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A pentacyclic condensation product from 2,4-dimethyl-7-nitro-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acid

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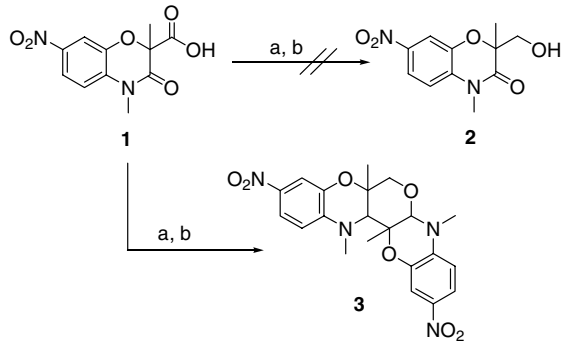
Abstract—2,4-Dimethyl-7-nitro-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acid on preparation of a mixed anhydride, followed by reduction with sodium borohydride, affords 5,7a,13,13b-tetramethyl-2,10-dinitro-5a,7,7a,13,13a,13b-hexahydro-5*H*-[1,4]benzoxazino[3′,2′:4,5]pyrano[3,2-*b*][1,4]benzoxazine (**3**), the structure of which was established unambiguously by X-ray analysis.

2*H*-1,4-Benzoxazin-3-(4*H*)-ones and 3,4-dihydro-2*H*-1,4-benzoxazines are widely used scaffolds in organic and medicinal chemistry.[1] In the course of our research directed toward a novel class of antithrombotic compounds with dual functions,[2] 2-(hydroxymethyl)-2,4-dimethyl-7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one (**2**) was required as a key intermediate. Since 2*H*-1,4-benzoxazin-3-(4*H*)-ones are readily reduced to 3,4-dihydro-2*H*-1,4-benzoxazines by strong reducing agents such as lithium aluminum hydride or borane, we attempted to synthesize **2** from the readily available 2,4-dimethyl-7-nitro-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acid (**1**)[3] through sodium borohydride reduction of the mixed anhydride formed by reaction with isobutyl chloroformate (Scheme 1). Reduction of mixed anhydrides is a convenient approach for the synthesis of alcohols from carboxylic acids bearing functional groups, which would also be reduced with strong reducing agents such as lithium aluminum hydride or borane dimethyl sulfide complex. Thus, a mixed anhydride can be reduced to an alcohol with sodium borohydride, even in the presence of a nitroxide free radical moiety, which is very sensitive to reductive conditions.[4]

The spectroscopic and elemental analysis of the reaction product showed that the desired alcohol **2** was not isolated and, unexpectedly, a new pentacyclic product **3**, containing two 3,4-dihydro-2*H*-1,4-benzoxazine units fused to a tetrahydropyran ring, was obtained. The structure of compound **3** was unambiguously determined by X-ray crystallography.

The new heterocyclic skeleton **3** supplements the already known heterocyclic scaffolds **4**, **5**, **6**, and **7** comprising two 1,4-benzoxazine units connected by a 2,2′, 2,3′, or 3,3′ bond and possessing a central five-, six-, or seven-membered ring. Compound **4** was prepared from *o*-quinone monoimide and 1-carboxymethoxypyrrole[5] and **5** was obtained as an aldolized polymeric product from unstable 2-(2-aminophenoxy)acetaldehyde.[6] Heterocycle



Scheme 1. Reagents and conditions: (a) *i*BuOCOCl, Et_3N, Et_2O, 0 °C, 3 h; (b) $NaBH_4$, EtOH, rt, overnight.

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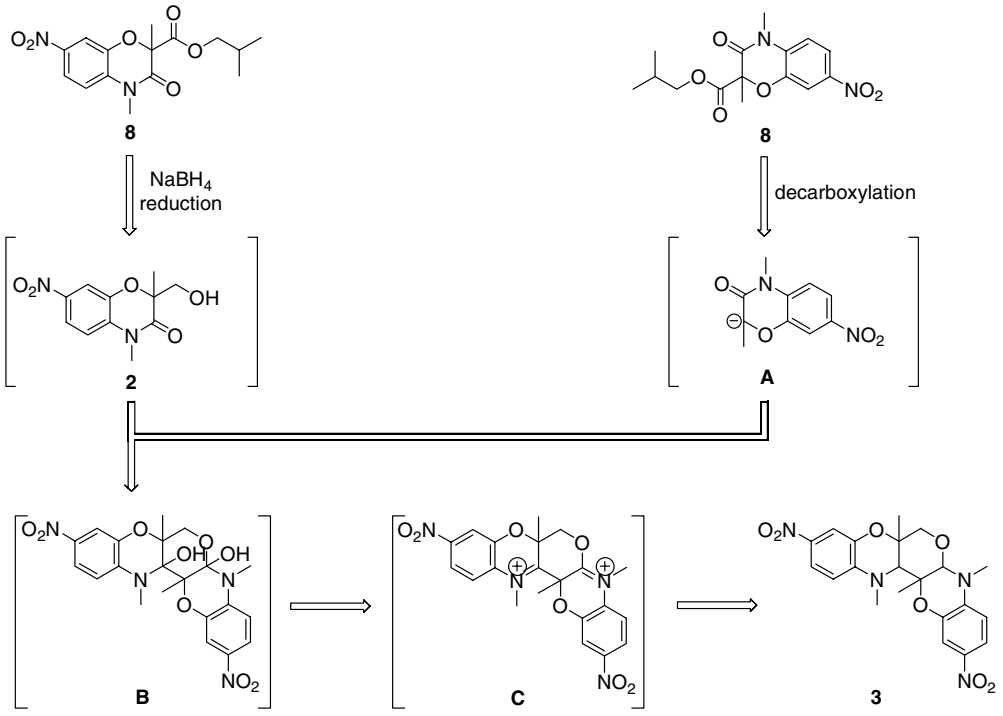
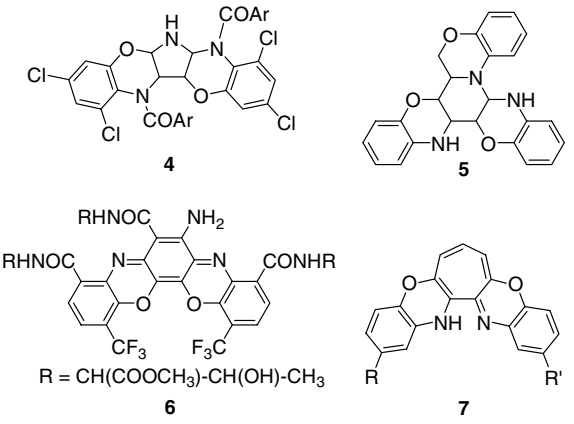


Scheme 2. Proposed reaction mechanism for the formation of compound **3**.

6 resulted from oxidative mixed condensation of a 3-hydroxy-2-nitro-4-(trifluoromethyl)benzoic acid derivative[7] and **7** was a product of an intermolecular heterocyclic exchange reaction.[8] However, there is no report in the literature on the formation of such pentacyclic heterocycles from two 1,4-benzoxazin-3(4*H*)-one units.



Analysis of the structure of **3** (Scheme 2) shows that formally one of two molecules of the mixed anhydride **8** has been decarboxylated to form carbanion **A**, whereas the other molecule was reduced to 2-hydroxymethyl derivative **2**. Attack of the C-2 reactive center of **A** at the lactam carbonyl group of **2** and reaction of the hydroxy group of **2** at the lactam carbonyl group of **A** resulted in the formation of intermediate **B** containing a new six-membered ring. Protonation, elimination of water and reduction of imine **C** finally afforded compound **3**. However, it is also feasible that conversion of the intermediately formed mixed anhydride **8** to **3** involves a concerted process mediated by chelation with borohydride anions. Decarboxylation of malonic acids and alkyl malonates is a well known approach for the synthesis of carboxylic acid derivatives.[9] Therefore, decarboxylation of **8**, comprising a substituted malonate moiety, to carbanion **A** could follow a similar mechanism.

Proton and ^{13}C NMR spectra of **3**[10] did not show any duplication of resonance signals, indicating that the isolated product was not a mixture of diastereomers. The X-ray crystal structure (Fig. 1) revealed the presence of two enantiomers with absolute configuration C5a (*S*), C7a (*S*), C13a (*R*), C13b (*R*) and C5a (*R*), C7a (*R*), C13a (*S*), C13b (*S*) in the crystal. Two crystals were

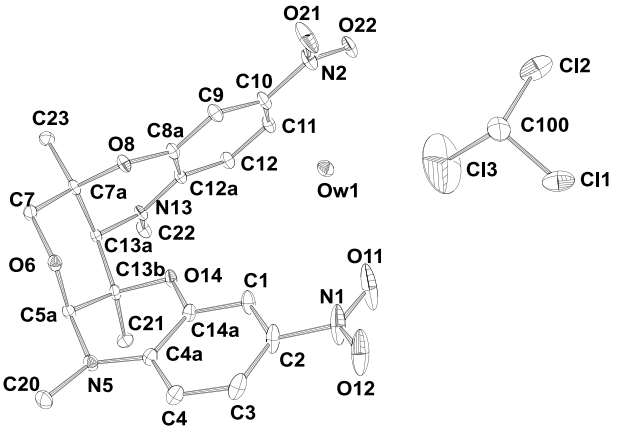


Figure 1. X-ray crystal structure of compound **3** as the hemisolvate with chloroform.[12] An additional water molecule is present with occupancy of 0.25. The displacement ellipsoids are drawn at the 30% probability level and H atoms are omitted for clarity.

analyzed by X-ray crystallography and in both cases the same enantiomers were found in the unit cell. Other crystals were examined by microscope and no morphological difference in structure was observed. This suggests that the reaction proceeded in a diastereoselective manner, yielding **3** as the major, if not the only diastereomer. Diastereoselectivity in the formation of **3** is not surprising, since all four chiral centers are located at ring junctions of the tetrahydropyran ring, which defines the conformation of the molecule. Recently, high diastereoselectivity was also observed in the formation of 5a,6,11a,12-tetrahydro[1,4]benzoxazino[3,2-*b*][1,4]benzoxazine propelanes, which, in contrast to **3**, comprise condensed cyclohexane and two 1,4-benzoxazine rings.[11] The bent conformation of **3** is responsible, due to the anisotropic effect of the benzene ring, for a high-field shift of H-1 (6.75 ppm) as compared to the chemical shift of H-9 (7.43 ppm). Other aromatic protons in the two benzoxazine rings have similar chemical shifts (H-4 and H-12 differ by 0.04 ppm and H-11 and H-3 by 0.14 ppm).

A novel pentacyclic ring system **3**, containing two 3,4-dihydro-2*H*-1,4-benzoxazine units fused to a tetrahydropyran ring, was obtained from 2,4-dimethyl-7-nitro-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acid. This is the first report of dimerization of two 1,4-benzoxazin-3(4*H*)-one derivatives with the formation of a new pentacyclic heterocyclic skeleton.

Acknowledgments

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10. *Synthesis of 5,7a,13,13b-tetramethyl-2,10-dinitro-5a,7,7a,13,13a,13b-hexahydro-5H-[1,4]benzoxazino[3′,2′:4,5]pyrano[3,2-b][1,4]benzoxazine* (**3**): A solution of isobutyl chloroformate (3.54 g, 25.92 mmol) in 100 mL of anhydrous diethyl ether was added dropwise over a period of 0.5 h to a stirred suspension of 2,4-dimethyl-7-nitro-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acid (**1**) (6.90 g, 25.92 mmol) and triethylamine (2.62 g, 25.92 mmol) in 500 mL of anhydrous diethyl ether, cooled on an ice bath. After 3 h, when completion of the reaction was observed by TLC (silica gel; petroleum ether:diethyl ether = 1:1), precipitated triethylammonium chloride was filtered off, and the filtrate was concentrated under vacuum. The resulting solid was added to a stirred suspension of sodium borohydride (1.37 g, 36.29 mmol, 1.4 equiv) in anhydrous ethanol (250 mL) over a period of 10 min. After 4 h another portion of sodium borohydride (1.37 g, 36.29 mmol, 1.4 equiv) was added and the mixture was left overnight at room temperature. The ethanol was removed under vacuum, 200 mL of 0.1 M NaOH was added to the suspension, and the product extracted with ethyl acetate (4 × 150 mL). Organic fractions were collected, washed with 10% citric acid (100 mL) and brine. The solvent was removed under vacuum to give 4.83 g of crude product as a yellow powder, which was purified by column chromatography on silica gel using dichloro methane/methanol (50:1→9:1) as eluant; yield: 2.48 g (44%), yellow crystals, mp 326–329 °C; IR (KBr) 3420, 2954, 1752, 1601, 1513, 1439, 1308, 1040, 1009, 969, 877, 826, 744 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6)[13] δ 1.05 (s, 3H, 7a-CH_3), 1.32 (s, 3H, 13b-CH_3), 3.15 (s, 3H, 5-CH_3), 3.39 (s, 3H, 13-CH_3), 3.78 (d, AB, 1H, $J = 13.0$ Hz, 7-CH_2), 3.87 (s, 1H, 13a-CH), 4.02 (d, AB, 1H, $J = 13.0$ Hz, 7-CH_2), 4.77 (s, 1H, 5a-CH), 6.75 (d, 1H, $J = 2.6$ Hz, 1-H), 6.86 (d, 1H, $J = 9.0$ Hz, 4-H), 6.90 (d, 1H, $J = 9.0$ Hz, 12-H), 7.43 (d, 1H, $J = 2.6$ Hz, 9-H), 7.74 (dd, 1H, $J = 2.6$ Hz, $J = 9.0$ Hz, 3-H), 7.88 (dd, 1H, $J = 2.6$ Hz, $J = 9.0$ Hz, 11-H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6)[13] δ 142.47 (12a-C), 142.38 (8a-C), 141.39 (14a-C), 139.87 (4a-C), 139.26 (2-C), 137.51 (10-C), 119.31 (11-C), 119.06 (3-C), 112.11 (4-C), 110.85, 110.82, 110.78, (12-C, 9-C, 1-C), 87.24 (5a-C), 77.15 (13b-C), 71.06 (7a-C), 70.98 (7-C), 64.95 (13a-C), 43.17 (13-CH_3), 38.34 (5-CH_3), 21.24 (13b-CH_3), 20.54 (7a-CH_3) ppm. MS (FAB): *m/z* (%) 443 (M+H, 29), 391 (6), 307 (20), 206 (34), 154 (100), 136 (76), 71 (73), 55 (75). Anal. Calcd for $C_{21}H_{22}N_4O_7$: calculated[14] C, 57.01; H, 5.01; N, 12.66; found C, 56.74; H, 4.85; N, 12.61.
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12. Crystallographic data (excluding structure factors) for **3** hemisolvate with chloroform have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 661430. Copies of this data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]. Crystal data of $C_{21}H_{22}N_4O_7 \times 0.5\ CHCl_3 \times 0.25\ H_2O$: triclinic, $P\bar{1}$, $a = 8.6396(9)$, $b = 10.2863(9)$, $c = 13.9204(9)$ Å, $\alpha = 85.727(1)°$, $\beta = 80.723(1)°$, $\gamma = 73.282(1)°$, λ (Mo-Kα) = 0.71073 Å, $V = 1168.80(18)$ Å^3, $T = -123$ °C, moiety formula $2(C_{21}H_{22}N_4O_7) \times CHCl_3 \times 0.48(H_2O)$, $D_x = 1.438$ g cm^{-3}, $Z = 1$, μ (mm^{-1}) = 0.272, absorption method: multiscan, $T_{min} = 0.92$, $T_{max} = 0.95$; $\theta_{max} = 27.10°$, completeness: 99.5%, $\Delta\rho_{min} = -0.36$, $\Delta\rho_{max} =$

+0.83 e. Å^3; $R = 0.0565$ for 3670 refls [$I > 2\sigma(I)$]; $wR_2 = 0.1532$ for all 5103 refls, $S = 1.034$, number of parameters: 337, refinement on F^2. The molecular geometry of the molecule is normal. The chloroform molecule is disordered across the center of inversion with an occupancy of 0.5. The position of the water molecule is only partially occupied. Several attempts were made to obtain better crystal data, but were unsuccessful. There are two centrosymetrically related molecules (racemic mixture) of **3** in the crystal structure with C5a (*S*), C7a (*S*), C13a (*R*), C13b (*R*) chirality in the first, and C5a (*R*), C7a (*R*), C13a (*S*), C13b (*S*) in the second molecule.

13. NMR spectra were recorded on a Bruker DRX 300 spectrometer at 300 MHz (^{1}H) and 75 MHz (^{13}C), with TMS as internal standard. Each assignment is based on 2D-COSY, 2D-HMQC and 2D-HMBC spectra obtained using the standard Bruker pulse programs INV4GS and INV4GSLPLRND.
14. Elemental analysis of crystals, which were dried at 60 °C and used for X-ray analysis, gave the following results: Anal. Calcd for $C_{21}H_{22}N_4O_7 \times 1/2\ CHCl_3 \times 1/2\ H_2O$: C, 50.52; H, 4.63; N, 10.66; found C, 50.75; H, 4.27; N, 10.80. Additional drying at 170 °C for 10 h gave a dry substance without any solvate present, as indicated by elemental analysis.