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CRYSTAL AND MOLECULAR STRUCTURE OF A 4-OXIMINO-5-IMINO-PYRAZOLINE ACTIVE ESTER

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The crystal structure of an active 4-oximino-5-imino-pyrazoline ester has been determined by single-crystal X-ray diffraction methods. The possible reasons for its high reactivity towards nucleophilic reagents are briefly discussed.

We have recently discussed (1,2,3,4) the use in peptide synthesis of active 4-oximino-5-imino-pyrazoline esters I, which are obtained from 1-phenyl-3-methyl-4-nitroso-5(N-benzyloxycarbonyl)-glycyl-amino-pyrazole II (Fig. 1).

A peculiarity of these active esters is their high reactivity towards nucleophilic reagents which cleave the NO-CO ester bond. In the most favourable cases the aminolysis reaction in organic solvents is completed in a few seconds, as it is easily detected by the change of colour of the solution. In an attempt to explain the unusual reactivity of these compounds, we have undertaken the determination of the crystal structure of the active ester of the p-bromo-benzoic acid, i.e. 1-phenyl-3-methyl-4(p-bromobenzoyloximino)-5(N-benzyloxycarbonyl)-glycyl-imino-2-pyrazoline.

Crystal data $C_{27}H_{22}O_5N_5Br$, mol.wt. = 576.4, triclinic, reduced cell parameters: a = 9.73(4), b = 8.751(4), c = 19.270(8) Å, α = 102.44(4), β = 107.72(4), γ = 115.16(4)°; D_m = 1.48 g cm^{-3} (by flotation), D_c = 1.48 g cm^{-3}, Z = 4; space group $P\bar{1}$ (C_i^1, No. 2). All the refinement has been carried out in the space group $C\bar{1}$ (a = 17.699(10), b = 8.751(4), c = 16.836(9) Å, α = 91.52(6), β = 91.46(4), γ = 88.57(5)°, Z = 4) to take advantage of the orthogonality of axis. A crystal with a cross section 0.30 × 0.22 mm was mounted along the *b* axis. The unit cell dimensions were refined by least-squares fit from the powder pattern. Intensity data were collected from equi-inclination Weissenberg photographs with Ni-filtered Cu Kα radiation. A combination of the multiple-film and multiple-exposure techniques was used. Intensities were measured by photometric integration of reflections, integrated one dimensionally by the Weissenberg camera. A total of 1,735 independent observed reflections were collected. The intensities were not corrected for absorption (μ = 0.4). The structure was solved by the Patterson & Fourier methods. Least squares refinement with anisotropic temperature factor for Br atom and isotropic tem-

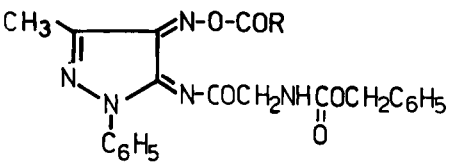
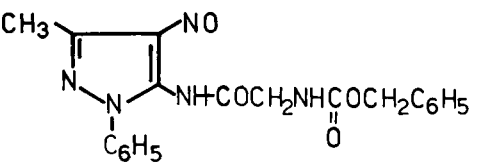


FIGURE 1



II

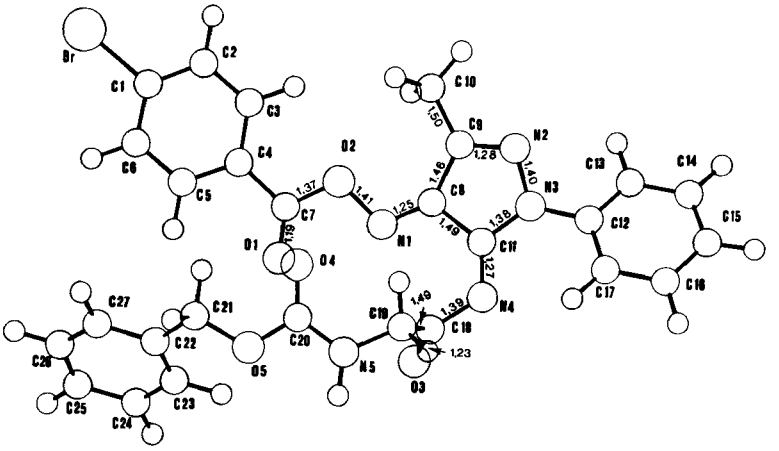
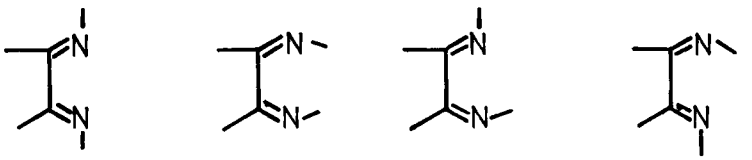


FIGURE 2



A B C D

FIGURE 3

perature factors for all the other non-hydrogen atoms yielded an R factor of 0.088. The phenyl rings were refined as rigid bodies with C-C distances of 1.392 Å. Positions of the H atoms were calculated assuming the accepted values for C-H and N-H distances.

An overall view of the molecule, with the most important interatomic distances in Å, is shown in Fig. 2.

All the observed bond distances are in the expected range of lengths. The e.s.d.'s are of the order of magnitude of .009–.012 Å. Owing to the existence of syn-anti isomerism in such a molecule, the four following structures were theoretically possible (Fig. 3).

It can be seen that the actual molecule corresponds to the form C. The two acyl chains are nearly parallel and the acyloximino group bonded to the N(1) atom is "anti" to the imino function.

The pyrazoline ring is strictly planar and displacements from the least-squares plane of the N(1), N(4) and 0(2) atoms are .016, .021 and .083 Å, respectively.

The distances between the C(7) atom and the N(4) and O(3) atoms are 5.06 and 4.60 Å, respectively, admitting the free rotation around the single bonds in solution, the first contact distance can not change noticeably, while the second one can be reduced to 3.15 Å. That is, the possibility of a nucleophilic attack on the carbonyl C(7) atom, based on a mechanism of anchimeric assistance, seems to be ruled out for the N(4) atom, but not for the O(3) atom. In fact, the minimum C(7)–O(3) distance of 3.15 Å is in the range of the admitted values for the N-H- - -O hydrogen bond (2.57–3.22 Å)(5). The general pattern of the bond distances from the O(2) atom to the N(4) atom, through the pyrazoline ring, shows that the contribution to the ground state of the molecule of polar forms, causing a shifting of the conjugated double bond, is very low.

Obviously it can not be excluded that these forms play an important role during the nucleophilic attack in solution, particularly in view of the noticeable planarity of the ring and of the O(2), N(1) and N(4) atoms.

In addition, the relative positions of the O(19) and N(1) atoms explain the transformation of the compounds I and II into cyclic pyrazolodihydro-pyrazine derivatives (2) which occurs in alkaline media.

EXPERIMENTAL PROCEDURES

0.786 g (2 mM) of 1-phenyl-3-methyl-4-nitroso-5(N-benzyloxycarbonyl)-glycyl-imino pyrazole(3) in 60 ml of chloroform were reacted with 0.440 g (2 mM) of p-bromobenzoylchloride and 0.28 ml (2 mM) of triethylamine.

The reaction mixture was kept under stirring for 3 h, then repeatedly washed with water, 1N $NaHCO_3$ solution and water.

The organic phase was anhydrified and evaporated to give an oily residue which was crystallized from ethyl ether. The separated product was purified on an LH 20 Sephadex column using chloroform as an eluent, and finally crystallized from chloroform and ethyl ether, m.p. 115–116.5°C.

Elemental analysis for $C_{27}H_{22}O_5N_5Br$;

Calc. % C, 56.26; H, 3.85; N, 12.15; Br, 13.86

Found % C, 56.44; H, 3.75; N, 12.17; Br, 13.96

To obtain a single crystal for X-ray analysis the product has been crystallized from chloroform and ethyl ether by means of the vapour diffusion method.

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