Conversion of 3,7-Dialkoxy-4*H*,8*H*-benzo[1,2-*c*:4,5-*c'*]diisoxazole-4,8-dione into New Heterocyclic Systems

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Treatment of **1a** or **1b** with concentrated acids yielded the acid **3**, with alkali hydrogen carbonates the sodium salt **7** and the potassium salt **8**; by reacting with phosphorus pentachloride the vinylogous acid chloride **9** was isolated. Reactions of **9** with amines such as *N*-nucleophiles led to the corresponding amides **10, 11, 14, 15,** and with alcohols such as *O*-nucleophiles to the corresponding alkoxyderivatives **16a, 16b,** which are isomeric compounds to **1a, 1b** and **2a, 2b.**

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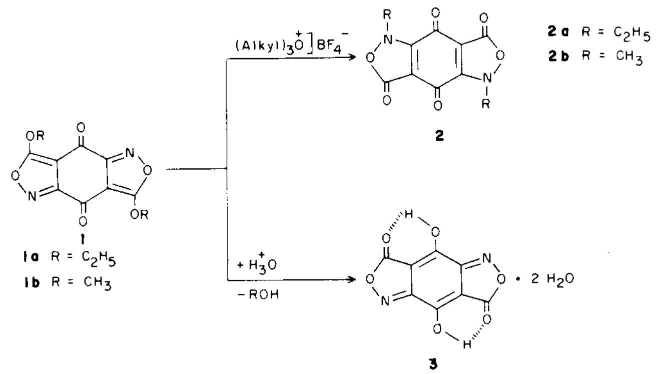
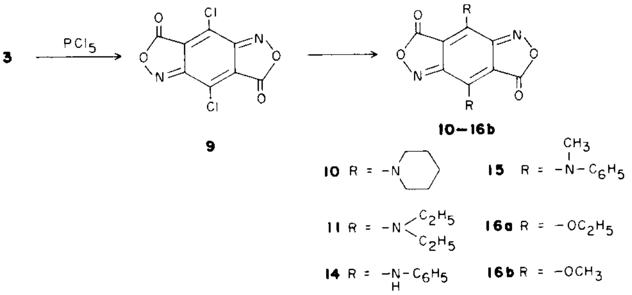
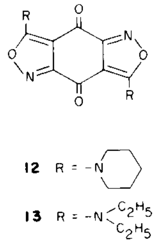
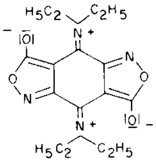
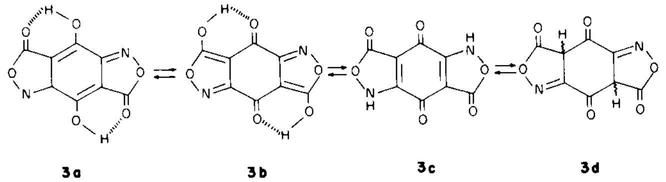
Some time ago we reported (2) the conversion of 3,7-dialkoxy-4*H*,8*H*-benzo[1,2-*c*:4,5-*c'*]diisoxazole-4,8-diones **1a** and **1b** into the isomeric compounds **2a, 2b** by treatment with trialkyloxonium tetrafluoroborates. Compounds **1a** and **1b** could by converted under substitution of the *O*-alkyl groups by strong acids, *e.g.* hydrobromic acid, hydrochloric acid into the vinylogous dicarboxylic acid **3**; as a derivative of an isoxazolin-5-one (3,4), **3** can exist in four tautomeric structures namely **3a-d**. The ^{13}C-nmr-spectrum of **3** shows four signals indicating that in deuterium oxide solution there is only one tautomeric form present. The values of these signals are listed in Table 1 and compared to those of a compound with the structure **4** (2).

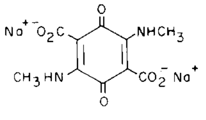







11a

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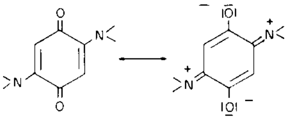

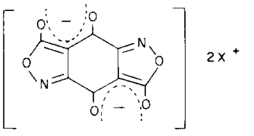

6 $X^+ = H_2\overset{+}{N}[CH(CH_3)_2]_2$
7 $X^+ = Na^+$
8 $X^+ = K^+$

Table 1

^{13}C-nmr-Spectra Data (a) of Compounds **3** and **4**

Compound	Chemical Shifts			
3	96.8	163.2	174.9	175.8
4	109.8	149.9	176.6	178.5

(a) Deuterium oxide solutions using 3-(trimethylsilyl)propionic acid sodium salt-d_4 as external standards.

Especially the similar values of the carbonyl groups of **3** and **4** might lead to the conclusion that **3** exists in deuterium oxide solution as tautomeric structure **3c**. Yet,

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it is known from the 2,5-diaminoquinones **5** that the mesomeric **5a** is of great importance for the description of the real state of these substances (5,6). It is our opinion, that the tautomeric structures **3a, 3b** have to be considered too; **3** is a strong acid (a 0.04 *N* solution has a *p*H value of 1.17) and probably **3** exists in water or in deuterium oxide in the dissociated structure of a *bis*-anion.

Unfortunately, a ^{13}C-nmr spectrum of any salt of **3** [or of a dialkali salt neither of a diammonium salt (6)] was not possible because the solubility in deuterium oxide in all cases was not sufficient. The ^{1}H-nmr spectrum of **3** in DMSO-d_6 solution only shows one singlet at $\delta = 7.41$ ppm; this signal contains the acidic protons of **3** and those of water of crystallization. The uv spectrum of **3** resembles that of compound **16b** and is practically identical with that of the *bis*diisopropylammonium salt **6** (1,2) (see Table 2).

Table 2

UV Data of **3**, **16b** and **6**

Compound	λmax	Solution
3	236, 282, 346	H_2O
16b	203, 239, 283, 348	CH_3OH
6 (1,2)	234, 282, 346	H_2O

The ir spectrum of **3** shows a very large O-H absorption vibration from 3500-2000 cm^{-1} resulting from the water of crystallization and chelated protons; absorption at 1607 and 1521 cm^{-1} may result from C=C and C=N vibrations.

By neutralization of an aqueous solution of **3** with sodium bicarbonate the disodium salt **7** precipitates, containing 2 moles of water of crystallization with potassium bicorbonate, we isolated the analogous potassium salt **8**.

With phophorus pentachloride **3** could be converted into the vinylogous acid chloride **9**; the existence as a pure quinonediimide derivative has been proved by reacting **9** with amines and alcohols: the reaction of **9** with piperidine or diethylamine in the presence of triethylamine exclusively yielded **10** and **11** respectively. The spectral data differ from those of the formerly synthesized isomeric compounds **12** and **13** (8). The low frequency of the carbonyl group in the ir spectrum of **11** and the ^{1}H- and ^{13}C-nmr spectra show that the mesomeric zwitterionic structure **11a** contributes much to the real state of the molecules **10** and **11**.

On the other hand **9** reacts also with aromatic amines to form compounds **14** and **15**; there were some difficulties with the purification of **14**, so that the elementary analysis of **14** has been additionally ascertained by peak matching. The low frequency of the N-H vibration in the ir spectrum of **14** (3243 cm^{-1}) in connection with the C=O vibration (1695 cm^{-1}) indicates a hydrogen bridge between the nitrogen of aniline and the carbonyl group (7) in the direct neighbourhood. The two chlorine atoms in **9** can also be substituted by aliphatic alkoxy groups yielding compounds **16a** and **16b**. The large chemical shifts of the CH_2-protons in **16a** ($\delta = 5.16$ ppm) and the CH_3 protons in **16b** ($\delta = 4.73$ ppm) are caused by the anisotropic effect of the neighbouring carbonyl group (7). The ir absorption frequencies of the carbonyl vibrations in **16a/16b** indicate an unconjugated five-membered lactone ring as in the case of **2a/2b**.

EXPERIMENTAL

Melting points were determined on a mp microscope "Reichert" and are uncorrected. All ir spectra were recorded on a Perkin- -Elmer 325 spectrophotometer using potassium bromide pellets. ^{1}H-nmr spectra were taken on a Bruker HX-90 E spectrometer at 90 MHz, ^{13}C-nmr spectra at 22.63 MHz, uv spectra were obtained on a Carl Zeiss spectrophotometer DMR 10 mass spectra were run on a Varian mat 311 A spectrophotometer.

4.8-Dihydroxy-3*H*,7*H*benzo[1,2-*c*:4,5-*c*′]diisoxazole-3,7-dione (**3**).

Method A

Compound **1a** (1.11 g, 4 mmoles) or 1.00 g (4 mmoles) of **1b** were heated with 35 ml of aqueous concentrated hydrobromic acid (48%) for 30 minutes. After cooling and filtering, the residue was washed with ether and extracted twice with 15 ml of hot acetonitrile to remove unchanged starting material; 0.94 g (91%) of **3** was obtained as a yellow powder, decomposing above 170°.

Method B

Compound **1a** (556 mg, 2 mmoles) or 500 mg (2 mmoles) of **1b** were heated with 20 ml of concentrated hydrochloric acid for 1 hour and 50 minutes and purified as described in method A to give 450 mg (87%) of **3**; uv (water): λmax (log ϵ) = 236 (3.66), 283 (3.80), 348 nm (3.89); ^{1}H-nmr (DMSO-d_6): $\delta = 7.41$ (s, OH, H_2O); ^{13}C-nmr (deuterium oxide TSPNa-d_4 external): $\delta = 96.8$ (C=C-OH), 163.2 (C=N), 174.9 and 175.8 (C=O, =C-OH); ms: (100 °C) m/e = 222 (9%, M^+), 178 (12), 94 (32), 68 (81), 44 (100); ir: (potassium bromide) 3500-2000 (H_2O and O-H), 1690 (C=O), 1607 (C=C), 1521 cm^{-1} C=N).

Anal. Calcd. for $C_8H_6N_2O_8$: C, 37.22; H, 2.34; N, 10.85. Found: C, 37.24; H, 2.31; N, 10.96.

Disodium-3,7-dioxo-3*H*,7*H*-benzo[1,2-*c*:4,5-*c*′]diisoxazole-4,8-diolate with water (**7**).

A solution of 620 mg (2.4 mmoles) of **3** in 40 ml of water was neutralized with a saturated solution of sodium bicarbonate, the precipitate was filtered and dried; 700 mg (96%) of **7** was obtained as a yellow powder mp above 300°; ir: 3475, 3355 (H_2O), 1682 (C=O), 1588 (C=C), 1508 cm^{-1} (C=N).

Anal. Calcd. for $C_8H_4N_2Na_2O_8$: C, 31.80; H, 1.33; N, 9.27. Found: C, 31.52; H, 1.39; N, 9.30.

Dipotassium-3,7-dioxo-3*H*,7*H*-benzo[1,2-*c*:4,5-*c*′]diisoxazole-4,8-diolate (**8**).

Compound **8** was synthesized analogously to **7** from **3** in a saturated potassium bicarbonate solution. Yellow needles were obtained in a yield of 565 mg (79%), mp above 300°; ir: (potassium bromide): 1690 (C=O), 1600 (C=C), 1510 cm^{-1} (C=N).

Anal. Calcd. for $C_8K_2N_2O_6$: C, 32.21; H, -; N, 9.39. Found: C, 32.52; H, -; N, 9.35.

4,8-Dichloro-3*H*,7*H*-benzo[1,2-*c*:4,5-*c*′]diisoxazole-3,7-dione (**9**).

A suspension of 1.033 g (4 mmoles) of **3** in 30 ml of carbon tetrachloride was heated to reflux for 3.5 hours with 3.32 g (16 mmoles) of phosphorus pentachloride. It was cooled and filtered and the residue was crystallized from trichloromethane to give 560 mg (54%) of yellow crystals, decomposing above 150°; ir: (potassium bromide) 1782 (C=O), 1590 (C=C), 1522 cm^{-1} (C=N); ms (70°C)m/e = 258 (100%, M$^+$), 200 (62), 170 (32), 135 (44), 107 (43).

Anal. Calcd. for $C_8Cl_2N_2O_4$: C, 37.10; N, 10.81; Cl, 27.38. Found: C, 36.93; N, 11.08; Cl, 27.13.

4,8-Dipiperidino-3*H*,7*H*[1,2-*c*:4,5-*c'*]diisoxazole-3,7-dione (**10**).

A solution of 189 mg (2.2 mmoles) of piperidine in 10 ml of trichloromethane was added dropwise to a suspension of 159 mg (1 mmole) of **9** in 10 ml of trichloromethane. One hour later, a solution of 222 mg (2.2 mmoles) of triethylamine in 10 ml of trichloromethane was added dropwise, the solution stirred for another two hours, evaporated and the residue washed with 20 ml of warm water and crystallized from acetonitrile, yielding 280 mg (79%) of brown-yellow needles decomposing above 210°; uv (methanol): λmax (log ε) = 203 (3.85), 225 (3.60), 302 (3.44) and 396 nm (3.49); H-nmr (deuteriochloroform): δ = 1.85 (mc, 12H, H-5, H-3, H-4), 4.23 (mc, 8H, H-2, H-6); ms: (190°) m/e = 356 (49%, M$^+$), 293 (40), 267 (87), 239 (95), 184 (100), 55 (99); ir (potassium bromide): 1714 (C=O), 1578 (C=C), 1503 cm^{-1} (C=N).

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.56; H, 5.60; N, 15.86.

4,8-*Bis*diethylamino-3*H*,7*H*-benzo[1,2-*c*:4,5-*c'*]diisoxazole-3,7-dione (**11**).

Compound **9** (259 mg, 1 mmole), 162 mg (2.2 mmoles) of diethylamine and 222 mg (2.2 mmoles) of triethylamine were allowed to react as described for **10** crystallization from acetone yielded 240 mg (72%) of brown-yellow needles, mp 203.5-205.5°; uv (methanol): λmax (logε) = 211 (4.09), 294 (3.90), 384 (3.97) and 3.98 (3.98); ^{1}H-nmr (acetone-d$_6$): δ = 1.38 (t, 12H, CH$_3$), 4.31 (q, 8H, -CH$_2$-); ^{13}C-nmr (deuteriochloroform): δ = 13.8 (-CH$_2$CH$_3$), 52.2 (-*C*H$_2$-N-), 88.3 (-N-*C*=C-), 156.5 (-*C*=N-), 167.8 (-*C*=O); ms: 175°C) m/e = 332 (52%, M$^+$), 255 (40), 227 (73), 201 (100); ir (potassium bromide): 1708 (C=O), 1562 (C=C), 1498 cm^{-1} (C=N).

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.86; H, 6.07; N, 16.86. Found: C, 57.83; H, 6.06; N, 16.90.

4,8-Dianilino-3*H*,7*H*-benzo[1,2-*c*:4,5-*c'*]diisoxazole-3,7-dione (**14**).

A solution of 202 mg (2.0 mmoles) of triethylamine and 186 mg (2.0 mmoles) of aniline in 15 ml of toluene was added dropwise to a suspension of 259 mg (1 mmole) of **9** in 15 ml of toluene, stirred overnight, filtered, the residue washed twice with 15 ml of hot water and extracted twice with 20 ml of methanol to yield 230 mg (62%) of brown-red needles, decomposing above 250°; ms: (250°) m/e = 374 (7%, M$^+$ + 2), 372 (18, M$^+$), 284 (64), 93 (37), 77 (100); ir (potassium bromide): 3243 (NH), 1695 (C=O), 1620 cm^{-1}; exact mass measurement Calcd. for $C_{20}H_{12}N_4O_4$: 372.0859.Found: 372.0873.

Anal. Calcd. for $C_{20}H_{12}N_4O_4$: C, 64.51; H, 3.25; N, 15.05. Found: C, 63.48; H, 3.47; N, 14.78.

4,8-*Bis*(N-methylanilino)-3*H*,7*H*-benzo[1,2-*c*:4,5-*c'*]diisoxazole-3,7-dione (**15**).

Compound **9** (259 mg, 1 mmole) g, 236 mg (2.2 mmoles) of *N*-methylaniline and 222 mg (2.2 mmoles) of triethylamine were allowed to react as described for **14**. Reapeated crystallization from dimethylformamide yielded 170 mg (47%) of red needles, mp 228-229°, ms: (230°C) m/e = 400 (16%, M$^+$), 312 (45), 311 (68), 77 (100); ir (potassium bromide): 1712 (C=O), 1560 (C=C), 1502, 1490 cm^{-1}.

Anal. Calcd. for $C_{22}H_{16}N_4O_4$:C, 66.00; H, 4.03; N, 13.99. Found: C, 65.92; H, 4.17; N, 13.19.

4,8-Diethoxy-3*H*,7*H*-benzo[1,2-*c*:4,5-*c'*]diisoxazole-3,7-dione (**16a**).

A suspension of 259 mg (1 mmole) of **9** in 15 ml of ethanol was stirred for 1 hour, then heated under reflux for 5 minutes cooled, filtered and the residue crystallized from toluene to give 140 mg (50%) yellow crystals decomposing above 180°; ^{1}H-nmr (deutoriochloroform): δ = 1.58 (t, 6H, CH$_3$), 5.16 (q, 4H, -CH$_2$-); ms: (135°C) m/e = 278 (83%, M$^+$), 250 (16), 222 (86), 138 (25), 112 (73), 94 (65), 67 (100); ir: (potassium bromide): 1767 (C=O), 1585 (C=C), 1540 cm^{-1} (C=N).

Anal. Calcd. for $C_{12}H_{10}N_2O_6$: C, 51.81; H, 3.60; N, 10.07. Found: C, 51.80; H, 3.57; N, 9.83.

4,8-Dimethoxy-3*H*,7*H*-benzo[1,2-*c*:4,5-*c'*]diisoxazole-3,7-dione (**16b**).

A solution of 222 mg (2.2 mmoles) of triethylamine in 10 ml of methanol was added dropwise to a suspension of 259 mg (1 mmole) of **9** in 10 ml of methanol at -30°, stirred for 15 minutes, allowed to warm gradually to room temperature and filtered after 1.5 hours. The residue was washed with water and crystallized from acetone to give 100 mg (40%) of yellow needles, decomposing above 160°; uv (methanol): λ max (log ε) = 203 (3.80), 239 (3.65), 283 (3.67), 348 nm (3.80); ^{1}H-nmr (acetone-d$_6$): δ = 4.73 (s, OCH$_3$); ms: (155°C) m/e 250 (100%, M$^+$), 205 (27), 138 (38), 80 (49); ir (potassium bromide): 1780 (C=O), 1595 (C=C), 1545 cm^{-1} (C=N).

Anal. Calcd. for $C_{10}H_6N_2O_6$: C, 48.01; H, 2.42; N, 11.20. Found: C, 47.82; H, 2.43; N, 10.85.

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