The epidioxycholestenol (2) is reported to show a cytotoxicity against mouse lymphopenia and anti-tumor activity against KB cells derived from human epidermoid carcinoma in mice (Matsueda & Katsukura, 1985). The MNDO calculation of the epidioxycholestenol shows that HOMO has bonding π orbitals and LUMO has antibonding π orbitals at the carbon–carbon double bond. Rather small coefficients were found at epidioxy O atoms. It is suggested that the double bond is more reactive both as an electrophile and as a nucleophile than the peroxide for 5,8α-epidioxy-5α-cholest-6-en-3β-ol.

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Structure and Conformation of a Hetero-Substituted Cyclooctane

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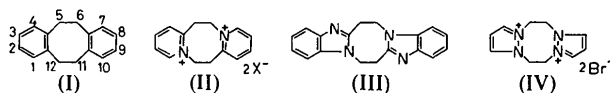AND PILAR CABILDO, ROSA MARIA CLARAMUNT AND JOSE ELGUERO

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Abstract. 5,6,12,13-Tetrahydrobispyrazolo[1,2-*a*:-1',2'-*e*][1,2,5,6]tetrazocinium dibromide, $C_{10}H_{14}N_4^{2+}$.-2Br$^-$, $M_r = 350 \cdot 06$, monoclinic, $C2/c$, $a = 12 \cdot 7119$ (5), $b = 6 \cdot 9016$ (2), $c = 14 \cdot 6312$ (5) Å, $\beta = 105 \cdot 755$ (3)°, $V = 1235 \cdot 41$ (8) Å^3, $Z = 4$, $D_x = 1 \cdot 882$ g cm^{-3}, λ(Cu $K\alpha$) = $1 \cdot 5418$ Å, $\mu = 82 \cdot 48$ cm^{-1}, $F(000) = 688$, $T = 298$ K, R (wR) = $0 \cdot 038$ ($0 \cdot 048$) for 999 observed reflections with $I > 3\sigma(I)$. The title compound contains a central eight-membered ring with an internal crystallographic center of symmetry and is in a chair conformation. The lateral pyrazole rings support the cationic charge and the bromide anions present short contacts with some hydrogen atoms.

Introduction. One of the cornerstones of conformational analysis is that concerning medium-sized rings (Hendrickson, 1967; Dunitz, 1979). Among these, one of the most fascinating compounds is dibenzo-1,5-cyclooctadiene (5,6,11,12-tetrahydrodibenzo[*a,e*]-cyclooctene) (I) (Ollis, Stoddart & Sutherland, 1974), since the two aromatic rings simplify the conformational problem (two dihedral angles equal to 0°). Most heterocyclic analogs of (I) have the hetero-atoms in place of the saturated carbons (positions 5, 6, 7 or 12) (Moore & Anet, 1984). Among the rare heterocycles with heteroatoms on the fused benzene rings, 6,7,13,14-tetrahydrodipyrido[1,2-*a*:1',2'-*e*]di-azocinium salts (II) (crystal structure unknown) (Glover, Pointer, Wilford & Elder, 1981) and 6,7,14,15-tetrahydrobisbenzimidazo[1,2-*a*:1',2'-*e*]dia-zocine (III) (structure reported) (Elguero, Katritzky, El-Osta, Harlow & Simonsen, 1976) have been described. The structure and conformation of 5,6,-12,13-tetrahydrobispyrazolo[1,2-*a*:1',2'-*e*][1,2,5,6]-tetrazocinium dibromide (IV) is presented here.

Experimental. The title compound (IV) was prepared by reacting 1,2-bis(pyrazol-1-yl)ethane (Torres, Lavandera, Cabildo, Claramunt & Elguero, 1988) with 1,2-dibromoethane in excess (5 cm³ for 2·4 mmol) without solvent. After 24 h reflux, a dark precipitate was formed which was purified by successive crystallization in water, m.p. 552–554 K. Yield of white pure crystalline compound, 23%. The compound was characterized by mass spectrometry using the fast atom bombardment (FAB) technique with glycerol matrix: m/z 269, 271 $[C_{10}H_{14}N_4Br]^+$ and m/z 281, 283, 285 $[C_7H_{11}N_2Br_2]^+$. UV (EtOH): λ_{max} 281 nm (log$\varepsilon = 4\cdot57$). NMR (D$_2$O), ^{1}H: 5·23 (s) (CH$_2$), 6·76 (t) (H-4), 8·32 (d) (H-3 and H-5) ($J_{34} = J_{45} = 2\cdot8$ Hz); ^{13}C: 50·7 (CH$_2$) ($^1J = 148\cdot9$ Hz), 109·6 (C-4) ($^1J = 191\cdot7$, $^2J = 6\cdot6$ Hz) and 141·7 p.p.m. ($^1J = 202\cdot6$, $^2J = {}^3J = 6\cdot4$ Hz).

The main characteristics of the structural determination are given in Table 1.* The absorption correction was empirical (*DIFABS*; Walker & Stuart, 1983). The thermal factors of the H atoms, equivalent to those of the attached atoms, were kept fixed in the last cycles of refinement. The *XRAY*76 system (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976) was used on a VAX 6410 computer. The scattering factors were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV).

Discussion. Table 2 presents the final atomic coordinates, and Tables 3 and 4 geometrical features; the atom numbering is shown in Fig. 1 (Johnson, 1965). The molecule has a crystallographically imposed symmetry center. Moreover, it presents a pseudo-mirror plane and corresponding pseudo-twofold axis (see Fig. 1). The bromide anions are situated quite symmetrically on that plane, almost over the center of the five-membered rings (the pyrazolium cations) [0·23 (1) Å from the centroid towards the N(1)—N(2) bond] and at 3·684 (5) Å from the plane through one of them. The bromide and the H atoms are involved in a series of interatomic contacts (Table 4). Among them, those marked with an asterisk correspond to contacts shorter than the van der Waals radii (Vainshtein, Fridkin & Indenbom, 1982).

The tetrazocine ring adopts a chair conformation around the symmetry center. The central part of the chair makes an angle of 61·72 (2)° with the two lateral ones. In Ollis notation (Ollis, Stoddart & Sutherland, 1974) this conformation is noted $C(+ - + - + -)$ and in Hendrickson notation,

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Table 1. *Crystal analysis parameters at room temperature*

Crystal habit	Rhombic prism, transparent, colorless
Crystal size (mm)	0·07 × 0·33 × 0·33
Experimental data	
Unit-cell determination*	
Number of reflections	66
θ (°)	< 45
Diffractometer	Philips PW1100 four-circle diffractometer, bisecting geometry
Scans	$\omega/2\theta$
Scan width (°)	1·5
θ_{max} (°)	65
Reflections	1 reflection per minute
h,k,l range	$0 < h < 14$, $-8 < k < 8$, $-16 < l < 16$
Number of reflections	
Measured	1088
Independent	1048
Observed	999 $[I > 3\sigma(I)]$
R_{int}	0·091
Standard reflections	2 reflections every 90 min, no variation
Min., max. absorption corrections	0·726, 1·623
Solution and refinement†	
Number of variables	94 (H-atom U values fixed)
Degrees of freedom	905
Ratio of freedom	10·6
Final Δ/σ	0·08
Weighting scheme	Empirical‡
Max. thermal value (Å²)	$U_{11}[C(4)] = 0\cdot043$ (2)
Final ΔF peaks (e Å^{-3})	0·52
Final R, wR, S	0·038, 0·048, 1·14

* Unit cell determined by least-squares fit.
† Structure solved by Patterson methods and refined by full-matrix least squares on F_o. H atoms located from difference Fourier synthesis.
‡ No trends in $\langle w\Delta^2F\rangle vs\langle|F_{obs}|\rangle$ and $\langle\sin\theta/\lambda\rangle$.

Table 2. *Final atomic coordinates and thermal parameters*

$$U_{eq} = \tfrac{1}{3}\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j\cos(a_i,a_j).$$

	x	y	z	U_{eq}(Å²)
Br	0·17601 (3)	−0·05253 (7)	−0·16860 (3)	0·0350 (2)
N(1)	0·0528 (3)	0·2478 (5)	−0·0056 (2)	0·023 (1)
N(2)	−0·0375 (3)	0·2128 (5)	−0·0771 (2)	0·023 (1)
C(3)	−0·0392 (4)	0·3345 (6)	−0·1486 (3)	0·029 (1)
C(4)	0·0528 (4)	0·4516 (6)	−0·1222 (3)	0·030 (1)
C(5)	0·1081 (4)	0·3924 (6)	−0·0327 (4)	0·029 (1)
C(6)	0·0819 (4)	0·1417 (6)	0·0846 (3)	0·026 (1)
C(7)	0·1198 (3)	−0·0654 (6)	0·0736 (3)	0·025 (1)
H(3)	−0·089 (6)	0·331 (11)	0·199 (6)	0·028†
H(4)	0·070 (6)	0·551 (11)	−0·158 (6)	0·029†
H(5)	0·159 (7)	0·427 (11)	0·006 (6)	0·028†
H(6A)	0·020 (6)	0·149 (10)	0·108 (5)	0·025
H(6B)	0·135 (6)	0·201 (11)	0·121 (5)	0·025
H(7A)	0·182 (6)	−0·101 (10)	0·125 (5)	0·026
H(7B)	0·138 (6)	−0·090 (10)	0·017 (5)	0·026

† Fixed in the last cycles of refinement.

$C(0\overset{+}{\underset{-}{}}\overset{-}{\underset{+}{}}\overset{+}{\underset{-}{}}0)$ (Hendrickson, 1967). Compound (III) adopts a similar structure in the solid state. More precisely, the Hendrickson torsional description of compounds (III) and (IV) is:

$$2\cdot4\;(3)\;\frac{69\cdot3\;(2),\,-101\cdot2\;(2),73\cdot7\;(2)}{-73\cdot7\;(2),101\cdot2(2),\,-69\cdot3\;(2)}\;-2\cdot4\;(3)\qquad\text{(III)}$$

$$0\cdot9\;(6)\;\frac{71\cdot9\;(5),\,-104\cdot8\;(4),74\cdot8\;(5)}{-74\cdot8\;(5),104\cdot8\;(4),\,-71\cdot9\;(5)}\;-0\cdot9.\qquad\text{(IV)}$$

Table 3. *Selected geometrical characteristics* (Å, °)

indicates the centrosymmetric atoms completing the molecule.

N(1)—C(5)	1·341 (6)	N(2)—C(3)	1·338 (6)
C(5)—C(4)	1·370 (6)	C(3)—C(4)	1·388 (6)
N(1)—C(6)	1·466 (5)	N(2)—C(7′)	1·469 (5)
N(1)—N(2)	1·348 (4)	C(6)—C(7)	1·531 (6)

Br—N(1)	3·804 (4)	Br—N(2)	3·807 (4)
Br—C(5)	3·881 (5)	Br—C(3)	3·891 (5)
Br—C(4)	3·949 (5)	Br—C(10)	3·690 (5)

N(2)—N(1)—C(5)	108·0 (3)	N(1)—N(2)—C(3)	108·9 (3)
N(2)—N(1)—C(6)	124·2 (3)	N(1)—N(2)—C(7′)	124·2 (3)
C(5)—N(1)—C(6)	127·8 (4)	C(3)—N(2)—C(7′)	127·0 (4)
N(1)—C(5)—C(4)	109·3 (4)	N(2)—C(3)—C(4)	108·4 (4)
C(5)—C(4)—C(3)	105·5 (4)	N(2)—C(7′)—C(6′)	113·3 (4)
N(1)—C(6)—C(7)	112·4 (3)		

C(7′)—N(2)—N(1)—C(6)	0·9 (6)	N(1)—C(6)—C(7)—N(2′)	−104·8 (4)
N(2)—N(1)—C(6)—C(7)	71·9 (5)	N(1)—N(2)—C(7′)—C(6′)	−74·8 (5)

Least-square planes through   (i) C(6), N(1), C(5), C(4), C(3), N(2), C(7′)
                            (ii) C(6), C(7), C(6′), C(7′)

Least-square lines through   (iii) Br, C(10)
                            (iv) Br, Br′

Br—(i)	3·684 (5)	Br—(ii)	3·425 (5)
(i)—(ii)	61·7 (2)	(i)—(iii)	3·7 (1)
(i)—(iv)	37·0 (1)	(ii)—(iii)	65·4 (2)
(ii)—(iv)	24·7 (2)	(iv)—(iii)	40·7 (1)

Table 4. *Main interatomic contacts* (Å, °)

	Symmetry	Br···H	C—H···Br	C—H
Br H(3)	−½ + x, ½ + y, z	3·24 (8)	112 (7)	0·84 (7)
Br H(3)	− x, y, −½ − z	3·29 (7)	127 (6)	0·84 (7)
Br H(4)	x, 1 + y, z	3·08 (8)	164 (4)	0·92 (8)
Br H(5)	½ − x, ½ − y, − z	2·84 (7)*	171 (9)	0·78 (7)
Br H(6A)	− x, − y, − z	2·93 (8)*	164 (6)	0·95 (8)
Br H(6B)	x, − y, ½ + z	3·16 (7)	110 (6)	0·84 (7)
Br H(7A)	½ − x, −½ − y, − z	2·96 (7)*	135 (5)	0·96 (7)
Br H(7A)	x, − y, ½ + z	3·22 (8)	115 (6)	0·96 (7)
Br H(7B)	x, y, z	2·90 (8)*	164 (6)	0·93 (8)

* See Fig. 2.

Thus, in the solid state, chair conformations are preferred over boat [B(−0+ −0+)] or twist-boat ones [TB(+ − + + − +)], for diazocines and tetrazocines. In solution, at room temperature, the isochrony of the methylene protons (a sharp singlet at 5·23 p.p.m.) is not compatible with a static chair conformation. Probably, as with compound (I) (Ollis, Stoddart & Sutherland, 1974), several species, including C, B and TB, are rapidly interconverting in solution. Unfortunately, low-temperature NMR studies are prevented by the insolubility of compound (IV) in low-melting point solvents.

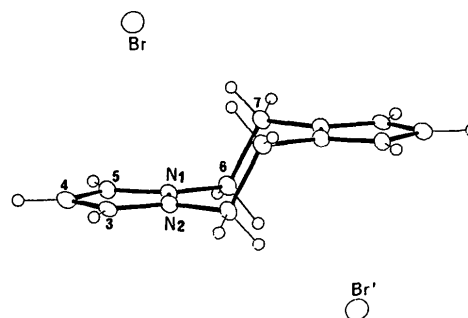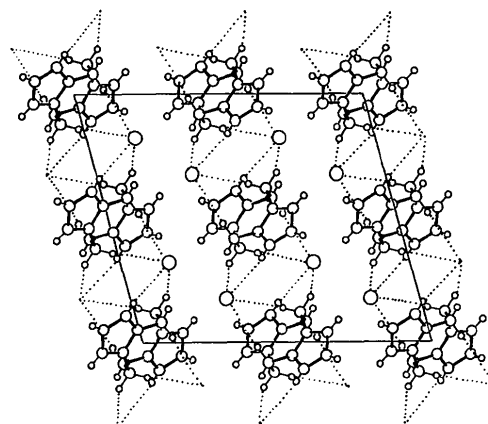Fig. 2. Shows the crystal packing, projected along the b axis.

Fig. 1. An *ORTEP* (Johnson, 1965) view of the salt (IV), showing the atomic numbering and the conformation of the central eight-membered ring.

Fig. 2. An *ORTEP* (Johnson, 1965) view of the crystal packing as projected along the *b* axis. Only the contacts marked with an asterisk in Table 4 are shown.

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