α-Oxolactam enamines as new synthons in the Nenitzescu reaction

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α-Oxolactam enamines, namely, 3-piperidino-5,6-dihydropyridin-2(1*H*)-one (**1a**) and 3-piperidino-1,5,6,7-tetrahydroazepin-2-one (**1b**), were introduced for the first time into the Nenitzescu reaction. The processes yield cyclic adducts **3a—e**, **6**. On heating in acetic acid, they are transformed into benzofuropyridone **7** and benzofuroazepinones **10a,d**, and **12** and, unexpectedly, into chromenopyrrole **8** and chromenopyridines **9a—d** and **11**.

Key words: α-oxolactam enamines, Nenitzescu reaction, benzofuropyridines, benzofuroazepines, chromenopyridines.

The Nenitzescu reaction is the most important classical method for the synthesis of 5-hydroxyindole and 5-hydroxybenzofuran derivatives playing an important role in chemistry and biology.[1—3] The key advances in developing the synthetic potential of this reaction and investigating its complicated mechanism stem from broad variation of the structures of the initial substrates, quinones and enamines.[1,2] The first step of this reaction is the Michael addition involving the electron-deficient quinone carbon atom and the enamine β-carbon atom bearing a partial negative charge. Only a few examples of using enamines containing α-electron-withdrawing substituents, which reduce this charge, have been described in the literature.[4,5] However, this approach appears quite promising because it would finally allow one to outline the scope of this reaction and to obtain unconventional results for both the first and the subsequent steps of the process. This study is devoted to the condensation of quinones with α-oxolactam enamines **1a,b**;[6] the presence of the electron-withdrawing lactam carbonyl group in these compounds is expected to induce a certain electron density deficiency in the β-position with respect to the electron density in usual enamines.

The condensation of enamines **1a,b** with *p*-benzoquinone (**2a**) was found to smoothly proceed in acetone at room temperature but to give cyclic adducts **3a,b** instead of the "hydroquinone adducts" (HQA),[1,2] usual for this reaction. The ^{1}H NMR spectra of compounds **3a,b** exhibit one signal for the hydroxy group (δ 8.79 and 8.66 ppm, respectively). The high-field parts of the spectra contain signals for fifteen and seventeen protons, respectively.

Few examples of synthesis of adducts of this type have been described in the literature.[5,7,8] The ease of cyclization of HQA into adducts **3a,b** is, undoubtedly, due to the increase in the partial positive charge at the α-enamine carbon atom caused by the electron-withdrawing effect of the lactam carbonyl group. The possibility of this nucleophilic attack of α-oxolactam enamines was first demonstrated by their transamination with arylhydrazines.[9]

Enamine **1b** was also introduced in the reaction with halo-substituted benzoquinones such as chlorobenzoquinone (**2b**) and 2,6-dibromoquinone (**2c**) (Scheme 1). In all cases, the reactions gave rise to cyclic adducts **3c—e**, respectively. A specific feature observed in the reaction between enamine **1b** and chloroquinone **2b** deserves attention. Usually, reactions of this type involve positions 5 and 6 of quinone **2b**.[10] In this case, the reaction also affords a mixture (adducts **3c,d**) but positions 3 and 5 of quinone **2b** are the reaction sites. According to ^{1}H NMR spectra, the **3c** to **3d** isomer ratio in the mixture was ~8 : 2. Only the minor isomer **3d** was isolated from the mixture and identified.

A heterocyclic quinone, *viz.*, 3-methyl-4,7-dioxo-4,7-dihydrobenzofuran (**4**), was also made to condense with enamine **1b** (Scheme 2). The possibility of formation of isomeric benzofuran and indole systems with asymmetrical quinone **4** has been described in detail in our previous study.[11] In this study, only one of the possible isomers, compound **6**, can be isolated. The structure of the cyclic adduct **6** was established using the HMBC procedure:* the correlation peaks at 6.49/143.2 ppm (H(5)/C(11a))

* Heteronuclear multiple bond correlation.

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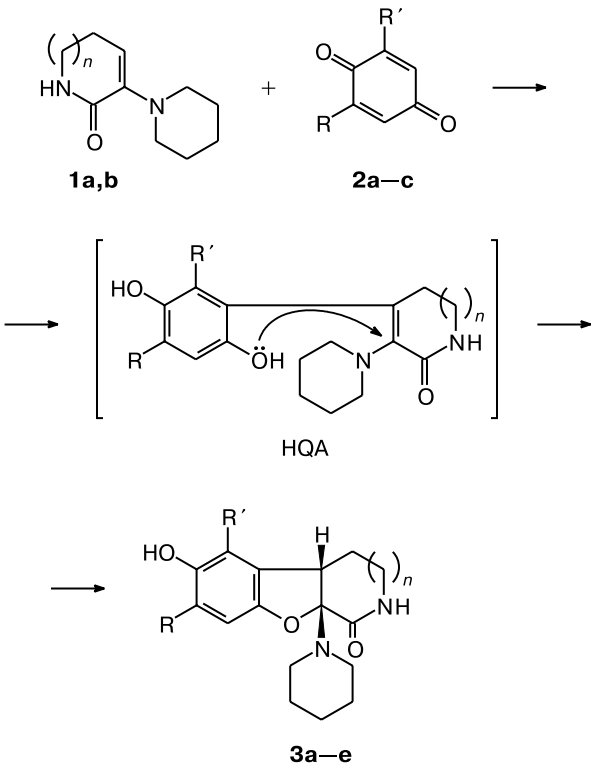
Scheme 1

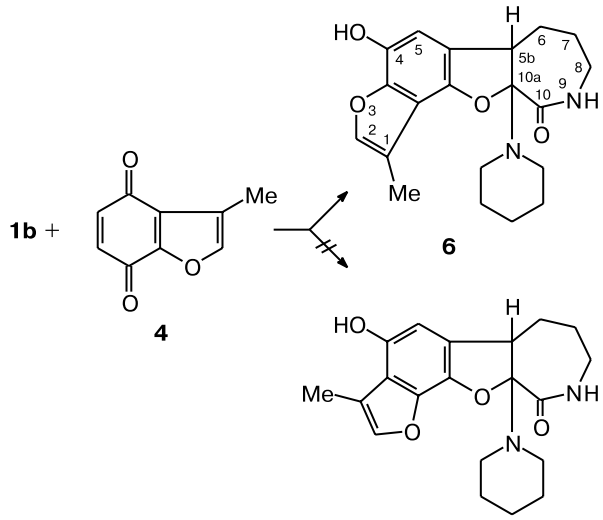


n = 1 (**1a**, **3a**), 2 (**1b**, **3b—e**)

R = R′ = H (**2a**, **3a,b**); R = Cl, R′ = H (**2b**, **3c**); R = H, R′ = Cl (**3d**); R = R′ = Br (**2c**, **3e**)

and 6.49/144.8 ppm (H(5)/C(3a)) observed in the spectra are in line with the proposed structure. For the other isomer, one peak would correlate with a carbon atom displayed in a higher field (116—120 ppm).

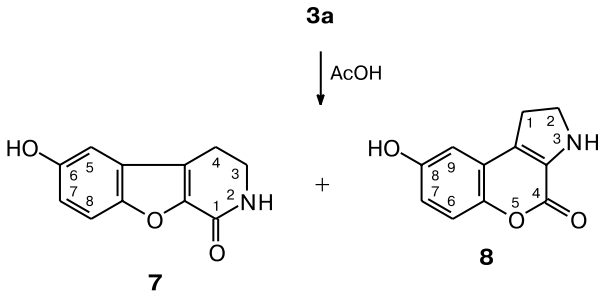
Scheme 2



The formation of cyclic adducts like **3** has also been described in the above-cited publications[5,7] and the reasons for their stability explaining the difficulty of elimination of amine to give the aromatic furan ring have been considered comprehensively in another publication.[12] In view of these data, we suggested that stability of our adducts is due to the fact that the piperidine residue and the hydrogen atom occupy *cis*-positions relative to each other, which may markedly hamper elimination of piperidine. This was confirmed previously for compound **3e**.[13] The NOESY NMR spectrum of adduct **3a**, containing a piperidone fragment, also points to a *cis*-configuration. The spectrum of compound **3a** exhibits a correlation peak with δ 2.64/3.64 (2 H(6″), 2 H(2″)/H(4a)). The signals in the spectra of **3a** and **3e** were assigned on the basis of the COSY spectra (see Experimental).

The possible *cis* → *trans* transformation is known[5] to be facilitated by treatment with an acid. Heating adduct **3a** in acetic acid gave rise to two compounds with identical molecular masses ($M^{\bullet+}$ 203). The major compound was the product of piperidine elimination, 6-hydroxy-3,4-dihydrobenzofuro[2,3-*c*]pyridin-1(2*H*)-one (**7**). According to NMR data, the minor reaction product was 8-hydroxy-2,3-dihydrochromeno[3,4-*b*]pyrrol-4(1*H*)-one (**8**) (Scheme 3).

Scheme 3

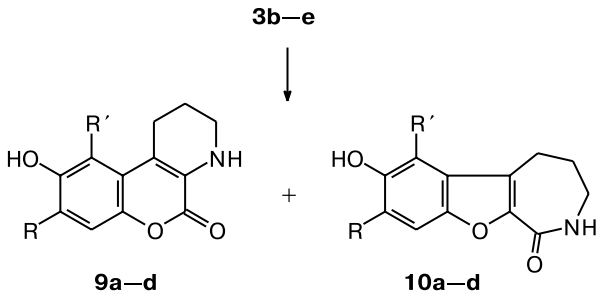


A similar heating in acetic acid of adducts **3b—e**, **6** also furnishes a mixture of chromenopyridine **9a—c**, **11** and benzofuroazepine **10a—d**, **12** derivatives. In these cases, however, the compounds were formed in an inverse ratio, chromene derivatives being the major products and fused benzofurans being the minor ones (Scheme 4 and 5).

In all cases, the obtained mixtures were separated by column chromatography and the compound structures were proved by spectral data. On acid treatment of a mixture of compounds **3c,d**, of the two possible chromene isomers, only the major isomer **9b** was isolated; the mixture of benzofuran derivatives **10b,c** was isolated in trace amounts.

The structures of chromenopyridines and azepinobenzofurans were established by HMBC spectra using

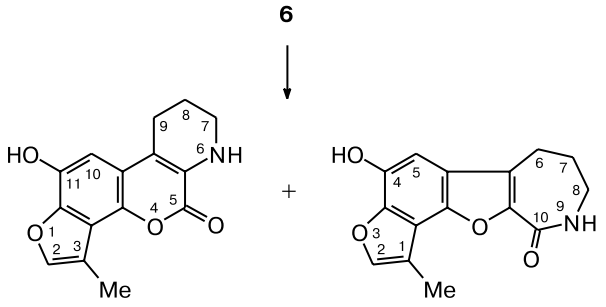
Scheme 4



9a—d **10a—d**

R = R′ = H (**a**); R = Cl, R′ = H (**b**); R = H, R′ = Cl (**c**); R = Br, R′ = H (**9d**); R = R′ = Br (**10d**)

Scheme 5



11 **12**

compounds **9a** and **10a** as examples.[13] In the ^{1}H NMR spectra of these compounds, all signals for like protons differ by 0.02—0.32 ppm (see Experimental). The proton signals for the NH group provide an exception: the amide proton of compound **10a** is displayed in a markedly lower field, 8.00 ppm, than the NH proton of the pyridine fragment in **9a**, which is at 5.77 ppm. We employed this pronounced difference between the chemical shifts of NH group protons to establish the structures of cyclic compounds **7**, **8**, **9b,d**, **10d**, **11**, and **12**.

Undoubtedly, it is a peculiar fact that acid treatment of adduct **3e** yields chromene derivative **9d**, containing only one bromine atom (in position 8).

To summarize the foregoing, it should be noted that, at least, two aspects need to be interpreted. The first one is the pathway to chromene derivatives and the second, debromination during refluxing of adduct **3e** in acetic acid.

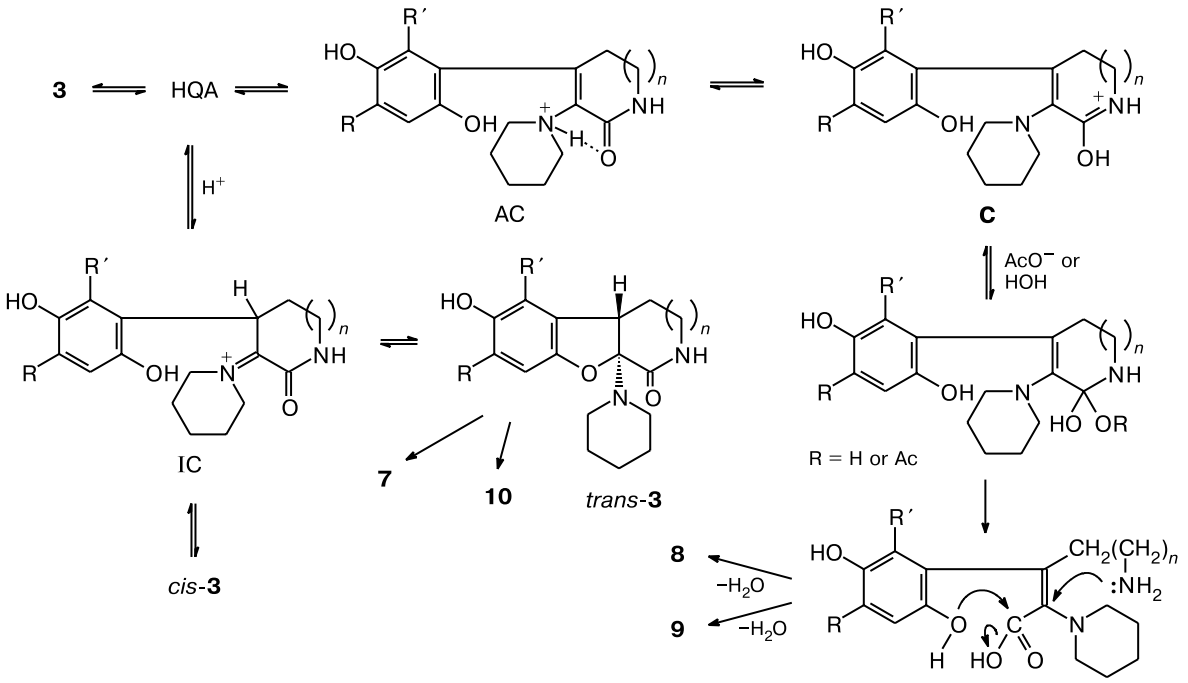
The basic assumption that appears necessary for solving these problems is the occurrence of equilibrium between the cyclic adducts and usual HQA in an acetic acid solution. To confirm this hypothesis, we studied the ^{1}H NMR spectra of solutions of cyclic adduct **3e** in deuterioacetic acid immediately after dissolution and after a 1.5—7-h refluxing. The spectrum of compound **3e** dissolved in CD_3COOD was found to exhibit two low-field singlets at δ 7.00 and 7.18; the former is due to the initial adduct **3e**, while the latter can be assigned to the open HQA (~3 : 1 ratio). During the refluxing, signals for chromene **9d** and benzofuran **10d** gradually appear, while the intensity of the signals due to the cyclic adduct **3e** and the signal at 7.18 ppm, which we assign to the HQA (see Scheme 1, R = R′ = Br), correspondingly decreases. The ^{1}H NMR spectrum (in DMSO-d_6) of the substance obtained after 1.5 h of refluxing of adduct **3e** in AcOH followed by evaporation of acetic acid *in vacuo* exhibits proton signals corresponding to chromene **9d**, benzofuran **10d**, and adduct **3e**. Simultaneously, signals at δ 7.05 (s, 1 H, H(6)) and δ 8.22 and 8.18 (both br.s, each 1 H, C(1)OH and C(4)OH), matching each other in intensity are recorded; these can be assigned with high probability to a HQA type compound. Thus, ^{1}H NMR monitoring of the transformation of cyclic adduct **3e** provided evidence for the presence of **3e** $\rightleftharpoons$ HQA equilibrium.

Hydroquinone adducts are enamines and their properties should fit appropriately in the properties of this class of compound. Enamines are known[14—16] to undergo fast N-protonation in acid solutions followed by slow transformation of the resulting ammonium cation into the immonium cation (C-protonated form), which proceeds *via* the initial uncharged enamine. Presumably, these transformations and the presence of either one or the other protonated form in solutions are exactly the factors that dictate the predominant pathway of the reactions under interest (Scheme 6).

In conformity with the proposed pattern, the HQA is rapidly converted in acetic acid into the ammonium cation (AC) whose NH proton is involved in an intramolecular hydrogen bond with the lactam carbonyl group. As a result, this proton would probably undergo a reversible transfer to the oxygen atom to give cation **C**; this can be followed by nucleophilic attack on the carbonyl carbon of the lactam ring, ring opening, cyclization to chromenone and, finally, transamination with piperidine elimination and one more cyclization to give compounds **8** and **9**. Probably, in other above-listed cases, chromene derivatives are formed along the same route.

The other reaction route is associated with the formation of the immonium cation (IC) (C-protonation).[14] This cation may be closed in two ways, namely, to give the initial cyclic adducts *cis*-**3**, which are unlikely to give off piperidine, or to give a different adduct, *trans*-**3**, which is rapidly transformed into benzofuran derivative **10**. If C-protonation *via* the immonium cation is the rate-limiting step of benzofuran formation, then $sp^2 \rightarrow sp^3$ rehybridization of the C(4) atom of the lactam fragment takes place. This is energetically favorable for six- but unfavorable for five- or seven-membered rings.[17,18] This accounts for the accelerated benzofuran cyclization for the adducts with the six-membered dihydropyridine fragment (**3a** $\rightleftharpoons$ HQA $\rightarrow$ **7**) and for the predominance of chromene formation from the adducts contain-

Scheme 6

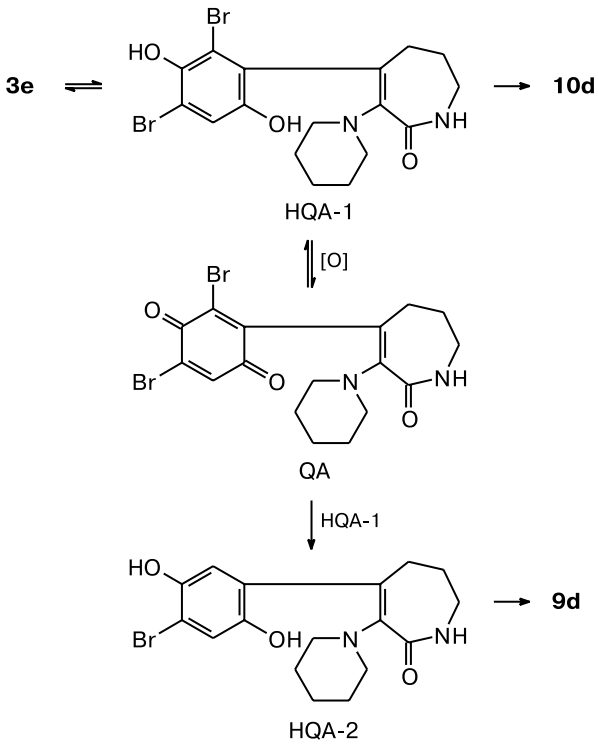


ing the seven-membered tetrahydroazepine fragment (**3b—e** ⇌ HQA → **9a—d**; **6** ⇌ HQA → **11**).

The proposed hypothetical scheme indicates that acceleration of the transformation of the initial enamines into the C-protonated form (immonium cation) should promote their transformation into aromatic derivatives of benzofuran with piperidine elimination. These conclusions imply that it may be possible to change the product ratio toward the benzofuran derivative. The transformation of the N-protonated form into the C-protonated form can be accelerated by increasing the temperature at which the cycloadduct is added to acetic acid. Indeed, if adduct **3b** (or **3e**) is suspended in acetic acid preheated to 30—40 °C, the suspension is kept at this temperature for 1 h, and only after that, the refluxing is started, the reaction affords azepinobenzofuran **10a** (or, correspondingly, **10d**) as the major product. Perhaps, in addition to accelerating the N→C-prototropic shift, the higher temperature displaces the HQA ⇌ **3b** (**3e**) equilibrium to the right and thus deteriorates the conditions for the transformation resulting in chromene synthesis.

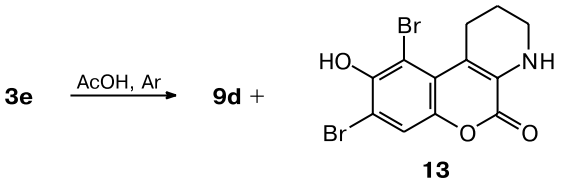
The other, very unusual process associated with the formation of monobromochromene derivative **9d** from dibrominated adduct **3e** might also be based on a **3e** ⇌ HQA type equilibrium. It appears likely that in this case, we are dealing with redox processes, generally typical of the Nenitzescu reaction,[1,2] in which the HQA are reversibly converted into quinone adducts (QA) where the bromine atoms are activated by two electron-withdrawing carbonyl groups of the quinone fragment. Apparently, the HQA reduces the QA with elimination of a bromine atom and subsequently the chromene cyclization takes place according to the above Scheme 6 (Scheme 7).

Scheme 7



To confirm our assumption that a redox process takes place resulting in transformation of HQA into QA, we carried out the reaction of adduct **3e** in acetic acid in an argon flow to exclude, as far as possible, the presence of oxygen in the reaction mixture (no other oxidants are present). As a result of this reaction, we obtained dibromochromene derivative **13**, which is not virtually formed in the presence of atmospheric oxygen (Scheme 8); the ratio of chromenes **9d** and **13** in the isolated mixture was ~6 : 4, according to NMR data. Among the signals corresponding to compound **13** in the ^{1}H NMR spectrum of this mixture, no signal for the proton in position 10 was found (δ 6.90 in compound **9d**), while in other respects, the signal multiplicities and chemical shifts for compounds **9d** and **13** were similar, although the signals for NH-group protons and for the H(7) proton in compound **13** were shifted downfield, apparently, due to the influence of the second bromine atom.

Scheme 8



Thus, in a study of the Nenitzescu reaction with α-oxolactam enamines and various quinones as the initial compounds, we found that, in addition to the formation of benzofuropyridines and benzofuroazepines, a transformation unusual for this reaction takes place giving rise to chromenopyrrole and chromenopyridine derivatives. The results were interpreted in terms of an equilibrium existing in acetic acid between the cyclic adducts we isolated and the hydroquinone adducts typical of the Nenitzescu reaction.

Experimental

Mass spectra were recorded on a Finnigan SSQ-710 mass spectrometer with direct sample injection into the ion source. The ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer, and HMBC 2D NMR spectra were measured on a Bruker DRX-500 spectrometer in DMSO-d_6 using standard Bruker procedures. Commercial reagents and solvents of the Lancaster Synthesis company were used. The reactions were monitored and the substance purity was checked by TLC on Silufol UV-254 plates with ethyl acetate elution and UV visualization. The physicochemical characteristics and the yields of products are presented in Tables 1—3.

6-Hydroxy-9a-piperidino-3,4,4a,9a-tetrahydrobenzofuro[2,3-*c*]pyridin-1(2*H*)-one (3a). A suspension of quinone **2a** (0.67 g, 6.2 mmol) and enamine **1a** (1.12 g, 6.2 mmol) in 4.5 mL of acetone was stirred for 6 h at 20 °C. The precipitate was filtered off and washed with acetone to give 0.87 g of adduct **3a**. ^{1}H NMR, δ: 1.43 (m, 7 H, 2 H(3″), 2 H(4″), 2 H(5″), H(4)); 2.20 (m, 1 H, H(4′)); 2.64 (m, 4 H, 2 H(6″), 2 H(2″)); 3.02 (m, 1 H, H(3′)); 3.17 (m, 1 H, H(3)); 3.64 (dd, 1 H, H(4a), J_1 = 7.2 Hz, J_2 = 9.2 Hz); 6.49—6.59 (m, 3 H, H(5), H(7), H(8)); 7.96 (br.s, 1 H, N(2)H); 8.79 (br.s, 1 H, C(6)OH).

7-Hydroxy-10a-piperidino-2,3,4,5,5a,10a-hexahydrobenzofuro[2,3-*c*]azepin-1(1*H*)-one (3b). The reaction of quinone **2a** (7.88 g, 73 mmol) and enamine **1b** (14.19 g, 73 mmol) gave 18.15 g of adduct **3b**. The synthesis was carried out similarly to the synthesis of compound **3a** but in ethanol instead of acetone.

8-Chloro-7-hydroxy-10a-piperidino-2,3,4,5,5a,10a-hexahydrobenzofuro[2,3-*c*]azepin-1(1*H*)-one (3c) and 6-chloro-7-hydroxy-10a-piperidino-2,3,4,5,5a,10a-hexahydrobenzofuro[2,3-*c*]azepin-1(1*H*)-one (3d). A suspension of quinone **2b** (1.67 g, 12 mmol) and enamine **1b** (2.58 g, 13 mmol) in 30 mL of acetone was stirred for 6 h at 20 °C. The precipitate was filtered off and washed with acetone to give 2.7 g of a mixture of adducts **3c** and **3d**. The mixture was refluxed in acetone (50 mL) and filtered hot. The acetone mother liquor was cooled and the precipitate was filtered off to give 0.18 g of adduct **3d**.

6,8-Dibromo-7-hydroxy-10a-piperidino-2,3,4,5,5a,10a-hexahydrobenzofuro[2,3-*c*]azepin-1(1*H*)-one (3e). The reaction of quinone **2c** (2.48 g, 9.3 mmol) and enamine **1b** (1.8 g, 9.3 mmol) gave 3.46 g of adduct **3e**. The synthesis was carried out similarly to the synthesis of compound **3b**.

4-Hydroxy-1-methyl-10a-piperidino-6,7,8,9,10,10a-hexahydro-5b*H*-furo[2′,3′:6,7][1]benzofuro[2,3-*c*]azepin-10-one (6). The reaction of 3-methyl-4,7-dioxobenzofuran (**4**) (1.46 g, 9 mmol) with enamine **1b** (1.75 g, 9 mmol) gave 1.55 g of adduct **6**. The synthesis was carried out similarly to the synthesis of compound **3a**. ^{1}H NMR, δ: 1.44—1.99 (m, 10 H, 2 H(3″), 2 H(4″), 2 H(5″)), H(7), H(7′), H(6), H(6′)); 2.50 and 2.68 (both m, 4 H, 2 H(6″), 2 H(2″)); 2.70 (s, 3 H, C(1)Me); 2.98 (m, 1 H, H(8′)); 3.29 (d, 1 H, H(5b), J = 11.4 Hz)); 3.90 (m, 1 H, H(8)); 6.49 (s, 1 H, H(5)); 7.49 (s, 1 H, H(2)); 7.54 (br.s, 1 H, N(9)H); 9.00 (br.s, 1 H, C(4)OH).

6-Hydroxy-3,4-dihydrobenzofuro[2,3-*c*]pyridin-1(2*H*)-one (7) and 8-hydroxy-2,3-dihydrochromeno[3,4-*b*]pyrrol-4(1*H*)-one (8). A solution of adduct **3a** (0.3 g, 1.04 mmol) in 5 mL of AcOH was refluxed for 4 h and concentrated. The dry residue was triturated with a slight amount of acetone and the precipitate was filtered off and washed with acetone to give 0.1 g of compound **7**. The acetone mother liquor was concentrated and the residue was dissolved in ethyl acetate and chromatographed on a column with SiO_2 (ethyl acetate as the eluent). Successive elution gave 0.025 g of compound **8** and 0.01 g of compound **7**. The total yield of compound **7** is 0.11 g. ^{1}H NMR, δ **7:** 3.22 (t, 2 H, 2 H(4), $J_1 = J_2$ = 9.2 Hz); 4.04 (t, 2 H, 2 H(3), $J_1 = J_2$ = 9.2 Hz); 6.86 (d, 1 H, H(5), J = 2.7 Hz); 7.00 (dd, 1 H, H(7), J_1 = 8.8 Hz, J_2 = 2.7 Hz); 7.31 (d, 1 H, H(8), J = 8.8 Hz); 9.30 (s, 1 H, C(6)OH); 9.75 (br.s, 1 H, N(2)H). ^{1}H NMR, δ **8:** 3.07 (t, 2 H, 2 H(1), $J_1 = J_2$ = 9.7 Hz); 3.58 (t, 2 H, 2 H(2), $J_1 = J_2$ = 9.7 Hz); 5.62 (br.s, 1 H, N(3)H); 6.66 (d, 1 H, H(9), J = 2.7 Hz); 6.73 (dd, 1 H, H(7), J_1 = 8.8 Hz, J_2 = 2.7 Hz); 7.16 (d, 1 H, H(6), J = 8.8 Hz); 9.47 (s, 1 H, C(8)OH).

9-Hydroxy-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-*b*]pyridin-5-one (9a) and 7-hydroxy-2,3,4,5-tetrahydro-1*H*[1]benzofuro[2,3-*c*]azepin-1-one (10a). ***A.*** A suspension of adduct **3b** (9.23 g, 30.6 mmol) in 50 mL of AcOH was refluxed for 3 h. The resulting solution was cooled to 20 °C and diluted with ~300 mL

Table 1. Physicochemical characteristics of the synthesized compounds

Compound	M.p. (solvent)	Yield (%) (Synthetic procedure)	Found / Calculated (%)				Molecular formula	Mass spectrum, m/z (I_{rel} (%))
			C	H	N	Br (Cl)		
3a	180—182	49	66.73 66.65	7.10 6.99	10.00 9.71	—	$C_{16}H_{20}N_2O_3$	288 $[M]^+$ (48) 230 $[M - CONHCH_3]^+$ (100) 204 $[M - N(CH_2)_5]^+$ (33)
3b	258—260	82	67.60 67.52	7.36 7.34	9.26 9.26	—	$C_{17}H_{22}N_2O_3$	302 $[M]^+$ (30) 230 $[M - CONHCH_2CH_3]^+$ (100) 204 $[M - N(CH_2)_5]^+$ (33)
3d	224—225	4.6	60.28 60.62	6.37 6.28	7.87 8.32	11.00 10.52	$C_{17}H_{21}ClN_2O_3$	336 $[M]^+$ (100) 264 $[M - CONHCH_2CH_3]^+$ (95) 251 $[M - N(CH_2)_5]^+$ (80)
3e	173—175	81	44.32 44.37	4.69 4.38	5.72 6.09	—	$C_{17}H_{20}Br_2N_2O_3$	460 $[M]^+$ (100) 388 $[M - CONHCH_2CH_3]^+$ (92) 375 $[M - N(CH_2)_5]^+$ (62)
6	213—215	48	67.28 67.39	6.90 6.79	7.50 7.86	—	$C_{20}H_{24}N_2O_4$	356 $[M]^+$ (68) 284 $[M - CONHCH_2CH_3]^+$ (100) 271 $[M - N(CH_2)_5]^+$ (39)
7	309—311 (AcOH)	52	65.00 65.02	4.50 4.46	6.99 6.89	—	$C_{11}H_9NO_3$	203 $[M]^+$ (100) 175 $[M - CO]^+$ (13) 158 $[M - COOH]^+$ (37) 147 $[M - CON{=}CH_2]^+$ (67)
8	262—263 (EtOH)	12	65.32 65.02	4.40 4.46	6.80 6.89	—	$C_{11}H_9NO_3$	203 $[M]^+$ (100) 175 $[M - CO]^+$ (75)
9a	213—216 (Pr^iOH)	54 (*A*) 4.0 (*B*)	66.08 66.35	5.20 5.11	6.03 6.45	—	$C_{12}H_{11}NO_3$	217 $[M]^+$ (100) 188 $[M - COH]^+$ (62) 161 $[M - CON{=}CH_2]^+$ (62)
9b	228—232 (Pr^iOH)	52	56.99 57.26	4.20 4.00	6.04 5.57	(14.12) (14.09)	$C_{12}H_{10}ClNO_3$	251 $[M]^+$ (100) 222 $[M - COH]^+$ (17) 227 $[M - CON{=}CH_2]^+$ (19)
9d	191—193 (EtOH)	23 (*A*) 11 (*B*)	48.24 48.67	3.30 3.40	4.26 4.73	27.40 26.99	$C_{12}H_{10}BrNO_3$	297 $[M]^+$ (100) 269 $[M - CO]^+$ (10) 239 $[M - CON{=}CH_2]^+$ (19)
10a	244—247 (Pr^iOH)	6.0 (*A*) 80 (*B*)	66.30 66.35	5.06 5.11	6.72 6.45	—	$C_{12}H_{11}NO_3$	217 $[M]^+$ (100) 189 $[M - CONHCH_3]^+$ (33)
10d	230—232 (EtOH)	14 (*A*) 30 (*B*)	38.74 38.43	2.40 2.42	3.63 3.73	43.08 42.62	$C_{12}H_9Br_2N_2O_3$	374 $[M]^+$ (Br^{79}) (100) 346 $[M - CO]^+$ (84)
11	244—245	23	66.48 66.41	4.97 4.83	4.96 5.16	—	$C_{15}H_{13}NO_4$	271 $[M]^+$ (100) 256 $[M - CH_3]^+$ (32) 227 $[M - CO_2]^+$ (18)
12	277—278 (EtOH)	5.6	66.28 66.41	4.99 4.83	5.11 5.16	—	$C_{15}H_{13}NO_4$	271 $[M]^+$ (73) 242 $[M - COH]^+$ (100) 226 $[M - COOH]^+$ (56) 215 $[M - CON{=}CH_2]^+$ (30)

of water. The precipitate was filtered off and washed with water to give 5.3 g of a mixture of compounds **9a** and **10a**. The mixture was suspended in 300 mL of hot ethyl acetate and chromatographed on a column with SiO_2 (elution with ethyl acetate) to give 5.29 g of compound **9a**. Subsequent elution with isopropyl alcohol gave 0.39 g of compound **10a**.

B. Adduct **3b** (0.93 g, 3 mmol) was suspended in 5 mL of AcOH heated to 35±5 °C and the mixture was stirred at this temperature for 1 h and refluxed for 3 h. The precipitate formed upon cooling was filtered off and washed with AcOH and water to give 0.52 g of compound **10a**. The acetic acid mother liquor was concentrated and the residue was recrystallized from Pr^iOH with carbon to give 0.05 g of compound **9a**.

8-Chloro-9-hydroxy-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-*b*]pyridin-5-one (9b). The reaction of a mixture of adducts **3c,d** (0.98 g, 2.9 mmol) and 10 mL of AcOH gave 0.38 g of compound **9b**. The synthesis was carried out similarly to the synthesis of compound **9a** by procedure *A*.

8-Bromo-9-hydroxy-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-*b*]pyridin-5-one (9d) and 6,8-dibromo-7-hydroxy-2,3,4,5-tetrahydro-1*H*-[1]benzofuro[2,3-*c*]azepin-1-one (10d). ***A.*** The reaction of adduct **3e** (3.92 g, 8.5 mmol) and 130 mL of AcOH

Table 2. ^{1}H NMR spectra of compounds **3b—e**[a], **10a**, and **10d**

Compound	δ, *J*/Hz								
	N(2)H	H(3), H(3′) (m, 1 H)	H(4), H(4′), H(5), H(5′), H(3″), 2 H(4″), 2 H(5″)	H(5a) (d, 1 H, J = 11.0)	H(6)	H(8)	H(9)	C(7)OH (s, 1 H)	2 H (2″), 2 H (6″) (m, 2 H)
3b	7.52 (t, 1 H, J_1 = J_2 = 7.5)	2.96 3.96	1.42—1.93 (m, 10 H)	3.28	6.51 (m, 3 H)			8.66	2.47 2.65
3c[b]	7.57 (t, 1 H, J_1 = J_2 = 7.5)	2.99 3.91	1.43—1.91 (m, 10 H)	3.32	6.72 (s, 1 H)	—	6.75 (s, 1 H)	9.21	2.45 2.63)
3d	7.53 (t, 1 H, J_1 = J_2 = 7.5)	3.00 3.85	1.42—1.71 (m, 9 H), 2.32 (m, 1 H)	3.31	—	6.56 (d, 1 H, J = 8.7)	6.74 (d, 1 H, J = 8.7)	9.21	2.48 2.60
3e	8.21 (t, 1 H, J_1 = J_2 = 7.5)	3.23 4.16	1.32—1.82 (m, 9 H), 2.56 (m, 1 H)	3.52	—	—	7.10 (s, 1 H)	—	2.82 2.91
10a	8.00 (br.s, 1 H)	[c]	2.00 (m, 2 H), 2.90 (t, 2 H, J_1 = J_2 = 6.0)	—	6.95 (m, 2 H)		7.40 (d, 1 H, J = 8.0)	9.40	—
10d	8.19 (br.s, 1 H)	[c]	2.09 (m, 2 H)[c]	—	—	—	7.96 (s, 1 H)	9.60	—

[a] The spectrum of compound **3e** was recorded in Py-d_5.
[b] Chemical shifts were taken from the spectrum of a mixture of **3c** and **3d**.
[c] The signals for 2 H(3) in **10a** and 2 H(3), 2 H(5) in **10d** are overlapped by the signal of water in DMSO-d_6 (δ_H 3.26).

Table 3. ^{1}H NMR spectra of compound **9a,b,d** and **13**

Compound	δ, *J*/Hz						
	2 H(1) (t, 1 H, J_1 = J_2 = 6.2)	2 H(3), 2 H(2)[a] (m, 2 H)	N(4)H (br.s, 1 H)	H(7)	H(8)	H(10)	C(9)OH (br.s, 1 H)
9a	2.59	1.88	5.77	7.08 (d, 1 H, J = 8.7)	6.67 (dd, 1 H, J_1 = 8.7, J_2 = 2.5)	6.74 (d, 1 H, J = 2.5)	9.32
9b	2.57	1.89	5.91	7.30 (s, 1 H)	—	6.91 (s, 1 H)	10.00
9d	2.58	1.89	5.96	7.44 (s, 1 H)	—	6.90 (s, 1 H)	10.07
13[b]	2.54	1.76	5.31	7.53 (s, 1 H)	—	—	9.8

[a] The signal is covered by the signal of water from the solvent δ_H 3.26.
[b] The chemical shifts taken from the spectrum of a mixture of **9d** and **13** are given.

gave 0.56 g of compound **9d** and 0.44 g of compound **10d**. The synthesis was carried out similarly to the synthesis of compounds **9a** and **10a** by procedure *A* (the solution was, however, refluxed for 7 h).

B. The reaction of adduct **3e** (3.46 g, 7.5 mmol) and 115 mL of AcOH gave 0.25 g of compound **9d** and 0.84 g of compound **10d**. The synthesis was carried out similarly to the synthesis of compounds **9a** and **10a** by procedure *B*.

11-Hydroxy-3-methyl-6,7,8,9-tetrahydro-5*H*-furo[2′,3′:7,8]chromeno[3,4-*b*]pyridin-5-one (11) and 4-hydroxy-1-methyl-6,7,8,9-tetrahydro-10*H*-furo[2′,3′:6,7][1]benzofuro[2,3-*c*]azepin-10-one (12). The reaction of adduct **6** (1.42 g, 4 mmol) and 30 mL of AcOH gave 0.25 g of compound **11** and 0.06 g of compound **12**. The synthesis was carried out similarly to the synthesis of compounds **9a** and **10a** by procedure *A*.

8-Bromo-9-hydroxy-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-*b*]pyridin-5-one (9d), 6,8-dibromo-7-hydroxy-2,3,4,5-tetrahydro-1*H*-[1]benzofuro[2,3-*c*]azepin-1-one (10d) and 8,10-dibromo-9-hydroxy-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-*b*]pyridin-5-one (13). Adduct **3e** (1.38 g, 3 mmol) was added in an argon flow to 40 mL of AcOH. The reaction mixture was refluxed for 7 h, cooled to 20 °C, and diluted with water. The precipitate was filtered off, washed with water, dried, and dissolved in 75 mL of ethyl acetate. The solution was chromatographed on a column with SiO_2 (elution with ethyl acetate) to give 0.2 g of a mixture of compounds **9d** and **13**. Subsequent elution with isopropyl alcohol gave 0.1 g of compound **10d**.

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