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REACTION OF 1,2,3,4-TETRAHYDRO-ISOQUINOLINE ENAMINES WITH QUINONES

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

The reaction of p-benzoquinone with enamino amides derived from 2,2-dimethyl-1,2,3,4-tetrahydrobenzo[f]isoquinoline proceeds through a Michael addition. The reaction of this quinone with the base of drotaverine leads to a derivative of indolo[2,1-a]isoquinoline. Fusion of isoquinoline enamines by the action of 2,3-dichloro-1,4-naphthoquinone leads to pentacyclic benzo[g]naphtho-[2,3-b]indolyzine-8,13-dione.

Keywords: benzo[*g*]naphtho[2,3-*b*]indolyzine-8,13-diones, *p*-benzoquinone, 2,3-dichloro-1,4-naphtho-quinone, indolo[2,1-*a*]isoquinoline, 1,2,3,4-tetrahydroisoquinoline enamines, donor–acceptor complexes, Michael addition, Nenicescu reaction.

Condensed isoquinolines are the basic structure of many natural products and drugs. Some of these compounds have been patented as pesticides, photographic agents, and light-sensitive materials etc. [1].

The classical reaction of *p*-benzoquinone enamines leading to 5-hydroxyindole derivatives (Nenicescu reaction) is well known [2, 3]. 2,3-Dichloro-1,4-naphthoquinone has also found common use in the synthesis of condensed systems [4]. The reaction of these quinones with cyclic enamines has hardly been studied. In the present work, we investigated the feasibility of the synthesis of condensed systems by the reaction of these quinones with cyclic enamines. Study of the reactions of enamines **1a**,**b** with *p*-benzoquinone showed that the structure of the products depends on the structure of the starting enamines. In all cases, dark coloration typical of donor–acceptor complexes was noted upon mixing of the reagents. Further reaction of the reagents proceeds through two pathways: 1) simple Michael addition and 2) the Nenicescu reaction. The reaction of *p*-benzoquinone with enamines **1a**,**b** proceeds through pathway 1 to give dihydric phenols **2a**,**b**. On the other hand, the reaction with the base of drotaverine (no-spa) (**3**) leads to a condensed derivative of 5-hydroxyindole **4**, i.e., the normal product of the Nenicescu reaction. The difficulty in forming the indole ring in the case of amides **1a**,**b** may be attributed to steric hindrance by the methyl groups at $C_{(2)}$.

Upon mixing *p*-benzoquinone with enamines **5**, we observe only darkening of the solution and formation of almost black precipitates of the complexes. Reaction products have not been preparatively isolated.

Gavrilov et al. [5] reported that derivatives of 1,2,3,4-tetrahydroisoquinoline form colored donor–acceptor complexes with chloranil. Similar properties might have been expected for 2,3-dichloro-1,4-naphthoquinone. Indeed, all the enamines studied (**1, 3, 5**, and similar compounds) give dark-colored complexes upon mixing with this quinone. We should especially note the base of drotaverine, which gives brilliant green complexes, which gradually darken in the air. The specific color of this complex may be attributed to the electron-donor effect of the ethoxy groups.

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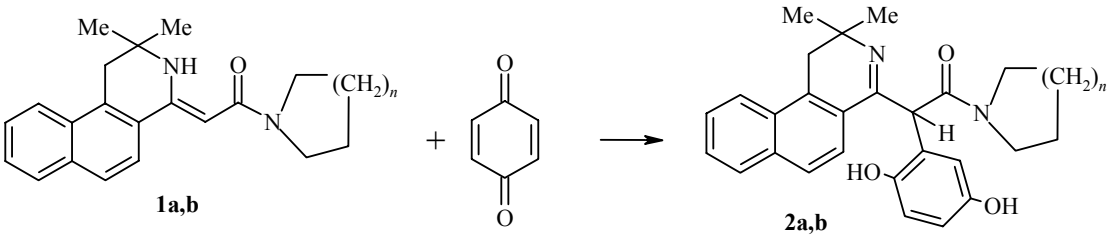
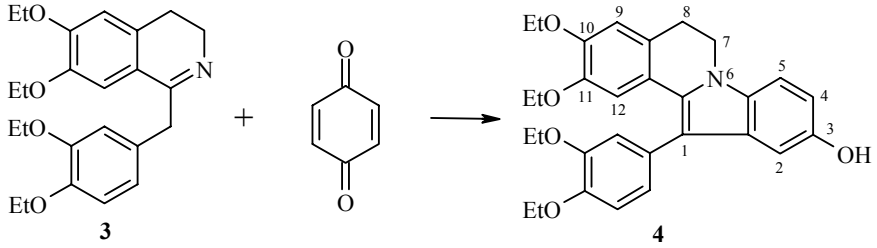
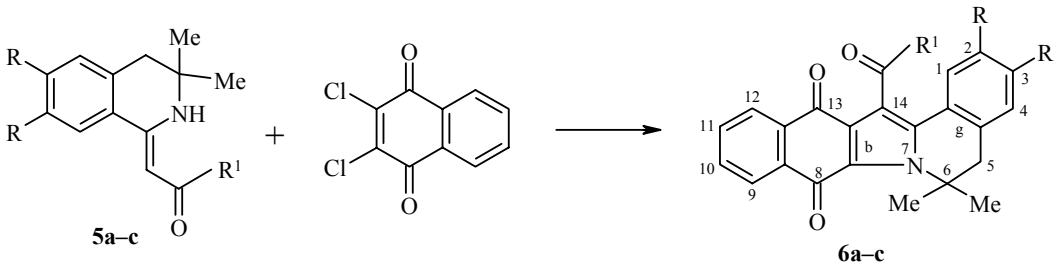
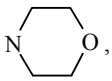


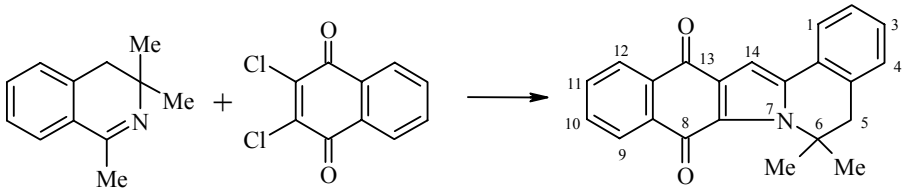


Our studies showed that not only complexes, but also condensed compounds may be obtained by altering the conditions of the reaction with 2,3-dichloro-1,4-naphthoquinone. A similar reaction was carried out in our earlier work on amides **2a**,**b** [6, 7].

The major reaction products obtained when using **5a-c** as the starting compound in the presence of triethylamine were the corresponding condensed quinones **6a-c**, whose formation was observed upon heating at reflux in benzene. Product **5d** does not give condensed quinones in the presence of triethylamine. However, the corresponding condensed product could be obtained in benzene at 20°C in the absence of triethylamine, naturally with a much reduced yield of reaction product since starting compound **5d** binds two equivalents of liberated HCl. The yield is approximately doubled when the amount of **5d** is tripled. The absence of preparative amounts of condensed product in the reaction of **5d** in the presence of triethylamine may be attributed to the high basicity of the imino group in comparison with the enamino group (**5a-c**). The formation of donor–acceptor complex may predominate in this reaction due to its high stability.



5, 6 a R = MeO, **b–c** R = H; **a** R^1 =  ; **b** R^1 =  , **c** R^1 = OEt



Thus, condensation upon the action of 2,3-dichloro-1,4-naphthoquinone may be achieved both for compounds, in which enamine structure has already been fixed (**5a-c**), and "azomethine" compounds such as **5d**.

Phenols **2a**,**b** are almost colorless compounds, which dissolve in aqueous solutions of alkali. Condensed quinones **6a-d** are bright-yellow. Halochromism is observed upon their dissolution in concentrated sulfuric acid and the solutions turn dark-blue. These solutions gradually turn red upon their gradual dilution by adding more water (Table 1). The structure of these compounds was demonstrated by elemental analysis, IR and ^{1}H NMR spectroscopy, and mass spectrometry.

The ^{1}H NMR spectra of phenols **2a**,**b** (Table 2), in contrast to the spectra of the starting enamines [8], lack singlets for ring NH protons, indicating transition to the imino form. Proton H-4, which gives a singlet in the vicinity of 5.6-5.7 ppm, is at a chiral site. Thus, in contrast to the case of the starting compound, the 2-CH_3 groups become diastereotopic and their proton signals are seen as two singlets (at 1.2 and 1.3 ppm). The spectrum of condensed indolo[2,1-*a*]isoquinoline **4** lacks the benzilic methylene group singlet characteristic for drotaverine base but has a phenol hydroxyl group singlet at 4.9 ppm. The spectra of condensed quinoxalines **6** lack the singlets for the enamine NH and CH group protons (enamines **5a-c**) and 1-CH_3 (**6d**) found in the spectra of the starting enamines.

The IR spectra of dihydric phenols have phenolic hydroxyl bands at 3350-3370 cm^{-1}, while the phenolic hydroxyl band for **4** is found at 3340 cm^{-1}. The band at about 1670 cm^{-1} corresponds to the amide carbonyl group in **2a,b, 6a,b,** while the band at 1710 cm^{-1} corresponds to the ester carbonyl group in **6c** and the band at 1640 cm^{-1} corresponds to the quinone carbonyl group in **6a-d.**

The mass spectra of amides **2a**,**b** feature a common low-intensity peak, corresponding to the loss of a tertiary amine (pyrrolidine or piperidine) with the loss of two protons (most likely, phenolic protons). The intensity of this band for amides **2a**,**b** is 5 and 30%, respectively (*m/z* 357).* This hypothesis is supported by the finding of strong peaks for pyrrolidine (*m/z* 70, 50%) and piperidine (*m/z* 84, 60%). The mass spectrum of drotaverine derivative **4** contains a molecular ion peak (M^+ 487, 100%).

TABLE 1. Characteristics of Synthesized Products

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{27}H_{28}N_2O_3$	75.6 / 75.7	6.5 / 6.6	6.6 / 6.5	210-211	58
2b	$C_{28}H_{30}N_2O_3$	75.9 / 76.0	6.7 / 6.8	6.3 / 6.3	198-199	57
4	$C_{30}H_{33}NO_5$	73.8 / 73.9	6.6 / 6.8	3.0 / 2.9	182-183	48
6a	$C_{29}H_{28}N_2O_5$	71.8 / 71.9	5.7 / 5.8	5.9 / 5.8	195-197	62
6b	$C_{27}H_{24}N_2O_4$	73.5 / 73.6	5.4 / 5.5	6.3 / 6.4	225-227	60
6c	$C_{25}H_{21}O_4$	75.1 / 75.2	5.2 / 5.3	3.6 / 3.5	197-199	67
6d	$C_{22}H_{17}NO_2$	80.6 / 80.7	5.1 / 5.2	4.3 / 4.3	160-162	27

* Here and subsequently, the *m/z* values are given for the ion peaks.

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

Com-pound	Chemical shifts, δ, ppm. (*J*, Hz)				
	2(6)-$(CH_3)_2$	1(5)-CH_2	aromatic protons	CH_3O, EtO and R^1 protons	other protons
		3.1 (br. s)	6.3-6.6 (3H, m, phenol); 7.3-8.7 (6H, m, napthyl)	1.7-1.9 (4H, m, $C(CH_2)_2C$); 3.3-3.6 (4H, m, NCH_2)	—* 5.7 (1H, s, 4-CH)
2b	1.2 (s); 1.3 (s)	3.1 (br. s)	6.2-6.6 (3H, m, phenol); 7.3-8.7 (6H, m, napthyl)	1.4-1.8 (6H, m, $C(CH_2)_3C$); 3.4-3.5 (4H, m, NCH_2)	—* 5.6 (1H, s, 4-CH)
4	—	—	6.7-7.3 (8H, m)	1.2-1.5 (12H, 4 t, *J* = 7.4, $C\underline{H}_3CH_2$); 4.0-4.2 (8H, 4 q, *J* = 7.4, $CH_3C\underline{H}_2$)	3.1-3.7 (4H, m, $ArCH_2CH_2N$); 4.9 (1H, s, OH)
6a	1.6 (s)	2.9 (s)	6.6 (s, H-4); 7.1 (s, H-1); 7.2-8.1 (4H, m)	3.7 s and 3.8 s ($2CH_3O$); 1.7-1.9 (4H, m, CCH_2CH_2C); 3.1-3.2 (4H, m, NCH_2)	—
6b	1.6 (s)	3.1 (s)	7.2-7.9 (8H, m)	3.2-3.7 (8H, m, CH_2 morpholine)	—
6c	1.5 (s)	2.9 (s)	6.9-7.9 (8H, m)	1.2 (3H, t, *J* = 6.9, $C\underline{H}_3CH_2$); 4.1 (2H, q, *J* = 6.9, $CH_3C\underline{H}_2$)	—
6d	1.5 (s)	2.9 (s)	7.1-7.9 (8H, m)	—	6.8 (1H, s, H-14)

* OH group protons are in exchange with water present in the solvent.

EXPERIMENTAL

The ^{1}H NMR spectra of **4** were taken on a Varian Mercury-300 spectrometer (300 MHz), while the spectra of the other compounds were taken on a Tesla BS 567 spectrometer (100 MHz) in DMSO-d_6 (amides **2a**,**b**) or CCl_4 (**4, 6a-d**) with HMDS as the internal standard (δ 0.05 ppm). The IR spectra were taken on a Specord-80 spectrometer in vaseline mull. The electron-impact mass spectra were taken on a MAT-311 spectrometer at 70 eV. The purity of the products were checked by thin-layer chromatography on Silufol UV-254 plates using 1:3:6 acetone–ethanol–chloroform as the eluent and development by iodine vapor.

Amides **2a**,**b** were recrystallized from acetonitrile, while quinones **6a**,**d** were recrystallized from petroleum ether (70-100°C fraction). The other products were recrystallized from 2-propanol.

Derivatives **5a,b** [9]**,** and **5d** [10] were prepared according to reported procedures.

Pyrrolidyl Amide (2a) and Piperidyl Amide of 2-(2',2'-Dimethyl-1',2'-dihydrobenzo[*f*]isoquinolyl-4')-2-(2",5"-dihydroxyphenyl)ethanoic Acid and 1-(3',4'-Diethoxyphenyl)-10,11-diethoxy-7,8-dihydro-indolo[2,1-*a*]isoquinoline (4) (General Method). A solution of *p*-benzoquinone (1.08 g, 10 mmol) in dry methylene chloride (20 ml) was added to a solution of corresponding starting enamine (10 ml) in dry methylene chloride (50 ml). The solution turns dark-blue. The mixture was heated at reflux for 1 h and the solvent was distilled off. Treatment of the residue with hexane gave a precipitate, which was filtered off, dried, and recrystallized.

14-Piperidinocarbonyl- (6a), 14-Morpholinocarbonyl- (6b), and 14-Ethoxycarbonyl-6,6-dimethyl-5,6-dihydrobenzo[*g*]naphtho[2,3-*b*]indolyzine-8,13-dione (6c) (General Method). A sample of 2,3-dichloro-1,4-naphthoquinone (2.27 g, 10 mmol) was added to a mixture of corresponding enamine **5a-c** (10 mmol) with triethylamine (2.80 ml, 22 mmol) in benzene (100 ml). The resultant dark-blue solution was heated at reflux for 1 h and the triethylamine hydrochloride precipitate was filtered off. The solvent was removed in vacuum and then treated as in the procedures for **2a,b,** and **4**.

6,6-Dimethyl-5,6-dihydrobenzo[*g*]naphtho[2,3-*b*]indolyzine-8,13-dione (6d). A sample of 2,3-dichloro-1,4-naphthoquinone (2.27 g, 10 mmol) was added to a solution of enamine **5d** (1.73 g, 10 mmol) in benzene (10 ml). The resultant dark-blue solution was left stand for 3-4 h at 20°C. A precipitate formed. The mixture was diluted by adding hexane (50 ml) and then treated as in the procedure for **2a,b,** and **4**.

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