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A REINVESTIGATION OF THE REACTION OF N-(2-BROMOETHYL)ISATOIC ANHYDRIDE WITH METHYLAMINE. ISOLATION AND CRYSTAL STRUCTURE OF 1-(2-HYDROXYETHYL)-3-METHYL-2,4-(1H,3H)-QUINAZOLINEDIONE

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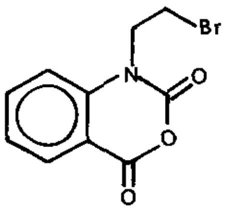
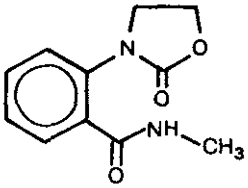
Abstract - The reaction of N-(2-bromoethyl)isatoic anhydride with methylamine affords 1-(2-hydroxyethyl)-3-methyl-2,4-(1H,3H)-quinazolinedione, the structure of which has been determined by single crystal X-ray diffraction.

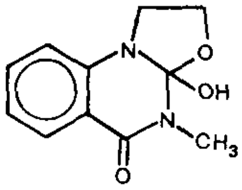
In the context of our studies on the conformation and ring-chain tautomerism of 9- and 10-membered cyclotripeptides[1], the new heterocyclic system (4) described by Barcza et al.[2] caught our interest. The 9-membered ring of 2,3-dihydro-6-methyl-4,1,6-benzoxadiazonine-5,7-(1H,6H)-dione (4) contains in fact a free amino group (N-1) and a potentially reactive N-acylurethane carbonyl (C-5) suitably located for studying endoannular interactions and related tetrahedral adducts.

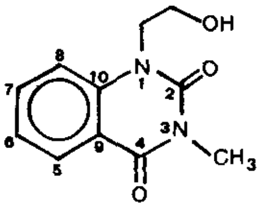
4,1,6-Benzoxadiazonine (4) was obtained by treating N-(2-bromoethyl)isatoic anhydride (1) with methylamine[2]. According to the proposed reaction mechanism[2], oxazolidinylbenzamide (2) is the species initially formed; this compound, however, is an elusive intermediate which reacts further to give, through the tetrahedral adduct (3), a new heterocyclic system to which structure (4) was assigned on the basis of ^{1}H-nmr and ir data. The alternative breakdown of the adduct (3) producing N-(2-hydroxyethyl)quinazolinedione (5), the ring-chain tautomer of (4), is not discussed by the authors.

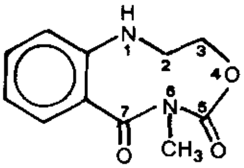
We repeated the reaction of (1) with methylamine by following the procedure of Barcza et al.[2] Melting point, ir absorptions and ^{1}H-nmr data of the compound isolated by us[3] are in accordance with the corresponding data reported for (4)[4]. The reaction product, however, does not show basic properties and gives an O-acetyl-


(1)


(2)


(3)


(5)


(4)

derivative when treated with acetic anhydride/pyridine. Moreover the ir carbonyl frequency (ν_{CO}= 1700-1690 cm^{-1}) seems in accordance with (5) and rather low for a cyclic N-acylurethane such as (4)[5]. Since chemical methods are in general unreliable for the determination of the structure of ring-chain tautomeric compounds and the reported ^{1}H-nmr data are not decisive to discriminate between (4) and (5), we decided to ascertain the structure of the reaction product by X-ray crystallographic analysis. The molecular structure reported below shows that the isolated product does not correspond to the expected benzoxadiazonine (4) but to its ring-chain tautomer (5).

Crystal structure of 1-(2-hydroxyethyl)-3-methyl-2,4-(1H,3H)-quinazolinedione (5). Suitable single crystals of (5) were obtained by slow evaporation from ethyl acetate[6]. Crystal data: $C_{11}H_{12}N_2O_3$, M=220.2, tetragonal, s.g. P $\bar{4}2_1c$, Z=8, a=b=17.008 (5), c=7.081(3) Å, V=2048(1)$Å^3$, D_c=1.43 g/cm^3, F(000)=928, λ(Cu-Kα)=1.5418 Å, μ(Cu-Kα)=0.9 mm^{-1}, R=0.044 and R_w=0.065 for 1023 observed independent reflections with $I > 1.5\sigma(I)$. Intensity data were recorded on an automatic Syntex $P2_1$ diffractometer equipped with Cu-Kα radiation up to a 2ϑ value of 138° by the ϑ-2ϑ scan technique. The structure has been solved by direct methods using the programme MULTAN 80[7]. An E-map computed with the phases of the set having the highest figures of merit revealed the non hydrogen atoms. A difference Fourier map, computed after isotropic refinement by full-matrix least-squares method, showed a residual electronic density peak of ca. 2 e·$Å^{-3}$ in the vicinity of the hydroxyl group of the N-hydroxyethyl chain. This was interpreted as due to a secondary conformation assumed by the terminal hydroxyl. Refinement was then continued anisotropically, assuming two different positions for the hydroxylic oxygen, with 3/4 and 1/4 occupancy factor respectively. A successive Fourier difference synthesis allowed to detect the hydrogen atoms.

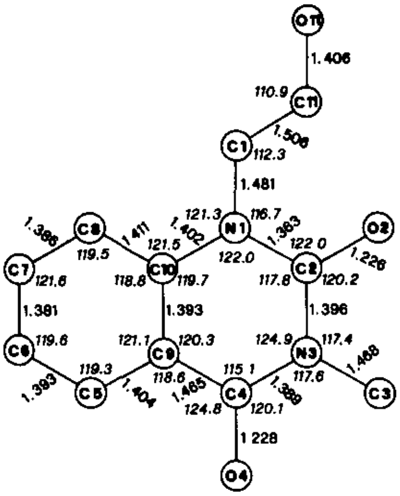


Fig. 1

Atomic numbering, valence bond lengths and angles of (5).

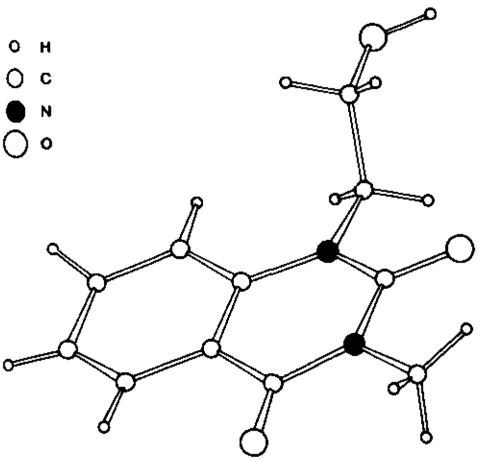


Fig. 2

Perspective molecular view of (5)

The atomic numbering together with the bond lengths and angles and a perspective molecular view of compound (5) are reported in Figure 1 and 2 respectively for the major conformer. The atoms of the heterocyclic ring lie on a plane, the largest deviation from the least squares plane through these atoms, being 0.039 Å for N(3). The hydroxymethyl group is out of the plane of the heterocyclic system with the C(10)-N(1)-C(1)-C(11) torsion angle equal to 90°. In the major conformer the N(1) and O(11) atoms are trans-coplanar with the torsion angle N(1)-C(1)-C(11)-O(11)= -172°, while in the minor conformer the corresponding torsion angle is -78°. Full details of the crystal structure will be given elsewhere.

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2. S.Barcza, G.M.Coppola, and M.J.Shapiro, J.Het.Chem., 1979, **16**, 439.
3. Mp 165 - 167°C ($CHCl_3$); 60% yield; ir(nujol): 3480, 1700-1690, 1655, 1610 cm^{-1}; ir($CHCl_3$): 3480, 1700, 1655, 1610 cm^{-1}; ^1H-nmr (Varian EM-390, 90 MHz, DMSO-d_6): δ = 3.3 (3H,s,CH_3), 3.6-3.8 (2H,m,CH_2O), 4.2 (2H,t,J=6.0Hz,CH_2N), 4.9 (1H,br. t, OH), 7.15-8.2 ppm (4H,m,ArH); ^{13}C-nmr (Bruker WP 200, 50.28 MHz, $CDCl_3$): δ=161.9 (C-4), 152.1(C-2), 140.1(C-10), 135.1(C-7), 129.0(C-5), 123.1(C-6), 115.6(C-9), 113.9(C-8), 60.6(CH_2O), 46.0(CH_2-N), 28.4 ppm (CH_3).
   ^1H- and ^{13}C-nmr spectra do not show evidence of ring-chain tautomeric equilibria. Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.05; H, 5.52; N, 12.68%.
4. Mp 166-168°C ($CHCl_3$); ir(nujol): 3480, 1685, 1640 cm^{-1}; ^1H-nmr (60 MHz, DMSO-d_6): δ = 3.3 (3H,s), 3.7 (2H,m), 4.2 (2H,t), 4.9 (1H,br.t), 7.1-8.2 ppm (4H,m). See reference 2.
5. (a) N-Benzoyl-N-methyl-tert-butylurethane $C_6H_5CO-N(CH_3)-COO-Bu^t$ shows ir carbonyl frequency (nujol) at 1730 and 1670 cm^{-1} (F.Pinnen and G.Lucente, unpublished results); (b) P.A.Grieco, D.L.Flynn, and R.E.Zelle, J.Am.Chem.Soc., 1984, **106**, 6414; (c) C.Shin, Y.Yonezawa, and E.Watanabe, Tetrahedron Lett., 1985, **26**, 85.
6. These crystals show melting point and spectral data identical to those obtained from chloroform.
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