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Positional isomerization of quinine and quinidine via rhodium on alumina catalysis: practical one-step synthesis of $\Delta^{3,10}$-isoquinine and $\Delta^{3,10}$-isoquinidine

David E. Portlock,[a,*] Dinabandhu Naskar,[b] Laura West,[a] William L. Seibel,[a] Titan Gu,[a] Howard J. Krauss,[a] X. Sean Peng,[a] Paul M. Dybas,[a] Edward G. Soyke,[a] Stephen B. Ashton[a] and Jonathan Burton[a]

[a]*Combinatorial Chemistry Section, Procter & Gamble Pharmaceuticals, Health Care Research Center, 8700 Mason Montgomery Road, Mason, OH 45040, USA*

[b]*Chembiotek Research International, Block BN, Sector-V, Salt Lake City, Calcutta 700 091, India*

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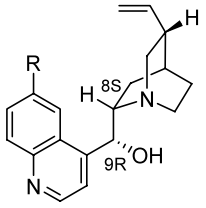
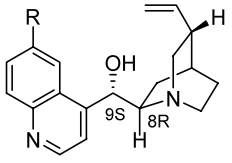
Abstract—The synthesis of $\Delta^{3,10}$-isoquinine (**5*Z*,5*E***) and $\Delta^{3,10}$-isoquinidine (**6*Z*,6*E***) was achieved in one-step through positional isomerization of the terminal alkene in the parent *cinchona* alkaloids using catalytic amounts of 5% Rh/Al_2O_3 and excess hydrochloric acid in refluxing 50% aqueous EtOH. The products were obtained in good yields as a mixture of *E* and *Z* geometric isomers and fully characterized using spectroscopic methods.

Since quinine (**1**) has historically been prescribed for the treatment of malaria,[1] there has been substantial interest in the isolation, structural characterization, synthesis, and biological profiles of its human metabolites.[2] This is also the case for quinidine (**3**), which has found clinical utility for many years in the treatment of atrial fibrillation.[3,4] Within this context we wished to develop a concise synthetic method for the preparation of the positional isomers of quinine and quinidine, i.e. $\Delta^{3,10}$-isoquinine (**5*Z*,5*E***)[5] and $\Delta^{3,10}$-isoquinidine (**6*Z*,6*E***),[6] for their utility as key synthetic intermediates. In this regard, Carroll and co-workers have elaborated (**6*Z*,6*E***) into an important (pharmacologically active) human metabolite of quinidine.[4a,7] Furthermore, much attention has been drawn to quinine (**1**), cinchonine (**2**), quinidine (**3**), and cinchonidine (**4**) analogues for their useful properties as chiral ligands in the catalytic asymmetric dihydroxylation[8] and aminohydroxylation[9] of olefins, as well as the enantioselective phase transfer catalyzed alkylation of enolates,[10] epoxidation of α,β-unsaturated ketones,[11] and the asymmetric Michael reaction.[12] Therefore, mild synthetic methods which are effective in modifying these alkaloids are of considerable interest for the rational and combinatorial design of new catalysts.



1, R = OCH_3, quinine
2, R = H, cinchonine



3, R = OCH_3, quinidine
4, R = H, cinchonidine

Although $\Delta^{3,10}$-isoquinine (**5*Z*,5*E***) and $\Delta^{3,10}$-isoquinidine (**6*Z*,6*E***) have been isolated from a complex mixture of products formed in the reaction of the parent alkaloids with boiling concentrated sulfuric acid, the yields are low and the method is impractical for synthesis.[13] To our knowledge there have not been any other reported methods for the synthesis of (**5*Z*,5*E***) and there is only one synthetically feasible method for the conversion of quinidine (**3**) to $\Delta^{3,10}$-isoquinidine (**6*Z*,6*E***). This was developed by Carroll et. al. in 1976[4a,7] and subsequently improved by Hoffmann et. al. in 1996.[14a] This four-step sequence employs the regioselective addition of fuming 62% HBr (ca. 6 equiv.) to the terminal side-chain double bond in **3**, followed by acetylation of the secondary alcohol, elimination of HBr with DBU, and finally deacetylation to give a mixture of **6*Z*** and **6*E*** in moderate to good overall

* Corresponding author. Present address: Wright State University, Department of Chemistry, Dayton, OH 45435, USA. E-mail: portlockde@aol.com

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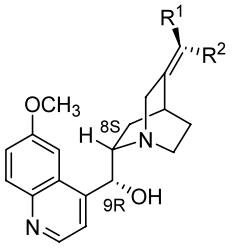
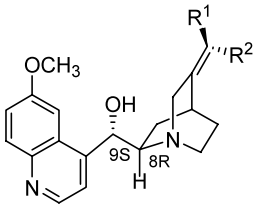
Table 1. Extent of double bond isomerization in quinine by various catalysts

Entry	Catalyst	Reaction times (2 h)			Reaction times (24 h)		
		% Quinine	% **5*Z***	% **5*E***	% Quinine	% **5*Z***	% **5*E***
1	5% Pd/C	90	8	2	81	14	5
2	5% Pd/Al_2O_3	90	8	2	85	11	4
3	5% Rh/Al_2O_3	79	18	3	0	72	28
4	5% Rh/C	60	24	16	0	72	28

yield. Although this reaction sequence has found extensive application for small scale laboratory work,[14] for our purposes we sought to develop a one-step catalytic process for the isomerization of both quinine (**1**) and quinidine (**3**).



5Z, $R^1 = CH_3$, $R^2 = H$
5E, $R^1 = H$, $R^2 = CH_3$



6Z, $R^1 = CH_3$, $R^2 = H$
6E, $R^1 = H$, $R^2 = CH_3$

In 1968 Cheung et. al.[15] observed the presence of two impurities in dihydroquinine, which were formed during the commercial hydrogenation of quinine with Pd–C in ethanol (2–7% yield). Careful isolation using preparative TLC and structural characterization by ^1H NMR spectroscopy, demonstrated that these contaminants were **5*Z*** and **5*E***.[15] Apparently, they were formed as a result of double bond migration via transition metal catalysis and were resistant to subsequent hydrogenation under these reaction conditions. Based on this literature precedent we wondered if quinine and quinidine could be *preparatively* converted to **5*Z***,**5*E*** and **6*Z***,**6*E*** in one synthetic step through the positional isomerization of the terminal alkene in the parent alkaloids using Pd–C or some other heterogeneous or homogeneous catalyst. In this paper we describe the results of these studies. Furthermore, we have qualitatively compared Pd versus Rh supported on both alumina and activated carbon for catalytic efficiency.

Transition metal reagents have been used extensively to catalyze the positional isomerization of carbon–carbon double bonds.[16,17] Practical synthetic applications have most frequently been realized with Wilkinson's catalyst[17,18] and $RhCl_3$ hydrate.[19] This isomerization approach is predicated empirically upon the preference for a double bond to migrate into conjugation and/or to a more highly alkyl substituted position. In this regard, the conversion of quinine (**1**) and quinidine (**3**) to $\Delta^{3,10}$-isoquinine (**5*Z***/**5*E***) and $\Delta^{3,10}$-isoquinidine (**6*Z***/**6*E***), respectively, should be favored thermodynamically (Saytzev's Rule), since a terminal mono-substituted double bond is isomerizing to an internal tri-substituted position. The observations of Cheung et. al.[15] are consistent with this expectation, but it was not clear a priori whether this approach could be used for *practical synthetic application* with an inexpensive hydrogenation catalyst such as 5% Pd–C. For example, it is well documented that multi heteroatom (basic) substrates can coordinate to commercial Pd/C and poison the catalytic activity.[20] We have now observed in our laboratory (as predicated by the results of Cheung et. al.[15]) that when quinine is solubilized in 50% aqueous ethanol with 10 equiv. of hydrochloric acid, treated with 5% Pd–C catalyst (5% by weight) under an atmosphere of argon, and then heated to 90°C for 24 h, that it is slowly but incompletely converted (Table 1, entry 1) to two new products (as detected by HPLC).[21] Preparative separation of the reaction components followed by structural characterization revealed that peak one is **5*Z*** and peak two is **5*E***.[22] Modifying reaction conditions to include a different catalytic support (i.e. 5% $Pd–Al_2O_3$), did not significantly improve these results (Table 1, entry 2). Although no efforts were made to drive the isomerization to completion by longer reaction times, increased temperature, or variation of solvent, we did explore additional catalysts. Remarkably, when quinine was treated with 5% Rh/Al_2O_3 or 5% Rh/C (5% by weight), complete conversion to **5*Z*** and **5*E*** was observed during a 24 h period (Table 1, entries 3 and 4). The reaction was readily performed on a larger scale (10 g) providing a 95% yield of a mixture of **5*Z***/**5*E***. Very similar results were obtained for the isomerization of quinidine (**3**) to a mixture of **6*Z*** and **6*E***.[23]

In summary, we have developed a mild and efficient one-step preparative procedure to convert quinine and quinidine to their $\Delta^{3,10}$ positional isomers.[24] This method should provide ready access to these useful synthetic intermediates.[5–12]

References

1. For leading references related to clinical applications of quinine, see: Tracy, J. W.; Webster, L. T., Jr. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th ed.; Hardman, J. G.; Limbird, L. E.; Molinoff, P. B.; Ruddon, R. W.; Gilman, A. G., Eds.; McGraw-Hill: New York, 1996; Chapter 40, pp. 978–981.
2. For examples of work related to metabolites of quinine, see: (a) Bannon, P.; Yu, P.; Cook, J. M.; Roy, L.; Villeneuve, J.-P. *J. Chromat. B.: Biomed. Sci. Applications* **1998**, *715*, 387; (b) Wanmimolruk, S.; Wong, S.-M.;

Zhang, H.; Coville, P. F.; Walker, R. J. *J. Pharmacy Pharm.* **1995**, *47*, 957.
3. For leading references related to clinical applications of quinidine, see: Roden, D. M. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th ed.; Hardman, J. G.; Limbird, L. E.; Molinoff, P. B.; Ruddon, R. W.; Gilman, A. G., Eds.; McGraw-Hill: New York, 1996; Chapter 35, pp. 869–871.
4. For examples of work related to metabolites of quinidine, see: (a) Carroll, F. I.; Abraham, P.; Gaetano, K.; Mascarella, S. W.; Wohl, R. A.; Lind, L.; Petzoldt, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3017; (b) Guengerich, F. P.; Muller-Enoch, D.; Blair, I. A. *Mol. Pharm.* **1986**, *30*, 287 and references cited therein.
5. (a) (*E*)-$\Delta^{3,10}$-Isoquinine (**5*E***) and α-isoquinine are synonyms for (3*E*,8α,9*R*)-3,10-didehydro-10,11-dihydro-6′-methoxy-cinchonan-9-ol (Chemical Abstracts 9CI, registry number: 16934-08-0); (b) (*Z*)-$\Delta^{3,10}$-Isoquinine (**5*Z***) and β-isoquinine are synonyms for (3*Z*,8α,9*R*)-3,10-didehydro - 10,11 - dihydro - 6′ - methoxy - cinchonan - 9 - ol (Chemical Abstracts 9CI, registry number: 16934-07-9).
6. $\Delta^{3,10}$-Isoquinidine (**6*Z*,6*E***) and apoquinidine methyl ether are synonyms for (9*S*)-3,10-didehydro-10,11-dihydro-6′-methoxy-cinchonan-9-ol (Chemical Abstracts 9CI, registry number: 139237-97-1). The separated **6*Z*** geometric isomer has also been reported (registry number: 60801-73-2).
7. Carroll, F. I.; Philip, A.; Coleman, M. C. *Tetrahedron Lett.* **1976**, *17*, 1757.
8. (a) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483; (b) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448.
9. Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1483 and references cited therein.
10. (a) Corey, E. J.; Bo, Y.; Busch-Peterson, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000; (b) Lygo, B. *J. Am. Chem. Soc.* **1999**, *40*, 1389.
11. Lygo, B.; Wainwright, G. P. *Tetrahedron Lett.* **1998**, *39*, 1599.
12. Alvarez, R.; Hourdin, M.-A.; Cave, C.; d'Angelo, J.; Chaminade, P. *Tetrahedron Lett.* **1999**, *40*, 7091.
13. Henry, T. A.; Solomon, W.; Gibbs, E. M. *J. Chem. Soc.* **1937**, 592. As reviewed in: Turner, R. B.; Woodward, R. B. In *The Alkaloids*; Manske, R. H. F.; Holmes, H. L., Eds.; Academic Press: New York, 1953; Vol. 3, pp. 20–21.
14. (a) von Riesen, C.; Jones, P. G.; Hoffmann, H. M. R. *Chem. Eur. J.* **1996**, *2*, 673; (b) von Riesen, C.; Hoffmann, H. M. R. *Chem. Eur. J.* **1996**, *2*, 680; (c) Langer, P.; Hoffmann, H. M. R. *Tetrahedron* **1997**, *53*, 9145; (d) Frackenpohl, J.; Langer, P.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1998**, *81*, 1429; (e) Braje, W.; Frackenpohl, J.; Langer, P.; Hoffmann, H. M. R. *Tetrahedron* **1998**, *54*, 3495; (f) Langer, P.; Frackenpohl, J.; Hoffmann, H. M. R. *J. Chem. Soc., Perkin 1* **1998**, 801.
15. Cheung, A. P.; Benitez, A.; Lim, P. *J. Org. Chem.* **1968**, *33*, 3005.
16. For reviews, see: (a) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*; John Wiley & Sons: New York, 1988; p. 188; (b) Yamamoto, A. *Organotransition Metal Chemistry: Fundamental Concepts and Applications*; Wiley: New York, 1986; p. 372; (c) Davies, S. G. *Organotransition Metal Chemistry: Applications to Organic Synthesis*; Pergamon Press: Oxford, 1982; Chapter 7.
17. (a) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 3775; (b) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224.
18. Birch, A. J.; Subba Rao, G. S. R. *Tetrahedron Lett.* **1968**, *9*, 3797.
19. (a) Calabi, L.; Danieli, B.; Lesma, G.; Palmisano, G. *Tetrahedron Lett.* **1982**, *23*, 2139; (b) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin 1* **1977**, 359; (c) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102; (d) Bertele, E.; Schudel, P. *Helv. Chim. Acta* **1967**, *50*, 2445; (e) Harrod, J. F.; Chalk, A. J. *J. Am. Chem. Soc.* **1964**, *86*, 1776.
20. For leading references, see: (a) Sajiki, H.; Hattori, K.; Hirota, H. *J. Org. Chem.* **1998**, *63*, 7990; (b) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron Lett.* **2000**, *41*, 5711; (c) Ulan, J. G.; Maier, W. F.; Smith, D. A. *J. Org. Chem.* **1987**, *52*, 3132.
21. HPLC analyses were performed on a Waters (Milford, MA, USA) Alliance HPLC/PDA chromatography system equipped with a 996 photodiode array UV detector and a 2690 separations module controlled by the Waters Millennium 2020 data system. All peaks were detected at a wavelength of 250 nm. For analytical HPLC of the quinine reaction, a 10 μL sample (1 mg/mL concentration in MeOH) was injected on a Chiralcel OJ-R (150×4.6 mm, 5 μm) column and the two isomers were separated at ambient temperature by an isocratic elution with a mobile phase consisting of MeOH:H_2O:HCO_2-H:Et_3N:THF (3/95/0.2/0.2/2, v/v/v/v/v). At a flow rate of 1 mL/min, quinine was eluted at 11.0 min, the *Z* isomer at 16.5 min, and the *E* isomer at 17.8 min.
22. Milligram samples of pure **5*Z*** and **5*E*** were isolated with difficulty using a preparative scale chiral stationary phase HPLC column as described for the analytical method.[21] NMR spectra were taken on a Bruker Avance DRX 600 spectrometer at room temperature. Chemical shift values are reported relative to tetramethylsilane (TMS) as the external standard. One-dimensional ^{1}H NOE difference, two-dimensional ^{1}H COSY and NOESY, as well as ^{1}H–^{13}C HMQC experiments were performed to assign proton and carbon resonances. **(*Z*)-$\Delta^{3,10}$-Isoquinine (5*Z*)**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.21 (m, H7^a, 1H), 1.48 (d, $J=7$ Hz, H11, 3H), 1.87 (m, H5^a, 1H), 2.24 (m, H5^b, 1H), 2.31 (m, H7^b, 1H), 2.59 (m, H4, 1H), 3.20 (m, H6^a, 1H), 3.37 (m, H8, 1H), 3.82 (s, H11′, 3H), 3.86 (m, H2, 2H), 4.58 (m, H6^b, 1H), 5.40 (m, $J=7$ Hz, H10, 1H), 6.43 (s, H9, 1H), 6.84 (d, $J=2$ Hz, H5′, 1H), 7.04 (dd, $J=2$, 9 Hz, H7′, 1H), 7.67 (d, $J=4$ Hz, H3′, 1H), 7.74 (d, $J=9$ Hz, H8′, 1H), 8.60 (broad s, H12, 1H), 8.71 (s, H2′, 1H). Important NOE: H-10 with H-4 (strong), H-2 with H-11 (strong), and no NOE observed between H-2 and H-10. ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.3 (1°, C-11), 24.6 (2°, C-7), 25.5 (2°, C-5), 32.7 (3°, C-4), 45.9 (2°, C-6), 56.8 (2°, C-2), 57.5 (1°, C-11′), 62.7 (3°, C-8), 68.1 (3°, C-9), 99.0 (3°, C-5′), 118.5 (3°, C-3′), 120.0 (3°, C-10), 122.2 (3°, C-7′), 131.8 (3°, C-8′), 147.6 (3°, C-2′).
(*E*)-$\Delta^{3,10}$-Isoquinine (5*E*). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.16 (m, H7^a, 1H), 1.54 (d, $J=7$ Hz, H11, 3H), 1.83 (m,

H5[a], 1H), 2.24 (m, H5[b], 1H), 2.33 (m, H7[b], 1H), 2.97 (m, H4, 1H), 3.23 (m, H6[a], 1H), 3.34 (m, H8, 1H), 3.64 (s, H11′, 3H), 3.82 (m, H2, 2H), 4.60 (m, H6[b], 1H), 5.30 (m, $J=7$ Hz, H10, 1H), 6.42 (s, H9, 1H), 6.85 (d, $J=2$ Hz, H5′, 1H), 7.04 (dd, $J=2$, 9 Hz, H7′, 1H), 7.67 (d, $J=4$ Hz, H3′, 1H), 7.75 (d, $J=9$ Hz, H8′, 1H), 8.60 (broad s, H12, 1H), 8.71 (d, $J=4$ Hz, H2′, 1H). Important NOE: H-11 with H-4 (strong), H-10 with H-2 (strong). ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.4 (1°, C-11), 23.5 (2°, C-7), 24.3 (2°, C-5), 25.3 (3°, C-4), 44.7 (2°, C-6), 56.4 (1°, C-11′), 57.5 (2°, C-2), 61.1 (3°, C-8), 66.9 (3°, C-9), 100.5 (3°, C-5′), 119.2 (3°, C-3′), 120.9 (3°, C-10), 122.7 (3°, C-7′), 132.0 (3°, C-8′), 147.9 (3°, C-2′).

23. For analytical HPLC of the quinidine reaction, a 10 μL sample (1 mg/mL concentration in MeOH) was injected on a Waters Symmetry Shield RP 18 (3.9×150 mm, 5 μm) column and the two isomers were separated at ambient temperature by an isocratic elution with a mobile phase consisting of CH_3CN:H_2O:HCO_2H:Et_3N (5/95/0.2/0.2, v/v/v/v). At a flow rate of 1 mL/min, quinidine was eluted at 22.2 min, the *Z* isomer at 21.0 min, and the *E* isomer at 24.0 min. For preparative HPLC of the quinidine isomerization mixture, 100 μL of sample (50 mg/mL in MeOH) was injected on a Waters Symmetry Prep C18 (7.8×300 mm, 7 μm) column with a flow rate of 6 mL/min. Using 5% Rh/Al_2O_3, the result obtained at 2 h for the isomerization of quinidine (**3**) to a mixture of **6*Z*** and **6*E*** were 49, 17 and 34%, respectively, while after 24 h, 0% quinidine (**3**), 36% **6*Z*** and 64% **6*E*** were obtained.
24. **Representative procedure for double bond isomerization**: **(a) analytical scale**: A magnetically stirred mixture of quinine or quinidine free base (1.0 g, 3.08 mmol, 1.0 equiv.), 50% aqueous EtOH (50 mL), concentrated (37%, 12N) HCl (2.56 mL, 30.8 mmol, 10.0 equiv.), and the catalyst (50 mg) was heated with an oil bath (90°) under an atmosphere of argon. Aliquot samples were removed periodically and syringe filtered through a disposable LC13 PVDF Acrodisc (pore size 0.45 μm filter, diameter 13 mm) to remove catalyst prior to HPLC analysis. The reaction was monitored by analytical HPLC.[21,23] **(b) Preparative scale**: A stirred mixture of quinine dihydrochloride or quinidine dihydrochloride salt (10.0 g, 25.2 mmol) and 5% rhodium/Al_2O_3 catalyst (500 mg) in 50% aqueous ethanol (500 mL) was refluxed under an atmosphere of nitrogen. In a typical experiment isomerization was shown by HPLC to be complete after 24 h. At this time the reaction mixture was cooled, the catalyst filtered through Celite, and the filtrate evaporated to a residue, which was dissolved in water (250 mL). The pH was adjusted to 9 with conc. NH_4OH and the resulting white precipitate washed well with water and dried to a constant weight in a vacuum desiccator. Purification of this crude product isomer mixture by preparative HPLC eluting with THF gave a mixture of the *E* and *Z* isomers as a white solid in both cases (7.8 g, 95%). Final purification to the pure individual *E* or *Z* isomers can be achieved with difficulty as described.[22,23] **$\Delta^{3,10}$-Isoquinine (5*Z*/5*E* mixture)**: CHN calcd for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.63; Found: C, 73.85; H, 7.49; N, 8.53; MS (EI): 324 (M+); NMR data.[22] **$\Delta^{3,10}$-isoquinidine (6*Z*/6*E* mixture)**: ^{1}H NMR (MeOH-d_4): δ 1.57 (m, 1H), 1.67 (d, $J=7$ Hz, 3H), 1.92 (m, 1H), 1.98 (m, 2H), 2.40 (m, 1H), 2.70 (s, 1H), 3.10–3.63 (m, 3H), 3.96 (m, 1H), 4.12 (m, 3H), 5.02 (m, 1H), 5.58 (m, 1H), 6.30 (s, 1H), 7.63 (d, 1H), 7.74 (dd, 1H), 8.11 (d, 1H), 8.16 (d, 1H), 8.94 (d, 1H). ^{13}C NMR (MeOH-d_4): 13.1, 24.2, 25.0, 33.3, 50.3, 51.9, 53.6, 57.5, 68.9, 103.2, 119.6, 121.4, 127.5, 128.8, 132.2, 133.1, 139.3, 144.8, 153.9, 163.3; HRMS: 325.191911 [calcd for $C_{20}H_{24}N_2O_2$ 325.191603 $(M+H)^+$].