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Key indicators

Single-crystal X-ray study
 $T = 293\text{ K}$
Mean $\sigma(\text{C}-\text{C}) = 0.004\text{ \AA}$
 R factor = 0.042
 wR factor = 0.126
Data-to-parameter ratio = 12.7For details of how these key indicators were
automatically derived from the article, see
<http://journals.iucr.org/e>.The dipolar cycloaddition of methyl acrylate
to 5,6-diethyl-1-methyl-3-oxidopyrazinium

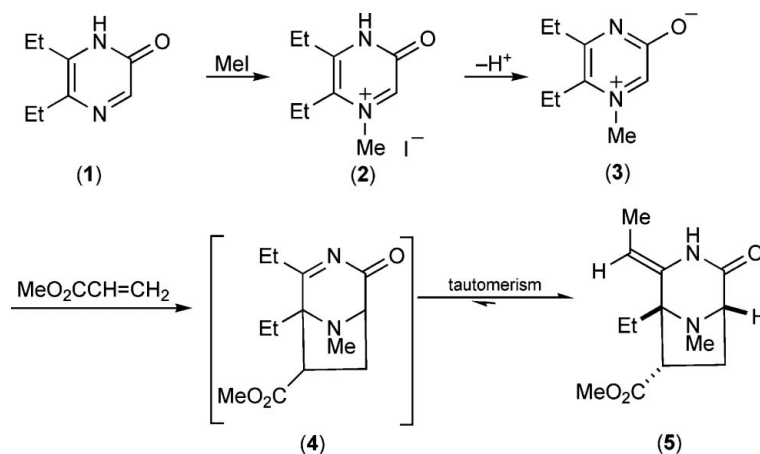
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5,6-Diethylpyrazin-2-one reacts with iodomethane to give a quaternary salt, deprotonation of which, *in situ*, liberates a 3-oxidopyrazinium which undergoes a 1,3-dipolar cycloaddition with methyl acrylate to form methyl (*Z*)-5-ethyl-4-ethylidene-8-methyl-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-*endo*-6-carboxylate. The crystal structure revealed (i) the existence of the imine product as its enamine tautomer, (ii) the *Z* geometry of the exocyclic double bond, and (iii) the *endo* orientation of the ester group. Pairwise hydrogen bonding between the NH H atom and the amide carbonyl group links the molecules into centrosymmetric dimers.

Comment

In our investigations of the 1,3-dipolar cycloaddition chemistry of 3-oxidopyraziniums (Kiss *et al.*, 1987; Allway *et al.*, 1990; Yates *et al.*, 1995; Helliwell *et al.*, 2006), we have demonstrated that these reactions efficiently produce bridged bicyclic systems – 3,8-diazabicyclo[3.2.1]octanes – which comprise key structural components of such biologically active natural products as anticancer quinocarcin (Takahashi & Tomita, 1983; Tomita *et al.*, 1983; Hirayama & Shirahata, 1983) and antibiotic lemomycin (He *et al.*, 2000).



In a series of benchmark papers by Katritzky and co-workers (for reviews, see Dennis *et al.*, 1976; Katritzky & Dennis, 1989) on the cycloadditions of 3-oxidopyridiniums, there were no examples of adduct formation using dipoles in which either one or two substituents were located on the 1,3-dipole at the future ring-junction positions. We have shown that one methyl group, so located, is not deleterious to the cycloaddition process using 1,5,6-trimethyl-3-oxidopyrazinium (Helliwell *et al.*, 2006). This report describes our investigation of the reactivity of 5,6-diethyl-1-methyl-3-oxidopyrazinium, (3), in which a larger ethyl group is located at one of the future

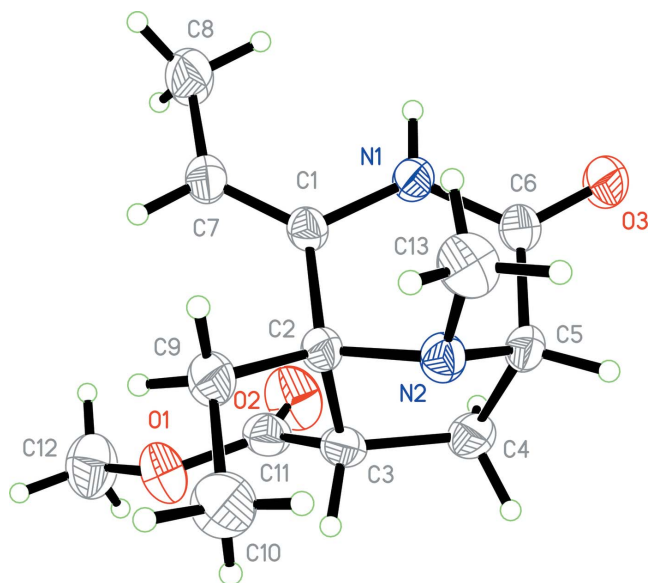


Figure 1
The molecular structure of (5), with displacement ellipsoids drawn at the 50% probability level.

ring-junction positions and, in addition, this group is adjacent to another relatively bulky ethyl group.

5,6-Diethylpyrazin-2-one, (1), was prepared by the condensation of hexane-3,4-dione with glycineamide following the established method (Jones, 1949; Karmas & Spoerri, 1952; Yates *et al.*, 1995). Reaction of (1) with iodomethane produced the methiodide (2), treatment of which with triethylamine allowed the generation of the zwitterion (3), *in situ*, and in the presence of methyl acrylate. As in all previous cases, the immediate products of such cycloadditions [(4) in this case] are not isolated but tautomerize to the more stable enamide structures, (5) in this case. Thus, the presence of even an ethyl group at a future ring-junction position does not prevent cycloaddition. It is noteworthy that, with increasing bulk, a greater proportion of *endo* isomer is formed, actually the only stereoisomer isolated in this case. The *Z* stereochemistry of the exocyclic double bond was established by the crystal structure study. Suitable crystals of the adduct were examined crystallographically, confirming the structure and stereochemistry (Fig. 1). Intermolecular hydrogen bonding between the NH H atom and the amide carbonyl group leads to the formation of centrosymmetric dimers (Table 1).

Experimental

To hexane-3,4-dione (4.80 g, 0.04 mol) in water (5 ml) was added sodium metabisulfite (7.60 g, 0.04 mol) and the mixture stirred for 1 h at room temperature. An addition compound was precipitated as a gummy solid on addition of methanol (18 ml) and ethanol (6 ml) and separated by filtration. The solid was dissolved in water (5 ml) and glycineamide hydrochloride (2.27 g, 0.02 mol) was added. The pH was then adjusted to 8 with 10 M KOH and the mixture maintained at 333–353 K for 2 h. The pH was adjusted to 10 and the mixture kept at 323–333 K for 30 min. The mixture was cooled and adjusted to pH 6 with concentrated HCl, then cooled to 273 K. 5,6-Diethylpyrazin-3-

one was precipitated as square white crystals (1.34 g, 44%; m.p. 443–445 K), δ_{H} (300 MHz, CDCl_3) 1.26 (3H, *t*, $J = 7.5$ Hz, CH_2CH_3), 1.34 (3H, *t*, $J = 7.5$ Hz, CH_2CH_3), 2.63 (2H, *q*, $J = 7.5$ Hz, CH_2CH_3), 2.66 (2H, *q*, $J = 7.5$ Hz, CH_2CH_3), 8.07 (1H, *s*, H-2), 13.32 (1H, *s*, NH); analysis found: C 62.64, H 7.95, N 16.25%; $\text{C}_8\text{H}_{12}\text{N}_2\text{O}$ requires C, 63.13; H, 7.95; N, 18.41%.

5,6-Diethylpyrazin-2-one (500 mg, 3.3 mmol) and iodomethane (1.2 ml, 16.5 mmol) were heated under reflux in acetonitrile (25 ml) under N_2 for 24 h. The solvent was removed under vacuum. The residue was extracted with CH_2Cl_2 and the solid was filtered off to give the methiodide as a greenish crystalline solid (548 mg, 57%) which was used in the next step without further purification: Analysis: δ_{H} (300 MHz, D_2O) 1.20 (3H, *t*, $J = 7.6$ Hz, CH_2CH_3), 1.25 (3H, *t*, $J = 7.6$ Hz, CH_2CH_3), 2.80 (2H, *q*, $J = 7.6$ Hz, CH_2CH_3), 2.90 (2H, *q*, $J = 7.6$ Hz, CH_2CH_3), 4.20 (3H, *s*, NCH_3), 8.15 (1H, *s*, H-2).

A solution of 1-methyl-5,6-diethylpyrazin-3-onium iodide (100 mg, 0.725 mmol) with triethylamine (0.22 ml, 1.45 mmol) and methyl acrylate (0.33 ml, 3.63 mmol) in dry acetonitrile (5 ml) was heated at reflux for 1.5 h to give an orange solution. The solvent and excess methyl acrylate were evaporated under vacuum. From the residue a pure sample of methyl 5-ethyl-8-methyl-(*Z*)-4-ethylidene-2-oxo-3,8-diazabicyclo[3.2.1]octane-6-*endo*-6-carboxylate was obtained by flash chromatography (silica, *n*-hexane–EtOAc 7:3) as colourless plates (15 mg, 9%). Analysis: δ_{H} (300 MHz, CDCl_3) 1.01 (3H, *t*, $J = 7$ Hz, CH_2CH_3), 1.56 (3H, *d*, $J = 7$ Hz, CHCH_3), 1.02 1.66 (1H, *m*, one of CH_2CH_3), 2.13 1.03 (1H, *m*, one of CH_2CH_3), 2.25 (3H, *s*, NCH_3), 1.04 2.33 (1H, *m*, H-7), 2.48 (1H, *dd*, $J = 5, 13$ Hz, H-7), 1.05 3.21 (1H, *dd*, $J = 5, 11$ Hz, H-6), 3.58 (1H, *d*, $J = 8$ Hz, H-1), 1.06 3.64 (3H, *s*, OCH_3), 4.53 (1H, *q*, $J = 7$ Hz, CHCH_3), 1.07 6.95 (1H, *s*, NH).

Crystal data

$\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_3$
 $M_r = 252.31$
Monoclinic, $P2_1/c$
 $a = 10.00$ (2) Å
 $b = 8.842$ (10) Å
 $c = 14.693$ (10) Å
 $\beta = 90.36$ (8)°
 $V = 1300$ (3) Å³

$Z = 4$
 $D_x = 1.290$ Mg m⁻³
Mo $K\alpha$ radiation
 $\mu = 0.09$ mm⁻¹
 $T = 293$ (2) K
Plate, colourless
0.4 × 0.3 × 0.2 mm

Data collection

Rigaku R-Axis diffractometer
 φ scans
Absorption correction: none
10171 measured reflections

2173 independent reflections
1840 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.042$
 $\theta_{\text{max}} = 25.0^\circ$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.042$
 $wR(F^2) = 0.126$
 $S = 1.06$
2173 reflections
171 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.078P)^2 + 0.2408P]$
where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\text{max}} < 0.001$
 $\Delta\rho_{\text{max}} = 0.18$ e Å⁻³
 $\Delta\rho_{\text{min}} = -0.18$ e Å⁻³

Table 1
Hydrogen-bond geometry (Å, °).

| $D-H\cdots A$ | $D-H$ | $H\cdots A$ | $D\cdots A$ | $D-H\cdots A$ |
|--|----------|-------------|-------------|---------------|
| $\text{N1}-\text{H1}\cdots\text{O3}^i$ | 0.89 (2) | 2.10 (2) | 2.975 (3) | 170.9 (16) |

Symmetry code: (i) $-x + 1, -y, -z + 1$.

H atoms bonded to carbon were included in calculated positions using the riding model, with C–H distances of 0.93–0.98 Å and with $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$ for methyl H atoms and $1.2U_{\text{eq}}(\text{C})$ for the other H atoms; H1 was found by difference Fourier methods and refined isotropically.

Data collection: *MSC RAXISII Control Software* (Molecular Structure Corporation, 1992); cell refinement: *DENZO* (Otwinowski & Minor, 1988); data reduction: *DENZO*; program(s) used to solve structure: *SHELXS86* (Sheldrick, 1985) and *TEXSAN* (Molecular Structure Corporation, 1995); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL* (Bruker, 2001).

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