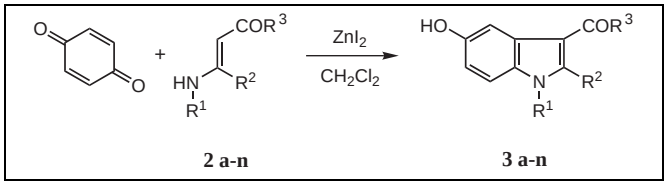
Valeriya S. Velezheva*, Albert G. Kornienko, Sergey V. Topilin, Ascar D. Turashev, Alexander S. Peregudov, and Patrick J. Brennan[a]

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilov Str, 119991 GSP-1 Moscow, Russia
Fax: (7-095)135-5085.
E-mail: vel@ineos.ac.ru

[a] Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, Colorado 80523-1682 U.S.A
Fax: (970) 491-1815.
E-mail: Patrick.Brennan@ColoState.edu

Received August 5, 2005



2 a-n **3 a-n**

A novel method for Lewis acid catalyzed Nenitzescu indole syntheses of 5-hydroxyindoles bearing different substituents in positions 1 (Alk, Bn, Ar), 2 (Me, Et, Ph), and 3 (COOEt, COMe, CONHPh) as well as tricyclic derivatives are reported. The method is simple, rapid, efficient, and allows preparation of hydroxyindoles from 1,4-benzoquinone and enamines in good to excellent yields with the use of low-polar solvents in the presence of weak Lewis acids catalysts. The formation of 5-hydroxyindoles under such mild conditions is explained in terms of a non-redox mechanism.

J. Heterocyclic Chem., **43**, 873 (2006).

Introduction.

5-Hydroxyindoles are found in nature and display a wide variety of biological activities [1,2]. A series of polysubstituted 5-hydroxyindole-based agents have been developed recently including the antiviral and immunomodulatory drug arbidol, ethyl 6-bromo-4-dimethylaminomethyl-5-hydroxy-1-methyl-2-phenylthio-methylindole-3-carboxylate hydrochloride [3] (and its 4-substituted derivatives [4]), as well as compounds of potential value as drugs. For example, N-benzyl substituted analogues of the anti-inflammatory drug indometacin and indometacin-related N-benzyl indoleacetamide exhibit selective cyclooxygenase (COX-2) inhibitory [5] and multidrug resistance related-protein 1 (MRP-1) modulatory activities [6,7], respectively. The antitumor agent E 09 (a fully synthetic indolequinone with 1,2,3,5-substituent pattern) and its analogues are good substrates for human DT-diaphorase which possibly is a molecular target for enzyme-directed bioreductive drug development [8,9]. Syntheses of medicinally interesting 2,4-diamino-8*H*-pyrimido[4,5-*b*]indol-6-ols were carried out recently *via* the Nenitzescu reaction [10].

The discovery of the above synthetically challenging and medicinally useful compounds has intensified the search for new effective drugs with broad clinical applications. The Nenitzescu reaction followed by functional group interconversions has proved to be the simplest synthetic entry into 5-hydroxyindole-based key intermediates of pharmacologically active molecules and drugs [11,12], including those cited above. For example, the facile synthesis of an advanced E 09 intermediate comprises five steps including the Nenitzescu indolization, in contrast to the 15-step synthesis starting from 3-chlorophenol [13]. The reaction, as well as Fisher indole synthesis, plays a prominent role in classical indole ring formation due to readily available precursors. The Fisher indolization, with rare exceptions, proceeds smoothly and furnishes good yields of target products but is very seldom suitable for preparation of polysubstituted 5-hydroxyindoles [14]. On the contrary, the Nenitzescu reaction, in principle, provides the possibility of solving the latter problem to a great extent. However the reaction has been fickle since at times it proceeds with good yields of indoles while at other times yields are low or the reaction may even fail altogether [15]. It was noted that the Nenitzescu reaction is highly affected by the nature of the substituents on the starting compounds and the reaction medium [5,7,9,15,16]. The 5-hydroxy derivatives of 3-acylbenzofurans are often obtained instead of the corresponding 3-acyl-5-hydroxyindoles. In many cases, the simultaneous formation of indole and benzofuran derivatives has been observed [15]. The scope of the reaction has mainly been restricted to the synthesis of 5-hydroxyindoles with 3-carboxylic ester groups. With

those, however, being at other times, low [5,7,9,10,16-18]. The corresponding N-benzylaminoacrylic esters when reacted with benzoquinone in nitromethane gave 2-methyl-1-benzyl-5-hydroxyindole-3-carboxylates in 47% yield and its 2-ethyl homologue in 53% yield [7]. Moreover, under such conditions the reaction goes slowly (16 - 48 hr) and fails altogether with enaminoanilides as enamino components in CH_2Cl_2 [19]. Even as lately as 2002, ethyl 5-hydroxy-2-propyl-indole-3-carboxylate was reported to be obtained by the Nenitzescu reaction in acetic acid, in 6% yield only [12]. Thus, large-scale production of the Nenitzescu indoles should be expensive. Previously**,** the application of the Nenitzescu reaction was somewhat limited due to not only low yields of 5-hydroxyindoles, but also difficulties in their isolation as pure compounds because of contamination with numerous by-products including those of characteristic dark red colour [15].

Recently, advances in the efficiency of the Nenitzescu indole synthesis were made. These came from the choice of proper solvents and the application of a solid-phase method described by Ketcha *et al.* [16]. The authors were the first to solve the problem of regioselective synthesis of 1,2,3,6-pentasubstituted 5-hydroxyindoles *via* the reaction of mono-substituted quinones with the corresponding enaminoamides. However, this solid-phase method employing nitromethane as the solvent and applied for the preparation of only 5-hydroxyindole 3-carboxamides, does not seem entirely satisfactory since it is a multi-stage procedure, employs hazardous and expensive chemicals and, in some cases, gives low yields of target 5-hydroxyindoles. Hence the problem of 5-hydroxyindole yields still remains topical. All of this underlines the need for a flexible strategy that could reduce the reaction time, provide good yields of 5-hydroxyindoles and use inexpensive reagents and solvents.

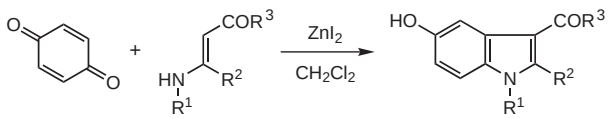
In order to develop improved methods we dwelt on catalytic interactions of 1,4-benzoquinone **1** with enaminoesters, enaminoketones and enaminoanilide **2a-n**, typical enamino components for the reaction. As to the Lewis acid catalyzed reactions of enaminoesters with 1,4-benzoquinones, only those of N-substituted aminofumarates have been reported by Domschke *et al.* [20]. These aminofumarates react with 1,4-benzoquinone in diethyl ester under $BF_3{\cdot}Et_20$ catalysis to afford N-substituted 5-hydroxyindole-2,3-dicarboxylates in 21 – 90% yields. Engler *et al.* extensively used Lewis acid promotion under addition of enol esters and styrenes to benzoquinones and their imines in syntheses of either 2-aryl-2,3-dihydrobenzofurans or 2-aryl-2,3-dihydroindoles, pterocarpanes, and highly substituted tetrahydro-β- or γ-carbolines, and also, benzofuran analogs [21].

Since the Nenitzescu reaction includes two steps of nucleophilic addition (conjugation of an enamino component to quinone and ring closure due to the nitrogen-to-carbonyl carbon addition) one could expect that, as in other similar nucleophilic addition reactions, the application of acidic catalysis would facilitate both of them. We believed that Lewis acids would not impede the interaction of enamines with benzoquinones. We also expected Lewis acids to be most effective for processes conducted in low-polar solvents. At present, nitromethane and AcOH are considered as the best solvents for the Nenitzescu reaction. In these solvents, however, the process occurs *via* an oxidation-reduction pathway generally marked by the formation, along with 5-hydroxyindoles, of many by-products.

Results and Discussion.

We chose the interaction of 3-methylaminocrotonate **2a** with quinone **1** furnishing 5-hydroxyindole **3a** as the first prototypical reaction. We did obtain high purity indole **3a** in good yield (> 80%) from the reaction carried out in benzene in the presence of catalytic amounts of $ZnCl_2$ (Table 1, Scheme 1).

Scheme 1



1 **2 a-n** **3 a-n**

2,3a: R^1=R^2=Me, R^3=OEt
b: R^1=H, R^2=Me, R^3=OEt
c: R^1=CH_2Ph, R^2=Me, R^3=OEt
d: R^1=Ph, R^2=Me, R^3=OEt
e: R^1=Me, R^2=Et, R^3=OEt
f: R^1=H, R^2=Ph, R^3=OEt
g: R^1=Me, R^2=Ph, R^3=OEt
h: R^1+R^2=$(CH_2)_5$, R^3=OEt
i: R^1=H, R^2=Me, R^3=Me
j: R^1= R^2= R^3=Me
k: R^1 = CH_2Ph, R^2= R^3=Me
l: R^1=Ph, R^2= R^3=Me
m: R^1=4-Br-Ph, R^2= R^3= Me
n: R^1= CH_2Ph, R^2=Me, R^3=NHPh

To assess how catalysts and their quantities, as well as how solvents affect the reaction we also used other Lewis acids ($AlCl_3$, $BF_3{\cdot}Et_2O$, and ZnI_2) as well as a protic acid, CF_3CO_2H (TFA), and solvents (toluene, carbon tetrachloride, methylene dichloride). Our experiments demonstrated that in the absence of catalyst, the yields of indole **3a** in benzene and CH_2Cl_2 achieved 30 and 21%, respectively, with the isolated compound purity being < 98% as shown by ^{1}H NMR. Earlier, Kucklender *et al.* obtained a mixture of indole **3a** with the corresponding hydroquinone adduct on heating a benzene solution of the same species [22]. In all cases when we used our method for producing indole **3a** (and later on indoles **3b-n**) a benzene or CH_2Cl_2 solution of enamine was gradually added to a boiling solution of an equimolar amount of

quinone **1** in the same solvent after introduction of a catalyst. The reaction mixture was then boiled for additional 40 - 60 minutes (method *A*). We obtained pure indole **3a** in good yields (80 – 87%) from the reaction carried out in the presence of catalytic amounts of $ZnCl_2$ or ZnI_2 (1 – 10 mol %) (Table 1, entries 3-6, 15-16).

Table 1

Yields of indole **3a** depending on catalysts and reaction conditions.

Entry	Solvent	t[a], min	Mp, (°C)	Catalyst MX_n (mol %)	Yield %
1	C_6H_6	45	200-203	None	30
2	CH_2Cl_2	40	197-199	None	21[b]
3	C_6H_6	40	208-209	$ZnCl_2$ (8)	81
4	CH_2Cl_2	60	208-209	$ZnCl_2$ (8)	87
5	C_6H_6	40	208-209	$ZnCl_2$ (1)	82
6	C_6H_6	40	208-209	$ZnCl_2$ (5)	81
7	C_6H_6	40	208-209	$ZnCl_2$ (10)	80
8	C_6H_6	40	208-209	$ZnCl_2$ (20)	80
9	C_6H_6	45	207-208	$ZnCl_2$ (50)	78
10	C_6H_6	60	196-198	$ZnCl_2$ (200)	64[b]
11	C_6H_6	105	195-198	$ZnCl_2$ (400)	37[b]
12	C_6H_6	40	195-198	$ZnCl_2$ (0.1)	42[b]
13	CH_2Cl_2	300	195-198	$ZnCl_2$ (0.2)	55[b]
14	CH_2Cl_2	40	197-199	ZnI_2 (0.2)	68[b]
15	CH_2Cl_2	40	207-208	ZnI_2 (10)	83
16	CH_2Cl_2	40	207-208	ZnI_2 (1)	83
17	CCl_4	40	180-190	$ZnCl_2$ (8)	19[b]
18	toluene	45	195-198	$ZnCl_2$ (8)	67[b]
19	CH_2Cl_2	120	177-178	$AlCl_3$ (1)	65[b]
20	CH_2Cl_2	60	206-207	$AlCl_3$ (8)	65
21	CH_2Cl_2	60	207-208	$BF_3{\cdot}Et_2O$ (1)	45
22	CH_2Cl_2	40	205-206	$BF_3{\cdot}Et_2O$ (8)	66

[a] method **A**. [b] the crude indole **3a**.

We found the yield of indole **3a** to be appreciably dependent on the amount of the catalyst applied. In benzene, high yields of the product, 80-82%, were achieved when $ZnCl_2$ was used in amounts of 1-20% (Table 1). An increase in the amount to 50 mol % did not virtually influence the yield (78%) whereas it was reduced to 64% with 200 mol % of the catalyst. With 4-fold excess, the yield was noticeably less - 37%. The reaction responded almost similarly to a decrease in the amount of $ZnCl_2$ to 0.1 mol % producing the product in 42% yield. With this catalyst, the highest indole **3a** yield of 87% was reached when quinone **1** and enamine **2a** were heated in CH_2Cl_2 in the presence of 8 mol % for 1 hour. We observed a drop in the yield to 55% with a decrease in amount of the catalyst to 0.2 mol %. The same proved to be valid for the ZnI_2/CH_2Cl_2 system; reducing the amount of the catalyst from 8 to 0.2 mol % lowered the yield from 83 to 68%. With that, prolongation of the heating of the components from 40 minutes up to several hours did not noticeably affect the reaction. However, the best yield (92%) of **3a** was gained when the process was conducted in CH_2Cl_2 in the presence of ZnI_2 at -45° - -30 ° C for 15 hours (method *B*). Additional amount of the indole **3a** was contained in the slightly colored mother liquor obtained after separation of the product in the form of a white powder. If the reaction time was limited to 2 hours the yield was reduced to 80%.

The application of Lewis acid catalysis allowed preparation of indoles under conditions milder than those used before. With that, there were neither 5,5-dihydroxydiindoles, nor hydroquinone, *etc.*, characteristic of the classical Nenitzescu reaction performed in polar solvents and believed to proceed *via* the oxidation-reduction pattern [15]. Without the catalysts, the reaction either did not go at the low temperatures or produced indole **3a** in small yield at heating. When passing from CH_2Cl_2 to both CCl_4 and toluene, with ZnI_2 in amount of 8 mol %, the yield decreased to 19 and 67%, respectively. We believe this to have occurred since the reaction mixture was more heterogeneous in these solvents and underwent resinification to a greater extent. When the reaction was carried out by procedure A with $AlCl_3$ or $BF_3{\cdot}Et_2O$ as catalysts, the yields of indole **3a** turned out to be moderate. The samples of the crude indole **3a** listed under entries 1, 2, 10-14 and 17-19 in Table 1 contained some impurities and their melting points were below that of the pure compounds mentioned under entries 3-9, 15, 16 and 20-22.

The ZnI_2 catalyzed reaction effected by procedure A was also employed for the synthesis of indoles **3b-n** bearing different substituents at 1, 2, and 3 positions of the indole ring (Scheme 1, Table 2). With all enamines **2a-n**, the process went smoothly and the direct product crystallization occurred as the reaction progressed. In all cases the best yields of indoles **3a-n** (between 62 and 95%) resulted when equimolar amounts of the quinone and enamine were taken.

Table 2

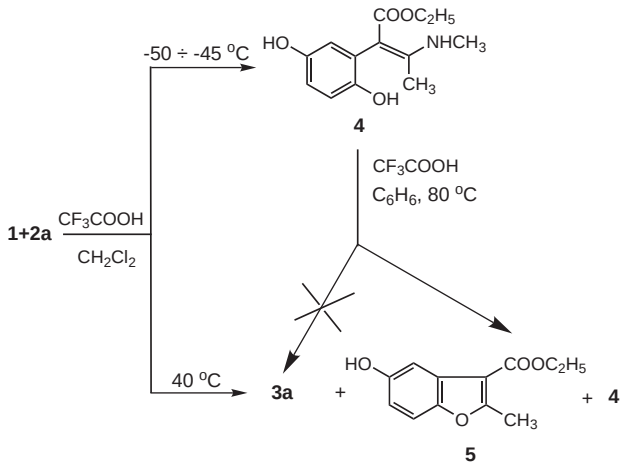
ZnI_2 catalyzed Nenitzescu Indole **3a-n** Synthesis.

Product	Yield % [a]	[c]	Mp (°C)
3a	83 92[b]	60[27]	208-209
3b	77	53[27]	204-205
3c	95	44[27]	197-198
3d	69	53[27]	203-204
3e	67		172-174
3f	72	46[28]	174-175
3g	63		205-207
3h	78		195-197
3i	79	53[30]	294-295
3j	87	30[30]	247-248
3k	77		243-244
3l	78	53[29]	230-231
3m	76		292-293
3n	62		220-221

[a] method **A**; [b] method **B**; [c] max. reported.

All indoles obtained are feasible for further use without additional purification. In the case of enaminoester **2d**, the yield of 1-phenylindole **3d** did not exceed 69% with the lack, however, of isomeric 6-hydroxyindole characteristic of the Nenitzescu reaction in AcOH [15,23]. The reactions with **2i-m** gave 3-acetyl-5-hydroxyindoles **3j-n** instead of 5-hydroxybenzofurans typical for the interaction between benzoquinones and enaminoketones in acidic media, *e.g.*, AcOH [15,24]. With TFA taken as an example, we further studied whether protic acid catalysts could be employed in the process. For the reaction of enamine **2a** with quinone **1**, the results turned out to be temperature dependent. At -50° C to -45° C in CH_2Cl_2, only product **4** was formed in 94% isolated yield whereas a mixture of indole **3a**, benzofuran **5**, and adduct **4** was obtained on heating (Scheme 2).

Scheme 2

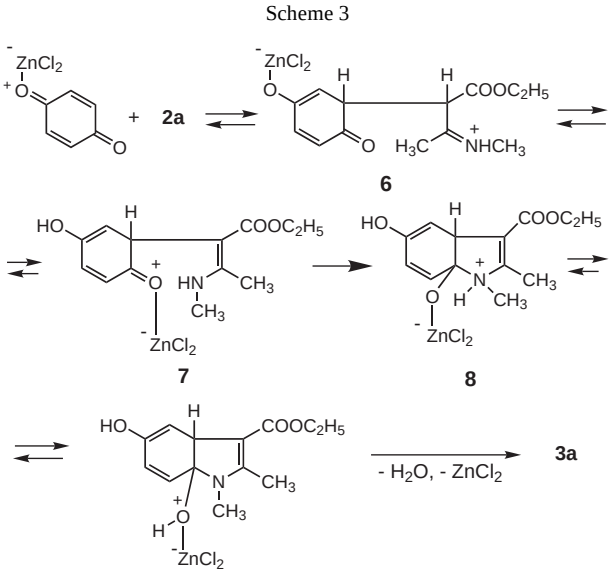


These results prompted us to examine whether indole **3a** could be formed from adduct **4** in both the TFA and Lewis acid promoted reactions and if so, whether it depended on the presence or absence of benzoquinone and the catalysts at different temperatures. According to Allen's data [15], a hydroquinone adduct was transformed into the corresponding indole in 55% yield in AcOH in the presence of 10 mol % benzoquinone *via* a redox mechanism. We found that without quinone **1**, adduct **4** did not transform into indole **3a** in the presence of ZnI_2 or TFA in both cases, on heating and cooling. Moreover adduct **4** was left intact in the presence of either 10 or even 100 mol % of quinone **1** at -50°C to -30°C with or without ZnI_2. However, it furnished indole **3a** in low yields (21 - 23%), when heated in benzene with 10 or 100 mol % of quinone **1** in the presence or absence of ZnI_2. The reaction mixture also contained a rather large amount of brick-red colored products typical for the classical conditions. At the same time, boiling of a benzene solution of adduct **4** without quinone **1** in the presence of ZnI_2 or TFA for 4 h afforded benzofuran **5** in 9% and 70% yields, correspondingly.

Thus the experiments showed TFA to be unsuitable as a catalyst for the indole synthesis. However the low temperature reaction in the presence of TFA provided the possibility to obtain pure adduct **4** and to study its behavior under conditions of the Lewis acid catalyzed indolization. This turned out to be important in elucidating the reaction mechanism.

An internal oxidation-reduction mechanism has been proposed and is now commonly accepted for the Nenitzescu reaction [15,25]. It involves the oxidation of an intermediate Michael adduct of type **4** by a quinone. Hence, the high yields of indole **3a** secured by us in the $ZnCl_2$ or ZnI_2 catalyzed reactions did not fit in with the redox pattern since adduct **4** either does not react at all or reacts to a small extent under the catalytic conditions. All these findings count in favor of the hypothesis that the catalytic Nenitzescu reaction occurs *via* a non-redox mechanism presented in Scheme 3.

Scheme 3



The conjugate Michael addition is a reversible process, so that complexing carbonyl oxygen of substrate **1** by the metal atom of a Lewis acid can shift the equilibrium towards intermediate **6** or increase the rate of the direct reaction. This increases the amount of intermediate **6**, which undergoes fast prototropic isomerization at its imino site to give intermediate **7** with the enamino moiety. The rearrangement seems plausible to proceed owing to the absence of any additional base capable of proton abstraction from the hydroxydienone site of **6**. By contrast, as shown by Bernatek [26], in the presence of $ZnC1_2$ and AcOH, the corresponding hydroxydienone intermediate (formed from quinone **1** and acetoacetic ester) is converted to a type **4** Michael adduct followed by cyclocondensation of the latter into

benzofuran **5,** obviously *via* proton abstraction by AcO^- as a base. The benzofuran synthesis is considered to follow a non-redox mechanism. Besides, the closing of the 5-membered ring into intermediate **8** is favored according to Baldwin's rules (five-Exo-Tet process) and thus, should be quick. The finding already mentioned that the yields of indole **3a** were higher in the presence of more weak Lewis acids ($ZnC1_2$ or ZnI_2) than those in the presence of $AlCl_3$ or $BF_3{\cdot}Et_2O$ can be attributed to the ability of the latter to deactivate the enamino component (Table 1). The same effect of deactivation probably occurred when we increased the amounts of $ZnC1_2$ or ZnI_2 up to 4-fold excess (Table 1).

A general characterization of the target compounds **3a-n** was accomplished using ^{1}H NMR spectroscopy. A salient feature in the spectra of these compounds is the appearance of characteristic groups of signals: two doublets (δ *ca*. 7.3 and 7.4 ppm), a doublet of doublets (δ *ca*. 6.7 - 6.8 ppm) or a multiplet (δ *ca*. 6.4 - 7.8 ppm) that are assigned to the protons - 4, 7, and 6 of the 5-hydroxyindole ring and protons of one or two aromatic rings attached to positions 1 and/or 2 of the ring, respectively.

Conclusion.

Thus, one can suggest that, depending on the conditions, the Nenitzescu reaction goes *via* at least two different mechanisms. The first of those is valid for the reactions performed in polar solvents. The alternative is realized when the reactions are conducted in low-polar solvents in the presence of weak Lewis acids. Thus we have defined experimental conditions for the realization of the Nenitzescu reaction *via* a second, non-redox mechanism that was first theoretically proposed by G. R. Allen in 1966 [27]. On the basis of the latter, we offer a simple and rapid method to afford polysubstitited 5- hydroxyindoles in good to excellent yields based on a catalytic version of the Nenitzescu reaction and applicable to a variety of enamines; the method does not require expensive solvents. The products obtained are of high purity so that they can be further used without purification.We think that the method will be useful for those chemists who are in search of biologically active 5-hydroxyindole derived compounds.

EXPERIMENTAL

Materials.

1,4-Benzoquinone, $ZnCl_2$, ZnI_2, $AlCl_3$, and $BF_3{\cdot}Et_2O$ were purchased commercially and used as received ($ZnCl_2$ was dried before used). Ethyl 3-methylaminocrotonate [28] **2a**, ethyl 3-aminocrotonate [29] **2b**, ethyl 3-benzylaminocrotonate [30] **2c**, ethyl 3-phenylamino-crotonate [31] **2d**, ethyl 3-methylamino-2-pentenoate [32] **2e**, ethyl-3-aminocinnamate [33] **2f**, ethyl-3-methyl-aminocinnamate [34] **2g**, ethyl 2-(hexahydro-2H-azepin-2-yliden)-acetate [35] **2h**, 4-amino-pent-3-en-2-one [36] **2i**, 4-methylamino-pent-3-en-2-one [37] **2j**, 4-benzyl-amino-pent-3-en-2-one [38] **2k**, 4-anilino-pent-3-en-2-one [39] **2l**, 4-(4-bromophenylamino)-3-penten-2-one [38] **2m**, 3-benzylamino-crotonanilide [40] **2n** were prepared according to literature procedures.

General Methods.

The ^{1}H NMR spectra were recorded on a Bruker AMX – 400 spectrometer at 400 MHz. The chemical shifts are reported in the δ scale (ppm) basing on the residual proton signal from $(CD_3)_2SO$ (δ 2.50).

General Procedure for the Synthesis of 5-Hydroxyindoles **3a-n** (Method A).

To a solution of quinone **1** (1.08 g, 10.00 mmoles) in CH_2Cl_2 (30 ml) was added ZnI_2 (0.32 g, 1.00 mmole). The temperature was raised to boiling, and a solution of enamine **2a-n** (10 mmoles) in CH_2Cl_2 (20 ml) was added drop by drop at stirring for 5-10 minutes. The mixture was then stirred under boiling for 40 minutes and cooled to 0-5° for 2-3 hours. The precipitated crystals were filtered off and washed with CH_2Cl_2 (2 x 1 ml) and acetone (2 x 1 ml) (Scheme 1, Tables 1, 2).

Ethyl 1,2-dimethyl-5-hydroxy-indole-3-carboxylate (**3a**).

Method A. To a solution of 1,4-benzoquinone (1.08 g, 10.00 mmoles) in CH_2Cl_2 (30 ml) was added $ZnCl_2$ (1.11 g, 8.00 mmoles). The resulting mixture was heated to boiling and then a solution of enamine **2a** (1.43 g, 10.00 mmoles) in CH_2Cl_2 (20 ml) was added drop by drop at stirring for 5-10 minutes. The mixture was stirred under boiling for additional 40 minutes and cooled to 0-5° for 2-3 hours. The precipitated crystals were filtered off and washed with CH_2Cl_2 (2 x 1 ml) and acetone (2 x 1 ml) to afford 2.03 g (87%) of **3a**, mp 208-209° (Table 1, entry 4); 209° according to [41]; ^{1}H nmr (DMSO-d_6): δ 1.33 (t, 3H, CH_3), 2.66 (s, 3H,CH_3-2), 3.64 (s, 3H, NCH_3), 4.24 (q, 2H, C*H*$_2$CH$_3$), 6.65 (dd, 1H, ArH-6), 7.26 (d, 1H, ArH-7), 7.35 (d, 1H, ArH-4), 8.92 (s, 1H, OH).

Method B. To a solution of 1,4-benzoquinone (1.08 g, 10.00 mmoles) in CH_2Cl_2 (30 ml) was added ZnI_2 (0.32 g, 1.00 mmole). After cooling the mixture to -30 - -45° a solution of **2a** (2.86 g, 20.00 mmoles) in CH_2Cl_2 (20 ml) was added drop by drop at stirring for 6 minutes. The mixture was then stirred at -30° for 15 hours. The precipitated crystals were filtered off and washed with CH_2Cl_2 (2 x 1 ml) and acetone (2 x 1 ml) to afford 2.14 g (92%) of the product, mp 208-209°; the ^{1}H nmr spectrum was suitable.

Ethyl 2-(2,6-dioxyphenyl)-3-methylaminocrotonate (**4**).

To a solution of 1,4-benzoquinone (2.16 g, 20.00 mmoles) in CH_2Cl_2 (15 ml) was added TFA (0.2 ml) and then, after cooling to -45 - -50°, a solution of methylaminocrotonate **2a** (3 ml, 20.00 mmoles) in CH_2Cl_2 (5 ml) was added drop by drop at stirring for 5-10 minutes. The mixture was further stirred at -30° for 17 hours. The precipitated crystals were collected by filtration and washed with CH_2Cl_2 (2 x1 ml) and acetone (2 x 1 ml). The product was recrystallized from MeOH to afford 4.70 g (94%) of **4**, mp 138-139°; 137-138° according to [42]; ^{1}H nmr

(DMSO-d_6): δ 1.06 (t, 3H, CH_3), 1.66 (s, 3H, =CCH_3), 2.89 (d, 3H, NCH_3), 3.90 (q, 2H, C$H_2$$CH_3$), 6.31 (d, 1H, ArH-3), 6.43 (dd, 1H, ArH-5), 6.55 (d, 1H, ArH-6), 7.99 (s, 1H, OH), 8.47 (s, 1H, OH), 9.29 (br s, 1H, NH).

Interaction of 1,4-Benzoquinone **1** and Ethyl 3-methylaminocrotonate **2a** in the presence of TFA on heating.

To a solution of **1** (2.16 g, 20.00 mmoles) in CH_2Cl_2 (30 ml) was added TFA (0.15 ml). The solution was heated to boiling, and a solution of **2a** (2.86 g, 20.00 mmoles) in CH_2Cl_2 (20 ml) was added drop by drop under stirring for 6 minutes. The mixture was then stirred at 40° for 40 minutes and cooled to 0-5° for 2 hours. The precipitated crystals were collected by filtration and washed with CH_2Cl_2 (2 x 1 ml) and acetone (2 x 1 ml). The solid (2.14 g) contained 27% of indole **3a** and 18% of adduct **4** and 52% of benzofuran **5** as shown by the comparison between the integral intensities of 2-CH_3 group signals for **3a** (δ 2.66), **5** δ 2.68), and adduct **4** (δ 1.66) in the ^{1}H nmr spectrum. The mother liquor was dried *in vacuo*, the solid residue washed with CH_2Cl_2 (2 x 0.5 ml) and acetone (2 x 0.5 ml) to give ethyl 5-hydroxy-2-methyl-benzofuran-3-carboxylate **5**, isolated yield 0.64 g (14%), mp 142-144°. 143-144° according to [43]; ^{1}H nmr (DMSO-d_6): δ 1.35 (t, 3H, CH_3), 2.68 (s, 3H, CH_3), 4.31 (q, 2H, CH_2CH_3), 6.73 (dd, 1H, ArH-6), 7.25 (d, 1H, ArH-7), 7.36 (d, 1H, ArH-4), 9.35 (s, 1H, OH). The filtrate contained unidentified products.

Interactions of Adduct **4** with ZnI_2 or TFA.

To a solution of 0.50 g (2 mmoles) of aminocrotonate **4** in 80 ml of benzene was added ZnI_2 (0.064 g, 0.2 mmoles), and the reaction mixture was then stirred for 40 minutes at boiling. The solvent was evaporated *in vacuo*. The mixture contained 81% of starting adduct **4** and 9% of benzofuran **5**. It was displayed by the comparative analysis of signals from the 2-CH_3 and N-CH_3 groups of adduct **4** at δ 1.66 and 2.89 accordingly and that from the 2-CH_3 group of benzofuran **5** at δ 2.68 in the ^{1}H nmr spectrum. The reaction carried out with the same amounts of **4** and the solvent in the presence of TFA (0.15 ml, 0.2 mmoles) produced 0.31 g (70% isolated yield) of benzofuran **5** after 4 hours boiling.

Interaction of Adduct **4** with 1,4-Benzoquinone.

To a solution of 0.50 g (2 mmoles) adduct **4** in 80 ml of benzene was added ZnI_2 (0.064 g, 0.2 mmoles) and then, under boiling and stirring, a solution of 1,4 benzoquinone (0.216 g, 2 mmoles) in benzene (5 ml). The mixture was stirred for additional 40 minutes, allowed to cool down to room temperature and left overnight. The precipitated crystals were collected by filtration and washed with CH_2Cl_2 (2 x 1 ml) and acetone (2 x 1 ml) to afford 0.11g (23%) of the crude indole **3a**, mp 198-201°. Under the same conditions in the presence of 0.022 g, (0.20 mmoles) of 1,4 benzoquinone indole **3a** was obtained in 21% yield. Without ZnI_2, in both cases, mixtures of compounds containing indole **3a** were obtained as determined by ^{1}H nmr analysis basing on signals of the 2-CH_3 group at δ 2.66 and the N- CH_3 group at δ 3.64.

Ethyl 2-ethyl 5-hydroxy-1-methyl-indole-3-carboxylate (**3e**).

Isolated as a colorless solid, mp 172-174°; ^{1}H nmr (DMSO-d_6): δ 1.18 (t, 3H, CH_2C*H*$_3$), 1.35 (t, 3H, $COOCH_2C$*H*$_3$), 3.13 (q, 2H, C$H_2$$CH_3$) 3.68 (s, 3H, NCH_3), 4.25 (q, 2H, $COOCH_2CH_3$), 6.69 (dd, 1H, ArH-6), 7.29 (d, 1H, ArH-7), 7.37 (d, 1H, ArH-4), 8.95 (s, 1H, OH).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 67.94; H, 6.87; N, 5.66. Found: C, 67.97; H, 7.01; N, 5.64.

Ethyl 5-hydroxy-1-methyl-2-phenyl-indole-3-carboxylate (**3g**).

Isolated as a colorless solid, mp 205-207°; ^{1}H nmr (DMSO-d_6): δ 1.05 (t, 3H, CH_2C*H*$_3$), 3.48 (s, 3H, NCH_3), 4.02 (q, 2H, C$H_2$$CH_3$), 6.78 (dd, 1H, ArH-6), 7.36-7.49 (m, 7H, ArH), 9.10 (s, 1H, OH).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.22; H, 5.76; N, 4,75. Found: C 73.00; H 5.68; N 4.74.

Ethyl 8-hydroxy-2,3,4,5-tetrahydro-1*H*-azepino[1,2-*a*]indole-11-carboxylate (**3h**).

Isolated as a colorless solid, mp 195-197°; ^{1}H nmr (DMSO-d_6): δ 1.33 (t, 3H, $COOCH_2C$*H*$_3$), 1.80-4.00 (m, 8H, 4 CH_2), 4.24 (m, 4H, 2 CH_2), 6.65 (dd, 1H, ArH-6), 7.32 (d, 1H, ArH-7), 7.36 (d, 1H, ArH-4), 8.93 (s, 1H, OH).

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.33; H, 6.96; N, 5.13. Found: C, 70.25; H, 6.99; N, 5.16.

3-Acetyl-1-benzyl-5-hydroxy-2-methylindole (**3k**).

Isolated as a colorless solid, mp 243-244°; ^{1}H nmr (DMSO-d_6): δ 2.49 (s, 3H, $COCH_3$), 2.66 (s, 3H, CH_3), 5.45 (s, 2H, CH_2Ph), 6.59-7.45 (m, 8H, ArH), 9.03 (s, 1H, OH).

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.42; H, 6.09; N, 5.02. Found: C, 77.39; H, 6.07; N, 4.99.

3-Acetyl-1-(4-bromophenyl]-5-hydroxy-2-methylindole (**3m**).

Isolated as a colorless solid, mp 243-244°; ^{1}H nmr (DMSO-d_6): δ 2.49 (s, 3H, $COCH_3$), 2.66 (s, 3H, CH_3), 5.45 (s, 2H, CH_2Ph), 6.59-7.45 (m, 8H, ArH), 9.03 (s, 1H, OH).

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.42; H, 6.09; N, 5.02. Found: C, 77.39; H, 6.07; N, 4.99.

1-Benzyl-5-Hydroxy-2-methylindole-3-carboxanilide (**3n**).

Isolated as a colorless solid, mp 292-293°; ^{1}H nmr (DMSO-d_6): δ 2.50 (s, 3H, $COCH_3$), 2.57 (s, 3H, CH_3), 6.40-7.84 (m, 7H, ArH), 9.12 (s, 1H, OH).

Anal. Calcd. for $C_{17}H_{14}BrNO_2$: C, 59.30; H, 4.07; N, 4.07. Found: C, 59.36; H, 4.04; N, 3.99.

Acknowledgements.

The authors would like to thank Dr. Yu. Lyakhovetsky for his assistance in speculations concerning the non-redox Nenitzescu reaction mechanism. Financial support provided by the U.S. Civilian Research & Development Foundation (RB 2 2032) and Russian Foundation for Basic Research (01-03-332518) is greatfully acknowledged.

REFERENCES

[1] H. Y. Meltzer, *Neuropsychopharmacology*, **21**, 106 (1999); B. E. Leonard, *CNS Drugs*, **4**, 1 (1995); T. C. R.Vijayalaxmi, C. R. Thomas, J. R. Reiter and S. H. Terence, *J. Clin. Oncol*., **20**, 2575 (2002); S. Kaneko, K Okumura , Y. Numaguchi , H. Matsui, K. Murase, S. Mokuno, I. Morishima, K. Hira, Y. Toki, T. Ito and T. Hayakawa. *Life Sciences*, **67**, 101 (2000).

[2] R. D. E. Sewell, in "Introduction to the Principles of Drug Design and Action", H. J. Smith ed.; Harwood Academic Publishers, Amsterdam, B.V., 1998, pp 391-410.

[3] T. A. Gus'kova, *Pharmaceutical Chemistry Journal*, **35**, 527 (2001), Springer Verlag New York; J. A. McCullers, *Expert Opin. on Investigational Drugs*, **14**, 305 (2005), Ashley Publications; R. G. Glushkov, T. A. Gu'skova, *Pharm. Chem. J. (Engl. Trans.)*, **33**, 115 (1999).

[4] D. Wang, Y. U. De Sheng, F. Qin, L. Fang and P. Gong, *Chinese Chem. Lett.*, **15**, 19 (2004).

[5] Y. Leblanc, W. C. Black, C.-C. Chan, S. Charleson, D. Delorme, D. Denis, C. Bayly, J. Y. Gauthier, R. Grimm, R. Gordon, D. Guay, P. Hamel, S. Kargman, C. K. Lau, J. Mancini, M. Ouellet, D. Percival, P. Roy, K. Skorey, P. Tagari, P. Vickers, E. Wong, L. Xu and P. Prasit, *Bioorg. Med. Chem. Lett*., **6**, 731 (1996).

[6] A. Roller, O. K. Bahr, J. Streffer, S. Winter, M. Heneka, M. Deininger, R. Meyermann, U. Naumann, E. Gulbins and M. Weller, *Biochem. and Biophys. Res. Comm*., **259**, 600 (1999).

[7] A. R. Maguire, S. J. Plunkett, S. Papot, M. Clynes, R. O' Connor and S. Touhey, *Bioorg. Med. Chem*., **9**, 745 (2001).

[8] R. M. Philips, M. A. Naylor, M. Jaffar, S. W. Doughty, S. A. Everett, A. G. Breen, G. A. Choudry and I. J. Stratford, *J. Med. Chem*., **42,** 4071 (1999).

[9] J. M. Pawlak, V. V. Khau, D. R. Hutchinson and M. J. Martinelli, *J. Org. Chem.*, **61**, 9055 (1996).

[10] B. Dotzauer and R. Troschutz, *Synlett*, 1039 (2004).

[11] H. D. Beall, S. Winski, E. Swann, A. R. Hudnott, A. S. Cotteril, N. O'Sullivan, S. J. Green, R. Bien, D. Siegel, D. Ross and C. J. Moody, *J. Med. Chem*., **41**, 4755 (1998).

[12] T. M. Bohme, C. E. Augelli-Szafran, H. Hallak, T. Pugsley, K. Serpa and R. D. Schwarz, *J. Med. Chem*., **45**, 3094 (2002).

[13] M. A. Naylor, M. Jaffar, J. Nolan, M. A. Stephens, S. Butler, K. B. Patel, S. A. Everett, G. E. Adams and I. J. Stratford, *J. Med. Chem*., **40**, 2335 (1997).

[14] R. J. Sundberg, in Indoles. Best synthetic methods series. Academic Press, New York, pp 54-63 (1996); N. N. Suvorov, V. G. Avramenko, V. N. Shkilkova and L. I. Zamyshlyaeva, British Patent 1.174.034 (1968); *Chem. Abstr*., 66814m (1970).

[15] G. R. Allen, in Org. React., 1973, 20, pp 337-454.

[16] D. M. Ketcha, L. J. Wilson and D. E. Portlock, *Tetrahedron Lett.*, **41**, 6253 (2000).

[17]M. Kinugawa, H. Arai, H. Nishikawa, A. Sakaguchi, T. Ogasa, S. Tomioka, M. Kasai, *J. Chem. Soc., Perkin Trans. 1*, 2677 (1995).

[18] J. B. Patrick and E. K. Saunders, *Tetrahedron Lett*., **20**, 4009 (1979).

[19] E. K. Panisheva, L. M. Alekseeva, A. S. Shashkov, V. G. Granik, *Chem. Heterocycl. Comp. (Russ.)*, **8**, 1164 (2003).

[20] G. Domschke, *J. Prakt. Chem.*, **311**, 807 (1969).

[21] T. A. Engler and J. Wanner, *Tetrahedron Lett*., **38**, 6135 (1997); T. A. Engler, K. O. Lynch, W. Chai and S. P. Meduna, *Tetrahedron Lett.*, **36**, 2713 (1995); T. A. Engler, M. A. Letavic, R. Iyengar, K. O. LaTessa and J. P. Reddy, *J. Org. Chem*., **64**, 2391 (1999).

[22] U. Kucklander, *Tetrahedron*., **29**, 921 (1973).

[23] V. I. Shvedov, E. K. Panisheva, T. F. Vlasova and A. N. Grinev, *J. Gen. Chem. USSR (Engl. Trans.)*, **9**, 1225 (1973).

[24] G. S. Gadaginamath, R. R. Kavali and S. R. Pujar, *Synthetic Comm.*, **33**, 2285 (2003).

[25] J. J. Li, in Name Reactions: A Collection of Detailed Reaction Mechanisms, Springer, Berlin, 2002, p. 255.

[26] E. Bernatek and T. Ledaal, *Acta Chem. Scand*., **12**, 2053 (1958).

[27] J. R. Allen, Jr. C. Pidacks, and M. J. Weiss, *J. Am. Chem. Soc.*, **88**, 2536 (1966).

[28] E. Knoevenagel, E. Reinecke, *Chem. Ber*., **32**, 423 (1899).

[29] M. C. Bagley; J. W. Dale, J. W. Bower, *Synlett*, 1149 (2001).

[30] R. Moehlau, *Chem. Ber*., 27, 3377 (1894).

[31] S. Coffey, J. K. Thomson, F. J. Wilson, *J. Chem. Soc*., 856 (1936).

[32] J. Decombe, *Ann. Chim*., **18**, 81 (1932).

[33] M. C. Bagley, C. Brace, J. W. Dale, M. Ohnesorge, N. G.; Phillips, X. Xiong, J. Bower, J. *Chem. Soc. Perkin Trans. 1*, 14, 1663 (2002).

[34] C. Goldschmidt, *Chem. Ber*., **29**, 105 (1896).

[35] J-P. Celerier, E. L. Deloisy., G. Hommet., P. Maitte, *J. Org. Chem*., **44**, 3089 (1979).

[36] B. Singh, G. Y.Lesher, *J. Heterocyclic Chem*., **27**, 2085 (1990).

[37] A. P. Terent'ev, E. A.Viktorova, B. M. Eselson, A. N. Kost, V. V. Ershov, *J. Gen. Chem. USSR (Engl. Transl.)*, **30**, 2402 (1960).

[38] G. R. Cook, L. G. Beholz, J. R. Stille, *J. Org. Chem*., **59**, 3575 (1994).

[39] A. D. Garnovskii, V. L. Abramenko, *J. Gen. Chem. USSR (Engl. Transl.)*, 55, 1630 (1985).

[40] A. N. Grinev, V. N. Ermakova, I. A Mel'nikova, A. P. Terent'ev, *J. Gen. Chem. USSR (Engl. Transl.)*, **31**, 2146 (1961).

[41] A. N. Kost, L. G. Iudin, E. J Zinchenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **9**, 306 (1973).

[42] A. N. Grinev, V. N. Ermakova, A. P. Terent'ev, *J. Gen. Chem. USSR (Engl. Transl.)*, **32**, 1928 (1962).

[43] H. L. Mc. Pherson, B. V. Ponder, *J. Heterocyclic Chem*., **15**, 43 (1978).