Chemistry of Natural Compounds, Vol. 46, No. 3, 2010

OXIDATION OF QUINOPIMARIC ACID DERIVATIVES BY DIMETHYLDIOXIRANE

O. B. Kazakova,* E. V. Tret′yakova, A. R. Abdrakhmanova, N. N. Kabal′nova, O. S. Kukovinets, G. A. Tolstikov, and T. I. Nazyrov

UDC 547.824:542.91:548.737

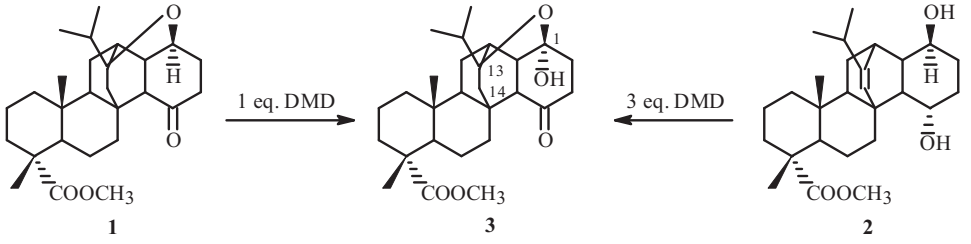
Successful application of dimethyldioxirane for selective oxidation of an oxygen-containing tertiary C atom to form a hemiacetal, the preparation of which is inaccessible by other methods, was demonstrated using dihydroquinopimaric acid derivatives as examples.

Keywords: levopimaric acid, quinopimaric acid, oxidation, dimethyldioxirane.

Abietane diterpenoids have recently aroused interest primarily because of the development of new drugs based on them. The sodium salt of 12-sulfodehydroabietinic acid (ekabet sodium) is used as an antiulcer drug [1]. Podocarpic acid derivatives are promising as platforms for preparing compounds that are effective atherosclerosis agents [2]. Quinopimaric acid and its derivatives exhibit anti-inflammatory and antiulcer activity [3, 4].

Oxidative transformations represent one type of modification of levopimaric acid derivatives. As a rule, the reaction of diene adducts of levopimaric acid (maleopimaric and fumaropimaric acids, etc.) with ozone, $KMnO_4$, and H_2O_2 produced a mixture of products in low yields [5, 6]. Recent studies have shown that dimethyldioxirane (DMD) is highly effective and selective for oxidation of steroids, terpenoids, and alkaloids [7].

Quinopimaric acid derivatives **1** and **2** (Scheme 1) have become targets for DMD oxidation. The reaction of saturated ester **1** with one equivalent of DMD in acetone involved an addition mechanism and occurred with selective oxidation of the C(1)–H bond with formation of hemiacetal **3** in quantitative yield. Reaction of unsaturated diol **2** with DMD was expected to produce the 1,4-diketo-13(14)-epoxide. However, the presence in the reaction mixture of a weak acid formed by DMD decomposition [8] apparently facilitated the formation of a –C(1)–O–C(13)– ether, analogously to that described before [9]. Oxidation of the alcohol on C(4) to a ketone produced saturated ester **1**. Then, oxidation of the C(1)–H bond was analogous to the pathway from **1** to **3**.



Scheme 1

Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, 450054, Ufa, prosp. Oktyabrya, 71, Russia, fax: (347) 235 60 66, e-mail: obf@anrb.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 328–329, May–June, 2010. Original article submitted September 29, 2009.

 0009-3130/10/4603-0388

The structure of **3** was established using NMR spectral data. Thus, the ^{13}C NMR spectrum showed a resonance for tertiary C atom C(1) at δ 100.4 ppm in contrast with the resonance at δ 72.2 ppm in the spectrum of **1** [9]. A broad resonance in the PMR spectrum at δ 2.65 ppm corresponded to the OH proton. A resonance for proton H(1) at δ 3.92 that was characteristic of **1** was missing.

Thus, the successful application of DMD for oxidation of oxygen-containing tertiary C atom into hemiacetal that is inaccessible by other methods was demonstrated using dihydroquinopimaric acid derivatives.

EXPERIMENTAL

Melting points were determined on a Boetius microstage. ^{13}C NMR (75.5 MHz) and PMR (300 MHz) spectra in $CDCl_3$ were recorded on a Bruker AM-300 spectrometer with $SiMe_4$ internal standard. Optical density was measured on a Perkin–Elmer 241 MC polarimeter in a 1-dm tube. TLC was performed on Sorbfil plates (Krasnodar, Russia) using $CHCl_3$:MeOH (25:1) with detection by H_2SO_4 solution (10%) and subsequent heating for 2–3 min at 100–120°C. Compounds **1** and **2** were synthesized as before [9, 10]. DMD solution in acetone (~0.08 M) was prepared as before [7].

Methyl-1-hydroxy-13-isopropyl-7,10a-dimethyl-4-oxo-1-oxahexacyclo[11.8.0.0^{4a,4b}.0^{12,13}.0^{1,12a}.0^{6a,10a}]-henicosan-7-carboxylate (3). Compound **1** or **2** (1 mmol, 0.43 g) in acetone (10 mL) was stirred continuously at room temperature, treated in small portions with DMD solution (1 or 3 eq.), stirred until DMD was completely consumed (monitoring by iodometry for the presence of peroxide) and the starting material disappeared (TLC monitoring). Solvent was vacuum distilled. The solid was crystallized from acetone. Yield 0.39 g (90% of **1**) and 0.37 g (84% of **2**), R_f 0.23, mp 192–194°C, $[\alpha]_D^{20}$ +52° (*c* 1.35, $CHCl_3$), $C_{27}H_{40}O_5$, MW 444.608.

PMR spectrum (δ, ppm, J/Hz): 0.91 (3H, s, H-18), 0.97 and 0.99 (2 × 3H, both d, J = 7.11, H-16/H-17), 1.09 (3H, s, H-19), 1.11–1.85 (12H, m), 1.99–2.30 (6H, m), 2.41–2.53 (5H, m), 2.65 (1H, br.s, OH), 3.61 (3H, s, H-21).

^{13}C NMR spectrum (δ, ppm): 212.0 (C-4), 178.9 (C-20), 100.4 (C-1), 86.6 (C-13), 60.2, 55.3, 51.9, 51.8, 49.9, 47.9, 47.1, 43.0 (C-14), 38.7, 38.6, 37.8, 36.4, 36.0, 35.7, 34.7, 34.0, 31.9, 21.0, 17.8, 16.9, 16.6, 16.4, 15.4.

ACKNOWLEDGMENT

The work was supported financially by the RFBR (Project No. 09-03-00831).

REFERENCES

1. Y. Ito, K. Shibata, A. Hongo, and M. Kinosita, *Eur. J. Pharmacol.*, **19**, 193 (1998).
2. W. Liu, S. Chen, J. Dropinski, L. Colwell, M. Robins, M. Szymonifka, N. Hayes, N. Sharma, K. MacNaul, M. Hernandez, C. Burton, C. P. Sparrow, J. G. Menke, and S. B. Singh, *Bioorg. Med. Chem. Lett.*, **15**, 4574 (2005).
3. O. B. Flekhter, E. V. Tret′yakova, N. S. Makara, S. F. Gabdrakhmanova, N. Zh. Baschenko, F. Z. Galin, F. S. Zarudii, and G. A. Tolstikov, *Khim.-farm. Zh.*, **37**, 71 (2003) [*Pharm. Chem. J.*, **37**, 142 (2003)].
4. O. B. Flekhter, E. V. Tret′yakova, F. Z. Galin, L. T. Karachurina, L. V. Spirikhin, F. S. Zarudii, and G. A. Tolstikov, *Khim.-farm. Zh.*, **36**, 29 (2002) [*Pharm. Chem. J.*, **36**, 428 (2002)].
5. L. H. Zalkow, M. V. Kulkarni, and N. N. Girotra, *J. Org. Chem.*, **30**, 1679 (1965).
6. W. Herz and R. C. Balckstone, *J. Org. Chem.*, **34**, 1257 (1969).
7. D. V. Kazakov, A. I. Voloshin, V. P. Kazakov, V. V. Shereshovets, and N. N. Kabal′nova, *Chemistry and Chemiluminescence of Dioxiranes* [in Russian], Nauka, Moscow, 1999.
8. S. L. Khursan, S. A. Grabovskii, N. N. Kabal′nova, E. G. Galkin, and V. V. Shereshovets, *Izv. Akad. Nauk Ser. Khim.*, **8**, 1344 (2000) [*Russ. Chem. Bull. Int. Ed.*, **8**, 1338 (2000)].
9. I. E. Smirnova, E. V. Tret′yakova, O. B. Kazakova, and Z. A. Starikova, *Zh. Strukt. Khim.*, **2**, 379 (2009).
10. I. E. Smirnova, I. V. Tret′yakova, O. B. Flekhter, L. V. Spirikhin, F. Z. Galin, G. A. Tolstikov, Z. A. Starikova, and A. A. Korlyukov, *Zh. Org. Khim.*, **44**, 1623 (2008).