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AZOCOUPLING REACTION OF 1-BENZYL-3,4-DIHYDROISOQUINOLINES WITH DIAZONIUM SALTS AND THE PROPERTIES OF ITS PRODUCTS

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It has been shown that drotaverine base and 1-benzyl-3,3-dimethyl-3,4-dihydroisoquinoline react with diazonium salts to form hydrazones. The position of the K-band in the UV spectra of the compounds obtained depends on the nature of the substituenst in the aromatic ring and the absorption frequency correlates with its Hammett constant.

Keywords: 1-benzyl-3,4-dihydroisoquinolines, hydrazones, enamines, diazonium salts, Hammett constant correlations, UV absorption spectra.

The azocoupling of 1,2,3,4-tetrahydroisoquinoline enamines with diazonium salts has been studied previously [1, 2]. In chemistry and pharmacology 1-benzyl-3,4-dihydroisoquinolines are widely known and also show enamine properties [3], in particular drotaverine base (nospa) [4]. The azocoupling reaction of 1-benzyl-3,4-dihydroisoquinolines with diazonium salts has not been studied to this time.

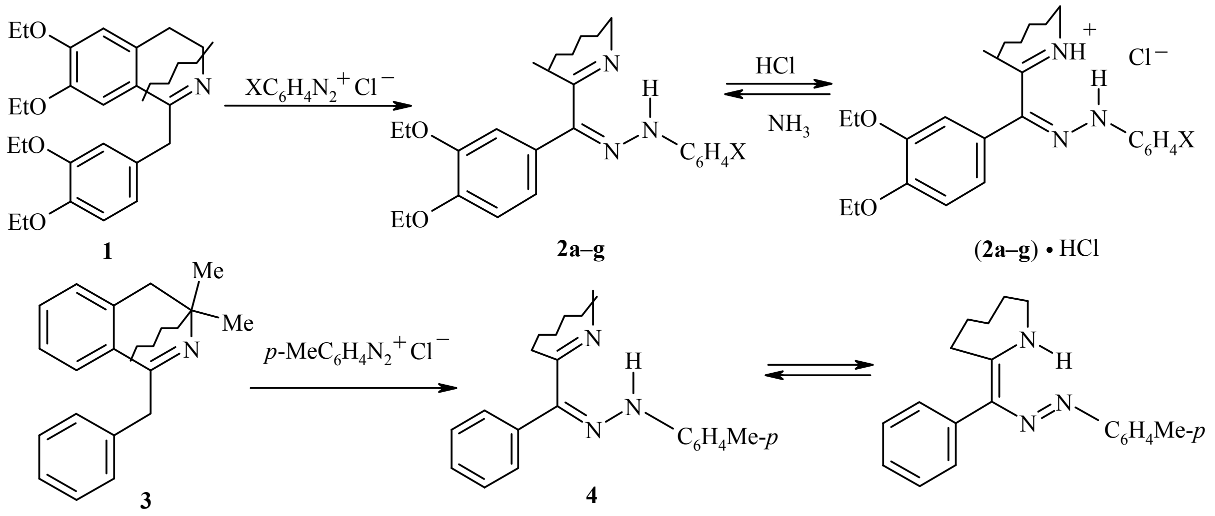

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	X	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
			C	H	Cl	N		
2a	H	$C_{30}H_{35}N_3O_4$•HCl	66.8 67.0	6.5 6.7	6.5 6.6	7.9 7.8	140-142	80
2b	*p*-NO_2	$C_{30}H_{34}N_4O_6$	65.7 65.9	6.2 6.3	—	10.4 10.3	143-145	62
2c	*m*-NO_2	$C_{30}H_{34}N_4O_6$•HCl	61.7 61.8	5.9 6.1	5.8 6.1	9.7 9.6	124-126	65
2d	*p*-CO_2Et	$C_{33}H_{39}N_3O_6$•HCl	64.8 65.0	6.5 6.6	3.7 3.8	6.9 6.9	147-148	67
2e	*m*-Cl	$C_{30}H_{34}ClN_3O_4$•HCl	62.8 62.9	6.1 6.2	12.3 12.4	7.5 7.3	142-143	55
2f	*p*-Me	$C_{31}H_{37}N_3O_4$•HCl	67.3 67.4	6.7 6.9	6.2 6.4	7.6 7.6	190-192	70
2g	*p*-MeO	$C_{31}H_{37}N_3O_5$•HCl	65.4 65.5	6.6 6.7	6.1 6.2	7.2 7.4	105-107	66
4	—	$C_{25}H_{25}N_3$•HCl	74.3 74.4	6.3 6.4	8.7 8.8	10.5 10.4	280 (dec.)	78

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

Compound	Chemical shifts, δ, ppm (*J*, Hz)								
	4$C\underline{H}_3CH_2O$, (12H, 4t)	$CH_3C\underline{H}_2O$, (2H, q)	3$CH_3C\underline{H}_2O$, (6H, 3q)	H-4, (2H, m)	CH_2–N, (2H, m)	Ar, m	Hydrazone NH	Ring NH$^+$	Remaining protons
2a	1.2-1.5 (*J* = 6.8)	3.8 (*J* = 6.8)	4.0-4.3 (*J* = 6.8)	3.2	3.9	6.5-7.5 (10H)	8.9	12.1	—
2b	1.1-1.5 (*J* = 7.0)	3.9 (*J* = 7.0)	4.0-4.3 (*J* = 7.0)	3.1	4.2	6.7-8.3 (9H)	9.7	–	—
2c	1.1-1.7 (*J* = 7.1)	3.8 (*J* = 7.1)	4.0-4.2 (*J* = 7.1)	3.1	4.2	6.7-8.2 (9H)	9.5	11.7	—
2d	1.1-1.5 (*J* = 6.9)	3.8 (*J* = 6.9)	3.9-4.2 (*J* = 6.9)	3.2	4.1	6.7-8.2 (9H)	9.8	—*	$C\underline{H}_3CH_2OCO$, t, *J* = 7.3, in region 1.1–1.5; $CH_3C\underline{H}_2OCO$, q, *J* = 7.3, in region 3.8–3.9
2e	1.1-1.6 (*J* = 7.0)	3.7 (*J* = 7.0)	4.0-4.2 (*J* = 7.0)	3.0	4.1	6.7-8.1 (9H)	9.3	11.7	–
2f	1.2-1.5 (*J* = 6.9)	3.9 (*J* = 6.9)	4.1-4.3 (*J* = 6.9)	3.3	4.1	6.8-7.4 (9H)	9.1	12.3	2.3 (s, CH_3–Ar)
2g	1.2-1.6 (*J* = 7.0)	3.6 (*J* = 7.0)	4.0-4.2 (*J* = 7.0)	3.0	4.0	6.6-7.2 (9H)	8.7	11.6	3.7 (s, CH_3O)
4	—	—	—	—	—	—	—	—	1.1 (3H, s) and 1.4 (3H, s); 3-$(CH_3)_2$; 2.3 (3H, s, CH_3–Ar); 2.8 (1H, s) and 2.9 (1H, s), H-4

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* Proton exchanges with water in solvent.

The aim of this work was the synthesis and study of the structure of the reaction products of the azocoupling of the 1-benzyl-3,4-dihydroisoquinolines with diazonium salts.

Studies have shown that coupling of the drotaverine base **1** with diazonium salts gives the hydrazones **2a-g**. An analogous reaction of the base **3** with *p*-tolyldiazonium chloride gives the hydrazone **4**.

The azocoupling products are orange or red crystalline materials characterized as the hydrochlorides with the exception of the *p*-nitro derivative **2b** for which the base is stable (Table 1). All of the hydrochlorides are hardly soluble in water.

The ^{1}H NMR spectra of the drotaverine derivatives **2a-g** (Table 2) support a hydrazone structure. In contrast to the spectrum of the starting drotaverine base the spectra of these substances show the absence of the singlet for the benzyl group methylene protons and the presence of singlets for the hydrazone NH group protons (8.7-9.7) and ring NH^+ (11.6-12.3 ppm). In the spectrum of base **2b** the ring NH^+ group signal is absent. In the spectra of the bases of these materials separated by the action of 25% ammonia solution on the hydrochlorides the ring NH^+ is also absent and a singlet for the hydrazone NH group protons appears at about 9.5 ppm. One of the methylene groups in the $OC\underline{H}_2CH_3$ appears as a quartet at somewhat higher field than the rest (3.7-3.9 ppm). This is probably due to a direct polar conjugation of ethoxy groups with the positively charged center.

The spectrum of base **4** (Table 2), also separated from the hydrochloride by treatment with ammonia, shows two singlet for the methyl groups at position 3, two singlets for the H-4 group protons and a multiplet for the aromatic protons. In addition two signals are seen for the NH group at 9.1 and 10.5 ppm. This facts suggest that the base **4** exists in solution as azohydrazone tautomers. Judged by the integrated intensities of the signals both tautomers exist in about equal proportions. The predominance of the hydrazone forms in compounds **2a-g** can be explained by the presence of four electron-donor ethoxy groups stabilizing the π deficient diazadiene fragment.

The IR spectra of the bases of compounds **2a-g** and **4** show C=N stretching bands at 1620-1630 and NH at 3120 cm^{-1}.

The UV absorption spectra of the hydrochlorides of the substances obtained (Table 3) were recorded for 0.01 molar solutions in aqueous HCl and started at a wavelength of 200 nm. All of the spectra were characterized by the presence of an aromatic β-band π-π* transition [5-7] with a maximum near 200 nm and a log ε of 4.66-4.84. The aromatic *p*-band appears in the region 236-260 nm (log ε 4.26-4.43) and the *K*-band for the overall chain of π-conjugation [8, 9] is found at 305-450 nm (log ε 3.91-4.28). It is apparent from the data presented that the position of the *K*-bands depends strongly on the nature of the substituent in the aromatic ring of the phenylazo group. The literature contains examples of the correlation of the frequency of the absorption in the UV spectra with substituent constants [10, 11]. Comparison of the values of the absorption frequency with the Hammett constants of the terminal substituents [12] shows that a deviation from this correlation occurs for terminal substituents having maximum electron-donor or acceptor properties (MeO and NO_2). With their exclusion the series of hydrochlorides of compounds **2a-g** follows the relationship:

$$\Delta\nu = 0.32\ \nu\ (r = 0.98;\ s = 0.08,\ n = 4)$$

where Δν is the shift in the absorption frequency (cm^{-1}) relative to unsubstituted phenyl. Overall, increase in the donor properties of the substituent gives a bathochromic shift of the conjugated *K*-band. The comparatively small value of ρ (0.32) points to a moderate effect of the substituent on the electron excitation energy of the ionized hydrazone molecule.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker-300 (300 MHz) instrument using DMSO-d_6 (compounds **2b,d**) or $CDCl_3$ (all of the remainder) and with HMDS (0.05 ppm from TMS) as internal standard. IR spectra

TABLE 3. UV Spectroscopic Absorption for the Synthesized Compounds

Compound*	λ, nm (log ε)			*K*-band, $\nu\bullet10^3$ cm^{-1}	
	β (at 200 nm)	*p* (λ_{max})	*K* (λ_{max})	ν	Δν
2a	200 (4.83)	254 (4.41)	430 (4.08)	23.27	0
2c	200 (4.68)	237 (4.26)	305 (4.02)	34.23	+10.4
2d	200 (4.73)	236 (4.39)	310 (4.24)	32.27	+9.0
2e	200 (4.74)	236 (4.43)	314 (4.26)	31.83	+8.56
2f	200 (4.84)	250 (4.31)	450 (4.28)	22.23	-1.04
2g	200 (4.69)	260 (4.32)	458 (3.91)	21.83	-1.44
4	200 (4.66)	245 (4.31)	455 (4.27)	—	—

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* Compound **2b** is insoluble in these conditions.

were taken on a Specord-80 spectrometer using vaseline oil. UV spectra were obtained on an SF-2000 spectrometer at a concentration of 0.5×10^{-4} molar. Monitoring of the purity of the compounds obtained was carried out by TLC on Silufol UV-254 plates in the system acetone–ethanol–chloroform (1:3:6), the starting materials and products being colored in the visible part of the spectrum.

Compound **3** has been described in [13]. All of the compounds were recrystallized from acetonitrile.

3,4-Diethoxyphenyl (6,7-Diethoxy-3,4-dihydroisoquinol-1-yl) Ketone Arylhydrazones 2a-g and Phenyl (3,3-dimethyl-3,4-dihydroisoquinol-1-yl) Ketone *p*-Tolylhydrazone (4). The diazotization and azo-coupling were carried out in a mixture of alcohol and water (1:1 volume).

Diazotization was carried out by the method reported in [2].

Azocoupling. The azo component base (10 mmol) was dissolved with refluxing in an aqueous alcohol mixture (100 ml) and the temperature taken to 5-7ºC. The diazonium salt was added to the cooled solution and the mixture was held at this temperature for 30 min. A saturated solution of sodium acetate was added slowly dropwise and a colored precipitate formed. After addition of excess sodium acetate solution the mixture was held for a further 1 h with the cooling removed and periodically shaken. The precipitate was filtered off, carefully washed with water, dried, and recrystallized.

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