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4-HYDROXY-2-QUINOLONES 146*. SYNTHESIS AND STRUCTURE OF 1,1'-DIALLYL-4,4'-DIHYDROXY-1H,1'H-[3,3']BIQUINOLINYL-2,2'-DIONE

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The methyl ester of N-allyl-2-methoxycarbonylsuccinanilic acid is partially converted to 1,1'-diallyl-4,4'-dihydroxy-1H,1'H-[3,3']biquinolinyl-2,2'-dione in refluxing toluene in the presence of metallic sodium. A possible mechanism for the occurrence of these chemical processes is discussed.

Keywords: biquinolines, 4-hydroxy-2-oxo-1,2-dihydroquinolines, succinanilic acids, X-ray structural analysis, ester condensation.

The most convenient starting compounds for the synthesis of natural furo- and pyranoquinoline alkaloids are 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-acetic acids. In turn, these are prepared from methyl 2-alkoxycarbonylsuccinanilic acid esters. The succinic acid residue in such compounds contains two reaction centers similar in nucleophilic properties. Hence carrying out an ester condensation in refluxing toluene in the presence of metallic sodium always ends in the formation of a mixture of the two methyl esters of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-acetic and 2,5-dioxo-2,3,4,5-tetrahydro-1H-benzo[*b*]azepine-4-carboxylic acids. With subsequent work up using an aqueous solution of potassium hydroxide the first of these is hydrolyzed and the second additionally undergoes a recyclization to give finally the same corresponding quinoline-3-acetic acid [2-4].

However, after repeating the method described as reported in detail in the study [2] we have found that heterocyclization of the methyl N-allyl-2-methoxycarbonylsuccinanilic acid (**1**) gives an unexpected further product together with these quinoline and benzazepine derivatives. The yield is quite low (around 4%) and thus is hardly likely to have a preparative value. None the less, for broadening the theoretical basis of the features of formation of azaheterocycles in ester condensation conditions, the observation is undoubtedly of interest.

Unfortunately, ^{1}H NMR spectroscopy proved of little value in establishing the structure of the compound synthesized. However, an unambiguous answer to this question came from X-ray structural analysis which showed that the sample investigated is 1,1'-diallyl-4,4'-dihydroxy-1H,1'H-[3,3']biquinolinyl-2,2'-dione (**2**), i.e. consisting of a dimer containing two fragments (**A** and **B**) joined by the $C_{(8a)}$–$C_{(8b)}$ chemical bond and twisted relative to one another (torsional angle $C_{(7a)}$–$C_{(8a)}$–$C_{(8b)}$–$C_{(9b)}$ = -43.0(3)º). This mutual positioning of the

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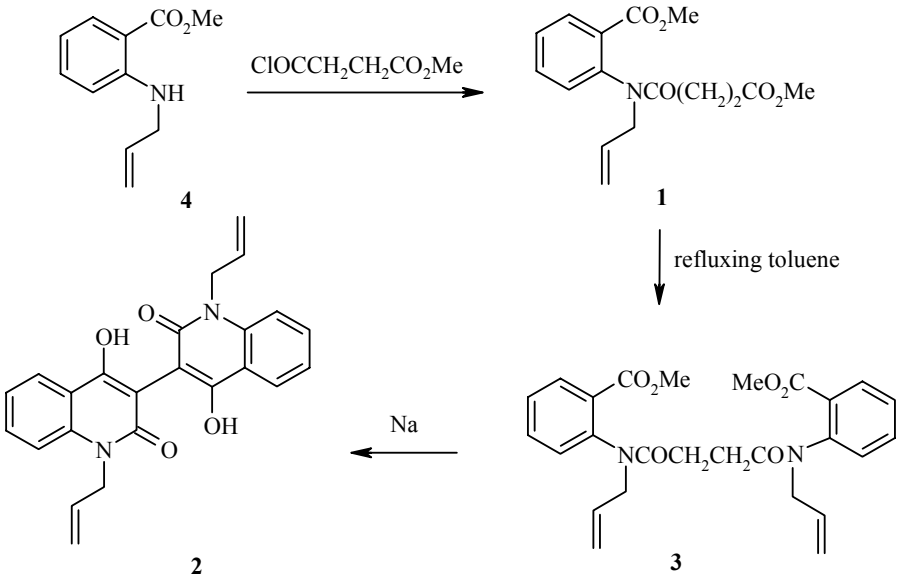
A and **B** fragments (see Fig. 1) is stabilized by strong intramolecular hydrogen bonds $O_{(2a)}$–$H_{(2Oa)}$···$O_{(1b)}$ H···O 1.54(3) Å, O–H···O 169(3)º, and $O_{(2b)}$–$H_{(2Ob)}$···$O_{(1a)}$ H···O 1.55(3) Å, O–H···O 158(3)º. In addition, the formation of the hydrogen bonds leads to a marked lengthening of the bond $O_{(1)}$–$C_{(9)}$ to 1.265(2) in **A** and 1.264(2) Å in **B** (mean value 1.210 Å [5]) and $C_{(7)}$–$C_{(8)}$ to 1.380(3) in **A** and 1.379(3) Å in **B** (1.331 Å) together with a simultaneous shortening of the $O_{(2)}$–$C_{(7)}$ bond to 1.341(2) in **A** and 1.343(3) Å in **B** (1.362 Å) and $C_{(6)}$–$C_{(7)}$ to 1.437(3) in **A** and 1.435(3) Å in **B** (1.470 Å).



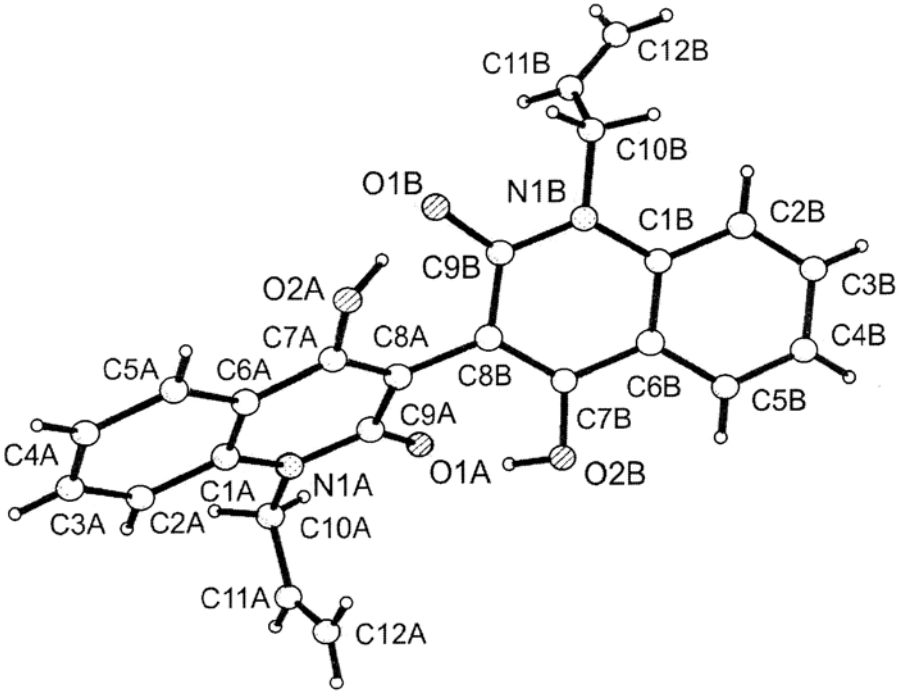


Fig. 1. Structure of the biquinoline **2** with atomic numbering.

TABLE 1. Bond Lengths (*l*) in the Biquinoline Structure **2**

Bond	*l*, Å	Bond	*l*, Å
$N_{(1A)}$–$C_{(9A)}$	1.370(3)	$N_{(1A)}$–$C_{(1A)}$	1.391(3)
$N_{(1A)}$–$C_{(10A)}$	1.468(3)	$O_{(1A)}$–$C_{(9A)}$	1.265(2)
$O_{(2A)}$–$C_{(7A)}$	1.341(2)	$C_{(1A)}$–$C_{(2A)}$	1.395(3)
$C_{(1A)}$–$C_{(6A)}$	1.400(3)	$C_{(2A)}$–$C_{(3A)}$	1.375(3)
$C_{(3A)}$–$C_{(4A)}$	1.387(3)	$C_{(4A)}$–$C_{(5A)}$	1.366(3)
$C_{(5A)}$–$C_{(6A)}$	1.411(3)	$C_{(6A)}$–$C_{(7A)}$	1.437(3)
$C_{(7A)}$–$C_{(8A)}$	1.380(3)	$C_{(8A)}$–$C_{(9A)}$	1.447(3)
$C_{(8A)}$–$C_{(8B)}$	1.496(3)	$C_{(10A)}$–$C_{(11A)}$	1.488(3)
$C_{(11A)}$–$C_{(12A)}$	1.290(3)	$N_{(1B)}$–$C_{(9B)}$	1.370(3)
$N_{(1B)}$–$C_{(1B)}$	1.392(3)	$N_{(1B)}$–$C_{(10B)}$	1.474(3)
$O_{(1B)}$–$C_{(9B)}$	1.264(2)	$O_{(2B)}$–$C_{(7B)}$	1.343(3)
$C_{(1B)}$–$C_{(2B)}$	1.401(3)	$C_{(1B)}$–$C_{(6B)}$	1.406(3)
$C_{(2B)}$–$C_{(3B)}$	1.372(3)	$C_{(3B)}$–$C_{(4B)}$	1.387(4)
$C_{(4B)}$–$C_{(5B)}$	1.365(3)	$C_{(5B)}$–$C_{(6B)}$	1.403(3)
$C_{(6B)}$–$C_{(7B)}$	1.435(3)	$C_{(7B)}$–$C_{(8B)}$	1.379(3)
$C_{(8B)}$–$C_{(9B)}$	1.448(3)	$C_{(10B)}$–$C_{(11B)}$	1.492(4)
$C_{(11B)}$–$C_{(12B)}$	1.261(4)		

TABLE 2. Valence Angles (ω) in the Biquinoline Structure **2**

Angle	ω, deg	Angle	ω, deg
$C_{(9A)}$–$N_{(1A)}$–$C_{(1A)}$	122.7(2)	$C_{(9A)}$–$N_{(1A)}$–$C_{(10A)}$	116.9(2)
$C_{(1A)}$–$N_{(1A)}$–$C_{(10A)}$	120.4(2)	$N_{(1A)}$–$C_{(1A)}$–$C_{(2A)}$	122.0(2)
$N_{(1A)}$–$C_{(1A)}$–$C_{(6A)}$	118.6(2)	$C_{(2A)}$–$C_{(1A)}$–$C_{(6A)}$	119.3(2)
$C_{(3A)}$–$C_{(2A)}$–$C_{(1A)}$	120.1(2)	$C_{(2A)}$–$C_{(3A)}$–$C_{(4A)}$	121.1(3)
$C_{(5A)}$–$C_{(4A)}$–$C_{(3A)}$	119.6(2)	$C_{(4A)}$–$C_{(5A)}$–$C_{(6A)}$	120.6(2)
$C_{(1A)}$–$C_{(6A)}$–$C_{(5A)}$	119.2(2)	$C_{(1A)}$–$C_{(6A)}$–$C_{(7A)}$	119.3(2)
$C_{(5A)}$–$C_{(6A)}$–$C_{(7A)}$	121.5(2)	$O_{(2A)}$–$C_{(7A)}$–$C_{(8A)}$	123.5(2)
$O_{(2A)}$–$C_{(7A)}$–$C_{(6A)}$	114.9(2)	$C_{(8A)}$–$C_{(7A)}$–$C_{(6A)}$	121.6(2)
$C_{(7A)}$–$C_{(8A)}$–$C_{(9A)}$	117.5(2)	$C_{(7A)}$–$C_{(8A)}$–$C_{(8B)}$	124.0(2)
$C_{(9A)}$–$C_{(8A)}$–$C_{(8B)}$	118.6(2)	$O_{(1A)}$–$C_{(9A)}$–$N_{(1A)}$	118.0(2)
$O_{(1A)}$–$C_{(9A)}$–$C_{(8A)}$	121.9(2)	$N_{(1A)}$–$C_{(9A)}$–$C_{(8A)}$	120.0(2)
$N_{(1A)}$–$C_{(10A)}$–$C_{(11A)}$	114.3(2)	$C_{(12A)}$–$C_{(11A)}$–$C_{(10A)}$	126.6(2)
$C_{(9B)}$–$N_{(1B)}$–$C_{(1B)}$	122.5(2)	$C_{(9B)}$–$N_{(1B)}$–$C_{(10B)}$	117.0(2)
$C_{(1B)}$–$N_{(1B)}$–$C_{(10B)}$	120.4(2)	$N_{(1B)}$–$C_{(1B)}$–$C_{(2B)}$	122.1(2)
$N_{(1B)}$–$C_{(1B)}$–$C_{(6B)}$	118.4(2)	$C_{(2B)}$–$C_{(1B)}$–$C_{(6B)}$	119.4(2)
$C_{(3B)}$–$C_{(2B)}$–$C_{(1B)}$	119.9(2)	$C_{(2B)}$–$C_{(3B)}$–$C_{(4B)}$	120.8(3)
$C_{(5B)}$–$C_{(4B)}$–$C_{(3B)}$	120.1(2)	$C_{(4B)}$–$C_{(5B)}$–$C_{(6B)}$	120.7(2)
$C_{(5B)}$–$C_{(6B)}$–$C_{(1B)}$	118.9(2)	$C_{(5B)}$–$C_{(6B)}$–$C_{(7B)}$	121.7(2)
$C_{(1B)}$–$C_{(6B)}$–$C_{(7B)}$	119.4(2)	$O_{(2B)}$–$C_{(7B)}$–$C_{(8B)}$	123.5(2)
$O_{(2B)}$–$C_{(7B)}$–$C_{(6B)}$	114.7(2)	$C_{(8B)}$–$C_{(7B)}$–$C_{(6B)}$	121.8(2)
$C_{(7B)}$–$C_{(8B)}$–$C_{(9B)}$	117.2(2)	$C_{(7B)}$–$C_{(8B)}$–$C_{(8A)}$	122.9(2)
$C_{(9B)}$–$C_{(8B)}$–$C_{(8A)}$	119.8(2)	$O_{(1B)}$–$C_{(9B)}$–$N_{(1B)}$	117.1(2)
$O_{(1B)}$–$C_{(9B)}$–$C_{(8B)}$	122.4(2)	$N_{(1B)}$–$C_{(9B)}$–$C_{(8B)}$	120.5(2)
$N_{(1B)}$–$C_{(10B)}$–$C_{(11B)}$	112.7(2)	$C_{(12B)}$–$C_{(11B)}$–$C_{(10B)}$	126.8(3)

All of the non-hydrogen atoms of the biquinoline **2** lie in a single plane in each of the monomer fragments with the exception of $C_{(11)}$ and $C_{(12)}$. An attractive interaction $H_{(5)}\cdots O_{(2)}$ occurs (2.43 in **A** and 2.42 Å in **B**, sum of van der Waal radii 2.46 Å [6]). There is a marked repulsion between the allyl substituent on the nitrogen atom, the neighboring carbonyl group, and the benzene ring atoms (shortened intramolecular contacts $H_{(2)}\cdots C_{(10)}$ 2.55 in **A** and 2.56 in **B** (2.87), $H_{(2)}\cdots H_{(10a)}$ 2.05 in **A** and 2.04 in **B** (2.34), $H_{(10a)}\cdots C_{(2)}$ 2.57 in **A** and 2.55 in **B** (2.87), and $H_{(10b)}\cdots O_{(1)}$ 2.25 in **A** and 2.28 Å in **B** (2.46 Å)) which causes the terminal vinyl fragments in the N-allyl groups to be placed virtually perpendicular to the quinolone ring planes (torsional angle $C_{(9)}$–$N_{(1)}$–$C_{(10)}$–$C_{(11)}$ 93.9(2) in **A** and -89.8(2)º in **B**) and situated in an *sp*-conformation relative to the $N_{(1)}$–$C_{(10)}$ bond in fragment **A** and an *ac*-conformation relative to this bond in fragment **B** (torsional angle $N_{(1)}$–$C_{(10)}$–$C_{(11)}$–$C_{(12)}$ -4.9(4) in **A** and -131.4(3)º in **B**). A shortened intramolecular contact $H_{(12b)}\cdots N_{(1)}$ 2.56 Å (2.67 Å) arises in fragment **A**. An increase in the valence angle $C_{(12)}$–$C_{(11)}$–$C_{(10)}$ to 126.6(2) in **A** and 126.8(3) Å in **B** should also be noted.

In conclusion, it is necessary to stress that the synthetic precursor of the biquinoline **2** can only be the corresponding symmetrical succinic acid N,N'-dianilide **3**. Its formation is feasible by two routes, during the acylation of the N-allylanthranilate **4** by methylsuccinyl chloride (under conditions where the acylating agent contains an admixture of the succinic acid dichloride) or directly at the heterocyclization stage. Chromato-mass spectrometric monitoring confirmed the high purity of the acyl halide used in the synthesis. Hence partial conversion of the monoanilide **1** to N,N'-dianilide **3** occurs upon treatment with sodium in refluxing toluene. The reason for this transformation is likely due to several factors, one of which is the rather high reflux temperature of the solvent. A similar effect has repeatedly been seen by us for similarly structured malonic [7, 8] and methanetricarboxylic [8] acid derivatives upon thermolysis or refluxing in DMF. However, carrying out a similar conversion of, for example, ethyl 2-methoxycarbonylmalonanilate in the presence of strong bases proved impossible because of the very ready occurrence of a Dieckmann condensation. But in the case of the closely structured succinanilic acid ester **1** the formation of the symmetrical N,N'-dianilide **3** in these conditions accounts for a marked competition to ester condensation. In other words a second, and evidently more significant, factor contributing to formation of the N,N'-dianilide **3** is the fact that the reactivity of the methylene chain in the succinic acid derivatives is considerably less than that of the highly nucleophilic malonates. As a result part of the monoanilide **1** is successfully converted to the N,N'-dianilide **3** before heterocyclization and after that the suspended metallic sodium catalyzes the subsequent closing of the two quinolone rings of biquinoline **2** (since the generation of a dianion by this basis is unlikely).

EXPERIMENTAL

The ^{1}H NMR spectrum of the biquinoline **2** was recorded on a Varian Mercury VX-200 spectrometer (200 MHz) using DMSO-d_6 and with TMS as internal standard.

1,1'-Diallyl-4,4'-dihydroxy-1H,1'H-[3,3']biquinolinyl-2,2'-dione (2). Methylsuccinyl chloride (16.56 g, 0.011 mol) was added with stirring and cooling in running water to a mixture of the N-allyl-substituted methylanthranilate **4** (19.12 g, 0.1 mol) and triethylamine (15.4 ml, 0.011 mol) in dry toluene (100 ml) and left at room temperature for 10-12 h. The reaction mixture was diluted with water and stirred thoroughly. The organic layer was separated and dried over anhydrous $CaCl_2$. The solution of monoanilide **1** obtained was added dropwise with vigorous stirring to refluxing toluene (150 ml) containing metallic sodium (3.45 g, 0.15 mol) and then refluxed for 3.5 h. Excess sodium was decomposed by the addition of absolute methanol (20 ml). The reflux condenser was exchanged for a direct and the solvent was evaporated *in vacuo*. The residue was cooled and treated with ether (100 ml). The precipitated biquinoline **2** was filtered off, washed with ether, and dried. Yield 0.84 g (4.2%); mp 174-176ºC (DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.07 (2H, s, 4,4'-OH); 7.99 (2H, dd, *J* = 8.0 and *J* = 1.4, H-5,5'); 7.59 (2H, td, *J* = 7.6 and *J* = 1.8, H-7,7'); 7.40 (2H, d, *J* = 8.2, H-8,8'); 7.24

(2H, t, J = 7.6, H-6,6'); 5.90 (2H, m, 2C<u>H</u>=CH_2); 5.20-5.08 (4H, m, $2NCH_2CH$=C<u>H_2</u>); 4.86 (4H, s, $2NCH_2$). Found, %: C 71.87; H 5.09; N 7.07. $C_{24}H_{20}N_2O_4$. Calculated, %: C 71.99; H 5.03; N 7.00.

X-Ray Crystallographic Investigation. Crystals of the biquinoline **2** are triclinic (DMF), at 20ºC: a = 8.801(2), b = 10.009(2), c = 11.528(2) Å, α = 89.97(2), β = 69.21(2), γ = 85.10(2)º, V = 945.4(3) $Å^3$, M_r = 400.42, Z = 2, space group $P\bar{1}$, d_{calc} = 1.407 g/cm^3, μ(MoKα) = 0.097 mm^{-1}, F(000) = 420. The unit cell parameters and intensities of 7825 reflections (4314 independent, R_{int} = 0.038) were measured on an Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω-scanning to $2\theta_{max}$ = 55º). The structure was solved by a direct method using the SHELXTL program package [10]. The positions of the hydrogen atoms were revealed in electron density difference synthesis and refined using the "riding" model with U_{iso} = 1.2 U_{eq} for the non-hydrogen atom bound to the given hydrogen. The hydroxyl group hydrogens taking part in the formation of the hydrogen bonds were refined isotropically. The structure was solved using F^2 full matrix least squares analysis for non-hydrogen atoms to wR_2 = 0.127 for the 4246 reflections (R_1 = 0.049 for 2060 reflections with $F > 4\sigma$ (F), S = 0.928). The full crystallographic information has been placed in the Cambridge structural data bank (reference CCDC 631478). The interatomic distances and valence angles are given in Tables 1 and 2.

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