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OXIDATIVE COUPLING OF 4α,9-DIAZA-1,2,4α,9α-TETRAHYDRO-FLUORENES. 5*. REACTION WITH *o*-AMINOPHENOL AND *o*-AMINOTHIOPHENOL

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Oxidative coupling of 4α,9-diaza-1,2,4α,9α-tetrahydro-9H-fluorenes with o-aminophenol and o-aminothiophenol in the presence of MnO_2 gives o-hydroxyphenyl- and o-mercaptophenylquinonediimines, cyclization of which gives derivatives of phenoxazine and phenothiazine.

Keywords: phenoxazines, phenothiazines, quinonediimines, oxidative coupling.

The oxidative coupling of 4α,9-diaza-1,2,4α,9α-tetrahydro-9H-fluorenes with primary amines gives quinonediimines of the 4α,9-diaza-1,2,4α,9α-tetrahydro-6H-fluorene series [2]. It is of interest to study similar oxidative coupling with primary amines containing additional O-, S-, and N- nucleophilic centers since, in this case, there is the possibility of an intramolecular cyclization to give phenoxa(thia)zine structures possessing potential biological activity [3].

We have examined the reaction of the compound **1a,b** derivatives with aromatic *o*-binucleophiles (*o*-aminophenol, *o*-aminothiophenol, and anthranilic acid) in the presence of MnO_2 to give the quinonediimines **2a,b, 3a,b, 4a**. Along with compounds **3a,b** there were formed in small amounts the disulfides **7a,b** and **8a,b** but it was not possible to separate them from compounds **3a,b** due to their very similar chromatographic properties.

Treatment of compounds **2a,b** with acetic acid (and compounds **3a,b** with NaOH in ethanol) caused an intramolecular cyclization to form the phenoxazine **5b** and phenothiazine **6a,b** products. The cyclization product from compound **2a** could not be isolated although a reaction did occur. Compound **5b** had been prepared before by the reaction of the corresponding quinonemonoimine of the diazatetrahydrofluorene series with *o*-aminophenol but in significantly lower yield [4]. Compound **4** did not cyclize in the conditions indicated above.

The IR spectra of all of the compounds prepared (Table 1) showed absorption bands for enamine [$C_{(3)}$–$C_{(4)}$] bonds and a quinoid structure typical of the quinoid system of diazatetrahydrofluorene. The spectra of compounds **2a,b** showed a band for a hydrogen bonded OH group and the spectrum of compound **4a** an absorption for the carboxylic C=O group. There are also weak absorption bands for an NH_2 group in the spectra of compounds **3a,b** due to the admixture of compounds **7a,b**.

* For Communication 4 see [1].

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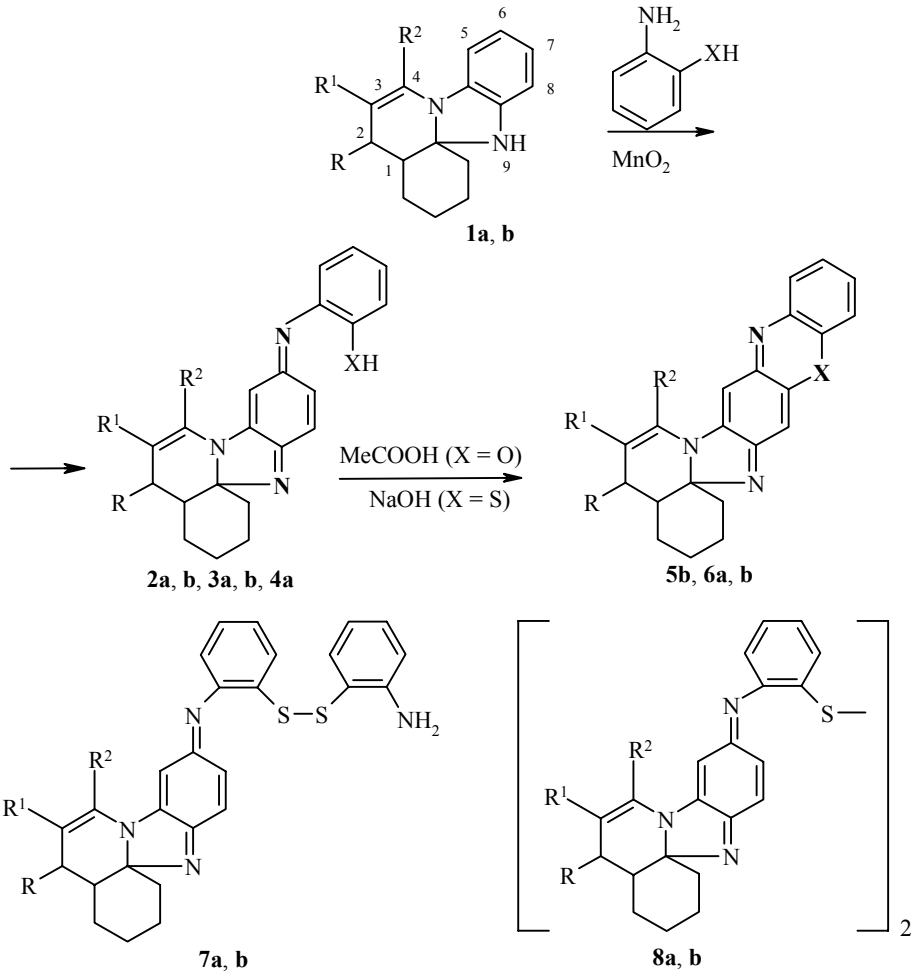

1a, **b**

2a, **b**, **3a**, **b**, **4a**

5b, **6a**, **b**

7a, **b**

8a, **b**

1-8 a R = H, $R^1+R^2 = (CH_2)_4$; **b** R = R^2 = Ph, R^1 = H, **2**, **5** X = O; **3**, **6** X = S; **4** X = COO

In their ^{1}H NMR spectra of the prepared compounds the quinoid proton signals are generally similar to the analogous data for quinoid compounds previously obtained in this series [2, 4]. The spectra of compounds **2a,b, 4a** show doubling of the signals for the 5-H protons. A similar doubling of the signals had been observed before in the spectra of the N-arylquinonediimine series of diazatetrahydrofluorene [2]. We propose that these compounds are a mixture of the *Z*- and *E*-forms; a similar picture being observed for N-aryl(aroyl)quinoneimines [5, 6].

With the aim of comparing the relative stability of the quinonediimine stereomers we have carried out quantum chemical calculation of the overall energy of the *Z*- and *E*-forms of 6-phenylimino-4α,9-diaza-1,2,4α,9α-tetrahydro-6H-fluorene using the AM1 method with complete geometrical optimization. A full component analysis showed a high stability for the *Z*-form, which is explained by the greater value for the interaction of the $N_{(4a)}$ unshared electron pair with the π-antibonding orbital of the $C_{(4b)}$–$C_{(5)}$ bond. From the calculated data, the phenyl substituent is turned at an angle of 56° relative to the plane of the quinoid ring both for the *Z*- and the *E*-forms. This agrees with data for the N-aroylbenzoquinonemonoimines in which the non-planar conformation is energetically more favored with the aroyl fragment perpendicular to the plane of the quinoid ring [7]. In the study [8] it was shown that 2,6-di-*tert*-butyl-N-*p*-nitrophenylbenzoquinoneimines exist at room temperature as a mixture of stereomers with an experimentally determined inversion barrier of 75.5 kJ/mole. The calculated barrier for *Z*,*E*-inversion in our case is 80 kJ/mole and the enthalpy of formation -3.7 kJ/mole and this is sufficient for the existence of a mixture of stereomers with the *Z*-form predominating.

TABLE 1. IR and NMR Data for the Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}				^{1}H NMR spectrum, δ, ppm (*J*, Hz) ($I_{rel.}$ signal)					
	$C_{(3)}=C_{(4)}$	C=N	C=C quin.	Other	2-H	3-H	5-H	8-H	Ar–H	Other
2a	1668	1631	1584, 1522	3400 br. (OH)	*	—	6.04 s (*Z*) (5) 6.12 s (*E*) (1)	*[2]	6.80-7.15 m	—
2b	1648	1628	1580, 1520	3380 (OH)	3.84 dd (10.0; 3.0)	5.44 d (3.0)	5.21 s (*Z*) (8) 5.00 s (*E*) (1)	*[2]	6.80-7.50 m	—
3a	1669	1632, 1625	1587, 1572	3449, 3370 weak (NH_2)	*	—	6.08 d (2.0) (3) 6.02 d (2.0) (1) 5.58 d (2.0) (0.7) 5.47 br. s (2)	*[2]	6.60-7.80 m	4.28 br. s (NH) (2H)
3b	1648	1629	1588, 1573	3436, 3380 weak (NH_2)	3.82 dd (10.0; 3.0)	5.47 d (3.0) 5.36 d (3.0)	5.13 d (2.0) (1) 4.50 br. s (6) 4.48 br. s (1) 4.42 br. s (0.7)	7.25 d (10.0)	6.80-7.45 m	6.36 dd (8.0; 2.0)
4a	1660	1630	1574, 1565	3435 br., 1700 (COOH)	*	—	6.30 s (*Z*) (5) 6.12 s (*E*) (1)	*[2]	8.35 d (8.5) (1H) 7.50 t (8.5) (1H) 7.07-7.37 m	—
5b	1649	1606	1578	—	—	—	—	—	—	—
6a	1668	1616	1586	—	*	—	6.18 s	6.90 s	7.05-7.60 m	—
6b	1642	1618	1566	—	7.82 dd (10.0; 3.0)		5.27 s	*[2]	7.05-7.50 m	—

* Overlapping with the signals of the CH_2 protons.

*[2] Overlapping with the signals of the ArH protons.

TABLE 2. Characteristics for the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{25}H_{27}N_3O$	78.34 / 77.92	7.23 / 7.01	10.87 / 10.91	145-146	68
2b	$C_{33}H_{29}N_3O$	82.11 / 81.99	6.26 / 6.00	8.83 / 8.70	133-134	62
4a	$C_{26}H_{27}N_3O_2$	75.92 / 75.55	6.31 / 6.54	9.87 / 10.17	Did not melt	88
5b	$C_{33}H_{27}N_3O$	82.41 / 82.33	5.95 / 5.61	8.54 / 8.73	280-282	72
6a	$C_{25}H_{25}N_3S$	75.65 / 75.19	6.03 / 6.27	10.67 / 10.53	156-158	80
6b	$C_{33}H_{27}N_3S$	80.10 / 79.68	5.14 / 5.43	8.41 / 8.45	295-297	62

The spectra of compounds **3a,b** containing an admixture of compounds **7** and **8** showed four signals for the 5-H proton and the spectrum of compound **3b** two signals for the 3-H vinyl proton. We propose that the signals of the 5-H proton with greatest intensity are assigned to the *Z*- and *E*-forms of compounds **3a,b** and the low intensity signals to compounds **7** and **8**, each of which exists as a single stereomer.

The mass spectroscopic data for the molecular ions correspond to those calculated for the molecular masses of the compounds. In the mass spectra of **3a,b** (see Experimental), along with strong molecular ion peaks corresponding to the given compounds, there are observed peaks which agree with compounds **7** and **8**. Using HPLC it was shown that a mixture of three compounds exists with very closely similar retention times.

EXPERIMENTAL

IR spectra were obtained on a Spectrum-1000 BX-11 instrument for KBr tablets and CH_2Cl_2 solutions and NMR spectra on a Bruker WM-250 (250 MHz) instrument using $CDCl_3$ or DMSO-d_6 solvent and TMS internal standard. Chromatograms and mass spectra were taken using liquid chromatography with an HP LC-MSD 1100, API-ES-positive ionization-electrospray, and fragmentor voltage varying in the range 5-250 V. Monitoring of the reaction course and the purity of the obtained products was carried out on Silufol and Sorbfil plates.

Characteristics for the synthesized compounds are given in Table 2.

Oxidative Coupling of 4α,9-Diaza-1,2,4α,9α-tetrahydro-9H-fluorenes 1a,b with Binucleophiles. MnO_2 (10-12 mmol) was added with stirring to a solution of compound **1a** or **1b** (1 mmol) and the reagent (*o*-aminophenol, *o*-aminothiophenol, anthranilic acid, 1.1 mmol) in acetone (50 ml) and stirring was continued at room temperature until the TLC spot for starting material had disappeared. The MnO_2 was filtered off, washed with acetone. The filtrate was diluted threefold with water and Na_2CO_3 (compounds **2a,b, 3b**) or NaCl (compound **3a**) was added, and the precipitate was filtered off, dried, and chromatographed on an Al_2O_3 column. In the case of compound **3a** it was eluted with a mixture of petroleum ether and acetone, for compound **4** a mixture of chloroform and ethanol, and in the remaining examples a mixture of petroleum ether and ethyl acetate. Mass spectrum, *m/z*, for the mixture **3a**, **7a**, **8a**: 402 (**3a**), 525 (**7a**), 801 (**8a**), $[M^+]$; for the mixture **3b**, **7b**, **8b**: 500 (**3b**), 623 (**7b**), 997 (**8b**), $[M^+]$.

Cyclization of Compounds 2,3. A. A solution of the quinonediimine **2a** (0.3 mmol) in acetic acid (5 ml) was held at room temperature for 3 days, water (15 ml) was added, and the product was neutralized with Na_2CO_3 solution, extracted with ether, the extract evaporated at room temperature, and the residue was triturated with hexane. Pure compound **5b** was obtained and it was identical to that obtained previously [4] chromatographically and in its IR spectrum.

B. A solution of compound **3a,b** (3 mmol) (containing an admixture of compounds **7** and **8**) in 5 ml of a 5% solution of NaOH in ethanol was held for 1 day at room temperature (in the case of compound **3a**) or refluxed for 2 h (for compound **3b**), diluted with water (15 ml), and neutralized with an aqueous solution of acetic acid (10%). The precipitate formed was filtered off, dried, and chromatographed on Al_2O_3 using petroleum ether–ethyl acetate as eluent.

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