ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 9, pp. 1410–1411. © Pleiades Publishing, Ltd., 2009.
Original Russian Text © S.G. Polonik, N.S. Polonik, V.A. Denisenko, O.P. Moiseenko, V. F. Anufriev, 2009, published in Zhurnal Organicheskoi Khimii, 2009, Vol. 45, No. 9, pp. 1423–1424.

SHORT COMMUNICATIONS

Synthesis and Transformation of 2-Amino-3-hydroxynaphthazarin

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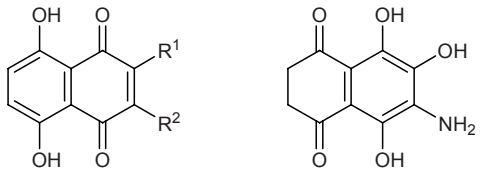
Received March 2, 2009

DOI: 10.1134/S1070428009090164

Aminonaphthoquinones constitute a group of compounds that are rarely encountered in nature [1]. Some aminonaphthoquinone derivatives were found to exhibit cytotoxic [2] and antimalarial activity [3]. Aminohydroxynaphthazarins (5,8-dihydroxy-1,4-naphthoquinones), specifically echinamines A and B, have been isolated recently from the sea urchin *Scaphechinus mirabilis* and synthesized [4]. These compounds displayed high antioxidant activity *in vitro*. Although the structure of echinamines A and B was proved by their total synthesis [4, 5], no convenient preparative procedures for the synthesis of analogous aminohydroxynaphthazarins have been developed so far.



I–**V**, **VII** **VI**

I, $R^1 = R^2 = Cl$; **II**, $R^1 = ONa$, $R^2 = NO_2$; **III**, $R^1 = OH$, $R^2 = Cl$; **IV**, $R^1 = OH$, $R^2 = NO_2$; **V**, $R^1 = OH$, $R^2 = NH_2$; **VII**, $R^1 = R^2 = OH$.

In the present communication we describe the synthesis of 2-amino-3-hydroxynaphthazarin and its acid-catalyzed transformation into spinazarin that is the natural pigment of echinoderms [6]. For this purpose, commercial 2,3-dichloronaphthazarin (**I**) was treated in acetone–methanol with 6 equiv of sodium nitrite over a period of 1 h [7]. The precipitate of sodium salt **II** was acidified with hydrochloric acid, and by preparative thin-layer chromatography we isolated 3% of known chloroquinone **III** [8] (resulting from attack on dichloronaphthazarin **I** by oxygen atom of nitrite ion) and 87% of the target 2-hydroxy-3-nitronaphthazarin (**IV**). The latter was reduced with sodium dithionite to obtain 2-amino-3-hydroxynaphthazarin (**V**) (78%) and product of its further reduction, dihydro derivative **VI** (10%). Amine **V** was converted into spinazarin (**VII**, 80%) by heating in boiling 30% aqueous sulfuric acid over a period of 1.5–2 h.

The structure of quinones **II**–**VII** was confirmed by the IR, ^{1}H NMR, and mass spectra.

2,5,8-Trihydroxy-3-nitro-1,4-dihydronaphthalene-1,4-dione (IV). 2,3-Dichloronaphthazarin (**I**), 0.258 g (1 mmol), was dissolved in 20 ml of a 1:1 (by volume) acetone–methanol mixture, 0.345 g (6 mmol) of powdered sodium nitrite was added, and the mixture was stirred for 1 h. The precipitate was filtered off, acidified on a filter with concentrated hydrochloric acid, and colored substances were washed off from the precipitate with acetone. The filtrate was evaporated to dryness with addition of toluene, and the residue was subjected to preparative thin-layer chromatography on silica gel using hexane–benzene–acetone (2:1:1 by volume) as eluent (four elutions) to isolate 0.007 g of 2-chloro-3-hydroxynaphthazarin (**III**), R_f 0.85, and 0.219 g of nitroquinone (**IV**), R_f 0.81, mp 227–229°C (from acetone), red prisms. IR spectrum ($CHCl_3$), ν, cm^{-1}: 3373, 1715, 1677, 1620, 1577, 1546, 1457, 1388, 1321, 1264, 1213, 1198, 1145, 1086. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 7.33 d and 7.40 d (6-H, 7-H, J = 9.5 Hz), 11.60 s and 12.30 s (5-OH, 8-OH). Mass spectrum, m/z (I_{rel}, %): 251 (84) $[M]^+$, 233 (8), 221 (100), 204 (42), 193 (41), 176 (37), 162 (22), 147 (14), 134 (17), 119 (23), 108 (25), 92 (16), 79 (14), 58 (25), 43 (60). Found: M 251.0057. $C_{10}H_5NO_7$. Calculated: M 251.0066.

2-Amino-3,5,8-trihydroxy-1,4-dihydronaphthalene-1,4-dione (V). Nitronaphthazarin **IV**, 0.251 g (1.0 mmol), was dissolved in 40 ml of water, and 4–5 mmol of finely ground $Na_2S_2O_4$ was added in portions under stirring over a period of 1 h. The precipitate was filtered off, washed with water, dried, and dissolved in acetone. By preparative TLC (see above) we isolated 0.173 g of aminonaphthazarin **V**, R_f 0.78, mp 237–240°C (from acetone), brown needles. IR spectrum ($CHCl_3$), ν, cm^{-1}: 3015, 2965, 2937, 2876, 1464, 1381, 1245, 1067, 1026. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 4.78 br.s (2H, NH_2), 6.40 s (1H, 3-OH), 7.10 d and 7.14 d (1H each, 6-H, 7-H, J = 9.4 Hz), 11.92 s and 12.03 s (1H each, 5-OH, 8-OH). Mass spectrum, m/z (I_{rel}, %): 221 (100) $[M]^+$, 204 (15), 193 (83), 176 (26), 165 (8), 147 (19), 137 (6), 120 (18), 108 (5), 92 (12), 81 (8), 63 (5), 53 (7). Found: M 221.0329. $C_{10}H_7NO_5$. Calculated: M 221.0324.

6-Amino-5,7,8-trihydroxy-1,2,3,4-tetrahydronaphthalene-1,4-dione (VI) was isolated as by-product. Yield 0.022 g, R_f 0.75, mp 206–208°C (decomp., from acetone), brown prism-like crystals. IR spectrum (CCl_4), ν, cm^{-1}: 3458 (OH), 3367 (NH_2), 2365, 1633 (C=O), 1606 (C=O), 1446, 1409, 1384, 1295, 1201, 1149, 1100, 1019, 943. ^1H NMR spectrum (250 MHz, $CDCl_3$), δ, ppm: 2.98 m (4H, CH_2), 4.64 br.s (2H, NH_2), 6.01 br.s (1H, 7-OH), 11.42 s and 12.70 s (1H each, 5-OH, 8-OH). Mass spectrum, m/z (I_{rel}, %): 223 (100) $[M]^+$, 205 (30), 194 (6), 177 (19), 149 (11), 139 (15), 121 (13), 93 (15), 65 (9). Found: M 223.0478. $C_{10}H_9NO_5$. Calculated: M 223.0481.

Spinazarin (VII). A mixture of 0.221 g of amine **V** and 10 ml of 30% aqueous sulfuric acid was heated for 1.5–2 h under reflux. Red needles separated and were filtered off, washed with water, dried, and identified by comparing with an authentic sample [6]. Yield 0.178 g.

This study was performed in the framework of State contract no. 02522.11.2013 (June 21, 2007).

REFERENCES

1. Thomson, R.H., *Naturally Occurring Quinones III: Recent Advances*, London: Chapman and Hall, 1987, 3rd ed.; Thomson, R.H., *Naturally Occurring Quinones IV: Recent Advances*, London: Blackie Academic & Professional, 1997, 4th ed.
2. Esteves-Souza, A., Figueiredo, D.V., Esteves, A., Camara, S.A., Vargas, M.D., Pinto, A.C., and Echevarria, A., *Braz. J. Med. Biol. Res*., 2007, vol. 40, p. 1399.
3. Kapadia, G.J., Azuine, M.A., Balasubramanian, V., and Sridhar, R., *Pharmacol. Res*., 2001, vol. 43, p. 363.
4. Pokhilo, N.D., Shuvalova, M.I., Lebed'ko, M.V., Sopelnyak, G.I., Yakubovskaya, A.Y., Mishenko, N.P., Fedoreev, S.A., and Anufriev, V.Ph., *J. Nat. Prod*., 2006, vol. 69, p. 1125.
5. Pokhilo, N.D., Yakubovskaya, A.Y., Denisenko, V.A., and Anufriev, V.Ph., *Tetrahedron Lett*., 2006, vol. 47, p. 1385.
6. Yakubovskaya, A.Ya., Pokhilo, N.D., Mishchenko, N.P., and Anufriev, V.F., *Izv. Ross. Akad. Nauk, Ser. Khim*., 2007, p. 788.
7. Ulrich, H. and Richter, R., *Methoden der organischen Chemie (Houben–Weyl)*, Müller, E., Bayer, O., Meerwein, H., and Ziegler, K., Eds., Stuttgart: Georg Thieme, 1977, 4th ed., vol. 7/3a, p. 533.
8. Glazunov, V.P., Yakubovskaya (Chizhova), A.Ya., Pokhilo, N.D., Bochinskaya, N.V., and Anufriev, V.F., *Izv. Ross. Akad. Nauk, Ser. Khim*., 2003, p. 186.