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Structural Determination of a Dimeric Side-Product Accompanying Dihydropyrazine Preparation

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The identity of a major side-product of attempted 2,3-dihydropyrazine dehydrogenation has been elucidated using a geminal dimethyl analog [2,2,5,6-tetramethyl-2,3-dihydropyrazine (**1**)] which cannot aromatize. ^{1}H, ^{13}C NMR and GC–MS analyses were consistent with the formulation of the product as a symmetrical dimer of **1**, but did not allow unambiguous distinction between two possible isomers, each of which could exist as either *syn* or *anti* diastereoisomers. X-Ray diffraction studies identified the product as the *anti* isomer of 3,3,5a,8,8,10a-hexamethyl-1,2,3,5,5a,6,7,8,10,10a-decahydropyrazino[2,3-*g*]quinoxaline (**2**). Compound **2** crystallizes in the tetragonal space group $I4_1/a$ (No. 88) with $a = 12.090(1)$, $c = 22.007(3)$ Å, $V = 3216.8(7)$ Å^3 and $Z = 8$. The solid-state structure also displays extensive hydrogen bonding between molecules of **2**. A likely mechanism for the formation of **2** is presented.

In a project designed to develop a method for the monoalkylation of symmetrical 1,2-diketones via the corresponding 1,2-diimines, we had the opportunity to review the literature on 2,3-dihydropyrazines, which result from the condensation of 1,2-diketones with 1,2-diamines. 2,3-Dihydropyrazines are of importance in that they can be dehydrogenated to substituted pyrazines, most useful as flavorants.[1,2] The two-step preparation of pyrazines via the intermediate 2,3-dihydropyrazines has traditionally not been a high yield process, owing to variable yields in the dehydrogenation step, which was traditionally achieved by autoxidation, by heating in the presence of base.[2–5] Efforts to facilitate dehydrogenation by addition of a suitable oxidant have resulted in better pyrazine yields,[1] presumably by averting one or more side reactions which compete with dehydrogenation under the base-mediated autoxidation reaction conditions. There has been no information on the nature of the side-reactions which contribute to low yields of pyrazines using traditional dehydrogenation conditions.

In this paper, we report on the structure of what we conclude to be a major side-product formed during attempted dehydrogenation of 2,3-dihydropyrazines. The quaternary center in 2,2,5,6-tetramethyl-2,3-dihydropyrazine (**1**), prepared from 2,3-butanedione and 2-methylpropane-1,2-diamine, precludes dehydrogenation and should thus be a good precursor to an analog of the unknown side-product. We could distil **1** without decomposition; however, neat samples of **1** after some lag time formed a solid substance **2** which then increased in quantity in an apparently autocatalytic manner. Re-distillation of **1** resulted in a sample which had increased stability. Spectroscopic and single crystal diffraction studies are presented in this work which now shed light on the structure of the solid **2**.[6]

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Experimental

Synthesis. 2,2,6,6-Tetramethyl-2,3-dihydropyrazine was prepared by combining equimolar amounts of 2,3-butanedione and 2-methylpropane-1,2-diamine and 1 mol% of *p*-toluenesulfonic acid in refluxing benzene, with azeotropic removal of water until the calculated amount had been collected. Following distillation (50 °C at 10 mmHg), the neat liquid obtained developed crystals of **2**, which were collected by filtration after dilution with hexane, and washed with hexane. X-Ray suitable crystals were obtained by slow recrystallization from benzene: m.p. 226–228 °C; EIMS: m/z M^+ 276; ^{1}H NMR ($CDCl_3$): δ 1.16 (s, 6 H), 1.22 (s, 6 H), 1.24 (s, 6 H), 1.43 (br, 2 H, NH), 2.16 (d, 2 H, $J = 13.3$ Hz), 2.62 (d, 2 H, $J = 13.3$ Hz), 2.66 and 2.70 (2 d, 2nd-order signal, 4 H, $J = 13.1$ Hz). ^{13}C NMR ($CDCl_3$, with APT designations in parentheses) δ 24.83 (–), 27.42 (–), 27.85 (–), 49.19 (+), 49.42 (+), 53.44 (+), 54.40 (+), 168.54 (+).

Crystallographic details. Data collection and reduction. Crystals suitable for X-ray investigation were obtained by crystallization from benzene solution. A crystal was mounted on a glass fiber using epoxy glue. The X-ray data were collected on a Siemens P4 diffractometer with Mo Kα X-rays (λ = 0.71073 Å). The crystal was judged to be acceptable on the basis of rotation photography and preliminary scans. Cell lengths were confirmed by axial photographs. Tetragonal crystal symmetry was corroborated by examination on the diffractometer. The settings of 49 general reflections were used in a least-squares fit to determine the unit-cell parameters. Semiempirical absorption corrections from psi scans were applied. No decay corrections were necessary. Further details concerning crystallographic data and experimental conditions are summarized in Table 1.

Structure determination and refinement. The structure was solved by direct methods (SHELXTL PLUS, PC version 5),[7] which gave atomic coordinates of non-hydrogen atoms. Hydrogen atoms were located in successive least-squares refinements and refined isotropically with thermal parameters 1.2 times that of the attached carbon atoms. All non-hydrogen atoms were refined anisotropically. Refinement was carried out against F^2, and final refinement by a full-matrix least-squares method of the 134 variables and 1259 data for which $I > 4\sigma(I)$ gave $R = 0.0505$ and $wR2 = 0.0949$. Final fractional coordinates and equivalent displacement parameters are given in Table 2.

Table 1. Crystal data collection information.

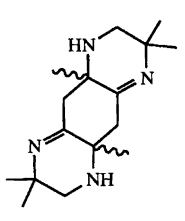
Formula	$C_{16}H_{28}N_4$
Formula weight/g mol^{-1}	276.42
Crystal dimensions/mm^3	0.32 × 0.22 × 0.20
Density calculated/Mg m^{-3}	1.142
Linear absorption coefficient/ mm^{-1}	0.070
F(000)	1216
Space group	$I4_1/a$ (No. 88)
Z	8
a/Å	12.090(1)
c/Å	22.007(3)
V/Å^3	3216.8(7)
Diffractometer	Siemens P4
Radiation	Mo Kα
Wavelength/Å	0.71073
Monochromator	Graphite
T/K	288
Scan mode	θ–2θ
Scan speed	Variable
2θ range/°	3.84–48.00
Background/scan ratio	0.5
No. of reflections measured	1778
No. of unique reflections [$I > 4\sigma(I)$]	1259 ($R_{int} = 0.0224$)
Stability monitoring	3 test refl./97 measured
$R = \Sigma\|\|F_o\| - \|F_c\|\|/\Sigma\|F_o\|$	0.0505
$wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$	0.0949
$S = \{\Sigma[w(F_o^2 - F_c^2)^2]/(n-p)\}^{1/2}$	1.178

Table 2. Fractional atomic coordinates and equivalent isotropic displacement parameters. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

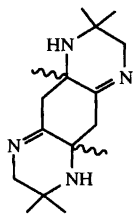
	x	y	z	U_{eq}
N(2)	0.1447(2)	0.5023(2)	0.1015(1)	0.041(1)
N(1)	−0.1807(2)	0.3754(2)	0.0047(1)	0.038(1)
C(8)	−0.2671(2)	0.3799(2)	−0.0430(1)	0.037(1)
C(6)	0.0025(2)	0.4085(2)	0.0433(1)	0.037(1)
C(5)	0.0482(2)	0.5226(2)	0.0629(1)	0.035(1)
C(7)	−0.0853(2)	0.4167(2)	−0.0056(1)	0.033(1)
C(4)	0.2172(2)	0.5981(3)	0.1050(1)	0.044(1)
C(3)	−0.0433(3)	0.5864(3)	0.0960(2)	0.049(1)
C(2)	−0.3242(3)	0.2673(3)	−0.0426(2)	0.060(1)
C(1)	−0.3493(3)	0.4701(3)	−0.0260(2)	0.060(1)

Results and discussion

^{1}H and ^{13}C NMR spectral and GC–MS measurements on the crystalline material originating from compound **1** were consistent with a symmetrical dimer, but could not distinguish unambiguously between the possible isomers **2** and **3** (below). Each dimer could also exist as either *syn* or *anti* diastereoisomers. Single crystal diffraction studies resolved this issue and confirmed that the compound was the *anti* isomer of 3,3,5a,8,8,10a-hexamethyl-1,2,3,5,5a,6,7,8,10,10a-decahydropyrazino[2,3-g]-quinoxaline, **2**.



2



3

Fig. 1 shows the results of the structural determination and the numbering scheme. Important bond lengths and angles in the molecule are listed in Table 3. A crystallographically imposed center of inversion relates the two halves of **2** to one another. The C=N distance of 1.277(3) Å is close to the average value for C=N bonds of 1.279 Å.[8] The C–N bond lengths in **2** are much longer and span 1.455(3) to 1.481(3) Å. The hydrogen atoms were successfully located and an NH distance of

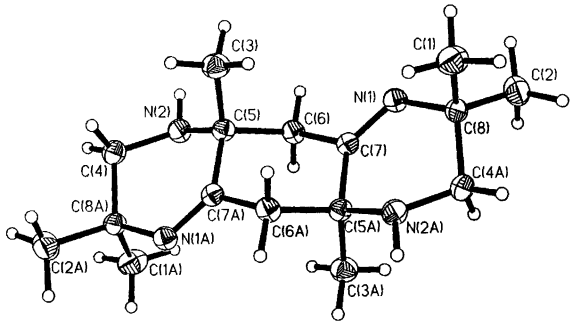


Fig. 1. Thermal ellipsoid plot for compound **2**.

Table 3. Selected interatomic distances (Å) and angles (°) with e.s.d.s in parentheses.

N(2)–C(4)	1.455(3)
N(2)–C(5)	1.463(3)
N(2)–H(201)	0.85(3)
N(1)–C(7)	1.277(3)
N(1)–C(8)	1.481(3)
C(8)–C(4)A	1.517(4)
C(8)–C(1)	1.522(4)
C(8)–C(2)	1.526(4)
C(6)–C(7)	1.515(3)
C(6)–C(5)	1.547(3)
C(5)–C(7)A	1.527(3)
C(5)–C(3)	1.531(4)
C(7)–C(5)A	1.527(3)
C(4)–C(8)A	1.517(4)
C(4)–N(2)–C(5)	112.3(2)
C(4)–N(2)–H(201)	112(2)
C(5)–N(2)–H(201)	110(2)
C(7)–N(1)–C(8)	119.8(2)
N(1)–C(8)–C(4)A	111.3(2)
N(1)–C(8)–C(1)	108.2(2)
C(4)A–C(8)–C(1)	110.8(2)
N(1)–C(8)–C(2)	106.3(2)
C(4)A–C(8)–C(2)	110.0(2)
C(1)–C(8)–C(2)	110.0(3)
C(7)–C(6)–C(5)	113.0(2)
N(2)–C(5)–C(7)A	109.0(2)
N(2)–C(5)–C(3)	112.6(2)
C(7)A–C(5)–C(3)	111.2(2)
N(2)–C(5)–C(6)	107.3(2)
C(7)A–C(5)–C(6)	107.6(2)
C(3)–C(5)–C(6)	108.9(2)
N(1)–C(7)–C(6)	118.8(2)
N(1)–C(7)–C(5)A	126.9(2)
C(6)–C(7)–C(5)A	114.3(2)
N(2)–C(4)–C(8)A	109.3(2)

0.85(3) Å was determined. Other bond lengths and angles are within established norms.

Analysis of the packing of **2** (Fig. 2) reveals an extensive network of hydrogen bonds aligned along the *c* axis of the crystal. Each molecule of **2** is bridged by two NH···N′ donor bonds and two N···HN′ acceptor bonds occurring at 2.47(3) Å. Typical N···H hydrogen bonds range from 1.73 to 2.23 Å and point out the presence of only moderately strong N···H bonding in **2**, perhaps owing to the presence of geminal dimethyl substitution α to the hydrogen-bond accepting nitrogen atoms.

A likely mechanism leading from **1** to **2** (Scheme 1) is a sequence of two enamine–imine aldol-like condensations. This would require initial isomerization of the diimine form of **1** with the imine–enamine **A**. Such equilibration would be catalyzed by base, explaining the slowing of the formation of **2** with increased purification of **1**. The fact that product **2** is an amine, being more basic than the starting **1**, also explains the apparent autocatalytic nature of the conversion. Since the pathway considered in Scheme 1 includes multiple instances where there are alternative regiochemical and stereochemical choices, we believe the various steps shown must be reversible, and that the nature of product actually formed might be determined either by overall thermodynamics and/or by crystal lattice forces in the solid **2** that forms.

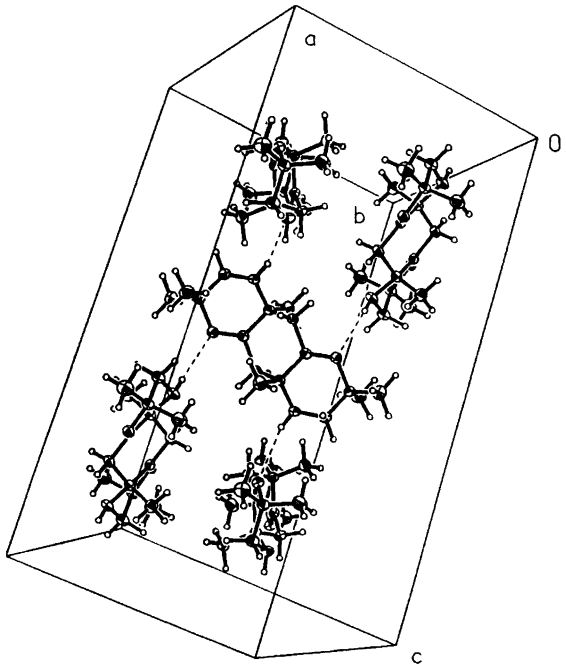


Fig. 2. Packing diagram for compound 2.

Overall, our finding indicates that any preparative reaction designed to induce autoxidation of 2,3-dihydropyrazine to pyrazine using basic conditions would be susceptible to the dimerization we have seen here, and this could well contribute to the poor yields of pyrazines obtained in previous synthetic enterprises.

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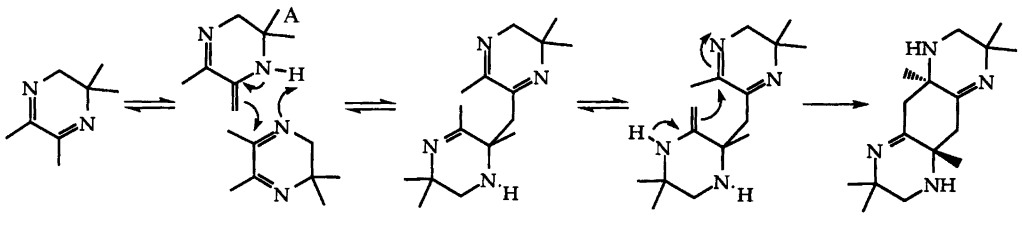

1 **2**

Scheme 1.

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