There are no hydrogen bonds between water molecules. The shortest inter-ion contact is 3·173 (3) Å between pyrrolyl nitrogen N1 (which would have a formal positive charge in canonical form 1*a*) and nitro oxygen O19 of a symmetry-related cation (at $1-x, y, \frac{1}{2}-z$).

We thank NSERC Canada for financial support through the award of an Operating Grant.

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Structures of Leukotriene Antagonists: Racemic 2-Hydroxy-3-[2-(8-phenyloctyl)phenyl]-4-thiaheptanedioic Acid, SK&F 103944

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(*Received* 21 *April* 1989; *accepted* 19 *September* 1989)

Abstract. $C_{26}H_{34}O_5S$, $M_r = 458{\cdot}62$, monoclinic, $C2/c$, $a = 26{\cdot}686$ (7), $b = 16{\cdot}479$ (4), $c = 11{\cdot}988$ (5) Å, $\beta = 105{\cdot}37$ (3)°, $V = 5083{\cdot}1$ (10) Å^3, $Z = 8$, D_m (flotation in aqueous $ZnCl_2$) = 1·20 (2), $D_x = 1{\cdot}198$ g cm^{-3}, λ(Mo $K\bar{\alpha}$) = 0·71073 Å, $\mu = 1{\cdot}516$ cm^{-1}, $F(000) = 1968$, $T = 293$ K, $R = 0{\cdot}048$, $wR = 0{\cdot}054$ for 2726 observations, $I \geq 3\sigma(I)$. The 2-hydroxy-3-[2-(8-phenyloctyl)phenyl]-4-thiaheptanedioic acid molecule, a member of a novel class of selective leukotriene receptor antagonists, has its all-*trans* phenyloctyl and mercaptopropionate chains each fully extended. In the hydroxyacetate chain both the carboxylic and hydroxyl groups are *gauche* to the phenyl ring. The interphenyl dihedral angle is 67·3 (3)°. Hydrophobic and hydrophilic groups are segregated by the molecular packing. Lipophilic chains pack in a head-to-tail fashion. There are three intermolecular, and possibly two intramolecular, hydrogen bonds clustered in a channel parallel to **c**. The molecular conformation resembles that which we reported for a prototype of the related dithia class of antagonists.

Introduction. Leukotrienes LTC_4, D_4 and E_4 are released upon antigenic challenge of sensitized human lung tissue and are known to be causative agents of bronchoconstriction (Dahlen, Hedquist, Hammarstrom & Samuelsson, 1980), mucous production (Marom, Shelhamer, Bach, Morton & Kaliner, 1982) and microvascular permeability (Peck, Piper & Williams, 1981; Woodward, Weichman, Gill & Wasserman, 1983). These substances are involved in the pathophysiology of allergic asthma and are implicated in certain non-immunologically driven diseases (Lefer, 1986; Feuerstein, 1985). Leukotrienes exert their pharmacological effects *via* receptor-mediated events. The identification of LTD_4-specific binding sites in human and animal tissues (Lewis, Mong, Vessella & Crooke, 1985; Mong, Wu, Hogaboom, Clark & Crooke, 1984; Pong & DeHaven, 1983) has spurred considerable research efforts toward the design and synthesis of high-affinity peptidoleukotriene receptor antagonists (Gleason *et al.*, 1983; Gleason *et al.*, 1987; Perchonock *et al.*, 1985*a*; Ku, McCarthy, Weichman & Gleason 1985; Perchonock *et al.*, 1985*b*). These efforts have resulted in the identification of a series of [(phenyloctyl)phenyl]-propionic acids as novel, potent, specific, high-affinity leukotriene receptor antagonists. We report

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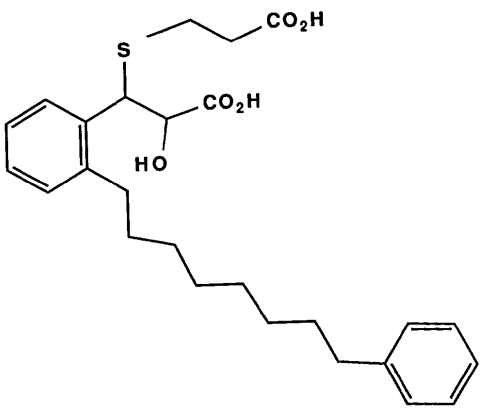
0108-2701/90/071244-05$03.00

here the solid-state structure of the racemate (1) (SK&F 103944), which exhibits substantial affinity for the LTD_4 receptor [K_i = 5 (2) nm] on both guinea pig and human lung membranes.



(1)

Experimental. Colorless needles were grown by slow evaporation from diethyl ether and the crystal used for data collection had approximate dimensions 0·40 × 0·25 × 0·30 mm after cleavage from a longer parent, and was mounted on a glass fiber with epoxy. Enraf–Nonius diffractometer, graphite monochromator; cell constants from least-squares analysis of 25 reflections with $30 \le 2\theta(\text{Mo}) \le 35°$ measured on the diffractometer. Systematic absences, *h*0*l* for *l* odd, *hkl*, for *h* + *k* odd. Intensity data were collected in an ω–2θ scan mode using variable speed scans (2·5 to 6·7 °min^{-1}) to $2\theta_{max} = 56°$. Of the 6410 intensities scanned ($0 \le h \le 35$; $0 \le k \le 21$; $-15 \le l \le 15$), 6118 were unique after averaging, R_{int} = 0·023 on *I*. Data were corrected for Lorentz and polarization effects and for absorption. The absorption correction was applied using *DIFABS* (Walker & Stuart, 1983); correction factors were 0·824 min, 1·083 max. Intensities of three standard reflections (8,12,0; 7,11,2; $\bar{1}5$,3,7), measured at the beginning, end and every three hours of exposure (35 times) did not vary significantly. Average values and deviations for F_o of the standards were 76·8 (9), 101·3 (10) and 69·6 (9), respectively. The structure was solved with *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). All H-atom positions were located from difference Fourier maps and were refined. Isotropic thermal parameters for hydrogens were held fixed at 1·3 × B_{eq} for the atom to which they were attached except for hydrogens involved in hydrogen bonding, for which thermal parameters were refined. Refinement by full-matrix least squares minimized the function $\sum w(|F_o| - |F_c|)^2$ where weights *w* were eventually assigned as $4F_o^2/\sigma^2(I)$ with $\sigma(I)$ as defined by Corfield, Doedens & Ibers (1967) and the instrument instability factor,

Table 1. *Table of positional parameters for* (1) *with e.s.d.'s in parentheses*

	x	*y*	*z*	*B*(Å^2)*
S	0·85386 (3)	0·91558 (5)	0·80189 (7)	3·02 (2)
O1	0·77800 (8)	0·9421 (1)	0·4111 (2)	3·24 (5)
O2	0·74371 (9)	1·0574 (1)	0·4501 (2)	4·29 (5)
O3	0·75831 (8)	1·0183 (1)	0·6770 (2)	3·15 (5)
O4	0·7806 (1)	0·6722 (2)	0·8511 (2)	8·24 (9)
O5	0·8121 (1)	0·6876 (2)	1·0360 (2)	8·03 (8)
C1	0·8710 (1)	1·0157 (2)	0·6426 (2)	2·42 (6)
C2	0·9095 (1)	1·0071 (2)	0·5823 (2)	2·70 (6)
C3	0·9434 (1)	1·0721 (2)	0·5865 (3)	3·68 (8)
C4	0·9403 (1)	1·1428 (2)	0·6454 (3)	3·86 (7)
C5	0·9019 (1)	1·1510 (2)	0·7039 (3)	3·47 (8)
C6	0·8680 (1)	1·0873 (2)	0·7015 (2)	2·91 (6)
C7	0·8355 (1)	0·9454 (2)	0·6504 (2)	2·39 (6)
C8	0·7763 (1)	0·9635 (2)	0·6057 (2)	2·59 (5)
C9	0·7639 (1)	0·9933 (2)	0·4819 (2)	2·71 (6)
C10	0·8178 (2)	0·8231 (2)	0·7992 (3)	4·13 (8)
C11	0·8316 (2)	0·7891 (2)	0·9197 (3)	4·25 (9)
C12	0·8049 (2)	0·7114 (2)	0·9295 (3)	4·16 (9)
C13	0·9167 (1)	0·9319 (2)	0·5177 (3)	3·22 (7)
C14	0·9526 (1)	0·8694 (2)	0·5914 (3)	3·81 (8)
C15	0·9621 (1)	0·7955 (2)	0·5232 (3)	3·65 (8)
C16	1·0032 (2)	0·7390 (2)	0·5941 (3)	5·7 (1)
C17	1·0183 (1)	0·6679 (2)	0·5301 (3)	4·59 (9)
C18	1·0564 (2)	0·6109 (3)	0·6084 (4)	6·0 (1)
C19	1·0770 (1)	0·5424 (2)	0·5485 (3)	4·62 (9)
C20	1·1139 (2)	0·4876 (3)	0·6323 (4)	6·3 (1)
C21	1·1361 (1)	0·4153 (2)	0·5850 (3)	4·13 (8)
C22	1·1569 (1)	0·3517 (2)	0·6590 (3)	4·62 (9)
C23	1·1792 (2)	0·2853 (2)	0·6211 (4)	5·0 (1)
C24	1·1818 (2)	0·2816 (2)	0·5081 (4)	5·1 (1)
C25	1·1613 (2)	0·3438 (3)	0·4337 (3)	5·4 (1)
C26	1·1387 (2)	0·4100 (2)	0·4715 (3)	5·0 (1)

* For aniosotropically refined atoms the isotropic equivalent displacement parameters are given as: $B_{eq} = (4/3)\sum_i\sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

p = 0·04. Refinement converged (max. Δ/σ = 0·01) to values of the standard crystallographic residuals, R = 0·0483, wR = 0·0542, S = 1·44 for 2726 observations with $I \ge 3\sigma(I)$, 394 variables. A final difference Fourier map showed maximum positive and negative features of 0·231 and 0·243 e Å^{-3}. Neutral atom scattering factors from *International Tables for X-ray Crystallography* (1974), for hydrogen from Stewart, Davidson & Simpson (1965). All programs used were from the locally modified Enraf–Nonius *SDP* (Frenz, 1987). All metrical parameters are calculated based on coordinates in Table 1 which were obtained from refinement using the 3σ data. Refinement using 4529 observations with $I \ge 0{\cdot}01\sigma(I)$ gave R = 0·092, wR = 0·064, S = 1·21. These latter data are tabulated as 'observed' in the structure factor listings.* The remaining 1589 data were considered unobserved based on a prescan acceptance parameter in which the reflection was flagged weak if $\sigma(I)/I$ of the prescan was greater than 2·0.

Discussion. The structure of the 2(*S*), 3(*R*) diastereoisomer of this racemic compound is displayed as Fig.

* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52673 (39 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

1. This stereochemistry corresponds to that of the natural agonist, LTD_4, as well as to the more biologically active isomer (SK&F 104353). Principal bond lengths and angles are listed in Table 2. Bond distances about the central phenyl ring range from 1·410 (3) to 1·376 (4) Å with an average of 1·391 (1) Å. Distances range from 1·390 (4) to 1·373 (5) Å about the terminal phenyl ring with an average of 1·38 (1) Å. The terminal phenyl-ring distances are shortened, undoubtedly due to effects of thermal motion. One exceptional exterior angle for the central ring is noteworthy. The C(1)—C(2)—C(13) angle of 123·9 (2)° is widened appreciably from a 120° trigonal value, reflecting perhaps adjustment to minimize steric interactions involving protons on C(13). Concomitantly, the C(1)—C(2)—C(3) angle of 117·2 (3)° is notably compressed from a normal value. In the terminal phenyl ring the interior angle of 117·8 (3)° at the point of attachment for the alkane chain, C(21), also is notably compressed.

Both phenyl rings are planar. Atom C(7) is displaced 0·112 (3) Å out-of-plane from the central ring whereas C(13) is nearly in the plane, its displacement being only 0·024 (3) Å to the opposite side of the plane from C(7). The C(7)—C(1)—C(2)—C(13) torsion angle is 3·1 (4)°. The methine H atom at C(7) lies nearly in the phenyl ring plane [C(2)—C(1)—C(7)—HC(7) torsion angle −9·5 (5)°] suggesting that its resonance would be deshielded in an NMR experiment were the solid-state conformation to persist in solution.

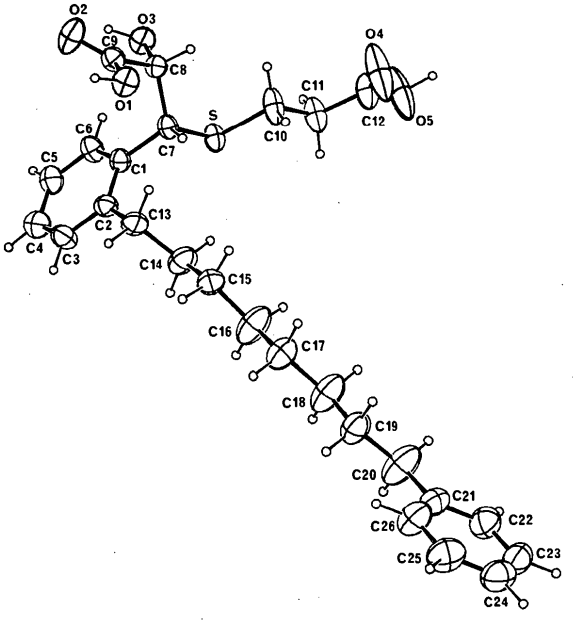


Fig. 1. Labeled *ORTEP* (Johnson, 1976) drawing of (1). Thermal ellipsoids are drawn at the 50% probability level; H atoms as small spheres of arbitrary size.

Table 2. *Bond distances* (Å) *and angles* (°) *for* (1)

S—C7	1·819 (3)	C10—C11	1·501 (4)
S—C10	1·799 (3)	C11—C12	1·484 (4)
O1—C9	1·320 (3)	C13—C14	1·519 (4)
O2—C9	1·202 (3)	C14—C15	1·524 (4)
O3—C8	1·412 (3)	C15—C16	1·516 (4)
O4—C12	1·183 (4)	C16—C17	1·513 (5)
O5—C12	1·301 (4)	C17—C18	1·514 (5)
C1—C2	1·410 (3)	C18—C19	1·517 (5)
C1—C6	1·389 (4)	C19—C20	1·505 (5)
C1—C7	1·517 (4)	C20—C21	1·509 (5)
C2—C3	1·396 (4)	C21—C22	1·390 (4)
C2—C13	1·501 (4)	C21—C26	1·383 (5)
C3—C4	1·376 (4)	C22—C23	1·380 (5)
C4—C5	1·392 (4)	C23—C24	1·376 (5)
C5—C6	1·382 (4)	C24—C25	1·373 (5)
C7—C8	1·555 (4)	C25—C26	1·380 (5)
C8—C9	1·514 (4)		

C7—S—C10	102·1 (1)	C10—C11—C12	113·4 (3)
C2—C1—C6	119·7 (2)	O4—C12—O5	121·4 (3)
C2—C1—C7	120·5 (2)	O4—C12—C11	125·6 (3)
C6—C1—C7	119·7 (2)	O5—C12—C11	113·0 (3)
C1—C2—C3	117·2 (3)	C2—C13—C14	114·1 (2)
C1—C2—C13	123·9 (2)	C13—C14—C15	113·4 (2)
C3—C2—C13	118·8 (2)	C14—C15—C16	112·8 (3)
C2—C3—C4	122·8 (3)	C15—C16—C17	116·2 (3)
C3—C4—C5	119·5 (3)	C16—C17—C18	113·1 (3)
C4—C5—C6	118·8 (3)	C17—C18—C19	115·9 (3)
C1—C6—C5	121·9 (3)	C18—C19—C20	112·6 (3)
S—C7—C1	105·1 (2)	C19—C20—C21	118·4 (3)
S—C7—C8	112·1 (2)	C20—C21—C22	119·0 (3)
C1—C7—C8	115·2 (2)	C20—C21—C26	123·2 (3)
O3—C8—C7	113·1 (2)	C22—C21—C26	117·8 (3)
O3—C8—C9	111·4 (2)	C21—C22—C23	121·4 (3)
C7—C8—C9	109·8 (2)	C22—C23—C24	119·9 (3)
O1—C9—O2	122·6 (3)	C23—C24—C25	119·4 (3)
O1—C9—C8	113·5 (2)	C24—C25—C26	120·7 (4)
O2—C9—C8	124·0 (2)	C21—C26—C25	120·8 (3)
S—C10—C11	107·7 (2)		

All appendages from the central phenyl ring adopt maximally extended conformations. The octyl phenyl chain adopts an all-*trans* zigzag conformation similar to that observed previously in the structure of a related antagonist, SK&F 102316, with an undecyloxy tail (Eggleston & Perchonock, 1986). The dihedral angle between the plane of the terminal phenyl ring and the plane of the central ring is 67·3 (3)°. The central phenyl ring bisects the C(8)—C(7)—S bond junction with S—C(7)—C(1)—C(6) and C(8)—C(7)—C(1)—C(6) torsion angles of −63·7 (3) and 60·2 (3)°, respectively. The mercaptopropionate chain also adopts a fully extended all-*trans* conformation with C(7)—S—C(10)—C(11) and S—C(10)—C(11)—C(12) torsion angles of 177·1 (3) and −179·1 (3)°, respectively. The rotational disposition of the hydroxyacetate chain places both the carboxylic and hydroxyl groups *gauche* to the central phenyl ring. The hydroxyl also then is *gauche* to the S atom while the carboxylic acid group lies *trans* to sulfur. Relevant torsion angles are C(1)—C(7)—C(8)—O(3) = −69·0 (3), C(1)—C(7)—C(8)—C(9) = 56·2 (3), S—C(7)—C(8)—O(3) = 51·2 (3) and S—C(7)—C(8)—C(9) = 176·3 (2)°.

A diagram of the unit-cell packing is presented in Fig. 2. A distinct separation of hydrophobic and hydrophilic groups occurs within the crystal. The

lipophilic groups pack in a head-to-tail fashion with the terminal ring pointed nearly perpendicularly to the central ring. In this orientation the C(26)—H bond points almost directly to the middle of the central ring of a screw-related molecule along **c**. The octyl chains are partially interdigitated one to another extending approximately parallel to the *b* axis. There are three apparent intermolecular, and possibly two intramolecular, hydrogen bonds all clustered in a channel parallel to the *c* axis. The carboxylic acid groups do not form dimers. Instead the pairwise interaction occurs between the carboxylate of the mercaptopropionate chain and the hydroxyl oxygen O(3) and ketonic oxygen O(2) of the hydroxyacetate chain. This interaction occurs between molecules related by translation along the *a* and *c* axes. The associated distances are O(3)···O(4), 2·727 (3) Å; HO(3)···O(4), 1·89 (4) Å with an angle at hydrogen of 153 (3)°; O(5)···O(2), 2·641 (3) Å; HO(5)···O(2), 1·68 (5) Å with an angle at hydrogen of 175 (4)°. The orientation of the hydroxyl hydrogen, synperiplanar to O(2), additionally suggests the possibility of an intramolecular hydrogen bond to the adjacent carboxyl oxygen, O(2). Distances for this interaction are O(3)···O(2), 2·721 (3) Å; HO(3)···O(2), 2·33 (4) Å with an angle at hydrogen of 106 (3)°. In addition, the C(6)···O(3) distance of 3·081 (4) Å and the HC(6)···O(3) distance of 2·45 Å with an angle at hydrogen of 120° all are suggestive of an intramolecular C—H···O hydrogen bond, meeting all criteria denoted by Taylor & Kennard (1982) in their discussion of such interactions. The hydrogen-bonding scheme is completed by an intermolecular hydrogen bond, also involving the hydroxyl oxygen as an acceptor, from carboxylic acid oxygen O(1). The distances are O(1)···O(3), 2·792 (3) Å; HO(1)···O(3), 1·91 (4) Å with an angle at hydrogen of 159 (4)°. In the proposed scheme one of the ketonic oxygens, O(2), may accept two hydrogen bonds while the other, O(4), accepts only one. The environment of the hydroxylic oxygen O(3) is particularly interesting in that it may involve four stabilizing interactions.

Overall, the conformation observed for (1) is analogous to that reported in a prototype of a related series of dithianonanedioic acid antagonists (Eggleston & Perchonock, 1986). The lipophilic octylphenyl group, which replaces the unsaturated triene moiety of LTD_4, consistently adopts a highly extended conformation. In addition, the methine H atom at C(7) is very close to the plane of the central aromatic ring in both structures while the mercaptopropionate chains adopt highly extended conformations. These features may be indicative of key structural forms required for high-affinity binding at leukotriene receptors.

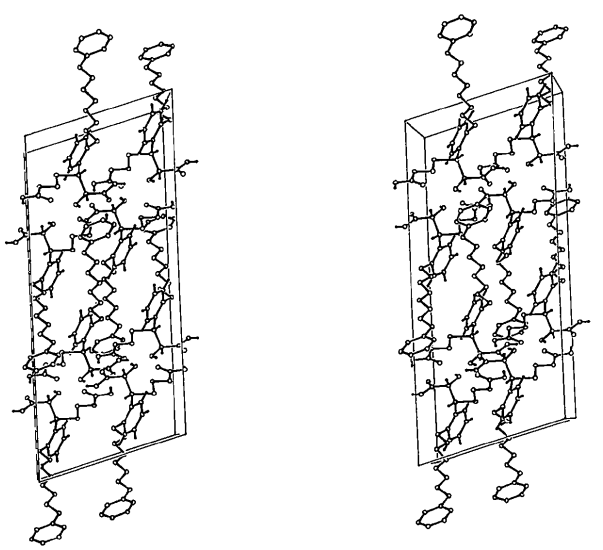


Fig. 2. Stereoview of the unit-cell packing in the crystal of (1). The view has **a** vertical and **c** nearly horizontal in the plane of the page.

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6-Bromo-2,3-dihydro-5,7-dimethyl-1,4-diazepinium Picrate and 6-Bromo-2,3-dihydro-1,4-diazepinium Picrate

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(*Received* 20 *July* 1989; *accepted* 12 *September* 1989)

Abstract. (1) $C_7H_{12}BrN_2^+.C_6H_2N_3O_7^-$, $M_r = 432{\cdot}2$, triclinic, $P\bar{1}$, $a = 7{\cdot}760\ (3)$, $b = 9{\cdot}139\ (2)$, $c = 12{\cdot}262\ (4)$ Å, $\alpha = 100{\cdot}24\ (2)$, $\beta = 98{\cdot}32\ (3)$, $\gamma = 93{\cdot}63\ (3)°$, $V = 843\ (1)$ Å^3, $Z = 2$, $D_x = 1{\cdot}70$ g cm^{-3}, λ(Mo $K\alpha$) = 0·70926 Å, $\mu = 24{\cdot}6$ cm^{-1}, $F(000) = 436$, $T = 294$ K, $R = 0{\cdot}039$, $wR = 0{\cdot}046$ for 2045 observed data. (2) $C_5H_8BrN_2^+.C_6H_2N_3O_7^-$, $M_r = 404{\cdot}1$, monoclinic, $C2/c$, $a = 21{\cdot}501\ (6)$, $b = 10{\cdot}685\ (4)$, $c = 13{\cdot}255\ (5)$ Å, $\beta = 90{\cdot}47\ (2)°$, $V = 3045\ (3)$ Å^3, $Z = 8$, $D_x = 1{\cdot}76$ g cm^{-3}, λ(Mo $K\alpha$) = 0·70926 Å, $\mu = 27{\cdot}2$ cm^{-1}, $F(000) = 1616$, $R = 0{\cdot}044$, $wR = 0{\cdot}046$ for 1562 observed data. Both crystal structures contain discrete diazepinium cations and picrate anions which are linked by N—H···O hydrogen bonds to form centrosymmetric tetrameric rings in (1) (N···O 2·779–3·166 Å) and infinite chains in (2) (N···O 2·863–3·020 Å). The seven-membered ring of each cation contains a five-membered delocalized 1,5-diazapentadienium chain [N—C—C—C—N; mean C—C 1·413 (6), mean C—N 1·306 (5) Å in (1), mean C—C 1·390 (7), mean C—N 1·304 (7) Å in (2)] in a helical conformation. The picrate ring dimensions in both (1) and (2) are consistent with significant contributions from a resonance form with an essentially normal C=O bond.

Introduction. Interest in the 2,3-dihydro-1,4-diazepinium cation has centred on the delocalized nature of its 1,5-diazapentadienium, or vinamidinium, system and on its 'quasi-aromatic' character (Lloyd & Marshall, 1964, 1971). Because of this character, it was suprising that the Br atom of the 6-bromo-5,7-dimethyl derivative (1) underwent ready nucleophilic displacement (Lloyd & Marshall, 1958; Gorringe, Lloyd, Wasson, Marshall & Duffield, 1969). The unmethylated derivative (2) was found not to take part in such reactions, and rationalization of these reactions has invoked steric crowding between the geminal bromo and methyl groups in (1) (Lloyd, McNab & Marshall, 1975) which would be absent in (2). X-ray analyses of the bromo compounds (1) and (2) were therefore desirable to allow us to compare them with each other and with the corresponding 6-hydrogeno-5,7-dimethyl analogue (Ferguson, Marsh, Lloyd & Marshall, 1980). The 1,4-diazepinium picrate derivatives were obtained from the corresponding bases by reaction with picric acid in acetone (Lloyd & McNab, 1989).

Experimental. (1) Yellow crystals, 0·30 × 0·20 × 0·35 mm, CAD-4 diffractometer, graphite-monochromatized Mo $K\alpha$ radiation, 25 reflections with θ in range $10 < \theta < 15°$ used to determine lattice parameters; for data collection $2 < \theta < 25°$ (h −9 to 9, k −10 to 10, l 0 to 14), ω–2θ scans, ω-scan width $(0{\cdot}60 + 0{\cdot}35\tan\theta)°$; intensities of three reflections monitored every 2 h of exposure time showed no significant decay; Lorentz, polarization and

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0108-2701/90/071248-04$03.00