Formation of an Unusual Dimeric Compound by Lead Tetraacetate Oxidation of a Corynanthe-Type Indole Alkaloid, Mitragynine

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Lead tetraacetate oxidation of a Corynanthe-type indole alkaloid, mitragynine, produced mainly 7-acetoxyindolenine derivative (2) together with a dimeric compound (4) as a minor product. The novel structure having a bridge between the C-11′ and C-7 positions in the respective indolenine parts and its formation mechanism were studied.

Key words indole alkaloid; oxidation; dimerization; lead tetraacetate; indolenine; reaction mechanism

In the recent chemical[1—9] and pharmacological[10—15] studies on the Rubiaceous plant, *Mitragyna speciosa*,[16—20] which has been traditionally used in tropical areas as a substitute for opium,[21] we have found that mitragynine (**1**), a major Corynanthe-type indole alkaloid of this plant, exhibited potent analgesic activity mediated by μ- and δ-opioid receptors.[22] Further, 7-hydroxymitragynine (**3**),[23] an oxidative derivative of **1**, was found as a novel opioid agonist with higher potency than that of morphine.[24] This remarkable opioid ligand was prepared from mitragynine (**1**) by conventional procedure, *i.e.*, oxidation of **1** with lead tetraacetae [$Pb(OAc)_4$] followed by alkaline hydrolysis of the resultant 7-acetoxyindolenine (**2**). In investigating the first oxidation step in detail, we found a structurally and mechanistically novel dimerization product, as described in this publication.

Results and Discussion

In general, 7-acetoxyindolenine derivatives are prepared from the corresponding indoles by oxidation with $Pb(OAc)_4$.[25,26] When yohimbine was treated with $Pb(OAc)_4$, we obtained the 7-acetoxyindolenine derivative in a quantitative yield. However, in the case of mitragynine (**1**) the yield of the desired indolenine (**2**) was up to 50%, and the presence of side products was shown on thin-layer chromatography. By careful purification of the reaction residue, we isolated **2** together with an unusual compound (**4**) in 3% yield, which showed molecular weight of 852 by mass spectrum. The UV absorption curve of **4** exhibited close resemblance to that of 7-acetoxyindolenine derivative (**2**), but the large log ε value at 234 nm (log ε=4.68) together with the molecular formula ($C_{48}H_{60}O_{10}N_4$) obtained from high-resolution FAB-MS spectrum indicated the presence of two units of indolenine chromophore derived from mitragynine (**1**). The ^{1}H- and ^{13}C-NMR spectra of **4** clearly showed the presence of two sets of the fundamental structural units in the mother compound, mitragynine (**1**), *i.e.*, two β-methoxyacrylic acid methyl ester residues, two ethyl groups and two 9-methoxy groups on the aromatic ring. Further, the presence of one acetoxy group was shown by the ^{1}H-NMR (δ 2.09, 3H, s) and ^{13}C-NMR (δ 168.3, 20.8) spectra. In the ^{13}C-NMR spectrum, two characteristic signals due to indolenine carbons at C-2 or C-2′ (δ 187.1, 181.1) as well as two newly formed quaternary carbons at C-7 or C-7′ (δ 61.7, 84.5) were observed. Therefore, it became clear that compound (**4**) had the usual acetoxyindolenine unit in the molecule. In the ^{1}H-NMR spectrum, a set of three aromatic protons at δ 6.65 (doublet), 7.22 (doublet of doublet), and 7.32 (doublet) same as those of **1** and a set of *meta*-coupled protons at δ 6.07 (singlet-like) and 7.35 (singlet-like) were observed. This indicated that one of the two indolenine units had a substituent at the C-11 position and the other one was intact as regards the substituent mode on the benzene ring. In the ^{1}H-detected heteronuclear multiple-bond correlation (HMBC) spectrum, clear long-range connectivities were observed between both two *meta*-coupled protons (δ 6.07, 7.35) and a newly formed quaternary carbon (δ 61.7), which could be assigned as C-7 based on the fact that this carbon showed long-range coupling with the protons on C-3, C-5 and C-6. All the above spectroscopic analyses enabled us to construct the dimeric structure that had a bridge between C-7 in one indolenine part and C-11′ on the aromatic part in theother indolenine unit. The stereochemistry at C-7 and C-7′ was respectively deduced by the nuclear Overhauser effect (NOE) observations between H-10′ and H-3 and H-6α, and between H-3′ and the protons on the acetyl group as shown in Fig. 1.

For the carbon–carbon bond formation between C-7 and C-11′ to produce the dimeric compound (**4**), two possible mechanisms can be considered, *i.e.*, an electrophilic aromatic substitution at C-11 on the indole ring (Type I) or a common

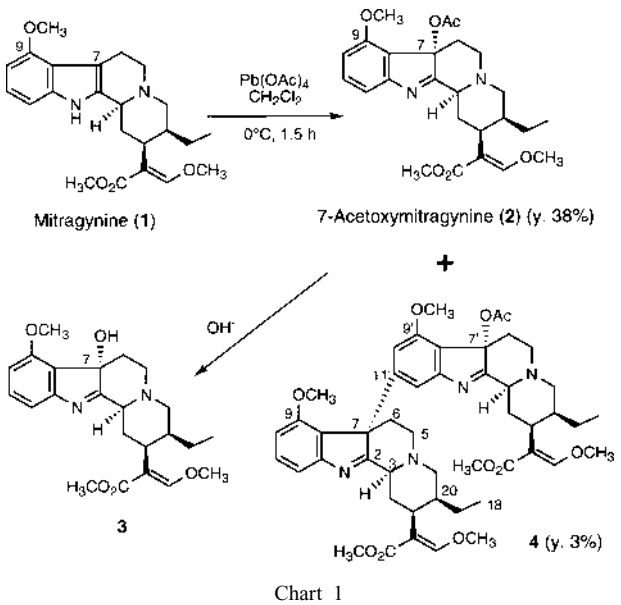

Chart 1

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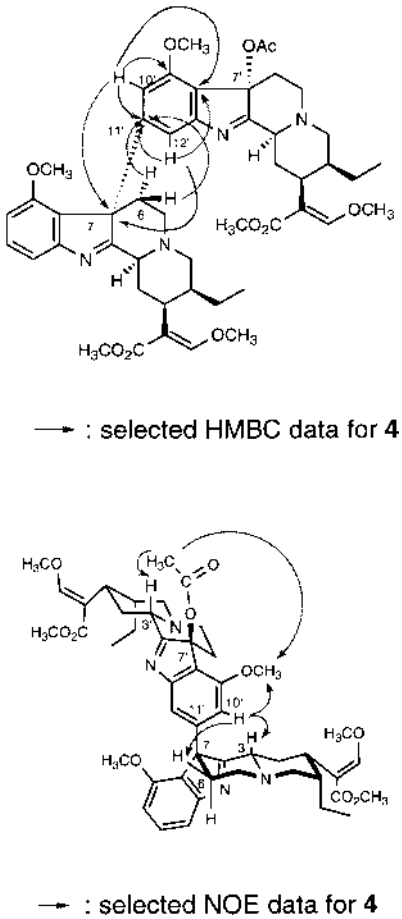

Fig. 1. Selected HMBC Data for Compound **4** and Selected NOE Data for Compound **4**

electrophilic substitution at the β-position (C-7) of the indole nucleus (Type II) as shown in Fig. 2.

To formulate the reaction mechanism, $Pb(OAc)_4$ oxidation of mitragynine (**1**) was performed in the presence of 1,3-dimethoxybenzene, which has high ability to react as a nucleophile. The formation of 1,3-dimethoxybenzene adducts (**5**) or (**6**) could be anticipated, if the reaction would respectively proceed under the mechanisms Type-I or -II. As the result, we obtained the adduct (**5**) in 6% yield along with the 7-acetoxyindolenine (**2**) and dimeric compound (**4**), indicating that the mechanism of Type-I would be plausible for this dimerization process. The indolenine residue of the upper part in **4** would be formed by subsequent $Pb(OAc)_4$ oxidation of the indole portion in the dimer produced by the first step (Type-I mechanism). Hereupon, a possibility of Type-II mechanism could not be excluded entirely, if 1,3-dimethoxybenzene would function as an electrophilic species, as depicted in Chart 2, that would be generated by the contact with $Pb(OAc)_4$.[27] But, when 1,3-dimethoxybenzene was treated with one equivalent of $Pb(OAc)_4$ under the same reaction conditions above (CH_2Cl_2, 0 °C, 1.5 h), more than 90% of the starting material was recovered. This fact would support our mechanistic consideration described above. Quite recently, the production of the dimers and trimers of 1-trimethylacetylindole in the presence of aluminum chloride was reported,[28] in which nucleophilicity of the benzene part (C-6) in the indole ring under the particular condition was

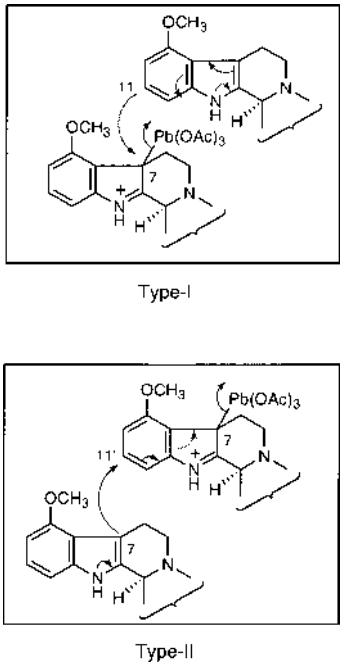

Fig. 2. Possible Mechanisms for the Formation of Dimeric Compound **4**

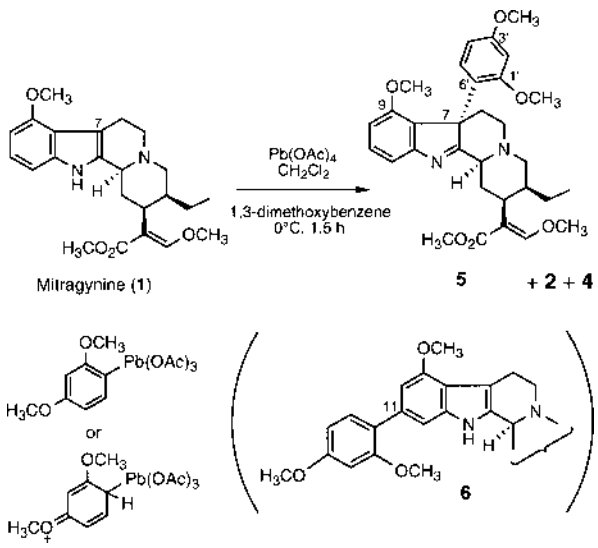

Chart 2

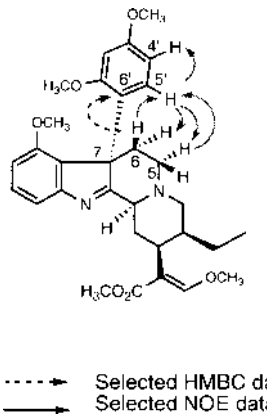

Fig. 3. Selected HMBC Data for Compound **5** (⇢) and Selected NOE Data for Compound **5** (→)

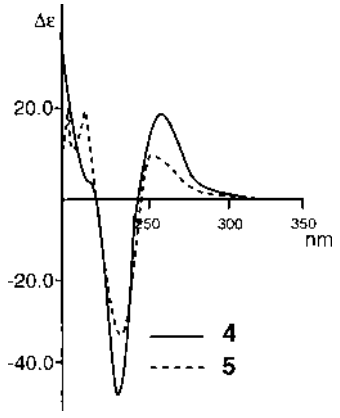

Fig. 4. CD Spectra of Compounds **4** and **5**

proposed. An interesting dimerization of the simple indole derivatives with anodic oxidation is also reported.[29] The structure of **5** was elucidated by spectroscopic analysis. Particularly, the HMBC correlation between H-6 and C-6′ on the benzene ring and the NOE observations depicted in Fig. 3 made clear the proposed structure. The dimeric compound **4** and the 1,3-dimethoxybenzene adduct (**5**) displayed almost the same CD curves as shown in Fig. 4.

Further studies on the coupling reactions of indole derivatives are in progress in our laboratory to develop new methods for the synthesis of biologically active dimeric natural alkaloids or their derivatives.

Experimental

General UV: recorded in MeOH, JASCO V-560. ^{1}H- and ^{13}C-NMR spectra: recorded at 500 and 125.65 MHz, respectively, [ppm, *J* in Hz with tetramethylsilane (TMS) as internal standard], JEOL JNM A-500. Electron impact (EI)-MS: direct probe insertion at 70 eV, JEOL JMS-AM20. FAB-MS: JEOL JMS-HX110. CD: JASCO J-720WI. TLC: precoated Kieselgel 60 F_{254} plates (Merck, 0.25 mm thick). Column Chromatography: Kieselgel 60 [Merck, 70—230 (for open chromatography) and 230—400 mesh (for flash chromatography)].

$Pb(OAc)_4$ Oxidation of Mitragynine (1) To a stirred solution of mitragynine (**1**) (500 mg, 1.26 mmol) in dry CH_2Cl_2 (11 ml) was added $Pb(OAc)_4$ (1547 mg, 91% purity, 3.15 mmol) at 0 °C under argon atmosphere. After the reaction mixture was stirred for 1.5 h, the reaction mixture was poured onto chilled water and was extracted with CH_2Cl_2 five times. The combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was separated by Al_2O_3 column chromatography (AcOEt/*n*-hexane=1 : 1) to give 7-acetoxyindolenine (**2**) (218 mg, 38%) as an amorphous powder and dimer (**4**) (16.3 mg, 3%) as an amorphous powder. UV λ_{max} (MeOH) nm: 311 (sh), 234 (log ε 4.683). IR ($CHCl_3$) cm^{-1}: 3020, 1697, 1598, 1521, 1423. ^{1}H-NMR ($CDCl_3$) δ: 7.44 (2H, s, H-17, H-17′), 7.35 (1H, br s, H-12′), 7.32 (1H, d, *J*=7.7, H-12), 7.22 (1H, dd, *J*=8.2, 7.7, H-11), 6.65 (1H, d, *J*=8.2, H-10), 6.07 (1H, br s, H-10′), 3.82 (6H, s, 17-OCH_3, 17′-OCH_3), 3.69 (9H, s, 9-OCH_3, 22-OCH_3, 22′-OCH_3), 3.62 (3H, s, 9′-OCH_3), 3.30 (1H, br d, *J*=14.1, H-6α), 3.07 (1H, br d, *J*=14.0, H-21′), 3.00 (3H, m, H-14, H-14′, H-15′), 2.96 (1H, m, H-21), 2.92 (1H, m, H-15), 2.90 (1H, m, H-3), 2.74 (1H, br d, *J*=9.0, H-3′), 2.73 (1H, br d, *J*=14.5, H-6′α), 2.65 (2H, m, H-5α, H-5′β), 2.55 (2H, m, H-5α, H-5′α), 2.40 (1H, br d, *J*=11.4, H-21′), 2.21 (1H, br d, *J*=11.7, H-21), 2.09 (3H, s, 7′-$O_2CC\underline{H}_3$), 1.90 (2H, m, H-14, H-14′), 1.72 (2H, m, H-19, H-19′), 1.67 (1H, m, H-6β), 1.60 (1H, m, H-20′), 1.53 (1H, m, H-20), 1.45 (1H, br d, *J*=3.1, H-6′β), 1.25 (2H, m, H-19, H-19′), 0.80 (6H, m, H-18, H-18′). ^{13}C-NMR ($CDCl_3$) δ: 187.1 (C-2), 181.1 (C-2′), 169.2 and 169.4 (C-22 or C-22′), 168.3 (7′-$O_2\underline{C}CH_3$), 160.7 (C-17, C-17′), 155.9 (C-13′), 155.5 (C-13), 155.3 (C-9, C-9′), 139.6 (C-11′), 133.2 (C-8), 128.9 (C-11), 121.4 (C-8′), 114.2 (C-12), 113.9 (C-12′), 111.3 (C-16), 111.1 (C-16′), 108.6 (C-10), 107.4 (C-10′), 84.5 (C-7′), 62.3 (C-3), 62.1 (C-3′), 61.7 (C-7, 17-OCH_3, 17′-OCH_3), 58.2 (C-21′), 57.9 (C-21), 55.5 (9-OCH_3), 55.2 (9′-OCH_3), 51.3 (C-5′, 22-OCH_3, 22′-OCH_3), 50.1 (C-5), 40.5 (C-20, C-20′), 39.3 (C-15′), 39.1 (C-15), 35.3 (C-6′), 32.0 (C-6), 26.3 (C-14), 25.8 (C-14′), 20.8 (7′-$O_2C\underline{C}H_3$), 19.1 (C-19′), 18.9 (C-19), 12.8 (C-18, C-18′). FAB-MS (NBA) *m/z*: 853 ([M+1]$^+$). High resolution (HR)-FAB-MS: Calcd for $C_{48}H_{61}O_{10}N_4$ [MH$^+$]: 853.4388, Found 853.4349. CD (0.13 mM, MeOH, 24 °C), nm ($\Delta\varepsilon\lambda$): 330 (0), 257 (+22.5), 233 (−44.3), 218 (+2.0), 200 (+38.0).

$Pb(OAc)_4$ Oxidation of Mitragynine (1) in the Presence of 1,3-Dimethoxybenzene To a stirred mixture of mitragynine (**1**) (100 mg, 0.25 mmol) and 1,3-dimethoxybenzene (173 mg, 1.25 mmol) in dry CH_2Cl_2 (1 ml) was added $Pb(OAc)_4$ (230 mg, 91% purity, 0.38 mmol) at 0 °C under argon atmosphere. After the reaction mixture was stirred for 1.5 h, the reaction mixture was poured onto chilled water and was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was separated by SiO_2 column chromatography (45% AcOEt/*n*-hexane) to give 7-acetoxyindolenine (**2**) (34 mg, 29%), dimer (**4**) (3.2 mg, 3%), and the adduct (**5**) (8.0 mg, 6%) as an amorphous powder. UV λ_{max} (MeOH) nm: 286 (sh), 235, 205. ^{1}H-NMR ($CDCl_3$) δ: 7.60 (1H, br d, H-5′), 7.45 (1H, s, H-17), 7.30 (1H, dd, *J*=7.6, 0.6, H-12), 7.20 (1H, dd, *J*=7.9, 7.9, H-11), 6.61 (1H, d, *J*=7.6, H-10), 6.57 (1H, dd, *J*=8.5, 2.4, H-4′), 6.29 (1H, d, *J*=2.4, H-2′), 3.84 (3H, s, 17-OCH_3), 3.80 (3H, s, 3′-OCH_3), 3.68 (3H, s, 22-OCH_3), 3.62 (3H, s, 9-OCH_3), 3.40 (1′-OCH_3), 3.25 (1H, br d, *J*=14.3, H-6α), 3.02 (1H, br dd, *J*=13.4, 11.0, H-14), 2.93 (1H, br d, *J*=9.5, H-21), 2.89 (1H, ddd, *J*=13.7, 3.4, 3.4, H-15), 2.68 (1H, br d, *J*=2.4, H-3), 2.61 (1H, br d, *J*=11.6, H-5β), 2.42 (1H, br dd, *J*=11.3, 11.3, H-5α), 2.21 (1H, br d, *J*=2.8, H-21), 1.88 (1H, br d, *J*=13.4, H-14), 1.76 (1H, m, H-19), 1.53 (1H, m, H-20), 1.50 (1H, m, H-20), 1.34 (1H, br ddd, *J*=12.8, 12.8, 3.7, H-6β), 1.23 (1H, m, H-19), 0.78 (3H, dd, *J*=4.0, 3.4, H-18). ^{13}C-NMR ($CDCl_3$) δ: 188.7 (C-2), 169.6 (C-22), 160.9 (C-17), 159.7 (C-3′), 158.3 (C-1′), 156.7 (C-13), 155.5 (C-9), 130.6 (C-8), 128.5 (C-11), 117.8 (C-6′), 114.0 (C-12), 111.4 (C-16), 108.3 (C-10), 104.8 (C-4′), 99.1 (C-2′), 62.5 (C-3), 61.9 (17-OCH_3), 58.7 (C-7), 57.9 (C-21), 55.6 (9-OCH_3), 55.3 (1′-OCH_3, 3′-OCH_3), 51.3 (C-5), 51.1 (22-OCH_3), 40.7 (C-20), 39.6 (C-15), 34.7 (C-6), 26.6 (C-14), 19.1 (C-19), 12.9 (C-18). FAB-MS (NBA) *m/z*: 535 ([M+1]$^+$). HR-FAB-MS: Calcd for $C_{31}H_{39}O_6N_2$ [MH$^+$]: 535.2808, Found 535.2816. CD (0.14 mM, MeOH, 24 °C), nm ($\Delta\varepsilon\lambda$): 350 (0), 251 (+9.5), 234 (−33.8), 219 (+17.2), 203 (+15.9), 200 (+14.5).

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