lar frame is nearly planar with the largest deviation from the plane being 0.027 Å for N.

The conformation of the *meso* form of DMSA in the solid state is staggered. The two sulfhydryl groups are opposite each other as are the two carboxylic acid groups and the two H atoms. The steric repulsions are minimized by having the bulky carboxylic acid groups between the sulfhydryl group and the H atom. The most notable feature of this adduct is the hydrogen bonding between two dimethylformamide units and the hydroxyl group of the carboxylic acid forming a DMF–DMSA–DMF adduct. The O1—HO1—O3 bond lengths are 0.990 and 1.591 Å, respectively. There are no other unusually short intermolecular contacts.

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Acta Cryst. (1992). C**48**, 2009–2013

Structures of Two Crystalline Modifications of Lapachol

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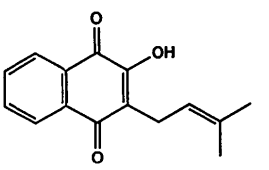
(*Received* 30 *December* 1991; *accepted* 19 *March* 1992)

Abstract. 2-Hydroxy-3-(3-methyl-2-butenyl)-1,4-naphthalenedione, $C_{15}H_{14}O_3$, $M_r = 242.26$. Triclinic (LAPA I), $P\bar{1}$, $a = 5.960$ (1), $b = 9.569$ (2), $c = 10.679$ (2) Å, $\alpha = 96.82$ (2), $\beta = 98.32$ (2), $\gamma = 90.32$ (2)°, $V = 598.2$ (3) Å^3 at 105 K, $Z = 2$, $D_x = 1.345$ Mg m^{-3}, λ(Mo $K\alpha$) = 0.71073 Å, $\mu = 0.087$ mm^{-1}, $F(000) = 256$, $T = 105$ K, final $R = 0.028$ for 1249 unique observed reflections. Monoclinic (LAPA II), $P2_1/c$, $a = 6.035$ (1), $b = 9.427$ (2), $c = 20.918$ (5) Å, $\beta = 98.27$ (2)°, $V = 1177.7$ (5) Å^3 at 105 K, $Z = 4$, $D_x = 1.366$ Mg m^{-3}, λ(Mo $K\alpha$) = 0.71073 Å, $\mu = 0.088$ mm^{-1}, $F(000) = 512$, $T = 105$ K, final $R = 0.027$ for 739 unique observed reflections. In both crystalline modifications of lapachol the naphthoquinone ring system is approximately planar, and the planar unsaturated side chain is twisted about 90° with respect to the ring system. The crystal packings of LAPA I and II show that the molecules, in both cases, form dimers through OH···O hydrogen bonds around centres of symmetry.

Introduction. Lapachol (LAPA) is a natural pigment derived from the heart wood of certain tropical plants (Hooker, 1896). It has been known for several years that the compound is an active antineoplastic agent (Rao, McBride & Oleson, 1968), but the anticoagulant effects encountered during the clinical testing of lapachol have prevented its use as an



LAPA

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anticancer drug (Block, Serpick, Miller & Wiernik, 1974). The anticoagulant action of lapachol is probably a result of its action as a potent reversible inhibitor of enzymes involved in vitamin-K-dependent carboxylation of clotting factors, *i.e.* the enzymes vitamin K epoxide reductase (Preusch & Suttie, 1984) and DT-diaphorase (Preusch, 1986).

The mode of cytostatic action of lapachol is not known. The main target of action might be the enzyme ribonucleotide reductase, as the *E. coli* ribonucleotide reductase has been reported to be effectively inhibited by lapachol (Smith & Douglas, 1986). The molecular mechanism of the blocking of this enzyme is not known. The X-ray structure of the smaller of the two proteins of ribonucleotide reductase of *E. coli* has been determined recently (Nordlund, Sjöberg & Eklund, 1990).

Lapachol is also a strong inhibitor of glyoxalase I, an enzyme which has been suggested as target enzyme for anticancer drug action (Douglas, Gohel, Nadvi, Quilter & Seddon, 1985). It has been proposed that 1,4-naphthoquinones interfere with biological electron-transfer processes, and the redox potential has been found to be the most important physico-chemical property determining the antitumour activity of a series of quinones, including lapachol (Hodnett, Wongwiechintana, Dunn & Marrs, 1983; Pisani, Elliott, Hinman, Aaronson & Pardini, 1986).

Lapachol is a strong Fe chelator (de Lima, de Araujo, DuFresne & Knudsen, 1971), and rapidly reduces the free radical salt $(KO_3S)_2NO^{\cdot}$, which has been used as a model for the small tyrosyl-radical-containing protein of ribonucleotide reductase (Kjøller Larsen, Sjöberg & Thelander, 1982). These properties, together with an apparent steric requirement of planarity, are important for effective inactivators of the small protein (Larsen, 1990). In this report, the crystal structures of two crystalline modifications of lapachol are described.

Experimental. Lapachol (from Aldrich) was recrystallized from ethanol. Single crystals of LAPA I (triclinic) were obtained by slow evaporation from a solution in an ethanol–ether mixture, and of LAPA II (monoclinic) from a solution in an ethanol–water mixture. The crystals of LAPA I are yellow plates, m.p. 406–407 K, and those of LAPA II are yellow needles with *a* as the needle axis, m.p. 411–412 K. Single crystals of LAPA I (0.15 × 0.25 × 0.04 mm) and of LAPA II (0.20 × 0.40 × 0.05 mm, cut out of a needle) were chosen for data collection on an Enraf–Nonius CAD-4 diffractometer equipped with graphite monochromator and Nonius low-temperature device. The temperature was kept constant within ±0.5 K from an estimated value of 105 (5) K. The cell dimensions were determined by least-squares fit of angular settings of 18 reflections in the θ range 15.22–21.17° in the case of LAPA I, and 11.08–20.87° in the case of LAPA II. The intensities were measured by the $\omega/2\theta$-scan method for $\theta \le 25°$ with hkl ranges $-7 \le h \le <7$, $-11 \le k \le 11$, $-12 \le l \le 12$ for LAPA I, and $0 \le h \le 7$, $-11 \le k \le 11$, $-24 \le l \le 24$ for LAPA II. Three standard reflections, measured every 10^4 s, showed no significant variations in the case of LAPA I, whereas the data of LAPA II were corrected for a total gain of intensity of 7% (0.12% h^{-1}). Intensities of 4745 reflections of LAPA I were measured, 2182 being unique (symmetry equivalent reflections were averaged, $R_{int} = 0.033$, based on I), and 1256 of these were considered observed [$I > 3.0\sigma_c(I)$, where $\sigma_c(I)$ is based on counting statistics]. Intensities of 4554 reflections of LAPA II were measured, 2066 being unique ($R_{int} = 0.103$ for all, and 0.040 for observed reflections, based on I), and 739 of these were considered observed [$I > 3.0\sigma_c(I)$]. No absorption corrections were made. The structures were solved by direct methods using *MULTAN*80 (Main *et al.*, 1980). Full-matrix least-squares refinement (on F) of positional parameters for all atoms was performed, with anisotropic displacement factors for non-H atoms and isotropic displacement factors for H atoms kept fixed ($B = 2.0$ Å^2). All H atoms were located in successive difference Fourier maps. The quantity minimized was $\sum w(|F_o| - k|F_c|)^2$, where $w = 4F^2[\sigma_c^2(F^2) + (pF^2)^2]^{-1}$, and $p = 0.06$ for LAPA I and 0.08 for LAPA II. The average and maximum values of Δ/σ in final refinement cycles were 0.004 and 0.06 for LAPA I, and 0.006 and 0.05 for LAPA II. The final error indicators are $R = 0.028$, $wR = 0.037$, $S = 1.01$ for LAPA I, and $R = 0.027$, $wR = 0.034$, $S = 0.72$ for LAPA II. The fluctuations in the final $\Delta\rho$ maps were ± 0.2 e Å^{-3} in both cases. Scattering factors for atoms were as implemented in the *SDP* program package (Frenz, 1982), which was used for all calculations.

Discussion. The final atomic parameters of LAPA I and LAPA II are listed in Table 1.* Bond lengths and angles are given in Table 2. The atomic numbering scheme and molecular conformations are shown in Fig. 1, and the molecular packing arrangements are illustrated in Fig. 2.

In both modifications of lapachol the molecules are found to be composed of two nearly planar parts,

* Lists of structure factors, anisotropic displacement parameters, H-atom parameters, bond distances and angles involving H atoms, and parameters of least-squares planes have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55311 (16 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: AB0274]

Table 1. *Fractional atomic coordinates and equivalent isotropic thermal parameters* (Å^2) *for non-*H *atoms of LAPA* I *and LAPA* II

$B_{eq} = (4/3)\sum_i\sum_j \beta_{ij} \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}
LAPA I				
O1	0.8997 (2)	0.1316 (1)	0.0743 (1)	1.50 (2)
O2	0.7028 (2)	0.0004 (1)	−0.1514 (1)	1.58 (2)
O4	0.0799 (2)	0.2930 (1)	−0.1214 (1)	1.71 (2)
C1	0.7166 (3)	0.1761 (2)	0.0297 (2)	1.20 (3)
C2	0.5947 (3)	0.1068 (2)	−0.0928 (2)	1.26 (3)
C3	0.3854 (3)	0.1420 (2)	−0.1435 (2)	1.23 (3)
C4	0.2701 (3)	0.2589 (2)	−0.0773 (2)	1.25 (3)
C5	0.2883 (3)	0.4475 (2)	0.1083 (2)	1.43 (3)
C6	0.4027 (3)	0.5212 (2)	0.2186 (2)	1.65 (3)
C7	0.6195 (3)	0.4839 (2)	0.2671 (2)	1.65 (3)
C8	0.7225 (3)	0.3709 (2)	0.2062 (2)	1.40 (3)
C9	0.6082 (3)	0.2970 (2)	0.0947 (2)	1.15 (3)
C10	0.3908 (3)	0.3357 (2)	0.0445 (2)	1.23 (3)
C11	0.2654 (3)	0.0663 (2)	−0.2671 (2)	1.40 (3)
C12	0.3323 (3)	0.1249 (2)	−0.3820 (2)	1.36 (3)
C13	0.2010 (3)	0.1929 (2)	−0.4650 (2)	1.35 (3)
C14	−0.0430 (3)	0.2250 (2)	−0.4581 (2)	1.87 (4)
C15	0.2910 (3)	0.2422 (2)	−0.5777 (2)	2.04 (4)
LAPA II				
O1	0.1049 (3)	0.6228 (2)	0.4647 (1)	1.39 (5)
O2	0.2931 (3)	0.5174 (2)	0.5791 (1)	1.45 (5)
O4	0.9210 (3)	0.8020 (3)	0.5645 (1)	1.62 (5)
C1	0.2881 (5)	0.6731 (3)	0.4878 (1)	1.13 (6)
C2	0.4045 (5)	0.6161 (3)	0.5495 (2)	1.13 (6)
C3	0.6134 (5)	0.6555 (3)	0.5755 (2)	1.12 (6)
C4	0.7307 (5)	0.7633 (3)	0.5421 (2)	1.18 (6)
C5	0.7244 (5)	0.9281 (4)	0.4474 (2)	1.36 (7)
C6	0.6156 (6)	0.9903 (3)	0.3921 (2)	1.52 (7)
C7	0.3972 (5)	0.9508 (4)	0.3677 (2)	1.47 (7)
C8	0.2909 (5)	0.8477 (4)	0.3994 (2)	1.26 (7)
C9	0.3994 (5)	0.7854 (3)	0.4548 (1)	1.06 (6)
C10	0.6179 (5)	0.8266 (3)	0.4801 (1)	1.14 (6)
C11	0.7289 (5)	0.5941 (4)	0.6382 (2)	1.40 (7)
C12	0.6739 (5)	0.6771 (3)	0.6957 (2)	1.14 (6)
C13	0.8087 (5)	0.7590 (4)	0.7356 (2)	1.29 (7)
C14	1.0517 (5)	0.7875 (4)	0.7292 (2)	1.82 (7)
C15	0.7273 (5)	0.8350 (4)	0.7905 (2)	1.68 (7)

Table 2. *Bond lengths* (Å), *bond angles* (°) *and hydrogen-bond geometry* (Å, °) *of LAPA* I *and LAPA* II

	LAPA I	LAPA II
O1—C1	1.225 (2)	1.237 (3)
O2—C2	1.347 (2)	1.350 (4)
O4—C4	1.225 (2)	1.232 (3)
C1—C2	1.481 (2)	1.477 (4)
C1—C9	1.479 (2)	1.478 (4)
C2—C3	1.348 (2)	1.352 (4)
C3—C4	1.478 (2)	1.471 (5)
C3—C11	1.508 (2)	1.510 (4)
C4—C10	1.498 (2)	1.499 (4)
C5—C6	1.384 (2)	1.376 (4)
C5—C10	1.392 (2)	1.387 (5)
C6—C7	1.387 (2)	1.394 (4)
C7—C8	1.387 (2)	1.385 (5)
C8—C9	1.394 (2)	1.378 (4)
C9—C10	1.398 (2)	1.404 (4)
C11—C12	1.511 (3)	1.512 (5)
C12—C13	1.328 (2)	1.326 (4)
C13—C14	1.498 (3)	1.515 (4)
C13—C15	1.509 (3)	1.496 (5)
O1—C1—C2	119.8 (1)	119.3 (3)
O1—C1—C9	122.5 (1)	122.1 (3)
C2—C1—C9	117.7 (1)	118.5 (2)
O2—C2—C1	115.9 (1)	116.4 (2)
O2—C2—C3	120.4 (1)	120.1 (3)
C1—C2—C3	123.7 (1)	123.5 (3)
C2—C3—C4	119.4 (1)	118.9 (3)
C2—C3—C11	121.8 (1)	122.1 (3)
C4—C3—C11	118.8 (1)	118.9 (3)
O4—C4—C3	120.7 (1)	120.7 (3)
O4—C4—C10	120.5 (1)	119.6 (3)
C3—C4—C10	118.9 (1)	119.7 (2)
C6—C5—C10	120.2 (1)	120.6 (3)
C5—C6—C7	120.4 (2)	120.4 (3)
C6—C7—C8	120.2 (1)	119.4 (3)
C7—C8—C9	119.5 (2)	120.3 (3)
C1—C9—C8	119.8 (1)	120.5 (3)
C1—C9—C10	119.8 (1)	119.2 (3)
C8—C9—C10	120.5 (1)	120.4 (3)
C4—C10—C5	120.3 (1)	121.1 (3)
C4—C10—C9	120.6 (1)	120.1 (3)
C5—C10—C9	119.2 (1)	118.8 (3)
C3—C11—C12	112.3 (1)	111.5 (3)
C11—C12—C13	127.0 (2)	128.0 (3)
C12—C13—C14	124.5 (2)	124.2 (3)
C12—C13—C15	120.9 (2)	121.4 (3)
C14—C13—C15	114.6 (1)	114.3 (3)

	$D\cdots A$	$H\cdots A$	D—$H\cdots A$	Symmetry code (A)
LAPA I				
O2—H2···O1	2.685 (2)	2.21 (2)	114 (1)	x, y, z
O2—H2···O1	2.758 (2)	1.97 (2)	149 (2)	$-x+2, -y, -z$
C11—H111···O2	2.826 (2)	2.51 (2)	97 (1)	x, y, z
C11—H112···O4	2.842 (2)	2.50 (2)	101 (1)	x, y, z
LAPA II				
O2—H2···O1	2.688 (3)	2.21 (3)	116 (3)	x, y, z
O2—H2···O1	2.779 (3)	2.02 (3)	149 (3)	$-x+2, -y+1, -z+1$
C11—H111···O2	2.835 (4)	2.50 (3)	100 (2)	x, y, z
C11—H112···O4	2.842 (4)	2.52 (3)	99 (2)	x, y, z

the aromatic ring system and the allylic side chain, which are almost perpendicular to each other. The side chain C11–C15 is planar in both cases, to within ±0.010 (3) Å, and the torsion angles C2—C3—C11—C12 are −84.6 (2) and −87.7 (4)° for LAPA I and LAPA II, respectively (*cf.* Fig. 1). This molecular conformation of lapachol may be determined by weak CH···O hydrogen bonding, as the distances of the H atoms at C11 to O2 and O4 in all cases are about 2.5 Å (*cf.* Table 2).

As it appears, the lapachol molecule as a whole is not planar, as normally required for potent inactivators of the small protein of the enzyme ribonucleotide reductase (see *Introduction*). This is in agreement with the result of the recently performed testing of lapachol on the small protein of the *E. coli* enzyme (Sykes, 1991), when it was found that lapachol does not inactivate this protein (reduce the tyrosyl free radical). The testing of the effect of lapachol on the larger protein of the enzyme has not yet been performed.

The naphthoquinone ring system of lapachol is approximately planar, with average deviations from the least-squares plane through C1–C10 being 0.019 (2) and 0.021 (3) Å for LAPA I and LAPA II, respectively. The exocyclic O atoms are more or less out of this plane. The quinone O atom O1 is displaced −0.135 (1) and 0.172 (2) Å in LAPA I and LAPA II, respectively, while the other quinone O atom, O4, is situated almost in the ring plane in both structures with displacements of −0.001 (1) and −0.031 (2) Å, respectively. The phenol O atom O2 is displaced 0.045 (1) and −0.021 (2) Å, respectively.

Good agreement is observed between corresponding bonds and angles of LAPA I and LAPA II. In both molecules the ring C5–C10 is appreciably

aromatic, while in the quinone ring the C1—O1, C4—O4 and C2—C3 bonds are more or less localized double bonds. This is in accordance with the three 2-hydroxy-1,4-naphthoquinones found in the Cambridge Structural Database (CSD, July 1991 release; Allen *et al.*, 1979), *i.e.* 2-hydroxy-3-iodo-1,4-naphthoquinone (Courseille, Geoffre & Schvoerer, 1971), 2,5-dihydroxy-3,8-dimethoxy-7-methyl-1,4-naphthoquinone (Cannon, Lojanapiwatna, Raston, Sinchai & White, 1980) and bis(2-hydroxy-1,4-naphthoquinone)bis(pyridine)copper(II) (Peng, Wang, Chang, Tang & Wang, 1981). In all the structures differences of the angles at the C1=O1 bonds are observed (*cf.* Table 2) and to a lesser degree at the C2—O2 bonds (contractions of the angles O1—C1—C2 and O2—C2—C1). This is probably a consequence of the hydrogen-bonding systems, except in the case of the Cu complex, where the quinone and hydroxy O atoms are ligated to Cu. Both angles at C4=O4 are near to 120° in all cases (119.5–122.4°). The dimensions of the naphthoquinones referred to above were calculated on the basis of the parameters stored in the CSD.

The crystal packing of lapachol (Fig. 2) is in both polymorphs determined primarily by stacking forces (π interactions between aromatic rings) and van der Waals forces. Only one intermolecular hydrogen bond is found in each structure, *i.e.* O2—H2···O1 (see Table 2), in both cases forming dimers around centres of symmetry. The hydrogen bonds are three-centred (bifurcated), as the H2 atom also has a short intramolecular contact to the O1 atom in both cases (*cf.* Table 2). Of the 2-hydroxynaphthoquinones found in the CSD, one forms dimers in the same way as in lapachol (Cannon *et al.*, 1980), and the other forms infinite chains through O2—H2···O1 hydrogen bonding along screw axes (Courseille *et al.*, 1971). The stacking forces seem to be more dominant in LAPA II than in LAPA I, as the interplanar distance between adjacent naphthoquinone ring planes is 3.29 Å in LAPA II and 3.75 Å in LAPA I. The closer packing of the molecules in LAPA II is also reflected in the higher density of the crystals of this modification of lapachol (1.366 Mg m^{-3} for LAPA II and 1.345 Mg m^{-3} for LAPA I).

Lisbet Aamand Andersen was NORDPLUS student at the University of Oslo. PharmaBiotec Research Centre is acknowledged for financial support. The authors thank Mr Flemming Hansen for

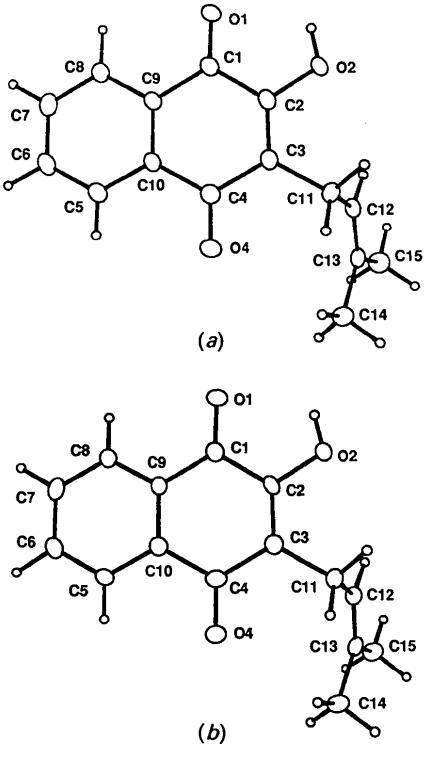

Fig. 1. Molecular structures of (*a*) LAPA I and (*b*) LAPA II with thermal ellipsoids at the 50% probability level for non-H atoms (Johnson, 1976).

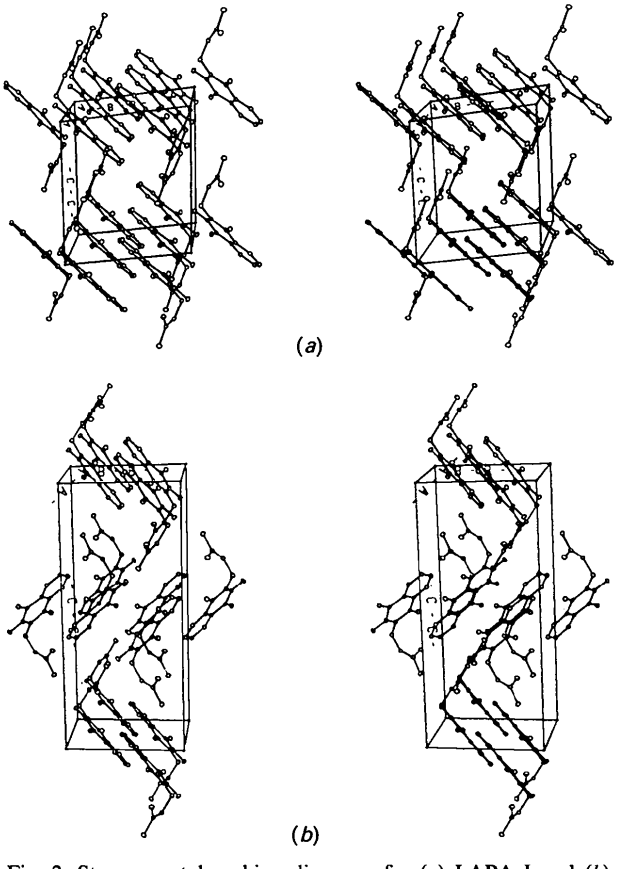

Fig. 2. Stereo crystal-packing diagrams for (*a*) LAPA I and (*b*) LAPA II.

collecting the X-ray data. The diffractometer and an X-ray generator were acquired by means of grants from the Danish National Science Research Council.

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Acta Cryst. (1992). C**48**, 2013–2016

Structure of *N,N′,N″*-Triphenylbiuret

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(*Received* 27 *November* 1991; *accepted* 6 *April* 1992)

Abstract. $C_{20}H_{17}N_3O_2$, $M_r = 331.37$, monoclinic, $P2_1/n$, $a = 12.619$ (1), $b = 8.285$ (1), $c = 16.469$ (1) Å, $\beta = 94.39$ (6)°, $V = 1716.7$ (3) Å^3, $Z = 4$, $D_x = 1.28$ g cm^{-3}, Cu $K\alpha$ radiation, $\lambda = 1.54184$ Å, $\mu = 0.647$ cm^{-1}, $F(000) = 696$, $T = 293$ (2) K, final $R = 0.038$ and $wR = 0.049$ for 2664 observed reflections and 294 refined parameters. The title molecule consists of three phenyl rings connected to the three N atoms of the biuret. Both intra- and intermolecular hydrogen bonds stabilize the molecular and crystal structure.

Introduction. Interest in biuret (NH_2—CO—NH—CO—NH_2) and biuret derivatives arose long ago (Wiedemann, 1848) because of the well known violet color (the 'biuret color') shown by alkaline solutions containing Cu^{2+} ions and biuret. In more modern times, this class of compounds has been investigated mainly by coordination chemists and biochemists because biuret is one of the simplest compounds mimicking a polypeptide chain (Siegel & Martin, 1982; Veersai & Rode, 1981). The biuret system may be viewed as made up of two amidic arms attached to a common N atom. Such a unique arrangement allows interaction between the two arms which directly affects the conformation of the biuret system. Studies addressing such problems are of relevance owing to the following points: (i) amide-based hydrogen bonding is a topic of ever-growing interest in molecular recognition (Jorgensen, 1991); (ii) several compounds related to biuret show a potent activity which may well depend on their conformation (Barton, Paluchowska, Mokrosz & Szneler, 1987; Al Sabbagh, Calmon & Calmon,

0108-2701/92/112013-04$06.00