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DEHYDRATION REARRANGEMENTS OF DERIVATIVES OF METHYLENEDIHYDRO-BENZOFURAN – A NEW PATH TO SUBSTITUTED BENZOFURANS

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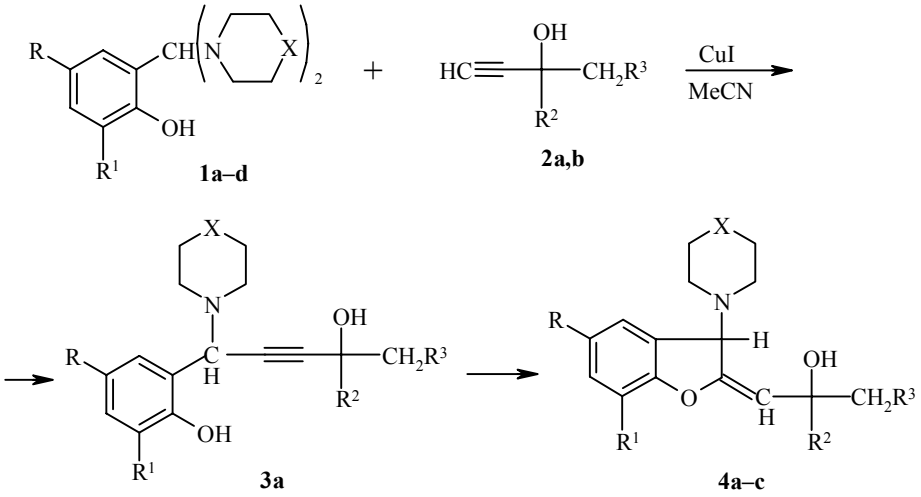
When heated with acidic agents derivatives of 3-amino-2-(hydroxydialkylmethyl)methylene-2,3-dihydrobenzofuran undergo rapid dehydration and rearrangement to substituted 2-alkenyl-3-aminobenzofurans.

Keywords: 2-alkenyl-3-aminobenzofurans, salicylaldehyde aminals, 2-alkylidene-3-amino-2,3-dihydrobenzofuran acetylenes.

Earlier [1] we showed that the aminals of salicylaldehydes **1** in the presence of copper(I) iodide react with terminal acetylenes, including the homologs of propargyl alcohol **2**, and form propargylamines **3**. The latter undergo cyclization to derivatives of 3-amino-2-methylene-2,3-dihydrobenzofuran **4**. [The synthesis of compounds **4a**,**b** was described in [1], and that of **4c** is described in the present paper.]



1 a R = H, **b** R = NO_2, **c** R = Cl, **d** R = Br; **a**, **b** R^1 = H, **c** R^1 = Cl, **d** R^1 = Br; **a** X = CH_2, **b-d** X = O; **2 a** R^2 = Me, R^3 = H, **b** R^2+R^3 = $(CH_2)_4$; **3 a** R = R^1 = H, R^2 = Me, R^3 = H; **4 a** R = H, **b**, **c** R = NO_2; **a-c** R^1 = H, **a**, **b** R^2 = Me, **c** R^2+R^3 = $(CH_2)_4$; **a**, **b** R^3 = H; **a** X = CH_2, **b**, **c** X = O

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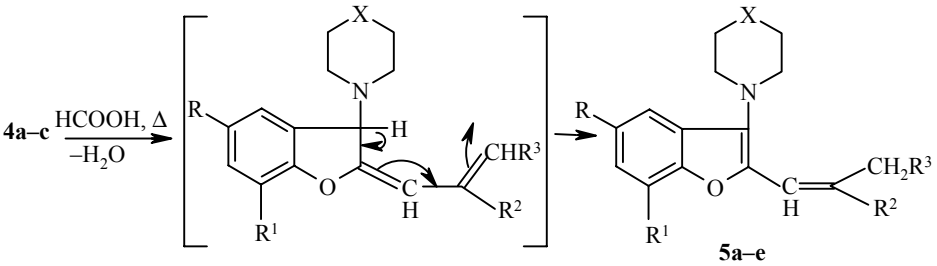
It can be concluded from the results in [1] that cuprous iodide catalyzes not only the Mannich reaction – the formation of propargylamines **3** – but also cyclization of the latter to methylenedihydrobenzofurans **4**. However, further investigations showed that in individual cases the cyclization was caused by impurities present in the samples of the employed CuI. In the absence of such impurities the reaction of the aminal **1a** with the acetylene **2a** stops at the formation of propargylamine **3a**. It was established that the rapid cyclization of **3a** to **4a** was caused by catalytic amounts of silver salts and also of the base. [Procedures for the synthesis of **4a** using silver nitrate and potassium hydroxide are described in the experimental section.]

It was suggested that further aromatization of compounds **4** does not occur on account of orbital prohibition on the 1,3-migration of hydrogen [2], while the introduction of an additional double bond, conjugated with the methylene group, would make the permitted 1,5-migration of hydrogen possible [2, 3]. Such a conjugated system of double bonds must be formed during dehydration of the hydroxy derivatives **4**.

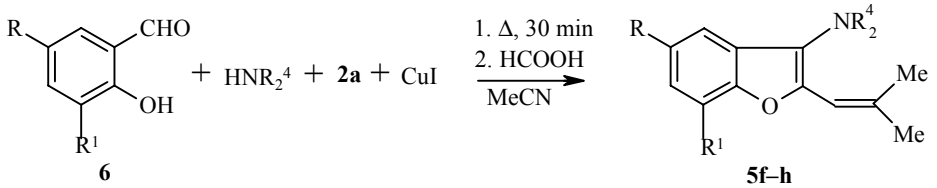
It was in fact found that the action of heat on compounds **4a-c** in formic acid led to rapid dehydration and rearrangement to the respective benzofuran derivatives **5a-c** (see the preliminary data in [4]):



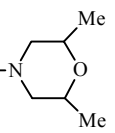
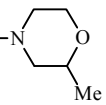
a R = H, **b**,**c** R = NO_2, **d** R = Cl, **e** R = Br; **a-c** R^1 = H, **d** R^1 = Cl, **e** R^1 = Br; **a**, **b** R^2 = Me, **c-e** $R^2 + R^3 = (CH_2)_4$; **a**, **b** R^3 = H; **a** X = CH_2, **b-e** X = O

Compound **5b** was also isolated after boiling from solutions of **4b** in dimethoxyethane containing catalytic amounts of sulfuric acid or *p*-nitrobenzoic acid. Dehydration and rearrangement under the same conditions is also brought about by 2-formyl-4-nitrophenol, which is easily separated from the reaction products on aluminum oxide.

It is not essential to start from previously isolated hydroxyl derivatives **4** to produce the benzofurans **5**. In certain cases "one-pot" syntheses from aminals **1**, in which compounds **4** are formed *in situ*, are more convenient. The benzofurans **5d**,**e** were obtained by such a method. If, however, it is not possible to isolate even the aminal **1**, it is possible to attempt the reaction starting from the respective salicylaldehyde **6** with the formation *in situ* of both the aminal **1** and the hydroxyl derivative **4**:



5 f R = NO_2, **g**, **h** R = Cl; **f** R^1 = H, **g**, **h** R^1 = Cl;

f, **g** $-NR_2^4$ =  , **h** $-NR_2^4$ = 

In the last case (the benzofuran **5h**) the crystalline product could only be isolated in the form of the perchlorate.

The ^{1}H NMR spectra of the benzofurans **5** show that the reaction results in the formation of one geometric isomer (presumably the *E*-isomer). 2,6-Dimethylmorpholine from Fluka, which is a mixture of configurational isomers, was used in the synthesis of compounds **5f**, **g**. In these cases a mixture of compounds **5** with the two isomers of 2,6-dimethylmorpholine in approximately the same ratio (3:1) as in the initial amine was formed. By a single recrystallization of **5f** from ethanol it was possible to remove the minor isomer almost completely. After a single recrystallization of **5g** from methanol, according ^{1}H NMR, the substance remained a mixture of the isomers in a ratio of ~4:1.

EXPERIMENTAL

The IR spectra were recorded in vaseline oil on a Specord IR-75 instrument. The ^{1}H NMR spectra were recorded on a Varian UNITY-300 instrument at 300 MHz.

1-(2'-Hydroxyphenyl)-4-methyl-1-piperidino-2-pentyn-4-ol (3a). A mixture of the aminal **1a** (2.74 g, 10 mmol) and the alcohol **2a** (1 ml, 10.3 mmol) in acetonitrile (15 ml) was heated until the precipitate had dissolved, and CuI (1.91 g, 10 mmol) was added. The mixture was boiled for 30 min and filtered while hot. The filtrate was cooled, and concentrated NH_4OH (20 ml) and water (40 ml) were added. The separated oil was cooled with ice, rubbed with a rod, and left on ice for 2 h. The precipitate was filtered off and recrystallized from hexane (25 ml). Yield 1.75 g (64%). The product formed pale-yellow crystals melting at 87-90°C (hexane). IR spectrum, ν, cm^{-1}: 3433, 3380 (OH); 1694 (w), 1607, 1587, 1494 (arom.); 1154 (C–O); 754 (*o*-disubstituted benzene ring). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 11.12 (1H, s, C(2')OH); 7.37 [1H, d, *J* = 7.5, C(6')H]; 7.10, (1H, m, C(4')H); 6.74 (1H, m, C(5')H); 6.64 (1H, d, *J* = 8.0, C(3')H); 5.21 (1H, s, OH); 4.87 (1H, s, CH); 2.50 (4H, m, NCH_2); 1.62-1.38 (12H, m, $3CH_2$, $2CH_3$). Found %: C 74.50; H 8.31; N 5.43. $C_{17}H_{23}NO_2$. Calculated %: C 74.73; H 8.42; N 5.13.

2-(2'-Hydroxy-2'-methylpropylidene)-3-piperidino-2,3-dihydrobenzofuran (4a). A. A mixture of the aminal **1a** (2.3 g, 8.4 mmol) and the alcohol **2a** (0.9 ml, 9.3 mmol) in acetonitrile (15 ml) was heated until the aminal had dissolved, and CuI (1.2 g, 6.3 mmol) was added. The mixture was boiled for 25 min, and silver nitrate (0.2 g, 0.74 mmol) was added. It was boiled for a further 15 min and was then filtered from the red precipitate. The filtrate was cooled, and concentrated NH_4OH (20 ml) and water (40 ml) were added. The oil that separated together with the precipitate soon began to crystallize on cooling and rubbing. The precipitate was filtered off, washed with water, dried, and recrystallized from isooctane (40 ml) after being filtered hot from the dark residue. Yield 1.55 g (67.7%); mp 100-103°C (twice from isooctane). IR spectrum, ν, cm^{-1}: 3347 (OH); 1714 (sh); 1694 (=CH–); 1607, 1594 (arom.); 1154 (C–O); 747 (*o*-disubstituted benzene ring). ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz): 7.37 (1H, d, *J* = 7.2, C(4)H); 7.23 (1H, m, C(6)H); 6.98 (1H, m, C(5)H); 6.90 (1H, d, *J* = 8.0, C(7)H); 5.15 (1H, s, OH); 4.78 (1H, s, =CH; 3.05 (1H, s, CH); 2.58 (2H, m, CH_2N); 2.38 (2H, m, CH_2N); 1.70-1.30 (12H, m, $3CH_2$, $2CH_3$). Found %: C 75.12; H 8.17; N 5.37. $C_{17}H_{23}NO_2$. Calculated %: C 74.73; H 8.42; N 5.13.

B. A mixture of compound **3a** (0.27 g, 1 mmol) in acetonitrile (3 ml) was boiled with silver nitrate (0.027 g, 0.1 mmol) for 15 min. A precipitate and an oil were separated with water, and the oil soon crystallized when rubbed. It was filtered off, washed with water, and dried. Yield 0.17 g (63%). A mixed melting test on the substance recrystallized from isooctane did not give a melting point depression with an authentic sample. The IR spectra fully agreed.

C. A mixture of compound **3a** (0.27 g, 1 mmol) in methanol (5 ml) with potassium hydroxide (0.2 g, 3 mmol) was boiled for 40 min. The oil that separated with water began to crystallize when rubbed with a rod and was kept on ice for 1 h. The precipitate was filtered off, washed with water, and dried. Yield 0.2 g (74%). The substance was identified by its IR spectrum and its melting point in a mixed melting test.

2-[(1'-Hydroxycyclohexyl)methyl]-3-morpholino-5-nitro-2,3-dihydrobenzofuran (4c). A mixture of the aminal **1c** (1.62 g, 5 mmol) [1], 1-ethynylcyclohexanol **2b** (0.9 g, 7 mmol), and cuprous iodide (1 g, 5 mmol) in acetonitrile (10 ml) was boiled for 30 min and cooled, and concentrated NH_4OH and water (50 ml) were added. The oil that separated was removed and passed through a column of aluminum oxide (chloroform). The solvent was evaporated, and the oil was boiled with petroleum ether and rubbed with a rod until it was converted into a solid white precipitate. The product was cooled and filtered off. Yield 0.7 g (39%); mp 115-117°C. IR spectrum, ν, cm^{-1}: 3407 (OH); 1700 (C=C); 1614, 1594 (arom.); 1514, 1341 (NO_2). ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz): 8.27 (1H, d, *J* = 2.4, C(4)H); 8.23 (1H, dd, ^3J = 8.8, ^4J = 2.4, C(6)H); 7.02 (1H, d, *J* = 8.8, C(7)H); 5.22 (1H, d, *J* = 1.5, =CH); 4.87 (1H, d, *J* = 1.5, C(3)H); 3.66 (4H, t, *J* = 4.5, CH_2O); 2.55 (1H, s, OH); 2.56 (4H, m, CH_2N); 1.64 (6H, m, CH_2); 1.44 (4H, m, CH_2). Found %: C 63.67; H 6.58; N 7.45. $C_{19}H_{24}N_2O_5$. Calculated %: C 63.33; H 6.66; N 7.77.

2-(2'-Methyl-1'-propenyl)-3-piperidinobenzofuran (5a). A 0.55-g sample of compound **4a** (2 mmol) was dissolved by heating in formic acid (3 ml). The solution was cooled, and a precipitate and an oil were separated with water. The oil began to crystallize when cooled with ice and rubbed with a rod. The precipitate was filtered off, washed with water, and dried. The yield of the impure product was 0.38 g (74.5%). After recrystallization from a small amount of methanol 0.19 g of the analytically pure product was obtained; mp 100-103°C. IR spectrum, ν, cm^{-1}: 1654 (C=C); 1607, 1581, 1560 (arom.); 741 (*o*-disubstituted benzene ring). ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz): 7.63 (1H, d, *J* = 8.5, C(7)H); 7.35 (1H, d, *J* = 8.5, C(4)H); 7.14 (2H, m, C(5)H, C(6)H); 6.30 (1H, s, CH=); 3.15 (4H, m, CH_2N); 2.14 (3H, s, CH_3); 1.95 (3H, s, CH_3); 1.4-1.8 (6H, m, CH_2). Found %: C 80.12; H 8.31; N 5.17. $C_{17}H_{21}NO$. Calculated %: C 80.00; H 8.24; N 5.49.

2-(2'-Methyl-1'-propenyl)-3-morpholino-5-nitrobenzofuran (5b). A 0.1-g sample (0.3 mmol) of compound **4b** [2] was dissolved by heating in formic acid (2 ml). The solution was boiled for 20 min and cooled. The precipitate that separated with the addition of water (5 ml) was filtered off and dried. The yield of the impure product was 0.076 g (85%). The product formed yellow crystals, which melted at 150-153°C (methanol). IR spectrum, ν, cm^{-1}: 1650, 1627, 1567 (C=C, arom.); 1521, 1341 (NO_2); 1114 (C–O–C). ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz): 8.53 (1H, d, *J* = 2.3, C(4)H); 8.13 (1H, dd, ^3J = 8.9, ^4J = 2.3, C(6)H); 7.44 (1H, d, *J* = 8.9, C(7)H); 6.28 (1H, s, CH=); 3.88 (4H, m, CH_2O); 3.20 (4H, m, CH_2N); 2.18 (3H, s, CH_3); 2.00 (3H, s, CH_3). Found %: C 63.85; H 5.97; N 9.60. $C_{16}H_{18}N_2O_4$. Calculated %: C 63.58; H 5.96; N 9.27.

2-(Cyclohexylidenemethyl)-3-morpholino-5-nitrobenzofuran (5c). A mixture of the carbinol **4c** (0.2 g, 0.55 mmol) in formic acid (2 ml) was heated to boiling and cooled. The precipitate and tar that were separated with water (5 ml) were recrystallized from ethanol. Yield 0.1 g (53%). The product formed yellow crystals melting at 134-136°C (ethanol). IR spectrum, ν, cm^{-1}: 1647, 1621, 1581, 1560 (C=C, arom.); 1514, 1341 (NO_2). ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz): 8.50 (1H, d, *J* = 2.3, C(4)); 8.11 (1H, dd, ^3J = 9.0, ^4J = 2.3, C(6)H); 7.42 (1H, d, *J* = 9.0, C(7)H); 6.20 (1H, s, CH=); 3.85 (4H, m, CH_2O); 3.20 (4H, m, CH_2); 2.70 (2H, m, CH_2N); 2.30 (2H, m, CH_2N); 1.64 (6H, m, CH_2). Found %: C 66.76; H 6.73; N 8.27. $C_{19}H_{22}N_2O_4$. Calculated %: C 66.66; H 6.43; N 8.19.

5,7-Dichloro-2-(cyclohexylidenemethyl)-3-morpholinobenzofuran (5d). To a solution of the aminal **1c** (1.74 g, 5 mmol) and the alcohol **2b** (1 ml, 7.8 mmol) in acetonitrile (10 ml), heated to boiling, we added cuprous iodide (0.5 g, 2.5 mmol). The mixture was boiled for 30 min, and formic acid (1.5 ml) was added. It was boiled for a further 2 min and filtered while hot. The filtrate was cooled with ice, and the precipitate was filtered off and washed with cold acetonitrile. Yield 1 g (54%). The product formed colorless crystals melting at 158-160°C (acetonitrile). IR spectrum, ν, cm^{-1}: 1647, 1601, 1560, 1541 (C=C, arom.); 1107 (C–O–C). ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz): 7.50 (1H, d, *J* = 1.8, C(6)H; 7.20 (1H, d, *J* = 1.8, C(4)H); 6.29 (1H, s, CH=C); 3.90 (4H, m, CH_2O); 3.19 (4H, m, CH_2); 2.76 (2H, m, CH_2N); 2.31 (2H, m, CH_2N); 1.65 (6H, m, CH_2). Found %: C 62.27; H 6.08; Cl 19.22; N 4.12. $C_{19}H_{21}Cl_2NO_2$. Calculated %: C 62.29; H 5.74; Cl 19.40; N 3.83.

5,7-Dibromo-2-(cyclohexylidenemethyl)-3-morpholinobenzofuran (5e). To a boiling mixture of the aminal **1d** (1.45 g, 3.3 mmol) and the alcohol **2b** (1 ml, 7.8 mmol) in acetonitrile (10 ml) we added cuprous iodide (0.5 g, 2.5 mmol). The mixture was boiled for 30 min, and formic acid (1.5 ml) was added. The mixture was boiled for a further 2 min and filtered while hot. The precipitate was washed with hot acetonitrile. The colorless crystalline precipitate that separated when the filtrate was cooled with ice was filtered off and washed with cold acetonitrile. Yield 0.8 g (53%); mp 138-140°C (ethanol). IR spectrum, ν, cm^{-1}: 1647, 1601, 1554, 1541 (C=C, arom.); 1107 (C–O–C). ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz): 7.68 (1H, d, *J* = 1.8, C(6)H); 7.47 (1H, d, *J* = 1.8, C(4)H); 6.25 (1H, s, CH=C); 3.87 (4H, m, CH_2O); 3.16 (4H, m, CH_2); 2.78 (2H, m, CH_2N); 2.29 (2H, m, CH_2N); 1.64 (6H, m, CH_2). Found %: C 49.73; H 4.89; Br 35.47; N 3.45. $C_{19}H_{21}Br_2NO_2$. Calculated %: C 50.11; H 4.62; Br 35.16; N 3.08.

3-(2',6'-Dimethylmorpholino)-2-(2'-methyl-1'-propenyl)-5-nitrobenzofuran (5f). A mixture of 5-nitrosalicylaldehyde (1.2 g, 7.2 mmol) and 2,6-dimethylmorpholine (1.75 ml, 15 mmol) in acetonitrile (10 ml) was heated to boiling, and the alcohol **2a** (1 ml, 10.3 mmol) was added. The mixture was boiled for 5 min, and cuprous iodide (0.3 g, 1.5 mmol) was added. The mixture was boiled for 30 min, formic acid (1.5 ml) was added, and the mixture was filtered while hot. The filtrate was cooled with ice, and the yellow crystalline precipitate that separated was filtered off and washed with cold ethanol. Yield 1.15 g (49%) (ethanol). IR spectrum, ν, cm^{-1}: 1654, 1621, 1567 (C=C, arom.); 1527, 1341 (NO_2); 1081 (C–O–C). ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz): 8.48 (1H, d, *J* = 2.3, C(4)H); 8.11 (1H, dd, ^3J = 9.0, ^4J = 2.3, C(6)H); 7.42 (1H, d, *J* = 9.0, C(7)H); 6.24 (1H, t, *J* = 1.3, CH=C); 3.84 (2H, m, CHO); 2.94 (4H, m, CH_2N); 2.15 (3H, s, CH_3); 1.98 (3H, s, CH_3); 1.23 (3H, s, CH_3); 1.21 (3H, s, CH_3). Found %: C 65.98; H 7.00; N 8.73. $C_{18}H_{22}N_2O_4$. Calculated %: C 66.26; H 6.75; N 8.59.

3-(2',6'-Dimethylmorpholino)-5,7-dichloro-2-(2'-methyl-1'-propenyl)benzofuran (5g). A mixture of 0.8 g (4.2 mmol) of 3,5-dichlorosalicylaldehyde and 1.25 ml (11 mmol) of 2,6-dimethylmorpholine in 10 ml of acetonitrile was heated to boiling, 1 ml (10.3 ml) of the alcohol (**2a**) was added, 0.25 g (1.25 mmol) of cuprous iodide was added, and the mixture was boiled for 30 min. Formic acid (1.5 ml) was added, and the mixture was filtered while hot and cooled with ice. The crystalline precipitate that separated after rubbing with a glass rod was filtered and washed with cold methanol. Yield 0.77 g (52%). The product formed colorless crystals melting at 110-116°C (from methanol). IR spectrum, ν, cm^{-1}: 1654, 1601, 1560 (C=C, arom.); 1081 (C–O–C). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 7.45 (1H, d, *J* = 2.1, C(6)H); 7.18 (1H, d, *J* = 2.1, C(4)H); 6.23 (1H, s, CH=); 4.12 (0.4H, m, CH_2O); 3.80 (1.6H, m, CH_2O); 3.18 (0.8H, m, CH_2N); 2.88 (3.2H, m, CH_2N); 2.19 (3H, s, CH_3); 1.97 (3H, s, CH_3); 1.34 (0.6H, s, CH_3); 1.31 (0.6H, s, CH_3); 1.21 (2.4H, s, CH_3); 1.11 (2.4H, s, CH_3). Found %: C 60.78; H 6.21; Cl 19.70; N 4.12. $C_{18}H_{21}Cl_2NO_2$. Calculated %: C 61.02; H 5.93; Cl 20.06; N 3.95.

5,7-Dichloro-3-(N-methylpiperazino)-2-(2'-methyl-1'-propenyl)benzofuran Perchlorate (5h). A mixture of 3,5-dichlorosalicylaldehyde (0.8 g, 4.2 mmol) and N-methylpiperazine (1.1 ml, 7.6 mmol) in acetonitrile (10 ml) was heated to boiling, the alcohol **2a** (1 ml, 10.3 mmol) was added, cuprous iodide (0.25 g, 1.25 mmol) was added, and the mixture was boiled for 30 min. Formic acid (1.5 ml) was added to the boiling mixture, the solution was filtered while hot, the filtrate was cooled, water (30 ml) was added, the precipitate was filtered off, and concentrated NH_4OH (10 ml) was added to the filtrate. The released dark oil was separated and passed through a column of aluminum oxide (chloroform). The solvent was evaporated, the light oil was dissolved in ether, and 70% perchloric acid (0.5 ml) was added. The crystalline precipitate was filtered off (0.7 g) and recrystallized from 2-propanol (30 ml). The yield of the pure product was 0.52 g (28%); mp 225-230°C (decomp.). IR spectrum, ν, cm^{-1}: 3080 (NH^+); 1647, 1600, 1567 (C=C, arom.); 1100 (ClO_4). ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz): 8.96 (1H, s, NH^+); 7.45 (1H, s, C(6)H); 7.17 (1H, s, C(4)H); 6.16 (1H, s, CH=C); 3.80 (4H, m, CH_2N); 3.20 (1H, m, CH_2N); 3.08 (3H, s, NCH_3); 2.19 (3H, s, CH_3); 1.90 (3H, s, CH_3). Found %: C 46.20; H 5.08; Cl 24.25; N 6.23. $C_{17}H_{20}Cl_2N_2O{\cdot}HClO_4$. Calculated %: C 46.42; H 4.78; Cl 24.23; N 6.37.

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