References

BURLEY, S. K. & PETSKO, G. A. (1986). *J. Am. Chem. Soc.* **108**, 7995–8001.
DESIRAJU, G. R. (1991). *Acc. Chem. Res.* **24**, 290–296.
Enraf–Nonius (1989). *CAD-4 Software*. Enraf–Nonius, Delft, The Netherlands.
GAVEZZOTTI, A. (1989). *J. Am. Chem. Soc.* **111**, 1835–1843.
GAVEZZOTTI, A. (1990). *J. Phys. Chem.* **94**, 4319–4325.
GOLDBERG, I., BERNSTEIN, J. & KOSOWER, E. M. (1982). *Acta Cryst.* B**38**, 1990–2000.
GOLDBERG, I., BERNSTEIN, J., KOSOWER, E. M., GOLDSTEIN, E. & PAZHENCHEVSKY, B. (1983). *J. Hetercyc. Chem.* **20**, 903–912.
GREEN, B. S., LAHAV, M. & RABINOVICH, D. (1979). *Acc. Chem. Res.* **12**, 191–197.
JOHNSON, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak-Ridge National Laboratory, Tennessee, USA.
KAUPP, G. & HAAK, M. (1993). *Angew. Chem. Int. Ed. Engl.* **32**, 694–695.
KLEBE, G. & DIEDERICH, F. (1993). *Phil. Trans. R. Soc. Lond. A*, **345**, 37–48.
NARDELLI, M. (1983). *Comput. Chem.* **7**, 95–98.
ROUGHTON, A. L., MUNEER, M. & DEMUTH, M. (1993). *J. Am. Chem. Soc.* **115**, 2085–2087.
SAKAMOTO, M., HOKARI, N., TAKAHASHI, M., FUJITA, T., WATANABE, S., IIDA, I. & NISHIO, T. (1993). *J. Am. Chem. Soc.* **115**, 818.
SEKINE, A., HORI, K., OHASHI, Y., YAGI, M. & TODA, F. (1989). *J. Am. Chem. Soc.* **111**, 697–699.
SHELDRICK, G. M. (1976). *SHELX*76. *Program for Crystal Structure Determination*. Univ. of Cambridge, England.
SHELDRICK, G. M. (1985). *SHELXS*86. *Crystallographic Computing* 3, edited by G. M. SHELDRICK, C. KRUGER & R. GODDARD, pp. 175–189. Oxford Univ. Press.
STEINER, T. (1994). *J. Chem. Soc. Chem. Commun.* pp. 2341–2342.
TANAKA, K., KAKINOKI, O. & TODA, F. (1992). *J. Chem. Soc. Chem. Commun.* pp. 1053–1054.
THOMAS, J. M., MORSI, S. E. & DESVERGNE, J. P. (1977). *Adv. Phys. Org. Chem.* **15**, 63–151.
TODA, F. & AKAGI, K. (1971). *Tetrahedron*, **27**, 2801–2810.
TODA, F. & FUJITA, J. (1972). *Bull. Chem. Soc. Jpn*, **45**, 1928–1929.
TODA, F., ISHIHARA, H. & AKAGI, K. (1969). *Tetrahedron Lett.* pp. 2531–2534.
TODA, F. & MIYAMOTO, H. (1993). *J. Chem. Soc. Perkin Trans.* 1, pp. 1129–1132.
TODA, F., NAKAOKA, H., YUWANE, K. & TODO, E. (1973). *Bull. Chem. Soc. Jpn*, **46**, 1737–1740.
TODA, F., SODA, S. & YAGI, M. (1987). *J. Chem. Soc. Chem. Commun.* pp. 1413–1414.
VAIDA, M., POPOVITZ-BIRO, R., LEISEROWITZ, L. & LAHAV, M. (1990). *Photochemistry in Organized and Constrained Media*, edited by V. RAMAMURTHY, pp. 247–302. Weinheim: Verlag-Chemie.
WILSON, K. R. & PINCOCK, R. E. (1975). *J. Am. Chem. Soc.* **97**, 1474–1478.
WINTER, W. & TODA, F. (1975). Unpublished results.

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Structure of 5-(3,4,5-Trimethoxyphenyl)-2-iodomethyltetrahydrofuran: A Precursor of Acetylcholinesterase Inhibitors with Platelet-Activating Factor Antagonistic Activity

BY LAURENCE LE TEXIER, EDITH FAVRE AND JEAN-JACQUES GODFROID

Laboratoire de Pharmacochimie Moléculaire, Unité de Recherche Chimie et Pharmacologie, Université Paris 7 Denis Diderot, 2 Place Jussieu, 75251 Paris CEDEX 05, France

AND SABINE HALUT-DESPORTES

Laboratoire de Chemie des Métaux de Transition, UA No. 419, Université Paris 6 Pierre et Marie Curie, 4 Place Jussieu, 75252 Paris CEDEX 05, France

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Abstract

The *trans* configuration of an iodomethyltetrahydrofuran derivative (2) has been determined as part of a structure–activity relationships study of acetylcholinesterase inhibitors with correlated platelet-activating factor antagonistic activity. Synthesis of tetrahydrofurfuryloxypyridinium bromide *via* the key intermediate (2) is described. $C_{14}H_{19}IO_4$, $M_r = 378.2$, monoclinic, space group $P2_1/n$, $a = 7.686(1)$, $b = 8.113(2)$, $c = 24.249(6)$ Å, $\beta = 99.96(2)°$, $V = 1489(1)$ Å^3, $Z = 4$, $D_x = 1.69$ Mg m^{-3}, $T = 293$ K, $F(000) = 752$, μ(Mo $K\alpha$) = 21.3 cm^{-1}, $R = 0.034$ for 2494 independent reflexions with $I > 3\sigma(I)$.

Introduction

The structure of iodomethyltetrahydrofuran (2) (Fig. 1) was determined as part of the investigation into structure–activity relationships in 2,5-disubstituted tetrahydrofuran derivatives with dual activity, *i.e.* acetylcholinesterase inhibition combined with platelet-activating factor antagonistic activity in the same molecule (Le Texier *et al.*, 1995). The final aim is to find potent drugs as palliative treatment of Alzheimer's disease.

Alzheimer's disease (AD) is a progressive dementia which results in severe memory loss and cognitive decline. Memory impairments in AD result from a deficit

of cholinergic function in the central nervous system (Perry, 1986). Postmortem findings show significantly low levels of acetylcholine in the brain (Wilkerson, Kergaye & Tam, 1993), consistent with extensive neurodegeneration of the cholinergic system (Vogels *et al.*, 1990) and marked reduction of acetylcholine synthesis (Sims *et al.*, 1983). One strategy for the palliative treatment of AD is to inhibit acetylcholinesterase (AChE), the enzyme responsible of the metabolic degradation of acetylcholine. Tacrine (Knapp *et al.*, 1994), a potent AChE inhibitor, is the first drug approved against AD in the USA (Villalobos *et al.*, 1994) in spite of its hepatoxicity noted in clinical studies (Summers, Koehler, Marsh, Tachiki & Kling, 1989).

Platelet-activating factor (PAF) is a potent endogenous ether-phospholipid mediator found in a large variety of cells implicated in inflammatory and immune processes (Braquet, Touqui, Shen & Vargaftig, 1987). PAF is also implicated in the brain: the biosynthesis of PAF occurs in neural tissues (Goracci, Francescangeli, Dreyfus, Boila & Freysz, 1994). The presence of specific binding sites are detected in the brain (Domingo, Spinnewyn, Chabrier & Braquet, 1988) and PAF may play a physiological role in neural development, but may also be involved in pathological events (Kornecki & Ehrlich, 1991). It has been demonstrated that PAF is an important mediator of ischemia-induced damages in the central nervous system (Bazan, Squinto, Braquet, Panetta & Marcheselli, 1991; Lindsberg, Hallenbeck & Feuerstein, 1991). In addition, the administration of PAF antagonists attenuates both the functional and histological results in experimental cerebral ischemia and improves cerebral metabolism (Krieglstein, Beck & Siebert, 1986).

A combination of anti-PAF and anti-AChE activities in the same molecule is related to the neuroprotective effect of PAF antagonists against cerebral ischemia and excitotoxic damage in cultured neurons (Prehn & Krieglstein, 1993).

2,5-Disubstituted tetrahydrofuran derivatives present *cis–trans* isomerism; the separation and structure determination of each isomer are of prime importance for biological study. The synthesis and X-ray analysis of intermediate (2) allowed us to prepare *cis* and *trans* isomers of the acetylcholinesterase inhibitor (6).

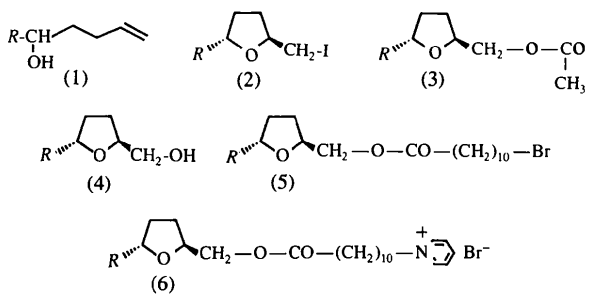

Fig. 1. Synthetic intermediates and acetylcholinesterase inhibitor structures. Only *trans* configurations are shown. R = 3,4,5-Trimethoxyphenyl, $(MeO)_3Ph$.

Experimental

Synthesis of 11-[5-(3,4,5-*trimethoxyphenyl*)*tetrahydrofurfuryloxy*]*undecanoyl pyridinium bromide* (6)

Five steps were necessary to achieve the synthesis of (6). Synthetic intermediates and acetylcholinesterase inhibitors formulae are shown in Fig. 1.

Preparation of the iodomethyltetrahydrofuran (2)

Conventional Grignard reaction using 3,4,5-trimethoxybenzaldehyde and a magnesium derivative of 1-bromo-4-butene provided the ethylenic alcohol (1). The iodocyclization of (1) according to Bartlett (Bartlett & Holmes, 1983) gave the iodomethyltetrahydrofuran (2) as a mixture of *cis* and *trans* isomers. Yield 60%; ratio *cis/trans* 30/70 determined from ^1H NMR spectra. Crystallization in petroleum ether/diethyl ether, 35:65 *v/v*, afforded the pure major *trans* isomer as a white powder, m.p. = 332.5 K. The *trans* configuration was determined by the X-ray study presented in this paper. ^1H NMR: δ 1.75–2.33 (*m*, 4H, $CH_2—CH_2$ THF ring), 3.22 (*dd*, 1H, $CH_2—I$), 3.32 (*dd*, 1H, $CH_2—I$), 3.75 (*s*, 3H, OCH_3), 3.79 (*s*, 6H, OCH_3), 4.25 (*m*, 1H, O—C<u>H</u>—CH_2I), 4.98 (*dd*, 1H, O—C<u>H</u>—Ph), 6.48 (*s*, 2H, H_{ar}).

Isolation of the pure *cis* isomer, as a pale yellow oil, was conducted by preparative high pressure liquid chromatography (HPLC) performed on a Precision Instrument Axial Compression System using petroleum ether/diethylether, 45:55 *v/v*, as eluant. The *cis*-iodide compound was isolated as a pale yellow oil, $R_f = 0.47$ (diethylether); ^1H NMR: δ 1.81–2.31 (*m*, 4H, $CH_2—CH_2$ THF ring), 3.36 (*dd*, 1H, $CH_2—I$), 3.39 (*dd*, 1H, $CH_2—I$), 3.76 (*s*, 3H, OCH_3), 3.81 (*s*, 6H, OCH_3), 4.05 (*m*, 1H, O—C<u>H</u>—CH_2I), 4.86 (*dd*, 1H, O—C<u>H</u>—Ph), 6.61 (*s*, 2H, H_{ar}).

Preparation of the acetoxymethyltetrahydrofuran (3)

1 g of the *trans*-iodide isomer (2) (2.64 mmol) was treated at 353 K for 6 d with 0.882 g of silver acetate (2 eq., 5.28 mmol) in 20 ml of dry dimethylformamide (DMF). After filtration of silver iodide and partial elimination of DMF under reduced pressure, water was added and the mixture was extracted with diethylether. After standard work up, the crude product was chromatographed on a silica gel column using petroleum ether/diethylether, 60:40 *v/v*, as eluant to obtain the *trans*-acetate compound (3) as a dark yellow oil. Yield 30%; $R_f = 0.39$ (diethylether).

The *cis*-acetate derivative was obtained using the same procedure as for the *trans* isomer, starting with the *cis*-iodide. Yield 30%; $R_f = 0.39$ (diethylether).

Preparation of the hydroxymethyltetrahydrofuran (4)

Saponification of each isomer of acetate (3) with potassium hydroxide in methanol, followed by purification on silica gel column using dichloromethane/methanol, 98:2 *v/v*, as eluant, led to the corresponding hydroxymethyltetrahydrofuran (4) as a yellow oil. Yield 78% *versus* acetate (3) and 23% *versus* iodide derivative (2); $R_f = 0.47$ (methanol/chloroform, 5:95, *v/v*).

Preparation of the title compound (6)

Each isomer of the hydroxymethyltetrahydrofuran (4) was esterified with 11-bromoundecanoyl chloride to give the *cis* and *trans*-bromoester (5), which were converted into the corresponding isomer of the acetylcholinesterase inhibitor (6) by heating with pyridine, as previously described.

Cis and *trans* compounds were isolated as waxy products. Yield 86%; $R_f = 0.52$ (chloroform/methanol/acetic acid, 70:35:12, *v/v/v*). ^{1}H NMR of *trans* isomer (6): δ 1.20 (*m*, 2H, $-C\underline{H}_2-CH_2-CO$), 1.31 [*m*, 12H, $-(CH_2)_6-$], 1.83 (*m*, 2H, $-CH-CH-$, THF ring), 2.01 (*m*, 2H, $-C\underline{H}_2-C-N^+$), 2.14–2.33 (*m*, 4H, $-CH-CH-$, THF ring + $CO-CH_2-$), 3.81 [1*s*, 3H, $(CH_3O)_{para}$], 3.85 [1*s*, 6H, $2(CH_3O)_{meta}$], 4.12 and 4.18 (2*dd*, 2H, CH_2-O-CO), 4.47 (*m*, 1H, $-O-C\underline{H}-CH_2-O-CO-$), 4.93 (*m*, 1H, $-C\underline{H}-Ph$), 4.99 (*t*, 2H, $-CH_2-N^+$), 6.56 (*s*, 2H, $-CH_{ar}$), 8.10 (*m*, 2H, $H_{meta\text{-pyridinium}}$), 8.48 (*t*, 1H, $H_{para\text{-pyridinium}}$), 9.47 (*d*, 2H, $H_{ortho\text{-pyridinium}}$). ^{1}H NMR of *cis* isomer (6): δ 1.20–1.36 [*m*, 12H, $-(CH_2)_6-$], 1.69 (*m*, 2H, $-C\underline{H}_2-CH_2-CO$), 1.81 (*m*, 3H, $-CH_2-CH-$, THF ring), 2.00 (*m*, 2H, $-C\underline{H}_2-C-N^+$), 2.08 (*m*, 1H, $-C-CH-$, THF ring), 2.31 (*t*, 2H, $CO-CH_2-$), 3.80 [1*s*, 3H, $(CH_3O)_{para}$], 3.84 [1*s*, 6H, $2(CH_3O)_{meta}$], 4.22 (*m*, 2H, CH_2-O-CO), 4.30 (*m*, 1H, $-O-C\underline{H}-CH_2-O-CO-$), 4.82 (*t*, 1H, $-C\underline{H}-Ph$), 4.98 (*t*, 2H, $-CH_2-N^+$), 6.57 (*s*, 2H, $-CH_{ar}$), 8.11 (*m*, 2H, $H_{meta\text{-pyridinium}}$), 8.49 (*t*, 1H, $H_{para\text{-pyridinium}}$), 9.49 (*d*, 2H, $H_{ortho\text{-pyridinium}}$).

Biological activities were evaluated for both *cis* and *trans* isomers as previously described. Antiaggregant-PAF activity was measured according to Born & Cross (1963) and acetylcholinesterase inhibition was determined using the Ellman photometric method (Ellman, Courtney, Andres, Featherstone & Featherstone, 1961).

Table 1 shows that *cis* and *trans* isomerism does not induce significant differences in both activities.

Table 1. *Anti-PAF and anti-acetylcholinesterase activities of* (6)

Isomer	IC_{50} μM Anti-PAF	IC_{50} μM Anti-AChE
Trans/cis (70/30)	15.0	0.38
Trans	12.0	0.35
Cis	19.0	0.57

X-ray analysis

Single crystals were grown in pentane. A colorless crystal was selected and set up on an automatic CAD-4F diffractometer using monochromated Mo$K\alpha$ radiation.

Unit-cell dimensions with e.s.d.'s were obtained from least-squares refinements of the setting angle of 25 well centered reflections. Two standard reflections were monitored periodically: they showed no change during data collection. 4061 reflections in total were collected in the range $4 < 2\theta < 50°$ using the $\omega/2\theta$ technique (scan width $= 0.8 + 0.34\text{tg}\,\theta$, scan speed in the range $1.8 < sp < 21° \text{ min}^{-1}$, background measurements at both ends of the scan for a total time 25% of the scan time), of which 3566 were unique (merging $R = 0.02$) and 2494 were considered as observed with $I > 3\sigma(I)$. Corrections were made for Lorentz and polarization effects. Empirical absorption corrections (*DIFABS*; Walker & Stuart, 1983) and a secondary extinction correction were applied. Computations were performed using *CRYSTALS* (Watkin, Curruthers & Betteridge, 1988) adapted on a MicroVAXII. The structure was solved by direct methods using the *SHELX*S86 progam (Sheldrick, 1985) and subsequent Fourier maps. H atoms were found on difference maps, their positions were not refined and they were given an overall isotropic thermal parameter. Non-H atoms were anisotropically refined. Least-squares refinements with 175 variable parameters, with approximation in three blocks to the normal matrix, were carried out by minimizing the function $\Sigma w(|F_o| - |F_c|)^2$, where F_o and F_c are the observed and calculated structure factors. Models reached convergence with $R = \Sigma(||F_o| - |F_c||)/\Sigma|F_o|$ and $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w(F_o)^2]^{1/2}$; unit weights were used. The final cycle converged with $R = 0.034$ and $R_w = 0.035$. Criteria for a satisfactory complete analysis were the ratios of r.m.s. shift to standard deviation being less than 0.1 and no significant features in the final difference map.

Results and discussion

Table 2 gives the atomic parameters of the non-H atoms, while interatomic distances and bond angles are given in Table 3.* Fig. 2 gives a view of the molecule with atom numbering, using *Cameron* (Pearce & Watkin, 1992).

The tetrahydrofuran has an envelope form. The four atoms O(1), C(2), C(4) and C(5) are coplanar and C(3) is out of the plane, the deviations from the plane being, respectively, 0.062, −0.038, 0.034, −0.058 and −0.574 Å.

The distances of C(6) and C(8) from the plane of tetrahydrofuran are, respectively, −0.830 and 0.985 Å

* Lists of structure factors, anisotropic thermal parameters, bond lengths and angles involving H-atoms and H-atom coordinates have been deposited with the IUCr (Reference: DU0397). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Fractional atomic coordinates with e.s.d.'s in parentheses*

	x	y	z	U_{eq}
I(7)	0.24193 (5)	0.21435 (5)	0.01825 (1)	0.0584
O(1)	0.5611 (4)	0.3889 (4)	0.1123 (2)	0.0463
O(14)	1.2448 (4)	0.7769 (4)	0.1233 (1)	0.0498
O(16)	1.1073 (4)	0.9559 (4)	0.1974 (1)	0.0465
O(18)	0.7890 (4)	0.8798 (4)	0.2231 (1)	0.0505
C(2)	0.5302 (6)	0.2203 (6)	0.1233 (2)	0.0460
C(3)	0.6602 (6)	0.1227 (5)	0.0959 (2)	0.0477
C(4)	0.8171 (6)	0.2417 (5)	0.1020 (2)	0.0469
C(5)	0.7249 (6)	0.4082 (5)	0.0922 (2)	0.0405
C(6)	0.3355 (6)	0.1828 (5)	0.1054 (2)	0.0474
C(8)	0.8264 (5)	0.5534 (5)	0.1207 (2)	0.0369
C(9)	0.9898 (6)	0.5939 (5)	0.1076 (2)	0.0409
C(10)	1.0837 (5)	0.7274 (5)	0.1335 (2)	0.0379
C(11)	1.0154 (5)	0.8207 (5)	0.1734 (2)	0.0362
C(12)	0.8502 (5)	0.7792 (5)	0.1858 (2)	0.0403
C(13)	0.7570 (5)	0.6454 (5)	0.1595 (2)	0.0415
C(15)	1.2998 (6)	0.7168 (6)	0.0740 (2)	0.0544
C(17)	1.1744 (6)	0.9392 (7)	0.2545 (2)	0.0559
C(19)	0.6159 (7)	0.8458 (7)	0.2344 (2)	0.0587

Table 3. *Interatomic distances* (Å) *and bond angles* (°), *with e.s.d.'s in parentheses*

I(7)—C(6)	2.126 (5)	O(1)—C(2)	1.420 (6)
O(1)—C(5)	1.434 (5)	O(14)—C(10)	1.364 (5)
O(14)—C(15)	1.421 (5)	O(16)—C(11)	1.377 (5)
O(16)—C(17)	1.398 (6)	O(18)—C(12)	1.360 (5)
O(18)—C(19)	1.430 (5)	C(2)—C(3)	1.515 (6)
C(2)—C(6)	1.515 (6)	C(3)—C(4)	1.531 (6)
C(4)—C(5)	1.523 (6)	C(5)—C(8)	1.512 (5)
C(8)—C(9)	1.387 (6)	C(8)—C(13)	1.377 (6)
C(9)—C(10)	1.389 (6)	C(10)—C(11)	1.400 (6)
C(11)—C(12)	1.396 (6)	C(12)—C(13)	1.391 (6)

C(5)—O(1)—C(2)	110.7 (3)	C(15)—O(14)—C(10)	117.6 (3)
C(17)—O(16)—C(11)	114.6 (3)	C(19)—O(18)—C(12)	116.8 (3)
C(3)—C(2)—O(1)	106.0 (4)	C(6)—C(2)—O(1)	109.2 (4)
C(6)—C(2)—C(3)	117.6 (4)	C(4)—C(3)—C(2)	101.3 (4)
C(5)—C(4)—C(3)	101.9 (3)	C(4)—C(5)—O(1)	105.2 (3)
C(8)—C(5)—O(1)	110.1 (3)	C(8)—C(5)—C(4)	115.4 (4)
C(2)—C(6)—I(7)	114.1 (3)	C(9)—C(8)—C(5)	119.7 (4)
C(13)—C(8)—C(5)	120.2 (4)	C(13)—C(8)—C(9)	120.1 (4)
C(10)—C(9)—C(8)	120.0 (4)	C(9)—C(10)—O(14)	124.3 (4)
C(11)—C(10)—O(14)	115.3 (4)	C(11)—C(10)—C(9)	120.4 (4)
C(10)—C(11)—O(16)	119.7 (4)	C(12)—C(11)—O(16)	121.4 (4)
C(12)—C(11)—C(10)	118.8 (4)	C(11)—C(12)—O(18)	115.5 (4)
C(13)—C(12)—O(18)	124.2 (4)	C(13)—C(12)—C(11)	120.3 (4)
C(12)—C(13)—C(8)	120.3 (4)		

and the angles between the plane of the tetrahydrofuran and the lines C(2)—C(6) and C(8)—C(5) are 31.5 and 43.6°, respectively. Therefore, the substituents C(6) and C(8) are equatorial, showing the *trans* configuration.

The aromatic ring is well planed as the deviations from the plane point out: −0.002 for C(8), −0.001 for C(9), 0.005 for C(10), −0.007 for C(11), 0.004 for C(12) and 0.001 Å for C(13). The angle between this plane and the plane of tetrahydrofuran is 129.7°.

The plane of the phenyl group contains the three O atoms and the atom C(19) is almost in the plane, while the atoms C(15) and C(17) are out of the plane. The distances of the three atoms are −0.102, −0.375 and 1.162 Å, respectively. This structural feature can be seen in Fig. 3.

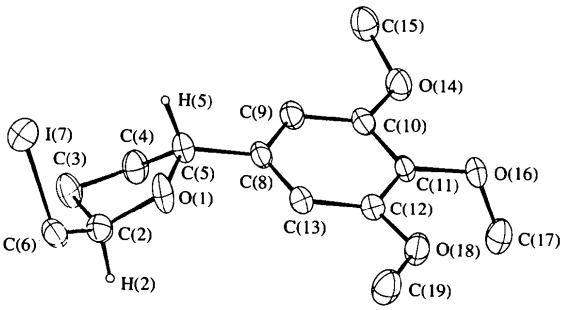

Fig. 2. View of the molecule, ellipsoids represent 30% probability.

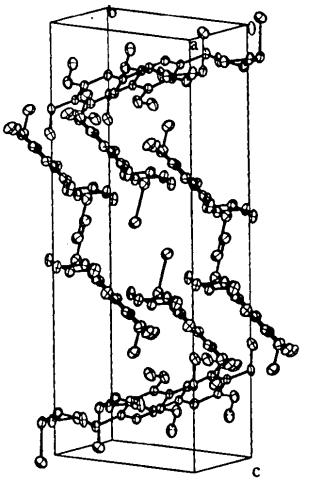

Fig. 3. Packing in the unit cell.

References

BARTLETT, P. A. & HOLMES, C. P. (1983). *Tetrahedron Lett.* **24**, 1365–1368.

BAZAN, N. G., SQUINTO, S. P., BRAQUET, P., PANETTA, T. & MARCHESELLI, V. L. (1991). *Lipids*, **26**, 1236–1242.

BORN, G. V. R. & CROSS, M. J. (1963). *J. Physiol.* **168**, 178–195.

BRAQUET, P., TOUQUI, L., SHEN, T. Y. & VARGAFTIG, B. B. (1987). *Pharmacol. Rev.* **39**, 97–145.

DOMINGO, M. T., SPINNEWYN, B., CHABRIER, P. E. & BRAQUET, P. (1988). *Biochem. Biophys. Res. Commun.* **151**, 730–736.

ELLMAN, G. L., COURTNEY, D., ANDRES, V., FEATHERSTONE, J. & FEATHERSTONE, R. (1961). *Biochem. Pharmacol.* **7**, 88–95.

GORACCI, G., FRANCESCANGELI, E., DREYFUS, H., BOILA, A. & FREYSZ, L. (1994). *J. Lip. Med.* **10**, 7–8.

KNAPP, M., KNOPMAN, D., SOLOMON, P., PENDLEBURY, W., DAVIS, C. & GRACON, S. (1994). *J. Am. Med. Assoc.* **271**, 985–998.

KORNECKI, E. & EHRLICH, Y. (1991). *Lipids*, **26**, 1243–1246.

KRIEGLSTEIN, J., BECK, T. & SIEBERT, A. (1986). *Life Sci.* **39**, 2237–2334.

LE TEXIER, L., FAVRE, E., REDEUILH, C., BLAVET, N., BELLAHSENE, F., DIVE, G., PIROTSKY, E. & GODFROID, J.-J. (1995). *J. Lip. Med.* Submitted.

LINDSBERG, P., HALLENBECK, J. & FEUERSTEIN, G. (1991). *Ann. Neurol.* **30**, 117–129.

PEARCE, L. & WATKIN, D. (1992). Personal communication. Chemical Crystallography Laboratory, Oxford.

PERRY, E. K. (1986). *Br. Med. Bull.* **42**, 63–69.

PREHN, J. & KRIEGLSTEIN, J. (1993). *J. Neurosci. Res.* **34**, 179–188.

SHELDRICK, G. M. (1985). *SHELXS86. Program for the Solution of Crystal Structures*. Univ. of Göttingen, Germany.
SIMS, N., BOWEN, D., ALLEN, S., SMITH, C., NEARY, D., THOMAS, D. & DAVISON, A. (1983). *J. Neurochem.* **40**, 503–509.
SUMMERS, W., KOEHLER, A., MARSH, G., TACHIKI, K. & KLING, A. (1989). *Lancet*, **1**, 729.
VILLALOBOS, A., BLAKE, J., BIGGERS, K., BUTLER, T., CHAPIN, D., CHEN, Y., IVES, J., JONES, S., LISTON, D., NAGEL, A., NASON, D., NIELSEN, J., SHALABY, I. & WHITE, W. (1994). *J. Med. Chem.* **37**, 2721–2734.
VOGELS, O., BROERE, C., TER LAAK, H., DONKELAAR, H., NIEUWENHUYS, R. & SCHULTE, R. (1990). *Neurobiol. Aging*, **11**, 3–13.
WALKER, N. & STUART, D. (1983). *Acta Cryst.* A**39**, 158–166.
WATKIN, D., CARRUTHERS, J. & BETTERIDGE, P. (1988). *An Advanced Crystallographic Computer Program*. Chemical Crystallography Laboratory, Oxford.
WILKERSON, W. W., KERGAYE, A. A. & TAM, S. W. (1993). *J. Med. Chem.* **36**, 2899–2907.

Acta Cryst. (1995). B**51**, 867–873

Structure of (*Z*,*Z*)-*N*-{[2-(4-Methylphenyl)-2-(4-methylphenyl)imino]ethylidene}aniline *N*-Oxide: Conjugation in Systems with the Nitrone Moiety

BY P. K. OLSZEWSKI, P. MILART AND K. STADNICKA

Faculty of Chemistry, Jagiellonian University, ul. Ingardena 3, 30-060 *Kraków, Poland*

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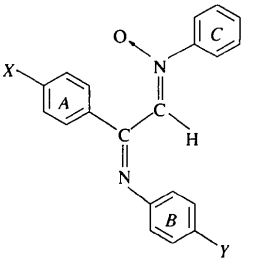
Abstract

The crystal structure of the title compound has been determined. The crystals are orthorhombic: $Pna2_1$, $a = 8.6190(6)$, $b = 10.9705(6)$, $c = 18.7157(6)$ Å, $V = 1769.7(2)$ Å^3, $Z = 4$. The structure was solved by direct methods and refined using 2127 reflections with $F^2 \geq 2\sigma(F^2)$ to a final $R = 0.0371$ and $wR(F^2) = 0.0865$. Second-harmonic generation (SHG) activity was checked by Kurtz powder method in relation to urea. The molecule reveals the *Z*,*Z*,*s*-*E*-configuration of the 1,4-diazabutadiene fragment with a N=C—C=N torsion angle of $-145.8(3)°$. All aryl rings are twisted against each other. The crystal packing is controlled by very weak C—H···O hydrogen bonding, coupling of dipoles and weak van der Waals interactions. An influence of π-electron conjugation on the geometry of the nitrone moiety in conjugated systems X=C—C=N → O (X = C, N or O) is discussed.

Introduction

This work is a continuation of the structural study of 1,2,4-triaryl-1,4-diazabutadiene N^4-oxides (see Scheme) with different substituents *X* and *Y* in *A* and *B* phenyl rings, respectively. The presented *N*-oxide (*N*22) has methyl groups in both positions *X* and *Y*, whereas the previously described compounds had *X* = H and either a methoxy (*N*11) or *N*,*N*-dimethylamino (*N*15) group in the *Y* position (Olszewski & Stadnicka, 1995). The ^{13}C NMR spectra of nitrones having the 1,4-diazabutadiene system, in addition to the nitrone group, showed distinct upfield shifts, which indicated conjugation of the two heteroen bonds and supported an almost coplanar arrangement of the azomethine and nitrone groups (Moskal & Milart, 1985). Although the planarity of the system is necessary for full conjugation, the nitrones cannot achieve planarity due to steric hindrance between the H atoms of the aldonitrone carbon and phenyl ring *B*. Therefore, a question arises if a degree of conjugation can be related to the geometry of the X=C—C=N(→ O) fragment with X = C, N or O. To answer this question the database study was performed. The structural data of two other nitrones, *N*25 and *N*65, which will be published elsewhere, are also taken into account.



*N*11 *X* = H, *Y* = OCH_3
*N*15 *X* = H, *Y* = $N(CH_3)_2$
*N*22 *X* = CH_3, *Y* = CH_3
*N*25 *X* = CH_3, *Y* = $N(CH_3)_2$
*N*65 *X* = Br, *Y* = $N(CH_3)_2$

Experimental

The title compound was obtained according to the procedure published earlier for the other conjugated nitrones (Moskal & Milart, 1984) and purified by repeated recrystallization from saturated (at boiling point) ethanol solution. Yield 62%, m.p. 464–465 K. *Elemental analysis*. Found: C 80.32, H 6.11, N 8.62; calc.