mg) in dimethoxyethane (1 ml) was stirred at room temperature under N_2 for 2 h. Work-up of the reaction mixture gave an oil (19 mg), which was crystallized from ether/hexane to yield **18** (17.0 mg, 89%) as colorless granules of mp 146—148 °C, shown to be identical with an authentic sample[2] by direct comparison.

References and Notes

1) Part XIV: H. Yamaguchi, Y. Harigaya, and M. Onda, *Chem. Pharm. Bull.*, **31**, 1601 (1983).
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6) This could be explained in terms of secondary orbital overlap between the 4-carbon and the carbonyl group of the inner ethyl carboxylate in the transition state.
7) Water may come from the solvent.
8) Preparative thin-layer chromatography.