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1-Benzyl-2-[(hydroxyimino)methyl]pyridinium Bromide and 1-Benzyl-2-[(hydroxyimino)methyl]pyridinium Methylsulphonate

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Abstract

$C_{13}H_{13}N_2O^+.Br^-$ is orthorhombic, *Pcab*, $Z = 8$, $a = 11{\cdot}649\ (5)$, $b = 12{\cdot}218\ (7)$, $c = 17{\cdot}775\ (10)$ Å; $d_c = 1{\cdot}539$ Mg m^{-3}, μ(Mo $K\alpha$) = 3·431 mm^{-1}. $R_w = 0{\cdot}041$ for 1634 reflections. $C_{13}H_{13}N_2O^+.CH_3SO_3^-$ is monoclinic, $P2_1/b$, $Z = 4$, $a = 7{\cdot}044\ (1)$, $b = 13{\cdot}113\ (7)$, $c = 16{\cdot}50\ (1)$ Å, $\gamma = 93{\cdot}10\ (2)°$; $d_c = 1{\cdot}416$ Mg m^{-3}, μ(Mo $K\alpha$) = 0·234 mm^{-1}. $R_w = 0{\cdot}042$ for 1960 reflections. The structure of the bromide was solved *via* heavy-atom techniques. The *MULTAN* solution of the methylsulphonate gave a translationally misplaced cation. The problem was solved using the Karle refinement option. Both molecules have their oxime moieties in the (*E*) configuration.

Introduction

Certain oxime derivatives of pyridine, *i.e.* the monoquaternary compound 2-[(hydroxyimino)methyl]-1-methylpyridinium chloride (pralidoxime) and the bisquaternary oximes 1,1′-(1,3-propanediyl)bis{4-[(hydroxyimino)methyl]pyridinium} dibromide (TMB4) and 1,1′-[oxybis(methylene)]bis{4-[(hydroxyimino)methyl]pyridinium} dichloride (obidoxime, Toxogonin®), are used or considered for use as antidotes against intoxication with organophosphate anticholinesterases, both of the pesticide and of the nerve-agent type (Ellin & Wills, 1964; Erdman & Clarmann, 1963; Sidell, 1974). These oximes reactivate phosphorylated acetylcholinesterase (AcChoE) by way of a nucleophilic displacement of the organophosphate moiety from the enzyme, thereby restoring the normal transmission of nerve impulses in the body.

AcChoE inhibited by the nerve agent ethyl dimethylphosphoramidocyanidate (tabun) is effectively reactivated by the bisquaternary compounds TMB4 and obidoxime, but is rather resistant to reactivation by monoquaternary oximes, *e.g.* pralidoxime (de Jong, Benschop, van den Berg, Wolring & de Korte, 1981). Recently, we found, however, that the monoquaternary 1-benzyl-2-[(hydroxyimino)methyl]pyridinium bromide (benzyl-P_2A bromide) and the corresponding methylsulphonate (benzyl-P_2A sulphonate) are highly effective reactivators of tabun-inhibited AcChoE. Moreover, preliminary *in vivo* experiments by Kepner of the Medical Biological Laboratory TNO showed that these compounds have a substantially higher protective effect as an oral prophylactic agent against tabun than pralidoxime or obidoxime (de Jong *et al.*, 1981).

In view of the unusual high activity of the monoquaternary benzyl-P_2A bromide and benzyl-P_2A sulphonate we have determined the structures of these oximes. So far, pralidoxime is the only reactivator of phosphorylated AcChoE for which the structure has been determined (Carlström, 1966).

Structure determinations and refinements

Benzyl-P_2A bromide was prepared from (*E*)-2-pyridinecarbaldehyde oxime (obtained from Aldrich) and benzyl bromide (de Jong *et al.*, 1981). Replacement of the bromide anion by the methylsulphonate anion yielded the benzyl-P_2A sulphonate. Colourless single crystals were obtained by slow evaporation at room temperature of an aqueous solution of the product.

The structures have been determined from data obtained at room temperature on an Enraf–Nonius CAD-4 diffractometer using Zr-filtered Mo radiation

Table 1. *Experimental data*

	Benzyl-P_2A bromide	Benzyl-P_2A sulphonate
Crystal dimensions (mm)	0·2 × 0·1 × 0·15	0·2 × 0·1 × 0·1
Number of reflections	2213	2677
Number of reflections in refinement with $I > 3\sigma(I)$	1634	1960
Method of measurement	ω/θ scan 3:2 speed ratio	pure ω scan
Scan angle (°)	0·8 + 0·35 tg θ	1·0 + 0·35 tg θ
Aperture of detection unit (mm)	1·0 + 1·0 tg θ	1·0 + 1·0 tg θ

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Table 2. *Positional parameters in fractions of the cell edges*

The e.s.d.'s given in parentheses refer to the last digit. Isotropic temperature parameters (Å²) of non-hydrogen atoms are calculated from the anisotropic temperature parameters assuming equal volume of the 50% probability region. All anisotropic thermal parameters were physically acceptable. H atom H(j,x) (j = 1, 2, 3) is attached to atom x. B_{iso} was calculated according to Lipson & Cochran (1968): $B_{iso} = 8\pi^2(U_{11}^0\ U_{22}^0\ U_{33}^0)$. E.s.d.'s are about 0·2 Å².

	x	y	z	B_{iso}
Benzyl-P_2A bromide				
Br	0·5520 (1)	0·1009 (1)	0·1442 (1)	4·01
O	0·4055 (3)	0·3154 (3)	0·1413 (2)	3·96
N(1)	0·2776 (3)	0·5484 (3)	−0·0462 (2)	2·74
N(2)	0·4136 (3)	0·3473 (3)	0·0674 (2)	3·49
C(1)	0·2778 (4)	0·5862 (4)	−0·1171 (3)	3·79
C(2)	0·3465 (5)	0·5407 (4)	−0·1699 (3)	4·61
C(3)	0·4156 (4)	0·4545 (4)	−0·1525 (3)	4·20
C(4)	0·4146 (4)	0·4164 (4)	−0·0812 (3)	3·44
C(5)	0·3455 (3)	0·4639 (3)	−0·0262 (2)	2·57
C(6)	0·1989 (3)	0·6007 (4)	0·0087 (2)	3·04
C(7)	0·3436 (4)	0·4243 (3)	0·0510 (2)	3·04
C(8)	0·2626 (4)	0·6775 (3)	0·0612 (2)	2·90
C(9)	0·2378 (5)	0·6741 (3)	0·1369 (3)	4·50
C(10)	0·2909 (5)	0·7472 (5)	0·1876 (3)	5·51
C(11)	0·3766 (5)	0·8222 (4)	0·1600 (3)	5·07
C(12)	0·3933 (4)	0·8273 (4)	0·0844 (3)	3·89
C(13)	0·3412 (4)	0·7556 (4)	0·0350 (2)	3·09
H(C1)	0·222 (3)	0·643 (3)	−0·125 (2)	
H(C2)	0·344 (3)	0·566 (3)	−0·211 (2)	
H(C3)	0·447 (3)	0·416 (3)	−0·200 (2)	
H(C4)	0·453 (3)	0·360 (3)	−0·072 (2)	
H(1,C6)	0·142 (3)	0·537 (3)	0·027 (2)	
H(2,C6)	0·136 (3)	0·637 (3)	−0·020 (2)	
H(C7)	0·282 (3)	0·452 (3)	0·089 (2)	
H(C9)	0·164 (3)	0·613 (3)	0·147 (2)	
H(C10)	0·271 (3)	0·756 (3)	0·249 (2)	
H(C11)	0·395 (3)	0·870 (3)	0·193 (2)	
H(C12)	0·456 (4)	0·888 (4)	0·063 (3)	
H(C13)	0·361 (3)	0·770 (3)	−0·018 (2)	
Benzyl-P_2A sulphonate				
S	0·3380 (1)	0·2191 (1)	0·3801 (1)	3·73
O(1)	0·6341 (2)	0·2289 (2)	0·5624 (1)	4·71
O(2)	0·5353 (2)	0·2284 (1)	0·4064 (1)	4·28
O(3)	0·3035 (3)	0·2868 (2)	0·3148 (1)	5·75
O(4)	0·2742 (4)	0·1162 (2)	0·3646 (2)	8·17
N(1)	1·1782 (3)	0·1667 (1)	0·7019 (1)	3·23
N(2)	0·7999 (3)	0·1776 (2)	0·5656 (1)	3·73
C(1)	1·3437 (4)	0·1206 (2)	0·7115 (2)	3·99
C(2)	1·3835 (4)	0·0373 (2)	0·6685 (2)	4·56
C(3)	1·2518 (4)	−0·0049 (2)	0·6153 (2)	4·88
C(4)	1·0827 (4)	0·0410 (2)	0·6069 (2)	4·15
C(5)	1·0451 (3)	0·1270 (2)	0·6488 (1)	3·11
C(6)	1·1483 (3)	0·2627 (2)	0·7476 (2)	3·60
C(7)	0·8690 (4)	0·1807 (2)	0·6368 (2)	3·61
C(8)	1·1715 (4)	0·3560 (2)	0·6945 (2)	3·73
C(9)	1·3429 (5)	0·3813 (2)	0·6573 (2)	5·14
C(10)	1·3584 (6)	0·4674 (3)	0·6094 (2)	7·12
C(11)	1·2087 (7)	0·5290 (2)	0·6004 (2)	7·37
C(12)	1·0409 (6)	0·5039 (3)	0·6377 (3)	7·63
C(13)	1·0230 (4)	0·4189 (2)	0·6842 (2)	5·55
C(14)	0·1995 (5)	0·2582 (3)	0·4592 (2)	6·17
H(O1)	0·608 (3)	0·232 (2)	0·511 (1)	
H(C1)	1·422 (3)	0·152 (1)	0·748 (1)	

Table 2 (*cont.*)

	x	y	z
H(C2)	1·489 (3)	0·011 (2)	0·676 (1)
H(C3)	1·277 (3)	−0·068 (2)	0·584 (1)
H(C4)	0·992 (3)	0·015 (2)	0·572 (1)
H(1,C6)	1·021 (3)	0·255 (2)	0·772 (1)
H(2,C6)	1·236 (3)	0·263 (2)	0·791 (1)
H(C7)	0·817 (3)	0·218 (2)	0·680 (1)
H(C9)	1·443 (3)	0·339 (2)	0·667 (1)
H(C10)	1·460 (3)	0·472 (2)	0·595 (1)
H(C11)	1·215 (3)	0·579 (2)	0·567 (1)
H(C12)	0·928 (3)	0·561 (2)	0·632 (1)
H(C13)	0·914 (3)	0·403 (2)	0·708 (1)
H(1,C14)	0·065 (3)	0·256 (2)	0·439 (1)
H(2,C14)	0·235 (3)	0·236 (2)	0·501 (1)
H(3,C14)	0·235 (3)	0·328 (2)	0·466 (1)

(λ = 0·71073 Å). All unique reflections with $\theta \leq 25°$ were measured. Cell parameters were evaluated by a least-squares procedure using 20 reflections. Relevant experimental details for the two compounds are summarized in Table 1. No absorption correction was applied.

The Br^- ion of benzyl-P_2A bromide was located by the Patterson method and all non-hydrogen atoms were found from subsequent Fourier difference maps. Most of the H atoms were placed either directly from difference electron density maps or at expected positions. Only the H atom attached to O(1) could not be located.

The structure of benzyl-P_2A sulphonate was solved using *MULTAN* 80 (Germain, Main & Woolfson, 1971). The most likely E map with 300 terms showed the S atom and a translationally misplaced benzyl-P_2A cation moiety. The translation problem could be solved using the Karle refinement option (Karle, 1968) of *MULTAN* 80. In doing so, we assumed that S was

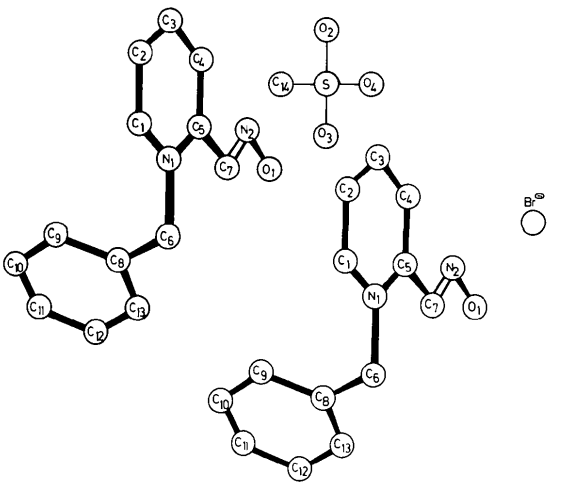

Fig. 1. The structures of (left) the methylsulphonate and (right) the bromide with the atom numbering.

correctly positioned, while the geometry and orientation of the cation were used as *a priori* information. The new resulting E map showed all non-hydrogen atoms. A subsequent difference electron density map revealed the positions of the H atoms.

In both refinements we employed the Gauss–Seidel block method (Sparks, 1974), gave each reflection a weight based on counting statistics and kept the Debye–Waller temperature factor of the H atoms fixed (4 Å^2 for the bromide and 3·7 Å^2 for the sulphonate).

After refinement of the isotropic extinction parameter (Zachariasen, 1963) to $r = 0{\cdot}78 \times 10^{-5}$ mm the R value for benzyl-P_2A sulphonate converged to 0·042. No extinction correction was applied for benzyl-P_2A bromide. The final R value $\{R = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}\}$ is 0·041 for observed reflections only.

The maximum noise level in the final difference Fourier map of benzyl-P_2A sulphonate is 0·15 e Å^{-3} and 0·3 e Å^{-3} for benzyl-P_2A bromide. Refined parameters are listed in Table 2, the numbering of the atoms is illustrated in Fig. 1.*

Discussion

The arrangement of the substituents at the C=N bond shows that the oxime moiety in both compounds is in the (E) configuration (indicated as the *syn* isomer in previous literature). Hence, this configuration is the same as in the 1-methyl analogue pralidoxime (Carlström, 1966) and probably also the same for the pairs of oxime moieties in the bis-quaternary compounds TMB4 (Schnekenburger, 1969), and obidoxime (Lüttringhaus & Hagedorn, 1964; Leitis, Shimanskaya & Varslavans, 1969). It is of interest that for 4-[(hydroxyimino)methyl]-1-methylpyridinium iodide, it has been shown that the (Z) isomer is inferior in reactivating potency to the (E) isomer (Poziomek, Kramer, Mosher & Michel, 1961). The (Z,Z) isomer of obidoxime seems to be more toxic than the (E,E) isomer (Leitis *et al.*, 1969). It could not be tested whether such behaviour also occurs with the 2-oximes, since to our knowledge quaternary derivatives of 2-pyridinecarbaldehyde oxime in which the oxime moiety has the (Z) configuration are not described in the literature.

The similarity in pharmacological properties of benzyl-P_2A bromide and benzyl-P_2A sulphonate is also displayed in their molecular geometries. We did not find significant differences in bond lengths and valence angles (see Tables 3 and 4). Nothing unexpected was noticed; all distances and angles have values close to those normally encountered in other pyridine derivatives and oximes. Our determinations show no clear indications of π-bond localization in the pyridinium

Table 3. *Bond distances* (Å) *in benzyl-P_2A bromide and benzyl-P_2A sulphonate with e.s.d.'s in parentheses*

	Benzyl-P_2A sulphonate	Benzyl-P_2A bromide
N(1)–C(1)	1·351 (2)	1·341 (2)
C(1)–C(2)	1·345 (2)	1·353 (3)
C(2)–C(3)	1·372 (2)	1·361 (3)
C(3)–C(4)	1·370 (2)	1·351 (3)
C(4)–C(5)	1·361 (2)	1·392 (3)
C(5)–N(1)	1·365 (2)	1·349 (2)
C(5)–C(7)	1·472 (2)	1·454 (3)
C(7)–N(2)	1·271 (2)	1·279 (2)
N(2)–O(1)	1·380 (1)	1·373 (2)
N(1)–C(6)	1·492 (2)	1·484 (2)
C(6)–C(8)	1·506 (2)	1·517 (3)
C(8)–C(9)	1·379 (2)	1·376 (3)
C(9)–C(10)	1·376 (3)	1·412 (3)
C(10)–C(11)	1·372 (3)	1·371 (4)
C(11)–C(12)	1·357 (3)	1·378 (4)
C(12)–C(13)	1·354 (3)	1·382 (3)
C(13)–C(8)	1·377 (2)	1·402 (3)
S–O(2)	1·454 (1)	
S–O(3)	1·426 (1)	
S–O(4)	1·421 (1)	
S–C(14)	1·723 (2)	
⟨C–H⟩	0·90 (7)	0·9 (1)

Table 4. *Valence angles* (°) *in benzyl-P_2A bromide and benzyl-P_2A sulphonate* (*e.s.d.'s in parentheses*)

	Benzyl-P_2A sulphonate	Benzyl-P_2A bromide
N(1)–C(1)–C(2)	121·5 (1)	120·7 (2)
C(1)–C(2)–C(3)	119·9 (2)	120·7 (2)
C(2)–C(3)–C(4)	118·2 (2)	118·3 (2)
C(3)–C(4)–C(5)	121·7 (2)	121·4 (2)
C(4)–C(5)–N(1)	118·7 (1)	118·2 (2)
C(5)–N(1)–C(1)	119·8 (1)	120·7 (2)
N(1)–C(5)–C(7)	118·9 (1)	119·7 (2)
C(4)–C(5)–C(7)	122·3 (1)	122·2 (2)
C(5)–C(7)–N(2)	116·1 (1)	116·8 (2)
C(7)–N(2)–O(1)	110·7 (1)	112·5 (2)
C(8)–C(9)–C(10)	118·9 (2)	120·9 (2)
C(9)–C(10)–C(11)	121·1 (2)	118·7 (3)
C(10)–C(11)–C(12)	119·7 (2)	121·3 (3)
C(11)–C(12)–C(13)	119·9 (2)	119·8 (2)
C(12)–C(13)–C(8)	121·5 (2)	120·4 (2)
C(13)–C(8)–C(9)	119·0 (2)	118·9 (2)
C(1)–N(1)–C(6)	118·8 (1)	118·1 (2)
C(5)–N(1)–C(6)	121·3 (1)	121·2 (2)
N(1)–C(6)–C(8)	112·2 (1)	111·7 (2)
C(6)–C(8)–C(9)	120·6 (1)	118·7 (2)
C(6)–C(8)–C(13)	120·4 (1)	122·4 (2)
O(2)–S–O(3)	111·55 (6)	
O(2)–S–O(4)	112·63 (7)	
O(2)–S–C(14)	107·64 (9)	
O(3)–S–O(4)	113·49 (9)	
O(3)–S–C(14)	105·62 (8)	
O(4)–S–C(14)	105·27 (10)	

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36305 (19 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 5. *Selected torsion angles* (°) *in benzyl-P_2A sulphonate and benzyl-P_2A bromide*

	Benzyl-P_2A sulphonate	Benzyl-P_2A bromide
N(2)=C(7)–C(5)–C(4)	32·5 (4)	3·9 (5)
C(5)–N(1)–C(6)–C(8)	74·1 (4)	77·8 (5)
C(13)–C(8)–C(6)–N(1)	61·8 (4)	44·5 (5)

Table 6. *Short* O–H···O *interaction in benzyl-P_2A sulphonate* (*A acceptor, D donor*)

D–H	*A*	Transformation	*D*–H (Å)	*A*–H (Å)	*D*···*A* (Å)	*D*–H···*A* (°)
O(1)···HO(1)	O(2)	*x,y,z*	0·86 (10)	1·81 (10)	2·666 (3)	173·6 (4)

ring nor signs of a less pronounced double-bond character of the C(7)=N(2) bond. Such behaviour was suggested in the closely related 2-[(hydroxyimino)-methyl]-1-methylpyridinium iodide (Carlström, 1966).

The benzyl, pyridinium and oxime parts of the two molecules are individually planar. Relative orientations of these parts can best be seen from the torsion angles given in Table 5. Some torsion angles differ up to 30° between the bromide and the sulphonate, but we believe that these differences only reflect changes in the crystal packing induced by the difference in the anions of the two molecules.

The methylsulphonate anion and the 1-benzyl-2-[(hydroxyimino)methyl]pyridinium cation are linked through a hydrogen bridge (Table 6). A similar interaction could exist in the bromide since the Br···O(1) distance (3·128 Å) is shorter than the normal van der Waals contact (3·28 Å). This could not be proved, however, because we were unable to locate a refinable H atom on O(1). In the 1-methyl analogue a short I···O distance was also noted.

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Discussion of an Order–Disorder Behaviour Near T_c in the Chloranil Displacive Transition

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Abstract

The study of the temperature variation of molecular rotations in chloranil (tetrachloro-*p*-benzoquinone) between 10 and 89 K [for T_c = 94 K; Baudour, Delugeard, Cailleau, Sanquer & Zeyen (1981). *Acta Cryst.* B**37**, 1553–1557] is extended above 89 K. First it is shown that between T_c − 5 K and T_c a classical determination of the structure based principally on superlattice reflexions cannot be realized because the atomic displacements δ decrease continuously as T_c is approached and become of the same order as the r.m.s. thermal amplitude u. So another method is proposed based on the measurements of some main reflexions

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