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SYNTHESIS AND STRUCTURE OF TRICYCLIC QUINAZOLINE ALKALOID OXALATES

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Oxalates of the alkaloids deoxyvasicinone, 2,3-tetra-, and their seven-membered analog 2,3-pentamethylen-3,4-dihydroquinazol-4-one and the complex of 2,3-pentamethylen-3,4-dihydroquinazol-4-one hydrochloride with oxalic acid were synthesized. It was found that 2:1, 2:1, and 1:1 alkaloid:oxalic acid complexes, respectively, were formed. The last complex had 2,3-pentamethylen-3,4-dihydroquinazol-4-one, oxalic acid, and HCl in a 2:1:2 ratio, respectively. X-ray crystal structures of single crystals were performed. The oxalate of 2,3-pentamethylen-3,4-dihydroquinazol-4-one and its hydrochloride formed salts with a protonated N1 atom and involvement of only one hydroxyl. The other alkaloids formed a complex with oxalic acid through N1...H–O H-bonds involving both acid hydroxyls.

Key words: deoxyvasicinone, 2,3-tetra-, -pentamethylene-3,4-dihydroquinazol-4-one, oxalates, x-ray crystal structure, complexes, protonation, H-bonds.

Natural tricyclic quinazolines and quinazol-4-ones and their synthetic analogs possess various physiological activities and are widely used in medicine as the water-soluble salts [1, 2].

We previously observed during a study of the crystal structure of deoxypeganine (DOP) oxalate that one of the oxalic acid (OA) hydroxyls was involved in protonation of DOP whereas the second free carboxylic acid formed an intermolecular H-bond with another OA molecule. The crystals contained a 1:1 ratio of alkaloid and acid [3].

The chemical and physicochemical properties of tricyclic quinazoline alkaloids differ sharply from those of the corresponding quinazolone alkaloids [1]. Thus, the aromatic rings of both systems have different nucleophilicities, which affects electrophilic substitution reactions. For example, deoxyvasicinone is nitrated only in the 6-position and a second nitro group cannot be introduced [4]. However, DOP can be nitrated at both C-6 and C-8 to give 6,8-dinitro-DOP.

These quinazoline alkaloids, their homologs, and the corresponding quinazolones also have different basicities. Quinazolines are more basic than quinazolone derivatives [5]. Therefore, complexation of tricyclic quinazolones with dicarboxylic acids, in particular oxalic acid, seemed especially interesting. Protonation of the alkaloid by hydrogens of both OA hydroxyls or by one hydrogen could occur, i.e., formation of 1:1 or 2:1 salts. Formation of complexes without protonation of the base was also possible.

In order to answer these questions, we synthesized complexes of OA with deoxyvasicinone (DOV, **1**), 2,3-tetramethylene-3,4-dihydroquinazol-4-one (**2**), and 2,3-pentamethylene-3,4-dehydroquinazol-4-one (**3**). The resulting single crystals were examined by x-ray diffraction. Crystals of the OA complex of 2,3-pentamethylene-3,4-dihydroquinazol-4-one hydrochloride (**4**) were also prepared and analyzed for comparison.

The x-ray crystal structures showed that each complex with OA (**1**, **2**, **3**) had a unique structure in the crystal with respect to formation of intermolecular H-bonds and salt formation. Figure 1 shows the resulting complexes, the ratio of alkaloid and acid molecules involved, and the arbitrary position of the labile H atom in the studied complexes.

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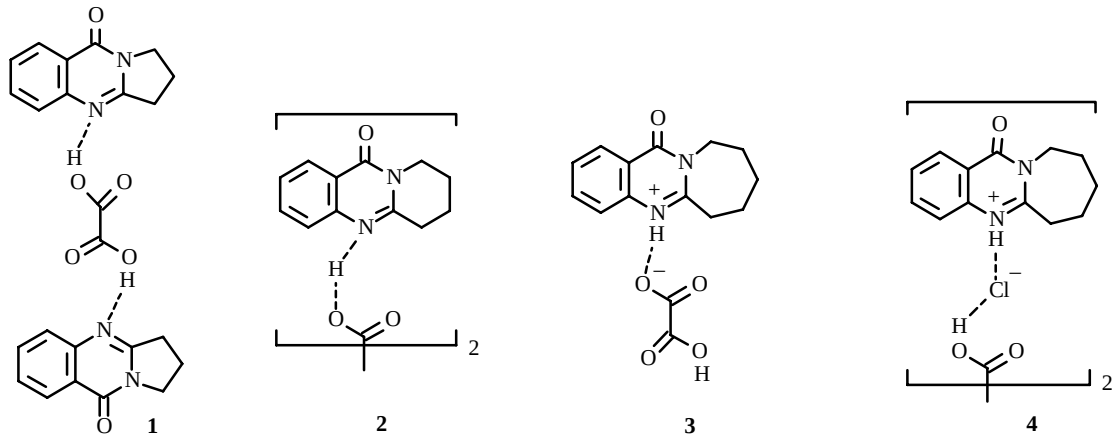

Fig. 1. Diagrams of complexes according to x-ray crystal structures.

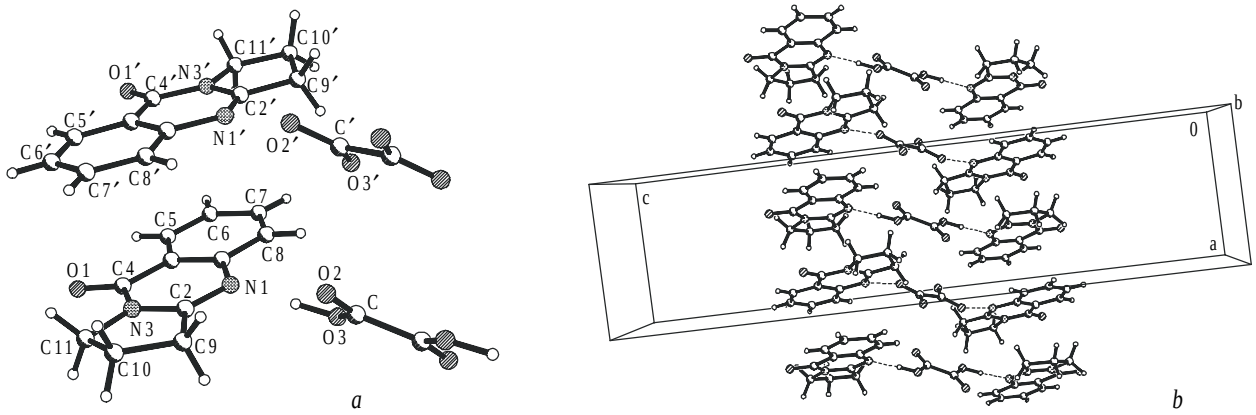

Fig. 2. Structure of **1**: asymmetric atom numbering (a) and molecular packing in the crystal (b).

Judging from the x-ray structure, the complex of DOV with OA in the crystal had two DOV and two halves of OA in the asymmetric unit (Fig. 2a). The location of the experimentally determined H atoms of OA revealed that **1** existed in the crystal as the base, i.e., in this instance the expected protonation of N1 by a H atom from an OA hydroxyl did not occur. The hydroxyl H atom of one of the crystallographically independent halves of OA was located on O3 [H–O3 distance 1.00(6) Å]. However, the hydroxyl H atom of the other independent OA half could not be located experimentally although peaks in an electron-density difference synthesis that corresponded to a H atom were disordered near O2′ and O3′ of OA. Transformation (center of symmetry) of both independent halves of OA and DOV molecules formed two chemically equivalent (but crystallographically different) complexes (Fig. 2, molecular packing).

Thus, a complex formed in the crystal of **1** through H-bonds between N1 of two alkaloid molecules and both OH groups of a single OA molecule (alkaloid:acid ratio 2:1). The parameters of the H-bonds were as follows (Fig. 2): distance O3...N1, 2.676(5) Å; H...N1, 1.69(7); angle O3–H...N1, 171(6)°. The O2′...N1′ distance in the second (upper) independent part was 2.780(3) Å.

The structure of the complex of 2,3-tetramethylene-3,4-dihydroquinazol-4-one with OA (**2**) did not differ markedly from that of **1**. The asymmetric unit contained a molecule of 2,3-tetramethylene-3,4-dihydroquinazol-4-one and one carboxylic acid of OA, i.e., the complex had a 2:1 ratio of alkaloid:acid (Fig. 3). The nature of the intermolecular H-bond was also similar to that of **1**. Two (one transformed by a center of symmetry) OH groups of OA were bonded to N1 atoms of the base through H-bonds to form the complex. However, the experimentally found H atom of OA was situated between N1 of the base [distance N1...H1, 1.51(5) Å] and O3 of OA [O3...H1, 1.15(5) Å] but closer to the OA oxygen.

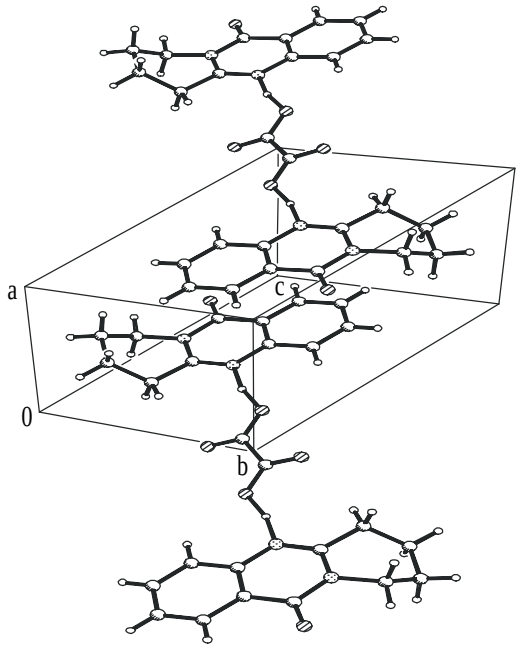

Fig. 3. Crystal structure of **2**.

The structure of the complex of 2,3-pentamethylene-3,4-dihydroquinazol-4-one with OA (**3**) differed from those of **1** and **2**. In this instance, N1 was protonated by one H atom of an OA hydroxyl to give a 1:1 alkaloid:acid complex. The x-ray structure located one of the OA H atoms on N1 of the base with a distance N1–H of 0.91(4) Å.

Therefore, the nature of the intermolecular H-bonds differed from those observed in the above structures. Crystals of **3** contained O–H...O and N–H...O H-bonds. The parameters of the H-bonds were as follows: distance O3...O3′, 2.638(5); H3...O3′, 1.76(5) Å; angle O3–H3...O3′, 170(4)°; and N1...O2′, 2.631(5); H1...O2′, 1.72(5) Å, angle N1–H1...O2′, 174(5)°. Thus, the H-bonds in the crystal of **3** formed an infinite chain along the crystallographic *b* axis, as was noted for the complex of DOP with OA [3].

Adding aqueous HCl to 2,3-pentamethylene-3,4-dihydroquinazol-4-one oxalate gave its hydrochloride (**4**), i.e., a complex involving HCl was formed. The asymmetric unit in the crystal structure included a cation of the protonated base, a chloride anion, and half (one of the carboxylic acids) of an OA. The OA was bonded on two sides through O–H...Cl H-bonds (a center of symmetry was located in the middle of the OA C–C bond); the Cl anion, to the protonated quinazol-4-one (Fig. 4). The parameters of these interactions were as follows: distance Cl...N1, 3.069(3); Cl...H1, 2.23(4) Å; angle Cl...H1–N1, 168(4)°; Cl...O3, 2.946(3), Cl...H3, 1.84(7) Å; angle Cl...H3–O3, 169(5)°. The complex was formed via transformation of the aforementioned asymmetric unit. Therefore, the alkaloid:OA:HCl ratio in the crystal was 2:1:2.

The bond lengths of the N1=C2–N3 fragment of the alkaloids and O–C=O of the OA confirmed the above description of **1**-**4** (Table 1). For example, the average distances N1=C2 (1.291 Å) and C2–N3 (1.383 Å) for starting deoxyvasicinone, 2,3-tetra-, and 2,3-pentamethylene-3,4-dihydroquinazol-4-ones [6] were identical within experimental uncertainty to those observed in **1** and **2**. On the other hand, the distances N1=C2 and C2–N3 in **3** and **4** were similar to the averages (1.310 and 1.335, respectively) observed in salts [6]. However, the bond lengths of one OA carboxylic acid of **1** (Table 1) did not fall within the range noted above.

Such differences in the complexation of DOV, 2,3-tetra- and -pentamethylene-3,4-dihydroquinazol-4-ones were apparently due to the relative difference in the charge on N1, i.e., to the basicity of the molecule.

TABLE 1. Bond Lengths r (Å) and Angles ω (deg) in **1**-**4**

Bond	r**1**	r**1′**	r**2**	r**3**	r**4**
O(1)-C(4)	1.227 (5)	1.224 (5)	1.215 (3)	1.207 (6)	1.214 (4)
N(1)-C(2)	1.295 (5)	1.298 (6)	1.299 (3)	1.314 (6)	1.320 (4)
N(1)-C(8a)	1.404 (6)	1.404 (5)	1.394 (3)	1.389 (6)	1.396 (4)
C(2)-N(3)	1.367 (5)	1.357 (6)	1.369 (3)	1.344 (5)	1.336 (4)
C(2)-C(9)	1.494 (6)	1.504 (6)	1.492 (4)	1.490 (6)	1.483 (4)
N(3)-C(4)	1.389 (6)	1.388 (6)	1.397 (3)	1.418 (6)	1.424 (4)
N(3)-C(11)	1.480 (6)	1.479 (6)			
N(3)-C(12)			1.486 (3)		
N(3)-C(13)				1.479 (5)	1.494 (4)
C(4)-C(4a)	1.460 (6)	1.459 (7)	1.460 (4)	1.459 (6)	1.454 (5)
C(4A)-C(5)	1.392 (6)	1.412 (6)	1.396 (4)	1.400 (6)	1.400 (5)
C(4A)-C(8a)	1.400 (6)	1.390 (6)	1.398 (4)	1.381 (6)	1.387 (4)
C(5)-C(6)	1.366 (7)	1.368 (7)	1.368 (4)	1.374 (7)	1.371 (5)
C(6)-C(7)	1.396 (7)	1.374 (7)	1.395 (5)	1.383 (8)	1.379 (5)
C(7)-C(8)	1.370 (7)	1.388 (6)	1.363 (4)	1.378 (7)	1.377 (5)
C(8)-C(8a)	1.408 (6)	1.403 (6)	1.398 (4)	1.390 (6)	1.392 (4)
C(9)-C(10)	1.525 (6)	1.506 (7)	1.523 (4)	1.537 (6)	1.525 (5)
C(10)-C(11)	1.506 (7)	1.510 (7)	1.520 (4)	1.515 (6)	1.524 (5)
C(11)-C(12)			1.504 (4)	1.509 (6)	1.519 (5)
C(12)-C(13)				1.521 (6)	1.505 (5)
O(2)-C		1.202 (5)	1.188 (3)	1.193 (5)	1.194 (4)
O(3)-C		1.315 (5)	1.276 (3)	1.289 (5)	1.310 (4)
C-C#1		1.527 (8)	1.532 (5)	1.541 (6)	1.534 (7)
O(2′)-C′		1.266 (8)		1.244 (5)	
O(3′)-C′		1.247 (8)		1.229 (5)	
C′-C′#2		1.496 (11)			

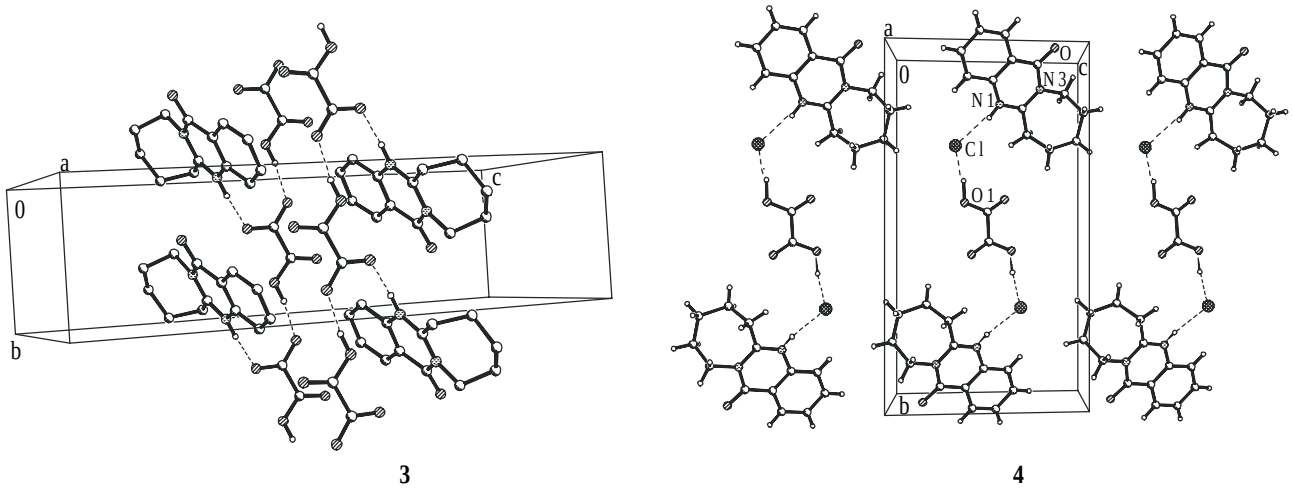

Fig. 4. Molecular packing in **3** and **4** (H atoms involved in H-bonds are shown for **3**).

Thus, H-bonds between N1 in **1** and **2** and both hydroxyls of OA formed 2:1 alkaloid:OA complexes for DOV and 2,3-tetra-3,4-dihydroquinazol-4-one with OA. The N1 nitrogen was protonated by the H atom from one of the hydroxyls for 2,3-pentamethylene-3,4-dihydroquinazol-4-one and its hydrochloride. Then the second OA hydroxyl was bonded to the other OA molecule through a H-bond.

The base was protonated by the HCl proton in the 2,3-pentamethylene-3,4-dihydroquinazol-4-one hydrochloride complex with OA (base + HCl + OA). The chloride formed an intermolecular H-bond with the OA hydroxyl.

TABLE 2. Crystallographic and X-ray Structure Data for **1-4**

	1	**2**	**3**	**4**
Molecular formula	$2(C_{11}H_{10}N_2O)\cdot C_2H_2O_4$	$C_{12}H_{12}N_2O\cdot 0.5(C_2H_2O_4)$	$C_{13}H_{14}N_2O\cdot C_2H_2O_4$	$C_{13}H_{14}N_2O\cdot HCl\cdot 0.5(C_2H_2O_4)$
MW, g/mol	462.46	245.25	304.30	295.74
Space group	P 2_1/n, Z = 4	P-1, Z = 2	P 2_1/n, Z = 4	P 2_1/n, Z = 4
a, Å	7.7580 (16)	7.2530 (15)	10.991 (2)	8.0680 (16)
b, Å	8.7060 (17)	8.6370 (17)	5.8790 (12)	17.898 (4)
c, Å	32.104 (6)	9.914 (2)	22.179 (4)	9.872 (2)
α	90	78.69 (3)	90.00	90.00
β	90.84 (3)	79.76 (3)	94.00 (3)	97.40 (3)
γ	90	69.87 (3)	90.00	90.00
V, $Å^3$	2168.1 (8)	567.7 (2)	1429.6 (5)	1413.7 (5)
ρ, g/cm^3	1.417	1.435	1.414	1.390
Crystal size, mm	0.65×0.50×0.20	0.65×0.30×0.10	1.00×0.20×0.20	0.75×0.30×0.30
2θ scan range	2.5≤θ≤26.0°	2.1≤θ≤25.2°	1.8≤θ≤22.6°	2.3≤θ≤27.5°
μ_{exp}, cm^{-1}	0.104	0.104	0.107	0.279
Number of reflections	3159	2006	1876	3124
Number of reflections with **I** > 2σ(**I**)	2090	1457	1168	2039
R1 (**I**>2σ (**I**) and total)	0.0776 (0.1522)	0.0563 (0.0823)	0.0647 (0.1278)	0.0687 (0.1180)
wR2	0.1194 (0.1744)	0.1327 (0.1529)	0.0914 (0.1147)	0.1244 (0.1290)
S	1.060	1.069	1.186	1.130
Difference peaks electron density, e. $Å^3$	0.33 and -0.33	0.22 and -0.21	0.21 and -0.21	0.25 and -0.24

Differences in IR spectra of the starting DOV, 2,3-tetra-, and -pentamethylene-3,4-dihydroquinazol-4-ones and their OA complexes (1:1 and 2:1 ratios) and 2,3-pentamethylene-3,4-dihydroquinazol-4-one hydrochloride confirmed these observations. The IR spectra showed several absorption bands of medium strength at 2500-2800 cm^{-1}, which are characteristic of the N^+H group [7], for 2,3-pentamethylene-3,4-dihydroquinazol-4-one oxalate and the complex of 2,3-pentamethylene-3,4-dihydroquinazol-4-one hydrochloride with OA. These absorption bands are missing in mixed crystals of DOV and 2,3-tetramethylene-3,4-dihydroquinazol-4-one with OA.

EXPERIMENTAL

DOV Oxalate (1). A solution of DOV and OA in acetone with 2:1 and 1:1 molar ratios was slowly evaporated at room temperature. In both instances colorless prismatic single crystals with the same mp 150-152°C were formed and used for x-ray analysis.

2,3-Tetramethylene-3,4-dihydroquinazol-4-one Oxalate (2). A solution of 2,3-tetramethylene-3,4-dihydroquinazol-4-one (40 mg) and OA (16 mg) in ethanol (1:1 molar ratio) was slowly evaporated at room temperature to produce colorless single crystals as plates with mp 144-148°C.

2,3-Pentamethylene-3,4-dihydroquinazol-4-one Oxalate (3). 2,3-Pentamethylene-3,4-dihydroquinazol-4-one (11 mg) was dissolved in acetone and treated with OA (5 mg) in acetone (1:1 molar ratio). Slow evaporation of the heated solution in a refrigerator produced colorless single crystals as plates with mp 143-146°C.

Complex of 2,3-Pentamethylene-3,4-dihydroquinazol-4-one with OA (4). A solution of 2,3-pentamethylen-3,4-dihydroquinazol-4-one (10.5 mg) in acetone was treated with OA (5 mg) in acetone (1:1 molar ratio) and dilute HCl solution (1 drop, 1:1). Slow evaporation of the solution in a refrigerator produced yellow single crystals as prisms with mp 130-133°C.

X-ray Crystal Structure. Unit-cell constants and intensities of reflections were determined on a STOE Stadi-4 four-circle diffractometer (θ-2θ-scanning) using Mo Kα-radiation (graphite monochromator). Absorption corrections were not applied. Table 2 gives the principal crystallographic and x-ray structure parameters.

The structures were solved by direct methods using the SHELXS-97 programs and were refined by isotropic and anisotropic full-matrix least-squares methods using the SHELXL-97 programs. Positions of H atoms were found geometrically

and were refined with fixed isotropic thermal parameters U_{iso} = nU_{eq}, where n = 1.5 for methyls and 1.2 for others and U_{eq} is the equivalent isotropic thermal parameter of the corresponding C atoms. H atoms of OA hydroxyls in **1**, **2**, and **4** and of N1 of the alkaloid in **3** and **4** were found in a difference electron-density synthesis and refined isotropically.

The data from the x-ray crystal structures were deposited as CIF files in the Cambridge Crystallographic Data Center (registry No. CCDC 634572-634575).

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