no unusually short contacts between the molecules. A perspective drawing of the molecule with the numbering scheme is shown in Fig. 2. Bond distances and angles are listed in Table 2. The NO_2 group is attached to the C(9) atom. The molecules are greatly distorted from a planar conformation because of the steric repulsion between H(C1)···H(C21), which is known as a 1,7 interaction, as in the structure of the parent 7*H*-dibenzo[*a*,*kl*]anthracen-7-one (10,11-BzBT). The mean planes of the two naphthalene moieties [(*a*,*b*) and (*d*,*e*) rings in Fig. 2] make an angle of 24·95 (5)°. The repulsion is released mainly by the enlargement of the C(1)–C(13)–C(12), C(11)–C(12)–C(13) and C(12)–C(11)–C(21) angles and the distortion from a planar conformation. We have defined the degree of distortion as the twisting angle around the line C(11)···C(13). The torsion angle C(1)–C(13)···C(11)–C(21) is 36·7 (3)°, which is larger than that in 10,11-BzBT [33·4 (6)°] (Fujisawa, Oonishi, Aoki, Ohashi & Sasada, 1985). The NO_2 group rotates around the C(9)–N bond from the coplanar conformation. The torsion angle O(2)–N–C(9)–C(8) is 30·1 (3)°.

References

FUJISAWA, S., OONISHI, I., AOKI, J. & OHASHI, Y. (1986). *Acta Cryst.* C**42**, 1872–1874.

FUJISAWA, S., OONISHI, I., AOKI, J. & OHASHI, Y. (1987). *Acta Cryst.* C**43**, 254–256.

FUJISAWA, S., OONISHI, I., AOKI, J., OHASHI, Y. & SASADA, Y. (1985). *Bull. Chem. Soc. Jpn*, **58**, 3356–3359.

International Tables for X-ray Crystallography (1974). Vol. IV, pp. 71–151. Birmingham: Kynoch Press. (Present distributor D. Reidel, Dordrecht.)

MAIN, P., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1978). *MULTAN*78. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. of York, England, and Louvain, Belgium.

OHASHI, Y. (1975). Unpublished version of original *HBLS* program by T. ASHIDA.

Acta Cryst. (1987). C**43**, 974–977

Structure of 4-(4-Methoxyphenyl)thiosemicarbazide

BY D. CHATTOPADHYAY, T. BANERJEE AND S. K. MAJUMDAR

Crystallography and Molecular Biology Division, Saha Institute of Nuclear Physics, Sector I, *Block 'AF', Bidhannagar, Calcutta*-700 064, *India*

S. GHOSH

Department of Inorganic Chemistry, Indian Association for the Cultivation of Science, Calcutta-700 032, *India*

AND R. KURODA*

CRC Biomolecular Structure Unit, The Institute of Cancer Research, Sutton, Surrey SM2 5PX, England

(*Received* 5 *September* 1986; *accepted* 10 *December* 1986)

Abstract. $C_8H_{11}N_3OS$, $M_r = 197·26$, monoclinic, $P2_1/c$, $a = 13·105$ (1), $b = 5·759$ (1), $c = 13·056$ (1) Å, $\beta = 99·71$ (2)°, $V = 971·4$ (2) Å^3, $Z = 4$, $D_m = 1·389$, $D_x = 1·349$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 26·354$ cm^{-1}, $F(000) = 416$, $T = 298$ K, final $R = 0·067$ for 1499 observed reflections. There is significant electron localization at the hydrazinic end of the thiosemicarbazide side chain. This is due to the presence of the electron-releasing methoxy group in the phenyl ring *para* to the thiosemicarbazide chain and as a result the antibacterial activity of the compound increases.

Introduction. Thiosemicarbazides and thiosemicarbazones exhibit a variety of metal-chelating capacities (Domiano, Gasparri, Nardelli & Sgarabotto, 1969; Nandi, Chaudhuri, Mazumdar & Ghosh, 1984*a*,*b*). The antibacterial, antiviral and anticancer activities possessed by substituted thiosemicarbazides and thiosemicarbazones have generated rapidly growing interest in the chemical, biochemical and structural aspects of these compounds (Johnson, Joyner & Perry, 1952; French & Blanz, 1966; Agrawal, Booth & Sartorelli, 1968; Agrawal, Cushley, McMurray & Sartorelli, 1970; Williams, 1972; Agrawal, Booth & Sartorelli, 1973; Kuroda, Neidle & Wilman, 1984). It has been suggested that the biological activities of these groups of N,S donor ligands originate from their metal-chelating and reductive capacities (Kirschner, Wei, Francis & Bergman, 1966; Palenik, Rendle & Carter, 1974). Comparative studies of the antibacterial activity of 4-phenylthiosemicarbazide and some of its ring-substituted derivatives revealed that the activity of the *para* methoxy and the *para* chloro derivatives

* Present address: Department of Chemistry, College of Arts and Sciences, The University of Tokyo, Komba, Meguro, Tokyo 153, Japan.

0108-2701/87/050974-04$01.50

increased significantly over that of 4-phenylthiosemicarbazide (Nandi, Chaudhuri, Mazumdar & Ghosh, 1984*c*; present work). The aim of the present work is to determine the crystal structure of 4-(4-methoxyphenyl)thiosemicarbazide to account for its increased antibacterial activity and to compare its activity and structural features with those of 4-(4-chlorophenyl)-thiosemicarbazide in order to arrive at a meaningful structure–activity relationship.

Experimental. Colourless needle-shaped crystals (from ethanol); density by flotation (benzene–bromoform); crystal size: 0·42 × 0·30 × 0·25 mm; symmetry from oscillation and Weissenberg photographs, $P2_1/c$ (systematic absences: $0k0$, k odd, $h0l$, l odd); Enraf–Nonius CAD-4 diffractometer; graphite-monochromated Cu $K\alpha$ radiation; cell parameters refined from setting angles of 25 reflections ($11 \leq \theta \leq 34°$), 1640 unique reflections ($-15 \leq h \leq 15$, $0 \leq k \leq 15$, $0 \leq l \leq 15$, $3 \leq 2\theta \leq 130°$), 1499 observed reflections [$I \geq 2{\cdot}5\sigma(I)$], intensities corrected for Lp, absorption ignored: $\omega/2\theta$ scan mode, scan angle $(0{\cdot}90 + 0{\cdot}14\tan\theta)°$, scan aperture $(2{\cdot}50 + 0{\cdot}50\tan\theta)$ mm, maximum scan time 90 s, three orientation control reflections (413, 224, 141) monitored every 200 reflections, structure solved by direct methods (*MULTAN*78; Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978); full-matrix least-squares refinement on F for non-H atoms with isotropic thermal parameters and then with anisotropic thermal parameters (*SHELX*76; Sheldrick, 1976); ten H atoms located from difference synthesis; further refinement with isotropic thermal parameters for H and anisotropic thermal parameters for non-H atoms; one H atom generated with fixed geometry, not refined at all; $R = 0{\cdot}067$, $wR = 0{\cdot}085$, $S = 1{\cdot}5$, $w = 1/[\sigma^2|F_o| + 0{\cdot}012|F_o|^2]$, $\Delta/\sigma < 0{\cdot}06$, $\Delta\rho$ excursions 0·30 to −0·26 e Å^{-3} in final difference synthesis except a large peak of 0·78 e Å^{-3} at 0·95 Å from the S atom, scattering factors from *International Tables for X-ray Crystallography* (1974). Refinement of the structure considering the disorder of the S atom was unsuccessful. This fact as well as the large thermal vibration of the methoxy carbon atom, C(8), may be the reason for the rather high R value.

Evaluation of antibacterial activity. The *in vivo* antibacterial activity of the following compounds against *Escherichia coli* was determined in nutrient broth by standard techniques. The minimum inhibitory concentrations (m.i.c. in μg ml^{-1}) of 4-phenylthiosemicarbazide, 4-(4-chlorophenyl)thiosemicarbazide and 4-(4-methoxyphenyl)thiosemicarbazide were found to be 55·5, 26·3 and 25·8 respectively.

Discussion. The molecular structure drawn by *ORTEP* (Johnson, 1965) is shown in Fig. 1 along with the numbering of atoms. Fig. 2 shows the crystal packing. Fractional atomic coordinates together with their isotropic thermal parameters are listed in Table 1.* Table 2 lists the bond lengths and bond angles. The net atomic charges computed by the CNDO/2 method (Pople & Beveridge, 1970) are shown in Table 3.

The S atom in the present structure, like that in unsubstituted thiosemicarbazide (Andreetti, Domiano, Gasparri, Nardelli & Sgarabotto, 1970) and various derivatives of thiosemicarbazide and thiosemicarbazone in their unprotonated and uncomplexed forms (Kálmán, Argay & Czugler, 1972; Palenik *et al.*, 1974; Nandi *et al.*, 1984*a*,*c*), lies *trans* to the hydrazinic nitrogen atom, N(3). The S–C(7)–N(2)–N(3) torsion angle is comparable to that in 4-phenylthiosemicarbazide (Kálmán *et al.*, 1972) and in its *para* chloro derivative (Nandi *et al.*, 1984*c*). This conformation of the molecule forces the N(1) atom to be *cis* to the N(3) atom and favours intramolecular hydrogen bonding between these N atoms [H(N1)···N(3) = 2·24 (4), N(1)···N(3) = 2·627 (4) Å, N(1)–H(N1)···N(3) = 108 (3)°].

The C–S bond length in various thiosemicarbazide and thiosemicarbazone derivatives varies in the range 1·678 (2)–1·707 (2) Å (Palenik *et al.*, 1974). The bond length in the present structure indicates that the molecule is in the thioketo form; this is further corroborated by the presence of a band around 750 cm^{-1} in the IR spectrum of the compound

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, bond distances and angles involving H atoms, and deviations from least-squares planes have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43634 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallograhy, 5 Abbey Square, Chester CH1 2HU, England.

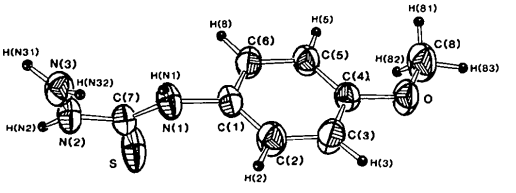

Fig. 1. View of the molecule with numbering of atoms.

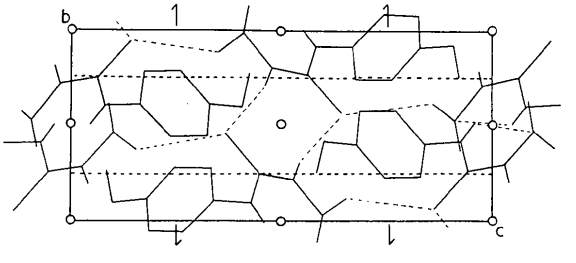

Fig. 2. View of the crystal packing.

assignable to ν(C=S). Although in thiosemicarbazones the C–S distance is apparently influenced by the parent aldehyde or ketone moieties it appears that a phenyl ring at the 4 position, N(1), of the thiosemicarbazide does not affect this bond length. The bond length is similar in unsubstituted thiosemicarbazide (Andreetti *et al.*, 1970), 4-phenylthiosemicarbazide (Kálmán *et al.*, 1972), 4-(4-chlorophenyl)thiosemicarbazide (Nandi *et al.*, 1984*c*) and in the present compound. The lengthening of the C–S bond from the normal C(sp^2)–S(sp^2) double-bond length of 1·59 Å is in agreement with the different canonical forms suggested for thiosemicarbazides (Domiano *et al.*, 1969).

The N(1)–C(7) bond length in the present molecule is similar to that in 4-phenylthiosemicarbazide; the charge densities computed by the CNDO/2 method (Pople & Beveridge, 1970) on the N(1) and C(7) atoms are only slightly different from those on the corresponding atoms of 4-phenylthiosemicarbazide (Nandi *et al.*, 1984*c*). However, the bond lengths at the hydrazinic terminal of the thiosemicarbazide side chain differ significantly from the corresponding lengths in 4-phenylthiosemicarbazide. The C(7)–N(2) and N(2)–N(3) bonds are considerably shorter than those in 4-phenylthiosemicarbazide and are comparable to those in 4-(4-chlorophenyl)thiosemicarbazide. This indicates an enhanced electron localization at this end of the molecule compared with that in 4-phenylthiosemicarbazide and is attributable to the effect of the electron-releasing methoxy group in the phenyl ring at the position *para* to the thiosemicarbazide chain.

None of the bond angles in the phenyl ring deviates much from the normal sp^2 value. The observed asymmetry in the exocyclic angles about C(4) is attributable to the steric interaction between the methyl group and the benzene ring [C(5)···C(8) = 2·800 (5), H(5)···H(81) = 2·35 (6), H(5)···H(82) = 2·30 (6) Å] resulting from the near-coplanarity of the methoxy group with the ring. Such asymmetry is a commonly observed phenomenon with a methoxy substituent in the phenyl ring (Eliopoulos, Sheldrick & Hamodrakas, 1983). The C(4)–O bond length agrees well with the average, 1·36 Å, calculated for similar bonds (Eliopoulos *et al.*, 1983). The molecules are packed by extensive hydrogen bonds between the N and S atoms. Molecules related by a centre of symmetry dimerize through N(2)–H(N2)···S hydrogen bonds [H(N2)···S = 2·52 (5), N(2)···S = 3·327 (3) Å, N(2)–H(N2)···S = 163 (5)°]. Glide-related molecules are linked together by N(3)–H(N31)···S hydrogen bonds resulting in a zigzag pattern [H(N31)···S = 2·86 (6), N(3)···S = 3·569 (3) Å, N(3)–H(N31)···S = 135 (5)°].

Structure–activity correlation studies on a series of substituted 1-formylisoquinolinethiosemicarbazones revealed that an electron-withdrawing substituent in the isoquinoline ring resulted in a reduction of antineoplastic activity while an electron-releasing group caused a pronounced increase in the activity (Agrawal *et al.*, 1968, 1970). Increased electronic charge on the terminal N atom is expected to increase the electron-donating capacity and metal-chelating ability of thiosemicarbazides. Comparison of the charge densities in 4-(4-chlorophenyl)thiosemicarbazide and 4-phenylthiosemicarbazide showed that the electron-releasing Cl atom led to an enhancement of negative charge on the terminal N atom. This resulted in an increased antibacterial activity of the former compound (Nandi *et*

Table 1. *Fractional coordinates of the atoms and their isotropic temperature factors with e.s.d.'s in parentheses*

$U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}(Å^2)
S	0·0764 (1)	0·4554 (2)	0·3641 (1)	0·067 (4)
O	0·4130 (2)	0·0873 (4)	0·0966 (2)	0·053 (7)
N(1)	0·1988 (2)	0·0942 (5)	0·4298 (2)	0·048 (7)
N(2)	0·0871 (2)	0·2075 (4)	0·5345 (2)	0·047 (7)
N(3)	0·1278 (2)	0·0309 (5)	0·6043 (2)	0·050 (8)
C(1)	0·2516 (2)	0·1023 (5)	0·3425 (2)	0·041 (8)
C(2)	0·2362 (2)	−0·0710 (5)	0·2691 (3)	0·054 (10)
C(3)	0·2910 (3)	−0·0688 (5)	0·1871 (3)	0·056 (11)
C(4)	0·3611 (2)	0·1053 (5)	0·1790 (2)	0·040 (8)
C(5)	0·3771 (2)	0·2797 (5)	0·2522 (2)	0·044 (9)
C(6)	0·3217 (2)	0·2766 (5)	0·3339 (2)	0·046 (8)
C(7)	0·1249 (2)	0·2430 (5)	0·4472 (2)	0·041 (8)
C(8)	0·4798 (3)	0·2695 (7)	0·0808 (3)	0·063 (12)

Table 2. *Bond distances* (Å), *bond angles* (°) *and some selected torsion angles* (°) *with e.s.d.'s in parentheses*

S–C(7)	1·687 (3)	C(4)–O–C(8)	117·6 (3)
O–C(4)	1·370 (4)	C(1)–N(1)–C(7)	125·0 (2)
O–C(8)	1·404 (5)	N(3)–N(2)–C(7)	120·6 (2)
N(1)–C(1)	1·430 (4)	N(1)–C(1)–C(6)	120·5 (2)
N(1)–C(7)	1·341 (4)	N(1)–C(1)–C(2)	120·0 (2)
N(2)–C(7)	1·333 (4)	C(2)–C(1)–C(6)	119·5 (2)
N(2)–N(3)	1·409 (4)	C(1)–C(2)–C(3)	120·1 (3)
C(1)–C(2)	1·371 (4)	C(2)–C(3)–C(4)	120·2 (3)
C(2)–C(3)	1·386 (6)	O–C(4)–C(3)	115·6 (2)
C(3)–C(4)	1·376 (4)	C(3)–C(4)–C(5)	120·2 (3)
C(4)–C(5)	1·378 (4)	O–C(4)–C(5)	124·2 (2)
C(5)–C(6)	1·388 (4)	C(4)–C(5)–C(6)	119·0 (3)
C(6)–C(1)	1·378 (4)	C(1)–C(6)–C(5)	120·9 (3)
		N(1)–C(7)–N(2)	115·5 (2)
S–C(7)–N(2)–N(3)	−179·7 (2)	S–C(7)–N(2)	120·5 (2)
S–C(7)–N(1)–C(1)	4·2 (4)	S–C(7)–N(1)	124·0 (2)

Table 3. *Net charges on the atoms in the* 4-(4-*methoxyphenyl)thiosemicarbazide molecule calculated by the CNDO/2 method (Pople & Beveridge,* 1970)

S	−0·4702	C(8)	0·1173
O	−0·2199	H(2)	0·0271
N(1)	−0·1711	H(3)	0·0194
N(2)	−0·0922	H(5)	0·0228
N(3)	−0·2369	H(6)	0·0174
C(1)	0·1157	H(81)	−0·0096
C(3)	−0·0257	H(82)	0·0008
C(3)	−0·0405	H(83)	0·0012
C(4)	0·1804	H(N1)	0·1246
C(5)	−0·0519	H(N2)	0·1501
C(6)	−0·0055	H(N31)	0·1263
C(7)	0·2698	H(N32)	0·1504

al., 1984*c*). Comparison of the atomic charge densities calculated for the present molecule with those for the 4-phenylthiosemicarbazide (Nandi *et al.*, 1984*c*) indicates that the electron-releasing methoxy group also increases the accumulation of negative charge on N(3). Consequently an increase in the reductive capacity and donor ability of the compound over 4-phenylthiosemicarbazide has been observed (Ray, 1981). The similarity in the charge-density distribution and the antibacterial activity of the *para* chloro and *para* methoxy derivatives of 4-phenylthiosemicarbazide indicate that the electron-releasing effect of the methoxy group is responsible for the increased antibacterial activity of 4-(4-methoxyphenyl)thiosemicarbazide over the 4-phenylthiosemicarbazide.

We thank Mr S. Chaudhuri of Bose Institute, Calcutta for many useful discussions.

References

AGRAWAL, K. C., BOOTH, B. A. & SARTORELLI, A. C. (1968). *J. Med. Chem.* **11**, 700–703.

AGRAWAL, K. C., BOOTH, B. A. & SARTORELLI, A. C. (1973). *J. Med. Chem.* **16**, 715–717.

AGRAWAL, K. C., CUSHLEY, R. J., MCMURRAY, W. J. & SARTORELLI, A. C. (1970). *J. Med. Chem.* **13**, 431–434.

ANDREETTI, G. D., DOMIANO, P., GASPARRI, G. F., NARDELLI, M. & SGARABOTTO, P. (1970). *Acta Cryst.* B**26**, 1005–1009.

DOMIANO, P., GASPARRI, G. F., NARDELLI, M. & SGARABOTTO, P. (1969). *Acta Cryst.* B**25**, 343–349.

ELIOPOULOS, E., SHELDRICK, B. & HAMODRAKAS, S. (1983). *Acta Cryst.* C**39**, 1693–1695.

FRENCH, F. A. & BLANZ, E. J. (1966). *J. Med. Chem.* **9**, 585–589.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor D. Reidel, Dordrecht.)

JOHNSON, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee.

JOHNSON, C. W., JOYNER, J. W. & PERRY, R. P. (1952). *Antibiot. Chemother. (Washington DC)*, **2**, 634–638.

KÁLMÁN, A., ARGAY, G. & CZUGLER, M. (1972). *Cryst. Struct. Commun.* **1**, 375–378.

KIRSCHNER, S., WEI, Y. K., FRANCIS, D. & BERGMAN, J. G. (1966). *J. Med. Chem.* **9**, 369–372.

KURODA, R., NEIDLE, S. & WILMAN, D. E. V. (1984). *Acta Cryst.* C**40**, 465–467.

MAIN, P., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1978). *MULTAN*78. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. of York, England, and Louvain, Belgium.

NANDI, A. K., CHAUDHURI, S., MAZUMDAR, S. K. & GHOSH, S. (1984*a*). *Acta Cryst.* C**40**, 1193–1196.

NANDI, A. K., CHAUDHURI, S., MAZUMDAR, S. K. & GHOSH, S. (1984*b*). *Inorg. Chim. Acta*, **92**, 235–240.

NANDI, A. K., CHAUDHURI, S., MAZUMDAR, S. K. & GHOSH, S. (1984*c*). *J. Chem. Soc. Perkin Trans.* 2, pp. 1729–1733.

PALENIK, G. J., RENDLE, D. F. & CARTER, W. S. (1974). *Acta Cryst.* B**30**, 2390–2395.

POPLE, J. A. & BEVERIDGE, D. L. (1970). In *Approximate Molecular Orbital Theory*. New York: McGraw-Hill.

RAY, P. K. (1981). PhD Dissertation, Univ. of Calcutta.

SHELDRICK, G. M. (1976). *SHELX*76. Program for crystal structure determination. Univ. of Cambridge, England.

WILLIAMS, D. R. (1972). *Chem. Rev.* **72**, 203–213.

Acta Cryst. (1987). C**43**, 977–979

Structure of Codeine

BY DENNIS V. CANFIELD, JAMES BARRICK* AND B. C. GIESSEN†

University of Southern Mississippi, Hattiesburg, MS 39406-10076, *USA*

(*Received* 14 *February* 1983; *accepted* 17 *December* 1986)

Abstract. 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol, $C_{18}H_{21}NO_3$, $M_r = 299{\cdot}4$, orthorhombic, $P2_12_12_1$, $a = 7{\cdot}491$ (7), $b = 13{\cdot}697$ (12), $c = 14{\cdot}775$ (14) Å, $V = 1516$ (2) Å^3, $Z = 4$, $D_x = 1{\cdot}312$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 0{\cdot}83$ cm^{-1}, $F(000) = 640$, $T = 296$ K, $R = 0{\cdot}038$ for 1205 unique reflections with $F^2 > 2\sigma(F^2)$. The crystal structure of codeine is related to that of morphine hydrate, which belongs to the same group, has the same rigid molecular skeleton, and closely similar cell parameters. Unlike morphine hydrate, the codeine structure lacks hydrogen bonds. This produces a different molecular packing, characterized by a small, approximately 3 Å, shift in the molecular centers, and a rotation of the codeine molecules of approximately 40°.

Introduction. The crystal-structure determination of codeine (I) was undertaken to establish the atomic and thermal parameters for later use in the calculation of a standard X-ray diffraction pattern for use in forensic-science laboratories. The basic configuration of codeine was originally determined by the structural analysis of codeine hydrobromide dihydrate (Lindsey & Barnes,

* Present address: 4517 Wingfield St., Columbus, OH 43229, USA.

† Present address: Institute of Chemical Analysis, Applications and Forensic Science and Department of Chemistry, Northeastern University, Boston, MA 02115, USA.

0108-2701/87/050977-03$01.50