SELECTIVE ACETYLATION OF BERBIN-8-ONE. SYNTHESIS OF 2-METHOXYBERBINE

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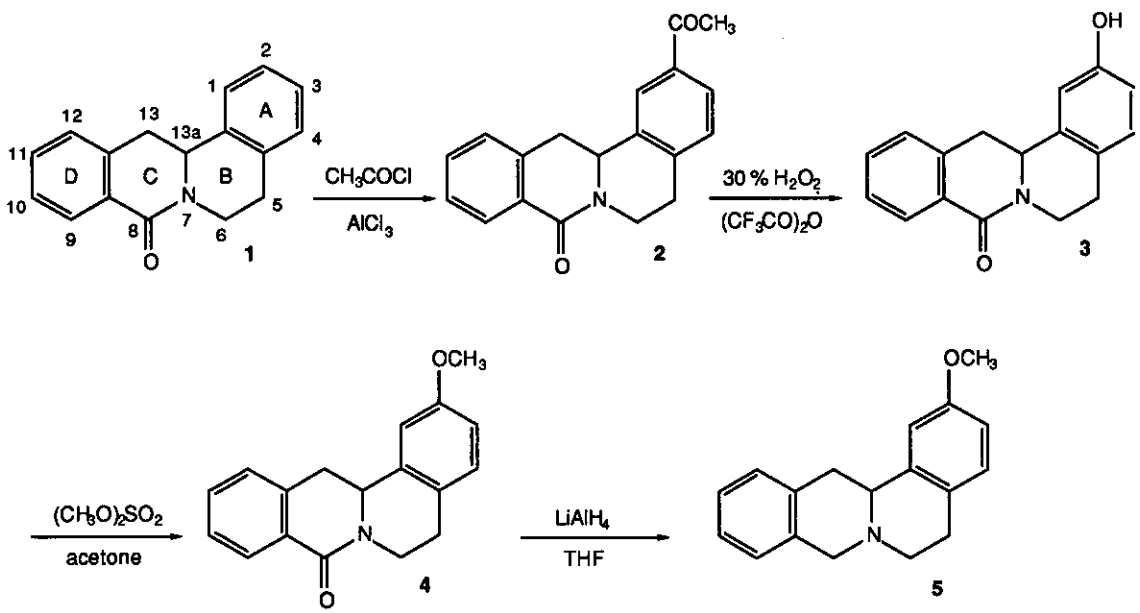
Abstract - In the presence of excess aluminum chloride, berbin-8-one (1) could be selectively acetylated at the C-2 position to give 2-acetylberbin-8-one (2) in good yield. In fact this exclusive orientation was due to a complex between the amide carbonyl and the Lewis acid which deactivated the aromatic ring D for electrophilic substitution. Further chemical degradation of the acetyl group afforded the corresponding phenol derivative (3) which was converted to 2-methoxyberbin-8-one (4). Reduction of this latter gave finally 2-methoxyberbine (5). Spectral data comparison of compound (4) and 3-methoxyberbin-8-one permitted us to conclude unambiguously in favour of the C-2 orientation of the acetylation.

In a previous paper we have described chemical properties of berbin-8-one (**1**) with regard to the functionalization of the C-13 position.[1] In the present study we investigated the directed substitution at the C-2 position in order to introduce a methoxy group on the berbin ring system and to evaluate its pharmacological influence.

The usual methods, involving Bischler-Napieralski or Pictet-Spengler reaction,[2] did not produce 2-methoxyberbine (**5**) in good yield. As a matter of fact, internal cyclization of *N*-(2-

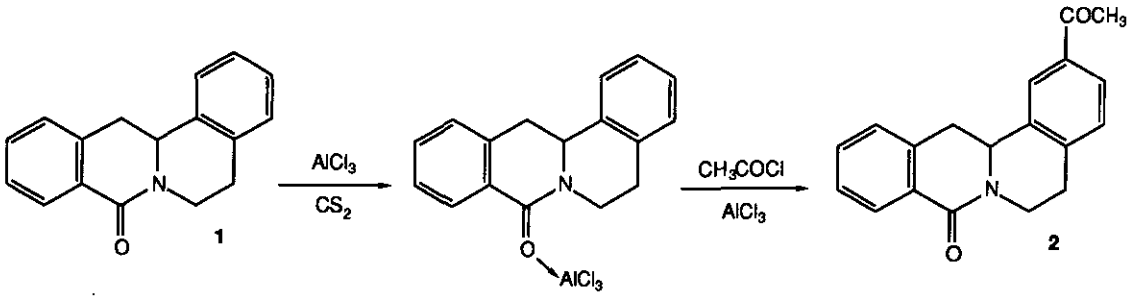
methoxyphenethyl)phenylacetamide is not favored in rate because of the *meta* position of the electon-donating methoxy group compared to the *para* position, leading to a mixture of isomeric isoquinolines.

So we tried to directly introduce a convenient group at the C-2 position of berbin-8-one (**1**) and to convert it into 2-methoxyberbine (**5**) in a few steps. Thus, the most synthetical useful strategy involved acetylation of berbin-8-one (**1**) followed by chemical degradation of the acetyl group of **2** by a modified Baeyer-Villiger reaction[3] leading to the phenol analogue (**3**). The resulting 2-hydroxyberbin-8-one (**3**) was methylated with dimethyl sulfate to give 2-methoxyberbin-8-one (**4**) which was then reduced with lithium aluminum hydride to afford the expected 2-methoxyberbine (**5**). (Scheme 1)



However, in a first assay of berbin-8-one (**1**) acetylation , using equimolar quantities of acetyl chloride and aluminum chloride as catalyst, we obtained a mixture of acetylated compounds. ^{1}H-Nmr spectral analyses showed that the acetyl group was attached to both aromatic rings A and D. In fact, the electron-withdrawing effect of the amide carbonyl was not sufficient to prevent acetylation of aromatic ring D. Thus, in order to avoid such a reaction, acetylation was carried out with excess aluminum chloride. Actually, it is known that Lewis acids are able to form complexes

with the carbonyl group of amides.[4] As a consequence, the electron-withdrawing aluminum atom enhanced the deactivation of the aromatic ring D and therefore prevent further attack of the acylating agent. So under these experimental conditions the electophilic substitution exclusively occurred in the ring A to lead to a pure monoacetylated derivative. (Scheme 2)



In order to give evidence of the right position of the acetyl group, a simple spectroscopic study of compound (**2**) was not sufficient. The signal of proton H_9 (δ = 8.15) of compound (**1**) did not change in comparison with this (δ = 8.15) of the acetylated compound (**2**), indicating an acylation of the ring A. The ABC pattern of the remaining three protons of the ring A did not exhibited a simple triplet ($J_{1,2,3}$ or $J_{2,3,4}$) with an ortho coupling constant, allowing us to deduce that the acetyl group was at the C-2 or C-3 position. But simple analysis of these spectral features did not permit us to determine exactly the acetyl position and there was a choice between these two possible C-2 or C-3 positions.

Thus, it was necessary to continue the synthesis until the methoxyberbin-8-one (**4**) was obtained and to compare their spectral data with those exhibited by 3-methoxyberbin-8-one, that we previously described.[5] As regards these spectral data, compound (**4**) and 3-methoxyberbin-8-one were different and so permitted us to conclude that the methoxy group was fixed at the C-2 position in compound (**4**). Consequently the acetylation of berbin-8-one (**1**) occurred unambiguously at the C-2 position.

In conclusion berbin-8-one (**1**) appears to be an interesting starting molecule in the selective substitution at the C-2 position by acetylation reaction and therefore permits the synthesis of 2-methoxyberbine (**5**) which is difficult to obtain in other ways.

EXPERIMENTAL

Melting points (mp) were determined on Kofler hot stage apparatus and are uncorrected. Proton nmr spectra were recorded on a Brucker AC 200 spectrometer. Infrared spectra were performed on a Beckman IR 4230 spectrophotometer. All new substances exhibited spectroscopic data consistent with the assigned structures. Analyses indicated by elemental symbols were within 0.4 % of the theorical values and were done by the Central Service of Microanalyses in Vernaison. All tlc were performed on Merck silica gel F-254 plates (chloroform, ethyl acetate, triethylamine / 25:25:1).

2-Acetyl-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizin-8-one (**2**)

To a solution of berbin-8-one (**1**)[5] (2 g, 8.03 mmol) in carbon disulfure (40 ml) was added anhydrous aluminum chloride (3 g, 22.50 mmol). The mixture was stirred at room temperature for 15 min. Then acetyl chloride (0.7 g, 8.92 mmol) was added and the whole was refluxed for 1.5 h. After cooling the supernatant was decanted and the residue was treated with cracked ice. Then water (30 ml) was added and the mixture was extracted with dichloromethan (40 ml). The organic phases were collected, washed with water, dried ($MgSO_4$) and evaporated *in vaccuo*. The residue was recrystallized from ethanol to give **2** (1.50 g, 68 %), mp 146°C. Ir ($CHCl_3$) cm^{-1}: 1680 ($\nu_{CO\ acetyl}$); 1640 ($\nu_{CO\ lactam}$). ^{1}H-Nmr ($CDCl_3$) δ: 2.64 (s, 3H, CH_3); 2.92-3.12 (m, 4H, $H_{5,5',6,13}$); 3.35 (dd, $J_{13,13'}$ = 15.6 Hz, $J_{13',13a}$ = 3.6 Hz, 1H, $H_{13'}$); 4.95-5.08 (m, 2H, $H_{6',13a}$); 7.30 (dd, $J_{11,12}$ = 7.2 Hz, $J_{10,12}$ = 1.6 Hz, 1H, H_{12}); 7.38 (d, $J_{3,4}$ = 8.2 Hz, 1H, H_4); 7.47 (td, $J_{9,10,11}$ = 7.4 Hz, $J_{10,12}$ = 1.6 Hz, 1H, H_{10}); 7.49 (td, $J_{10,11,12}$ = 7.2 Hz, $J_{9,11}$ = 1.6 Hz, 1H, H_{11}); 7.82 (dd, $J_{3,4}$ = 8.2 Hz, $J_{1,3}$ = 1.9 Hz, 1H, H_3); 7.93 (d, $J_{1,3}$ = 1.9 Hz, H_1); 8.16 (dd, $J_{9,10}$ = 7.4 Hz, $J_{9,11}$ = 1.6 Hz, 1H, H_9). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.4; H, 5.8; N, 4.8. Found: C, 77.9; H, 5.8; N, 4.8.

2-Hydroxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a,g*]quinolizin-8-one (**3**)

To a solution of 2-acetylberbin-8-one (**2**) (1.5 g, 5.45 mmol) in CH_2Cl_2 (6 ml) were added 30 % H_2O_2 (3 ml, 26.47 mmol) and dropwise trifluoroacetic anhydride (6 ml, 41.90 mmol). The mixture was refluxed for 6 h. Then water (20 ml) was added and the aqueous phase was neutralized with solid sodium bicarbonate. The organic phase was decanted, washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The solid residue was recrystallized from ethyl acetate to give **4** (1.01 g, 70 %), mp 214 °C. Ir ($CHCl_3$) cm-1: 3600 (ν_{OH}); 1640 (ν_{CO}). 1H-Nmr ($CDCl_3$) δ: 2.79-3.11 (m, 4H, $H_{5,5',6,13}$); 3.24 (dd, $J_{13,13'}$ = 15.7 Hz, $J_{13',13a}$ = 3.8 Hz, 1H, $H_{13'}$); 4.85-5.04 (m, 2H, $H_{6',13a}$); 6.72 (dd, $J_{3,4}$ = 8.5 Hz, $J_{1,3}$ = 2.6 Hz, 1H, H_3); 6.82 (d, $J_{1,3}$ = 2.6 Hz, 1H, H_1); 7.10 (d, $J_{3,4}$ = 8.5 Hz, 1H, H_4); 7.25 (dd, $J_{11,12}$ = 7.4 Hz, $J_{10,12}$ = 1.7 Hz, 1H, H_{12}); 7.39 (td, $J_{9,10,11}$ = 7.4 Hz, $J_{10,12}$ = 1.7 Hz, 1H, H_{10}); 7.47 (td, $J_{10,11,12}$ = 7.2 Hz, $J_{9,11}$ = 1.5 Hz, 1H, H_{11}); 8.15 (dd, $J_{9,10}$ = 7.4Hz, $J_{9,11}$ = 1.5 Hz, 1H, H_9); 9.02 (s, 1H, OH). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 77.0; H, 5.7; N, 5.7. Found: C, 77.1; H, 5.9; N, 5.2.

2-Methoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a,g*]quinolizin-8-one (**4**)

A mixture of **3** (1 g, 3.77 mmol), potassium carbonate (0.8 g, 5.79 mmol), dimethyl sulfate (1.5 ml, 15.85 mmol) and acetone (30 ml) was heated under reflux for 2 h. Then the solvent was evaporated *in vaccuo* and the residue was treated with water (30 ml) and extracted with CH_2Cl_2 (40 ml). The organic phases were separated , washed with water, dried ($MgSO_4$) and evaporated. The solid residue was recrystallized from cyclohexane to give **4** (1.01 g, 96 %), mp 116 °C. Ir ($CHCl_3$) cm-1: 1640 (ν_{CO}).1H-Nmr ($CDCl_3$) δ: 2.79-3.11 (m, 4H, $H_{5,5',6,13}$); 3.24 (dd, $J_{13,13'}$ = 15.7 Hz, $J_{13',13a}$ = 3.8 Hz, 1H, $H_{13'}$); 3.92 (s, 3H, OCH_3); 4.85-5.04 (m, 2H, $H_{6',13a}$); 6.71 (dd, $J_{3,4}$ = 8.5 Hz, $J_{1,3}$ = 2.6 Hz, 1H, H_3); 6.80 (d, $J_{1,3}$ = 2.6 Hz, 1H, H_1); 7.05 (d, $J_{3,4}$ = 8.5 Hz, 1H, H_4); 7.25 (dd, $J_{11,12}$ = 7.2 Hz, $J_{10,12}$ = 1.7 Hz, 1H, H_{12}); 7.39 (td, $J_{9,10,11}$ = 7.4 Hz, $J_{10,12}$ = 1.7 Hz, 1H, H_{10}); 7.47 (td, $J_{10,11,12}$ = 7.4 Hz, $J_{9,11}$ = 1.5 Hz, 1H, H_{11}); 8.15 (dd, $J_{9,10}$ = 7.4Hz, $J_{9,11}$ = 1.5 Hz, 1H, H_9). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.4; H, 6.1; N, 5.0. Found: C, 77.4; H, 6.1; N, 5.0.

2-Methoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine (**5**)

A solution of **4** (1 g, 3.58 mmol) in dry THF (25 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (0.2 g, 5.27 mmol) in anhydrous ether (20 ml). The mixture was kept at ambient temperature for 1 h. Then water (0.2 ml), 15 % aqueous NaOH (0.2 ml) and water (0.6 ml) were successively added. The resulting hydroxides were separated by filtration and thoroughly washed with THF. The combined filtrates were evaporated *in vaccuo*. The residual oil was recrystallized from diisopropyl ether to afford **5** (0.874 g, 92 %), mp 92 °C. Ir ($CHCl_3$) cm^{-1}: 2835-2720 (Bohlmann bands). ^{1}H-Nmr ($CDCl_3$) δ: 2.65-3.78 (m, 8H, $H_{5,5',6,6',8,13,13',13a}$); 3.78 (s, 3H, CH_3O); 4.04 (d, $J_{8,8'}$ = 14.9 Hz, 1H, H_8); 6.70 (dd, $J_{3,4}$ = 8.5 Hz, $J_{1,3}$ = 2.6 Hz, 1H, H_3); 6.78 (d, $J_{1,3}$ = 2.6 Hz, 1H, H_1); 7.10-7.25 (m, 5H, $H_{4,9,10,11,12}$). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.5; H, 7.2; N, 5.3. Found: C, 81.5; H, 7.2; N, 5.3.

REFERENCES

1. J. F. Stambach and L. Jung, Heterocycles, 1991, 32, 1571.

2. For a review of the Bischler-Naperialski cyclization, see W. M. Whaley and T. R. Govindachari, Org. React., 1951, 6, 74. For a review of the Pictet-Spengler synthesis, see W. M. Whaley and T. R. Govindachari, Org. React., 1951, 6, 151.

3. W. D. Emmons and G. B. Lucas, J. Am. Chem. Soc., 1955, 77, 2287.

4. D. P. N. Satchell and R. S. Satchell, Chem. Rev., 1969, 69, 251.

5. J. F. Stambach and L. Jung, Tetrahedron, 1985, 41, 169;

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