laquelle l'oxygène O(2) est simultanément engagé dans deux liaisons intramoléculaires avec les liaisons N(1)—H(N1) et N(3)—H(N3). La bande d'absorption infrarouge de la première liaison apparaît vers 344,0 mm⁻¹ et celle de la seconde liaison vers 332,0 mm⁻¹. Dans le second conformère minoritaire, la liaison amide médiane est de conformation *cis* et l'absence de toute liaison hydrogène intramoléculaire ne nous a pas permis de préciser la conformation de la molécule.

Les auteurs remercient Monsieur le Professeur J. Néel pour l'intérêt qu'il a porté à ce travail.

Références

AUBRY, A. (1976). Thèse Doctorat en Sciences. Université de Nancy I. CNRS N° AO-12610.

AUBRY, A., PROTAS, J., BOUSSARD, G. & MARRAUD, M. (1977). *Acta Cryst.* B33, 2399–2406.

BOUSSARD, G., MARRAUD, M. & AUBRY, A. (1979). A paraître.

BUSING, W. R., MARTIN, K. O. & LEVY, H. A. (1962). *ORFLS.* Report ORNL-TM-305. Oak Ridge National Laboratory, Tennessee.

CHANDRASEKARAN, R., LAKSHMINARAYANAN, A. V., PANDYA, U. V. & RAMACHANDRAN, G. N. (1973). *Biochim. Biophys. Acta,* 303, 14–27.

CHENG-SAN CHEN & PARTHASARATHY, R. (1978). *Int. J. Pept. Protein Res.* 11, 9–18.

CHOU, P. Y. & FASMAN, G. D. (1977). *J. Mol. Biol.* 115, 135–175.

GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1970). *Acta Cryst.* B26, 274–285.

IUPAC–IUB COMMISSION ON BIOCHEMICAL NOMENCLATURE (1970). *J. Mol. Biol.* 52, 1–17.

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

KARLE, I. L. (1975). *Peptides: Chemistry, Structure, Biology,* edited by R. WALTER & J. MEIENHOFER, pp. 61–84 et références citées. Ann Arbor: Science Publishers Inc.

KARLE, I. L. (1978). *J. Am. Chem. Soc.* 100, 1286–1289.

LEWIS, P. N., MOMANY, F. A. & SCHERAGA, H. A. (1973). *Biochim. Biophys. Acta,* 303, 211–219.

MARRAUD, M. & NÉEL, J. (1975). *J. Chim. Phys. Phys. Chim. Biol.* 72, 1173–1184.

RAMACHANDRAN, G. N., KOLASKAR, A. S., RAMAKRISHNAN, C. & SASISEKHARAN, V. (1974). *Biochim. Biophys. Acta,* 359, 298–302.

SHAMALA, N., NAGARAJ, R. & BALARAM, P. (1977). *Biochem. Biophys. Res. Commun.* 79, 292–298.

Structural Studies of Substituted 6,7-Benzomorphan Compounds.
I. The Absolute Configuration of (−)-2-Cyclopropylmethyl-2′-hydroxy-5-ethyl-9,9-dimethyl-6,7-benzomorphan (Gemazocine) Hydrobromide

BY Y. G. GELDERS AND C. J. DE RANTER*

Laboratorium voor Analytische Scheikunde, Instituut voor Farmaceutische Wetenschappen, KU Leuven, Van Evenstraat 4, B-3000 Leuven, Belgium

AND H. SCHENK

Laboratorium voor Kristallografie, Universiteit van Amsterdam, Nieuwe Achtergracht 166, Amsterdam, The Netherlands

Abstract

The hydrobromide salt of the biologically active laevorotatory form of gemazocine crystallizes in the orthorhombic space group $P2_12_12_1$ with $a = 11\cdot225$ (1), $b = 11\cdot817$ (1), $c = 14\cdot076$ (2) Å and $Z = 4$. The crystal structure of (−)-gemazocine.HBr [(−)-3-cyclopropylmethyl-6-ethyl-1,2,3,4,5,6-hexahydro-2,6-methano-11,11-dimethyl-3-benzazocin-8-ol hydrobromide] was determined by a Patterson method and was refined by block-diagonal least squares to $R = 0\cdot038$. The absolute configuration was determined by coordinate inversion, the lower R value giving the appropriate coordinates of the molecule, and checked with analogous measurements on (+)-gemazocine.HBr. The antagonist properties of the (−)

---

enantiomer on interaction with the narcotic opiate receptor could be attributed to the cyclopropylmethyl side chain, as in cyclazocine. However, attentive study of the three crystal structures [(−)-gemazocine.HBr, (−)-cyclazocine.HBr.H_2O and (−)-cyclazocine base] revealed the existence of three different conformations for the cyclopropylmethyl side chain. In the gemazocine.HBr crystal the molecules are linked by hydrogen bonds involving the Br, O and N atoms.

Introduction

The present study forms part of an investigation into the relation between molecular structure and physiological properties of morphine-related compounds. In this respect substituted 6,7-benzomorphans are of particular interest, because they show both structural rigidity, and a variety of different analgesic activities, possibly associated with less addicting properties than morphine.

This study describes the structure of (−)-gemazocine.HBr (ACF Chemiefarma NV, 1970), which appears to be an antagonist of the narcotic analgesics, while its optical antipode has no activity at all (ACF Chemiefarma NV, private communication). The results can be compared with those for related benzomorphans that have been determined already (Karle, Gilardi, Fratini & Karle, 1969; Fedeli, Giacomello, Cerrini & Vaciago, 1970; Cochran & Abola, 1975) and which have in common the presence of one methyl group at the 9-position, whilst (−)-gemazocine.HBr has two methyl groups at this position. Special attention will be paid to the conformation of the N−C−C−C side chain, one of the most important features in defining the interaction with the opiate narcotic receptor.

Experimental

Crystal data

$C_{20}H_{30}NO^+.Br^-$, M_r = 380.38, orthorhombic, $P2_12_12_1$, a = 11.225 (1), b = 11.817 (1), c = 14.076 (2) Å, V = 1867 Å^3, Z = 4, ρ_{calc} = 1.353, ρ_{meas} = 1.355 Mg m^{-3}, $F(000)$ = 800, $\alpha_D(DMF)$ = −133°, $\mu(Cu\ K\alpha)$ = 3.336 mm^{-1}.

Crystals of (−)-gemazocine.HBr were obtained by evaporation at room temperature from a solution in methanol/water. The crystals display a high degree of transparency and a well defined morphological habit. Preliminary photographic work indicated that the crystals were orthorhombic. The space group $P2_12_12_1$ was unambiguously determined from the systematic absences (h00, 0k0, 00l, for h, k and l odd respectively). The lattice constants were obtained from a least-squares calculation of the setting angles of 29 2θ

reflections measured on a Nonius CAD-4 automatic diffractometer with Cu $K\alpha$ radiation (λ = 1.54178 Å) at room temperature. 1870 independent intensities were collected using the θ–2θ scan; of these, 63 were rejected because of low intensity (I_o < 3σ). The net intensities of the reflections were corrected for Lorentz and polarization factors, but not for absorption.

With an identical procedure, intensity data for (+)-gemazocine.HBr were also collected. In this case 2020 independent reflections were above the significance level.

Determination and refinement of the structure

In the (−)-gemazocine.HBr molecule the bromide position was obtained from a three-dimensional Patterson function, and a subsequent superposition map (minimum function) gave the positions of all other non-hydrogen atoms. The structure was then refined anisotropically by block-diagonal least squares using the XRAY program system (Stewart, Kruger, Ammon, Dickinson & Hall, 1976). At the stage R = 0.061 a difference synthesis was made in which the positions of most non-methyl H atoms could be found. Positional parameters of the H atoms bonded to terminal C atoms and those of a missing H atom in the cyclopropyl ring, H(16,2), were calculated. The H atoms were all given the isotropic thermal parameters of the adjacent atoms and in this manner they were, although not refined, included in the subsequent calculations, which lowered the R value to 0.051.

The absolute configuration was established by inverting the signs of the atomic coordinates (Ibers & Hamilton, 1964). Two refinements to convergence were performed, one with the original coordinates yielding R = 0.044 and the other, with the inverted coordinates, resulting in R = 0.055, so that the correct structure of the molecule has to be attributed to the first set of coordinates, even at the 0.5% level of significance (Hamilton, 1965). These results were confirmed by refinements of data of the optical antipode, (+)-gemazocine.HBr. In this case the refinement with x,y,z positions led to an R value of 0.044, whilst the inverted coordinates gave R = 0.060.

After rejection of 36 reflections affected by extinction the final refinement of (−)-gemazocine.HBr yielded an R index of 0.038. The final positional parameters for the non-hydrogen atoms of the molecule are given in Table 1;* the coordinates and isotropic thermal parameters of the H atoms are listed in Table 2.

___

Table 1. *Atomic coordinates for the non-hydrogen atoms, with e.s.d.'s in parentheses*

	x	y	z
Br	0·8789 (1)	−0·0534 (0)	0·8468 (0)
O(2')	0·7370 (3)	0·7191 (3)	0·9090 (3)
C(1)	0·7320 (4)	0·2418 (4)	0·6806 (3)
N	0·8402 (3)	0·1847 (3)	0·7230 (3)
C(3)	0·8881 (5)	0·2470 (4)	0·8079 (3)
C(4)	0·7894 (4)	0·2628 (4)	0·8795 (3)
C(5)	0·6732 (4)	0·3168 (4)	0·8383 (3)
C(6)	0·7055 (4)	0·4358 (4)	0·8069 (3)
C(7)	0·7491 (4)	0·4544 (4)	0·7154 (3)
C(8)	0·7629 (4)	0·3589 (4)	0·6431 (4)
C(9)	0·6295 (4)	0·2458 (4)	0·7526 (3)
C(10)	0·5832 (5)	0·3153 (4)	0·9242 (4)
C(11)	0·4622 (5)	0·3719 (6)	0·9140 (4)
C(12)	0·5909 (5)	0·1249 (4)	0·7792 (4)
C(13)	0·5242 (5)	0·2975 (5)	0·6992 (4)
C(14)	0·9408 (4)	0·1580 (4)	0·6548 (4)
C(15)	0·9007 (5)	0·1001 (5)	0·5661 (4)
C(16)	0·9790 (6)	0·0063 (5)	0·5273 (5)
C(17)	0·8584 (6)	−0·0230 (6)	0·5708 (5)
C(1')	0·7024 (4)	0·5280 (4)	0·8689 (3)
C(2')	0·7389 (4)	0·6355 (4)	0·8417 (4)
C(3')	0·7753 (4)	0·6546 (4)	0·7497 (4)
C(4')	0·7818 (5)	0·5646 (4)	0·6880 (3)

Table 2. *Fractional coordinates and isotropic thermal parameters for the hydrogen atoms*

	x	y	z	U (Å² × 10³)
H(1)	0·7248	0·1998	0·6262	37
H(N)	0·8164	0·1024	0·7439	35
H(3,1)	0·9575	0·2001	0·8336	38
H(3,2)	0·9204	0·3265	0·7866	38
H(4,1)	0·8265	0·3090	0·9307	45
H(4,2)	0·7649	0·1916	0·9088	45
H(8,1)	0·8447	0·3616	0·6205	36
H(8,2)	0·7184	0·3748	0·5886	36
H(10,1)	0·6226	0·3528	0·9811	50
H(10,2)	0·5837	0·2372	0·9521	50
H(11,1)	0·4782	0·4572	0·8975	65
H(11,2)	0·4191	0·3326	0·8566	65
H(11,3)	0·4023	0·3709	0·9712	65
H(12,1)	0·5151	0·1269	0·8228	52
H(12,2)	0·5723	0·0778	0·7177	52
H(12,3)	0·6633	0·0894	0·8159	52
H(13,1)	0·5055	0·2504	0·6377	52
H(13,2)	0·4484	0·2996	0·7429	52
H(13,3)	0·5505	0·3800	0·6811	52
H(14,1)	1·0000	0·1000	0·6896	55
H(14,2)	0·9813	0·2323	0·6373	55
H(15)	0·8833	0·1574	0·5161	67
H(16,1)	0·9898	0·0082	0·4524	90
H(16,2)	1·0352	−0·0074	0·5884	90
H(17,1)	0·8529	−0·0569	0·6417	88
H(17,2)	0·8312	−0·0230	0·4938	88
H(1')	0·6714	0·5209	0·9455	30
H(3')	0·8128	0·7314	0·7330	38
H(4')	0·8054	0·5722	0·6240	37
H(O2')	0·7640	0·7667	0·8798	42
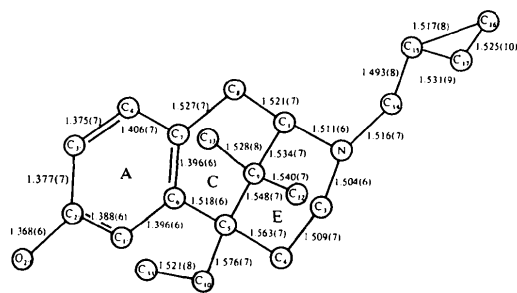
Fig. 1. Atomic numbering of the molecule with bond lengths (Å) and e.s.d.'s in parentheses.

Description and discussion of the molecule

Geometry

The atomic numbering of the gemazocine molecule (Fig. 1) is that commonly accepted for the benzo-morphan class, where the ring system shows a further simplification of the morphine and morphinan skeleton. For comparison, the same name is given to the rings as in the case of morphine (Gylbert, 1973). The benzo-morphans, however, do not have the ether bridge and the hydroaromatic ring D of the morphine molecule. In gemazocine the centres of chirality C(1) and C(5) can be designated as (1R,5R) for the narcotic antagonist and (1S,5S) for the inactive dextrorotatory molecule.

The bond angles (Table 3) indicate that the position of the phenolic O atom in the molecule shows a slight

Table 3. *Bond angles (°) with e.s.d.'s in parentheses for (−)-gemazocine.HBr*

N—C(1)—C(8)	111·2 (4)	C(1)—C(8)—C(7)	114·7 (4)
N—C(1)—C(9)	110·8 (4)	C(1)—C(9)—C(5)	107·0 (4)
C(8)—C(1)—C(9)	111·8 (4)	C(1)—C(9)—C(12)	110·0 (4)
C(1)—N—C(3)	112·4 (4)	C(1)—C(9)—C(13)	105·5 (4)
C(1)—N—C(14)	116·2 (4)	C(5)—C(9)—C(12)	113·8 (4)
C(3)—N—C(14)	109·8 (4)	C(5)—C(9)—C(13)	114·3 (4)
N—C(3)—C(4)	109·2 (4)	C(12)—C(9)—C(13)	105·8 (4)
C(3)—C(4)—C(5)	114·5 (4)	C(5)—C(10)—C(11)	119·6 (4)
C(4)—C(5)—C(6)	106·7 (4)	N—C(14)—C(15)	113·6 (4)
C(4)—C(5)—C(9)	109·4 (4)	C(14)—C(15)—C(16)	117·5 (5)
C(4)—C(5)—C(10)	104·2 (4)	C(14)—C(15)—C(17)	119·6 (6)
C(6)—C(5)—C(9)	110·5 (4)	C(16)—C(15)—C(17)	60·1 (4)
C(6)—C(5)—C(10)	112·8 (4)	C(15)—C(16)—C(17)	60·4 (4)
C(9)—C(5)—C(10)	112·8 (4)	C(15)—C(17)—C(16)	59·5 (4)
C(5)—C(6)—C(7)	119·9 (4)	C(6)—C(1')—C(2')	122·3 (4)
C(5)—C(6)—C(1')	122·4 (4)	O(2')—C(2')—C(1')	117·7 (4)
C(7)—C(6)—C(1')	117·6 (4)	O(2')—C(2')—C(3')	122·5 (4)
C(6)—C(7)—C(8)	122·3 (4)	C(1')—C(2')—C(3')	119·8 (4)
C(6)—C(7)—C(4')	119·3 (4)	C(2')—C(3')—C(4')	118·8 (4)
C(8)—C(7)—C(4')	118·4 (4)	C(7)—C(4')—C(3')	122·0 (4)

deviation from a strictly trigonal arrangement [O(2')—C(2')—C(1') = 117·7°]. This effect was also observed in morphine and cyclazocine (Karle, Gilardi, Fratini & Karle, 1969), the benzomorphan compound most closely related to gemazocine. If a methoxy group is
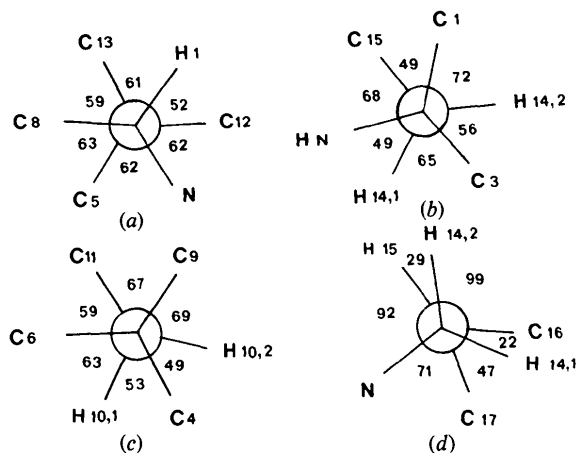
Fig. 2. Selected Newman projections along (a) C(1)–C(9), (b) N–C(14), (c) C(5)–C(10) and (d) C(14)–C(15).

Fig. 3. Stereoscopic view of the (−)-gemazocine cation with 50% probability thermal ellipsoids for the non-hydrogen atoms.

present, as in codeine (Kartha, Ahmed & Barnes, 1962) and dextrometorphan (Gylbert & Carlström, 1977), the deformation is even stronger and the same angle has values of 114·5 and 115·5° respectively. The bond lengths (Fig. 1) and most of the other bond angles are within the expected range, except for the angle C(5)–C(10)–C(11) which is closer to the trigonal than the tetrahedral value (119·6°). This observation, the slightly deviating bond lengths around C(5) and the conformation of the ethyl side chain, given in a Newman projection around the C(5)–C(10) bond in Fig. 2, reveal the considerable steric influence of the 9,9-dimethyl group. In this way, the distance of 2·28 Å [the shortest H···H interaction between the two terminal C atoms, C(11) and C(13)] can be understood.

In the (−)-gemazocine.HBr molecule, an ORTEP (Johnson, 1965) stereopair of which is shown in Fig. 3, the angle between the least-squares planes through the atoms of the aromatic ring A and the piperidine ring E is 84·6° while the angle between the plane through rings A and C and the plane of E is 87·6°, so that this three-ring system exhibits the well established T shape of the fairly rigid morphine-related molecules.

The torsion angles (Table 4) describe the stereochemical features of the molecule together with the comparable parts in (−)-cyclazocine.HBr.H₂O and (−)-cyclazocine base, as reported in the study of the racemate (Karle et al., 1969), which are all characterized by narcotic antagonist properties and a similar N side chain. The three structures have in common: the strictly planar aromatic A ring, the C ring in sofa form [only C(9) is on average 0·74 Å out of the plane through C(1)–C(5)–C(6)–C(7)–C(8)] and the E ring showing a slightly deformed chair conformation. From the misleading representation of Karle et al. (1969) it may be wrongly concluded that the side chains at the N
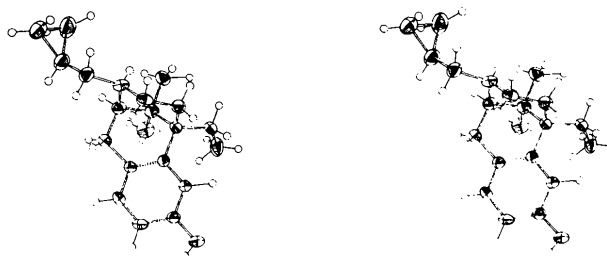
Table 4. *Torsion angles* (°) *with e.s.d.'s in parentheses for three comparative benzomorphans, with the atomic numbering of the gemazocine molecule*

	(−)-Gemazocine .HBr	(−)-Cyclazocine .HBr.H₂O	(−)-Cyclazocine
Ring A			
C(7)–C(6)–C(1')–C(2')	0·9 (8)	0·7 (11)	−0·9 (9)
C(6)–C(1')–C(2')–C(3')	2·7 (8)	−0·9 (12)	3·3 (9)
C(1')–C(2')–C(3')–C(4')	−3·9 (8)	−0·6 (12)	−3·7 (9)
C(2')–C(3')–C(4')–C(7)	1·6 (9)	2·3 (11)	1·8 (9)
C(3')–C(4')–C(7)–C(6)	2·0 (9)	−2·5 (11)	0·6 (9)
C(4')–C(7)–C(6)–C(1')	−3·2 (8)	0·9 (11)	−1·1 (9)
Ring C			
C(8)–C(1)–C(9)–C(5)	−63·2 (6)	−61·8 (8)	−63·8 (7)
C(1)–C(9)–C(5)–C(6)	60·2 (5)	59·6 (9)	58·6 (6)
C(9)–C(5)–C(6)–C(7)	−30·9 (6)	−28·7 (10)	−26·7 (7)
C(5)–C(6)–C(7)–C(8)	1·9 (8)	−3·0 (11)	0·1 (7)
C(6)–C(7)–C(8)–C(1)	−3·3 (8)	3·2 (10)	−5·1 (8)
C(7)–C(8)–C(1)–C(9)	34·6 (6)	30·1 (8)	36·1 (8)
Ring E			
C(9)–C(1)–N–C(3)	−61·9 (5)	−63·5 (10)	−59·9 (5)
C(1)–N–C(3)–C(4)	54·5 (5)	57·2 (9)	56·4 (5)
N–C(3)–C(4)–C(5)	−52·0 (6)	−56·3 (10)	−54·0 (6)
C(3)–C(4)–C(5)–C(9)	55·0 (6)	58·5 (10)	56·2 (5)
C(4)–C(5)–C(9)–C(1)	−57·0 (5)	−60·6 (9)	−60·0 (5)
C(5)–C(9)–C(1)–N	61·7 (5)	64·6 (9)	61·5 (5)
N side chain			
C(1)–N–C(14)–C(15)	−48·7 (6)	−167·1 (11)	−60·4 (6)
C(3)–N–C(14)–C(15)	−177·7 (5)	66·3 (14)	171·5 (5)
N–C(14)–C(15)–C(16)	−140·5 (5)	175·1 (12)	167·6 (6)
N–C(14)–C(15)–C(17)	−71·1 (7)	−96·1 (22)	96·9 (6)

atom in (−)-cyclazocine.HBr.H₂O and (−)-cyclazocine base have the same conformation. In fact, their conformations represent two of the main N–C–C–C-conformations which are plausible on the basis of steric considerations. A third possibility is found in the title compound (see Newman projections in Fig. 2). These results of the solid-state studies have been supported by the conformational-energy study of protonated gemazocine using PCILO calculations (Claverie et al., 1972). The energy map (Fig. 4) shows the regions of minimum energy for the cyclopropylmethyl side chain which, from the large extension of the contours, proves to be rather flexible. From this point of view it is expected that these minor conformational differences found in the three crystal structures do not have a significant influence on the pharmacological properties of the molecules.
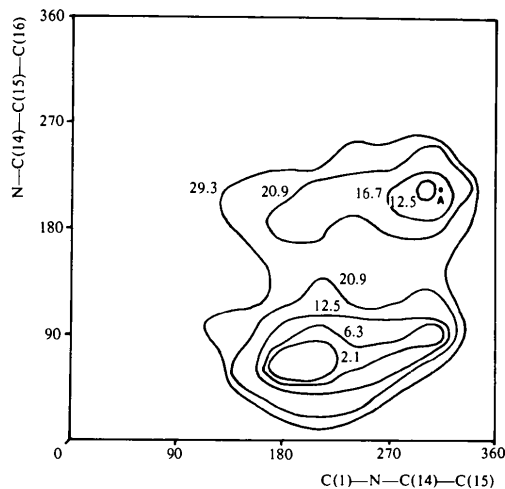
Fig. 4. Results of the *PCILO* calculations for protonated gemazocine. The dot *A* indicates the experimental value and the contours are in kJ mol⁻¹.
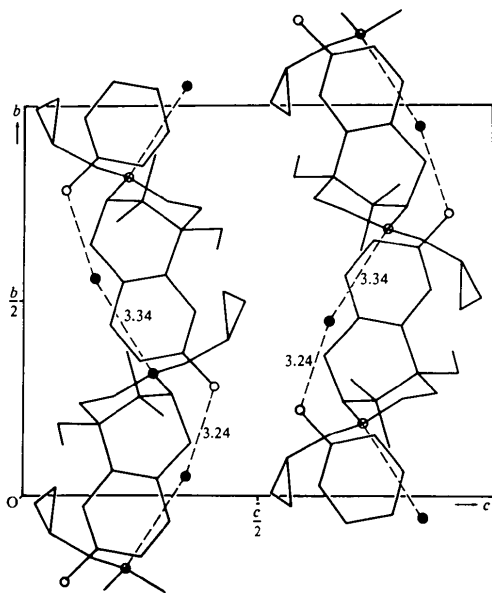

Fig. 5. Projection in the (100) plane of the (−)-gemazocine. HBr structure showing the packing and the hydrogen-bond scheme. Filled, open and crossed circles represent Br, O and N atoms respectively.

Molecular packing and hydrogen bonds

The packing of the molecules in the crystal and the hydrogen-bonding scheme of (−)-gemazocine. HBr can be seen in Fig. 5 where the $N^+ \cdots Br^-$ distance is 3·34 Å and $O(2') \cdots Br^-$ is 3·24 Å. From the positions of the H atoms involved in the bonding system it can be calculated that the $N^+ - H(N) \cdots Br^-$ angle is 148·2°, while $O(2') - H(O2') \cdots Br^-$ is 157·7°, both favourable for hydrogen-bond formation. These hydrogen bonds hold the gemazocine molecules together in endless chains parallel to the *b* axis. The corresponding $H \cdots Br^-$ distances are 2·71 and 2·53 Å respectively. No other short intermolecular distances which influence the molecular packing have been found.

References

ACF Chemiefarma NV (1970). US Patent 3764606. See *Chem. Abstr.* (1971), **74**, 125486X.

CLAVERIE, P., DAUDEY, J. P., DINER, S., GIESSNER-PRETTRE, C., GILBERT, M., LANGLET, J., MALRIEU, J. P., PINCELLI, U. & PULLMAN, B. (1972). *Quantum Chem. Program Exch.* **10**, 220.

COCHRAN, T. G. & ABOLA, J. E. (1975). *Acta Cryst.* B31, 919–921.

FEDELI, W., GIACOMELLO, G., CERRINI, S. & VACIAGO, A. (1970). *J. Chem. Soc. B*, pp. 1190–1195.

GYLBERT, L. (1973). *Acta Cryst.* B29, 1630–1635.

GYLBERT, L. & CARLSTRÖM, D. (1977). *Acta Cryst.* B33, 2833–2837.

HAMILTON, W. C. (1965). *Acta Cryst.* **18**, 502–510.

IBERS, J. A. & HAMILTON, W. C. (1964). *Acta Cryst.* **17**, 781–782.

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

KARLE, I. L., GILARDI, R. D., FRATINI, A. V. & KARLE, J. (1969). *Acta Cryst.* B25, 1469–1479.

KARTHA, G., AHMED, F. R. & BARNES, W. H. (1962). *Acta Cryst.* **15**, 326–333.

STEWART, J. M., KRUGER, G. J., AMMON, H. L., DICKINSON, C. & HALL, S. R. (1976). The XRAY system. Tech. Rep. TR-446. Computer Science Center, Univ. of Maryland, College Park, Maryland.