Chemistry of Heterocyclic Compounds, Vol. 42, No. 9, 2006

AZOCOUPLING REACTIONS OF ENAMINOCARBONYL DERIVATIVES OF 1,2,3,4-TETRAHYDROISOQUINOLINE WITH DIAZONIUM SALTS

N. N. Polygalova, A. G. MIkhailovskii, and M. I. Vakhrin

It has been shown that enamino amide and enamino ketone derivatives of 1,2,3,4-tetrahydroisoquinoline react with diazonium salts to form azo compounds. Depending on the enamine structure they can exist just as azo dyes or as azohydrazone tautomers.

Keywords: azo compounds, diazonium salts, secondary and tertiary enamines, 1,2,3,4-tetrahydroisoquinolines, azohydrazone tautomerization.

Up to this time the reactions of heterocyclic enamines with diazonium salts have been little studied. It has previously been shown [1] that the conjugation of an excess of a diazonium salt with 1,3,3-trimethyl-3,4-isoquinoline leads to the formation of formazans. Evidently the reaction products can also be an azo dye depending on the structural features of the enamine. The formation of dyes can also be expected from enaminocarbonyl compounds having only one hydrogen atom on the β-carbon atom of the enamine group in their structure (enamino amides and enamino ketones).

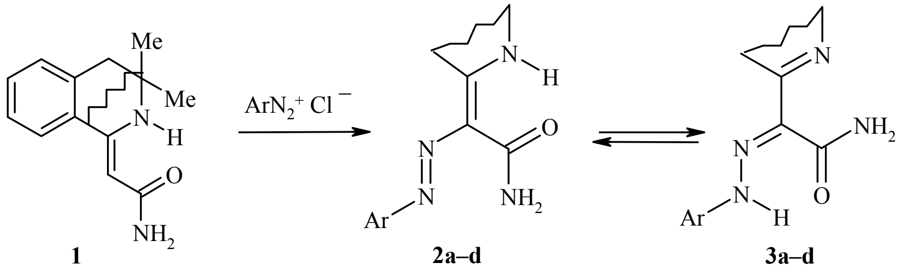
The aim of this work is a study of the structure of the azocoupling reaction products and the dependence on the structure of the starting 1,2,3,4-tetrahydroisoquinoline enaminocarbonyl derivatives.

This study has shown that the azocoupling of enamino amide **1** [2] with diazonium salts gives the azo dyes **2a-d** which exist in solution as a tautomeric equilibrium with the hydrazo form (compounds **3a-d**). The tertiary amide **4** [3] reacts similarly to give the azo dyes **5a,b** which show a similar solution equilibrium (hydrazones **6a,b**).

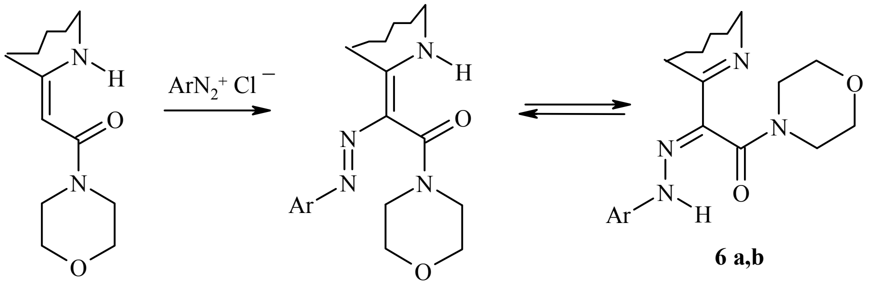
It is known [4] that amides of type **7** exist in the imino form. However, in the azocoupling of the named amide with p-nitrophenyldiazonium chloride it reacts as an enamine to give the azo dye **8**. It should be noted that the azo dye reaction product could only be separated for the *p*-nitro substituent. Attempts to use less active electrophiles as diazo component (such as the phenyl and *p*-tolyldiazonium chlorides) in the reaction did not give an azo conjugation product.

Coupling of diazonium salts with the enamino ketone **9** [5] gave the azo dyes **10a,b** and hydrazo formation was not seen in this case. The stability of the azo form can be explained by the greater electron-acceptor effect of a ketone group when compared with an amide. In the case where the azo component is a tertiary enamino ketone the azo dyes **11a,b** are also formed and exist in solution as a mixture of the two π-diastereomers (*Z* and *E*).

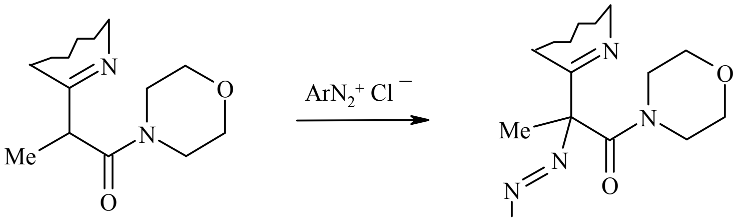
Perm State Pharmaceutical Academy, Perm 614990, Russia; e-mail: perm@pfa.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1382-1387, September, 2006. Original article submitted April 18, 2005.



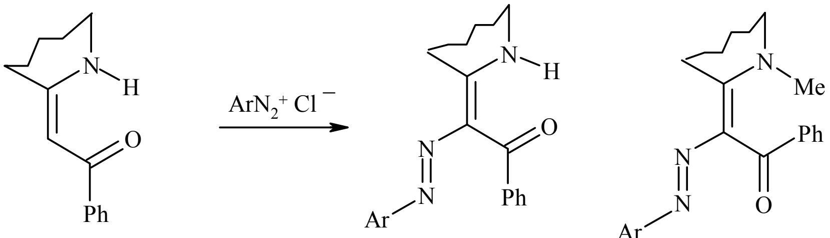
1 **2a–d** **3a–d**



4 **5a,b** **6 a,b**



7 **8**



9 **10a,b** **11a,b**

The azocoupling products are yellow-orange crystalline materials having sharp melting points (Table 1). They only give one spot on thin layer chromatographic analysis.

The ^{1}H NMR spectra (Table 2) show the presence of the azohydrazone tautomerism. In contrast to that of the starting amide **1** the spectra of compounds **2a-d** show doubling of the methyl and methylene group singlets. The proton of the ring NH group gives a signal in the region 9.0-10.5 ppm, this assignment being based on known data [2]. In the structures **3a-d** two hydrazo forms are seen which most likely correspond to the *s-cis-, trans* isomers:

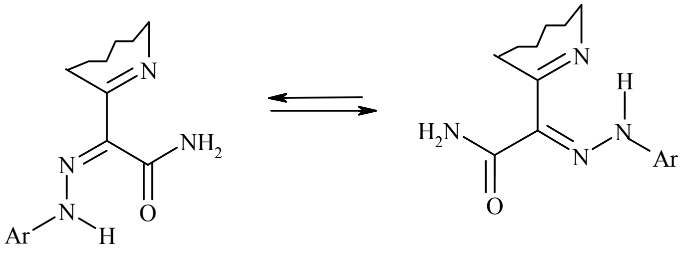


TABLE 1. Characteristics of the Compounds Synthesized (Ar = 4-XC_6H_4)

Compound	X	Empirical formula	Found, % Calculated, %			mp, °C	Yield, %
			C	H	N		
2a	H	$C_{19}H_{20}N_4O$	71.0 71.2	6.2 6.3	17.5 17.5	154-155	87
2b	Me	$C_{20}H_{22}N_4O$	71.8 71.6	6.6 6.4	16.8 16.9	150-151	89
2c	NO_2	$C_{19}H_{19}N_5O_3$	62.3 62.5	5.2 5.2	19.4 19.2	197-198	94
2d	Ac	$C_{21}H_{22}N_4O_2$	69.6 69.6	6.0 6.1	15.3 15.5	145-146	75
5a	Me	$C_{24}H_{28}N_4O_2$	71.2 71.3	6.9 7.0	14.0 13.9	162-164	54
5b	NO_2	$C_{23}H_{25}N_5O_4$	63.3 63.4	5.6 5.8	16.2 16.1	168-170	62
8	NO_2	$C_{24}H_{27}N_5O_4$	64.0 64.1	6.0 6.1	15.5 15.6	105-107	57
10a	Ac	$C_{27}H_{25}N_3O_2$	76.5 76.6	5.9 6.0	10.0 9.9	280 (dec.)	61
10b	NO_2	$C_{25}H_{22}N_4O_3$	69.9 70.4	5.1 5.2	13.2 13.1	214-216	53
11a	Ac	$C_{28}H_{27}N_3O_2$	76.8 76.9	6.1 6.2	9.7 9.6	168-170	63
11b	NO_2	$C_{26}H_{24}N_4O_3$	70.8 70.9	5.4 5.5	12.7 12.7	165-167	64

A similar spectroscopic picture is seen for the tertiary amides. The azo forms **5a,b** exist in equilibrium with the hydrazo forms **6a,b** as shown by the presence of two methyl group proton singlets and two CH_2 group proton singlets. The spectra of these compounds have only one singlet for the hydrazone proton (at 14.60 and 14.85 ppm for structures **6a,b**). A steric factor which stabilizes the predominance of one form of the hydrazone may be the repulsion between the isoquinoline and morpholine rings.

The molecule of compound **8** contains a chiral center and in the spectrum the methyl groups in position 3 are diastereotopically split as singlets at 1.0 and 1.18 ppm. The singlet for the CH_2 group is strongly broadened.

The ^1H NMR spectra of the ketones **10a,b** contain sharp CH_3 and CH_2 proton singlets and only one singlet for the ring NH proton group and this points to the presence of only the azo form. In the spectra of the enaminoketones **11a,b** there are two sets of methyl and methylene group singlets pointing to the two π-diastereomers.

The IR spectra of amides **2a-d** and **5a,b** show broad bands for H-chelated amide carbonyl (1605-1610) and ring NH group (3110-3180) and the primary amides bands are at 3375-3385 cm^{-1} (NH_2). The spectrum of amide **8** shows a band for a free amide carbonyl (1650), the spectra of the ketones **10a,b** bands for H-chelated carbonyl (1600) and ring NH (3010), and the tertiary enamino ketones **11a,b** shown a conjugated ketone carbonyl band (1640 cm^{-1}).

EXPERIMENTAL

^1H NMR spectra were recorded on a Tesla BS-567 instrument (100 MHz) using $CDCl_3$ and HMDS as internal standard (0.05 ppm from TMS). IR Spectra were recorded on a Specord-80 spectrometer using chloroform solvent (0.01 molar).

Monitoring of the purity of the substances obtained was carried out by TLC on Silufol UV-254 plates in the system acetone–ethanol–chloroform (1:3:6), compounds were colored in the visible region of the spectrum.

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

Compound	Chemical shifts, δ, ppm							
	3-$(CH_3)_2$	4-CH_2	$N(CH_2)_2O$, m	aromatic protons, m	NH amide, s,	ring NH, s	hydrazo NH, s	other protons
2a, 3a	1.15, s, 1.17, s,	2.74, s, 2.76, s,	—	6.50-7.76 (9H)	6.26	10.40	12.73, 14.0	—
2b, 3b	1.10, s, 1.20, s,	2.72, s, 2.73, s,	—	6.70-8.00 (8H)	5.84	10.07	12.5, 13.7	2.18, s, (CH_3–Ph)
2c, 3c	1.21, s, 1.22, s,	2.73, s, 2.74, s,	—	7.00-8.23 (8H)	5.87	9.0	10.6, 13.0	—
2d, 3d	1.28, s, 1.30, s,	2.70, br. s,	—	7.00-8.00 (8H)	5.95	10.50	12.5, 13.6	2.50, s, (CH_3CO)
5a, 6a	1.20, s, 1.21, s,	2.72, br. s,	3.25-3.95	6.80-7.35 (8H)	—	8.65	14.62	2.21, s, (CH_3–Ph)
5b, 6b	1.18, s, 1.20, s,	2.65, s, 2.70, s,	3.10-3.80	6.90-8.20 (8H)	—	9.40	14.85	—
8	1.0, s, 1.18, s,	2.60, br. s,	2.90-3.70	7.00-8.22 (8H)	—	—	—	1.90, s (CH_3)
10a	1.25, s,	2.70, s,	—	6.70-8.00 (13H)	—	12.70	—	2.52, s, (CH_3CO)
10b	1.50, s,	2.80, s,	—	6.80-7.45 (13H)	—	12.70	—	—
11a	1.30-1.60, br. s,	3.10-3.30, br. s,	—	6.90-8.10 (13H)	—	—	—	2.47, s, (CH_3CO), 3.40, s (CH_3N)
11b	1.40, s, 1.57, s,	3.05, s, 3.23, s,	—	7.00-8.10 (13H)	—	—	—	3.42, s (CH_3N)

All materials were recrystallized from isopropanol.

Amides 2a-d and 2-Arylazo-2-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolidene-1)ethanoic Acid Morpholides 5a,b, 2-(*p*-Nitrophenylazo)-2-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolidene-1)propanoic Acid Morpholide 8, 1-Arylazo-1-(3,3-aimethyl-1,2,3,4-tetrahydroisoquinolidene-1)-2-phenylethan-2-ones 10a,b, and 1-Arylazo-1-(2,3,3-trimethyl-1,2,3,4-tetrahydroisoquinolidene-1)- 2-phenylethan-2-ones 11a,b. Diazotization and azo conjugation were carried out in a 1:1 (by volume) mixture of water and alcohol.

Diazotization. Conc. HCl (1.5 ml) was added to a solution of the base or hydrochloride of the corresponding aniline (12 mmol) in the aqueous-alcohol mixture (100 ml). In the case of *p*-nitrophenylaniline a fine dispersion was diazotized. A solution of 1N sodium nitrite (starch-iodine assay) was added dropwise at 3-5°C with stirring to a solution of the aniline hydrochloride. The obtained solution of diazonium salt was held for a further 10 min at the same temperature. With the suspension the mixture was stirred vigorously. The excess HNO_2 was removed using urea.

Azo Conjugation. The azo component (10 mmol) was dissolved at reflux in the aqueous-alcohol mixture (150-200 ml) and then slowly taken to 5-7°C. The precipitated base was treated with conc. HCl (3-5 drops). A solution of the diazonium salt was added to the cooled solution of the azo component and the obtained mixture was held for a further 20 min at the same temperature (in the case of the suspension with stirring). A saturated solution of sodium acetate was slowly added dropwise and this precipitated a colored solid. After addition of excess sodium acetate solution the mixture was held for a further 1 h without the cooling and periodic stirring. The precipitate was filtered off, thoroughly washed with water, dried, and recrystallized.

REFERENCES

1. V. S. Shklyaev, B. B. Aleksandrov, I. I. Vakhrin, and G. I. Legotkina, Russian Patent 852865, *Byul. Izobr.*, No. 29, 114 (1981).
2. V. S. Shklyaev, B. B. Aleksandrov, A. G. Mikhailovskii, and M. I. Vakhrin, *Khim. Geterotsikl. Soedin.*, 1239 (1989). [*Chem. Heterocycl. Comp.*, **25**, 1038 (1989)].
3. A. G. Mikhailovskii and V. S. Shklyaev, *Khim. Geterotsikl. Soedin.*, 946 (1994). [*Chem. Heterocycl. Comp.*, **30**, 818 (1994)].
4. R. Z. Dautova, V. S. Shklyaev, B. Ya. Syropyatov, B. B. Aleksandrov, A. G. Mikhailovskii, and M. I. Vakhrin, *Khim.-Farm. Zh.*, **23**, No. 2, 172 (1989).
5. A. G. Mikhailovskii, V. S. Shklyaev, and B. B. Aleksandrov, *Khim. Geterotsikl. Soedin.*, 808 (1990). [*Chem. Heterocycl. Comp.*, **26**, 674 (1990)].