Chemistry of Heterocyclic Compounds, Vol. 39, No. 3, 2003

REACTIONS OF 4-ARYL-2-HYDRAZINO-3-NITRO-6-R-QUINOLINES WITH HNO_2

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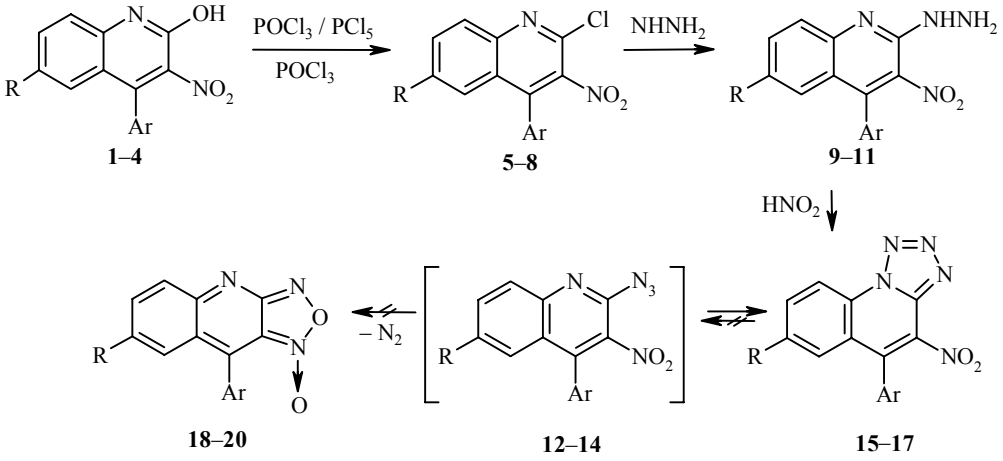
The reaction of 4-aryl-2-hydrazino-3-nitro-6-R-quinolines with $NaNO_2$ in AcOH gives the corresponding tetrazolo[1,5-a]quinolines. In contrast to tetrazolo[1,5-c]pyrimidines they cannot be converted to 6-R-4-phenyl[1,2,5]oxadiazolo[3,4-b]quinoline-3-oxides by heating in THF, toluene, or AcOH. Total energy quantum-chemical calculations using the MINDO/3 and MNDO methods show that [1,2,5]oxadiazolo[3,4-b]quinoline-3-oxides are significantly higher in energy (230-280 kcal/mol) than the mentioned tetrazolo[1,5-a]quinolines and hence their formation is unlikely.

Keywords: hydrazinoquinolines, oxadiazoloquinolines, tetrazoloquinolines, quinolines, ring-chain (azido-tetrazole) tautomerism.

We have previously reported the synthesis of 4-aryl-2-hydroxy-3-nitro-6-R-quinolines **1**, **2** (compounds **3**, **4** were obtained under analogous conditions during the course of this work) [1]. The aim of this study is the preparation of 2-chloro derivatives **5-8** of the previously reported compounds, 2-hydrazino-substituted quinolines **9-11** derived from them, and also to study the reaction products of compounds **9-11** with nitrous acid. The presence of an azide group and a nitro group in azides of type **12-14** can govern the formation of not only the corresponding tetrazolo[1,5-*a*]quinolines **15-17** [2] but also [1,2,5]oxadiazolo[3,4-*b*]quinolines **18-20** [3].



1, **5**, **9**, **15** R = Cl, Ar = Ph; **2**, **6, 10**, **16** R = Br, Ar = Ph; **3**, **7** R = Br, Ar = 2-ClC_6H_4; **4**, **8**, **11**, **17** R = NO_2, Ar = Ph

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 0009-3122/03/3903-0340$25.00

The conversion of compounds **1-4** to the halogenated products **5-8** was achieved by refluxing the starting derivatives either with an excess of $POCl_3$ or in a mixture of PCl_5 and $POCl_3$. The hydrazinolysis of these 2-chloroquinolines was carried out using an excess of hydrazine hydrate in refluxing ethanol or in DMSO at room temperature.

It was found that the reaction of hydrazines **9-11** with HNO_2 occurs almost instantaneously to give tetrazoloquinolines **15-17** but, in contrast to data in [3], prolonged refluxing the latter in glacial acetic acid, toluene, or THF did not lead to the formation of compounds **18-20**. The formation of structures related to **18-20** was possible only on prolonged heating of *o*-nitroaryl(heteryl)azides in the appropriate organic solvent medium either directly [4] or *via* the realization of a ring-chain tautomerism of the type **15-17** $\rightleftarrows$ **12-14** [5].

The fact that the expected furoxans **18-20** were not formed in this way points to the absence of such a tautomeric equilibrium at room temperature. This is also indicated by the absence of azide group stretching bands at 2120 cm^{-1} in the IR spectra of compounds **15-17**, both in the crystalline state and in $CHCl_3$ or CCl_4 solution [6].

In order to explain these facts we have carried out total energy quantum-chemical calculations for compounds **12-20**, the products of reaction of hydrazines **9-11** with nitrous acid. The semiempirical MINDO/3 and MNDO methods were used since it is known that they are fully suited for evaluation of the geometry and the energy of organic molecules containing polar groups (NO_2 in particular). The total energy calculations with geometry optimization were carried out using the "HyperChem 6.0" program*. The energy of furoxano[3,4-*b*]-quinolines **18-20** was found to be significantly (230-280 kcal/mol) higher than of all of the remaining products, and this is why the formation of compounds **18-20** is unlikely. The calculated results (Table 1) show that the energy of tetrazoles is lower than that of the corresponding azides. This is especially marked in the MNDO method calculations. It is of interest to note that the nature of the substituent R has virtually no effect on the energy difference (ΔE). Hence, in all likelihood, thermodynamic grounds are the deciding factor in the formation of tetrazoles **15-17** as the sole products of the reaction of hydrazines with nitrous acid.

Data of quantum-chemical calculation reflect the energy of the molecules in vacuo and do not take into consideration the effect of the medium. In our view it is unlikely that solvation effects have a decisive influence in the reaction discussed and so the qualitative conclusions made from the quantum-chemical calculations are the most plausible.

TABLE 1. Calculated Total Energy Values (kcal/mol) for Compounds **12-20**

R	Calculation method	$-E_1$ (azides)	$-E_2$ (tetrazoles)	$-E_3$ (furoxans)	$\Delta E = E_1 - E_2$	$\Delta E' = E_2 - E_3$
H	MINDO/3	3686	3692	3407	6	285
	MNDO	3561	3580	3347	19	233
Cl	MINDO/3	3670	3676	3391	6	285
	MNDO	3545	3563	3330	18	233
Br*	MNDO	3523	3541	3308	18	233
NO_2	MINDO/3	3886	3891	3606	5	285
	MNDO	3725	3742	3510	17	232

* Calculation by the MINDO/3 method was not carried out because of the absence of parameters for the Br atom.

* A fully working "trial" version of "HyperChem 6.0" is available from the Internet site of the HyperCube company: www.hyper.com.

TABLE 2. Characteristics for the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	IR spectrum, ν, cm^{-1}, KBr*[2]	M^+	Yield, %
		C	H	Hal	N				
3	$C_{15}H_8BrClN_2O_3$	47.50 / 47.46	2.18 / 2.12	30.34 / 30.39	7.33 / 7.38	320-322	1380, 1520, 1610, 1660, 2900-3550	378	21
4	$C_{15}H_9N_3O_5$	57.84 / 57.88	2.96 / 2.91		13.55 / 13.50	357-359	1325, 1515, 1600, 1660, 2800-3200	311	30.7
5	$C_{15}H_8Cl_2N_2O_2$	56.40 / 56.45	2.48 / 2.53	22.27 / 22.22	8.82 / 8.78	171-172	1380, 1515, 1640, 1670, 2800-3080	318	65
6	$C_{15}H_8BrClN_2O_2$	49.59 / 49.55	2.25 / 2.22	31.68 / 31.73	7.75 / 7.70	149-150	1370, 1520, 1640, 1660, 2800-3000	362	68
7	$C_{15}H_7BrCl_2N_2O_2$	45.31 / 45.26	1.81 / 1.77	37.93 / 37.88	7.00 / 7.04	185-186	1380, 1520, 1640, 1650, 2860-3075	396	96
8	$C_{15}H_8ClN_3O_4$	54.70 / 54.65	2.50 / 2.45	10.80 / 10.75	12.77 / 12.74	219-221	1330, 1515, 1600, 1645, 2780-3050	329	50
9	$C_{15}H_{11}ClN_4O_2$	57.28 / 57.24	3.56 / 3.52	11.21 / 11.26	17.22 / 17.18	202-204	1375, 1520, 1580, 1620, 2800-3200, 3320	314	51
10	$C_{15}H_{11}BrN_4O_2$	50.11 / 50.16	3.13 / 3.09	22.30 / 22.25	15.55 / 15.60	205-207	1340, 1520, 1590, 1620, 3050-3280, 3400	358	88
11	$C_{15}H_{11}N_5O_4$	55.44 / 55.39	3.46 / 3.41		21.49 / 21.53	208-210	1320, 1520, 1560, 1590, 3000-3290, 3300	325	96
15	$C_{15}H_8ClN_5O_2$	55.36 / 55.31	2.43 / 2.48	10.93 / 10.92	21.46 / 21.50	239-241	1040, 1060, 1360, 1520, 1610, 1640, 3050 (1020, 1080, 1355, 1540, 1610, 1680, 3080)	325	46.3
16	$C_{15}H_8BrN_5O_2$	48.62 / 48.67	2.22 / 2.18	21.54 / 21.59	18.87 / 18.92	239-241	1040, 1070, 1365, 1520, 1590, 1640, 3055 (1020, 1080, 1355, 1540, 1610, 1680, 3080)	369	97.6
17	$C_{15}H_8N_6O_4$	53.52 / 53.58	2.44 / 2.40		24.95 / 24.99	239-241	1020, 1080, 1320, 1530, 1600, 1680, 3055	336	45.2

* Solvents were: ethanol (compounds **3-6**,**15**) and benzene–heptane (compound **8**).

*[2] Values obtained in $CHCl_3$ are given in brackets for compounds **15** and **16**.

EXPERIMENTAL

IR spectra were recorded on a Specord M-80 instrument. Monitoring of the reaction course and the purity of the compounds obtained was carried out using TLC on Silufol UV-254 plates with acetone–hexane (1:2, 1:3, 1:4) as eluent. Mass spectra were taken on an MX-1321 mass spectrometer using a direct introduction system and irradiation ionization energy of 70 eV.

Physicochemical constants for the compounds prepared are given in Table 2.

6-Bromo-4-(2-chlorophenyl)-2-hydroxy-3-nitroquinoline (3) and **2-Hydroxy-3,6-dinitro-4-phenylquinoline (4)** were prepared as in method [1].

2,6-Dichloro-3-nitro-4-phenylquinoline (5), 6-Bromo-2-chloro-3-nitro-4-phenylquinoline (6), 6-Bromo-2-chloro-4-(2-chlorophenyl)-3-nitroquinoline (7), and **2-Chloro-3,6-dinitro-4-phenylquinoline (8). (General Method).** Mixture of the corresponding quinoline **1-4** (8.5 mmol) with the equivalent amount of PCl_5 was refluxed in $POCl_3$ (30 ml) to complete disappearance of the chromatographic spot for the starting quinoline (28-50 h). After the conclusion of the reaction the mixture was poured into ice. The precipitate formed was filtered off and washed with water. After drying, the precipitate was crystallized.

6-Chloro-2-hydrazino-3-nitro-4-phenylquinoline (9), 6-Bromo-2-hydrazino-3-nitro-4-phenylquinoline (10), and 2-Hydrazino-3,6-dinitro-4-phenylquinoline (11). (General Method). A. Mixture of the corresponding 2-chloroquinoline **5-8** (3.1 mmol) and 95% hydrazine hydrate (2 ml) was refluxed for 2 h in ethanol (50 ml). The precipitate formed was filtered off, washed with alcohol, and dried.

B. 95% $N_2H_4 \cdot H_2O$ (2 ml) was added to the corresponding chloride **5-8** (3.1 mmol) in DMSO (40 ml). The mixture was held for 3 h at room temperature and then poured into water. The precipitate formed was filtered off, washed with slightly acidified water, and dried.

A mixed sample of the materials obtained using methods A and B did not give a depression of melting point.

9-Chloro-6-nitro-7-phenyltetrazolo[1,5-*a*]quinoline (15), 9-Bromo-6-nitro-7-phenyltetrazolo-[1,5-*a*]quinoline (16), and **6,9-Dinitro-7-phenyltetrazolo[1,5-*a*]quinoline (17). (General Method).** Saturated aqueous solution of $NaNO_2$ (6.8 mmol) was poured into solution of the corresponding 2-hydrazinoquinoline (1.3 mmol) in AcOH (20 ml). The reaction mixture was stirred for 10 min. The precipitate formed was filtered, washed with slightly acidified water, dried, and crystallized from ethanol.

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