Communication

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Ivan V. Nechepurenko *, Nina I. Komarova , Nariman F. Salakhutdinov

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Synthesis of Tetrahydroberberine *N,N*-Derived *O*-Acetamides

Ivan V. Nechepurenko *, Nina I. Komarova and Nariman F. Salakhutdinov

Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences, Novosibirsk, 630090 Russia

* Correspondence: niv@nioch.nsc.ru; N.I.V.

Abstract: The reaction of berberine derivatives containing at *O*-9 position *N,N*-disubstituted acetamide fragments with sodium borohydride in methanol at 0 °C leads to a mild reduction of the "C" cycle with the formation of corresponding tetrahydroberberine derivatives with moderate to good yields.

Keywords: berberine; berberubine; tetrahydroberberine; tetrahydroberberrubine; acetamides

1. Introduction

The isoquinoline alkaloid berberine (berberine chloride, sulfate) is known to have a wide range of diverse biological activities. Currently, research on its hypolipidaemic [1–3], anti-inflammatory and antioxidant [4,5], anti-cancer [6,7] activities is being actively continued. Works on such types of berberine activity as anti-epileptic [8,9], antidepressant [10,11], antiallergic [12] are being developed. Berberine chloride contains in its structure an aromatic positively charged nitrogen atom, such a salt has low solubility and, as a result, low bioavailability. In order to increase the bioavailability of berberine, its water-soluble compositions are being developed [13] or complexes of berberine with Ag, Au nanoparticles [14,15], natural polymers such as chitosan [16,17], peptides [18], or hyaluronic acid [19] are used. A number of berberine derivatives have been found with activities exceeding that of the initial alkaloid, such as, hypolipidaemic [20], hypoglycemic [21], antibacterial [22] and antiviral [23].

The most common modification of berberine chloride involves its demethylation at the *O*-9 position to form the alkaloid berberubine **1** and further obtaining derivatives at this position by alkylation or acylation [20,24], *O*-9-arylation [25] or *C*-9 arylation [26]. Thus, earlier according to this scheme we synthesized aromatic acetamides **2** by reacting berberubine **1** with bromoacetic acid amides in the presence of a base (Scheme 1) [27,28]. A separate direction of berberine modification is the production of berberine-like molecules synthetically [29].

Another popular branch of chemical modification of berberine is the reduction of its isoquinolinium system. The resulting dihydro- or tetrahydro derivatives are less stable than the original berberines, but have much greater solubility and often have good bioactivity. Tetrahydroberberine itself has a pronounced lipid-lowering effect [30], although there is some evidence of hepatotoxicity [31]. Among tetrahydroberberine derivatives, examples with good lipid-lowering [32–34], antiproliferative [35], antibacterial (antifungal) activity [36] were found. Unusual examples of activity have been found. For example, we have shown that tetrahydroberberrubine polyfluoroaromatic sulfonates are inhibitors of tyrosyl-DNA phosphodiesterase 1 (Tdp1), an important enzyme of the DNA repair system [37].

The aim of the present work was to obtain new *N,N*-substituted *O*-acetamide derivatives of tetrahydroberberine.

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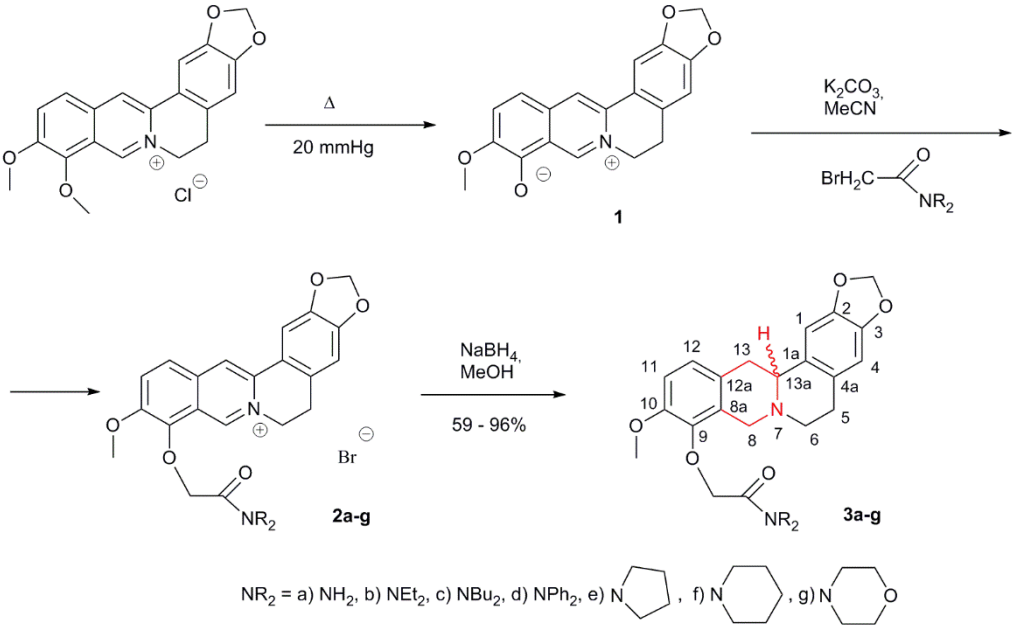
2. Results and Discussion

2.1. Synthesis of **3**

The synthesis of acetamides **2** by the interaction of berberubine **1** with bromoacetic acid amides in the presence of a base was described by us in [27,28]. Compounds **2** contains in their structure an aromatic heterocyclic ring (cycle "C") in the isoquinolinium system, which is reduced by the action of various reducing agents to form dihydro- or tetrahydro derivatives. We have shown that reaction of compounds **2a-g** with 4 mol-equivalents of sodium borohydride in methanol at 0 °C, results in a mild reduction of the "C" cycle occurs with the formation of tetrahydroberberine derivatives of **3a-g** (Scheme 1). The products were purified by column chromatography, followed by hexane re-precipitation from isopropanol. The best yields were achieved for compounds containing a dibutylamide fragment (**3c**, 96%), a diethylamide fragment (**3b**, 87%) and a piperidinamide fragment (**3f**, 80%). The yields of the remaining compounds were 59-66%, which is probably due to their greater solubility in the hexane-isopropanol system. To the best of our knowledge, compounds **3a-g** has not been previously described in the literature.



Scheme 1. Synthesis of tetrahydroberberine *N,N*-derived *O*-acetamides **3**.

2.2. Spectral Data of **3**

The structures of amides **3** were proved using spectral data. IR spectra exhibited vibrations in the range 1645–1698 cm^{-1} that corresponded to the vibrational frequency of tertiary amides. Mass spectra contained peaks (*m/z*) corresponding to $[M-H]^+$ positively charged molecular fragment. Among the fragmentation peaks there is a fragment with *m/z* 324.1, which corresponds to the tetrahydroberberrubine cation-radical $C_{19}H_{18}NO_4$, $[M-H]^+$.

^{1}H NMR spectra of **3** exhibited resonances for methylene protons of OCH_2CON as AB system with chemical shifts δ_H 4.20–4.80 ppm. Resonances of chemically identical protons of the alkyl substituents in the amide were nonequivalent. This was indicative of the hindered rotation that is characteristic of tertiary amides. The resonances of the carbon atoms of alkyl substituents in amide, e.g., dibutylamide **3c**, were also nonequivalent in ^{13}C NMR spectra. The corresponding chemical shifts were δ_C 45.38 and 46.76 ppm (NCH_2), 29.57 and 31.03 ppm ($NCH_2\underline{CH_2}CH_2CH_3$), 19.92 and 20.09 ppm ($NCH_2CH_2\underline{CH_2}CH_3$), 13.67 and 13.74 ppm ($NCH_2CH_2CH_2\underline{CH_3}$). This was consistent with the literature data for analogous amides [28,38].

^{1}H NMR and ^{13}C NMR spectra of compounds **3** showed characteristic resonances for the tetrahydroberberine skeleton. Let's consider these resonances using the example of compound **3b** for

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which standard one-dimensional and two-dimensional NMR experiments (COSY, NOESY, HSQC, HMBC) were recorded. When considering $^{1}H–^{13}C$ heteronuclear correlation (HSQC) spectrum (Figure S7 in supporting info), we determined the correspondence of signals from carbon atoms and protons. Thus, multiplet signal from proton at δ_H 3.46-3.52 ppm correspond to the signal at δ_C 59.32 ppm (C13a), multiplet signals at δ_H 2.73-2.81and 3.12-3.20 ppm (H13) correspond to the signal at δ_C 36.09 ppm (C13), doublet signals at δ_H 3.55 and 4.29 ppm (H8) correspond to the signal at δ_C 53.62 ppm (C8), which is typical for the signals of ring C in tetrahydroberberine systems.

3. Materials and Methods

3.1. General

Berberine chloride hydrate purchased from TCI company, the basic substance content is 81%. Commercially available organic and inorganic chemicals (reagent grade) from Khimservis Company (Russia) were used without additional purification. Solvents from Khimservis Company (Russia) were distilled prior to use. Column chromatography was performed on silica gel manufactured by Macherey-Nagel, fraction 63–200 μm. Berberrubine **1** was synthesized as the solvate with one EtOH molecule according to the literature procedure [27]. Berberrubine acetamides bromides **2a-g** were prepared as previously reported [27,28].

3.2. Instrumentation and Analysis

Spectral and analytical studies of products were carried out at the Multi-access Chemical Service Center of the Siberian Branch of the Russian Academy of Sciences. The UV spectra were recorded on a HP 8453 UV-Vis spectrophotometer in EtOH ($c = 10^{-4}$ mol/L). The IR spectra were measured on a Vector 22 FTIR spectrometer in KBr pellets. Melting points (mp) were obtained with Metler Toledo FP 900 instrument and Kofler stage. Elemental analyses were from Carlo Erba 1106. High-resolution mass spectra were obtained on a DFS-Thermo-Scientific spectrometer in a full scan mode (15-500 *m*/*z*, 70 eV electron-impact ionization, direct sample introduction). HPLC analyses were carried out on "Milichrome A-02" HPLC system (Econova, Russia) using ProntoSIL-120-5-C18AQ reversed-phase sorbent (particle size 5 μm, column 75 × 2 mm) at 35 °C, 3.0–3.6 MPa, and flow rate 150 μL/min with elution by a linear gradient of solvents from 100% A to 100% B over 25 min (solvent A, 0.1% TFA in H_2O; solvent B, MeOH) and simultaneous multiwave detection at six wavelengths (220, 240, 260, 280, 320 and 360 nm). ^{1}H and ^{13}C NMR spectra of 5–10% solutions of compounds in $CDCl_3$ or DMSO-d6 were recorded on Bruker AV-400, DRX-500 and AV-600 spectrometers. Solvent signals (δ_H 7.24 and δ_C 76.90 ppm for $CDCl_3$ or δ_H 2.50 and δ_C 39.52 ppm for DMSO-d6) were used as internal references. The numbering of carbon and hydrogen atoms in the spectra of compounds is shown on Scheme 1 and Figure S2. The assignments of the signals in the ^{1}H and ^{13}C NMR spectra marked with an asterisk (or a double asterisk) can be interchanged.

3.3. General Procedure for Tetrahydroderivatives 3a-g Synthesis

At a temperature 0 °C and stirring on a magnetic stirrer, 4 equivalents of sodium borohydride were added to a suspension of 0.6-1.5 mmol (1 eq.) of a derivative of berberine bromide **2** in 10 ml of methanol in portions. Stirred for 30 minutes while cooling and then for 4 hours at room temperature. The reaction mixture was evaporated and divided by column chromatography on silica gel. The eluent is methylene - methanol chloride, 100:2, 100:4. The fractions containing product **3** were combined, dissolved by heating in 5 ml of isopropanol, the precipitate was deposited with the addition of 10 ml of hexane.

2-[(9-Demethoxy-7,8,13,13a-tetrahydroberberine-9-yl)oxy]-acetamide 3a

According to the general procedure, 372 mg of compound 3a was obtained from 700 mg of compound 2a after chromatography on aluminum oxide (3rd degree of activity), yield 64%.

M.p. 230.9 °C. IR (neat, υ_{max}, cm^{-1}): 3435, 3161, 2910, 1683, 1494, 1483, 1280, 1246, 1225. UV (EtOH, λ_{max}, nm): 284, 352. MS (*m*/*z*): 381.1451, calculated for $C_{21}H_{21}O_5N_2^+$: 381.1445. EA (%): C 65.20, H 5.64,

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N 7.23, calculated for $C_{21}H_{22}O_5N_2$: C 65.96, H 5.80, N 7.33. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J* (Hz)): 2.40-2.64 m (3H, H5, H6, H13), 2.82-2.95 m (1H, H5), 3.03-3.11 m (1H, H13), 3.27-3.45 m (3H, H6, H8, H13a), 3.78 s (3H, OCH_3), 4.19 d (1H, H8, 16.0), 4.25 d (1H, OCH_2CO, 14.8), 4.32 d (1H, OCH_2CO, 14.8), 5.92-5.96 m (2H, OCH_2O), 6.66 s (1H, H4), 6.87-6.93 m (3H, H1, H11, H12), 7.44 d (2H, NH_2, 12.4). ^{13}C NMR (100 MHz, DMSO-d6, δ, ppm): 29.00 (C5), 35.69 (C13), 50.67 (C6), 53.16 (C8), 55.80 (OCH_3), 58.99 (C13a), 70.65 (OCH_2CO), 100.53 (OCH_2O), 105.72 (C1), 108.06 (C4), 111.07 (C11), 124.10 (C12), 127.49* (C4a), 127.67* (C12a), 128.31 (C8a), 130.86 (C1a), 142.67 (C9), 145.42** (C2), 145.71** (C3), 149.35 (C10), 170.58 (CO).

***N,N*-Diethyl-2-[(9-demethoxy-7,8,13,13a-tetrahydroberberine-9-yl)oxy]-acetamide 3b**

According to the general procedure, 460 mg of compound 3b was obtained from 618 mg of compound 2b in the form of an amorphous substance, yield 87%.

IR (neat, υ_{max}, cm^{-1}): 2934, 1645, 1487, 1276, 1248, 1222. UV (EtOH, λ_{max}, nm): 285, 341. MS (*m*/*z*): 437.2070, calculated for $C_{25}H_{29}O_5N_2^+$: 437.2071. EA (%): C 65.98, H 6.79, N 5.81, calculated for $C_{25}H_{30}O_5N_2+H_2O$: C 65.77, H 7.07, N 6.14. ^{1}H NMR (600 MHz, $CDCl_3$, δ, ppm, *J* (Hz)): 1.10-1.19 m (6H, $N(CH_2CH_3)_2$), 2.54-2.63 m (2H, H5, H6), 2.73-2.81 m (1H, H13), 3.00-3.10 m (1H, H5), 3.12-3.20 m (2H, H6, H13), 3.36-3.42 m (4H, NCH_2), 3.46-3.52 m (1H, H13a), 3.55 d (1H, H8, 16.2), 3.78 s (3H, OCH_3), 4.29 d (1H, H8, 15.6), 4.56 d (1H, OCH_2CO, 12.6), 4.66 d (1H, OCH_2CO, 12.6), 5.8-5.88 m (2H, OCH_2O), 6.53 s (1H, H4), 6.67 s (1H, H1), 6.73 d (1H, H11, 8.4), 6.82 d (1H, H12, 8.4). ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 12.75 q (NCH_2CH_3), 14.17 q (NCH_2CH_3), 29.24 t (C5), 36.09 t (C13), 39.87 t (NCH_2), 41.02 t (NCH_2), 51.05 t (C6), 53.62 t (C8), 55.74 q (OCH_3), 59.32 d (C13a), 70.62 t (OCH_2CO), 100.56 t (OCH_2O), 105.28 d (C1), 108.20 d (C4), 110.82 d (C11), 124.01 d (C12), 127.55 s (C4a, C12a), 128.37 s (C8a), 130.39 s (C1a), 143.37 s (C9), 145.72* s (C2), 145.92* s (C3), 149.58 s (C10), 167.29 s (CO).

***N,N*-Dibutyl-2-[(9-demethoxy-7,8,13,13a-tetrahydroberberine-9-yl)oxy]-acetamide 3c**

According to the general procedure, 359 mg of compound 3c was obtained from 435 mg of compound 2c in the oil form, yield 96%.

IR (neat, υ_{max}, cm^{-1}): 3452, 2957, 1647, 1485, 1279, 1248, 1223. UV (EtOH, λ_{max}, nm): 285, 341. MS (*m*/*z*): 493.2680, calculated for $C_{29}H_{37}O_5N_2^+$: 493.2700. EA (%): C 68.22, H 7.64, N 5.21, calculated for $C_{29}H_{38}O_5N_2+H_2O$: C 67.94, H 7.86, N 5.46. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J* (Hz)): 0.90 t (6H, $(N(CH_2CH_2CH_2CH_3)_2$), 7.2), 1.25-1.35 m (4H, $NCH_2CH_2CH_2$), 1.47-1.58 m (4H, NCH_2CH_2), 2.57-2.67 m (2H, H5, H6), 2.75-2.88 m (1H, H13), 3.05-3.22 m (3H, H5, H6, H13), 3.23-3.37 m (4H, NCH_2), 3.49-3.64 m (2H, H8, H13a), 3.78 s (3H, OCH_3), 4.32 d (1H, H8, 16.0), 4.58 d (1H, OCH_2CO, 12.8), 4.69 d (1H, OCH_2CO, 12.8), 5.87 s (2H, OCH_2O), 6.54 s (1H, H4), 6.67 s (1H, H1), 6.74 d (1H, H11, 8.3), 6.83 d (1H, H12, 8.3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 13.67 ($NCH_2CH_2CH_2CH_3$), 13.74 ($NCH_2CH_2CH_2CH_3$), 19.92 ($NCH_2CH_2CH_2CH_3$), 20.09 ($NCH_2CH_2CH_2CH_3$), 29.22 (C5), 29.57 ($NCH_2CH_2CH_2CH_3$), 31.03 ($NCH_2CH_2CH_2CH_3$), 36.08 (C13), 45.38 (NCH_2) 46.76 (NCH_2) 51.07 (C6), 53.65 (C8), 55.78 (OCH_3), 59.37 (C13a), 70.59 (OCH_2CO), 100.61 (OCH_2O), 105.33 (C1), 108.26 (C4), 111.00 (C11), 123.97 (C12), 127.58 (C4a, C12a), 127.82 (C8a), 129.89 (C1a), 143.55 (C9), 145.85* (C2), 146.02* (C3), 149.66 (C10), 167.67 (CO).

***N,N*-Diphenyl-2-[(9-demethoxy-7,8,13,13a-tetrahydroberberine-9-yl)oxy]-acetamide 3d**

According to the general procedure, 228 mg of compound 3d was obtained from 228 mg of compound 2d in the form of an amorphous substance, yield 66%.

IR (neat, υ_{max}, cm^{-1}): 2900, 1695, 1493, 1280, 1248, 1221. UV (EtOH, λ_{max}, nm): 284, 345. MS (*m*/*z*): 533.2067, calculated for $C_{33}H_{29}O_5N_2^+$: 533.2071. EA (%): C 73.51, H 5.56, N 5.08, calculated for $C_{33}H_{30}O_5N_2$: C 74.14, H 5.66, N 5.24. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J* (Hz)): 2.54-2.66 m (2H, H5, H6) 2.71-2.82 m (1H, H13), 3.10-3.22 m (3H, H5, H6, H13), 3.55-3.60 m (2H, H8, H13a), 3.70 s (3H, OCH_3), 4.32 d (1H, H8, 16.4), 4.49 d (1H, OCH_2CO, 14.7), 4.61 d (1H, OCH_2CO, 14.7), 5.88 s (2H, OCH_2O), 6.55 s (1H, H4), 6.68 s (1H, H1), 6.69 d (1H, H11, 8.3), 6.80 d (1H,H12, 8.3), 7.20-7.31 m (6H, Ph), 7.20-7.31 m (6H, Ph), 7.31-7.40 m (4H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 29.41 (C5), 36.24 (C13), 51.12 (C6), 53.79 (C8), 55.90 (OCH_3), 59.37 (C13a), 70.38 (OCH_2CO), 100.59 (OCH_2O), 105.34

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(C1), 108.25 (C4), 111.07 (C11), 123.79 (C12), 127.73 (C4a, C12a), 128.51 (C8a), 129.26 (C2',C3',C4',C5',C6'), 130.70 (C1a), 143.60 (C9), 145.71 (C2), 145.92* (C3), 149.28* (C10), 168.07 (CO).

2-[(9-Demethoxy-7,8,13,13a-tetrahydroberberine-9-yl)oxy]-1-(pyrrolidin-1-yl)ethan-1-one 3e

According to the general procedure, 2.00 g of compound 3e was obtained from 3.18 g of compound 2e in the form of an amorphous substance, yield 63%.

IR (neat, υ_{max}, cm^{-1}): 2922, 1649, 1491, 1248, 1222. UV (EtOH, λ_{max}, nm): 285. MS (*m*/*z*): 435.1911, calculated for $C_{25}H_{27}O_5N_2^+$: 435.1914. EA (%): C 68.98, H 6.58, N 6.25, calculated for $C_{25}H_{28}O_5N_2$: C 68.79, H 6.47, N 6.42. ^{1}H NMR (400 MHz, DMSO-d6, δ, ppm, *J* (Hz)): 1.78-2.00 m (4H, N($CH_2\underline{CH_2}$)$_2$), 2.53-2.70 m (2H, H5, H6), 2.70-2.88 m (1H, H13), 3.00-3.25 m (3H, H5, H6, H13), 3.40-3.65 m (6H, NCH_2, H13a, H8), 3.79 s (3H, OCH_3), 4.32 d (1H, H8, 16.0), 4.53 d (1H, OCH_2CO, 13.6), 4.66 d (1H, OCH_2CO, 13.6), 5.88 s (2H, OCH_2O), 6.55 s (1H, H4), 6.69 s (1H, H1), 6.75 d (1H, H11, 8.5), 6.84 d (1H, H12, 8.5). ^{13}C NMR (75 MHz, DMSO-d6, δ, ppm): 23.52 ($NCH_2\underline{CH_2}$) 25.45 (C5), 25.72 ($NCH_2\underline{CH_2}$) 32.05 (C13), 44.63 (NCH_2) 45.58 (NCH_2) 50.08 (C6), 51.43 (C8), 56.06 (OCH_3), 58.84 (C13a), 69.82 (O$\underline{CH_2}$CO), 101.20 (OCH_2O), 105.63 (C1), 108.20 (C4), 112.84 (C11), 122.79* (C4a), 123.79 (C12), 125.02* (C12a), 125.20* (C8a), 125.63* (C1a), 142.97 (C9), 146.61** (C2), 146.77** (C3), 149.62 (C10), 166.23 (CO).

2-[(9-Demethoxy-7,8,13,13a-tetrahydroberberine-9-yl)oxy]-1-(piperidin-1-yl)ethan-1-one 3f

According to the general procedure, 497 mg of compound 3f was obtained from 730 mg of compound 2f in the form of an amorphous substance, yield 80%.

IR (neat, υ_{max}, cm^{-1}): 3458, 2935, 1643, 1487, 1276, 1248, 1221. UV (EtOH, λ_{max}, nm): 285, 343. MS (*m*/*z*): 449.2068, calculated for $C_{26}H_{29}O_5N_2^+$: 449.2071. EA (%): C 66.71, H 6.30, N 5.81, calculated for $C_{26}H_{30}O_5N_2$+H_2O: C 66.65, H 6.88, N 5.98. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J* (Hz)): 1.51-1.68 m (6H, $NCH_2\underline{CH_2CH_2}$), 2.59-2.72 m (2H, H5, H6), 2.77-2.92 m (1H, H13), 3.06-3.25 m (3H, H5, H6, H13), 3.45-3.70 m (6H, NCH_2, H13a, H8), 3.79 s (3H, OCH_3), 4.33 d (1H, H8, 15.9), 4.60 d (1H, OCH_2CO, 12.8), 4.69 d (1H, OCH_2CO, 12.8), 5.88 s (2H, OCH_2O), 6.55 s (1H, H4), 6.68 s (1H, H1), 6.75 d (1H, H11, 8.4), 6.84 d (1H, H12, 8.4). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 24.54 ($NCH_2CH_2\underline{CH_2}$), 25.57 ($NCH_2\underline{CH_2}$), 26.51 ($NCH_2\underline{CH_2}$), 29.36 (C5), 36.19 (C13), 42.97 (NCH_2), 46.17 (NCH_2), 51.23 (C6), 53.79 (C8), 55.97 (OCH_3), 59.50 (C13a), 71.02 (O$\underline{CH_2}$CO), 100.78 (OCH_2O), 105.49 (C1), 108.42 (C4), 111.08 (C11), 124.28 (C12), 127.69 (C4a, C12a), 128.40 (C8a), 130.46 (C1a), 143.56 (C9), 145.98* (C2), 146.16* (C3), 149.86 (C10), 166.67 (CO).

2-[(9-Demethoxy-7,8,13,13a-tetrahydroberberine-9-yl)oxy]-1-morpholinoethan-1-one 3g

According to the general procedure, 380 mg of compound 3g was obtained from 750 mg of compound 2g, yield 59%.

M.p. 163.1 °C. IR (neat, υ_{max}, cm^{-1}): 2914, 1653, 1498, 1278, 1228. UV (EtOH, λ_{max}, nm): 285. MS (*m*/*z*): 451.1860, calculated for $C_{25}H_{27}O_6N_2^+$: 451.1864. EA (%): C 66.44, H 6.16, N 6.13, calculated for $C_{25}H_{28}O_6N_2$: C 66.36, H 6.24, N 6.19. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, *J* (Hz)): 2.56-2.68 m (2H, H5, H6), 2.74-2.86 m (1H, H13), 3.03-3.23 m (3H, H5, H6, H13), 3.48-3.74 m (10H, N$\underline{CH_2CH_2}$O, H13a, H8), 3.78 s (3H, OCH_3), 4.26 d (1H, H8, 15.9), 4.58 d (1H, OCH_2CO, 12.6), 4.66 d (1H, OCH_2CO, 12.6), 5.87 s (2H, OCH_2O), 6.55 s (1H, H4), 6.68 s (1H, H1), 6.74 d (1H, H11, 8.4), 6.84 d (1H, H12, 8.4). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 29.37 (C5), 36.19 (C13), 42.26 (NCH_2), 45.79 (NCH_2), 51.29 (C6), 53.77 (C8), 55.86 (OCH_3), 59.52 (C13a), 66.88 ($NCH_2\underline{CH_2}$O) 71.03 (O$\underline{CH_2}$CO), 100.80 (OCH_2O), 105.48 (C1), 108.43 (C4), 110.90 (C11), 124.54 (C12), 127.67* (C4a), 127.79* (C12a), 128.37 (C8a), 130.39 (C1a), 143.20 (C9), 146.01** (C2), 146.18** (C3), 149.79 (C10), 167.06 (CO).

4. Conclusions

New N,N-substituted O-acetamide derivatives of tetrahydroberberine were synthesized by reducing the corresponding derivatives of berberubine by the action of sodium borohydride. The structure of the compounds was determined by NMR and HRMS methods.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figures S1-S18: ^{1}H NMR and ^{13}C NMR spectrum of compounds **3a-g**.

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