Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2024, **34**, 396–397

Mendeleev Communications

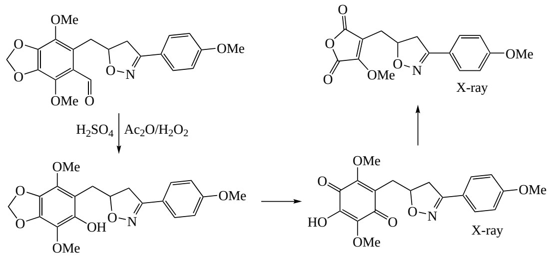
Baeyer–Villiger rearrangement of polyalkoxybenzaldehydes with benzene ring opening

Dmitry V. Tsyganov, Aida I. Samigullina and Victor V. Semenov*

*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
119991 Moscow, Russian Federation. E-mail: vs@zelinsky.ru*

DOI: 10.1016/j.mencom.2024.04.026

The Baeyer–Villiger oxidation of apiolaldehyde bearing *o*-(3-*p*-anisylisoxazolin-5-yl)methyl substituent proceeds first with the formation of the anticipated phenol. The subsequent oxidation of phenol with destruction of methylenedioxy ring leads to *p*-quinone derivative which would undergo opening of the benzene ring to finally produce maleic anhydride moiety. The structure of new compounds was proved by X-ray diffraction analysis.

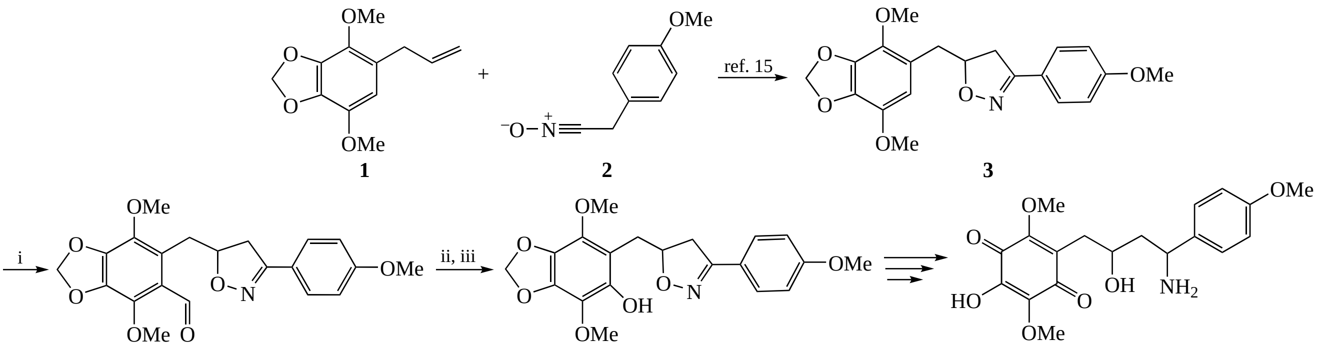


Keywords: Baeyer–Villiger rearrangement, apiol, quinone, isoxazole, maleic anhydride, antioxidant.

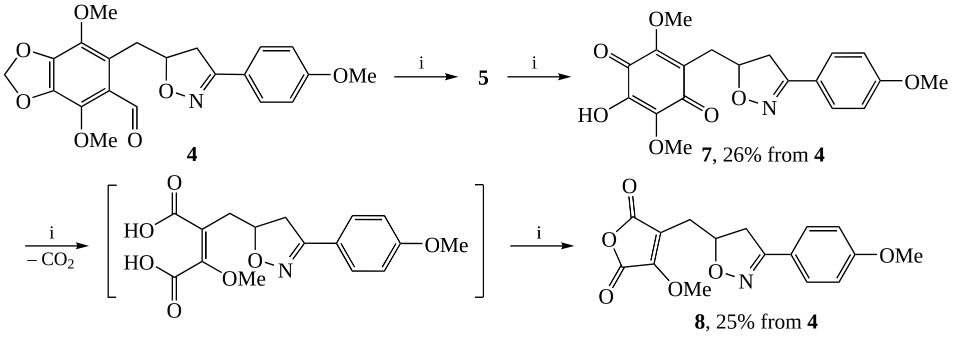
Polyhydroxy and polyalkoxy 1,4-naphthoquinones and hydroquinines are widespread in plants, animals and marine organisms.[1–4] They are of interest to medicine due to their diverse biological activity[1,5–8] such as antioxidant, antitumor or antibacterial. We have recently developed a convenient method for their synthesis using an oxidative Baeyer–Villiger rearrangements of polymethoxy(methylenedioxy)phenols[9,10] which are readily available from parsley and dill seed metabolites.[11,12] The transformation proceeded in two steps: first, the classical rearrangement of benzaldehydes into phenols occurred, which were further oxidized to quinones with the opening of the methylenedioxy moiety.[10] However, the selectivity of the reactions depended on the nature of the alkyl substituent *ortho* to the aldehyde group.

In the present work, such a rearrangement was studied using the example of apiolaldehyde bearing an *o*-(3-*p*-anisylisoxazolin-5-yl)methyl substituent (Scheme 1), which could be useful for the synthesis of quinones (like **6**) with biologically active α-amino-γ-hydroxyalkyl fragments. Quinones with such moieties as juglomycin C-amide isolated from the strain *S. coelicolor* A3(2) M145 belong to a family of promising juglomycin-type antibiotics.[13,14] Based on the reaction of dipolar cycloaddition of apiol **1** and nitrile oxide **2**, isoxazoline **3** was synthesized,[15] which was further formylated into aldehyde **4** according to the reported procedure.[10]

Aldehyde **4** normally undergoes the Baeyer–Villiger rearrangement in the presence of SeO_2 in H_2O_2/Bu^tOH system to form phenol **5** (see Scheme 1). However, phenol **5** being isolated could not be further oxidized to quinone **7** (Scheme 2) under standard conditions (H_2O_2–Ac_2O), similarly to most phenols with an apiol fragment.[9,10] Under these conditions, according to HRMS data, more than five products are formed, among which only traces of maleic anhydride derivative **8** (a decomposition product of quinone **7**) were detected. Fortunately, the *in situ* Baeyer–Villiger oxidation of compound **4** in the same medium (H_2O_2–Ac_2O) could proceed further with the formation of quinone **7** and maleic anhydride **8** derivatives in acceptable yields (totally 51%). Apparently, in the first case, at a high initial concentration of polymethoxyphenol **5**, a side interaction of the resulting highly reactive quinone **8** with the initial **5** occurs.



Scheme 1 *Reagents and conditions*: i, HCO_2Et, PCl_5, $SnCl_4$, CH_2Cl_2, room temperature, 5 h (ref. 10); ii, H_2O_2, SeO_2, Bu^tOH, 50–60 °C, 3 h; iii, MeOH, Et_3N, 20 °C, 1 h, then HCl/CH_2Cl_2, 20 °C.



Scheme 2 *Reagents and conditions*: i, H_2O_2, H_2SO_4, Ac_2O, room temperature, 6 h.

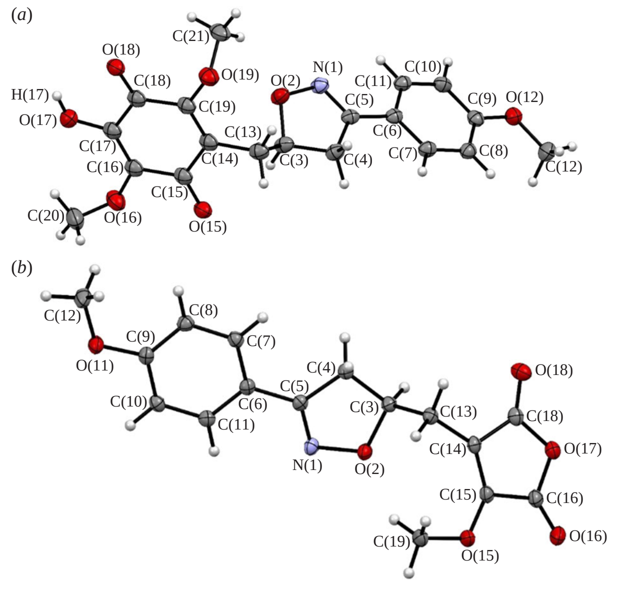


Figure 1 Structures of (*a*) compound **7** and (*b*) compound **8** in crystals. The thermal vibrations of atoms are represented by ellipsoids in anisotropic approximation (p = 50%).

Apparently, phenol **5** upon formation is further oxidized with methylenedioxy ring destruction to produce quinone **7**. Further oxidative degradation of the benzene ring and decarboxylation occur to form a maleic acid derivative, which would cyclize in an acid medium to maleic anhydride **8** (see Scheme 2). The structure of new products **7** and **8** was proved by X-ray diffraction analysis (Figure 1).†

In summary, polyalkoxybenzaldehydes in the Baeyer–Villiger rearrangement can undergo further oxidation with the decomposition of the benzene ring.

The authors gratefully acknowledge support from the Russian Science Foundation (grant no. 24-23-00024).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.04.026.

References

1 R. H. Thomson, *Naturally Occurring Quinones*, 2nd edn., Academic Press, London, 1971.
2 J. F. Pennock, in *Terpenoids in Plants*, ed. J. B. Pridham, Academic Press, London, 1967, pp. 129–146.
3 M. Ochi, H. Kotsuki, S. Inoue, M. Taniguchi and T. Tokoroyama, *Chem. Lett.*, 1979, **8**, 831.
4 R. J. Capon, E. L. Ghisalberti and P. R. Jeffereis, *Phytochemistry*, 1981, **20**, 2598.
5 Y. Hou, E. A. Vasileva, A. Carne, M. McConnell, A. El-Din Bekhit and N. P. Mishchenko, *RSC Adv.*, 2018, **8**, 32637.
6 C. L. L. Chai, J. A. Elix and F. K. E. Moore, *J. Org. Chem.*, 2006, **71**, 992.
7 K. Masuda, S. Funayama, K. Komiyama, I. Unezawa and K. Ito, *J. Nat. Prod.*, 1987, **50**, 418.
8 J. Daironas and I. N. Zilfikarov, *Prirodnye naftokhinony: perspektivy meditsinskogo primeneniya (Natural 1,4-Naphthoquinones: Prospects for Medical Use)*, OntoPrint, Moscow region, Schyolkovo, 2011 (in Russian).
9 F. Dallacker, *Monatsh. Chem.*, 1969, **100**, 742.
10 D. V. Tsyganov, D. V. Demchuk, O. I. Adaeva, L. D. Konyushkin, M. E. Minyaev, V. N. Khrustalev and V. V. Semenov, *Mendeleev Commun.*, 2023, **33**, 539.
11 V. V. Semenov, V. A. Rusak, E. M. Chartov, M. I. Zaretskii, L. D. Konyushkin, S. I. Firgang, A. O. Chizhov, V. V. Elkin, N. N. Latin, V. M. Bonashek and O. N. Stas'eva, *Russ. Chem. Bull.*, 2007, **56**, 2448 (*Izv. Akad. Nauk, Ser. Khim.*, 2007, 2364).
12 V. V. Semenov, A. S. Kiselyov, I. Y. Titov, I. K. Sagamanova, N. N. Ikizalp, N. B. Chernysheva, D. V. Tsyganov, L. D. Konyushkin, S. I. Firgang, R. V. Semenov, I. B. Karmanova, M. M. Raihstat and M. N. Semenova, *J. Nat. Prod.*, 2010, **73**, 1796.
13 K. Yoshioka, S. Kamo, K. Hosaka, R. Sato, Y. Miikeda, Y. Manabe, S. Tomoshige, K. Tsubaki and K. Kuramochi, *ACS Omega*, 2019, **4**, 11737.
14 J. Gubbens, H. Zhu, G. Girard, L.Song, B. I. Florea, P. Aston, K. Ichinose, D. V. Filippov, Y. H. Choi, H. S. Overkleeft, G. L. Challis and G. P. van Wezel, *Chem. Biol.*, 2014, **21**, 707.
15 D. V. Tsyganov, M. M. Krayushkin, L. D. Konyushkin, Y. A. Strelenko, M. N. Semenova and V. V. Semenov, *J. Nat. Prod.*, 2016, **79**, 923.

Received: 1st February 2024; Com. 24/7382

---

† *Crystal data for* **7**. $C_{19}H_{19}NO_7$ (M = 373.35), orthorhombic, space group $P2_12_12_1$, at T = 100(1) K, a = 4.79523(7), b = 8.20587(11) and c = 43.0852(6) Å, β = 90°, V = 1695.36(4) Å^3, Z = 4, d_{calc} = 1.463 g cm^{-3}, F(000) = 784, μ = 0.949 mm^{-1}. 13607 reflections (3493 independent reflections, R_{int} = 0.0435) were measured and used in the refinement. The refinement converged to R_1 = 0.0435 for 3277 observed reflections with $I > 2\sigma(I)$ and wR_2 = 0.1137 for all independent reflections, GOF = 1.075.

Crystal data for **8**. $C_{16}H_{15}NO_6$ (M = 317.29), monoclinic, space group $P2_1/n$, at T = 100(1) K, a = 8.29006(9), b = 14.54498(18) and c = 11.91274(13) Å, β = 94.3701(10)°, V = 1432.25(3) Å^3, Z = 4, d_{calc} = 1.471 g cm^{-3}, F(000) = 664, μ = 0.962 mm^{-1}. 16647 reflections (3102 independent reflections, R_{int} = 0.0311) were measured and used in the refinement. The refinement converged to R_1 = 0.0345 for 2886 observed reflections with $I > 2\sigma(I)$ and wR_2 = 0.0935 for all independent reflections, GOF = 1.046.

CCDC 2291864 (**7**) and 2291865 (**8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.