

parameters for the sequence C(1)—C(2)—C(3)—C(4)—C(5)—C(6) are $Q = 0.50$ Å, $\varphi = -171^\circ$ and $\theta = 125^\circ$ and Nardelli (1983) asymmetry parameters are $\Delta C_1[C(1)] = 0.041$ and $\Delta C_2[C(2)—C(1)] = 0.084$. The torsion angles around the C(4)—C(7) double bond are $\sim 179^\circ$.

Additional distortion of the cyclohexanedione ring is also due to the O(13) and O(15) substituents in equatorial positions; this agrees with previous results (de Kok & Romers, 1970; Nader, 1975) which show that substituents at C(3) and C(5) in equatorial positions affect the torsion angles and so the heterocycle conformation.

The *p*-nitrophenyl group is nearly planar [max. deviation to the mean-square plane 0.078 (10) Å]; although there is a slight tilt, 6.1 (7)° around N(2)—C(11), of the nitro group with respect to the phenyl plane of atoms.

The X-ray structure analysis of related compounds (Diáñez, López-Castro & Márquez, 1985, 1987) shows that the ZZE-enaminodione system is strictly planar and the close similarity between the IR spectra for solids and solutions of these compounds and for other compounds examined (Gómez-Sánchez, García Martín, Borrachero & Bellanato, 1987) indicates that the aminomethylene-5,5-dimethylcyclohexane-1,3-dione moiety of all of them has the same conformation.

As expected there is an intramolecular hydrogen bond between the N(1) atom and the carbonyl oxygen O(13). $N(1)\cdots O(13) = 2.606$ (11) Å and $N(1)—H\cdots O(13) = 133$ (1)°, showing a chelated structure. There are no intermolecular distances less than the sum of the van der Waals radii.

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Structure of 3-Methoxypyrazine-2-carbaldehyde 2,4-Dinitrophenylhydrazone

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Abstract. C₁₂H₁₀N₆O₅, $M_r = 318.25$, monoclinic, $P2_1/c$, $a = 7.1026$ (9), $b = 9.404$ (2), $c = 21.372$ (2) Å, $\beta = 108.246$ (9)°, $V = 1355.8$ (7) Å³, $Z = 4$, $D_x = 1.559$ g cm⁻³, $\lambda(\text{Cu } K\alpha) = 1.54178$ Å, $\mu = 10.26$ cm⁻¹, $F(000) = 656$, $T = 296$ K, $R = 0.087$ for 1083 observed [$I/\sigma(I) \geq 3$] reflexions. All skeletal atoms in the title phenylhydrazone lie in one plane,

including the methoxyl methyl and the nitro-group O atoms, with a mean deviation from the plane of only 0.0455 Å. The imine double bond has *Z* geometry and the benzenoid ring is oriented so that the *ortho*-nitro group is *syn* to the side-chain NH. The structure of the phenylhydrazone demonstrates that free-radical substitution of 2-methoxypyrazine in acid solution takes place *ortho* to the methoxyl and α to the more basic N atom.

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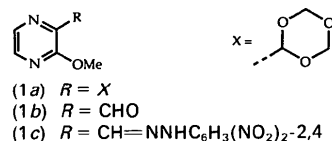
Introduction. The pK_a (Katritzky, 1963) of 4-methoxy-pyridine (6.62) shows it to be a stronger base than the parent base pyridine (5.23), an effect which must involve mesomeric donation from oxygen to stabilize the protonated heterocycle. 2-Methoxypyridine, in which the mesomeric effect can also stabilize adjacent protonation, is nonetheless a weaker base (3.28) presumably due to the larger influence of a combination of inductive and steric effects. In comparing the intrinsically weaker base pyrazine (pK_a 0.65) with its 2-methoxy derivative (0.75) it is difficult, then, to be sure whether the latter protonates at N-1 or N-4, for the mesomeric effect would be expected to be more important in this situation.

An important route for the introduction of carbon substituents into a pyridine α -position is the homolytic substitution of pyridinium salts with radicals having nucleophilic character – the introduction of alkyl (Castaldi, Minisci, Tortelli & Vismara, 1984), aryl (Minisci, Vismara, Fontana, Marini & Serravalle, 1986), aminocarbonyl (Minisci, Citterio, Vismara & Giordano, 1985), hydroxyalkyl (Citterio, Gentile, Minisci, Serravalle & Ventura, 1985) and trioxanyl (Giordano, Minisci, Vismara & Levi, 1986) into pyridine and/or benzo-fused pyridines has been demonstrated.

Our synthetic work required 6-methoxypyrazine-2-carbaldehyde and on the arguments given above we believed that there was a possibility that it would be available *via* the homolytic substitution of 2-methoxypyrazine, in acidic solution, with the trioxanyl radical. The radical carbamoylation (Minisci, Citterio, Vismara & Giordano, 1985), acylation (Gardini & Minisci, 1970; Houminer, Southwick & Williams, 1986, 1989) and alkylation (Tada & Momose, 1985) of pyrazines or quinoxalines have been described.

Experimental. Reaction of 2-methoxypyrazine with 1,3,5-trioxane in a degassed mixture of 3% sulfuric acid, 30% hydrogen peroxide and ferrous sulfate at 278 K produced a crystalline substitution product (1a), m.p. 381–382 K, in 13% isolated yield. The position of the introduced substituent was crucial to our synthetic plans. ^1H NMR measurements on the trioxanyl-substituted pyrazine revealed a small coupling constant, $J = 2.6$ Hz, between the two aromatic ring protons at δ 8.18 and 8.25, suggesting that they were oriented *meta* and that therefore the substitution had taken place as desired, at C-6.* Attempts to produce crystals of (1a) suitable for X-ray analysis were not successful; however, after room-temperature aqueous acidic hydrolysis, then

reaction of the resulting aldehyde (1b) with 2,4-dinitrophenylhydrazine, an orange 2,4-dinitrophenylhydrazone (1c) was obtained and crystallized from ethyl acetate to a m.p. 503–505 K. The coupling constant for the pyrazine ring protons, now at δ 8.23 and 8.41, was again 2.6 Hz.



A sample of (1c), of approximate dimensions $0.004 \times 0.074 \times 0.310$ mm, obtained from the thin flakes by cutting a section of clearer material from the long strip edges, was mounted on a glass fibre and used for data collection on a Rigaku AFC5R diffractometer with graphite-monochromated $\text{Cu } K\alpha$ radiation and a 12 kW rotating-anode generator. Cell constants and an orientation matrix were determined by least-squares refinement using the setting angles of 17 carefully centred reflexions in the range $12.81 < 2\theta < 42.89^\circ$. Data were collected at 296 (1) K using the $\omega/2\theta$ scan technique to a max. 2θ value of 120.1° . ω scans of several intense reflexions, made prior to data collection, had an average width at half-height of 0.24° with a take-off angle 6.0° . Scans of $(1.05 + 0.30 \tan \theta)^\circ$ were made at a speed of $4.0^\circ \text{ min}^{-1}$ (in ω). The weak reflexions [$I < 10.0\sigma(I)$] were rescanned and the counts accumulated to assure good counting statistics. Stationary background counts were recorded on each side of the reflexion. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm and the crystal was 400.0 mm from the detector. Of the 2345 reflexions, 2151 were unique ($R_{\text{int}} = 0.056$). Intensities of three representative reflexions, measured after every 150 reflexions, declined by 1.80%, so a linear correction factor was applied. The linear absorption coefficient for $\text{Cu } K\alpha$ is 10.3 cm^{-1} . An empirical absorption correction, using the program *DIFABS* (Walker & Stuart, 1983), was applied which resulted in transmission factors ranging from 0.81 to 1.24. The range of hkl was: h 0 to 7, k – 10 to 0, l – 23 to 22.

The structure was solved by direct methods [*MITHRIL* (Gilmore, 1984), *DIRDIF* (Beurskens, 1984)]. Non-H atoms were refined anisotropically. H-atom positions once found were restrained. The final cycle of full-matrix least-squares refinement was based on 1083 observed reflexions [$I > 3.00\sigma(I)$] and 208 variable parameters and converged (largest parameter shift was 0.01 times its e.s.d.) with unweighted and weighted factors of $R = 0.087$, $wR = 0.102$. The standard deviation, S , of an observation of unit weight was 2.92. The weighting scheme was

* The *meta*-related protons in 2-benzyloxy-6-(1,3-dithian-2-yl)-pyrazine coupled with $J = 3$ Hz (Allway & Joule, unpublished result).

based on counting statistics. Plots of $\sum w(|F_o| - |F_c|)^2$ versus $|F_o|$, reflexion order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The max. and min. peaks on the final difference Fourier map corresponded to 0.31 and $-0.30 \text{ e } \text{\AA}^{-3}$, respectively.

All calculations were performed using *TEXSAN* (Molecular Structure Corporation, 1985). Neutral atom scattering factors were taken from Cromer & Waber (1974), anomalous-dispersion effects were included in F_{calc} (Ibers & Hamilton, 1964) and the values of $\Delta f'$ and $\Delta f''$ were those of Cromer & Waber (1974).

Discussion. The atomic parameters for 3-methoxy-pyrazine-2-carbaldehyde 2,4-dinitrophenylhydrazine (1c) are listed in Table 1;* Fig. 1 shows a *PLUTO* (Motherwell & Clegg, 1978) drawing of the molecule and the numbering system used in Table 1. All atoms in the title phenylhydrazone lie in one plane, with a mean deviation from the plane of only 0.0455 Å, including the nitro-group O atoms and methoxyl methyl which is then necessarily oriented away from the 3-substituent. The imine double bond has *Z* geometry, presumably because of a hydrogen bond between the pyrazine ring N-1 and the side-chain N-H atoms which are 1.965 Å apart. The benzenoid ring is oriented so that a nitro O atom may also hydrogen bond to the N-H atom; here the distance between the relevant atoms is 1.976 Å.

While this work was in progress, radical acylation of 2-methoxypyrazine was reported to produce 2,3-disubstituted products (Houminer, Southwick & Williams, 1989); these products too had *ortho* coupling constants of 2.6 Hz. One may rationalize the regiochemistry of free-radical substitution of 2-methoxypyrazine in acid solution on the basis that (a) 2-methoxypyrazine is protonated at N-4 (see above), (b) that the attacking radical has nucleophilic character (see above) and (c) that of the two positions α to the protonated N-4, C-3 is rendered sufficiently further electron deficient by the *ortho*-methoxyl group as to overcome steric impediment to attack at the position, compared with the more accessible C-5 (*cf.* Caronna, Fronza, Minisci & Porta, 1972).

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* Lists of structure factors, anisotropic thermal parameters, intra- and intermolecular bond distances, intermolecular bond angles, torsion angles and special contacts and angles involving H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54268 (29 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Positional parameters for phenylhydrazone (1c) with e.s.d.'s in parentheses*

$$B_{\text{eq}} = (8\pi^2/3) \sum_i U_i a_i^* a_j^* a_i \cdot a_j$$

	x	y	z	B_{eq} (Å ²)
C1	0.116 (1)	0.239 (1)	0.4739 (4)	3.5 (4)
N2	0.203 (1)	0.3309 (8)	0.5187 (3)	3.8 (3)
N3	0.237 (1)	0.4620 (7)	0.4980 (3)	3.3 (3)
C4	0.329 (1)	0.559 (1)	0.5440 (4)	3.3 (4)
C5	0.372 (1)	0.700 (1)	0.5307 (4)	3.3 (4)
C6	0.460 (1)	0.796 (1)	0.5800 (5)	3.8 (4)
C7	0.510 (1)	0.753 (1)	0.6429 (4)	3.2 (4)
C8	0.472 (1)	0.616 (1)	0.6600 (4)	3.8 (4)
C9	0.383 (1)	0.522 (1)	0.6121 (4)	3.5 (4)
O10	-0.078 (1)	0.0141 (6)	0.3974 (3)	4.5 (3)
N11	-0.129 (1)	0.1393 (8)	0.3000 (3)	4.3 (4)
C12	-0.059 (1)	0.131 (1)	0.3647 (4)	3.4 (4)
C13	0.038 (1)	0.249 (1)	0.4020 (4)	3.3 (4)
N14	0.063 (1)	0.3706 (7)	0.3743 (3)	3.3 (3)
C15	-0.011 (1)	0.374 (1)	0.3081 (4)	4.5 (5)
C16	-0.105 (2)	0.263 (1)	0.2725 (4)	4.3 (5)
N17	0.322 (1)	0.752 (1)	0.4629 (4)	4.5 (4)
O18	0.252 (1)	0.6690 (7)	0.4170 (3)	5.1 (3)
O19	0.356 (1)	0.8747 (8)	0.4542 (3)	7.2 (4)
N20	0.602 (1)	0.8559 (8)	0.6957 (4)	4.2 (4)
O21	0.645 (1)	0.9727 (8)	0.6794 (4)	7.2 (4)
O22	0.634 (1)	0.8207 (7)	0.7529 (3)	6.1 (4)
C23	-0.165 (2)	-0.108 (1)	0.3578 (5)	5.3 (5)
H1	0.1011	0.1477	0.4910	4.3
H3	0.1968	0.4852	0.4524	4.0
H6	0.4863	0.8903	0.5694	4.5
H8	0.5059	0.5892	0.7050	4.5
H9	0.3562	0.4284	0.6240	4.2
H15	0.0020	0.4589	0.2857	5.3
H16	-0.1568	0.2715	0.2259	5.2
H231	-0.2945	-0.0856	0.3304	6.3
H232	-0.0851	-0.1341	0.3312	6.3
H233	-0.1703	-0.1854	0.3858	6.3

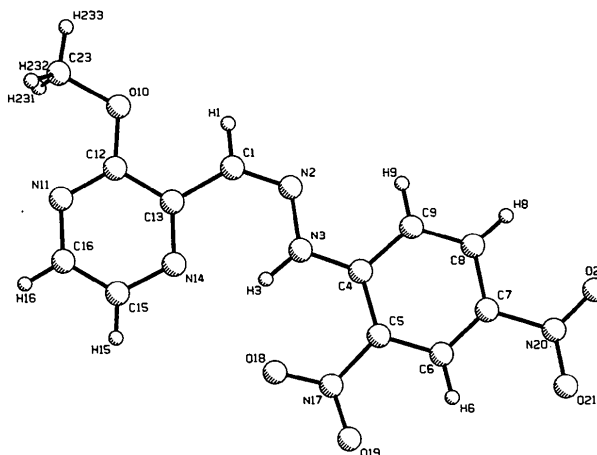


Fig. 1. *PLUTO* drawing of phenylhydrazone (1c), showing the numbering scheme used in Table 1.

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Structures of 3 β -Tetrahydropyranyloxy-5 α -cholesta-20(21),24-diene and 3 β -Tetrahydropyranyloxy-21-nor-5 α -ergost-24-en-20-one

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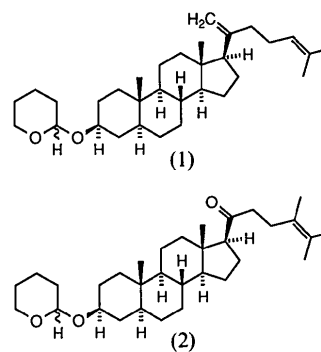
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Abstract. 3 β -Tetrahydropyranyloxy-5 α -cholesta-20(21),24-diene: C₃₂H₅₂O₂, $M_r = 468.77$, orthorhombic, $P2_12_12_1$, $a = 6.710$ (4), $b = 11.361$ (4), $c = 37.812$ (11) Å, $V = 2882$ (2) Å³, $Z = 4$, $D_x = 1.08$ g cm⁻³, $\lambda(\text{Cu } K\alpha) = 1.54178$ Å, $\mu = 4.60$ cm⁻¹, $F(000) = 1040$, $T = 224$ K, final $R = 0.088$ for 1729 unique observed reflections. 3 β -Tetrahydropyranyloxy-21-nor-5 α -ergost-24-en-20-one: C₃₂H₅₂O₃, $M_r = 484.77$, triclinic, $P1$, $a = 6.640$ (2), $b = 9.589$ (2), $c = 12.202$ (3) Å, $\alpha = 111.33$ (2), $\beta = 101.22$, $\gamma = 90.27$ (2)°, $V = 707.4$ (3) Å³, $Z = 1$, $D_x = 1.14$ g cm⁻³, $\lambda(\text{Mo } K\alpha) = 0.71069$ Å, $\mu = 0.8$ cm⁻¹, $F(000) = 268$, $T = 225$ K, final $R = 0.058$ for 2208 unique observed reflections. The configuration at C(17) of these synthetic sterol derivatives, which had been uncertain, is unambiguously established to be 'normal' (possessing a 17 α -H).

Introduction. The title compounds, 3 β -tetrahydropyranyloxy-5 α -cholesta-20(21),24-diene (1) (Rahman & Pascal, 1990) and 3 β -tetrahydropyranyloxy-21-nor-5 α -ergost-24-en-20-one (2), are key intermediates in the syntheses of certain inhibitors of ergosterol biosynthesis in parasitic protozoa. During the review of some of the synthetic and biological work for publication, a referee expressed concern that epimerization at C(17) might have occurred during the synthesis of compound (1), which employs

strong base in two steps when a carbonyl group is present at C(20). In order to establish unequivocally the configuration at C(17), we performed single-crystal analyses of compound (1) and the related compound (2) which is prepared in a similar way.



Experimental. Compound (1): A single crystal (from ethanol) with approximate dimensions 0.05 × 0.15 × 0.52 mm was used for data collection. Intensity measurements were made on a Nicolet R3m diffractometer, equipped with an LTII low-temperature device, at 224 K by using graphite-monochromated Cu $K\alpha$ radiation and a variable-speed 0.90° ω scan. Lattice parameters were determined by a least-squares fit of the 2θ values of 19 reflections having