Novel synthesis of chromene and benzofuran derivatives *via* the Nenitzescu reaction

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The condensation of 3-oxocaprolactam piperidine enamine with 2,6-dibromoquinone and quinone gave 6,8-dibromo-7-hydroxy- and 7-hydroxy-10*a*-piperidine-2,3,4,5,5*a*-hexahydro-1*H*-benzofuro[2,3-*c*]azepine-1-one adducts, the acid treatment of which afforded novel 9-hydroxy-1,2,3,4-tetrahydro-5*H*-chromene[3,4-*b*]pyridine-5-one derivatives.

The Nenitzescu reaction of enamines and quinones is the most important method for the synthesis of 5-hydroxyindole and 5-hydroxybenzofuran.[1,2] Obviously, the condensation rate is determined by a high electron density at the β-position of enamines and quinone electronegativity at the 2-position. Therefore, few examples of enamines having electron-withdrawing substituents at the α-position, which lower a partial negative charge at the β-position, were described for this reaction. These are α-diketone enamines of the carbocyclic series.[3–5] The first step is the condensation with quinones to form hydroquinone adducts.[1,2] However, further acid treatment at the second step leads not only to 5-hydroxyindole and 5-hydroxybenzofuran derivatives but also heterocycles such as benzoxazepines, benzoxazines or isoquinolines.[3–5]

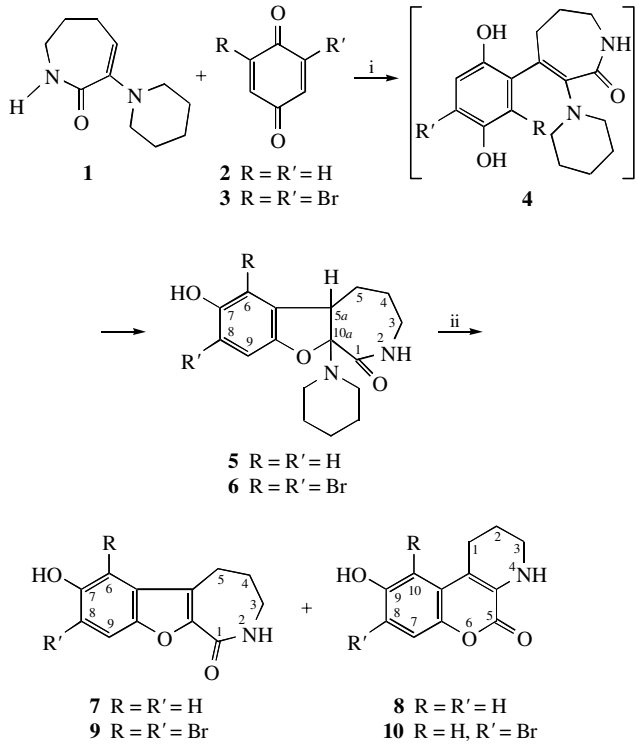
We used 3-piperidine-1*H*-2,5,6,7-tetrahydroazepine-2-one **1** with an electron-withdrawing lactam group at the α-position as an enamine component. Enamine **1** was used in cyclization with quinone **2** and 2,6-dibromoquinone **3** in order to obtain novel benzofuro[2,3-*c*]azepine derivatives. The condensation of enamine **1** with quinones **2** and **3** is readily achieved in acetone at room temperature. Apparently, under these conditions, hydroquinone adducts **4** are formed at the first step, immediately giving cyclic adducts 7-hydroxy-10*a*-piperidino-2,3,4,5,5*a*-hexahydro-1*H*-benzofuro[2,3-*c*]azepine-1-one **5** (73% yield, mp 258–260 °C, $M^{+\cdot}$ 302†) and 6,8-dibromo-7-hydroxy-10*a*-piperidino-2,3,4,5,5*a*-hexahydro-1*H*-benzofuro[2,3-*c*]azepine-1-one **6** (83% yield, mp 173–175 °C, $M^{+\cdot}$ 460‡), respectively.

The formation of such cyclic adducts was studied previously[4,5,7,8], and their stability was considered in detail.[9] On this basis, we assumed that the stability of adducts **5** and **6** is associated with the S-*syn*-positions of a piperidine fragment and a hydrogen atom in relation to each other, which may significantly hamper piperidine removal.[9] This was supported by spectroscopic data: a correlation peak with δ 2.91/3.52 ppm in the NOESY spectrum of **6** indicates that a proton at the 5*a*-position and the methylene protons of a piperidine ring 2″-CH_2 and 6″-CH_2 are spatially close, indicating the S-*syn*-conformation.

The adducts of this stereochemistry are known to form aromatic benzofurans upon acid treatment,[4] though some unexpected transformations were observed.[7,8] Adduct **5** was treated with acetic acid resulting in the formation of a benzofuran derivative as a product, namely, 7-hydroxybenzofuro[2,3-*c*]azepine-1-one **7** in 6% yield, mp 244–257 °C (isopropanol), $M^{+\cdot}$ 217.§

However, the major product was 9-hydroxy-1,2,3,4-tetrahydro-5*H*-chromeno[3,4-*b*]pyridine-5-one **8** in 58% yield, mp 213–216 °C (isopropanol), $M^{+\cdot}$ 217.¶

The structures of **7** and **8** were determined by HMBC spectrum analysis. The greatest difference between the spectra of **7** and **8**,



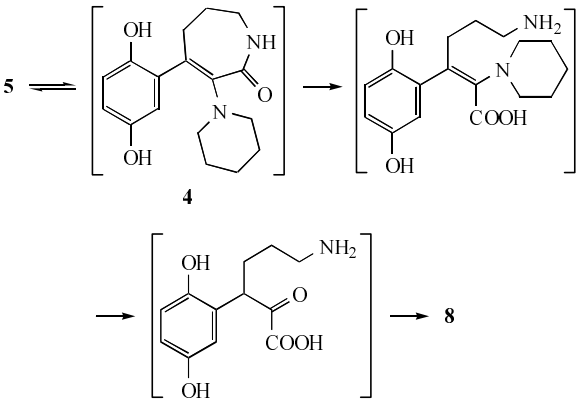
Scheme 1 *Reagents and conditions*: i, **1** was added to a solution of **2** (or **3**) in acetone, stirred (20 °C, 6 h), filtered (**5** or **6**); ii, **5** (or **6**) is refluxed in acetic acid for 2 h, then diluted with water, and a mixture of compounds **7**, **8** (or **9**, **10**) is filtered. The mixture was separated by column chromatography.

† For **5**: ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.42, 1.66, 1.93 (m, 10H, 3″-CH_2, 4″-CH_2, 5″-CH_2, 4′-CH, 4-CH, 5′-CH, 5-CH), 2.47–2.65 (m, 4H, 2″-CH_2, 6″-CH_2), 2.96 (m, 1H, 3′-CH), 3.28 (d, 1H, 5*a*-CH, *J* 11 Hz), 3.96 (m, 1H, 3-CH), 6.51 (m, 3H, 6-CH, 8-CH, 9-CH), 7.52 (t, 1H, 2-NH, *J* 7 Hz), 8.66 (br. s, 1H, 7-OH). Found (%): C, 67.60; H, 7.36; N, 9.26. Calc. for $C_{17}H_{22}N_2O_3$ (%): C, 67.52; H, 7.34; N, 9.26.

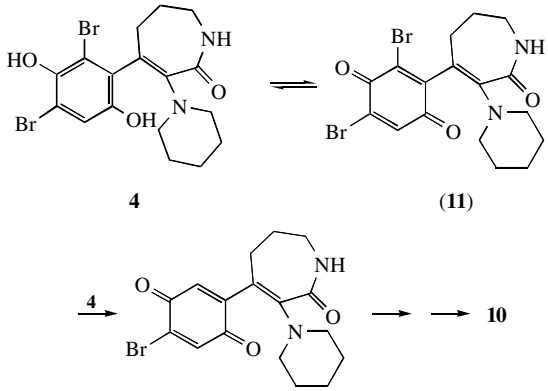
‡ For **6**: ^{1}H NMR ([$^2H_5$]pyridine) δ: 1.32 (m, 2H, 4″-CH_2), 1.45 (m, 4H, 3″-CH_2, 5″-CH_2), 1.69–1.82 (m, 3H, 4′-CH, 4-CH, 5-CH), 2.56 (m, 1H, 5′-CH), 2.82–2.91 (m, 4H, 2″-CH_2, 6″-CH_2), 3.23 (m, 1H, 3′-CH), 3.52 (d, 1H, 5*a*-CH, *J* 11 Hz), 4.16 (m, 1H, 3-CH), 7.10 (s, 1H, 9-CH), 8.21 (t, 1H, 2-NH, *J* 7 Hz). ^{13}C NMR ([$^2H_5$]pyridine) δ: 24.5 (4″-C), 25.8 (5-C), 26.2 (3″,5″-C), 27.5 (4-C), 47.3 (3-C), 48.9 (2″,6″-C), 50.6 (5*a*-C), 109.1 (10*a*-C), 109.7 (6-C), 111.8 (9-C), 112.5 (8-C), 129.7 (5*b*-C), 145.8 (7-C), 152.5 (9*a*-C), 169.6 (1-C). Found (%): C, 44.32; H, 4.69; N, 5.72. Calc. for $C_{17}H_{20}Br_2N_2O_3$ (%): C, 44.37; H, 4.38; N, 6.09.

§ For **7**: ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.00 (m, 2H, 4-CH_2), 2.90 (t, 2H, 5-CH_2, *J* 6.2 Hz), 3.23 (m, 2H, 3-CH_2), 6.95 (m, 2H, 6-CH, 8-CH), 7.40 (d, 1H, 9-CH, *J* 8.7 Hz), 8.00 (br. s., 1H, 2-NH), 9.40 (s, 1H, 7-OH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 23.8 (5-C), 26.3 (4-C), 40.8 (3-C), 104.7 (6-C), 111.9 (9-C), 116.4 (8-C), 123.1 (5*a*-C), 129.1 (5*b*-C), 143.8 (10*b*-C), 147.6 (9*a*-C), 153.4 (7-C), 161.5 (1-C). Found (%): C, 66.30; H, 5.06; N, 6.72. Calc. for $C_{12}H_{11}NO_3$ (%): C, 66.35; H, 5.11; N, 6.45.

¶ For **8**: ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.88 (m, 2H, 2-CH_2), 2.59 (t, 2H, 1-CH_2, *J* 6.2 Hz), 3.23 (m, 1H, 3-CH_2), 5.77 (br. s, 1H, 4-NH), 6.67 (q, 1H, 8-CH, J_1 8.7 Hz, J_2 2.5 Hz), 6.74 (d, 1H, 10-CH, *J* 2.5 Hz), 7.08 (d, 1H, 7-CH, *J* 8.7 Hz), 9.32 (br. s, 1H, 9-OH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 20.1 (2-C), 21.0(1-C), 39.8 (3-C), 105.9 (10-C), 112.9 (8-C), 114.3 (10*b*-C), 116.3 (7-C), 122.3 (10*a*-C), 129.2 (4*a*-C), 140.4 (6*a*-C), 154.0 (9-C), 157.5 (5-C). Found (%): C, 66.08; H, 5.20; N, 6.03. Calc. for $C_{12}H_{11}NO_3$ (%): C, 66.35; H, 5.11; N, 6.45.



Scheme 2



Scheme 3

displaying structural particularity, was observed for the quaternary carbon atoms. The most characteristic quaternary carbon atom correlation peaks of adduct **7**, δ/ppm: 3-CH_2/1-C = 3.23/161.5, 4-CH_2/5*a*-C = 2.00/123.1, 5-CH_2/5*a*-C = 2.90/123.1, 6-CH/5*a*-C = = 6.95/123.1, 9-CH/5*b*-C = 7.40/129.1, 5-CH_2/5*b*-C = 2.90/129.1, 6-CH/5*b*-C = 6.95/129.1, 4-NH/10*b*-C = 8.00/143.8, 5-CH_2/10*b*-C = = 2.90/143.8, 9-CH/9*a*-C = 7.40/147.6, 8-CH/9*a*-C = 6.95/147.6, 6-CH/9*a*-C = 6.95/147.6; adduct **8**, δ/ppm: 4-NH/5-C = 5.77/157.5, 1-CH_2/4*a*-C = 2.59/129.2, 7-CH/10*a*-C = 7.08/122.3, 1-CH_2/10*a*-C = = 2.59/122.3, 4-NH/10*b*-C = 5.77/114.3, 1-CH_2/10*b*-C=2.59/114.3, 10-CH/10*b*-C = 6.74/114.3, 7-CH/6*a*-C = 7.08/140.4, 8-CH/6*a*-C = = 6.67/140.4, 10-CH/6*a*-C = 6.74/140.4. Under the same conditions, adduct **6** also forms 6,8-dibromo-7-oxybenzofuro[2,3-*c*]-azepine-1-one **9** in 14% yield [mp 228–231 °C (EtOH), $M^{\pm}$ 375††] and 8-bromo-9-hydroxy-1,2,3,4-tetrahydro-5*H*-chromeno-[3,4-*b*]pyridine-5-one **10** in 22% yield [mp 191–193 °C (EtOH), $M^{\pm}$ 296‡‡].

Note that compound **10** contains only one bromine atom at the 8-position; therefore, the rearrangement in this case proceeds by halogen removal.

It is believed that the formation of chromene **8** is associated with an equilibrium in solution between adduct **5** with noncyclic hydroquinone adduct **4** (R = R′ = H), which is 'usual' for this reaction. The opening of a lactam ring in **4** (R = R′ = H) leads to chromene **8** according to Scheme 2.

Unexpected debromination with the formation of compound **10** is probably associated with the presence of hydroquinone adduct **4** (R = R′ = Br) in the reaction mixture. Compound **4** (R = R′ = Br) can undergo oxidation to quinone adduct **11**. An activated bromine atom at the 6-position is reduced by adduct **4** (with the transformation of **4** to a 'new portion' of quinone adduct **11**) (Scheme 3).

†† For **9**: ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.09 (m, 2H, 4-CH_2), 3.28 (m, 4-H, 5-CH_2, 3-CH_2), 7.96 (s, 1H, 9-CH), 8.19 (br. s, 1H, 2-NH), 9.60 (br. s, 1H, 7-OH). Found (%): C, 38.74; H, 2.40; Br, 43.00; N, 3.63. Calc. for $C_{12}H_9Br_2NO_3$ (%): C, 38.43; H, 2.42; Br, 42.62; N, 3.73.

‡‡ For **10**: ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.89 (m, 2H, 2-Me), 2.58 (t, 2H, 1-CH_2, *J* 6.2 Hz), 3.23 (m, 1H, 3-CH_2), 5.96 (br. s, 1H, 4-NH), 6.90 (s, 1H, 10-H), 7.44 (s, 1H, 7-H), 10.07 (br. s, 1H, 9-OH). Found (%): C, 48.24; H, 3.30; Br, 27.40; N, 4.26. Calc. for $C_{12}H_{10}BrNO_3$ (%): C, 48.67; H, 3.40; Br, 26.99; N, 4.73.

The mechanism of formation of chromene observed in the Nenitzescu reaction, as well as intriguing debromination in the transformation of dibromoadduct **6**, invite further investigation.

The structures of all compounds were determined by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis.

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