OXIDATIVE NITRATION AND BROMINATION OF BERBIN-8-ONE

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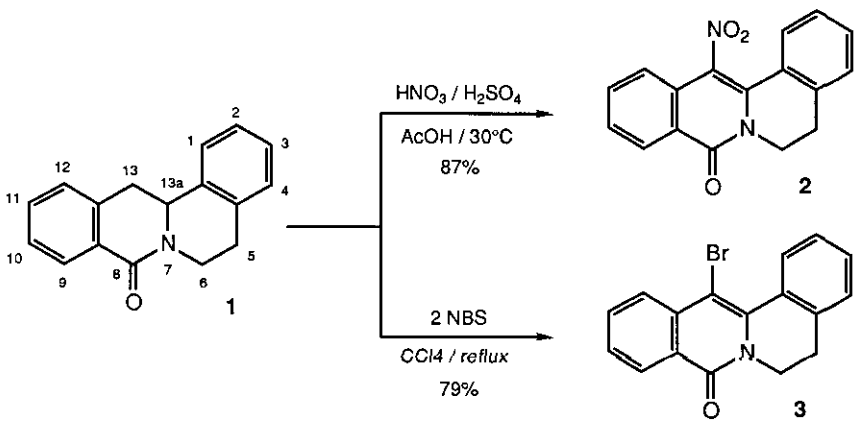
Abstract - In presence of two equivalents of nitric acid berbin-8-one (1) could be oxidized and nitrated to give 13-nitro-13,13a-dehydroberbin-8-one (2) in good yield. In the same way berbin-8-one (1) was made to react with N-bromosuccinimide to afford the 13-bromo analogue (3). The mechanism of the nitrative oxidation was studied. This oxidation is initiated by nitrogen dioxide from nitrous fumes included in the nitric acid. The oxidative nitration is accelerated by increasing the acidity or temperature of the medium. A radical mechanism which involves the 13,13a-dehydro-berbin-8-one (9) as intermediate of the reaction is postulated and discussed. The potential of this synthetic route was investigated.

During our synthetic work of berbine ring system,[1-4] we took a great interest in the chemical properties of the berbin-8-one or 5,6,13,13a-tetrahydro-8*H*-dibenzo[*a,g*]quinolizin-8-one (**1**). In attempting to nitrate this heterocycle we observed that a radical reaction took place to afford an oxidative nitration in the benzylic position 13. We report here the chemical study of the reaction mechanism and the further derivatives obtained this way.

Under appropriate reaction conditions of nitration, using nitric and sulfuric acids in acetic acid medium as described in the experimental part, berbin-8-one (**1**) could be transformated into the 13-nitro-13,13a-dehydro derivative (**2**) in good yield. The structure of the resulting nitro compound (**2**) was determined unambiguously from the ^{1}H-nmr and ir spectral data (Scheme 1).



Scheme 1

Induced by this interesting result, we have investigated the possible mechanism of this effect. Examination of the reaction behavior suggested that it may be explained by a radical mechanism. Thus, after some period of induction, the reaction started promptly. The temperature rised while evolution of nitrous fumes was observed. On immediate cooling the nitro compound (**2**) precipitated in the medium. So we investigated the kinetic study dealing with the effects of nitric acid, radical initiators and inhibitors, temperature, acidity, on the rate of the oxidative nitration (Table 1).

Table 1 - Results[a] of the induction periods[b] and the yields of the oxidative nitration in the presence of various added compounds.

Added compound	Quantity	Induction period min	Yield %
Conc. HNO_3	1 equivalent	17	52
Conc. HNO_3	2 equivalents	18	87
Fuming HNO_3	2 equivalents	8	81
Benzoyl peroxide	100 mg	15	81
Azobisisobutyronitrile	100 mg	17	83
Hydroquinone	200 mg	12	84
p-Cresol	200 mg	10	85
$NaNO_2$	10 mg	4	83
$NaNO_2$	50 mg	1.5	82
Urea	120 mg	no reaction	0
NO_2 gas	excess	0.5	82
Light	-	18	85
50°C	-	4	85
no H_2SO_4	-	40	78

[a] The values are the means of at least five experiments.

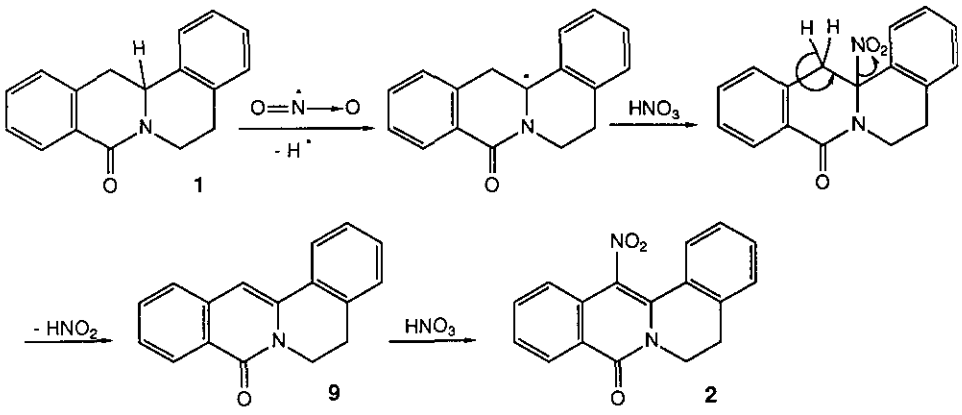
[b] The periods were determined when **2** began to precipitate.

The induction period was about 18 min with concentrated nitric acid solution at 30°C. Addition of an initiator of radical reaction, like benzoyl peroxide or α,α'-azobisisobutyronitrile did not change this period. Analogously irradiation of the medium with a low pressure mercury lamp did not reduce the induction time. Radical inhibitors such as hydroquinone or p-cresol were also capable of initiating the reaction. But a small amount of sodium nitrite started the reaction smoothly, while the reaction did not occur by the addition of urea, a scavenger of free radicals.[5] These results strongly suggested that the initiators were nitrous oxides (NO_2, N_2O_4) which are free stable radical entities. These oxides are commonly

present in commercial nitric acid. As a matter of fact the direct bubbling of nitrous dioxide gas from a cylinder into the acidic medium produced an immediate effect.

The commercial fuming nitric acid which usualy possesses nitrous vapors reduced the induction period. The effect of the concentration of nitric acid was examined and it was determined that two equivalents of nitric acid were required for this transformation. Indeed the reaction time was accelerated by increasing the acidity of the medium. In absence of sulfuric acid the induction time was twice longer. The temperature dependence was also studied. Activation was considerably high when the medium was heated to 50°C.

Thus the possible mechanism of the oxidative nitration is as follows:

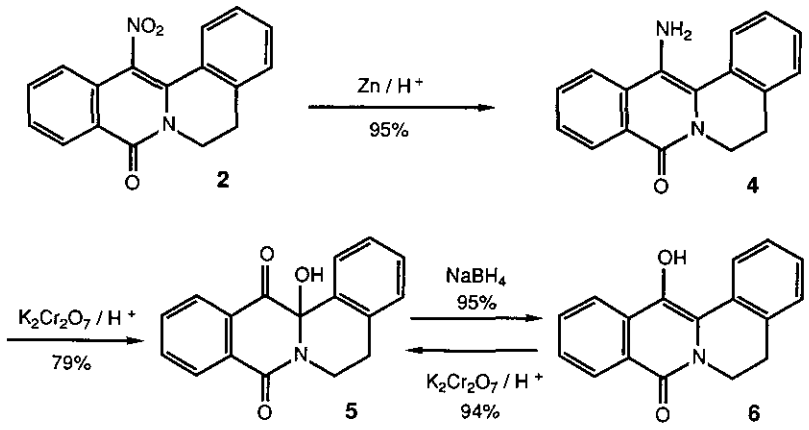


Scheme 2

That nitrogen dioxide is an effective initiator implies that it may be the attacking species.[6] The resulting radical formed from the berbinone at the 13a position is stabilized by extensive delocalization of the free electron. This latter can react and be oxidized by nitric acid to afford the dehydroberbinone (**9**). The second step is ionic. The resulting intermediate (**9**) is rapidly nitrated with a second equivalent of nitric acid. Actually the compound (**9**), obtained in another manner, could be easily nitrated in these same conditions to give the nitro compound (**2**) (Scheme 4).

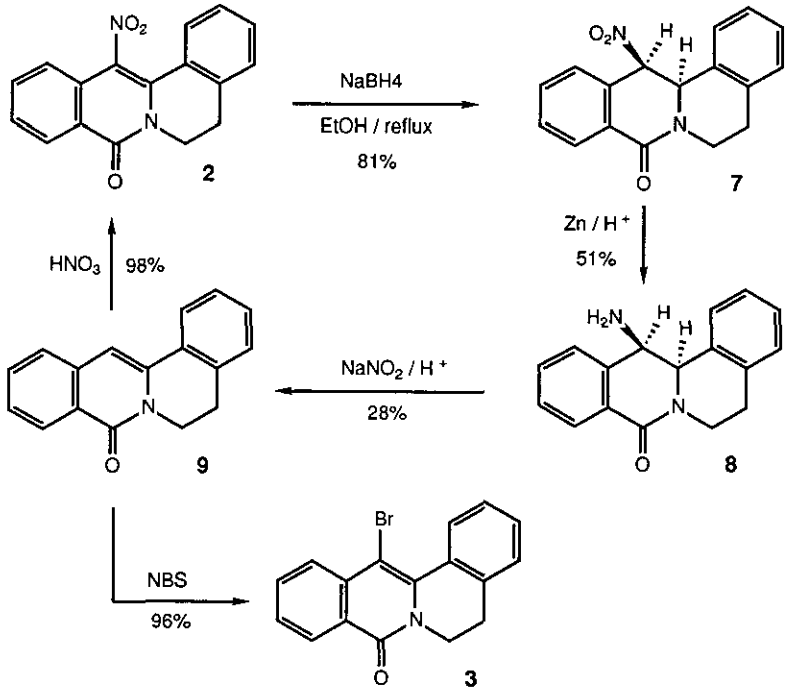
In order to confirm this radical mechanism we have studied the action of the *N*-bromosuccinimide with the berbin-8-one (**1**). The reaction proceeded in the same way. In presence of two equivalents of NBS the berbinone (**1**) was oxidized and brominated at the 13 position to afford the 13-bromo-13,13a-dehydroberbin-8-one (**3**) in good yield (**Scheme 1**). Likewise the 13,13a-dehydroberbinone (**9**) reacted with one equivalent of NBS to give the bromo compound (**3**) (Scheme 4).[7]

We were also interested in the potential of this synthetic route by further chemical transformations of the nitro compound (**2**). The nitro group could be reduced by zinc in acidic medium to give the 13-amino analogue (**4**). On treatment with chromic acid this latter was oxidized to the 13a-hydroxyberbine-8,13-dione (**5**). After sodium borohydride reduction in methanolic solution the enol derivative (**6**) was isolated which could be reoxidized to compound (**5**) (Scheme 3).[8]



Scheme 3

The active ethylenic double bond has been selectively reduced with sodium borohydride in hot ethanol to the partial saturated nitro compound (**7**), then reduced to the amino derivative (**8**). The 13,13a-dehydroberbinone (**9**) was the main product when this amine was made to react with nitrous acid (Scheme 4).



Scheme 4

The stereochemistry of the partial saturated nitro compound (**7**) was determined from the ^{1}H-nmr spectral data. As a matter of fact the vicinal constant coupling (AB type) between the protons of the 13 and 13a positions indicated a *cis* configuration as described for the 13-methyl-berbin-8-one.[9] Moreover the presence of strong Bohlmann bands in the ir spectrum indicated that the hydrogen atom in the 13a position is behind the molecule plan.[10]

In conclusion our results are relevant in the finding of oxidative nitration and bromination of berbin-8-one by a radical mechanism and of the development of synthetic applications for introducing various functionnal groups at the C-13 position of the berbinone heterocycle.

EXPERIMENTAL

Melting points (uncorrected) were taken on a Kofler hot stage apparatus. Infrared spectra were obtained on a Beckmann IR 4230 spectrophotometer. ^{1}H-Nmr spectra were taken on a Bruker AC 200 nmr spectrometer. Analyses were performed by Cent. Serv. Microan. Vernaison. All tlc were performed on Merck silica gel F-254 plates (chloroform - ethyl acetate, 1:1).

Oxidative nitration of the berbinone to 13-nitro-5,6-dihydro-8*H*-dibenzo[*a,g*]quinolizin-8-one (2) - The experiments summarized in Table 1 were carried out according to a standardized procedure. In glacial acetic acid (30 ml) was dissolved berbin-8-one (**1**) (2 g, 8.03 mmol).[1] To this stirred solution was added successively concentrated HNO_3 (1.2 ml, 17.33 mmol) and concentrated H_2SO_4 (2 ml, 37.5 mmol). The mixture was kept at 30°C in a water bath until the temperature began to rise. Then the solution was immediately cooled to 25°C in cold water and nitro compound (**2**) shortly precipitated (18 min). Then the mixture was allowed to stand at room temperature for 30 min. Water (20 ml) was added and the precipitate was isolated by filtration, washed with water and dried. Recrystallization from acetic acid gave yellow needles of **2** (2.04 g, 87%), mp 235°C. Ir (KBr): $\nu_{C=O}$ 1665, $\nu_{C=C}$ 1618, ν_{NO_2} 1518 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.05 (t, $J_{5,6}$= 5.8 Hz, 2H, H5); 4.31 (t, $J_{5,6}$= 5.8 Hz, 2H, H6); 7.35 (m, 2H, H3,4); 7.51 (td, $J_{1,2,3}$= 6.7 Hz, $J_{2,4}$= 1.2 Hz, 1H, H2); 7.61 (m, 3H, H1,10,12); 7.76 (td, $J_{10,11,12}$= 6.3 Hz, $J_{9,11}$= 1.4 Hz, 1H, H11); 8.52 (dd, $J_{9,10}$= 7.4 Hz, $J_{9,11}$= 1.4 Hz, 1H, H9). Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.11; N, 9.59. Found : C, 69.99; H, 4.08; N, 9.52.

Oxidative bromination of the berbinone to 13-bromo-5,6-dihydro-8*H*-dibenzo[*a,g*]quinolizin-8-one (3) - Berbin-8-one (**1**) (2 g, 8.03 mmol) was dissolved under reflux in CCl_4 (100 ml). *N*-Bromosuccinimide (2.90 g, 16.29 mmol) was then added. Reflux with stirring was continued for 1.5 h. The mixture was cooled, filtered and the filtrate was evaporated to dryness. The solid residue was recrystallized from cyclohexane to give the bromo compound (**3**) (2.07 g, 79%), mp 160°C. Ir ($CHCl_3$): $\nu_{C=O}$ 1640, $\nu_{C=C}$ 1615 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.95 (t, $J_{5,6}$= 6.0 Hz, 2H, H5); 4.30 (t, $J_{5,6}$= 6.0 Hz, 2H, H6); 7.27-7.45 (m, 3H, H2-4); 7.57 (td, $J_{9,10,11}$= 7.0Hz, $J_{10,12}$= 1.1 Hz, 1H, H10); 7.77 (td, $J_{10,11,12}$= 7.0 Hz, $J_{9,11}$= 1.4 Hz, 1H, H11); 8.14 (dd, $J_{1,2}$= 7.8 Hz, $J_{1,3}$= 1.2 Hz, 1H, H1); 8.35 (dd, $J_{11,12}$= 8.2 Hz, $J_{10,12}$= 1.4 Hz, 1H, H12); 8.50 (dd, $J_{9,10}$= 8.2 Hz, $J_{9,11}$= 1.4 Hz, 1H, H9). Anal. Calcd for $C_{17}H_{12}NOBr$: C, 62.58; H, 3.68; N, 4.29. Found: C, 68.66; H, 3.51; N, 4.22.

13-Amino-5,6-dihydro-8 *H*-dibenzo[*a,g*]quinolizin-8-one (4) - To a solution of nitro compound (**2**) (2 g, 6.85 mmol) in acetic acid (20 ml) and water (5 ml) was added zinc powder (2 g, excess). The mixture was stirred at 50-55°C in a water bath for 1.5 h. Then excess zinc was filtered, the filtrate was evaporated *in vacuo* and the residue was treated with water (25 ml) to crystallize the amino derivative (**4**) which was isolated by filtration, washed with water and dried. Recrystallization from ethanol gave yellow brown needles (1.7 g, 95%), mp 188°C decomp. Ir (KBr): ν_{NH_2} 3420 and 3350, $\nu_{C=O}$ 1640, $\nu_{C=C}$ 1610 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.92 (t, $J_{5,6}$= 5.6 Hz, 2H, H_5); 3.75 (m, 2H, NH_2); 4.30 (t, $J_{5,6}$= 5.6 Hz, 2H, H_6); 7.26-7.42 (m, 3H, $H_{1,3,4}$); 7.55 (td, $J_{1,2,3}$= 8.0 Hz, $J_{2,4}$= 3.5 Hz, 1H, H_2); 7.75 (m, 2H, $H_{10,11}$); 8.03 (d, $J_{11,12}$= 7.4 Hz, 1H, H_{12}); 8.55 (d, $J_{9,10}$= 7.9 Hz, 1H, H_9). Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.86; H, 5.34; N, 10.69. Found: C, 77.72; H, 5.48; N, 10.76.

13a-Hydroxy-5,6,13,13a-tetrahydro-8 *H*-dibenzo[*a,g*]quinolizine-8,13-dione (5) - Amino compound (**4**) (2.5 g, 9.54 mmol) was dissolved in a mixture of acetone (30 ml), water (30 ml) and concentrated HCl (5 ml). This solution was added dropwise for 15 min under stirring to a solution of potassium dichromate (2.85 g, 9.67 mmol) in water (100 ml) and concentrated HCl (3 ml). After the addition was complete, the reaction mixture was allowed to stand at room temperature for 10 min. The resulting precipitate was isolated by filtration, washed with water. Purification was carried out by chromatography on silica gel using $CH_3OH/CHCl_3$ (1:9) as eluant to afford rose coloured plates of compound (**5**) (2.66 g, 79%), mp 163°C decomp. Ir (KBr): ν_{OH} 3320, $\nu_{C=O}$(ketone) 1715, $\nu_{C=O}$(amide) 1625 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.85 (ddd, $J_{5a,5b}$= 16.5 Hz, $J_{5b,6b}$= 4.4 Hz, $J_{5b,6a}$= 1.3 Hz, 1H, H_{5b}); 3.18 (ddd, $J_{5a,5b}$= 16.5 Hz, $J_{5a,6a}$= 12.5 Hz, $J_{5a,6b}$= 5.9 Hz, 1H, H_{5a}); 3.69 (td, $J_{5a,6a,6b}$= 12.5 Hz, $J_{5b,6b}$= 4.4 Hz, 1H, H_{6b}); 4.38(s, 1H, OH); 4.87(ddd, $J_{6a,6b}$= 12.5 Hz, $J_{5a,6a}$= 5.9 Hz, $J_{5b,6a}$= 1.3 Hz, 1H, H_{6a}); 7.17-7.37 (m, 3H, H_{2-4}); 7.44 (dd, $J_{1,2}$= 8.3 Hz, $J_{1,3}$= 1.9 Hz, 1H, H_1); 7.72 (td, $J_{10,11,12}$= 7.4 Hz, $J_{9,11}$= 0.8 Hz, 1H, H_{11}); 7.77 (td, $J_{9,10,11}$= 7.4 Hz, $J_{10,12}$= 0.8 Hz, 1H, H_{10}); 8.07 (dd, $J_{9,10}$= 7.4 Hz, $J_{9,11}$= 0.8 Hz, 1H, H_9); 8.23 (dd, $J_{11,12}$= 7.4 Hz, $J_{10,12}$= 0.8 Hz, 1H, H_{12}). Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.12; H, 4.66; N, 5.02. Found: C, 72.98; H, 4.82; N, 4.94.

13-Hydroxy-5,6-dihydro-8 *H*-dibenzo[*a,g*]quinolizin-8-one (6) - After dissolving compound (**5**) (1g, 3.58 mmol) in methanol (30 ml), sodium borohydride (0.1g, 2.64 mmol) was added portionwise for 10 min. After the addition was complete the mixture was allowed to stand at room temperature for 30 min. Then water (30 ml) was added to precipitate the enol compound (**6**). Recristallization from ethanol gave pale yellow needles (0.90 g, 95 %), mp 240°C decomp. Ir (KBr): ν_{OH} 3560, $\nu_{C=O}$ 1635, $\nu_{C=C}$ 1610 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.17 (t, $J_{5,6}$= 5.7 Hz, 2H, H_5); 3.41 (t, $J_{5,6}$= 5.7 Hz, 2H, H_6); 6.57 (m, 3H, H_{2-4}); 6.67 (t, $J_{10,11,12}$= 7.4 Hz, 1H, H_{11}); 7.08 (t, $J_{10,11,12}$= 7.4 Hz, 1H, H_{10}); 7.28 (d, $J_{1,2}$= 8.05 Hz, 1H, H_1); 7.52 (d, $J_{11,12}$= 7.4 Hz, 1H, H_{12}); 7.67 (d, $J_{9,10}$= 7.4 Hz, 1H, H_9); 8.12 (s, 1H, OH). Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.56; H, 4.94; N, 5.32. Found: 77.52; H, 4.78; N, 5.43.

Oxidation of the enol compound (6) - Enol compound (**6**) (1 g, 3.80 mmol) was dissolved in acetone (25 ml). The mixture was added dropwise for 10 min under stirring to a solution of potassium dichromate (1.15 g, 3.91 mmol) in water (30 ml)

and concentrated HCl (1.5 ml). After addition was complete the reaction mixture was allowed to stand at room temperature for 10 min. The resulting precipitate was separated by filtration, washed with water and purified by chromatography on silica gel using $CH_3OH/CHCl_3$ (1:9) as eluant to give **5** (1.0 g, 94 %). Physical data were the same as those described above.

13-Nitro-5,6,13,13a-tetrahydro-8 *H*-dibenzo[*a,g*]quinolizin-8-one (7) - A mixture of nitro compound (**2**) (5g, 17.12 mmol) and ethanol (50 ml) was stirred under reflux for 30 min. Then the solution was evaporated to dryness and the residue was dissolved in tepid water and the solution was filtered. The filtrate was acidified with 10% HCl to precipitate the nitro derivate (**7**) which was isolated by filtration, washed with water and dried. Recristallization from n-butanol gave pale yellow plates (4.08 g, 81%), mp 130-132°C decomp. Ir ($CHCl_3$): $\nu_{C=O}$ 1655, ν_{NO_2} 1535 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.70-3.32 (m, 3H, $H_{5a,5b,6b}$); 5.13 (m, 1H, H_{6a}); 5.47 (d, $J_{13,13a}$= 4.0 Hz, 1H, H_{13a}); 6.00 (d, $J_{13,13a}$= 4.0 Hz, 1H, H_{13}); 7.22-7.80 (m, 7H, $H_{1\text{-}4,10\text{-}12}$); 8.31 (dd, $J_{9,10}$= 8.1 Hz, $J_{9,11}$= 2.6 Hz, 1H, H_9). Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.39; H, 4.76; N, 9.52. Found: C, 69.54; H, 4.48; N, 9.71.

13-Amino-5,6,13,13a-tetrahydro-8 *H*-dibenzo[*a,g*]quinolizin-8-one (8) - In a mixture of nitro compound (**7**) (4 g, 13.60 mmol), acetic acid (2 ml), concentrated HCl (9 ml) and water (30 ml) was added portionwise zinc powder (3 g, excess). The temperature of the reaction was kept at 50-55°C for 1 h. Then the excess zinc was filtered, the filtrate was made alkaline with concentrated NH_4OH and extracted with CH_2Cl_2. The organic layers were washed with water, dried ($MgSO_4$) and evaporated to dryness. The solid residue was recrystallized from ethanol to afford colorless plates of **8** (1.83 g, 51%), mp 208-210°C. Ir ($CHCl_3$): ν_{NH_2} 3380 and 3315, $\nu_{C=O}$ 1630 cm^{-1}.^{1}H-Nmr ($CDCl_3$) δ: 1.27 (s, 2H, NH_2); 2.60-3.22 (m, 3H, $H_{5a,5b,6b}$); 4.17 (d, $J_{13,13a}$= 2.4 Hz, 1H, H_{13a}); 5.02 (m, 2H, $H_{6b,13}$); 7.15-7.66 (m, 7H, $H_{1\text{-}4,10\text{-}12}$); 8.16 (dd, $J_{9,10}$= 7.4 Hz, $J_{9,11}$= 1.4 Hz, 1H, H_9). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.27; H, 6.06; N, 10.61. Found: C, 76.96; H, 6.18; N, 10.43.

5,6-Dihydro-8 *H*-dibenzo[*a,g*]quinolizin-8-one (9) - A solution of amino compound (**8**) (1.5 g, 5.68 mmol) in 10% HCl (30 ml) at 0-5°C was added dropwise for 10 min to another solution of sodium nitrite (0.395 g, 5.72 mmol) in water (10 ml). After addition was complete the resulting precipate was isolated by filtration, washed with water, dried and recrystallized from cyclohexane to give the dehydroberbinone (**9**) (0.393 g, 28%), mp 102°C (lit.[11] 102°C). Ir (KBr): $\nu_{C=O}$ 1640, $\nu_{C=C}$ 1615 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.03 (t, $J_{5,6}$= 6.2 Hz, 2H, H_5); 4.40 (t, $J_{5,6}$= 6.2 Hz, 2H, H_6); 7.05 (s, 1H, H_{13}); 7.25-7.45 (m, 3H, $H_{1,3,4}$); 7.51 (td, $J_{9,10,11}$= 6.5 Hz, $J_{10,12}$= 1.8 Hz, 1H, H_{10}); 7.58 (dd, $J_{11,12}$= 6.2 Hz, $J_{10,12}$= 1.6 Hz, 1H, H_{12}); 7.62 (td, $J_{10,11,12}$= 6.5 Hz, $J_{9,11}$= 1.6 Hz, 1H, H_{11}); 7.70 (td, $J_{1,2,3}$= 6.1Hz, $J_{2,4}$= 1.9 Hz, 1H, H_2); 8.45 (dd, $J_{9,10}$= 8.0 Hz, $J_{9,11}$= 1.5 Hz, 1H, H_9). Anal. Calcd for $C_{17}H_{13}NO$: C, 82.59; H, 5.26; N, 5.67. Found: C, 82.63; H, 5.33; N, 5.53.

Nitration of the dehydroberbinone (9) - To a solution of compound (**9**) (1 g, 4.05 mmol) in acetic acid (15 ml) were added successively concentrated HNO_3 (0.3 ml, 4.33 mmol) and concentrated H_2SO_4 (1 ml,18.7 mmol). The separated crystals of

2 were collected and recrystallized from acetic acid to give yellow needles of **2** (1.16 g, 98%). Physical data were the same as those exhibited by the nitro compound (**2**).

Bromination of the dehydroberbinone (9) - Dehydroberbin-8-one (**9**) (1.5 g, 6.07 mmol) was dissolved in CCl_4 (60 ml) and *N*-bromosuccinimide (1.10 g, 6.20 mmol) was added. The mixture was heated under reflux for 1h, then cooled and filtered. The filtrate was evaporated to dryness. The solid residue was recrystallized from cyclohexane to give the bromo compound (**3**) (1.90 g, 96 %). Physical data were the same as those described above.

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Received, 27th May, 1991