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SYNTHESIS AND STRUCTURE OF 6-BROMO-4-HYDROXY-2,3-TETRAMETHYLENE-3,4-DIHYDROQUINAZOLINE AND ITS MIXED CRYSTAL WITH 4-HYDROXY-2,3-TETRAMETHYLENE-3,4-DIHYDROQUINAZOLINE

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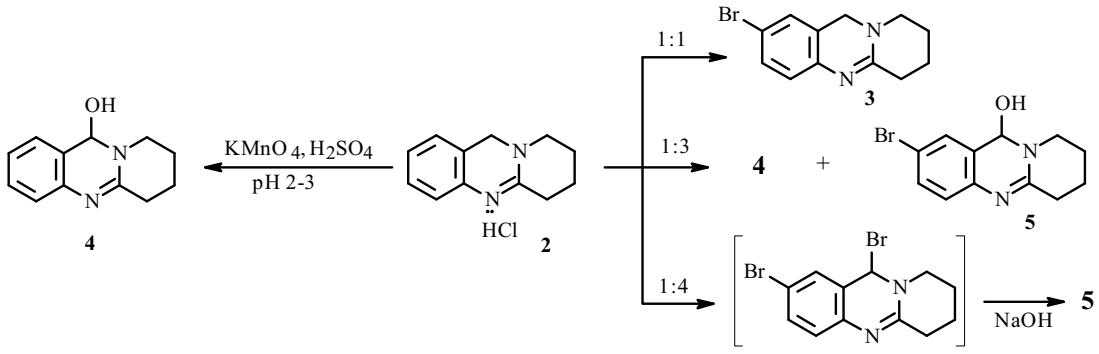
Bromination of the alkaloid 2,3-tetramethylene-3,4-dihydroquinazoline by N*-bromosuccinimide was studied. It was shown that either 4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline or 6-bromo-4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline was formed depending on the ratio of reagents. Oxidation of 2,3-tetramethylene-3,4-dihydroquinazoline by $KMnO_4$ produced 4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline. The crystal structures of 6-bromo-4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline and its mixed crystal with 4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline were studied by x-ray structure analysis. The enantiomeric molecules in all crystal structures formed associates owing to two opposing OH...N1 H-bonds.*

Key words: alkaloids, quinazolines, co-crystals, bromination, *N*-bromosuccinimide, oxidation, $KMnO_4$, x-ray structure analysis.

We have previously shown that deoxypeganine (DOP) reacts with *N*-bromosuccinimide (BSI) to form after work up with base peganol and 6-bromopeganol. It was also found that they crystallize from the reaction mixture as a two-component mixed crystal (solid solution) and form co-crystals in various ratios (0.72:0.28, 0.32:0.68, 0.08:0.92) [1]. These crystal structures typically form a centrosymmetric closed framework (associate) consisting of two different molecules with opposing centrosymmetric O–H...N1 H-bonds. The formation of such an associate is a reason behind the formation of mixed crystals of peganol and 6-bromopeganol.

Bromination of the six-membered analog of deoxypeganine 2,3-tetramethylene-3,4-dihydroquinazoline (**1**) by BSI was studied in order to expand the versatility of this approach for synthesizing quinazoline alkaloids containing a condensed six-membered ring. It also seemed interesting to determine if mixed crystals of the reaction products could form. Alkaloid **1** was isolated previously from *Mackinloya subulata* and *M. macnosciadia* (Araliacae) [2] and was later synthesized from anthranilic acid and δ-valerolactam with subsequent reduction by zinc in HCl [3, 4].



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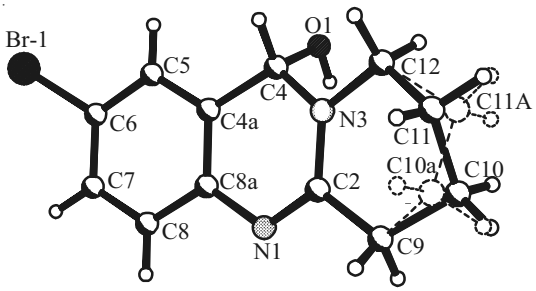

Fig. 1. Molecular structure and atom numbering of 6-bromo-4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline (equivalent methylene positions are shown by dashed lines).

2,3-Tetramethylene-3,4-dihydroquinazoline hydrochloride (**2**) reacted with BSI (1:1 ratio) to form 6-bromo-2,3-tetramethylene-3,4-dihydroquinazoline (**3**). Using a **2**:BSI ratio of 1:3 formed a mixture consisting of 4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline (**4**) and 6-bromo-4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline (**5**). A two-component crystal (**6**) was obtained from the mixture of reaction products. This was established by an x-ray structure analysis (XSA) of its structure. We synthesized **4** by oxidation of **2** using $KMnO_4$ in acidic medium in order to check the ability to form **4** in the reaction mixture and to prepare a standard sample. This produced 4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline (**4**) in 54.5% yield. The structures of the products were confirmed by spectral data.

Using a **2**:BSI ratio of 1:4 led to bromination of the 4- and 6-positions simultaneously to form 4,6-dibromo-2,3-tetramethylene-3,4-dihydroquinazoline, which converted upon work up with NaOH into 6-bromo-4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline (**5**).

Figure 1 shows the molecular structure of **5** from the XSA. Atoms C10 and C11 in the crystal are disordered over two positions (C10, C10A and C11, C11A). Refinement of the structure by least-squares methods with the FVAR instruction indicated that the populations of the disordered atoms were equal (0.5). Therefore, the positions of C10 and C11 indicated that 6-bromo-4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline in the crystal of **5** contained in two conformers of the piperidine ring in equal amounts.

According to the XSA, **6** was a mixed two-component crystal. The two-component nature of **6** was noticed during least-squares refinement of the structure where the population of the Br atom acquired a value of 0.86. For this reason HPTLC of the studied single crystal of **6** was performed independently. The chromatographic plate showed two spots, the heights of which coincided with those observed for **4** and **5**. Next, least-squares refinement of the Br positional parameter allowed the concentration of the molecules in the solid-solution mixture of **6** to be determined (such an approach was used to refine the structure of **7**, see below).

Therefore, the crystal of **6** was mixed and consisted of molecules of **4** and **5**. They were present in the crystal in a 0.15:0.85 ratio, respectively.

The geometric parameters of the molecules in the molecular structure of **6** did not differ from those in that of **5**. Therefore, an analogous disorder of C10 and C11 was observed. Refinement of the structure using the FVAR instruction showed that the molecules in the two-component crystal of **6** also had two equal populations of the tetramethylene conformers.

Compound **4** was added to the reaction mixture of **6** in a 1:10 ratio in order to obtain two-component cystals (solid solutions) with different ratios. A crystal of **7** that was grown from MeOH contained two components. However, the second component, 6-bromo-4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline, contributed only small quantities to the formation of the mixed crystal (solid solution). Traces of the second component appeared in the HPTLC. This feature appeared in the XSA in the difference electron-density (ED) synthesis of the last refinement cycles. The asymmetric unit of **7** included two alkaloid molecules. Least-squares refinement of the populations of the two approximately equal positions for the Br atom indicated that the ratio of the components (**4** and **5**) involved in the crystal was 0.97:0.03.

The structure of **7** also showed disorder of C10, C11 and C10′, C11′ of the tetramethylene moiety. However, in contrast with **5** and **6**, single positions of C10 and C11 predominated. The population of the C10 and C11 positions (C10A, C11A) and C10′, C11′ (C10B, C11B) had ratios for the two independent molecules of 0.83:0.17 and 0.89:0.11, respectively.

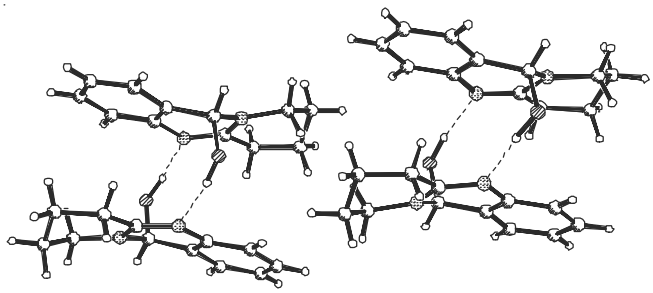

Fig. 2. Formation of associates in the crystal of **7** (equivalent methylene positions are not shown).

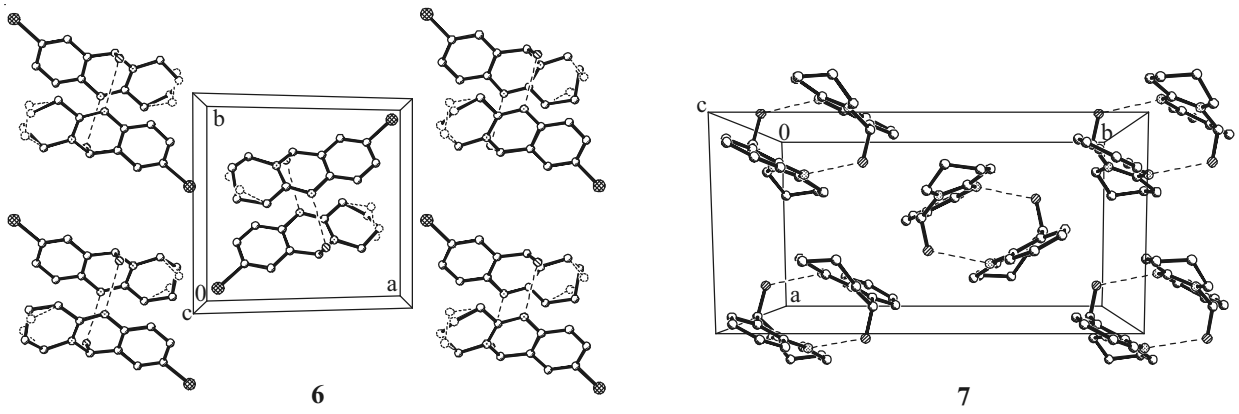

Fig. 3. Molecular packing in crystals of **6** and **7** (equivalent methylene positions are omitted).

The crystal structures of **5**, **6**, and **7** showed that enantiomers, the starting molecule and its transformation by a center of symmetry, in all structures formed a framework (associate) through opposed O–H...N1 H-bonds. Figure 2 shows this associate using **7** as an example. The H-bond parameters in the structures of **5**, **6**, and **7** were distances O...N1 2.801(5) Å, 2.792(9), 2.816 (5), 2.719(5) and H...N1 1.98, 1.98, 2.00, 1.99; angles O–H...N1 175°, 172, 170, and 163 for **5**, **6**, and **7**, respectively. The formation of the associate led to a common twist of the tricyclic molecular system around the N1 and C4 binding points. This could be seen by calculating the angle between planar fragments C4, C4a, C5, C6, C7, C8, C8a, N1 and N1, C2, N3, C4, C9, C12. This angle in the structures of **5** and **6** was 15.7° and 15.6, respectively; for the two independent molecules in **7**, 19.3° and 16.2 Such twisting of the tricyclic system was also observed in mixed crystals of 6-bromopeganol and peganol [1] where analogous centrosymmetric associates were formed. However, a similar twist was not observed in other known tricyclic quinazolines that do not form such associates. In particular, this angle was only 3.5° in 2,3-tetramethylene-3,4-dihydroquinazoline hydrochloride dihydrate [5].

These associates in the crystal of **5** were related through a Br···Br (3.604 Å) interaction. The crystal structures of **5** and **6** were isomorphous. This was evident from the similarity of the unit-cell constants and the identical space group. Therefore, the crystal of **6** also had a Br···Br interaction (3.544 Å) (Fig. 3).

The two independent associates in the crystal structure of **7** were situated at van-der-Waals distances (Fig. 3).

A similar formation of associates was observed previously in the related alkaloid peganol and bromopeganol in their mixed crystals [1, 6]. Therefore, it can be assumed that 6-bromo-4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline can also form mixed crystals (solid solutions) with 4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline in other ratios.

TABLE 1. Principal Crystallographic Parameters and Characteristics of X-ray Structure Analysis for **5**, **6**, and **7**

Parameters	**5**	**6**	**7**
Molecular formula	$C_{12}H_{13}N_2OBr$	$C_{12}H_{13}N_2OBr_{0.86}$	$C_{12}H_{13}N_2OBr_{0.03}$
MW/g·mol^{-1}	281.14	269.56	204.07
System	Monoclinic	Monoclinic	Monoclinic
Temperature, K	300 (1)	300 (1)	293 (1)
Wavelength	0.71073	0.71073	1.54184
Space group	P 2_1/c	P 2_1/c	P 2_1/n
Z	4	4	8
a, Å	11.246 (7)	11.181 (7)	7.617 (2)
b, Å	10.218 (10)	10.162 (8)	14.639 (3)
c, Å	10.743 (8)	10.747 (8)	18.743 (4)
α	90.00	90.00	90.00
β	112.57 (5)	112.36 (5)	101.17 (3)
γ	90.00	90.00	90.00
V, Å^3	1140.0 (16)	1129.3 (15)	2050.4 (8)
ρ, g/cm^3	1.638	1.586	1.322
Crystal size, mm	0.60×0.25×0.10	0.50×0.40×0.25	0.40×0.20×0.15
Scan range 2θ	1.96≤θ≤26.0°	1.97≤θ≤25.0°	3.86≤θ≤55.0°
$\mu_{exp.}$, cm^{-1}	3.585	3.106	0.816
Index range	0≤*h*≤13, –12≤*k*≤0, –13≤*l*≤12	0≤*h*≤13, –12≤*k*≤0, –12≤*l*≤11	–8≤*h*≤7, 0≤*k*≤15, 0≤*l*≤19
Number of reflections	2242	1981	2544
Number of reflections with I>2σ (I)	1631	1229	1602
R_1 (I>2σ (I) and total)	0.0531 (0.0876)	0.0906 (0.1587)	0.0647 (0.1131)
wR_2	0.0845 (0.0983)	0.1585 (0.1882)	0.1369 (0.1691)
GOOF	1.189	1.225	1.141
Difference ED peaks, e. Å^{-3})	0.312 and –0.362	0.506 and –0.453	0.121 and –0.150
CCDC	709176	709175	709174

EXPERIMENTAL

IR spectra in mineral oil were recorded on a Perkin–Elmer Model 2000 Fourier-IR spectrometer. Mass spectra were recorded in MX-1310 and Ms25 30 Rs (Kratos) spectrometers at ionizing potential 70 eV, source temperature 250 and 210°C, inlet temperature 120°C, and accelerating potential 4 kV. PMR spectra were taken from a Unity-400+ spectrometer at operating frequency 400 MHz for H nuclei. Samples were prepared in CD_3OD with TMS internal standard (0 ppm). Spectra were recorded at room temperature.

X-ray Structure Analysis. Unit-cell constants of crystals of **5**, **6**, and **7** were determined and refined on a Stoe Stadi-4 diffractometer (293 K, graphite monochromator). Table 1 lists the principal parameters of the XSA and the calculations. A three-dimensional data set of reflections was obtained on the same diffractometer by the ω/2θ-scanning method. Absorption corrections were applied to crystals of **5** and **7** using the Psi-Scan method.

The structures of **5**, **6**, and **7** were solved by direct methods using the program set SHELXS-97. The structures were refined using the SHELXL-97 program. All nonhydrogen atoms were refined by full-matrix least-squares methods (over F^2). Disorder of C10 and C11 in the structures of **5**, **6**, and **7** was refined using the FVAR instruction. Positions of H atoms were found geometrically and refined using fixed isotropic thermal parameters $U_{iso} = nU_{eq}$, where n = 1.5 for hydroxyls and 1.2 for others and *Ueq* is the equivalent isotropic thermal parameter of the corresponding C atoms. Lengths of identical bonds in the tetramethylene moiety in the structures of **5**, **6**, and **7** were significantly different from each other and the accepted value of 1.54Å. Therefore, the tetramethylene moiety was refined by the accepted DFIX values. Data from the XSA were deposited as CIF files in the Cambridge Crystallographic Data Centre (CCDC).

The compounds were analyzed by HPTLC on a CAMAG instrument. Samples (1 mg, accurate weight) were prepared by dissolution in MeOH (1 mL), placement on Sorbfil PTSKh-AF-UF plates of solution (4 μL) using a Linomat 5. The width of the tracks was 3 mm; distance between them, 7 mm. The eluent was $CHCl_3$:MeOH:$(CH_3)_2CO$:hexane (4:1:4:4). Elution was carried out in a dark glass chamber (distance 6 cm). Plates after elution were dried in air for 10 min. Chromatographic plates were scanned on an HPTLC Scanner 3 using the WinCATS program at wavelength 254 nm.

2,3-Tetramethylene-3,4-dihydroquinazol-4-one and -quinazoline were synthesized by the literature method [7].

Reaction of 2 with BSI: a) 1:1 ratio. Synthesis of 6-Bromo-2,3-tetramethylene-3,4-dihydroquinazoline (3). Compound **2** (0.44 g, 2 mmol) was placed in a 100-mL Ehrlenmeyer flask, dissolved in distilled water (30 mL), treated with BSI (0.36 g, 2 mmol), and stirred using a magnetic stirrer. The mixture turned light yellow after 15 min. Stirring was continued for 5 h. A suspension formed and succinimide floated on the water. The reaction mixture was treated with aqueous NaOH (50 mL, 5%) and stirred for 10–15 min. A precipitate formed upon standing, was filtered off and washed thoroughly with water until the rinsings were neutral, and was dried. Recrystallization from MeOH:H_2O (5:1) afforded **3** (0.24 g, 45%), mp 172–175°C, R_f 0.27.

IR spectrum (ν, cm^{-1}): 1600 (N=C), 817 (C–Br). PMR spectrum (δ, ppm, J/Hz): 4.70 (2H, s, 4-CH_2), 3.39 (2H, t, J = 6.0, α-CH_2), 1.80 –2.00 (4H, m, β-CH_2, γ-CH_2), 2.68 (2H, t, J = 6.0, δ-CH_2), 6.89 (1H, d, J = 8.0, H-8), 7.32 (1H, d, J = 2.0, H-5), 7.41 (1H, dd, J = 8.0, 2.0, H-7).

b) 1:3 ratio. A mixture of **6** consisting of 85% 6-bromo-4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline and 15% 4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline was obtained analogously as above from **2** (0.44 g, 2 mmol) and BSI (1.07 g, 6 mmol).

c) 1:4 ratio. The abvoe method was used with **2** (0.44 g, 2 mmol) and BSI (1.43 g, 8 mmol) to produce 6-bromo-4-hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline **(5)** (0.53 g, 78.3%), mp 164–166°C, R_f 0.52.

IR spectrum (ν, cm^{-1}): 1669 (N=C), 828 (C–Br). PMR spectrum (δ, ppm, J/Hz): 4.40 (1H, s, 4-OH), 5.80 (1H, s, H-4), 3.30–3.70 (2H, m, α-CH_2), 2.40–2.80 (2H, m, δ-CH_2), 1.75–2.05 (4H, m, β-CH_2, γ-CH_2), 6.80 (1H, d, J = 6.0, H-8), 7.35 (1H, d, J = 4.0, H-5), 7.20 (1H, dd, J = 8.0, 2.0, H-7).

Mass spectrum (*m*/*z*, %): 281 (5), 279 (19), 265 (27), 262 (100), 247 (3), 224 (8), 184 (14), 171 (7), 155 (7), 129 (6).

Synthesis of 4-Hydroxy-2,3-tetramethylene-3,4-dihydroquinazoline (4). Compound **2** (0.22 g, 1 mmol) was placed into a four-necked flask equipped with two dropping funnels, a reflux condenser, and a mechanical stirrer and was dissolved with stirring in water (10 mL). An aqueous solution (5%) of $KMnO_4$ (127 mg) was placed into one of the dropping funnels; H_2SO_4 solution (10%), into the other. The reaction mixture was stirred, treated dropwise from the funnels with $KMnO_4$ and H_2SO_4 over 30 min keeping the pH at 2–3, stirred another 30 min, and treated with NaOH solution (5%) until the solution was basic. The mixture was stirred for 1 h. The resulting precipitate was filtered off, washed thoroughly with water until the rinsings were neutral, and dried. Recrystallization from aqueous MeOH afforded **4** (0.11 g, 54.5%), mp 206–208°C, R_f 0.31.

IR spectrum (ν, cm^{-1}): 1673 (N=C). PMR spectrum (δ, ppm, J/Hz): 4.55 (1H, s, 4-OH), 5.90 (1H, s, H-4), 3.20–3.80 (2H, m, α-CH_2), 2.55–2.80 (2H, m, δ-CH_2), 1.70–2.00 (4H, m, β-CH_2, γ-CH_2), 7.05 (1H, d, J = 8.0, H-8), 7.11 (1H, td, J = 8.0, 2.0, H-7), 7.21 (1H, dd, J = 8.0, 1.5, H-5), 7.30 (1H, td, J = 8.0, 1.2, H-6).

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