Pergamon

Tetrahedron Letters 42 (2001) 5737–5740

TETRAHEDRON LETTERS

Synthesis of new 1,1-dimethyl-1,2,3,4-tetrahydrophenanthrene derivatives

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Received 22 August 2000; revised 13 October 2000; accepted 8 June 2001

Abstract—Four new 1,1-dimethyl-1,2,3,4-tetrahydrophenanthrene derivatives, 1-amino-2-(1-hydroxy-2-propyl)-8,8-dimethyl-5,6,7,8-tetrahydrophenanthrene-3,4-dione **2**, 3-amino-2-(1-hydroxy-2-propyl)-8,8-dimethyl-5,6,7,8-tetrahydrophenanthrene-1,4-dione **3**, 1,4,9,9-tetramethyl-4,5,9,10,11,12-hexahydro-1*H*-6-oxa-1,3-diaza-dicyclopenta[*a*,*c*]phenanthrene **4**, 2,4,9,9-tetramethyl-4,5,9,10,11,12-hexahydro-1,6-dioxa-3-aza-dicyclopenta[*a*,*c*]phenanthrene **5**, were synthesized by reactions of cryptotanshinone **1**, a bioactive component from *Salvia miltiorrhiza* Bunge, with amino compounds.

Naturally occurring diterpenoid tanshinones have attracted particular attention from medicinal chemists and clinicians because many of them exhibit interesting physiological properties.[1] Cryptotanshinone **1**, a typical diterpenoid tanshinone from *Salvia miltiorrhiza* Bunge, was found to exhibit enzyme inhibitory activities.[2] Tanshinone **1** is characterised by the presence of a dihydrofuran ring and an *o*-quinone moiety, which are able to react with nucleophilic agents. In this paper, we report the interaction of cryptotanshinone with NH_3, CH_3NH_2 and $C_2H_5NH_2$ (Scheme 1), which may afford more direct evidence for the mechanism of the inhibitory activity of tanshinones with various enzymes.

The reaction of **1** with NH_3 solution (room temperature) gave two products, compounds **2** and **3**. Mass spectra and elemental analysis[3] show both have the same formula, $C_{19}H_{23}NO_3$. The IR [ν_{max} cm^{-1} (KBr)] spectrum exhibited absorption bands at 3364, 3324, 1671 (α,β-unsaturated ketone) (compound **2**); 3500, 3333, 1699 (α,β-unsaturated ketone) (compound **3**). The UV spectrum shows characteristic maxima at 279, 349, 458 nm (compound **2**) and at 272, 294, 347 nm (compound **3**). These spectral properties suggest the presence of a 1,2-naphthoquinone moiety in compound **2** and a 1,4-naphthoquinone moiety in compound **3**. ^{13}C NMR and DEPT spectra (Table 1) showed the presence of a methylene group at δ_C 64.6 ppm (compound **2**) and 65.4 ppm (compound **3**). Signals for two protons with an ABX type splitting are found at δ_H 3.69 (dd, $J=10$, 5 Hz) and δ_H 3.77 (dd, $J=10$, 6 Hz) (compound **2**), δ_H 3.70 (dd, $J=11$, 5 Hz) and δ_H 3.79 (dd, $J=11$, 8 Hz) (compound **3**). These indicate that the dihydrofuran ring of compound **1** opened during the reaction. Hence, based on the spectroscopic evidence (Table 1) and comparison of NMR data with cryptotanshinone **1** (Table 1), the structures of compounds **2** and **3** were assigned as 1-amino-2-(1-hydroxy-2-propyl)-8,8-dimethyl-5,6,7,8-tetrahydrophenanthrene-3,4-dione and 3-amino-2-(1-hydroxy-2-propyl)-8,8-dimethyl-5,6,7,8-tetrahydrophenanthrene-1,4-dione, respectively.

Reactions of **1** with CH_3NH_2 solution (room temperature) gave the major product **4**, which had molecular formula $C_{21}H_{24}N_2O$, by mass spectra and elemental analysis.[4] The IR spectrum showed no active hydrogen. Comparing the ^{13}C NMR–DEPT spectra (Table 1) with that of compound **1**, compound **4** has an additional methyl and an additional methine but no carbonyl in the aromatic ring. The ^1H NMR data of **4** show two additional single peaks at δ_H 4.05 (3H) and a δ_H 7.86 (1H). These properties are clearly indicative of the presence of an aromatic hydrogen and a methyl attached to an atom with high electronegativity (–N). It seems a ring has formed at the position that the carbonyls occupied in compound **1**. Furthermore, the ^{13}C NMR and DEPT spectra of **4** showed the presence of a methylene with δ_C 79.3. Signals for two protons with an ABX type splitting are found at δ_H 4.91 (appr t, $J=9$ Hz) and 4.37 (dd, $J=6$, 10 Hz). These properties are similar to those of compound **1**, implying the presence

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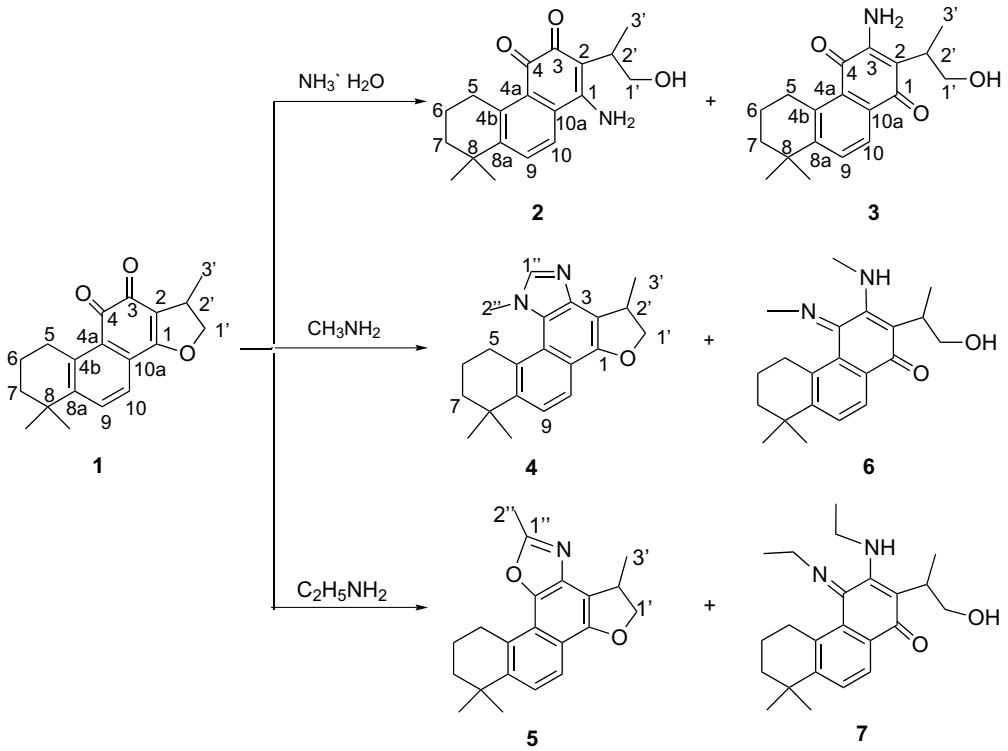
0040-4039/01/$ - see front matter
PII: S0040-4039(01)01034-6



Scheme 1.

of a dihydrofuran ring in **4**. The ^{13}C NMR–DEPT spectra also show a low-field shifting of $\delta_{C\text{-}5}$, $\delta_{C\text{-}6}$ and $\delta_{C\text{-}7}$ (numbered as Table 1, similarly hereinafter), the single peak of the six protons in the geminal dimethyl group was split into two single peaks (δ_H 1.38, 1.41). At the same time, $\delta_{C\text{-}5}$, $\delta_{C\text{-}6}$ and $\delta_{C\text{-}7}$ in compound **5** have no apparent low-field shifting, and the δ_H (1.37, 1.38) difference of protons in the geminal dimethyl group is smaller than that in compound **4**. All of these are apparently attributed to an anisotropic effect on the cyclohexane moiety, which prove that the methyl on the imidazole ring is attached to the N atom at C-4 position in **4**. Hence, the structure of compound **4** was assigned as 1,4,9,9-tetramethyl-4,5,9,10,11,12-hexahydro-1*H*-6-oxa-1,3-diazadicyclopenta[*a*,*c*]phenanthrene.

Major product **5** was obtained from the reaction of **1** with $C_2H_5NH_2$ solution (room temperature). Mass spectral and elemental analysis[5] indicated the formula to be $C_{21}H_{23}NO_2$. The IR spectrum shows no active hydrogen. Compared with compound **1**, compound **5** has an additional methyl and an additional quaternary carbon but no carbonyl in its aromatic ring. The ^1H NMR data of **5** show an additional single peak at δ_H 2.70 (3H), which means the presence of an additional methyl. As in compound **4**, a ring has formed at the position that the carbonyls occupied in **1**. However, it is not an imidazole ring, but an oxazole ring instead. Furthermore, just like compound **4** and **1**, the ^{13}C NMR and DEPT spectra (Table 1) showed the presence of a dihydrofuran ring in **5**. Based on these spectroscopic analyses, compound **5** has two possible structures: either that of 2,4,9,9-tetramethyl-4,5,9,10,11,12-hexahydro-1,6-dioxa-3-azadicyclopenta[*a*,*c*]phenanthrene or 2,4,9,9 - tetramethyl - 4,5,9,10,11,12 - hexahydro - 3,6-dioxa-1-azadicyclopenta[*a*,*c*]phenanthrene. We finally assigned it to the former since H-2′ showed correlation with C-3 in the ^{13}C–^1H COSY spectrum (Table 1).

The structure of **5** may also be supported by mechanistic analysis, the formation of the final product depending on which position (C-3 or C-4 in compound **1**) is attacked by $C_2H_5NH_2$ preferentially. Because C-1 is attached an electron-donating group (-OR), it is likely that $C_2H_5NH_2$ would attack the C-3 first leading to **5**.

Minor products **6** and **7** were also obtained from the reactions of **1** in CH_3NH_2 solution and in $C_2H_5NH_2$ solution. MS data showed molecular weights of **6** and **7** as 340 and 368, respectively; no other analysis was performed owing to limited availability. These minor products have been tentatively assigned the structures as shown in Scheme 1, R = Me, Et by analogy to structure **3**.

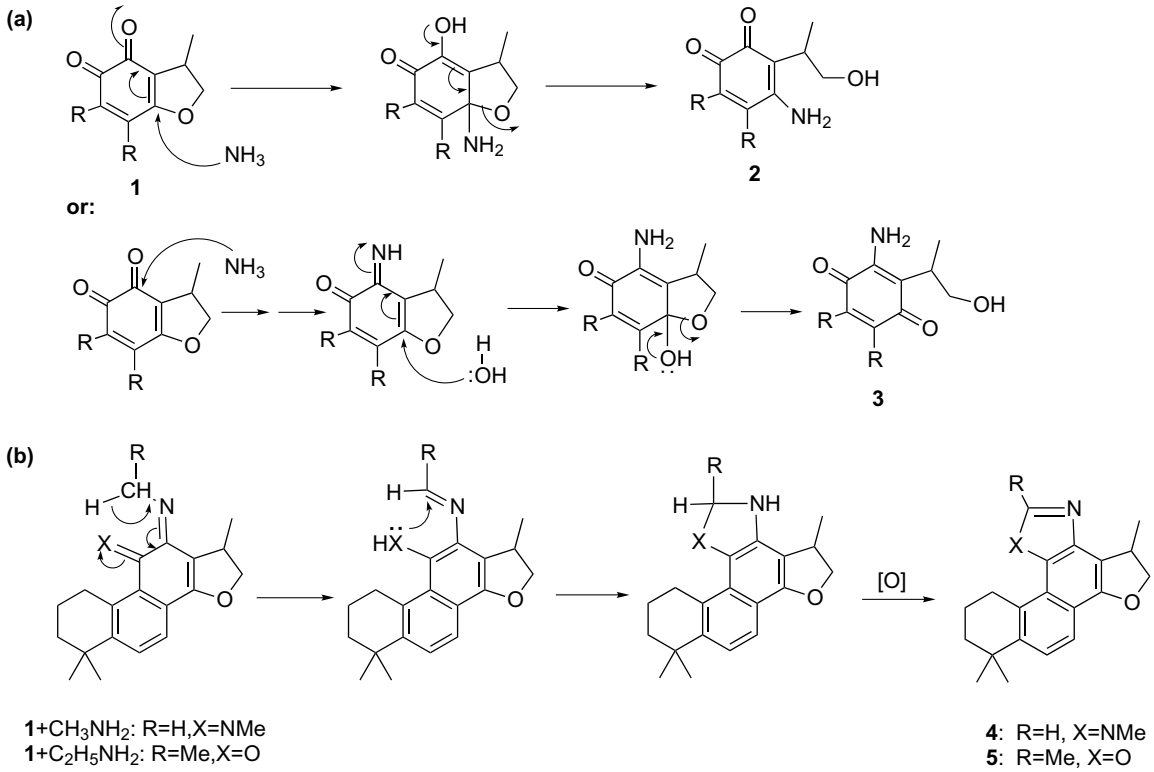
Based on the structures of the product, possible mechanisms of the reactions of **1** with NH_3, CH_3NH_2 and $C_2H_5NH_2$ are proposed (Scheme 2).

It is noticeable that compounds **4** and **5** have an imidazole ring and an oxazole ring respectively, which are formed under mild conditions. This may offer a new valuable strategy for the synthesis of imidazole ring or oxazole ring derivatives.

Table 1. NMR data for compounds **1**, **2**, **3**, **4** and **5** [500 Hz, **2**, **3** in $(CD_3)_2SO$, **1**, **4** and **5** in $CDCl_3$][a]

C	**1**			**2**		**3**			**4**		**5**		
No[b]	δ_H[c]	δ_C[c]	δ_C	HMQC δ_H	HMBC[d] δ_C	δ_C	HMQC δ_H	HMBC δ_C	δ_H	δ_C	HMQC δ_H	HMBC δ_C	δ_C
1		170.8s[e]	154.8s			184.2s				152.3s			153.0s
2		118.2s	112.8s			116.4s				115.2s*			115.2s
3		175.5s	176.9s			151.3s				143.2s*			135.6s
4		184.0s	186.3s			182.0s				140.0s*			143.0s
4a		126.1s	129.3s			128.4s				129.4s			129.4s
4b		152.3s	139.7s			139.4s				123.0s*			117.8s
5	3.22 (t, $J=7$ Hz, 2H)[f]	29.6t	29.5t	3.07 (m, 2H)	18.9, 37.6, 129.3, 139.7, 149.3	29.7t	3.09 (m, 2H)	19.7, 38.3, 128.4, 139.4, 149.0	3.27 (m, 2H)	34.3t	3.44 (t, $J=6$ Hz, 2H)	143.7, 129.4, 117.8	29.3t
6	1.78 (m, 2H)	19.3t	18.9t	1.75 (m, 2H)	29.5, 34.0, 37.6, 139.7	19.7t	1.79 (m, 2H)	29.7, 34.9, 38.3, 139.4, 19.7, 29.7	1.76 (m, 2H)	21.3t	1.98 (m, 2H)	29.3, 38.6	19.5t
7	1.64 (m, 2H)	37.8t	37.6t	1.61 (m, 2H)	18.9, 29.5, 31.2, 34.0, 149.3	38.3t	1.67 (m, 2H)	31.8, 34.9, 149.0	1.69 (m, 2H)	40.0t	1.76 (m, 2H)	31.7, 29.3	38.6t
8		34.7s	34.0s			34.9s				35.1s			34.4s
8a		143.6s	149.3s			149.0s				126.3s*			143.7s
9	7.64 (d, $J=8$ Hz, 1H)	132.5d	131.8d	7.73 (d, $J=9$ Hz, 1H)	34.0, 121.9, 131.2, 139.7	133.1d	7.80 (d, $J=8$ Hz, 1H)	34.9, 124.4, 128.0, 139.4	7.93 (d, $J=8.5$ Hz, 1H)	124.2d	7.84 (d, $J=9$ Hz, 1H)	143.7, 124.1	119.7d
10	7.51 (d, $J=8$ Hz, 1H)	122.5d	121.9d	7.91 (d, $J=8.5$ Hz, 1H)	129.3, 149.3, 154.8	124.4d	7.88 (d, $J=8$ Hz, 1H)	128.4, 149.0, 184.2	7.51 (d, $J=8.5$ Hz, 1H)	120.6d	7.49 (d, $J=9$ Hz, 1H)	116.8, 129.4	124.1d
10a		128.8s	131.2s			128.0s				118.3s*			116.8s
1′	4.90 (t, $J=9$ Hz, 1H), 4.37 (dd, $J=6$, 10 Hz, 1H)	81.5t	64.6t	3.69 (dd, $J=10$, 5 Hz, 1H), 3.77 (dd, $J=10$, 6 Hz, 1H)	14.0, 112.8	65.4t	3.70 (dd, $J=11$, 5 Hz, 1H), 3.79 (dd, $J=11$, 8 Hz, 1H)	14.4, 33.6, 116.4	4.91 (t, $J=9$ Hz, 1H), 4.37 (dd, $J=6$, 10 Hz, 1H)	79.3t	4.91 (t, $J=9$ Hz, 1H), 4.38 (dd, $J=6$, 9 Hz, 1H)	19.8	79.4t
2′	3.62 (ddq, $J=6$, 7, 9 Hz, 1H)	34.6d	32.5d	3.12 (m, 1H)	14.0, 64.6, 112.8, 154.8, 176.9	33.6d	3.12 (m, 1H)	14.4, 65.4, 116.4, 154.8, 151.3	4.10 (m, 1H)	37.1d	4.04 (m, 1H)	19.8, 79.4, 115.2, 135.6	36.8d
3′	1.36 (d, $J=7$ Hz, 3H)	18.7q	14.0q	1.14 (d, $J=7.5$ Hz, 3H)	32.5, 64.6, 112.8	14.4q	1.10 (d, $J=6$ Hz, 3H)	33.6, 65.4, 116.4	1.56 (d, $J=6.5$ Hz, 3H)	19.7q	1.52 (d, $J=6.5$ Hz, 3H)	36.8, 79.4, 115.2	19.8q
1″									7.86 (s, 1H)	145.7d			162.9s
2″									4.05 (s, 3H)	38.6q	2.70 (s, 3H)	162.9	14.9q
-OH				5.02 (s, 1H)	32.5		4.81 (s, 1H)	33.6					
$-NH_2$				7.84 (s, 2H)	131.2, 112.8		6.74 (s, 2H)	112.8, 182.0					
8-$(CH_3)_2$	1.31 (s, 6H)	31.7q	31.2q	1.31 (s, 6H)	34.0, 37.6, 149.3	31.8q	1.31 (s, 6H)	34.9, 38.3, 149.0	1.38 (s, 3H)	32.7q	1.37 (s, 3H)	143.7, 38.6, 34.4	31.7q
									1.41 (s, 3H)		1.38 (s, 3H)		

[a] All assignments were confirmed by HMQC, HMBC except **4**.
[b] Compounds are numbered for convenience, for systematic name, see abstract.
[c] Chemical shift is in ppm from TMS.
[d] H to C.
[e] Multiplicity was determined from DEPT spectrum.
[f] s, singlet; d, doublet; t, triplet; m, multiplet.
*Position not confirmed yet.



Scheme 2. (a) **1**+$NH_3 \cdot H_2O$; (b) **1**+CH_3NH_2 and **1**+$C_2H_5NH_2$.

Acknowledgements

We are indebted to the Guangdong Provincial Science Foundation and National Nature Science Foundation of China for financial support.

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3. Compound **2**: dark red powder, yield 50%, mp 186–188°C. $C_{19}H_{23}NO_3$, calcd: C, 72.82; H, 7.40; N, 4.47; found: C, 72.78; H, 7.43; N, 4.51. FABMS *m*/*z* (rel. int.): 314 $[M+1]^+$ (100), 296 $[M+1-H_2O]$ (10). UV λ_{max} nm (log ε) (EtOH) 217 (4.11), 242 (4.03), 279 (4.29), 349 (3.46), 458 (3.51). IR ν_{max} cm^{-1} (KBr): 3364, 3324, 2961, 2929, 2872, 1671, 1588, 1506, 1459, 1417, 1027, 680. δ_H, δ_C are shown in Table 1. Compound **3**: yellow powder, yield 28%, mp 62–64°C. $C_{19}H_{23}NO_3$, calcd: C, 72.82; H, 7.40; N, 4.47; found: C, 72.76; H, 7.45; N, 4.49. FABMS *m*/*z* (rel. int.): 314 $[M+1]^+$ (57), 296 $[M+1-H_2O]$ (30), 57 (100). UV λ_{max} nm (log ε) (EtOH) 217 (4.11), 240 (4.06), 272 (4.35), 294 (3.61), 347 (3.59). IR ν_{max} cm^{-1} (KBr): 3500, 3333, 2932, 2875, 1699, 1642, 1564, 1459, 1415, 1380, 1327, 1330, 1201, 1026, 644. δ_H, δ_C are shown in Table 1.
4. Compound **4**: colorless needles, yield 37%, $C_{21}H_{24}N_2O$, calcd: C, 78.71; H, 7.55; N, 8.74; found: C, 78.65; H, 7.63; N, 8.68. FABMS *m*/*z* (rel. int.): 321 $[M+1]^+$ (90), 55 (100). IR ν_{max} cm^{-1} (KBr): 2961, 2930, 2863, 1684, 1384. δ_H, δ_C are shown in Table 1. Compound **6**: FABMS *m*/*z* (rel. int.): 341 $[M+1]^+$ (25), 55 (100).
5. Compound **5**: colorless needles, yield 46%, $C_{21}H_{23}NO_2$, calcd: C, 78.47; H, 7.21; N, 4.36; found: C, 78.55; H, 7.14; N, 4.41. FABMS *m*/*z* (rel. int.): 322 $[M+1]^+$ (90), 55 (100). IR ν_{max} cm^{-1} (KBr): 2954, 2918, 2852, 1568, 1458, 1397, 1121, 956. δ_H, δ_C are shown in Table 1.