discussed by Clearfield, Sims & Singh (1972), and the present compound falls within their general conclusions.

As expected, the methyl group is oriented away from the lone pair of the N atom (Sax & Desiderato, 1967). The fact that the methyl C atom is nearly situated in the plane of the naphthyridine ring implies that some π bonding occurs between the O atom and the ring. The conformation of the methyl group and the distortion in the exocyclic angles result from the minimization of the steric interactions between the H atoms of the methyl group and atom H(3).

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7-Nitro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (Nitrazepam)

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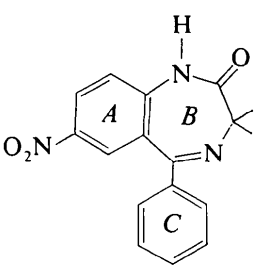
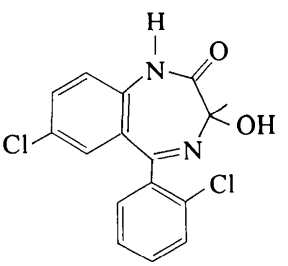
Abstract. Monoclinic, $C2/c$ (No. 15), $a = 27{\cdot}752$ (8), $b = 8{\cdot}251$ (3), $c = 13{\cdot}033$ (4) Å, $\beta = 116{\cdot}93$ (3)°, formula $C_{15}H_{11}N_3O_3$, $Z = 8$, $D_c = 1{\cdot}40$ g cm^{-3}, μ(Cu $K\alpha$) = 8·5 cm^{-1}. The structure consists of pairs of molecules linked by two hydrogen bonds through a crystallographic centre of symmetry. The seven-membered ring is in a boat conformation and a statistical comparison of the geometries of the benzodiazepine group in nitrazepam (I), lorazepam (II) and diazepam (III) has been carried out.

Introduction. The benzodiazepines were introduced as psychotherapeutic agents about fifteen years ago and are still widely used for this purpose. Moreover some of them, markedly diazepam, chlordiazepoxide, oxazepam and nitrazepam, have been shown to have anticonvulsant activity.

In recent years Camerman & Camerman (1970, 1974) have suggested that the biological activity of many anticonvulsant drugs is strictly related to particular steric features of the molecules or, in other words, to the similar arrangement in three-dimensional space of particular atoms or groups of atoms. They based their theory on the similarity of the space-filling characteristic of diazepam with those of other anticonvulsant drugs like diphenylhydantoin, phenobarbital, ethylphenacemide, procyclidine and trihexyphenidyl. On the other hand Sternbach, Sancilio & Blount (1974) have recently determined the crystal structure of two benzodiazepines (4′-fluorodiazepam



(I)



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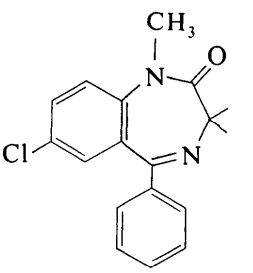


(III)

and 7-dechlorodiazepam), which, although biologically inactive, were found to be practically superimposable on the molecule of diazepam. According to these authors, these findings show that steric similarities do not necessarily imply similar biological properties, which may be affected by many other known or unknown factors.

What is evident, in our opinion, is that the problem of finding a relation between structure and activity in benzodiazepines is far from being totally elucidated and that it should be reconsidered in the future starting from as wide an experimental basis as possible.

The present paper reports the crystal and molecular structure of nitrazepam (I), a benzodiazepine having anticonvulsant properties and widely used as a hypnotic drug.

The compound, kindly provided by the pharmacological firm Prodotti Roche, Milan, was recrystallized from ethanol. A suitable crystal of dimensions 0·20 × 0·25 × 0·40 mm was mounted along **b**. Intensities were collected on an automatic Philips PW 1100 four-circle diffractometer by use of monochromated Cu $K\alpha$ radiation and the $\omega/2\theta$ scan technique. Of 1678 independent reflexions ($\theta \leq 55°$), 1346 having $I_o \geq 2\sigma(I_o)$ were considered to be observed. An appreciable intensity decay of the standard reflexions was observed during the data collection time and all the intensities were rescaled accordingly. Scattering factors for H atoms were taken from Stewart, Davidson & Simpson (1965) and for the other atoms from Cromer & Waber (1965). Computations were carried out mainly with the XRAY 72 system of crystallographic programs.

The structure was solved by direct methods with the *MULTAN* 74 system of computer programs (Main, Woolfson, Lessinger, Germain & Declercq, 1974) and refined by full-matrix least squares with anisotropic temperature factors used for all the non-hydrogen atoms. Although all the H atoms were located from the difference map made after the isotropic refinement, their positions were not refined but calculated with N–H and C–H bond lengths of 1·02 Å assumed. Unobserved reflexions were used only if $|F_c| > |kF_o|$. Weights for the last cycle were calculated as $w = 1/(4{\cdot}48 - 0{\cdot}139|F_o| + 0{\cdot}0018|F_o|^2)$. In this cycle the largest shift/error, R $(= \Sigma|\Delta|/\Sigma|F_o|)$ and R_w $[= (\Sigma w|\Delta|^2/\Sigma w|F_o|^2)^{1/2}]$ were 0·01, 0·056 and 0·056 respectively. The final values of the positional parameters are listed in Table 1.*

Table 1. *Positional* (×10⁴) *parameters of the non-hydrogen atoms, with e.s.d.'s in parentheses*

	x	*y*	*z*
C(1)	841 (1)	4288 (4)	767 (3)
C(2)	984 (2)	4011 (5)	−100 (3)
C(3)	1420 (2)	4832 (5)	−65 (3)
C(4)	1709 (1)	5920 (4)	825 (3)
C(5)	1552 (1)	6232 (4)	1686 (3)
C(6)	1104 (1)	5380 (4)	1633 (3)
C(7)	1820 (1)	7466 (4)	2593 (2)
C(8)	2681 (1)	6719 (4)	2821 (3)
C(9)	2614 (1)	7176 (4)	1651 (3)
C(10)	1478 (1)	8512 (4)	2926 (3)
C(11)	966 (1)	9017 (5)	2124 (3)
C(12)	665 (2)	10045 (5)	2448 (4)
C(13)	864 (2)	10570 (5)	3566 (4)
C(14)	1366 (2)	10054 (5)	4369 (3)
C(15)	1671 (1)	9054 (4)	4057 (3)
N(1)	369 (1)	3427 (5)	737 (3)
N(2)	2135 (1)	6753 (4)	751 (2)
N(3)	2332 (1)	7741 (3)	3116 (2)
O(1)	162 (1)	2370 (4)	17 (3)
O(2)	210 (1)	3802 (4)	1435 (3)
O(3)	2957 (1)	7919 (3)	1492 (2)

Discussion. A general view of the molecule is shown in Fig. 1 and bond lengths and angles are listed in Tables 2 and 3. The structure is built up of dimers consisting of

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32616 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

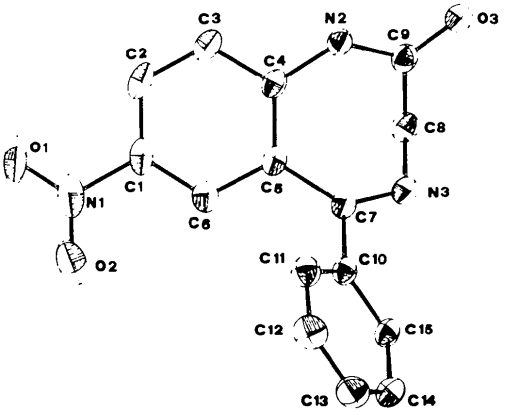
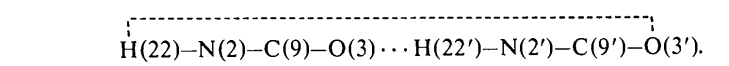


Fig. 1. A view of the molecule, showing the thermal ellipsoids at 40% probability (Johnson, 1965).

Table 2. *Bond distances* (Å) *with e.s.d.'s in parentheses*

C(1)–C(2)	1·377 (7)	C(8)–C(9)	1·499 (5)
C(1)–C(6)	1·368 (5)	C(9)–N(2)	1·362 (4)
C(1)–N(1)	1·474 (6)	C(9)–O(3)	1·225 (5)
C(2)–C(3)	1·370 (6)	C(10)–C(11)	1·393 (4)
C(3)–C(4)	1·397 (5)	C(10)–C(15)	1·393 (5)
C(4)–C(5)	1·399 (6)	C(11)–C(12)	1·384 (6)
C(4)–N(2)	1·406 (5)	C(12)–C(13)	1·373 (6)
C(5)–C(6)	1·403 (5)	C(13)–C(14)	1·377 (5)
C(5)–C(7)	1·480 (4)	C(14)–C(15)	1·369 (6)
C(7)–C(10)	1·487 (5)	N(1)–O(1)	1·217 (5)
C(7)–N(3)	1·289 (4)	N(1)–O(2)	1·217 (7)
C(8)–N(3)	1·460 (5)		

two molecules linked through a crystallographic centre of symmetry by two hydrogen bonds, forming an eight-membered ring:



The distance N(2)···O(3′) is 2·831 (4) Å and no other intermolecular short contact is observed.

The boat conformation of the seven-membered ring (ring *B*) can be described with reference to the least-squares plane (Table 4) through the C(1)–C(6) phenyl ring (ring *A*). Ring *A* is approximately planar and the displacements from this plane of the N(2) and C(7) atoms are very small, while the N(3), C(9) and C(8) atoms are out of the plane by 0·52, 0·59 and 1·41 Å respectively. The plane through the nitro group makes an angle of 6·6° with the phenyl plane.

The C(10)–C(15) phenyl ring (ring *C*) is strictly planar (χ^2 = 7·65) and the torsion angle C(5)–C(7)–C(10)–C(11) is 34·5°.

The geometry of the benzodiazepine group in the present structure has been compared with the geometry of the corresponding groups in lorazepam (Bandoli & Clemente, 1976) and diazepam (Camerman & Camerman, 1972), the two biologically active benzodiazepines whose structures have so far been reported. The comparison has been carried out by means of half-normal probability (HNP) plots (Abrahams & Keve, 1971; Hamilton & Abrahams, 1972) with all the intramolecular distances connecting each atom with its first, second and third neighbours, excluding third-neighbour distances related to the torsion angle between ring *B* and ring *C*. By this comparison nitrazepam is shown to be statistically indistinguishable from the two independent molecules in the asymmetric unit of lorazepam. The HNP plot is nearly linear with zero intercept; standard deviations (on average 0·012 Å in lorazepam and 0·005 Å in nitrazepam) are shown to be underestimated by a factor of two. Conversely, small differences are found between nitrazepam and diazepam (average standard deviation = 0·002 Å).

Table 3. *Bond angles* (°) *with e.s.d.'s in parentheses*

C(2)–C(1)–C(6)	122·7 (4)	C(8)–C(9)–N(2)	115·7 (3)
C(2)–C(1)–N(1)	118·7 (3)	C(8)–C(9)–O(3)	123·4 (3)
C(6)–C(1)–N(1)	118·5 (4)	N(2)–C(9)–O(3)	120·9 (3)
C(1)–C(2)–C(3)	118·0 (3)	C(7)–C(10)–C(11)	121·6 (3)
C(2)–C(3)–C(4)	120·8 (4)	C(7)–C(10)–C(15)	120·3 (3)
C(3)–C(4)–C(5)	120·9 (4)	C(11)–C(10)–C(15)	118·1 (4)
C(3)–C(4)–N(2)	116·2 (4)	C(10)–C(11)–C(12)	120·3 (3)
C(5)–C(4)–N(2)	122·7 (3)	C(11)–C(12)–C(13)	120·6 (3)
C(4)–C(5)–C(6)	117·3 (3)	C(12)–C(13)–C(14)	119·4 (4)
C(4)–C(5)–C(7)	122·8 (3)	C(13)–C(14)–C(15)	120·6 (4)
C(6)–C(5)–C(7)	119·8 (4)	C(10)–C(15)–C(14)	120·9 (3)
C(5)–C(6)–C(1)	120·1 (4)	C(1)–N(1)–O(1)	118·0 (4)
C(5)–C(7)–C(10)	118·5 (3)	C(1)–N(1)–O(2)	118·4 (3)
C(5)–C(7)–N(3)	125·3 (3)	O(1)–N(1)–O(2)	123·7 (4)
C(10)–C(7)–N(3)	116·2 (3)	C(4)–N(2)–C(9)	126·1 (3)
C(9)–C(8)–N(3)	109·3 (3)	C(7)–N(3)–C(8)	117·6 (3)

Table 4. *Displacements* (Å) *from the least-squares plane through the* C(1)–C(6) *phenyl ring*

C(1)	0·014	N(1)	0·001	C(8)	1·407
C(2)	−0·007	O(1)	0·123	N(3)	0·519
C(3)	−0·006	O(2)	−0·123	C(7)	−0·093
C(4)	0·012	N(2)	−0·051	C(10)	−0·973
C(5)	−0·005	C(9)	0·587		
C(6)	−0·008	O(3)	0·452		

χ^2 = 35·5 (5 degrees of freedom).

These differences are mainly due to the presence of the methyl group on the amidic nitrogen, which hinders the possibility of intermolecular hydrogen bonding present in nitrazepam as well as in lorazepam and causes small variations in the C(4)–N(2) bond distance [from 1·406 (5) to 1·427 (2) Å] and in the C(4)–N(2)–C(9) bond angle [from 126·1 (3) to 123·1 (2)°].

At present it seems difficult to state whether these steric similarities or small differences can be directly related to the biological activity of benzodiazepines, even if the analysis is confined to their anticonvulsant action. A reason for this is that drugs are metabolized in the body to form other compounds which may be, in their turn, biologically active. Diazepam is a typical case; it is metabolized to *N*-demethyldiazepam, 3-hydroxydiazepam and 3-hydroxy-*N*-demethyldiazepam (oxazepam), all of which are active to various degrees.

A point to be stressed is that the molecular structure of the parent drug may be unimportant if its activity is due to its metabolites. In the present case it has been proved that the parent compound, nitrazepam, accounts for the pharmacological activity in all the animal species studied (Randall & Kappell, 1973), so the determination of its molecular structure may be of interest in the elucidation of a structure–activity relation in benzodiazepines.

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(±)-Carbocamphenilone

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Abstract. $C_{10}H_{14}O_2$, $M_r = 166{\cdot}22$, m.p. 59–60°, monoclinic, $P2_1/c$, $Z = 4$, $a = 7{\cdot}785$ (2), $b = 10{\cdot}239$ (3), $c = 13{\cdot}510$ (4) Å, $\beta = 120{\cdot}06$ (4)°, $D_x = 1{\cdot}185$ g cm^{-3}, λ(Mo $K\alpha$) = 0·7107 Å, μ(Mo $K\alpha$) = 0·874 cm^{-1}, $R = 0{\cdot}051$ for 834 observed reflections. In the crystal the six-membered ring exists in the chair conformation and the dihedral angle between the two carbonyl groups is −34·0 (4)° in the (+)-enantiomer.

Introduction. (±)-Carbocamphenilone, m.p. 59–60°, was prepared from (±)-camphene by the method of Hückel (1947) and crystallized from ligroin. X-ray photographs of the chunky, yellow crystals indicated monoclinic symmetry and systematic absences consistent with the space group $P2_1/c$ ($h0l$ reflections absent when l odd and $0k0$ reflections absent when k odd). Because the substance is volatile and sensitive to moisture, the crystal (0·3–0·4 mm to a side) selected for the data collection was attached to the inside wall of a sealed, thin-walled glass capillary. Three-dimensional data were collected using a Syntex $P\bar{1}$ diffractometer, graphite-monochromated Mo $K\alpha$ radiation and a θ–2θ scan procedure, the details of which have been reported (Seccombe, Lee & Henry, 1975). Intensities were measured in shells of 2θ 0–20, 20–30, 30–35, 35–40, 40–43, and 43–47°. The data collection was terminated in the middle of the last shell because the intensities of the decay-monitoring reflections fell below 90% of the original values and because most of the intensities in this shell were undetectably low. There were 1064 reflections with $2\theta \leq 43°$, of which 834 reflections had $I > 3\sigma(I)$. These intensity data were corrected for the decay and reduced to the structure factors by the application of Lorentz and polarization corrections. No absorption or extinction correction was applied.

The structure was determined with *MULTAN* (Germain, Main & Woolfson, 1971) and refined by least-squares procedures, in which all non-hydrogen atoms were assigned anisotropic temperature factors. H

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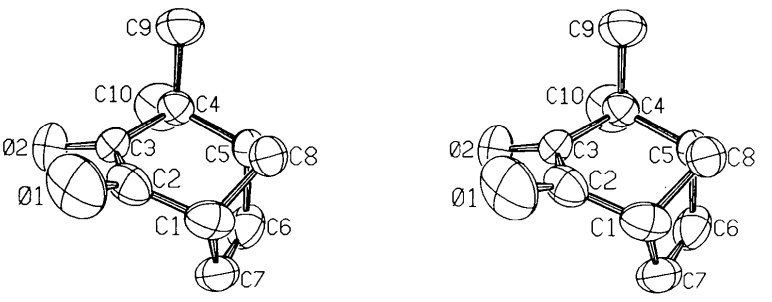

Fig. 1. Stereoview of the molecule (+)-carbocamphenilone.