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OXIDATIVE COUPLING IN A SERIES OF DERIVATIVES OF 4a,9-DIAZA-1,2,4a,9a-TETRAHYDROFLUORENE. 6*. REACTIONS WITH SUBSTITUTED 2-AMINOETHANOLS

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Oxidative coupling of derivatives of 4a,9-diaza-1,2,4a,9a-tetrahydro-9H-fluorene with 2-ethyl-, 2,2-dimethyl-, and 2-hydroxymethyl-2-methylaminoethanol in the presence of MnO_2 led to the selective formation of the corresponding mono- and di(hydroxymethyl)quinonediimines, subsequent cyclization of which gave the products of 6,7-annelation. Coupling with 2,2-di(hydroxymethyl)aminoethanol gave the annelation products directly.

Keywords: 2-aminoethanol, 4a,9-diaza-1,2,4a,9a-tetrahydrofluorene, quinonediimine, annelation, oxidative coupling.

In the preceding paper [1] we described the oxidative coupling of derivatives of 4a,9-diaza-1,2,4a,9a-tetrahydro-9H-fluorene (**1**) with aromatic *ortho*-binucleophiles (*o*-aminophenol and *o*-aminothiophenol) to give N-(2-hydroxyphenyl)-N-(2-mercaptophenyl)quinonediimines, cyclization of which gave products of 6,7-annelation – polycyclic compounds containing phenoxazine and phenothiazine units. In this paper we describe the oxidative coupling of compounds **1** with aliphatic derivatives of 2-aminoethanol which allows the introduction of the biologically active 2-aminoethanol group into the quinonoid structure. The possibility is studied of cyclization of the coupling products to give 6,7-annelated derivatives containing benzoxazine units. Annelation of quinoid compounds with aliphatic 1,2-binucleophiles has been seldom studied and is limited to an example of nucleophilic substitution of halogen by ethylenediamine in the quinoid nucleus with subsequent condensation at a quinoid carbonyl [2], but nucleophilic addition of 2-aminoethanol to 9-aza-3H-fluoren-3-one under oxidative conditions gave a 3,4-annelated oxazole ring [3].

Oxidative coupling of the derivatives **1a,b** with the 2-mono- and 2,2-disubstituted aminoethanols **2-5** in the presence of MnO_2 led to the selective formation of the corresponding mono- and di(hydroxymethyl)quinonediimines **6a,b** – **8a,b**.

Coupling with unsubstituted aminoethanol occurred in an extremely unselective manner; it was not possible isolate individual reaction products. Oxidative coupling of **1a,b** with 2,2-di(hydroxymethyl)aminoethanol gave the products of 6,7-annelation **10a,b**, directly. The intermediate quinonediimines **9a,b** were not observed.

* For part 5, see [1].

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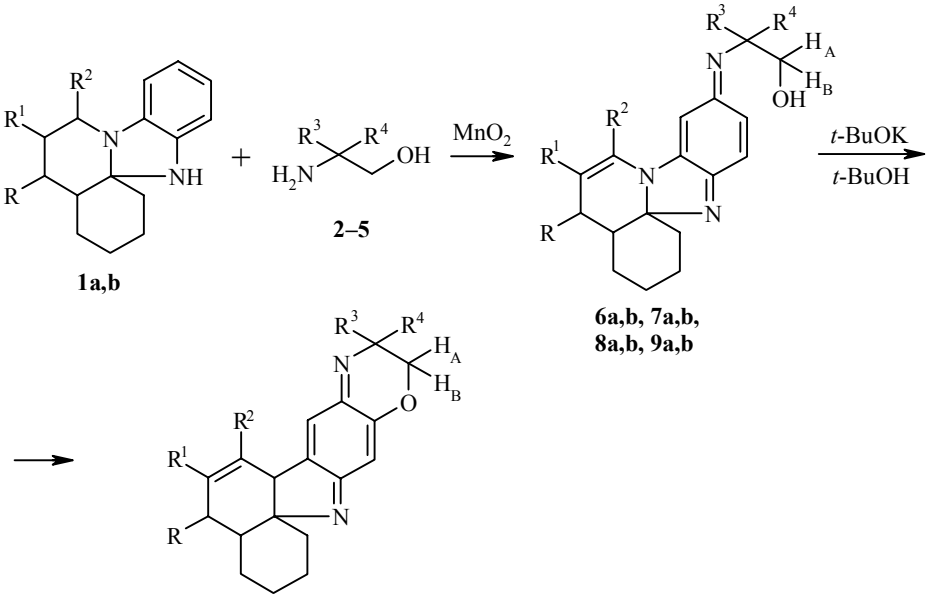
Compounds **6b**, **7a,b** cyclized into the corresponding compounds **11b, 12a,b** under the influence of potassium *tert*-butoxide, but compounds **6a, 8a,b** did not cyclize under these conditions. Note that the selectivity of the oxidative coupling reaction and the ease of cyclization increases with the number and volume of the substituents at atom $C_{(2)}$ in the aminoethanol unit.



1a,b **2–5** **6a,b, 7a,b, 8a,b, 9a,b**

1, 6–11 a R = H, $R^1 + R^2 = (CH_2)_4$; **b** R = R^2 = Ph, R^1 = H; **2, 6, 11** $R^3 = CH_2OH$, $R^4 = CH_3$; **3, 7, 12** $R^3 = R^4 = CH_3$; **4, 8** R^3 = H, $R^4 = C_2H_5$; **5, 9, 10** $R^3 = R^4 = CH_2OH$

Bands corresponding to the double bonds of the enamine ($C_{(3)}$–$C_{(4)}$) and quinoid structures were observed in the IR spectra of all the synthesized compounds (Table 2). Bands corresponding to hydrogen bonded hydroxyl groups were observed in the spectra of all compounds except **12a,b**. A hypsochromic shift of

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Mass spectrum, *m/z* $[M]^+$	Found, % / Calculated, %			mp, °C	Yield, %
			C	H	N		
6a	$C_{23}H_{31}N_3O_2$	382.3	72.44 / 72.75	8.14 / 7.96	11.02 / 11.10	191-193	76
6b	$C_{31}H_{33}N_3O_2$	479.9	77.66 / 78.11	6.96 / 6.51	8.77 / 9.08	166-168	71
7a	$C_{23}H_{31}N_3O$	366.3	75.62 / 75.37	8.49 / 8.22	11.51 / 11.60	190-192	73
7b	$C_{31}H_{33}N_3O$	464.4	80.35 / 80.00	7.13 / 7.49	9.07 / 9.35	213-215	71
8a	$C_{23}H_{31}N_3O$	366.2	75.62 / 76.04	8.49 / 8.23	11.51 / 11.27	147-149	69
8b	$C_{31}H_{33}N_3O$	463.8	80.35 / 80.81	7.13 / 6.82	9.07 / 8.83	217-219	71
10a	$C_{23}H_{29}N_3O_3$	396.3	69.87 / 70.15	7.34 / 7.71	10.63 / 10.52	232-234	72
10b	$C_{31}H_{31}N_3O_3$	494.1	75.46 / 75.29	6.29 / 6.65	8.52 / 8.84	226-228	62
11b	$C_{31}H_{31}N_3O_2$	478.3	77.99 / 77.58	6.50 / 6.42	8.81 / 8.89	112-114	76
12a	$C_{23}H_{29}N_3O$	364.2	76.03 / 76.45	7.99 / 7.81	11.57 / 11.51	79-81	40
12b	$C_{31}H_{31}N_3O$	462.3	80.69 / 80.50	6.72 / 6.93	9.11 / 9.02	248-250	43

TABLE 2. IR and Electronic Spectra of the Compounds Synthesized

Compound	IR spectra, ν, cm^{-1}				Electronic spectra, λ, nm
	$C_{(3)}=C_{(4)}$	C=N	$C=C_{quin}$	OH	
6a	1669	1634	1581, 1535	3337 br.	520, 313, 257
6b	1647	1630	1590, 1567	3351 br. 3253	465, 305, 245
7a	1671	1629	1590, 1540	3437 br.	515, 310, 258
7b	1648	1632	1590,1532	3444 br.	465, 310, 240
8a	1660	1630	1590, 1532	3170 br.	500, 305, 255
8b	1646	1630	1592, 1531	3334	450, 300, 245
10a	1670	1635	1605, 1589	3356 br.	465, 315, 265
10b	1652	1640	1603, 1587	3385 br.	455, 315, 240
11b	1652	1643	1604,1588	3400	458, 314, 230
12a	1667	1635	1601, 1590	—	480, 315, 258, 220
12b	1651	1640	1604, 1587	—	450, 312, 234

the absorption maximum in the visible region was observed in the electronic spectra (Table 2) of all the compounds on going from the **a**-derivatives to the **b**-derivatives, which is in agreement with previously published results [4] and is associated with the decreased coplanarity of the enamine unit with the quinone. A definite hypsochromic shift of the absorption band in the visible region is also observed on going from the "open" (**6a,7a,b**) to the "cyclic" (**11b, 12a,b**) forms of the corresponding quinonediimines, which is also probably connected with destruction of planarity on cyclization.

The chemical shifts and multiplicities of all the proton signals in the ^1H NMR spectra of the new compounds (Table 3) correspond to the proposed structures. In contrast to other results [1, 4], in this case the presence of *Z,E*-isomers at the C=N bond, which is revealed by doubling of the signals of the quinone protons, is observed only for compound **8a** which is evidently linked to a low barrier for *Z,E*-inversion and the negligible difference in enthalpies of formation of the stereoisomers for the remaining compounds. The molecular ion has the greatest intensity in the mass spectra. In most spectra fragmentation corresponding to loss of the CH_2OH group (M - 32) was observed.

EXPERIMENTAL

IR spectra of KBr disks or CH_2Cl_2 solutions were recorded with a Spectrum-1000 BX-II spectrometer, ^1H NMR spectra of $CDCl_3$ or DMSO-d_6 solutions with TMS as internal standard were recorded with a Bruker WM-250 (250 MHz) machine. Chromatograms and mass spectra were recorded on a liquid chromatograph with an HP LC-MSD 1100 mass spectrometric detector using API-CI-Positive chemical ionization and fragmentation current of 75 V. The column used was a reverse phase Shimpack FLC-NH_2 and the mobile phase was isopropanol, methanol. The course of the reaction and the purity of the products obtained was monitored on Silufol and Sorbfil plates. Melting points were determined with a Boetius apparatus.

Synthesis of the Quinonediimines 6-8 and 10. A 10-12-fold molar excess of MnO_2 was added to a solution of compound **1** (1 mmol) and compound **2-5** (1.1 mmol) in acetone (50 ml, for compounds **2-4**) or ethanol (50 ml, for compound **5**). The mixture was stirred at room temperature until the spot of starting material **1** on TLC had disappeared. MnO_2 was filtered off, washed with acetone or propanol until the washing solution was weakly colored. A precipitate formed on cooling the combined filtrate (in the cases of **6b, 7a,b, 8a,b**). To separate products **6a** and **10a,b** the filtrate was diluted threefold with water, a few ml of Na_2CO_3 solution was added, the precipitate was separated, washed with water and dried. Compound **8b** underwent additional column chromatography (Al_2O_3 sorbent, eluent hexane–ethyl acetate from 15:1 to pure ethyl acetate). In the remaining cases the precipitate was chromatographically pure.

TABLE 3. ^{1}H NMR Spectra of the Compounds Synthesized

Com-pound	^{1}H NMR spectra, δ, ppm (coupling constant *J*, Hz)							
	2-H	3-H, d	5-H	7-H	8-H	CH_3	Ar–H, m	Other
6a	—*	—	6.20 (s)	8.10 (d, J = 10.0)	7.23 (d, J = 10.0)	1.33 (3H, s)	—	3.84 (1H, d, J_{AB} = -12.0, H_A); 3.87 (1H, d, J_{BA} = -12.0, H_B); 4.09 (2H, d, J = -12.0, CH_2); 5.00 (1H, br. s); 10.70 (1H, br. s, OH)
6b	3.86 (dd, $J_{1\,2}$ = 11.0; $J_{2\,3}$ = 3.0)	5.40 (J = 3.0)	4.70 (d, J = 1.5)	6.79 (br. d, J = 10.0)	6.95 (d, J = 10.0)	0.68 (3H, s)	7.20-7.50	3.42 (4H, m, 2·CH_2)
7a	—*	—	5.80 (d, J = 2.0)	6.70 (dd, $J_{7\,8}$ = 10.0; $J_{5\,7}$ = 2.0)	6.86 (d, J = 10.0)	1.30 (6H, s)	—	3.39 (2H, s, CH_2)
7b	3.89 (dd, $J_{1\,2}$ = 10.0; $J_{2\,3}$ = 3.0)	5.48 (J = 3.0)	4.79 (s)	—*^{2}	6.90 (d, J = 10.0)	0.78 (3H, s); 0.89 (3H, s)	7.20-7.50	3.33 (2H, br. s, CH_2)
8a	—*	—	6.77 (0.5H, d, J = 2.0, *Z*-isomer); 6.80 (0.5H, d, J = 2.0, *E*-isomer)	6.97 (dd, $J_{7\,8}$ = 10.0; $J_{5\,7}$ = 2.0)	7.17 (d, J = 10.0)	0.95 (3H, t, J = 7.5)	—	3.79 (1H, dd, J_{AB} = -11.0; J_{AX} = 7.5, H_A) 3.82 (1H, dd, J_{BA} = -11.0; J_{BX} = 7.5, H_B)
8b	3.89 (dd, $J_{1\,2}$ = 10.0; $J_{2\,3}$ = 3.0)	5.59 (J = 3.0)	4.75 (d, J = 2.0)	—*^{2}	7.07 (d, J = 10.0)	0.62 (3H, t, J = 7,5)	7.20-7.50	3.00 (1H, m); 3.70 (2H, m)
10a	—*	—	6.45 (s)	—	6.52 (s)	—	—	3.80 (4H, m); 4.20 (2H, m)
10b	3.90 (dd, $J_{1\,2}$ = 10.0; $J_{2\,3}$ = 3.0)	5.70 (J = 3.0)	5.30 (s)	—	6.63 (s)	—	7.15-7.60	3.72 (4H, m); 4.08 (1H, d, J_{AB} = -12.0, H_A); 4.14 (1H, d, J_{BA} = -12.0, H_B)
11b	3.90 (dd, $J_{1\,2}$ = 10.0; $J_{2\,3}$ = 3.5)	5.72 (J = 3.5)	5.48 (s)	—	6.70 (s)	1.27 (3H, s)	7.15-7.75	4.00 (2H, d, J = -11.0, CH_2), 4.25 (2H, m)
12a	—*	—	5.76 (s)	—	6.26 (s)	1.27 (3H, s); 1.28 (3H, s)	—	—
12b	3.92 (dd, $J_{1\,2}$ = 10.0; $J_{2\,3}$ = 3.0)	5.52 (J = 3.0)	4.74 (s)	—	6.36 (s)	1.17 (3H, s); 1.19 (3H, s)	7.20-7.45	—

* Overlapped by signal of aliphatic protons.

*^{2} Overlapped by signals of aromatic protons.

Synthesis of Quinonediimines 11b, 12a,b. Potassium *tert*-butoxide (1.1 mmol) was added to a solution of compound **6b, 7a,** or **7b** (1 mmol) in *tert*-butanol (30 ml) and the solution was stirred at room temperature until the spot of the starting material on the TLC had disappeared (about 400 h). The mixture was diluted threefold with water, neutralized with AcOH solution, and extracted with water. The ether extract was dried over anhydrous $MgSO_4$ and evaporated at room temperature. The residue was triturated with a little hexane, filtered, and purified by preparative TLC (sorbent Al_2O_3, eluent petroleum ether, methylene chloride).

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